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SLOVENSKO ZDRUŽENJE
ZA GASTROENTEROLOGIJO
IN HEPATOLOGIJO

V tokratni dvojni številki strokovne revije Slovenskega združenja za gastroenterologijo in hepatologijo objavljamo štirinajst prispevkov, med katerimi sta dva raziskovalna članka, dvoje priporočil, trije pregledni, štirje strokovni članki in trije zanimivi prikazi primerov.

V prvem članku so avtorji želeli ugotoviti, kakšna je poraba bioloških zdravil v Sloveniji v zadnjih dveh letih. Analizirali so podatke o biološkem zdravljenju 2748 bolnikov s kronično vnetno črevesno boleznijo (KVČB), zbrane v UR-CARE registru v obdobju od oktobra 2020 do 1. oktobra 2022. Biološko terapijo je prejemalo 1014 bolnikov s Crohnovo boleznijo (CB) in 623 bolnikov z ulceroznim kolitisom (UK). Kot zdravilo prvega reda so bili najpogosteje predpisani zaviralci TNF-alfa: adalimumab pri CB (39,5 %) in infliximab pri UK (38,8 %). Kot zdravilo drugega in tretjega reda pa ustekinumab pri CB (28,9 % in 43,1 %) in vedolizumab pri UK (36,8 % in 43,3 %). Več kot polovica vseh bolnikov je bila ob zaključku analize na zdravilih prvega reda (CB 58,2 %, UK 57,8 %), pri čemer je bil delež bolnikov, zdravljenih z vedolizumabom pri CB 75,8 %, pri UK 75,1 % pri zdravljenju z ustekinumabom pri CB 75,2 %, pri UK 94,4 %. Pri zaviralcih TNF-alfa je bil delež zdravljenja prvega reda (infliximab: CB 55,8 %, UK 49,6 %, adalimumab: CB 49,9 %, UK 37,3 %). Raziskava je pokazala, da se vzorci predpisovanja bioloških zdravil bistveno ne razlikuje v obeh univerzitetnih in šestih regionalnih KVČB centrih, ki sodelujejo v UR-CARE registru in so zelo podobni vzorcem predpisovanja v drugih državah v Evropski uniji.

S pomočjo dihalnega testa sta avtorici v drugi raziskavi želeli ugotoviti pogostnost bakterijske razrasti tankega črevesa (SIBO) po resekciji želodca zaradi karcinoma želodca. Pri 11 od 37 bolnikih s subtotalno gastrektomijo ali totalno gastrektomijo sta z dihalnim testom potrdili SIBO. Ocenili sta, da je pojavnost SIBO podcenjena, in da njeno zgodnje odkrivanje in zdravljenje lahko zmanjša kratkoročne in dolgoročne zaplete po resekciji želodca.

Zdravljenje zapletenih perianalnih fistul pri CB je zahtevno in večdisciplinarno. V priporočilih za obravnavo bolnikov s perianalnimi fistulami je opisan algoritem diagnostike, zdravljenja in sledenja.

V predlogu priporočil za obravnavo bolnika z gastroparezo avtorji povzemajo evropska in ameriška priporočila o diagnostičnih postopkih in možnostih zdravljenja. Večina dosedanjih priporočil ni podkrepljena s študijami, temveč izhajajo predvsem iz strokovnih mnenj. V prispevku predlagamo, kako uporabiti dosedanja mednarodna priporočila v slovenskem prostoru.

V dveh preglednih člankih so obravnavali metilacijske označevalce v zunajcelični DNA in pomen nekodirajočih RNA, vključno z mikroRNA, pri prepoznavanju hepatoceličnega karcinoma (HCC).

Obravnava bolnika s krvavitvijo iz zgornjih prebavil se začne s hemodinamsko oceno. Za učinkovito in varno oskrbo bolnikov s krvavitvijo iz zgornjih prebavil je potrebno sodelovanje urgentnega zdravnika, intezivista/anesteziologa in gastroenterologa.

Menimo, da bodo prijetno branje tudi strokovni članki in predstavljeni zanimivi klinični primeri.

V imenu uredniška odbora in avtorjev prispevkov vam želim prijetno branje.

Prof. dr. Borut Štabuc,
urednik

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Castle Grad na Goričkem. Source: Shutterstock

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Utilisation of biologicals in inflammatory bowel disease in Slovenia – report from UR-CARE registry for the year 2022

Uporaba bioloških zdravil pri bolnikih s kronično vnetno črevesno boleznijo v Sloveniji – podatki iz UR-CARE registra za leto 2022

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***Keywords**: epidemiology, treatment patterns, persistence of biological therapy*

***Ključne besede**: epidemiologija, vzorci zdravljenja, vztrajanje z zdravljenjem*

ABSTRACT

Background. Due to the increasing incidence of inflammatory bowel disease (IBD) many patients are being treated with biological drugs. However, real-world treatment patterns with biologicals in Slovenian IBD patients have not yet been reported.

Aim. To characterise biological drug use in Slovenian IBD centres until the year 2022.

IZVLEČEK

Izhodišča. Zaradi naraščajoče incidence kronične vnetne črevesne bolezni (KVČB) je vse več bolnikov zdravljenih z biološkimi zdravili. Kljub temu v Sloveniji nimamo podatkov o vzorcih zdravljenja z biološkimi zdravili pri naših bolnikih.

Namen. Opredeliti uporabo bioloških zdravil v slovenskih centrih za KVČB v letu 2022.

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Material and Methods. We analysed data on the biological treatment of IBD patients from the UR-CARE Registry (initiated in October 2020) with data lock on 1st October 2022.

Results. Out of 2748 IBD patients treated in Slovenian IBD centres in the year 2022, 1014 of Crohn's disease (CD) and 623 of ulcerative colitis (UC) patients received biological therapy. TNF-alpha inhibitors were preferred as first-line therapy: adalimumab for CD (39.5%) and infliximab for UC (38.8%). Ustekinumab dominated second and third-line biological therapy in CD (28.9%, 43.1%, respectively) and vedolizumab in UC (36.8%, 43.3%, respectively). Over half of patients persisted with their first-line treatment (CD 58.2%, UC 57.8%) at the end of follow-up. Persistence rates were higher for first-line vedolizumab (CD 75.8%, UC 75.1%) and ustekinumab (CD 75.2%, UC 94.4%) than for TNF-alpha inhibitors (infliximab: CD 55.8%, UC 49.6%, adalimumab: CD 49.9%, UC 37.3%).

Conclusions. Biological treatment patterns in Slovenia were comparable with those in the European Union. TNF-alfa inhibitors remain the most common choice for first biological.

Metode. Analizirali smo podatke o biološkem zdravljenju bolnikov s KVČB, zbrane v UR-CARE registru v obdobju od formacije registra oktobra 2020 do 1. oktobra 2022.

Rezultati. Do leta 2022 je bilo v slovenski UR-CARE register vnesenih 2748 bolnikov iz 6 slovenskih KVČB centrov. Od tega je biološko terapijo prejelo 1014 bolnikov s Crohnovo boleznijo (CB) in 623 bolnikov z ulceroznim kolitisom (UK). Kot zdravilo prvega reda so bili najpogosteje predpisani zaviralci TNF-alfa: adalimumab pri CB (39,5 %) in infliximab pri UK (38,8 %). Kot zdravilo drugega in tretjega reda pa ustekinumab pri CB (28,9 % in 43,1 %) in vedolizumab pri UK (36,8 % in 43,3 %). Ob izvozu podatkov iz registra je več kot polovica vseh bolnikov vztrajala z zdravilom prvega reda (CB 58,2 %, UK 57,8 %), pri čemer je bil delež vztrajajočih višji na vedolizumabu (CB 75,8 %, UK 75,1 %) in ustekinumabu (CB 75,2 %, UK 94,4 %) kot na zaviralcih TNF-alfa (infliximab: CB 55,8 %, UK 49,6 %, adalimumab: CB 49,9 %, UK 37,3 %).

Zaključki. Vzorci predpisovanja bioloških zdravil v Sloveniji so podobni kot v drugih državah v Evropski uniji. Zaviralci TNF-alfa ostajajo najbolj pogosto predpisana biološka zdravila prvega reda do leta 2022.

INTRODUCTION

The incidence of inflammatory bowel disease (IBD) is increasing worldwide. It is estimated that currently 1 in 300 Europeans are affected (1). The disease is immune-mediated and may have a difficult course; therefore, many patients need treatment with biological drugs to prevent serious complications and intestinal failure. However, data on biological treatment in Slovenian IBD patients is lacking since these data have not been collected systematically until recently. In 2019 Slovenia started UR-CARE Registry. Until the year 2022, six Slovenian IBD centres joined the UR-CARE Registry. These six centres systematically enter data on patient characteristics and drug use into the registry. Consequently, data on biological drug use is now available in Slovenia.

This report aimed to analyse biological drug use until the year 2022 in Slovenia across all IBD centres included in the registry.

MATERIALS AND METHODS

In this study, we analysed the biological treatment of inflammatory bowel disease (IBD) patients in Slovenia in the year 2022. Patient data was prospectively collected from the UR-CARE Registry with data lock on 1st October 2022. The registry included data from the following medical centres: University Medical Centre Ljubljana (UMC Ljubljana), University Medi-

cal Centre Maribor (UMC Maribor), General Hospital Celje (GH Celje), General Hospital Jesenice (GH Jesenice), General hospital Izola (GH Izola) and Diagnostic centre Bled (DC Bled).

After the export of the data from the UR-CARE registry data collection and analyses were performed using Microsoft Excel software (version 2301, build 16.0.16026.20196). Descriptive statistics are presented as the means ± standard deviations for parametric variables and percentages for categorical variables. This study was approved by the National Medical Ethics Committee of Slovenia (ID 0120-576/2019/7).

RESULTS

Patient characteristics

At this data lock the UR-CARE Registry included 2748 patients with IBD. Most patients were diagnosed with Crohn's disease (51.1%), followed by ulcerative colitis (45.0%) and only a few who were diagnosed with IBD unclassified (3.5%). The genders were equally distributed. The median patient's age at diagnosis was 36.6 years (standard deviation (SD) 16.1). The majority of patients (42.6%) have never smoked. A minority of patients (6.4%) had a family history of inflammatory bowel disease. Patient demographics are shown in Table 1.

Disease phenotype

In most medical centres the majority of patients were diagnosed with Crohn's disease, except in GH Jesenice and in DC Bled, where more patients were diagnosed with ulcerative colitis. The proportion of Crohn's disease patients with risk factors for complications (i.e. ileal disease and perianal disease) was similar between all centres with exceptions again being GH Jesenice and DC Bled (more patients had ileal disease and fewer had perianal disease). In total, perianal disease was detected in 264 (18.8%) out of 1405 patients with Crohn's disease. Patients with Crohn's disease were generally a few years younger at the time of diagnosis than patients with ulcerative colitis and were diagnosed earlier in university clinical centres than in general hospitals or diagnostic centres. Overall characteristics of patients were similar between all medical centres. Phenotype data for every IBD centre are shown in Table 2.

Biological drug use in patients with Crohn's disease and ulcerative colitis

In total, 1014 patients with Crohn's disease received 1690 treatment episodes with biological drugs. The

Table 1. Patient characteristics

	All patients (n = 2748)
Current age [years]	47.3 ± 14.8
Age at diagnosis [years]	36.6 ± 16.1
Gender	
Male	1367 (49.7%)
Female	1358 (49.4%)
Missing information	23 (0.8%)
Diagnosis	
Crohn's disease	1405 (51.1%)
Ulcerative colitis	1237 (45.0%)
Unclassified inflammatory bowel disease	95 (3.5%)
Missing data	11 (0.4%)
Smoking	
Yes	293 (10.7%)
Previous smoker	406 (14.8%)
No	1170 (42.6%)
Info not available	458 (16.7%)
Missing info	421 (15.3%)
Family history of inflammatory bowel disease	
Yes	176 (6.4%)
No	1752 (63.8%)
Info not available	375 (13.6%)
Missing info	445 (16.2%)

Table 2. Disease phenotype in 6 inflammatory bowel disease centres in Slovenia

	University Medical Centre Ljubljana	University Medical Centre Maribor	General hospital Celje	General hospital Izola	General hospital Jesenice	Diagnostic centre Bled
Total number of patients with IBD***	1950	369	183	194	29	23
CD* - N (%)	967 (49.6%)	224 (61.5%)	95 (51.9%)	104 (53.6%)	10 (34.5%)	5 (21.7%)
UC** - N (%)	910 (46.7%)	130 (35.7%)	83 (45.4%)	81 (41.8%)	17 (58.6%)	16 (69.6%)
IBD-U*** - N (%)	73 (3.7%)	10 (2.7%)	4 (2.2%)	6 (3.1%)	1 (3.4%)	1 (4.3%)
Crohn's with isolated ileum disease - N (% of all CD)	248 (25.6%)	38 (17.0%)	17 (17.9%)	17 (16.3%)	4 (40.0%)	2 (40.0%)
Crohn's with ileocolonic disease - N (% of all CD)	62 (6.4%)	7 (3.1%)	7 (7.4%)	7 (6.7%)	1 (10.0%)	0
Crohn's perianal - N (% of all CD)	176 (18.2%)	53 (23.7%)	20 (21.0%)	14 (13.5%)	1 (10.0%)	0
Age at diagnosis CD	30.6±18.0	34.0±17.1	36.3±17.6	38.5±18.0	37.8±9.0	38.5±17.7
Age at diagnosis UC	35.4±17.4	39.4±17.1	36.3±14.2	39.4±17.2	31.6±15.2	41.8±16.9
Extraintestinal manifestitations - N (% of all IBD patients)	241 (12.4%)	38 (10.3%)	32 (17.5%)	19 (9.8%)	4 (13.8%)	4 (17.4%)

*****IBD-U – IBD – indeterminate*
**CD – Crohn's disease; **UC – ulcerative colitis; ***IBD – inflammatory bowel disease*

most commonly prescribed first-line treatments were TNF-alpha inhibitors adalimumab (39.5%) and infliximab (36.6%). As a second, third and fourth line of treatment, the most frequently prescribed biologic was ustekinumab (28.9%, 43.1%, 45.9%, respectively), followed by vedolizumab (17.1%, 23.4%, 23.0%, respectively). Detailed prescription sequence of biologics in CD is shown in Table 3.

In UC, 623 patients received 1010 treatment episodes with biologics in total. As a first-line treatment infliximab (38.8%) was the most common drug of choice. As a second and third-line drug vedolizumab was the most frequently prescribed among all biologic (36.8%, and 43.3%, respectively) and ustekinumab as a fourth and fifth line of treatment (50.0%, 66.7%, respectively). The detailed prescription sequence of biologics in UC is shown in Table 4.

Ongoing biological treatment in Crohn's disease and ulcerative colitis

Out of 1014 patients with CD 590 (58.2%) were still treated with a first-line biologic at the time of data export, 223 (22.0%) with a second line and 82 (8.1%) with a third-line biologic. The proportion of patients that persisted with the first-line biologic was the highest for vedolizumab (100/132, 75.8%), followed by ustekinumab (82/109, 75.2%), infliximab (207/371, 55.8%) and adalimumab (200/401, 49.9%). Several patients with CD that persisted on specific biological are shown in Table 5.

Out of 623 patients with UC 360 (57.8%) were still being treated with a first-line biologic, 106 (17.0%) with a second line and 50 (8.0%) with a third-line biologic. The proportion of patients that persisted with the first-line biologic was the highest for ustekinumab

Table 3. Number of prescriptions (treatment episodes) in respective lines of therapy for Crohn's disease

Line	All	Adalimumab/ biosimilars	Adalimumab/ Humira	Golimumab	Guselkumab	Infliximab/ biosimilars	Infliximab/ Ramicade	Natalizumab	Risankizumab	Ustekinumab	Vedolizumab
First line	1014	135 (13.3%)	266 (26.2%)	0 (0%)	0 (0%)	207 (20.4%)	164 (16.2%)	1 (0.1%)	0 (0%)	109 (10.7%)	132 (13.0%)
Second line	432	25 (5.79%)	97 (22.5%)	0 (0%)	0 (0%)	71 (16.4%)	40 (9.3%)	0 (0%)	0 (0%)	125 (28.9%)	74 (17.1%)
Third line	167	5 (3.0%)	20 (12.0%)	0 (0%)	0 (0%)	22 (13.2%)	8 (4.8%)	0 (0%)	1 (0.6%)	72 (43.1%)	39 (23.4%)
Fourth line	61	4 (6.6%)	5 (8.2%)	0 (0%)	1 (1.6%)	6 (9.8%)	3 (4.9%)	0 (0%)	0 (0%)	28 (45.9%)	14 (23.0%)
Fifth line	15	1 (6.7%)	2 (13.3%)	2 (13.3%)	0 (0%)	2 (13.3%)	0 (0%)	0 (0%)	0 (0%)	5 (33.3%)	3 (20.0%)
Sixth line	1	1 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total*	1690	171 (10.1%)	390 (23.1%)	2 (0.1%)	1 (0.06%)	308 (18.2%)	215 (12.7%)	1 (0.06%)	1 (0.06%)	339 (20.1%)	262 (15.5%)

Table 4. Number of prescriptions (treatment episodes) in respective lines of therapy for ulcerative colitis

Line	All	Adalimumab biosimilars	Adalimumab/ Humira	Golimumab	Guselkumab	Infliximab biosimilars	Infliximab Ramicade	Natalizumab	Risankizumab	Ustekinumab	Vedolizumab
First line	623	17 (2.7%)	50 (8.0%)	61 (9.8%)	0 (0%)	152 (24.4%)	90 (14.4%)	0 (0%)	0 (0%)	36 (5.8%)	217 (34.8%)
Second line	253	8 (3.2%)	40 (15.8%)	11 (4.3%)	0 (0%)	55 (21.7%)	22 (8.7%)	0 (0%)	0 (0%)	24 (9.5%)	93 (36.8%)
Third line	104	3 (2.9%)	7 (6.7%)	4 (3.8%)	0 (0%)	15 (14.4%)	3 (2.9%)	0 (0%)	1 (1.0%)	26 (25.0%)	45 (43.3%)
Fourth line	24	1 (4.2%)	0 (0%)	1 (4.2%)	0 (0%)	2 (8.3%)	4 (16.7%)	0 (0%)	0 (0%)	12 (50.0%)	4 (16.7%)
Fifth line	6	0 (0%)	1 (16.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (66.7%)	1 (16.7%)
Sixth line	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total*	1010	29 (2.9%)	98 (9.7%)	77 (7.6%)	0 (0%)	224 (22.2%)	119 (11.8%)	0 (0%)	1 (0.1%)	102 (10.1%)	360 (35.6%)

Table 5. Number of patients, who remained on biologic in respective line of treatment for Crohn's disease

Line	All	Adalimumab biosimilars	Adalimumab/ Humira	Golimumab	Guselkumab	Infliximab biosimilars	Infliximab Ramicade	Natalizumab	Risankizumab	Ustekinumab	Vedolizumab
First line	590	89 (15.1%)	111 (18.8%)	0 (0%)	0 (0%)	143 (24.2%)	64 (10.8%)	1 (0.2%)	0 (0%)	82 (13.9%)	100 (16.9%)
Second line	223	12 (5.4%)	23 (10.3%)	0 (0%)	0 (0%)	43 (19.3%)	6 (2.7%)	0 (0%)	0 (0%)	106 (47.5%)	33 (14.8%)
Third line	82	1 (1.2%)	0 (0%)	0 (0%)	0 (0%)	11 (13.4%)	1 (1.2%)	0 (0%)	0 (0%)	50 (61.0%)	19 (23.2%)
Fourth line	36	1 (2.8%)	4 (11.1%)	0 (0%)	1 (2.8%)	2 (5.6%)	1 (2.8%)	0 (0%)	0 (0%)	22 (61.1%)	5 (13.9%)
Fifth line	10	1 (10.0%)	0 (0%)	1 (10.0%)	0 (0%)	1 (10.0%)	0 (0%)	0 (0%)	0 (0%)	5 (50.0%)	2 (20.0%)
Sixth line	1	1 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total*	942	105 (11.1%)	138 (14.6%)	1 (0.1%)	1 (0.1%)	200 (21.2%)	72 (7.6%)	1 (0.1%)	0 (0%)	265 (28.1%)	159 (16.9%)

(34/36, 94.4%), followed by vedolizumab (163/217, 75.1%), infliximab (120/242, 49.6%), adalimumab (25/67, 37.3%) and golimumab (18/61, 29.5%). Number of patients with UC that persisted with biological treatment is shown in Table 6.

Table 6. Number of patients, who remained on biologic in respective line of treatment for ulcerative colitis

Line	All	Adalimumab biosimilars	Adalimumab/ Humira	Golimumab	Guselkumab	Infliximab biosimilars	Infliximab Ramicade	Natalizumab	Risankizumab	Ustekinumab	Vedolizumab
First line	360	9 (2.5%)	16 (4.4%)	18 (5.0%)	0 (0%)	89 (24.7%)	31 (8.6%)	0 (0%)	0 (0%)	34 (9.4%)	163 (45.3%)
Second line	106	5 (4.9%)	8 (7.5%)	2 (1.9%)	0 (0%)	24 (22.6%)	2 (1.9%)	0 (0%)	0 (0%)	17 (16.0%)	48 (45.3%)
Third line	50	0 (0%)	1 (2.0%)	1 (2.0%)	0 (0%)	6 (12.0%)	0 (0%)	0 (0%)	0 (0%)	20 (40.0%)	22 (44.0%)
Fourth line	11	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (9.1%)	1 (9.1%)	0 (0%)	0 (0%)	8 (72.7%)	1 (9.1%)
Fifth line	4	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (100.0%)	0 (0%)
Sixth line	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total*	531	14 (2.6%)	25 (4.7%)	21 (4.0%)	0 (0%)	120 (22.6%)	34 (6.4%)	0 (0%)	0 (0%)	83 (15.6%)	234 (44.1%)

DISCUSSION

In this study, we report on biological drug utilization in Slovenia until the year 2022. Our most important finding is that biological drug use in Slovenia follows that of Western Europe suggesting that Slovenia has good access to advanced treatments. More than half of patients were still approached with TNF-alpha inhibitors as a first-line treatment. However, an important proportion of patients received second-generation biological vedolizumab and ustekinumab as first-line treatment.

The strength of this study is that we reported data on drug use across 6 Slovenian IBD centres, 2 academic and 4 non-academic centres. Here we could observe that the disease phenotype of IBD patients was similar in all Slovenian IBD centres suggesting that IBD teams of respective centres were confident with treating different IBD phenotypes. This can be explained with good access to academic teams which regularly review applications for initiation of biologicals and also advice on tackling the loss of response to these drugs and offer support for severe disease complications.

In general, the disease phenotype of IBD and disease location of Slovenian patients were comparable with those reported by others (2). The same was observed for extraintestinal manifestations (3). Approximately one-quarter of CD patients had a perianal fistulizing disease which is in line with other cohorts (18.8%) (4–7).

Biological treatment patterns were in line with other studies (8). Namely, most patients received TNF-alpha inhibitors as a first-line treatment. In CD, adalimumab and infliximab were prescribed with equal frequencies. However, in UC infliximab was prescribed almost four times more frequently than adalimumab or golimumab, presumably due to its superior durability (9–11). As reported by others, ustekinumab was more commonly used than vedolizumab in Crohn's disease and the reverse was true for ulcerative colitis (9, 12, 13). Here it should be stressed that we only reported total drug use until 2022. Unfortunately, we were unable to analyse changing trends of drug choice over time in this early report. This might be relevant as drug prescription changed dramatically after the year 2019 when constraints on choice of first-line biological were released in Slovenia.

In both, Crohn's disease and ulcerative colitis, around 58% of patients were still being treated with their first-line biological at the time of data export. In other studies, persistence rates declined with every line of treatment (14, 15). The proportion of CD and UC patients that persisted with their first-line biologic was higher for vedolizumab and ustekinumab in comparison with TNF-alpha inhibitors. This is in line with the recent VARSITY trial (16) and several real-life cohorts (12, 14).

Our study has several limitations. The most important limitation of this early report is that data entry might not be complete in all IBD centres in Slovenia, particularly in those which only recently joined the URCARE registry. We also did not include data on Janus kinase inhibitors as in the year 2022 only a few patients (compared to biologicals) were treated with these molecules. Also, most IBD centres did not report on dose optimisation of biologicals although these data would be important for a more accurate understanding of biological drug utilisation in Slovenia. In addition, we failed to include data on conventional treatments, thus we were unable to assess the proportion of patients treated with biologicals in Slovenia.

In summary, the utilisation of biologicals in IBD in Slovenia is similar to that in other countries of the European Union. Inhibitors of TNF-alfa were the most common choice for first-line biological in Slovenia until 2022. After the failure of TNF-inhibitor(s), ustekinumab was the most prescribed drug for Crohn's disease and vedolizumab in ulcerative colitis until the year 2022.

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Small Intestinal Bacterial Overgrowth after total and subtotal gastrectomy; high incidence - not connected to gastrointestinal symptoms

Sindrom bakterijske razrasti v tankem črevesu po totalni ali subtotalni gastrektomiji; visoka incidenca, ki ni povezana z gastrointestinalnimi simptomi

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***Ključne besede**: prekomerna razrast bakterij (SIBO), karcinom želodca, totalna gastrektomija, subtotalna gastrektomija, simptomi, zapleti*

ABSTRACT

Background. Surgical resections of the gastrointestinal tract due to gastric carcinoma are connected to a higher risk of developing Small intestinal bacterial overgrowth (SIBO), which is a condition with an excessive number of bacteria in the small intestine, prompting a wide variety of symptoms and short and long-term complications. SIBO increases the incidence of nutritional deficiencies after gastrectomy and increases the overall incidence of complications.

IZVLEČEK

Izhodišče. Kirurške resekcije prebavil zaradi karcinoma želodca so povezane z večjim tveganjem za razvoj bakterijske razrasti tankega črevesa (SIBO), ki je stanje s prekomernim številom bakterij v tankem črevesu, kar povzroča različne simptome ter kratkoročne in dolgoročne zaplete. SIBO poveča pogostost prehranskih pomanjkljivosti po gastrektomiji in poveča splošno pogostost zapletov.

Namen študije. Namen te študije je bil oceniti natančno incidenco SIBO po totalni in subtotalni ga-

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Aims. This study aimed to evaluate the exact incidence of SIBO after total and subtotal gastrectomy due to gastric carcinoma and to compare symptoms, (neo)adjuvant chemo/radiotherapy treatment and eating patterns in patients with and without SIBO.

Methods. In an observatory randomised analytical cross-sectional study, patients after total and subtotal gastrectomy underwent a hydrogen (H_2) breathing test (BT) with glucose substrate (25 g/200 mL of water). Demographic, anthropometric data, symptoms, (neo)adjuvant chemo/radiotherapy treatment and eating patterns were analysed with a questionnaire.

Results. Of the 37 patients included, 7 had subtotal gastrectomy and 30 had total gastrectomy. H_2 BT was positive in 2/7 (29%) and 9/30 (30%) of patients after subtotal and total gastrectomy respectively. There was no statistically significant difference in demographic data, symptoms, eating patterns and treatment with chemo/radiotherapy.

Conclusions. The incidence of SIBO in patients who underwent subtotal and total gastrectomy is worryingly high, being 29 and 30 % respectively. SIBO occurs more frequently in patients with gastric cancer due to altered physiological defence mechanisms, cancer-related cachexia and nutritional disorders. SIBO further exacerbates and impairs the mechanisms triggered by surgery, chemotherapy and radiotherapy, with consequent micronutrient deficiencies and clinical signs. The incidence of SIBO is currently underestimated, which could be connected to developing systemic complications, malabsorption, and its consequences. The results of our study confirm that there is an urgent need to systematically address SIBO in patients undergoing total and subtotal gastrectomy already at high risk of post-surgical nutritional deficiency which would significantly improve treatment outcomes and prevent the development of short and long-term complications.

strektomiji zaradi karcinoma želodca ter primerjati simptome, (neo)adjuvantno zdravljenje s kemoterapijo/radioterapijo in vzorce prehranjevanja pri bolnikih s SIBO in brez nje.

Metode. V opazovalni randomizirani analitični presečni študiji so pri bolnikih po totalni in subtotalni gastrektomiji opravili test dihanja z vodikom (H_2) z glukoznim substratom (25 g/200 ml vode). Z vprašalnikom so analizirali demografske in antropometrične podatke, simptome, (neo)adjuvantno zdravljenje s kemoterapijo/radioterapijo in prehranjevalne navade.

Rezultati. Od 37 vključenih bolnikov jih je imelo 7 subtotalno gastrektomijo, 30 pa totalno gastrektomijo. H_2BT je bil pozitiven pri 2/7 (29 %) in 9/30 (30 %) bolnikov po subtotalni oziroma totalni gastrektomiji. V demografskih podatkih, simptomih, načinu prehranjevanja in zdravljenju s kemoterapijo/radioterapijo ni bilo statistično pomembnih razlik.

Zaključki. Pojavnost SIBO pri bolnikih, pri katerih je bila opravljena subtotalna in totalna gastrektomija, je zaskrbljujoče visoka in znaša 29 oziroma 30 %. SIBO se pogosteje pojavlja pri bolnikih z rakom želodca zaradi spremenjenih fizioloških obrambnih mehanizmov, z rakom povezane kaheksije in prehranskih motenj. SIBO dodatno poslabša in poslabša mehanizme, ki jih sprožijo operacija ter kemoterapija in radioterapija, zaradi česar se pogosteje in zgodnejše pojavijo znaki pomanjkanja mikrohranil in klinični znaki. Pojavnost SIBO je trenutno podcenjena, kar je povezano z razvojem sistemskih zapletov, malabsorpcije in njenih posledic. Rezultati naše študije potrjujejo, da je nujna sistematična obravnava SIBO pri bolnikih po totalni in subtotalni gastrektomiji, pri katerih že obstaja veliko tveganje za pooperativno presnovne pomanjkljivosti in zaplete; na takšen način bi lahko bistveno izboljšali rezultate zdravljenja ter preprečili razvoj kratkoročnih in dolgoročnih zapletov.

INTRODUCTION

Gastric cancer is the third leading cause of cancer death and fifth most prevalent worldwide, with a higher incidence in Asia, Central and South America and Eastern Europe, and a lower incidence in North America and Africa (1–3). All parts of the organ from the gastroesophageal junction to the pylorus may be affected and it has already been reported that some cancers are associated with infection by specific bacteria (3, 4). H. pylori is identified as an infectious agent related to carcinogenesis by inducing DNA mutation and causing chronic inflammation which may progress from atrophic gastritis to intestinal metaplasia, dysplasia, and gastric adenocarcinoma (3, 5). In recent decades, the incidence of gastric cancer has been declining due to the treatment of Helicobacter pylori infection and due to earlier detection and new treatment options (6).

Gastrectomy with or without lymphadenectomy and reconstruction of the gastrointestinal tract represents the mainstay of treatment for gastric carcinoma (3). The ongoing process in oncological gastric surgery has led to increased patient survival rates and improved quality of life, however after surgery, the five-year survival rate remains around 45%, with perioperative chemotherapy improving that rate only around 10% (3, 7). Improved cure rates for gastric cancer have increased focus on disease-related complications, development of health-related complications due to different treatment modalities and quality of life (HR-QL) in survivorship (2, 8, 9). Even so, nowadays efficient curative treatment for gastric carcinoma is still lacking (3, 5, 10, 11).

Despite considerable advances in gastric cancer surgeries the underestimated incidence of malabsorption, small intestinal bacterial overgrowth, and the consequences due to the surgery itself significantly reduce the quality of patient care, affect the incidence of postoperative and metabolic complications, irrespective of the type of surgical resection (10). Malnutrition may trigger weight loss, muscle mass reduction, and essential nutrient deficiencies, it increases the risk of tumour recurrence thus detrimentally impacting patients' quality of life and prognosis (10). In addition, gut and pancreatic insufficiency represent modifiable targets in the interdisciplinary approach to recovery of HR-QL (10).

Micronutrient deficiencies are also prevalent after gastric surgery, as functional and anatomical modification because surgical resection and reconstruction impact their absorption (10). Surprisingly, these deficiencies appear to be similarly prevalent in patients who have undergone surgery, with iron, vitamins A, B1, B12, D and E deficiencies commonly observed in up to 78,3% of patients (10). Recognizing and treating the distinct consequences associated with each type of deficiency underscores the importance of implementing preventive measures, early detection, and prompt management (10).

It remains to be elucidated whether changes in the gastric and gut microbiome have a role in gastric carcinogenesis or are a consequence of the surgery and tumour evolution (3). It was suggested that colonizing the stomach with commensal bacteria from other parts of the gastrointestinal region could promote gastric carcinogenesis associated with H. pylori (11). In animal models' gastric colonization with altered intestinal microbiota was correlated with pathology, immune responses, and mRNA expression for proinflammatory and cancer-related genes (11). Different composition of gastrointestinal microbiota is probably connected to different responses to H. pylori infection as well as to different pathological reactions and immunology status (11). The gut microbiome affects many types of cancer as well as gastric carcinoma cacinogenesis and the response and prognosis of gastric cancer treatment (3). The importance of the gut microbiome for the interactions between cancer and immunity is gaining attention, along with possible new treatment options targeting changed microbiota composition (7, 11).

The predominant phyla in normal gut microbiota are Bacteroidetes (19,7%), Firmicutes (40%), Actinobacteria (20%) and Proteobacteria (2,15%) (12–14). Small

intestinal bacterial overgrowth (SIBO) is a type of dysbiosis and a clinical condition, which is characterised as an excess number of colon-dominant bacteria in the small intestine, responsible for digestive symptoms such as bloating, abdominal pain, nausea, and diarrhoea (15–18). The suggested pathophysiologic mechanisms of SIBO in abdominal surgery include changes in anatomical features, such as adhesions after surgery, influx of substances in the intestine and changed gastric acidity (2, 19, 20).

Our study aimed to evaluate the exact incidence of SIBO after resections of the upper gastrointestinal tract due to gastric carcinoma and evaluate the presence of symptoms, comorbidities, and eating patterns in patients with and without SIBO. The goal of this study is to present the importance of diagnosing and treating SIBO after gastrectomy to prevent short- and long-term complications and improve the prognosis and quality of life.

METHODS

Study design

Observatory randomised analytical cross-sectional study was performed at University Medical Centre (UMC) Ljubljana between January 2021 and June 2022. Of the 37 patients included in the study, all had had a glucose hydrogen (H_2) breathing test (BT) and filled out the Questionnaire.

This study was approved by the Slovenian Republican Committee for Medical Ethics (national ethics committee) under the number 0120-515/2020/3, by Medical Faculty Ljubljana and UMC Ljubljana. All procedures performed in the study involving human participants were by the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Participants

Patients included were adults (> 18 years old), who had surgical resection of gastric carcinoma, being subtotal or total gastrectomy between January 2017 and June 2022, with or without gastrointestinal symptoms that signed the free consent form. We excluded patients who were incapable of preparing, executing or finishing the study, were using antibiotics, prokinetics and/or laxatives in the past two weeks and had basal concentration of H_2 at the start of the H_2BT in two different measures, 20 minutes apart, > 10 parts per million (ppm).

Glucose Hydrogen Breathing Test

Participants were instructed to ingest a low-fermentation diet 24 hours before the exam and to avoid smoking and physical activity on the day of the exam. Participants fasted overnight (12 h) and during the H_2 BT. At the start of the test, a basal sample of expired air was collected using an H_2BT device (Lactofan 2 Fischer®, Leipzig, Germany). The results were expressed as ppm. If the first measure (basal concentration) of H_2 was < 10 ppm, the participants ingested 25 g of glucose diluted in 200 mL of water. Every 20 min, in total of 120 min, 6 expired air samples were collected. An elevation of more than 12 ppm according to the basal value, within 120 min was deemed to be a positive result, indicating SIBO.

Questionnaire

Demographic and anthropometric data (age, gender, weight, educational level, socioeconomic status, time after surgery), symptoms and comorbidities (adjusted The Gastrointestinal Symptoms Rating Scale Questionnaire and adjusted SIBO Questionnaire), eating patterns (frequency of meals, snacks, breakfast, refined sugars, vegetable, fruit, fast food, and starch), treatment with (neo) adjuvant chemo/radiotherapy and quality of life (36-Item Short Form Survey (SF-36) Questionnaire) were analysed with the Questionnaire.

Table 1. Characteristics of patients according to positive or negative postoperative breath tests

Variable	Positive breath test (n = 11)	Negative breath test (n = 26)	p
Age (years)	59,2 ± 11,3	64,2 ± 11,3	0,272
Women (n, (%))	5 (45,5 %)	8 (30,8 %)	0,465
BMI (kg/m^2)	24,0 ± 4,3	23,4 ± 3,4	0,654
Education level	3,91 ± 1,38	4,15 ± 1,35	0,523
SE status	5,91 ± 1,97	6,08 ± 1,92	0,851
Time after S (months)	15,8 ± 14,9	28,8 ± 20,7	0,056
No complications (%)	90,9	76,9	0,649

The variables are expressed as mean ± SD (standard deviation); n (%) represents the number and percentage of variables. Statistical analysis was done using Mann-Whitney U and Fisher exact tests; p < 0,05
BMI – body mass index, S – surgery, SE – socioeconomic status

Surgical procedures

Surgical procedures were open or laparoscopic standard subtotal or total curative gastrectomy with lymphadenectomy performed by experienced surgeons with mainly Roux-en-Y reconstruction of the digestive tract.

STATISTICAL ANALYSIS

For statical analysis, categorical variables were expressed as number of participants and percentage (%) and numerical variables were expressed as mean value ± standard deviation. Categorical variables were analysed using the Chi-square test and Fischer exact test, depending on sample size. Numerical variables were analysed with a nonparametric test in case of non-sufficient sample size and with a parametric Student's t-test in the case of sufficient sample size. The Spearman correlation was used for small observed group statistical analysis. A 95% confidence interval was calculated and a p-value < 0,05 was considered statistically significant.

RESULTS

Characteristics of the population.

Out of 37 patients, 7 underwent subtotal gastrectomy and 30 underwent total gastrectomy, 24/37 (65,9%) were male and 13/37 (35,1%) were female. Mean age was 62,676 ± 11,36 years (range 33–81 years), mean body weight was 72,927 ± 12,42 kg (range 52–100 kg), mean BMI was 23,589 ± 3,62 kg/m^2 (range 15,8–34,6 kg/m^2), mean level of education was 2 (range 1–6), mean time after surgery was 24,956 ± 19,88 months (range 1,00–96,00).

Incidence of SIBO and Factors Associated with SIBO

Glucose H_2 BT was positive in 2/7 (29%) and negative in 5/7 (71%) patients after subtotal gastrectomy. Glucose H_2 BT was positive in 9/30 (30%) and negative in 21/30 (70%) patients after total gastrectomy. Characteristics of patients according to positive or negative postoperative BT are presented in Table 1. Symptoms according to positive and negative BT are presented in Table 2.

Table 2. Symptoms according to positive and negative postoperative breath tests after total and subtotal gastrectomy

Variable	Positive breath test (n = 11)	Negative breath test (n = 26)	p
Chronic pain	2,27 ± 1,85	2,27 ± 2,38	0,795
Diarrhoea	1,82 ± 1,33	2,42 ± 2,04	0,435
Frequent defecation	2,18 ± 0,60	1,98 ± 0,65	0,320
Obstipation	2,00 ± 2,72	1,54 ± 1,17	0,853
Floating stools	1,45 ± 0,52	1,77 ± 0,43	0,065
Abdominal cramps	2,23 ± 1,51	2,27 ± 2,38	0,580
Flatulence and bloating	6,18 ± 3,40	4,42 ± 2,67	0,107
Nausea	2,00 ± 1,79	1,85 ± 1,74	0,447
Vomiting	1,00 ± 0,00	1,77 ± 1,68	0,087
Belching	4,00 ± 3,35	2,65 ± 2,23	0,413
Loss of appetite	1,91 ± 2,39	2,31 ± 2,59	0,773
Bloating	4,27 ± 3,26	3,46 ± 2,55	0,465
Fever	1,00 ± 0,00	1,00 ± 0,00	NA
Joint pain	1,82 ± 1,83	2,69 ± 2,19	0,162
Fatigue	3,05 ± 3,10	3,54 ± 2,97	0,605
Skin lesions	1,64 ± 1,80	1,57 ± 1,45	0,942
Confusion and memory loss	1,73 ± 1,35	2,04 ± 2,01	0,789
Nausea with belching	2,00 ± 1,73	2,50 ± 2,10	0,399
Flatulence	2,5 ± 1,6	2,3 ± 1,0	0,524
Belching after meals	1,91 ± 1,51	2,04 ± 1,48	0,786
Pain and bloating	1,18 ± 1,54	1,40 ± 1,34	0,490
Obstipation	0,46 ± 1,21	0,46 ± 0,95	0,627
Diarrhoea and obstipation exchanging	0,36 ± 0,92	0,31 ± 0,68	0,817
Diarrhoea and obstipation	0,27 ± 0,65	0,31 ± 0,55	0,657

The variables are expressed as mean ± SD (standard deviation). Statistical analysis was done using Student's t-test

Neo (adjuvant) chemotherapy/radiotherapy

17/37 (45,9%) patients had neoadjuvant chemotherapy, 4/37 (10,8%) had neoadjuvant radiotherapy, 16/37 (43,2%) had adjuvant chemotherapy and 4/37 (10,8%) had adjuvant radiotherapy.

DISCUSSION

The main treatment for gastric cancer remains surgery that consists of gastric removal with/without lymphadenectomy and reconstruction of the gastrointestinal tract (3). Nowadays effective treatment is still lacking, with curative intent of gastric resections being nearly 50% with neoadjuvant therapy contributing to an improved survival rate up to 10% (3, 21). Although

gastrectomy aims to achieve radical resection of the primary tumour and the lymph nodes, it has been indicated that surgery, especially Roux-en-Y anastomosis affects gastrointestinal microbiota in diversity and community composition (15, 20, 22–24). Patients with gastrectomy are at higher risk of developing type II diabetes and metabolic syndrome, as well as developing metachronous cancer, including colorectal cancer (3). Additionally, the importance of the altered gut microbiota composition for the interactions between cancer and immunity is gaining attention, along with a further introduction of immunotherapies into clinical practice (3). Finally, despite significant progress in the field of gastric surgery, postoperative malnutrition with weight loss, muscle mass reduction, and essential nutrient deficiencies is detrimentally impacting patients' quality of life and prognosis (10). Therefore, new strategies to find effective treatment for gastric carcinoma are necessary.

It is known that some cancers are associated with infection by specific bacteria, for example, Helicobacter pylori, which has been found to contribute to the development of MALT lymphoma and gastric cancer by causing chronic inflammation (3). Gastric microbiome compromises a population of its own and it has been reported that H. pylori-infected in comparison to non-infected individuals exhibited significant differences between gastric bacterial communities (3, 21). In non-infected or with proton pump inhibitors treated patients, luminal microbiota consists of Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria (3). Mucosal microbiota mainly consists of acid-resistant species, such as Veillonella, Lactobacillus, and Clostridium (3), while in H. pylori-infected patients Streptococcus, Neisseria, Staphylococcus, and Roche were also identified (3, 25). It was suggested that colonizing the stomach with commensal bacteria from other parts of the gastrointestinal region could promote gastric carcinogenesis associated with H. Pylori (3). Microbiota in gastric carcinogenesis are changed in a way there is an increase in the functional characteristics of nitrosing, an aspect compatible with the microbial community with increasing genotoxic potential (3). This later implies the response and prognosis of gastric cancer treatment (3).

The historical and empirical safety limit of gut shortening procedures has been mainly based on maintaining absorptive physiological functioning of the gastrointestinal tract based on the lack of threatening clinical malabsorption features (26). However, gut shortening is related to impaired resorptive function due to withdrawal and/or exclusion of the part of the digestive tract where micronutrient resorption and altered absorption surfaces occur under physiological conditions (26, 27). Gastric resection and reconstruction lead to prominent changes in oxygen availability, intestinal pH, gastric acid secretion, food transit time, intestinal motility, and hormonal activity, affecting the microbiome and faecal metabolism (3). These significant changes in the intestinal environment could lead to the growth of certain species. Gut microbiota in patients after gastrectomy consists of different microbiome composition and metabolite profiles compared to the control group (3).

The altered gut microbiome affects many types of cancer and can also affect gastric carcinoma carcinogenesis and the response and prognosis of gastric cancer treatment (3). Surgery for gastric carcinoma influences the postoperative composition of the gut microbiome, in particular, distal gastrectomy is related to the great abundance of Escherichia/Shigella, Veillonella, and Clostridium XVIII and Bacteroidetes in lower quantities (28). Faecal microbiota alterations may be connected to different responses to H. Pylori infection, especially alterations in the Bacteroidetes, Firmicutes and Proteobacteria phyla may be implicated in the progression of gastric lesions associated with H. pylori infection (29).

The altered gut microbiota could be applied in gastric carcinogenesis through immunomodulation, and it may as well affect the effectiveness of chemotherapy in patients with gastric carcinoma (3). Qui et al showed a correlation between intestinal dysbiosis in gastric cancer patients to peripheral cellular immunity with CD3+T cells being linked to the relative abun-

dance of Lactobacillus and Streptococcus, while CD3+ T cells, CD4+ T cells, and NK cells are linked to Lachnospiraceae (30). These findings may suggest that Lachnospira and Lactobacillus may play vital roles in the alterations to the intestinal microbiota in gastric cancer patients and could be important targets for restoring the homeostasis of the intestinal bacterial community (30). Excessive amounts of the metabolic products of these bacteria characteristic of SIBO are associated with the extent of clinical signs in patients before and after gastrectomy, with an important impact of increased butyrate production.

The high prevalence of SIBO in patients who underwent gastrectomy has been reported, ranging from 15–83%, even reaching up to 96,2% in symptomatic patients after subtotal and total gastrectomy (31). Dysregulated intestinal microbiota in SIBO could be related to carcinogenesis by promoting inflammation which in the preoperative period contributes to the burden of disease with impaired peripheral cellular immunity (3). Inflammatory mediators due to the altered microbiome could facilitate cell proliferation, mutagenesis, angiogenesis, and oncogene activation related to gastric cancer but also other types of cancer such as metachronous liver, pancreatic, colon, oesophageal and pulmonary cancers (32). The candidate mechanism to promote carcinogenesis is cell proliferation via the activation of NF-κB and the inhibition of cellular apoptosis. Another important aspect is the relationship between gastric resection into the impairment of the oral microbiota and a consequent abundance of P. gingivalis and Aggregatibacter actinomycetemcomitans (A. actinomycetemcomitans), associated with a decreased relative abundance of Fusobacterium and its genus Leptotrichiae, which are connected to the increased risk of pancreatic cancer via cytokine signalization and receptor degradation (33).

In this present study we have found that in the cohort of symptomatic and asymptotic patients, SIBO is present in 29% of patients after subtotal gastrectomy and in 30% of patients after total gastrectomy, which is similar to the data found in the literature. We are aware that our study could have underestimated the incidence of SIBO after such surgery procedures as we have used lower amounts of glucose (25g) to avoid developing dumping symptoms in our patients, with most of the other studies having used higher amounts of glucose, ranging from 50–75 g. We conclude that the incidence of SIBO after total and subtotal gastrectomy is worryingly high and therefore necessary to address its diagnostics in such patients.

Surgical resection of the gastrointestinal tract changes its normal anatomy and leads to certain anatomical and physiological changes, which in turn may predispose to SIBO (20, 26, 34). Development of the blind loop after gastric reconstruction is such an anatomical change, although the literature on blind loop predisposing to SIBO is contradictory (26, 35). Another reason connected to developing SIBO after surgery is the delayed action of bile acids on the gastrointestinal tract due to the reconstruction and with it loss of their antimicrobial function (20). Other potentially important anatomic or physiologic mechanisms are also strictures, adhesions, reduced small bowel motility, gastroparesis, neuropathy, impaired transit time, impaired gastric acid secretion and impairment of immunological mechanisms (9, 20, 24, 26, 35). After all, systemic treatment such as the use of (neo)adjuvant chemo-radiotherapy which could harm the mucosa barrier either through direct effects or by causing diminished intestinal blood circulation could predispose to SIBO (36). Due to the bidirectional connection of the portal vein between the intestinal microbiome and the liver, intestinal dysbiosis can also affect the progression of liver disease to liver cirrhosis and its complications via the impairment of the so-called gut liver axis (37–39).

New therapies for gastric cancer have been developed recently, targeting gut microbiota, which has already been approved by FDA (3). It is proposed that the microbiome may have a role in cancer treatment with multiple mechanisms responsible for antineoplastic effects by which the bacteria could exert anticancer effects. In general, bacteria exhibit anticancer activity through four major mechanisms including improving the host immunity; decreasing the required tumour

metabolic and proliferation factors; biofilm formation and colonizing into the tumour; using as a target delivery vehicle and releasing relevant substances (40). Immunotherapy for gastric cancer based on immune checkpoint inhibitors (nivolumab, pembrolizumab) can be introduced in patients with high levels of microsatellite instability and/or mismatch repair gen and high tumour mutational burden, HER2 positive combined with trastuzumab (3). The introduction of immunotherapy to standard protocols of chemotherapy treatment for gastric carcinoma has an additional impact on the altered microbiota in the gastrointestinal tract, including both the altered microbiota in the gastric remnant after subtotal gastrectomy and the altered microbiota in the jejunum and ileum, as well as the oral microbiota (3). The literature also reveals that pre- and postoperative probiotics contribute to gut microbiota homeostasis with reduction of inflammation, maintenance of the intestinal barrier and improved immunity (3, 41).

Changes after gastric cancer surgery also have implications for postoperative nutrition. In the modern era, the prospects of cure and prolonged survivorship have improved in patients with gastric cancer, that are treated with curative intent and where radical resection is possible (22). As survivorship increases, other issues than oncologic outcomes must be considered in long-term follow-up, including nutritional well–being, which has an important influence on the prognosis (22). Maintaining body weight after upper gastrointestinal cancer surgery is a recognized significant challenge, but despite the prevalence and importance of weight loss, the incidence, severity, and specific causes of malabsorption are not well understood (22).

Malnutrition prevalence varies across different tumour sites ranging from 80–85% in pancreatic cancer, up to 74% for gastric cancer and 30–60% in colorectal cancer (10, 34, 42). Studies revealed before major gastric cancer surgery approximately 80% of patients with esophagogastric cancer experience significant weight loss and up to 27% of patients are already malnourished (10). Cancer-related sarcopenia (i.e., low muscle quantity and quality) contributes independently to the rate of postoperative complications and overall survival in gastric cancer (10). A grading system based on BMI and per cent weight loss (% WL) among cancer patients has shown that patients with higher % WL and lower BMI have notably shorter median survival, increased rate of surgical and non-surgical complications and prolonged hospitalization (10). Malnutrition also impacts neoadjuvant treatment being an independent predictor of chemotherapy dose–reduction of toxicity as malnourished patients are more likely to have their starting chemotherapy dose reduced from standard published dose (10, 42).

Malnutrition is connected to a variety of mechanisms due to local and systemic aspects of gastric carcinoma. Locally advanced disease is related to early satiety, therefore reduced intake of food, vomiting and anaemia due to bleeding and nutrient deficiency (10). Systemically, pro-inflammatory cytokines and chronic inflammation, lead to muscle wasting, and metabolic dysregulation with additional weight loss, known as cancer-induced cachexia (42). Neo-adjuvant chemo/radiotherapy combined with psychosocial factors related to cancer (i.e., fear, anxiety, depression) also contribute to additional weight loss (10, 42). Another possible and potentially treatable cause of malnutrition is the possibility of developing complications, such as small intestinal bacterial overgrowth (SIBO) (34).

The type of surgical reconstruction influences the development of micronutrient deficiency (6). It is the passage of food through the duodenum that appears to influence the micronutrient deficiency (6). After surgery reconstruction there is an accelerated passage of the contents through the gastrointestinal tract as well as diminished gastric acid availability in the small intestine due to the accelerated passage (10). The most commonly described deficiencies are iron (40–70%), copper and zinc (10–75%) (10), as well as calcium deficiency, due to several mechanisms, which include insufficient dietary intake, decreased dissolution of calcium salts due to hypochlorhydria and vitamin D deficiency (10). Calcium deficiency is one of the main causes of bone disorders following gastrec-

tomy (10). 75% of patients have diminished phosphate levels due to insufficient intake, bypass of the gastric absorption site, and vitamin D deficiency (10).

The jejunum and ileum are key absorption sites for fat-soluble vitamin, which includes vitamin A, D, E and K (6, 10). Undergoing gastrectomy patients are at risk of developing A, D and E deficiency (6, 10). After a total gastrectomy, there is an increased risk of lowered bone mineral density, probably due to vitamin D deficiency (10). Vitamin B_1 deficiency post-surgery is reported up to 49% resulting in duodenal and proximal jejunal exclusion as the primary absorption area (10). Vitamin B_{12} deficiency affects around one-third or more patients and is causing permanent megaloblastic anaemia. Folate deficiency also leads to megaloblastic anaemia and is far less common due to absorption across the entire small intestine (10). At lower incidence of B_{12} deficiency due to absorption across small intestinal areas (10).

Long-term changes in bowel function after gastric cancer surgical resection are common and are connected to decreasing the patient's quality of life (2). Also, altered microbiome pre- and post-surgery and neoadjuvant treatment contribute to the onset of clinical symptoms such as pain, diarrhoea and malabsorption, additional weight loss and cancer and malnutrition-related cachexia which is connected to poor life prognosis (2). Depending on which gastrointestinal functions are altered, a variety of different symptoms can present (43). Symptoms that are common in patients with SIBO condition are non-specific, such as non-specific abdominal pain, bloating, flatulence, obstipation, diarrhoea, malabsorption, and consequent unintentional weight loss (31). Non-specific abdominal symptoms are common after surgical resections of the upper gastrointestinal tract in patients with and without SIBO condition and they often trigger extensive diagnostic evaluation (31).

Careful evaluation of clinical symptoms in patients after total and subtotal gastrectomy presented, patients are more likely to manifest certain symptoms of SIBO. Besides, this study found that the symptoms were poor predictors of SIBO, as the symptom profiles were similar between SIBO negative and SIBO positive groups. We found that none of the symptoms were more frequent in the case of SIBO in symptomatic and asymptomatic patients after total and subtotal gastrectomy. In addition to the above, the recognition of symptoms in patients may also be subject to the patient's attitude towards knowledge of post-surgical complications. The extent to which the patient experiences these clinical symptoms certainly depends on the degree of symptom presence, knowledge of possible post-surgical complications, and assessment of quality of life. Targeted symptom-finding, considering the necessary nutritional treatment, could significantly improve treatment outcomes and also allow patients greater access to adjuvant treatment.

Literature reveals that symptoms are poor predictors for SIBO as most of the research did not find any connection to certain symptoms, with most of the research on symptomatic patients after RYGB surgery for morbid obesity treatment ((15, 18, 44)). Increasing evidence of microbiota involvement in different pathologies and disease burden offered new evidence-based data connecting gastric carcinoma and microbiota involvement (44). Besides, the characteristics of the microbial community play key roles as potential biomarkers and predictors of responses in cancer therapy (44).

Paik et al have found that abdominal fulness and borborygmus during glucose BT are positive predictive factors for SIBO (23). It is hard to compare their study with ours as we were trying to find the pretest symptoms that would help diagnose SIBO and not symptoms that are present during glucose BT. Paik et al suggested that SIBO could be associated with postprandial intestinal symptoms (23). Liang et al have proved that SIBO is connected to the severity or intensity of symptoms in patients with gastric cancer, also described and postulated with some other research groups; results are limiting due to a small number of included patients, poor description of observed groups or limited to SIBO detection preoperatively (36). Therefore, we have come to the conclu-

sion that none of the pretest symptoms is connected to SIBO after total and subtotal gastrectomy, therefore having a glucose BT is necessary for such patients. Regarding Paik et al and Liang et al, it is possible that SIBO-positive patients have a higher intensity of symptoms or that their symptoms are more severe postprandial, but more research is needed to prove this hypothesis.

The integrity of the intestinal mucosa barrier is damaged by chemotherapy and radiotherapy used in treatment protocols for gastric cancer either through direct effects on the epithelial stem cell compartments or by causing diminished intestinal blood circulation (36). Both mechanisms provoke ischemic hypoxia resulting in the activation of the xanthine oxidase and subsequently oxygen-free radical production (36). The ionizing radiation triggers intestinal cell necrosis, and consequent reduced function and survival of enterocytes (36). Effects of chemo/radiotherapy therefore result in making enterocytes less capable of counteracting bacterial growth and invasion (36).

In this present study, we have not found statistically significant differences between SIBO positive and negative groups in treatment with (neo)adjuvant chemo/radiotherapy. To the best of our knowledge, this is the first research to have analysed the influence of chemo/radiotherapy treatment on SIBO in post-gastrectomy treatment. In terms of explaining the phenomenon, the data presented here would be significantly more relevant if patients were tested preoperatively and, secondly, if the microbiome of positive patients was analysed. We need to conclude that more research is needed to find out whether there is a connection between SIBO to dose and type of chemo/radiotherapy and any other correlation.

SIBO is a well-known cause of malabsorption and malnutrition; given the explained altered physiological circumstances after subtotal and total gastrectomy and the proven metabolic disturbances in the SIBO state, we expect a more rapid occurrence of deficiencies of minerals and some vitamins, especially those whose key resorption or mechanisms take place in the duodenum. Accelerated passage of contents through the alimentary canal and triggering factors influencing the exacerbation of SIBO further exacerbate metabolic deficiencies; the introduction of antimicrobial agents for SIBO-related clinical signs may further exacerbate or mask the often-combative clinical signs. In addition, in the presence of SIBO, due to the rapid passage of the contents through the gastrointestinal tract, lower plasma levels of chemotherapeutic agents can be expected in patients treated with oral chemotherapeutic agents in adjuvant treatment regimens, thus blunting the otherwise reasonable chances of a complete response to treatment. It should also be noted that the recognition of SIBO in the early postoperative period is also underestimated because of the altered dietary regimen that might explain the appearance of certain clinical signs. Literature reports that up to 74% of post-gastrectomy patients have a BMI < 18,5 kg/m^2 and up to 58% have hypoproteinaemia and albuminemia (< 3,5 mg/dl) ((34, 45)). Aisa et al have found a trend towards lower levels of prealbumin and vitamin D, although the differences were not statistically significant (46). Extended meta-

Table 3. (Neo)adjuvant chemo/radiotherapy and antibiotic treatment according to positive and negative breath test

Variable	Positive breath test (n=11)	Negative breath test (n=26)	p
Chemotherapy before S	1,455 ± 0,52	1,577 ± 0,50	0,501
Chemotherapy after S	1,364 ± 0,50	1,654 ± 0,49	0.108
Radiotherapy before S	1,909 ± 0,30	1,885 ± 0,33	0,829
Radiotherapy after S	1,818 ± 0,40	1,924 ± 0,27	0,354

The variables are expressed as mean ± SD (standard deviation). Statistical analysis was done using the Mann-Whitney U test and Fisher exact test

bolic screening of patients has not been introduced in clinical protocols for post-operative follow-up, which could also account for the high incidence of late metabolic complications after gastrectomy.

In this present study SIBO positive and SIBO negative patients did not have important different eating patterns as eating profiles were similar in both groups. It is possible that eating patterns do not differ and that SIBO is one of the possible and treatable causes of malabsorption and malnutrition in patients after surgical removal of the gastrointestinal tract due to gastric cancer. Despite the rapid passage of contents through the gastrointestinal tract due to the tailored formula, ONS dietary treatment could have delayed the onset of metabolic disturbances; most patients in the observation group were prescribed pre-formulated formulas, but precise data on the actual consumption of fortified foods could not be obtained. At the same time, prescribing tailored nutritional formulas allows the patient to be able to resorb vitamins, minerals, and trace elements in a tailored way, which should be taken into account at least in the early postoperative period, until the adaptive environment has fully developed.

In conclusion regarding the high incidence of SIBO after total and subtotal gastrectomy, and its causal involvement in malabsorption and malnutrition it is necessary to diagnose and treat SIBO in such patients. Additional studies are needed to understand the exact connection between SIBO, malabsorption and its consequences in patients after gastrectomy and the impact of SIBO on the schemas of neoadjuvant treatment protocols for improved survival and QL.

The strength of this study is its focus on the connection between SIBO and surgical removal of the gastrointestinal tract after gastric cancer as this remains the mainstay treatment in these patients. We demonstrated the high incidence of SIBO after surgical resections for gastric carcinoma and mandatory early diagnosis and treatment.

The study had several limitations. First is the small number of participants, included in the study, but the interpretation of our results was based on significant data from the literature, therefore the importance of our study is increased even with the small cohort. The second limitation is the lack of a standardized methodology for diagnosing SIBO. The gold standard is a jejunal aspiration, which is very invasive and is therefore not suitable for our patients. The third limitation is the dose of glucose used for BT. In our study, we used 25 of glucose, because we wanted to avoid dumping symptoms in our patients. In the lite-

Table 4. Eating patterns according to positive and negative postoperative breathing tests after total and subtotal gastrectomy

Variable	Positive breath test (n = 11)	Negative breath test (n = 26)	p
Meals per day	4,636 ± 1,21	4,750 ± 0,97	0,958
Snacks per day	1,727 ± 1,01	2,000 ± 1,23	0,395
Sugars (n, (%))	0 (0,0)	2 (7,7)	0,744
Eating bread (n, (%))	9 (81,8 %)	20 (80,0%)	1,000
Drinking coffee (n, (%))	1 (9,1)	15 (57,7)	0,010*
Normal appetite	2 (22,2)	5 (19,2)	1,000
Fibres worsens symptoms	0,364 ± 0,67	0,2692 ± 0,83	0,300
Eating starch often	1,273 ± 1,49	1,423 ± 1,37	0,691
Starch worsens symptoms	0,546 ± 1,21	0,423 ± 0,95	0,808
Quit eating starch	0,636 ± 1,21	0,654 ± 1,02	0,938

rature, the glucose doses used in BT for the diagnosis of SIBO ranged from 25 to 100 g (15). There is a lack of standardization, but the North American consensus of 2017 suggests that a dose of 75 g of glucose appears to be the most practical dose for diagnosing SIBO (47). On the contrary, the European guideline on indications, performance, and clinical impact of hydrogen and methane breath tests in adult and paediatric patients of 2021 has suggested that this large dose is commonly associated with false positive diagnoses of SIBO (48). We are aware that due to smaller amounts of glucose, we could underestimate the prevalence of SIBO. The fourth limitation is that due to the study design, we did not have data on SIBO prevalence before surgical resection. The last limitation of our study is that we did not exclude patients with co-existing conditions, such as diabetes mellitus, connective tissue disease, chronic pancreatitis, thyroid disease, liver disease and some others that may be connected higher incidence of SIBO in our patients.

CONCLUSION

The incidence of SIBO in patients who underwent total and subtotal gastrectomy for gastric carcinoma is worryingly high, 30 and 29% respectively. The incidence of SIBO after total and subtotal gastrectomy is currently underestimated. SIBO is connected to systemic metabolic complications and their consequences. Symptoms are a poor predictor for SIBO, as the symptom profile is similar between SIBO positive and SIBO negative groups, therefore the diagnosis cannot be made based on clinical symptoms. Glucose BTs are useful and inexpensive tools for diagnosing SIBO but there is an urgent need for standardization.

The results of this observational study confirm there is an urgent need to systematically address SIBO after surgical resections of the gastrointestinal tract due to gastric cancer in subtotal and total gastrectomy to affect the clinical outcome and prevent the development of complications. Besides, SIBO as a clinical entity is implicated in the occurrence of gastric cancer, so there is also a diagnostic entity for disease confirmation and post-operative follow-up.

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Percutaneous endoscopic cecostomy: alternative solution in severe constipation – case report

Perkutana endoskopska cekostoma: alternativna možnost pri hudi obstipaciji – prikaz primera

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***Ključne besede**: perkutana endoskopska cekostomija, zaprtje, uvodna metoda*

ABSTRACT

Percutaneous endoscopic cecostomy (PEC) is a minimally invasive endoscopic procedure with the placement of the tube directly into the colon, that allows us therapeutic interventions. We present the case of a patient with tetraplegia, who suffered from chronic constipation. Chronic constipation is a common problem in patients with spinal and neuromuscular disorders. These patients are generally less favoured candidates for surgical interventions, so in patients where conservative measures fail, PEC represents a less invasive option for the improvement of symptoms.

IZVLEČEK

Perkutana endoskopska cekostomija (PEC) je minimalno invaziven endoskopski poseg z namestitvijo tubusa direktno v debelo črevo, kar nam omogoča terapevtske posege. Predstavljamo primer bolnika s tetraplegijo, ki je trpel za kroničnim zaprtjem. Kronično zaprtje je pogosta težava pri bolnikih s hrbteničnimi in živčno-mišičnimi obolenji. Ti bolniki so na splošno manj priljubljeni kandidati za kirurške posege, zato pri bolnikih, pri katerih konzervativni ukrepi ne uspejo, PEC predstavlja manj invazivno možnost za izboljšanje simptomov.

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INTRODUCTION

Chronic constipation is a frequent challenge in patients with spinal cord injuries, lesions, and neuromuscular disorders (1). The first step in the treatment of severe constipation is conservative management with dietary measures, discontinuation of medications that cause obstipation, correction of fluid and electrolyte disturbances, and use of laxatives. If symptoms persist, retrograde or antegrade lavage may be an option. Furthermore, the use of prokinetic agents and endoscopic decompression can also lead to resolution of symptoms, but results are often transient (2, 3, 4). Consequently, many patients need other therapeutic options, but since they usually have many comorbidities, they are at great risk for potential major complications following surgical interventions such as traditional surgical cecostomy. In these clinical settings, percutaneous endoscopic cecostomy (PEC) offers a less invasive treatment option, moreover, there is no risk of administering general anaesthesia (2, 5, 6).

Percutaneous endoscopic cecostomy was first described by Ponsky and colleagues in 1986 as an alternative to surgically or radiographically placed cecostomy (2, 7). Since then, the use of procedures has gradually increased. However, the procedure is still not widely used, most likely because of unfamiliarity with the procedure and its indications (2).

We report the case of a patient with severe constipation, whose symptoms were ultimately relieved by PEC placement.

CASE REPORT

A 56-year-old male with tetraplegia after a traumatic spinal cord injury in 2010 was admitted to our centre because of a urinary infection and evidence of prolonged constipation. He was administered intravenous antibiotics and showed a decrease in inflammatory parameters, nevertheless, his abdominal symptoms persisted. There were signs of abdominal distension and radiographic imaging (X-ray of the abdomen, abdominal CT) excluded mechanical obstruction or other organic pathology but showed meteorism and an excessively wide colon (Figure 1). During hospitalisation, extensive conservative measures were carried out (use of lactulose, prokinetic agents such as neostigmine, rectal tube insertion, repeated enemas), and several endoscopic decompressions were performed, but with a very limited effect. Surgical intervention was not feasible due to high perioperative risk assessment, therefore the decision for PEC placement was taken.

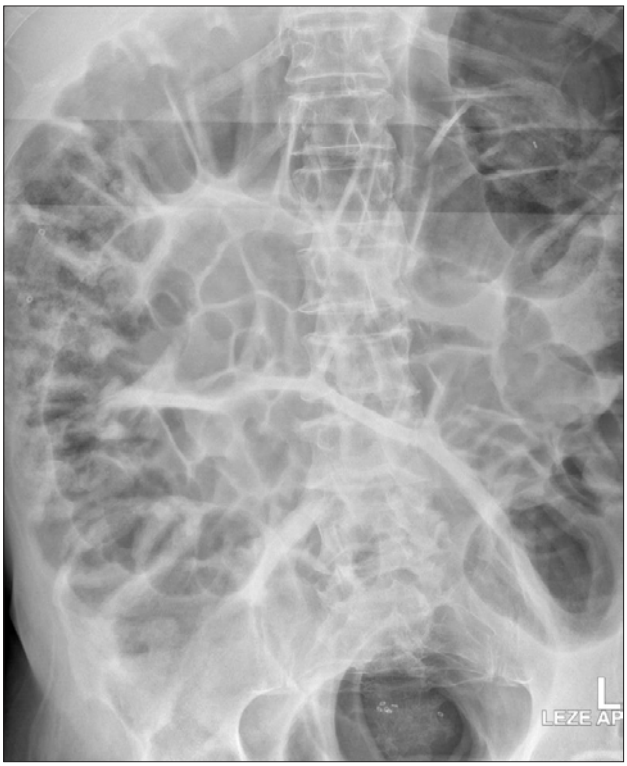

Figure 1. X-ray of the abdomen before the procedure showed meteorism and an excessively wide colon

The patient was given oral bowel preparation in a standard dose before the procedure and periprocedural antibiotic prophylaxis with intravenous metronidazole and gentamicin was administered. The procedure was conducted with conscious sedation with midazolam and fentanyl. The colonoscope was introduced into the right colon and then advanced to the cecum, with transillumination of the abdominal wall to identify a suitable puncture site. The correct position was verified by caecal indentation with direct digital pressure on the abdominal wall. The abdominal wall was prepared and anaesthetized in a sterile

fashion. Placement of four colopexy sutures, from the Pexact (Fresenius) gastrostomy system, was carried out under direct endoscopic vision. The centre of the colopexy site was punctured with an introducer needle and a thread was inserted (Figure 2). The thread was grasped with the snare and then withdrawn from the colon with the colonoscope. A standard percutaneous endoscopic gastrostomy tube (Freka Ch20) was then affixed to the thread and slowly pulled and trailed through the colon (pulled-through method), exiting the abdominal wall, where it was secured with external bolsters (Figure 3). The correct position was confirmed by reinsertion of the colonoscope.

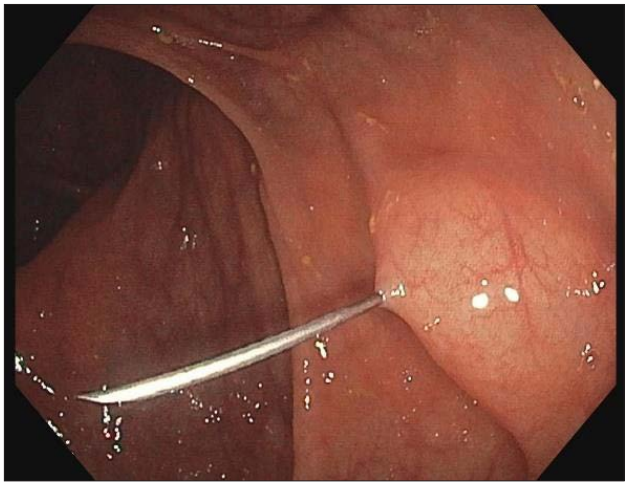

Figure 2. insertion of introducer needle

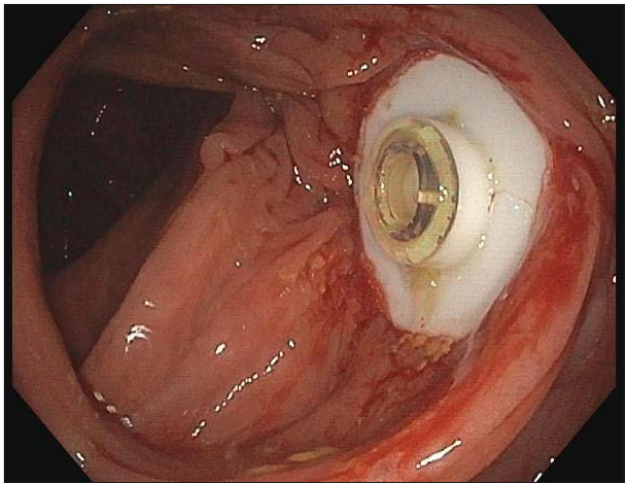

Figure 3. placement of percutaneous endoscopic tube

There were no adverse events after the procedure, and antibiotic prophylaxis was administered for a total of five days. Symptoms resolved quickly, and the patient was discharged to home care, with instructions to apply lactulose through the cecostomy tube for treatment of constipation.

DISCUSSION

PEC placement gives us another therapeutic option in patients with chronic constipation. However, there are many other indications for PEC placement, such as acute colonic pseudo-obstruction (Ogilvie's syndrome), chronic intestinal pseudo-obstruction, and for application of anterograde enemas in other colonic motility disorders (2, 3, 5). Contraindications for PEC placement are active colitis or ileocolitis, severe electrolyte disturbances, coagulopathy, anterior abdominal infection and sepsis, colonic ischemia, mechanical intestinal obstruction, and excessive abdominal wall fat with failure of transillumination (1, 8).

There was scarce information and guidelines other than case reports and retrospective case series on this topic. However, in 2020 the European Society of Gastrointestinal Endoscopy (ESGE) published guidelines for the endoscopic management of gastrointestinal motility disorders, which included patients with intractable constipation and Ogilvie's syndrome. Its main aim was to guide the technique and management of percutaneous endoscopic cecostomy tube placement. In patients with intractable constipation the recommendations state that before any endoscopic treatment, an extensive use of conservative treatment with medical therapies or retrograde enemas must take place. If the decision for PEC is made, the bowel must be properly prepared with diet and polyethylene glycol solution before the procedure. Antibiotic prophylaxis is recommended 1 hour before the procedure and for 3 days post-procedure given potential faecal contamination and should follow local protocol. There are three main techniques for percutaneous endoscopic cecostomy: the pull-through method, the introducer (push) method, and laparoscopically assisted percutaneous endoscopic cecostomy (LAPEC). In all techniques, ESGE recommends fixing the cecum to the abdominal wall to prevent leaks and infectious adverse events. If technically feasible the cecum is the pre-

ferred location for PEC placement (3). Albeit many advantages over surgery, this procedure is not without its risks. The complications following the procedure are usually minor, but serious complications, such as faecal peritonitis, may occur (2, 9). PEC is a viable treatment option, which should be reserved for selected patients after multidisciplinary assessment and should be performed by well-trained operators in tertiary referral centres (10).

CONCLUSION

PEC has been shown as a well-tolerated alternative for a selected group of patients with chronic constipation in which conservative treatment has failed or who are not candidates for surgical intervention.

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Idiopathic Myointimal Hyperplasia of the Mesenteric Veins as a Rare Cause of Chronic Diarrhoea

Idiopatska miointimalna hiperplazija mezenterialnih ven kot vzrok kronične driske

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***Keywords**: diarrhoea, myointimal hyperplasia, surgical resection*

***Ključne besede**: diareja, miointimalna hiperplazija, kirurško zdravljenje*

ABSTRACT

Idiopatic myointimal hyperplasia of the mesenteric veins (IMHMV) is a rare and poorly understood cause of chronic ischemic bowel disease. The pathognomonic findings consist of nonthrombotic and noninflammatory occlusion of the mesenteric veins secondary to intimal smooth muscle hyperplasia. It typically affects older and middle-aged men, who are often previously healthy. The pathogenesis and etiology of IMHMV is unknown. In most patients, the disease affects the rectosigmoid colon and presents with abdominal pain, hematochezia, diarrhoea, and weight loss. It represents a diagnostic challenge for pathologists and clinicians. Colonoscopy biopsy specimens are often non representative or misleading, since they show non specific findings or even suggest other diagnosis. Surgical resection is the treatment of choice. Although preoperative diagnosis of the disease is challenging, there are some mucosal pathological features

IZVLEČEK

Idiopatska miointimalna hiperplazija mezenterialnih ven (IMHMV) je redek in slabo poznan vzrok kronične ishemije črevesja. Gre za netrombotično in nevnetno zaporo mezenterialnih ven, ki je posledica proliferacije gladkih mišic v intimi. Pogosto so bolniki moški srednjih let ali starejši moški brez predhodno znanih bolezni. Etiologija in patogeneza bolezni nista poznani. Najpogosteje prizadene rektosigmo in se kaže z bolečinami v trebuhu, hemohezijo, drisko ter hujšanjem. Ker z endoskopijo neredko pridobimo nereprezentativne biopsije, ki kažejo nespecifične spremembe ali pa sugerirajo drugo diagnozo, predstavlja diagnostični izziv tako za klinike kot patologe, zato je bolezen pogosto pozno diagnosticirana. Zdravimo jo s kirurško resekcijo prizadetega dela črevesja. Pred operacijo in histopatološkim pregledom resektata je diagnozo težko postaviti, vendar poznamo histološke elemente, ki tudi v povrhnjih

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that suggest IMHMV. We report the case of a 64-year-old man with IMHMV as a cause of chronic diarrhoea.

endoskopskih biopsijah dajejo slutiti nanjo. Predstavljamo primer 64-letnega moškega s 15-mesečno anamnezo driske.

CASE REPORT

A 64-year-old male patient with arterial hypertension, type 2 diabetes mellitus, obstructive sleep apnea syndrome, psoriasis, history of transurethral resection of a bladder tumor and umbilical hernioplasty, was admitted to our gastroenterology clinic with chief complaint of chronic diarrhoea persisting for the past 15 months. He complained of multiple loose and watery bowel movements up to 10 times per day, accompanied by abdominal pain, hematochezia and unintentional weight loss of 7 kilograms during the last month before admission.

Colonoscopy, performed 4 months after onset of symptoms, only showed mucosal edema with diffuse loss of vascular pattern in the rectum and descending colon. Histopathological examination of biopsy specimens revealed edema of lamina propria, dilated capillaries in submucosa, with numerous eosinophilic granulocytes focally infiltrating the small vessels wall, suggesting possible systemic small-vessel vasculitis. Due to numerous eosinophilic granulocytes, eosinophilic granulomatosis with polyangiitis was suspected. 6 months after onset of symptoms, he underwent contrast enhanced computed tomography, which demonstrated circumferential, symmetrical wall thickening of sigmoid and descending colon with pericolic fat stranding. He temporarily received mesalazin, which had no effect.

Based on the previous histopathological findings, initial management during hospitalization was aimed at ruling out systemic vasculitis (eosinophilic granulomatosis with polyangiitis) and causes of colonic eosinophilia (parasitic infections). The patient had normal peripheral eosinophil count and no other organ involvement (lungs, kidneys, paranasal sinuses, peripheral nervous system). The laboratory results showed no significant abnormalities, inflammatory markers levels were not significantly elevated. Blood tests for systemic vasculitis (anti-neutrophil cytoplasmic antibody, ANCA) were negative. A repeat colonoscopy was performed, which revealed numerous ulcers in the sigmoid colon (Figure 1), and multiple biopsies were taken. Based on working diagnosis of eosinophilic colitis, the patient was treated with methylprednisolone, and some clinical improvement was observed. Histopathological analysis of biopsy specimen showed the presence of thick-walled hyalinized vessels in lamina propria, with plump endothelial cells and subendothelial fibrin deposits, subintimal edema, and in some cases complete occlusion of the vascular lumen. These findings were consistent with IMHMV. Treatment with methylprednisolone was discontinued.

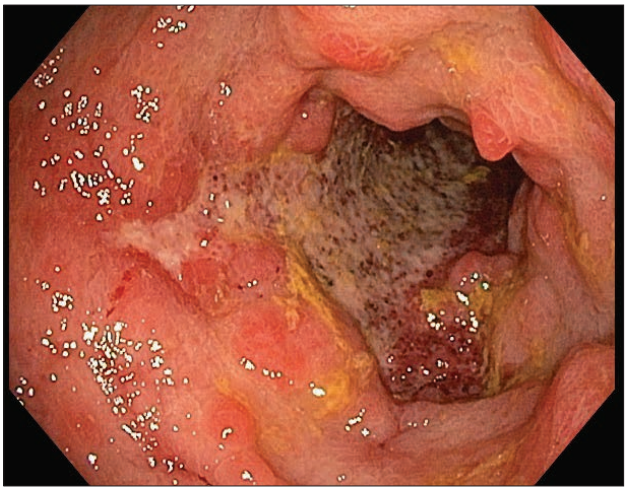

Figure 1. Endoscopic findings of sigmoid colon mucosa showed multiple ulcers

Under the guidance of the scope the bowel was tattooed distally and proximally to the abnormal region. The patient underwent laparoscopic surgical resection of the affected sigmoid segment. Histopathological examination of the resected bowel specimen confirmed the diagnosis of IMHMV. Veins with thickened

and hyperplastic wall, without signs of inflammation, were observed in subserosal fat, muscularis propria and submucosa. The findings involved irregular chronic ischemic colitis with erosions, shallow ulcers and regenerative changes in the mucosa, edema especially of the mucosa and submucosa, steatonecrosis of the pericolic fat and reactive changes in the lymph nodes in the pericolic fat. There were no ischemic changes in the resection margins. During one year follow-up period, there was no evidence of disease recurrence.

DISCUSSION

Etiology

Idiopatic myointimal hyperplasia of the mesenteric veins was first reported in 1991 by Genta and Haggitt. They described 4 patients with segmental ischemic colitis, who recovered completely after segmental resection of the ischemic portion of the colon and had no recurrence of intestinal symptoms on follow-up of up to 7 years (1). Since the histological features of the veins in IMHMV are similar to those of failed cardiac saphenous vein bypass grafts and stenosis of arteriovenous fistula (AVF) in patients undergoing dialysis (2, 3), Genta and Haggitt assumed that the formation of AVFs might increase venous blood flow and result in vascular remodeling that leads to myointimal hyperplasia (1).

Hui Li and his collegues performed a review of the literature from 1991 until February 2022 using electronic databases (Medline, EMBASE, Web of Science, PubMed, and The Cochrane Library – CENTRAL) and found 70 cases of IMHMV. Most patients were previously healthy and no arteriovenous malformation has been identified in the literature (4).

Clinical Features

The most common clinical features are recurrent, progressive abdominal pain (82,9 %), hematochezia (50 %), diarrhoea (37,1 %) and weight loss (18,6 %). Constipation alternating diarrhea (7,1 %) and constipation (7,1 %) were rarely reported. Left colon is affected in most cases, especially rectosigmoid colon, while small intestine, pancolon, ascending colon, transverse colon or only rectum are rarely affected. Clinical presentation depends on site of involvement. Regarding colonic IMHMV, the majority of patients suffer from persistent abdominal pain, hematochezia and diarrhoea. In contrast, small bowel IMHMV mostly presents with obstruction. The analysis of 70 reported cases showed that the meantime between symptom onset and surgery was 4,5 months (4).

Diagnosis

Historically, surgical resection and histopathological findings in resected specimen were considered the only method to diagnose IMHMV. Typical finding is the thickening of small and medium-sized intramural mesenteric veins, with the hallmark manifestation of intima and media smooth muscle proliferation, resulting in luminal occlusion, that leads to mucosal ischemic changes (5). The latter raises the possibility of endoscopic diagnosis. Because of the absence of concrete mucosal histopathological criteria of IMHMV, the preoperative diagnosis is still difficult, but there are some pathological features in endoscopy biopsy specimens reported in the literature that suggest the diagnosis. Those findings include the presence of ischemic pattern of mucosal damage, clustered, slightly dilated, "arteriolized" capillaries with myointimal thickening within the lamina propria, lined by plump endothelial cells and subendothelial fibrin deposits, and thickened submucosal veins (6–8). A hypothesis states that chronic mechanical stress on the mesenteric veins leads to vessel remodeling. The increased venous pressure is transmitted to the mucosal capillaries and causes endothelial injury, which results in fibrin extravasation in subendothelial space (7).

Endoscopic appearance of IMHMV is a result of ischemic changes of the mucosa and is non-specific, contributing to the high rate of misdiagnosis. The most common endoscopic findings are ulcers and mucosal congestion, while strictures are rarely seen (4). Early stages of disease result in edematous and

erythematous mucosa. Ulcers and inflammatory exudates develop with disease progression (9, 10).

Contrast enhanced computed tomography of the abdomen demonstrates the range of intestinal involvement and typically showes features of ischemic colitis: a segment of diffuse circumferential colonic wall thickening, poor mural enhancement, submucosal edema, and pericolic fat stranding. IMHMV is often misdiagnosed as inflammatory bowel disease (11).

Treatment

Surgical resection of the affected bowel is considered the treatment of choice. According to the available literature data, in follow-up duration up to 7 years after resection all patients appear to be cured, with no recurrence of disease-related activity or symptoms. Of the reported cases of IMHMV, Hui Li and his collegues observed complications in 20 out of 70 patients. They were mainly attributed to inflammatory bowel disease-related medication, delay of operation and need for emergent surgery. The most common complications were intestinal perforation and massive hematochezia (4).

CONCLUSION

Idiopatic myointimal hyperplasia of the mesenteric veins should be considered in middle-aged patients with subacute segmental colitis and symptoms characteristic of inflammatory bowel disease or chronic ischemic bowel disease, especially in those who do not improve with therapy. The preoperative diagnosis remains a challenge. Surgical resection of the ischemic portion of the bowel is curative. There is no known evidence of disease recurrence.

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Air embolism after insertion of a percutaneous endoscopic gastrostomy – case report

Zračna embolija po vstavitvi perkutane endoskopske gastrostome – prikaz primera

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***Ključne besede**: zračna embolija, perkutana endoskopska gastrostoma, endoskopski poseg, zaplet*

ABSTRACT

Percutaneous endoscopic gastrostomy is the method of choice in patients with long-term restriction of oral nutrition. Complications during percutaneous endoscopic gastrostomy insertion or immediately after the procedure include bleeding, perforation, peritonitis and damage of other internal organs. A very rare complication of endoscopic procedures is also air embolism. In the article, we present a case of cerebral air embolism in a 66-year-old patient after insertion of a percutaneous endoscopic gastrostomy.

IZVLEČEK

Perkutana endoskopska gastrostoma je metoda izbora pri bolnikih z dolgotrajno omejitvijo oralne prehrane. Zapleti med vstavitvijo perkutane endoskospske gastrostome ali takoj po posegu vključujejo krvavitev, perforacijo, peritonitis ter poškodbo drugih notranjih organov. Zelo redek zaplet endoskopskih posegov pa je tudi zračna embolija. V članku prikažemo primer možganske zračne embolije pri 66-letnem bolniku po vstavitvi perkutane endoskopske gastrostome.

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INTRODUCTION

Percutaneous endoscopic gastrostomy (PEG) was first described as a method to establish a nutritional route by Gauderer and colleagues in 1980 (1). Research shows that enteral nutrition has many advantages over parenteral nutrition. The decision to undergo the procedure must be considered on an individual level, as the benefits and risks must be analyzed in detail and the concerns of the patient and his relatives thoroughly assessed (2).

Complications during PEG insertion or immediately after the procedure are rare and include bleeding, perforation, peritonitis, damage to other internal organs. Attention should also be paid to complications due to the application of drugs used as part of sedation and analgesia during the procedure. Late complications are mostly related to care – local inflammation with infection, leakage, clogging of the tube, mucosal overgrowth over the stomach lining and aspiration of food (3, 4). Air embolism is a less frequently seen or described complication of endoscopic examinations (5).

CASE REPORT

We report a case of a 66 year old male patient without associated diseases or regular therapy and a medical history of the right lower lobe lung adenocarcinoma (T1bN2M0), after radical chemo- and radiotherapy until December 2020, with progression of the disease to the subcarineal lymph nodes in September 2022 (with a clinical picture of dysphagia) and repeated radiotherapy until December 2022 with a complete response. Since February 2023, he was treated several times in various medical facilities for outbreaks of infection. Most likely, due to the passage of food through a defect in the wall of the esophagus, which was never proven by radiological examinations.

In April 2023, he was treated at the Emergency Department of the University Clinical Center Ljubljana, due to fever over 38°C with chills and vomiting of blood. During hospitalization, a gastroscopy was performed, where fresh blood was present in the esophagus, and a shallow wall defect was visible at 30 cm. Transparency was poor, free perforation in the mediastinum or fistula with air bubbles was not recognized. The wall seemed very thin and soft, due to the risk of the wall puncture, hemostasis measures were not performed.

As the hemoglobin continued to drop, an urgent council of pulmonologist, thoracic surgeon and interventional radiologist decided to insert a stent graft into the aorta. The procedure was performed under general anesthesia. The thoracic aorta, just below the left subclavian artery, was covered with two stent grafts, approximately 20 cm long, and dilated with a balloon. After the procedure, patient was transferred to the Oncology Institute Ljubljana for further antibiotic therapy, parenteral nutrition and agreement regarding the insertion of a gastrostomy.

Approximately a week later, we performed a gastroscopy with the placement of a PEG with gastropexy. During the examination, mild bleeding was still visible at the site of the defect. There were no signs of complications during the procedure. Upon returning to the ward, the patient developed a mild disturbance of consciousness and a left-sided hemiparesis, as well as involuntary movements of the right limbs.

A head computed tomography (CT) with CT angiography of the aorto-cervical and cerebral arteries was performed, where there were no signs of a fresh infarction, but several very small hypodense air inclusions were visible in the right frontal and parietal lobes. 100% oxygen was administered via an OHIO mask, and he received benzodiazepines due to the clinical picture of an epileptic attack. The following day, the disturbance of consciousness deepened, he suffered a focal epileptic seizure again. He was transferred to the intensive care unit, where he was anglosedated and intubated. Control head CT showed resorption of gas bubbles in the right hemisphere, with the formation of edema. An ultrasound of the heart was also performed, which did not show air bubbles in the cardiovascular circulation or a possible open foramen ovale. Treatment in a hyperbaric chamber

was considered, but was not realized, due to the inability of the patient to cooperate and questionable effectiveness in the absence of bubbles on the control head CT.

During the treatment, epileptiform activity was ruled out with an EEG, no demarcated ischemia, herniation, bleeding or air inclusions were found on control imaging of the head, and the edema subsided. Antibiotic therapy was reintroduced due to the onset of the infection, patient also required vasoactive support and supplemental oxygen in inhaled air. Anticoagulant treatment was initiated in the presence of thrombosis of the right axillary vein. After 16 days, the patient was extubated. From the neurological deficits a left hand paresis remained, but it also gradually resolved. 12 days after transfer from the intensive care unit, patient had an episode of hematemesis and melena. Despite symptomatic supportive therapy, he died the same night.

DISCUSSION

An air embolism is a sudden clogging of a vessel with air, due to communication between the air source and the vessel and a pressure gradient that allows the passage of air into the bloodstream. It can occur with or without direct damage to the vessel (6, 7). It is a very rare complication of endoscopic examinations, the first description in the literature is from 1988 (8). Most commonly it is associated with endoscopic retrograde cholangiopancreatography (ERCP), but can result from any endoscopic procedure, including gastroscopy, enteroscopy, colonoscopy, and endoscopic ultrasound. Only one description of air embolism after PEG insertion is available in the literature, from 2013, where a 65-year-old male was diagnosed with portal vein air embolism 8 days after the procedure (9).

Air embolism is especially uncommon in upper gastrointestinal endoscopic procedures, because of the unique hepatic venous drainage. It may be limited to the portal venous system or develop into a systemic air embolism if the liver is bypassed (e.g. portosystemic bypasses, biliary-venous fistula, air flow directly into the hepatic veins or inferior vena cava). Arterial air embolism is even rarer and occurs in certain circumstances, such as the presence of an intracardiac bypass (most often an open foramen ovale), intrapulmonary right-left shunt, retrograde flow into the cerebral veins via the superior vena cava, or passage of air into the left atrium via pulmonary veins. These structural anomalies are usually not previously known, and often remain unrecognized even during diagnostics (in the event of a complication) (10, 11).

Risk factors for air embolism are inflammatory mucosal changes (e.g. inflammatory bowel disease, mesenteric ischemia), ulcer, tumor, postoperative gastrointestinal fistula, previous procedures or operations of the biliary system, transhepatic portosystemic shunt, special interventional techniques such as cholangioscopy, biliary sphincterotomy, placement of a metal stent, high-pressure air insufflation, increased volume and/or rate of air infusion (12).

The consequences of an air embolism depend on the speed and volume of air introduced into the bloodstream. Many cases are subclinical, but the clinical picture can be dramatic with cardiopulmonary instability and neurological symptoms. It may overlap with cardiopulmonary symptoms associated with sedation or neurological symptoms due to an ischemic or hemorrhagic event in the central nervous system (10). The diagnosis of air embolism is often difficult, because air can be absorbed from the circulation while the diagnosis is still ongoing. The presence of bubbles in the right atrium or pulmonary vein can be detected with cardiac ultrasound (preferably transesophageal). Potential structural anomalies of the heart, such as an open foramen ovale, can also be assessed. CT is the method of choice for detecting air inclusions in the portal system, lungs or brain parenchyma (11, 12).

The goal of treatment is to prevent further embolization and ischemia. Insufflation of the gastrointestinal tract should be stopped as soon as possible and excess gas should be aspirated. Application of 100% FiO2 is indicated. Patient can be tilted upside down by 30°

or placed in the left lateral position, thereby trying to prevent the further passage of air into the left heart and head. A possible therapeutic intervention is the insertion of a catheter into the central vein or pulmonary artery to aspire gas from the right ventricle. Treatment in a hyperbaric chamber is indicated, as the size of air bubbles can be reduced, nitrogen reabsorption is accelerated and the oxygen content of arterial blood is increased, which potentially reduces ischemia (13).

CONCLUSION

Air embolism is a rare endoscopic complication with a high mortality rate, presenting as cardiopulmonary instability and neurological symptoms. Diagnosis can be difficult.

We have presented a case of air embolism after gastroscopy with PEG insertion. It is not entirely clear whether the cause of the air embolism was the PEG insertion itself or insufflation in the presence of a defect in the esophageal wall.

Awareness, quick recognition and appropriate action by all who carry out such investigations and interventions in essential.

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Priporočila za obravnavo in napotitev bolnikov s perianalnimi fistulami pri Crohnovi bolezni

Recommendations for the treatment and referral of patients with perianal fistulas in Crohn's disease

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***Ključne besede**: kronična vnetna črevesna bolezen, Crohnova bolezen, kompleksne perianalne fistule, multidisciplinarna obravnava, kombinirano medikamentozno in kirurško zdravljenje*

***Keywords**: chronic inflammatory bowel disease, Crohn's disease, complex perianal fistulas, multidisciplinary treatment, combined medical and surgical treatment*

IZVLEČEK

Crohnova bolezen (CB) s perianalnimi fistulami predstavlja resen fenotip, povezan z znatno obolevnostjo. Bolniki s perianalno fistulizirajočo boleznijo imajo večjo verjetnost za hud potek bolezni, njihova kakovost življenja je občutno slabša. Poleg tega imajo ti bolniki povečano tveganje za nastanek raka rektuma in anusa. Kompleksnost in resnosti te skupine bolnikov zahteva večdisciplinarni pristop. Pri diagnozi in zdravljenju perianalne fistulizirajoče bolezni imata ključno vlogo gastroenterolog in kolorektalni kirurg (proktokirurg). Pregled v anestezji zagotovi pomembne informacije in je bistveni del obravnave zapletenih perianalnih fistul. Pomembno vlogo pri

ABSTRACT

Crohn's disease (CB) with perianal fistulas represents a serious phenotype associated with significant morbidity. Patients with perianal fistulizing disease are more likely to have a severe course of the disease, and their quality of life is significantly worse. In addition, these patients have an increased risk of rectal and anal cancer. The complexity and seriousness of this group of patients require a multidisciplinary approach. A gastroenterologist and a colorectal surgeon (proctologist) play a key role in the diagnosis and treatment of perianal fistulizing disease. Examination under anaesthesia provides important information and is an essential part of the management of complex

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opredelitvi poteka fistul in eventuelnih abscesnih kolekcij in ocenjevanju odziva na zdravljenje ima tudi radiolog z magnetno resonančnim slikanjem (MRI) male medenice, ki je preiskava izbora. Zdravljenje perianalne CB je medikamentozno in kirurško.

perianal fistulas. The radiologist also plays an important role in defining the course of fistulas and possible abscess collections and in evaluating the response to treatment with magnetic resonance imaging (MRI) of the pelvis, which is the examination of choice. Treatment of perianal CB is medical and surgical.

UVOD

Crohnova bolezen (CB) je kronična vnetna bolezen, ki prizadene kateri koli del prebavne cevi, od ust do anusa. Poznamo tri fenotipske oblike bolezni: vnetni, stenozantni in penetrantni. Penetrantno obliko lahko spremlja nastanek perianalnih fistul (1). Perianalne fistule predstavljajo najtežji fenotip CB, ki močno poslabša kakovost življenja bolnikov. Pojavijo se pri 20 do 40 odstotkih bolnikov (2). Tveganje za pojav perianalnih fistul se povečuje s trajanjem CB; po desetih letih je kumulativno tveganje 21-odstotno, po 20 letih 26-odstotno (2). Perianalne fistule so pogostejše pri bolnikih, ki imajo vnetje debelega črevesa (predvsem danke), in so redke pri bolnikih s terminalnim ileitisom. V petih odstotkih so perianalne fistule edina manifestacija CB (2). Klinično razdelimo perianalne fistule na enostavne in zapletene (kompleksne) (3). Enostavne fistule so vse nizke fistule, brez abscesov ali striktur, z eno samo zunanjo odprtino. Kompleksne fistule so opisane kot visoke fistule, z eno ali več zunanjimi odprtinami, s povezanimi abscesi ali strukturami ali brez njih, s pridruženo rektovaginalno fistulo ali brez nje (3). Razlikovanje med enostavnimi in zapletenimi je prognostično pomembno, saj imajo bolniki s kompleksnimi fistulami slabšo prognozo, nižjo stopnjo ozdravitve in ogroženo kontinenco za blato. Bolniki s perianalno boleznijo pogosteje potrebujejo hospitalizacijo, operacijo in eskalacijo medikamentozne terapije (4). Simptomi perianalne bolezni vključujejo perianalno bolečino, izcedek, nastanek abscesa in pojav sepse (5). Poleg tega je perianalna CB povezana z znatnim poslabšanjem kakovosti življenja, psihosocialno stisko in poslabšanjem spolnega življenja (6). Pri bolnikih s potrjeno Crohnovo boleznijo je bistveno zgodnje odkrivanje fistul, visoka stopnja pozornosti pa je potrebna pri bolnikih, ki imajo izolirano perianalno bolezen (7). Zaradi kompleksnosti in resnosti te skupine bolnikov mora zdravljenje perianalne Crohnove bolezni izvajati večdisciplinarna ekipa (8). Sodelovanje med gastroenterologom, kolorektalnim kirurgom, radiologom in patologom je bistveno za zagotovitev ravni oskrbe, potrebne za tako resen fenotip (8). V teh priporočilih je podan pregled večdisciplinarnega kliničnega pristopa k perianalni Crohnovi bolezni s posebnim poudarkom na perianalno fistulizirajočo bolezen z vidika kolorektalnih kirurgov in gastroenterologov ter napotitve v center odličnosti Univerzitetnega kliničnega centra (UKC) Ljubljana. Hitro zdravljenje in multidisciplinarni pristop sta namreč bistvenega pomena za uspeh zdravljenja in preprečevanje poškodbe sfinktrov in proktektomije (8).

POT NAPOTITVE

Pot napotitve bolnikov z zapletenimi perianalnimi fistulami pri CB mora biti dobro opredeljena in učinkovita. Zdravniki na primarni ravni, gastroenterologi, splošni in abdominalni kirurgi bi morali bolnike napotiti v specializiran center, v katerem lahko prejmejo večdisciplinarno oskrbo.

OCENA BOLNIKA

Ocena bolnikov z zapletenimi perianalnimi fistulami pri CB mora biti celovita in večdisciplinarna. Vključevati mora temeljito anamnezo, fizični pregled, laboratorijske, endoskopske in slikovne preiskave. Slikovne preiskave, kot je MRI ali endorektalni ultrazvok, lahko pomagajo pri opredelitvi obsega, vrste in kompleksnosti fistul (5, 7).

ZDRAVLJENJE ZAPLETENIH PERIANALNIH FISTUL

Zdravljenje zapletenih perianalnih fistul pri CB je zahtevno. Medikamentozno zdravljenje lahko vključuje antibiotike, imunosupresivno terapijo in biološka zdravila (6). Kirurško zdravljenje lahko vključuje vstavitev setona, kiretažo fistule ali obsežnejši kirurški poseg (ekscizijo fistule, LIFT (*ligiranje trakta intersfinkterne fistule*), reženj (*advancement flap*) itd.) in novejšo terapijo z mezenhimskimi matičnimi celicami (MMC) kot inovativno možnost, s katero se ohranja sfinkter in potencialno zagotavlja dolgoročna zacelitev (2. 6. 6. 7).

CENTER ODLIČNOSTI

V centru odličnosti za zdravljenje zapletenih perianalnih fistul pri CB mora delovati ekipa strokovnjakov z obsežnimi izkušnjami z zdravljenjem kompleksnih fistul. Ekipa mora biti večdisciplinarna, pri čemer mora vključevati v KVČB usmerjene gastroenterologe, kolorektalne kirurge, radiologe in v KVČB usmerjene medicinske sestre. Center mora imeti tudi dostop do najnovejše radiološke tehnologije in do opreme, potrebne za zdravljenje zapletenih perianalnih fistul (8).

PRIPOROČILA ZA OBRAVNAVO BOLNIKA S PERIANALNIMI FISTULAMI PRI CROHNOVI BOLEZNI (ALGORITEM)

Perianalne fistule lahko odkrije gastroenterolog, proktokirurg ali bolnik o njih pove sam. Zelo pomembno je proaktivno spraševanje bolnika o perianalni CB ob vsakem obisku in temeljit klinični pregled perianalnega predela ob načrtovanih kolonoskopijah.

- Gastroenterolog vodi bolnika s perianalno CB, zdravi luminalno bolezen in po potrebi spreminja ali prilagaja terapijo.
- Ob ugotovitvi perianalnih fistul lečeči zdravnik gastroenterolog napoti bolnika na MR male medenice.
- Po potrditvi perianalnih fistul gastroenterolog bolnika napoti h proktokirurgu oz. kolorektalnemu kirurgu.
- Proktokirurg opredeli zapletenost fistule glede na klinično sliko in MR preiskavo, kirurško oskrbi fistule, po potrebi vstavi seton in uvede antibiotično zdravljenje.
- Po vstavitvi setona proktokirurg bolnika napoti nazaj k lečečemu gastroenterologu.
- Če bolnik še ne prejema specifične terapije, ga gastroenterolog napoti na konzilij za kronično vnetno črevesno bolezen (KVČB) v UKC Ljubljana ali UKC Maribor za uvedbo primerne biološke terapije.
- Seton odstranimo po 8–14 tednih, če ni več sekrecije iz fistule oziroma nevarnosti za pojav abscesa (o tem presoja proktokirurg).
- V primeru poslabšanja perianalne CB ali nepričakovanega izpada setona svetujemo čimprejšni pregled pri proktokirurgu.
- Po približno 6–12 mesecih sledi ocena perianalne CB (endoskopija, MRI); gastroenterolog izključi proktitis, proktokirurg oceni stanje fistule (aktivnost, zacelitev).
- Če se je perianalna fistula zaprla, sledi vzdrževalno zdravljenje in spremljanje (redne kontrole pri proktokirurgu tudi v primeru zaceljenih fistul).
- Če je CB v remisiji, na MRI male medenice pa je še vedno prisotna zapletena perianalna fistula (zapletena/e fistula/e se ni/niso zaprle), bolnika lahko napotimo na KVČB- kirurški konzilij UKC Ljubljana za oceno primernosti zdravljenja z mezenhimskimi matičnimi celicami.
- Če je CB aktivna in se zapletena/e fistula/fistule ni/niso zaprle, lečeči gastroenterolog zdravljenje optimizira ali napoti bolnika ponovno na konzilij za KVČB za morebitno menjavo biološke terapije. Ko dosežemo luminalno remisijo ali minimalno aktivno bolezen, bolnika z ustrezno dokumentacijo lahko napotimo na KVČB – kirurški konzilij UKC Ljubljana za oceno primernosti zdravljenja z mezenhimskimi matičnimi celicami.

SPREMNA DOKUMENTACIJA ZA KVČB-KIRURŠKI KONZILIJ UKC LJUBLJANA:

- Gastroenterolog opiše luminalno stanje bolezni,
- Proktokirurg opiše stanje fistule (število in lega zunanjih in notranjih ustij/fistula drenira/ne drenira/ potencialno zaprtje fistule),
- Izvid MRI male medenice naj ne bo starejši od 3 mesecev,
- Izvid kolonoskopije naj ne bo starejši od 6 mesecev,
- Ostala relevantna medicinska dokumentacija in izvidi.

ZAKLJUČEK

Fistulizirajoča CB je poseben fenotip CB z veliko obolevnostjo in prizadene skoraj polovico vseh bolnikov s CB. Pogosto napoveduje večjo resnost bolezni s slabšo splošno prognozo in kvaliteto življenja. Ustrezna razvrstitev in anatomska opredelitev sta ključni za določanje učinkovitih strategij zdravljenja. Obravnava teh bolnikov je zelo kompleksna in zahteva večdisciplinarni pristop. Zdravljenje vključuje kombinacijo medikamentoznega zdravljenja in kirurških posegov. Terapija z mezenhimskimi matičnimi celicami je ena od obetavnih možnosti zdravljenja zapletenih perianalnih fistul pri CB. Večdisciplinarni tim zdravnikov poda oceno primernosti zdravljenja z njimi oziroma jih odobri za vsakega bolnika posebej na KVČB – kirurškem konziliju v UKC Ljubljani.

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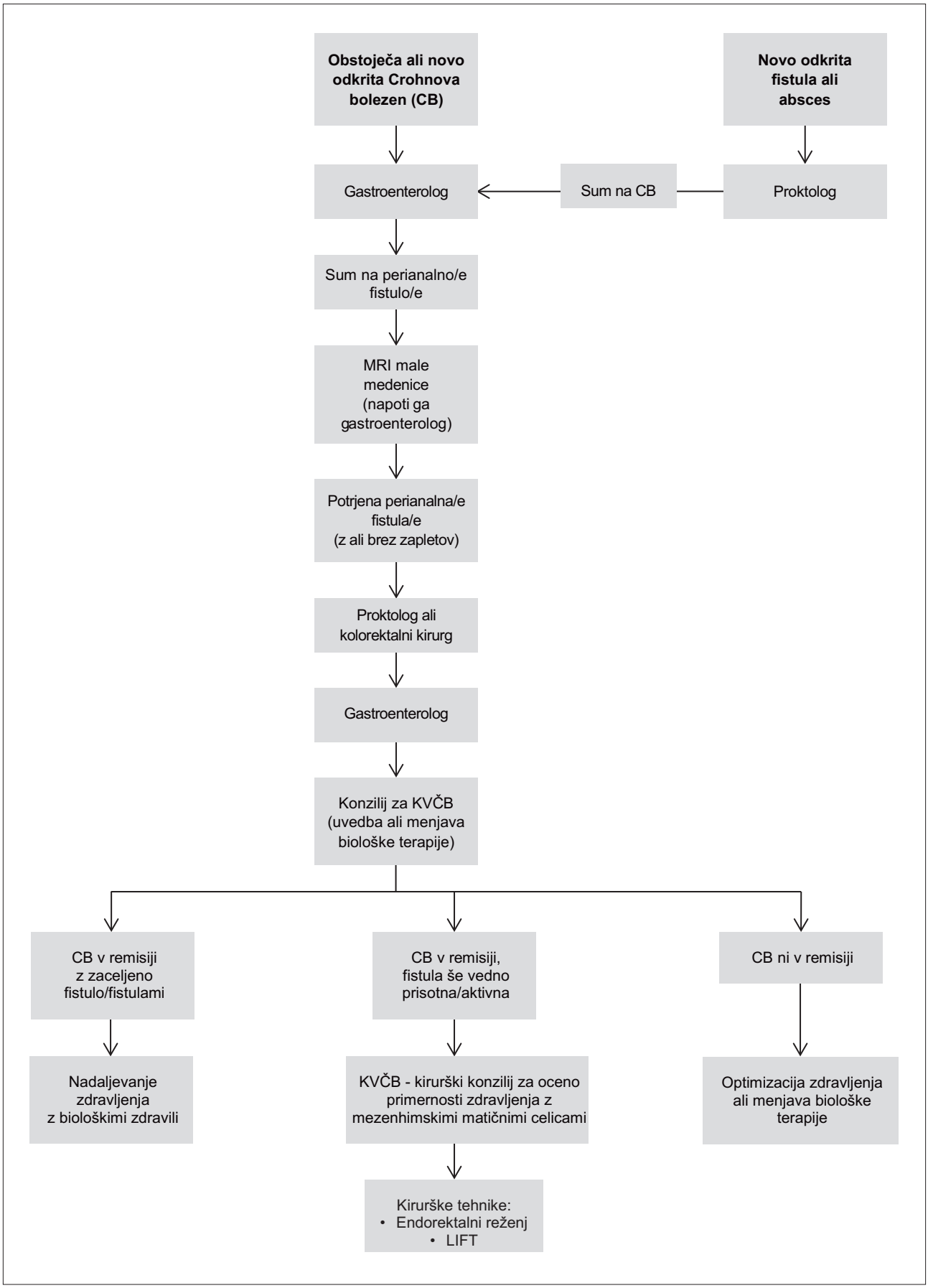

Algoritem obravnave bolnika s perianalnimi fistulami pri Crohnovi bolezni

Predlog priporočil za obravnavo bolnikov z gastroparezo

Recommendations for the management of patients with gastroparesis

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***Ključne besede**: gastropareza, diagnostika, zdravljenje, smernice*

***Keywords**: Gastroparesis, diagnostic, treatment, guidelines*

IZVLEČEK

Gastropareza je definirana kot simptom ali sklop simptomov, ki so povezani z objektivno dokazanim upočasnjenim praznjenjem želodca v odsotnosti mehanske ovire. Za postavitev diagnoze je poleg endoskopije ali slikovne diagnostike za izključitev obstrukcije potrebna scintigrafija praznjenja želodca. Možnosti zdravljenja vključujejo prehransko svetovanje, farmakoterapijo s metoklopramidom in domperidonom, endoskopske in kirurške posege ter nefarmakološke metode kot je akupunktura. V letih 2021 in 2022 sta Evropsko združenje za nevrogastroenterologijo in motiliteto v sodelovanju z Združeno evropsko gastroenterologijo ter Ameriški kolegij za gastroenterologijo izdala posodobljene smernice za obravnavo bolnikov z gastroparezo. Zaradi pomanjkanja dokazov in študij s področja zdravljenja gastropareze večina priporočil izhaja iz strokovnega konsenza ter se med evropskima in ameriškim združenjem razlikujejo. V prispevku povzemamo mednar-

ABSTRACT

Gastroparesis is defined as a symptom or set of symptoms associated with objectively proven delayed gastric emptying in the absence of a mechanical barrier. In addition to endoscopy or imaging to exclude obstruction, gastric emptying scintigraphy is required to make the diagnosis. Treatment options include nutritional counselling, pharmacotherapy with prokinetics, endoscopic and surgical interventions, and non-pharmacological methods such as acupuncture. In 2021 and 2022, the European Society for Neurogastroenterology and Motility in collaboration with the United European Gastroenterology and the American College of Gastroenterology issued updated guidelines for the management of patients with gastroparesis. Due to the lack of evidence and studies on the treatment of gastroparesis, most recommendations are based on expert consensus and differ between European and American associations. In this paper, we summarize the international recommen-

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odna priporočila s komentarjem in priporočili za klinično aplikacijo v slovenskem prostoru.

dations with commentary and recommendations for clinical application in the Slovenian context.

UVOD

Gastropareza je definirana kot simptom ali sklop simptomov, ki so povezani z objektivno dokazanim upočasnjenim praznjenjem želodca in z izrazito moteno motorično funkcijo želodca v odsotnosti mehanske ovire.

V letih 2021 in 2022 sta Evropsko združenje za nevrogastroenterologijo in motiliteto (European Society of Neurogastroenterology and Motility – ESNM) v sodelovanju z Združeno evropsko gastroenterologijo (United European Gastroenterology – UEG) ter Ameriški kolegij za gastroenterologijo (American College of Gastroenterology – ACG) izdala posodobljene smernice za obravnavo bolnikov z gastroparezo (1, 2). V prispevku povzemamo oboje smernice s komentarjem razlik med evropskim in ameriškim konsenzom ter možnostmi klinične aplikacije v slovenskem prostoru.

Skupne smernice obeh evropskih združenj so bile sprejete po načelu delfske metode z glasovanjem 40 strokovnjakov iz 19 evropskih držav, pri čemer je bil konsenz, in z njim vključitev posameznih trditev v smernice, opredeljen z več kot 80-odstotnim soglasjem. V ACG so avtorji smernic v sodelovanju z vodstvom ACG pripravili seznam ključnih vprašanj za klinično prakso v obliki PICO (Patient Intervention Comparison and Outcomes) in nato podali priporočila skozi večstopenjski pregled literature. Kakovost dokazov je v obeh smernicah ocenjena in predstavljena po kriterijih GRADE (Grading of Recommendations Assessment, Development and Evaluation). Kjer ni bilo dovolj dokazov za GRADE oceno, je bil tudi v ACG namesto tega uporabljen strokovni konsenz. Zaradi majhnega števila kvalitetnih študij s področja gastropareze je večina priporočil pogojnih in z nizko stopnjo dokazov.

Simptomi so kronični – po ESNM s trajanjem vsaj 3 mesece. Simptomi so po ACG lahko občutek polnosti po jedi, zgodnja sitost, slabost, bruhanje, napihnjenost in bolečina v zgornjem delu trebuha. ESNM opredeljuje kot glavna simptoma le slabost, ki je prisotna v več kot 95 % primerov, in bruhanje, ki je povezano s težjo okvaro motorične funkcije (3, 4). Slabost in bruhanje imata v študijah najboljšo korelacijo z objektivno izmerjeno upočasnitvijo praznjenja želodca in najbolje diferencirata gastroparezo od funkcionalne dispepsije (FD). Preostanek simptomov ima pomemben delež prekrivanja s simptomi FD, predvsem sindromom postprandialnega distresa, in bi lahko predstavljali posledico drugih tipov senzorično-motorične disfunkcije (oslabljena akomodacija želodca, preobčutljivost na raztezanje želodčne stene, neusklajena motorična aktivnost v proksimalnem delu tankega črevesa). Pomen razlikovanja med gastroparezo in FD poudarja tudi ACG, predvsem iz vidika ugodnejše pričakovane prognoze pri FD (5). Po ESNM ni jasne povezave med gastroparezo in simptomom hujšanja, zato je v primeru izgube telesne teže potrebno izključiti motnje hranjenja. Obe združenji kot pomemben moteč dejavnik pri postavitvi diagnoze gastropareze in opredelitvi povezanih simptomov, predvsem bolečine, izpostavljata široko razširjeno uporabo opioidov, ki jih ACG v povezavi z gastroparezo obravnava v ločenih smernicah (6). Ameriško združenje v komentarju kot potencialno pomemben simptom gastropareze izpostavlja še bolečino, predvsem ostro bolečino v epigastriju, ki naj bi se po validiranih vprašalnikih pojavljala pri do 90 % bolnikov z diabetično in idiopatsko gastroparezo (7, 8).

Epidemiologija in dejavniki tveganja

Epidemiologija gastropareze ni povsem jasna, saj je potrebno objektivno testiranje GE, ki na populacijski ravni še ni bilo izvedeno. Analiza bolnišničnih registrov v ZDA in VB ocenjuje incidenco na 1.9–6.3/100,000 bolnikov-let in prevalenco na 24.2–13,8/

100,000 (9, 10). Pojavlja se predominantno pri ženskah.

V Sloveniji aktualno uporabljena verzija mednarodne statistične klasifikacije bolezni (MKB) gastropareze ne vsebuje kot ločeno diagnozo in se lahko šifrira z K31.8 – druge opredeljene bolezni želodca in dvanajstnika, ali v primeru diabetične gastropareze z E10.43 oz. E11.43 - sladkorna bolezen tipa 1 oz. 2 z avtonomno nevropatijo, kar otežuje možnost ocene prevalence diagnoze v slovenski populaciji. Leta 2023 je Svetovna zdravstvena organizacija izdala posodobitev MKB, ki vsebuje gastroparezo kot ločeno diagnozo (11).

Obe združenji izpostavljata kot glavni dejavnik tveganja sladkorno bolezen. ESNM med dejavniki tveganja navaja še operativne posege (delna resekcija želodca, vagotomija, bariatrične in antirefluksne operacije), nekatere nevrološke motnje (Parkinsonova bolezen, multipla skleroza, amiloidna nevropatija), bolezni vezivnega tkiva ter zdravila (npr. opioidi). Kot možna dejavnika, glede katerih pa združenje ni doseglo konsenza, sta v študijah opisana še hipotiroza in okužba prebavil – v literaturi je opisan pojav motorične disfunkcije želodca po okužbi s parvovirusi, citomegalovirusi in virus Epstein-Barr, ter prisotnost enterovirusov v biopsijah želodčne sluznice (7).

Patofiziologija nastanka gastropareze ni poznana. Med mogočimi mehanizmi raziskujejo genetske dejavnike, spremembe v sluznici in mikrobioti dvanajstnika, okužbo s *H. pylori*, spremenjeno izločanje želodčne kisline in peptidnih hormonov, izgubo Cajalovih intersticijskih celic in enteričnih živčnih končičev, avtonomno disfunkcijo, spremembe v gladkem mišičju želodca ter moteno procesiranje živčnih signalov iz področja želodca in dvanajstnika. Prav tako ni jasen mehanizem nastanka simptomov, saj študije ne prikazujejo konsistentne povezave med simptomi in stopnjo upočasnjenega praznjenja želodca (1). ESNM glede vprašanj vzrokov za nastanek gastropareze in simptomov ni dosegel konsenza, medtem ko se ACG do vprašanja patofiziologije ne opredeljuje.

Obe združenji ocenjujeta, da gastropareza predstavlja veliko breme za bolnike, z znatnim poslabšanjem kakovosti življenja ter veliko stroškovno breme za zdravstveni sistem. Po podatkovnih zbirkah ZDA se je v letih 1997–2013 za 300 % povečalo število hospitalizacij in podvojilo število obiskov urgentnega centra v povezavi z gastroparezo, s hkratnim povišanjem stroškov posameznega obiska (12). Po ACG sta prisotna pri bolnikih z gastroparezo povečani morbiditeta in tudi mortaliteta, kar smernice ESNM zavračajo z utemeljitvijo, da povezava med gastroparezo in skrajšano pričakovano življenjsko dobo izgine, če pri analizah upoštevamo komorbidnosti (večino preseženih smrti predstavljajo srčno-žilni zapleti kot posledica diabetesa). Od pridruženih obolenj ESNM izpostavlja povezavo gastropareze s psihosocialnimi obolenji, kot sta anksioznost in depresija, pri čemer se do vzročno-posledične povezave ne opredeljuje.

Diagnostika

Po ESNM je pred postavitvijo diagnoze obvezna endoskopska preiskava zgornjih prebavil. Obstrukcijo tankega črevesa lahko izključimo tudi s slikovnimi preiskavami. Obe združenji se strinjata, da prisotnost hrane v želodcu na tešče med endoskopsko preiskavo ne zadostuje za postavitev diagnoze. V retrospektivnih študijah je imela prisotnost hrane v želodcu med gastroskopijo pozitivno napovedno vrednost za upočasnjeno praznjenje želodca 55 % (32 % pri bolnikih brez dejavnikov tveganja – 79 % pri bolnikih s sladkorno boleznijo tipa 1) (13) in senzitivnost 26 % (14) ter je bila pogosto povezana z jemanjem zdravil, predvsem opiatov. ACG za oceno prisotnosti gastropareze odsvetuje radiološko diagnostiko z radiopačnim kontrastnim sredstvom, ki je v primerjavi s scintigrafijo manj natančna za ocenjevanje praznjenja trdne hrane iz želodca in ne korelira z resnostjo simptomov (15).

Zlati standard za oceno hitrosti praznjenja želodca in s tem postavitev diagnoze gastropareze pri simptomatskih bolnikih je scintigrafija praznjenja želodca (SGE). Pri asimptomatskih bolnikih s patološkim izvidom SGE diagnoze ne moremo postaviti. Obe združenji poudarjata pomen pravilno izvedene preiskave,

s standardiziranim jajčnim obrokom z nizko vsebnostjo maščob, označenim z tehnecijem-99m, ter slikanjem v intervalih do 4 ure po zaužitju. ACG kot možen vzrok za nejasno korelacijo med simptomi, intenziteto simptomov in časom praznjenja želodca ter prekrivanje med diagnozami gastropareze in FD izpostavlja neoptimalno izvedene SGE, potencialno neprimerne mejne vrednosti in kompozicijo testnega obroka. Ukinitev zdravil, ki vplivajo na praznjenje želodca (opioidi, kanabinoidi, prokinetiki, antiemetiki, nevromodulatorji), svetujejo 48 ur pred izvedbo preiskave. SGE izvajajo v Sloveniji bolnišnični oddelki za nuklearno medicino (VZS šifra 2135).

Obe združenji kot primeren in zanesljiv diagnostični test pri simptomatskih bolnikih ocenjujeta tudi dihalni test s stabilnim izotopom ^{13}C. FDA je odobrila dihalni test in je preprostejši za izvedbo, cenejši in varnejši od SGE z vidika odsotnosti sevanja. Izvajamo ga s standardiziranim testnim obrokom, ki vsebuje s stabilnim ^{13}C izotopom označeno spirulino. Preiskovanec pred užitjem obroka in do tri ure po njem v vnaprej določenih časovnih intervalih zbira izdihan zrak preko cevke v epruvete. V izdihanem zraku izmerjen delež izotopa dobro korelira s hitrostjo praznjenja želodca, izmerjeno s SGE (16).

ACG kot možno ustrezno alternativo SGE ocenjuje tudi brezžično motilitetno kapsulo (WMC). Njeno prednost vidi v možnosti dodatne meritve amplitude krčenja želodca in hkratni diagnostiki motilitetnih motenj tankega in debelega črevesja. Po ESNM WMC zaradi slabše senzitivnosti in specifičnosti za diagnostiko gastropareze ni primerna. Dihalni test praznjenja želodca in WMC v Sloveniji zaenkrat nista dostopna. Kot možne diagnostične metode prihodnosti raziskujejo še elektrogastrografijo, UZ, analize protiteles v krvi ter biopsije celotne debeline želodca in pilorusa.

Zdravljenje

Konsenz ESNM kot učinkovite pri zdravljenju bolnikov z gastroparezo ocenjuje in priporoča le prehranske prilagoditve, antagoniste dopamin-2 receptorjev (metoklopramid, domperidon) in agoniste 5-HT4 (cisapride, prucalopride), pri čemer je farmakoterapija namenjena predvsem obvladovanju simptomov in ni jasno, če vpliva na hitrost praznjenja želodca. V primeru hude izgube telesne teže ali težko obvladljivega bruhanja svetuje prehransko podporo v obliki enteralne ali parenteralne prehrane. Glede vloge zaviralcev protonske črpalke, ki jih po študijah sicer prejema 70–80 % bolnikov z gastroparezo, najverjetneje zaradi prekrivanja s simptomi gastroezofagealne refluksne bolezni (GERB) (17), ni bilo doseženega konsenza, s prevladujočim mnenjem, da niso ustrezna terapija gastroparezo. Ocenili so še številne druge dietetske, farmakološke, nefarmakološke ter endoskopske in kirurške pristope k zdravljenju bolnikov, a jih zaradi pomanjkanja dokazov in študij v povezavi z bolniki z gastroparezo niso sprejeli v smernice.

Obe združenji priporočata prehransko svetovanje. Priporočata dieto z majhnimi delci in nizko vsebnostjo maščobe, ki zmanjša simptome in izboljša hitrost praznjenja želodca (18). Ob tem svarita pred tveganjem premajhnega vnosa kalorij ter motnjami hranjenja, povezanimi z omejevanjem in izogibanjem hrani. Pri bolnikih, kjer oralno hranjenje ni možno, s hudo izgubo telesne teže ali pomanjkanjem hranil, svetujejo enteralno hranjenje preko gastrojejunalne sonde in le izjemoma parenteralno hranjenje. Serije primerov bolnikov z diabetično gastroparezo s klinike Mayo in z idiopatsko gastroparezo iz Leuvna kažejo, da je postavitev perkutane gastrojejunalne sonde varna in omogoča povrnitev telesne teže. Sondo so pri bolnikih po povprečno 20 mesecih lahko odstranili (19, 20). ESNM svetuje parenteralno prehrano le v obliki kratkotrajnega zdravljenja, s katerim omogočimo hitro povrnitev telesne teže, in izogibanje njeni dolgotrajni uporabi zaradi tveganja katetrske sepse in hepatotoksičnosti. ACG pa ocenjuje, da je tudi dolgotrajno izključno parenteralno hranjenje lahko izvedljiva možnost za bolnike s hudo obliko gastropareze, z 68-odstotno stopnjo preživetja v 15-letni študiji, čeprav je bila parenteralna prehrana v kombinaciji z peroralnim vnosom povezana z višjo stopnjo preživetja (21). Tudi ACG za zmanjšanje tveganja obolevnosti in umrljivosti priporoča predvsem ohranitev ali ponovno vzpostavitev peroralnega vnosa.

Pri bolnikih z diabetično gastroparezo ACG svetuje optimizacijo nadzora glukoze v krvi za zmanjšanje tveganja za poslabšanje gastropareze. Dokazana je korelacija med nivojem glikiranega hemoglobina HbA1c in stopnjo retence v študijah praznjenja želodca, ter izboljšanje simptomov pri bolnikih z inzulinsko črpalko in kontinuiranim spremljanjem glukoze v krvi (22). Ni pa dokazov, da bi intenzivno zdravljenje diabetesa s pomembnim znižanjem HbA1c povzročilo izboljšanje hitrost praznjenja želodca (23).

Od farmakoterapije za izboljšanje simptomov in hitrosti praznjenja želodca ACG prav tako priporoča metoklopramid, domperidon ter agoniste 5-HT4 receptorjev. Vsa priporočila so pogojna in z nizko stopnjo dokazov. Metoklopramid, ki ga najnovejše študije testirajo tudi v intranazalni obliki, je edini, ki ga je odobrila FDA, vendar le za uporabo do 12 tednov in pri ljudeh mlajših od 65 let zaradi potencialnih stranskih učinkov. Po SMPC je metoklopramid prav tako odobren za zdravljenje gastropareze, s posebnim opozorilom, da ni namenjen za dolgotrajno zdravljenje, brez točnejše časovne opredelitve. Tveganje najhujšega izmed stranskih učinkov, tardivne diskinezije, je največja študija ocenila na 0,1 % na 1,000 bolnikov-let (24), kar je 10–100 x manj kot po predhodni oceni FDA. Nemir, zaspanost, utrujenost in razdražljivost naj bi se pojavili pri približno 10 % bolnikov, ter ekstrapiramidni nevrološki simptomi, ki so ob prenehanju jemanja metoklopramida reverzibilni, pri 0,1 % (25). Višje tveganje stranskih učinkov imajo starejše ženske, diabetiki, bolniki z odpovedjo delovanja ledvic ali jeter ali s hkratno terapijo z antipsihotiki. Domperidon po študijah zmanjša simptome in potencialno izboljša hitrost praznjenja želodca pri idiopatski, diabetični in pooperativni gastroparezi. Hudih stranskih učinkov v študijah, z najdaljšim trajanjem 4 let, ne opisujejo (26). FDA dovoljuje uporabo za zdravljenje gastropareze le v sklopu posebnih programov. Tudi po SMPC gastropareza ni vpisana kot terapevtska indikacija. Dober odziv na farmakoterapijo s prokinetiki lahko pričakujemo v skupinah bolnikov z virusno in dispeptično podvrsto idiopatske gastropareze, Parkinsonovi bolezni in večini bolnikov s sladkorno boleznijo. Slabši izid terapije pa pri bolnikih po vagotomiji, z boleznijo vezivnega tkiva, v podskupini diabetikov z dokazano vagalno nevropatijo in podskupini idiopatske gastropareze s prevladujočim simptomom bolečine v trebuhu ali anamnezo zlorabe (27).

Kot potencialne prokinetike ACG omenja še agoniste grelinskih receptorjev, za učinkovitost katerih zaenkrat ni dokazov in jih zato odpriporoča, ter agoniste motilina, kot so makrolidi (eritromicin, klaritromicin, azitromicin), ki se v praksi uporabljajo za zdravljenje bolnikov z gastroparezo, vendar so zaradi tahifilakse in izgube učinka primerni le za kratkotrajno uporabo (1–4 tedne). ACG za boljši nadzor simptomov predlaga tudi uporabo antiemetikov, čeprav ti ne izboljšajo hitrosti praznenja želodca. ESNM glede primernosti uporabe naštetih skupin zdravil ni dosegel konsenza. Obe združenji ne priporočata zdravljenja s centralno delujočimi nevromodulatorji, kot so triciklični antidepresivi, SSRI, mirtazapin in haloperidol. V študijah so obravnavani še številni drugi farmakoterapevtski pristopi, kot so imunske terapije z IVIg, itopride (kombiniran antagonist D2 receptorjev in holinesterazni inhibitor), 5-HT3 in NK1 antagonisti ter 5-HT1A agonisti.

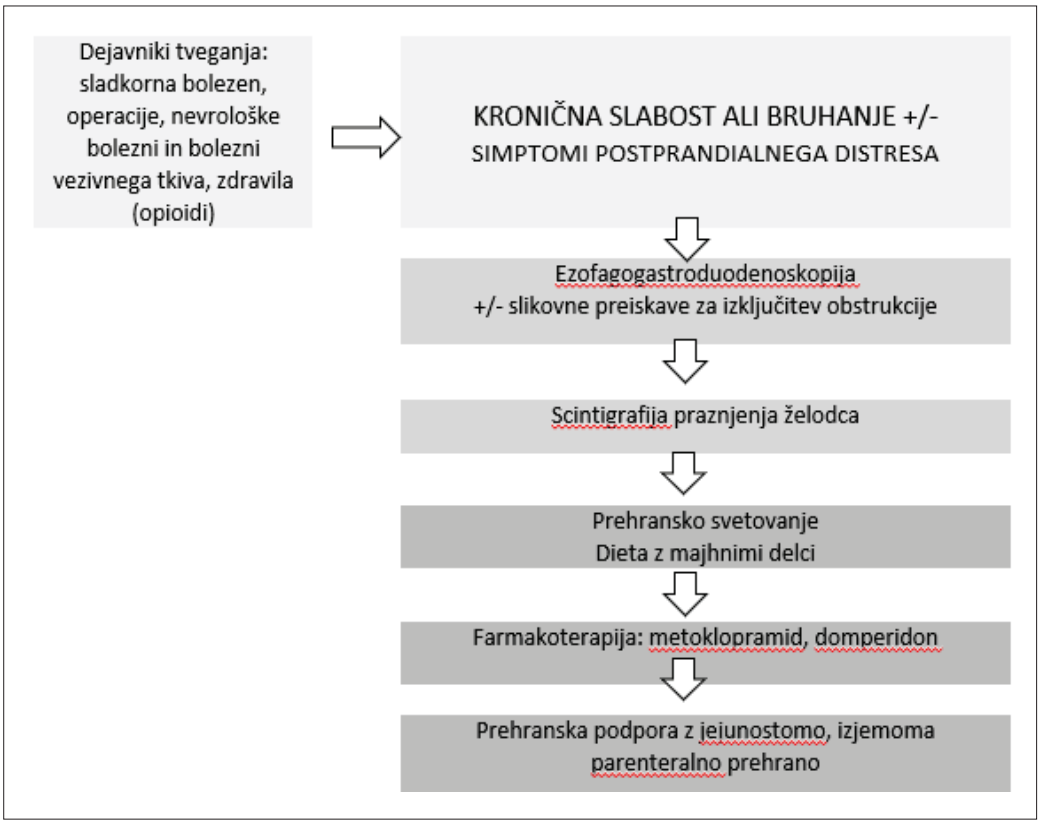
ACG za obvladovanje simptomov pri bolnikih, ki imajo hude simptome in se ne odzivajo na medikamentozno zdravljenje, svetuje piloromiotomijo. Endoskopska pilorotomija (Gastric peroral endoscopic myotomy – G-POEM) ima primerljivo učinkovitost kot kirurška, manj zapletov in krajšo hospitalizacijo (28, 29). Za oceno izida zdravljenja in boljši izbor bolnikov priporočajo pred pilorotomijo funkcionalne meritve pilorusa (premer, indeks razteznosti in kompliance) z EndoFLIP katetrom. ESNM ocenjuje, da za priporočila glede pilorotomije in uporabe EndoFLIP ni na voljo dovolj dokazov. Strinjajo se, da je dumpinški sindrom kot potencialen zaplet posegov redek; v literaturi je opisan le po laparoskopski piloroplastiki (30). Obe združenji glede na rezultate randomiziranih študij odpriporočata injekcije botulin toksina v pilorus. ESNM omenja študije na majhnem številu bolnikov, ki opisujejo tudi možnost subtotalne ali totalne gastrektomije, pri čemer so navajali visok

delež izboljšanja simptomov, vendar s spremljajočim visokim deležem neželenih učinkov in obolevnosti.

Kot možno simptomatsko zdravljenje pri medikamentozno refraktarni diabetični ali idiopatski gastroparezi ACG priporoča tudi električno stimulacijo želodca (GES). ESNM zaradi nezadostnih dokazov priporočila ni sprejel. Rezultati študij vpliva GES na simptome ter praznjenje želodca pri gastroparezi so heterogeni. Medtem ko prepričljivega vpliva GES na praznjenje želodca vse študije niso našle, je nedavna multicentrična študija z navidezno kontrolo iz Francije pri bolnikih z gastroparezo, zdravljenih z GES, opisovala zmanjšanje pogostosti bruhanja neodvisno od izmerjenega praznjenja želodca (31). Kot perspektivni metodi ACG omenja še vagalno in spinalno elektrostimulacijo, ki pa sta zaenkrat še v fazi raziskav.

Akupunkturo ocenjuje ACG kot koristno za lajšanje simptomov, vendar le pri bolnikih z diabetično gastroparezo, z zelo nizko kakovostjo dokazov. Učinkovitost akupunkture ugotavlja tudi sistematični pregled Cochrane (32), vendar zaradi nizke kakovosti vključenih študij ESNM sklepa ni sprejel. V uporabi so številne zeliščne terapije, kot so olje poprove mete, kumina, ingver, izvleček artičoke, Rikkunshito in STW5 (Iberogast). Kvalitetnih podatkov o njihovem vplivu je izredno malo, z izjemo ene s placebom nadzorovane študije, ki ni dokazala vpliva STW-5 na hitrost praznjenja želodca (33). ACG zato zeliščnih terapij ne priporoča (pogojno priporočilo, nizka kakovost dokazov), medtem ko ESNM o tem ni dosegel konsenza; le 23 % članov se je strinjalo s trditvijo, da zeliščni pripravki niso učinkoviti. ESNM je med predlogi obravnaval še hipnoterapijo, kognitivno-vedenjsko terapijo in čuječnost, vendar je bila podpora trditvi, da so primerne oblike zdravljenja za bolnike z gastroparezo, zelo nizka.

Prognoza je po ESNM odvisna od vzroka. Pri večini bolnikov simptomi in upočasnjeno praznjenje želodca vztrajajo več let. Če pride do izboljšanja, se to po navadi pojavi v prvem letu. Večja verjetnost izboljšanja je pri moških, starejših od 50 let, z anamnezo okužbe ali uporabo antidepresiva. Dejavniki tveganja za slabši potek so debelost, kajenje, uporaba protibolečinskih zdravil, zmerne ali hude abdominalne bolečine, hud GERB, zmerna ali huda depresija. V študiji s 6-letnim sledenjem bolnikov jih je v opazovanem obdobju 7 % umrlo in 22 % prejemalo dolgotrajno parenteralno hranjenje (34).



Slika 1. shematska predstavitev priporočil za obravnavo bolnikov s sumom na gastroparezo

ZAKLJUČEK

Gastropareza je bolezen s pomembnim vplivom na kvaliteto življenja bolnikov in porabo zdravstvenih virov, katere pojavnost v zahodnem svetu narašča. Pojavnost, patofiziologijo in možnosti zdravljenja zaenkrat slabo razumemo, za razjasnitev bodo potrebne še številne dodatne raziskave. Za pomoč v klinični obravnavi, diagnostiki in zdravljenju v prvi vrsti priporočamo upoštevanje evropskih smernic, ki so za naš prostor bolj smiselne. Pri obravnavi bolnikov zaradi njihove kompleksnosti priporočamo multidisciplinarno obravnavo.

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Tabela 1. Povzetek priporočil ESNM za obravnavo bolnikov z gastroparezo

Povzetek priporočil ESNM za obravnavo bolnikov z gastroparezo:
Gastropareza se definira kot simptom ali sklop simptomov, ki so povezani z upočasnjenim praznjenjem želodca v odsotnosti mehanske ovire in z izrazito moteno motorično funkcijo želodca. Glavna simptoma sta slabost in bruhanje.
Pri bolnikih z gastroparezo so pogosto prisotni dispeptični simptomi, kot so občutek polnosti po obroku, zgodnja sitost, bolečine v epigastriju, napihnjenost v zgornjem delu trebuha in spahovanje. Simptomi se prekrivajo predvsem s postprandialnim distresom in manj s sindromom epigastrične bolečine pri funkcionalni dispepsiji.
V primeru izgube telesne teže je potrebno izključiti motnje hranjenja.
Gastropareza je povezana z znatnim poslabšanjem kakovosti življenja, psihosocialnimi komorbidnostmi in predstavlja velik vir stroškov za zdravstveni sistem.
Dejavniki tveganja za gastroparezo so sladkorna bolezen, delna resekcija želodca, vagotomija, bariatrične in antirefluksne operacije, nekatere nevrološke motnje (npr. Parkinsonova bolezen, multipla skleroza, amiloidna nevropatija), bolezni vezivnega tkiva ter zdravila (npr. opioidi).
Za postavitev diagnoze je obvezna endoskopija zgornjih prebavil in nenormalen test praznjenja želodca - scintigrafska ocena praznjenja želodca ali dihalni test. Obstrukcijo tankega črevesa lahko izključimo s slikovnimi preiskavami.
Zdravljenje obsega prehranske prilagoditve v obliki diete z majhnimi delci, v primeru hude izgube telesne teže ali težko obvladljivega bruhanja prehransko podporo v obliki enteralne ali parenteralne prehrane. Od zdravil so učinkoviti antagonisti dopamin-2 receptorjev (metoklopramid, domperidon) in agonisti 5-HT4 (cisapride, prucalopride).
Prognoza je odvisna od vzroka.

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Metilacijski označevalci hepatocelularnega karcinoma v tekočinski biopsiji

Methylation biomarkers of hepatocellular carcinoma in liquid biopsy

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***Ključne besede**: hepatocelularni karcinom, tekočinska biopsija, zunajcelična DNA, cirkulirajoča tumorska DNA, DNA metilacija*

***Keywords**: hepatocellular carcinoma, liquid biopsy, cell-free DNA, circulating tumour DNA, DNA methylation*

IZVLEČEK

Hepatocelularni karcinom (HCC) je najpogostejše primarno maligno obolenje jeter, ki ostaja med petimi najpogostejšimi vzroki smrti zaradi raka po celem svetu. Njegov pojav je tesno povezan s kronično poškodbo jeter, ki je povezana s procesi vnetja, fibroze in ciroze, zaradi česar pride do okvare presnovne funkcije organa. Pomembni dejavniki tveganja za razvoj HCC so tudi virusne okužbe, pretirano uživanje alkohola in nealkoholna maščobna jetrna bolezen. Poleg genetskih sprememb, ki so pogosto opažene pri HCC, igrajo ključno vlogo tudi epigenetske spremembe, med katerimi je DNA metilacija najbolj preučevana. Naraščajoče število raziskav kaže na velik potencial DNA metilacije kot ključnega dejavnika pri različnih vidikih raka, vključno z diagnozo, napovedjo, spremljanjem bolezni in oceno odziva na zdravljenje. V zadnjih letih so tehnološki napredki omogočili odkrivanje sprememb DNA metilacije v vzorcih tekočinskih biopsij. Raziskave kažejo, da so metilacijski označevalci učinkoviti pri prepoznavanju HCC v zunajcelični DNA, kar je bilo še dodatno pod-

ABSTRACT

Hepatocellular carcinoma (HCC) is the most common liver cancer, consistently ranking among the top five causes of cancer-related mortality worldwide. Its emergence is linked to chronic liver damage stemming from processes such as inflammation, fibrosis, and cirrhosis, all of which contribute to the deterioration of liver function. HCC development is closely associated with risk factors including viral infections, excessive alcohol consumption, and non-alcoholic fatty liver disease. In addition to genetic alterations commonly observed in hepatocellular carcinoma, epigenetic changes, with DNA methylation being the most extensively studied, play a pivotal role. A growing body of research has underscored the substantial potential of DNA methylation as a key player in various facets of cancer, including diagnosis, prognosis, disease monitoring, and the assessment of treatment responses. Notably, advances in technology have facilitated the detection of DNA methylation changes in liquid biopsy samples. Methylation markers have demonstrated their effectiveness in identifying HCC

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krepljeno z odkritjem panelov metilacijskih označevalcev. Ti paneli so izboljšali občutljivost in specifičnost pri diagnosticiranju HCC, kar postavlja temelje za njihovo pomembno vlogo v diagnostiki HCC.

within cell-free DNA specimens, and this progress has been further augmented through the exploration of methylation marker panels. These panels have notably heightened the sensitivity and specificity of HCC detection, presenting promising avenues for improved diagnostics.

UVOD

HCC predstavlja najpogostejšo primarno maligno obolenje jeter, ki se uvršča med pet najpogostejših vzrokov raka in smrti po vsem svetu (1, 2). Nastane kot posledica kronične poškodbe jeter, vnetja, fibroze ali ciroze, kar vodi v oslabljeno presnovno funkcijo organa (3). Ta predstavlja nevarnost za pojav raka na več mestih v jetrih in ponovitev bolezni, bolniki pa so bolj dovzetni za jetrne in sistemske toksičnosti (1). Med dejavnike tveganja, ki povečujejo verjetnost kronične poškodbe jeter in s tem razvoj HCC, spadajo virusne okužbe, kot sta hepatitis B virus (HBV) in hepatitis C virus (HCV), dolgotrajno uživanje alkohola ter nealkoholna maščobna jetrna bolezen, ki je pogosto povezana z metaboličnim sindromom in diabetesom mellitusom (3–5). Povišano tveganje se pojavi tudi ob izpostavljenosti rakotvornim snovem v okolju ter prisotnosti presnovnih bolezni, kot so hemokromatoza, Wilsonova bolezen in druge (3–5). HCC se najpogosteje razvije v cirozno spremenjenih jetrih, kar predstavlja kar 80 % primerov v Sloveniji. Najpogosteje se pojavi v 50-letu starosti, pogosteje pri moških (6). Gre za bolezen z izrazito slabo prognozo in nizko petletno stopnjo preživetja (samo 18 %) (7). V Sloveniji smo leta 2018 zabeležili 231 novih primerov raka jeter (6).

MOLEKULARNO-GENETSKE ZNAČILNOSTI HCC

V diagnostiki raka igrajo vse večjo vlogo tudi novi pristopi, med katerimi izstopajo molekularno-genetske analize tkiv pacientov. Te analize se osredotočajo na identifikacijo najpogostejših sprememb na ravni DNA in RNA ter omogočajo karakterizacijo tumorjev glede na njihove genetske in epigenetske značilnosti ter spremembe v izražanju genov. Napredek je mogoč zaradi hitrega razvoja področja tehnologij molekularne biologije, kot je sekvenciranje nove generacije (NGS) ter razvoja metod za analizo podatkov. Vse to nam je omogočilo boljše razumevanje patogeneze, nastanka in napredovanja HCC.

Najpogostejše genetske spremembe pri HCC vključujejo somatske mutacije v onkogenih, tumor supresorskih genih in regulatornih poteh in druge strukturne spremembe v genomu, kot so genske fuzije, kromosomske preureditve, pomnožitve genov in virusne insercije, ki so posledica okužbe z virusi hepatitisa. Vsaj ena od teh sprememb je prisotna pri približno 80 % bolnikov s HCC. Študije so pokazale, da je pri 30–50 % bolnikov aktivirana Wnt-β-kateninska signalna pot, kar je posledica mutacij v genih *CTNNB1*, *AXIN1* ali *APC*. Druge pogoste mutacije pri HCC vključujejo gene *TP53*, *RB1*, *CCNA2*, *CCNE1*, *PTEN*, *ARID1A*, *ARID2*, *RPS6KA3* in *NFE2L2*, ki igrajo pomembno vlogo pri regulaciji celičnega cikla. Pogosto se pojavljajo tudi pomnožitve v genih, kot so *CCND1*, *FGF19*, *VEGFA*, *MYC* in *MET*, ki s prekomernim izražanjem povzročijo aktivacijo različnih onkogenih signalnih poti, vključno s receptorji tirozin kinaz. Prav tako so bile opažene različne mutacije genov, ki sodelujejo v mehanizmih oksidativnega stresa, AKT-MTOR in MAPK signalnih poti ter v epigenetski regulaciji (5).

EPIGENETSKE SPREMEMBE PRI RAKU

Epigenetika je področje molekularne biologije, ki preučuje spremembe v izražanju genov, ki niso povezane s spremembami v primarnem zaporedju DNA. Epigenetske modifikacije so del dedne genomske re-

gulacije izražanja genov preko DNA modifikacij, uravnavanja konformacije kromatina, pozicioniranja nukleosomov in uravnavanja zavijanja DNA z različnimi post-translacijskimi modifikacijami (acetilacija, metilacija, fosforilacija, ubikvitinacija, sumoilacija idr.). Vsi našteti mehanizmi omogočajo modulacijo interakcije transkripcijskega mehanizma z geni (dostop encimov, remodelacijskih kompleksov in transkripcijskih faktorjev) ter posredno nadzorujejo njihovo izražanje. V večceličnem organizmu epigenetski mehanizmi omogočajo vzpostavitev in ohranjanje identitete posamezne celice, pomembni so v razvoju in diferenciaciji celic (kot so vtisnjenje ali inaktivacija kromosoma X), obnovi matičnih celic, proliferaciji in ohranjanju stabilnosti genoma (4, 8, 9).

METILACIJA PRI RAKU

Ena izmed podrobneje preučenih epigenetskih sprememb je metilacija DNA. Gre za mehanizem regulacije izražanja genov v evkariontih, ki preko modifikacije osnovnega zaporedja nukleotidov daje informacijo, kje in kdaj naj pride do prepisa genske informacije. Metilacija je kovalentna modifikacija, ki poteče na nukleotidu citozinu, praviloma znotraj CpG otokov, nastane 5-metilcitozin (5-mC). Reakcijo katalizirajo encimi iz družine metiltransferaz DNA. Približno 70 % promotorjev genov v človeškem genomu vsebuje CpG otočke, ki uravnavajo več kot 50 % protein kodirajočih genov. Metilacija DNA v regulatornih in promotorskih regijah je praviloma povezana z zaviranjem izražanja genov (8).

Spremembe v vzorcu metilacije lahko igrajo pomembno vlogo pri razvoju raka. Kombinacija epigenetskih dogodkov lahko spremeni vzorec izražanja onkogenov ali tumor supresorskih genov in s tem pripomore k razvoju tumorskega fenotipa (8, 10, 11). Spremenjen metilacijski status pogosto najdemo v genih, ki igrajo pomembno vlogo v procesih regulacije celičnega cikla, zaviranja rasti in delitvi celic, apoptoze, uravnavanja metastatskega potenciala tumorja ter geni vključeni v DNA popravljalni mehanizem (12). Genom raka je globalno hipometiliran, medtem ko je hipermetilacija tumor supresorskih genov zgodnji dogodek pri kancerogenezi in spodbuja napredovanje raka (8). Metilacija je tkivno specifična – edinstven metilacijski profil celic omogoča identifikacijo izvornega tkiva DNA, prav tako pa raziskave kažejo, da omogoči ločitev rakavih celic od zdravega tkiva (13, 14). Danes je metilacija DNA zaradi svoje stabilnosti in informativne narave pomemben potencialen epigenetski označevalec v diagnostiki raka, pri postavljanju prognoze, spremljanju bolezni, oceni progresije in napovedovanju ter oceni odziva na zdravljenje (15).

TEKOČINSKA BIOPSIJA

Tekočinsko biopsijo sestavljajo zunajcelične molekule DNA in RNA, cirkulirajoče tumorske celice in zunajcelični vezikli. Zunajcelična DNA (cfDNA, ang. *cell-free DNA*) je mešanica majhnih fragmentov DNA, ki prosto kroži v krvnem obtoku. Nastane kot posledica odmiranja celic in spontanega izločanja DNA iz živih celic ter tako odraža trenutno stanje telesa, vključno z možno prisotnostjo malignosti (16). Del cfDNA je tudi cirkulirajoča tumorska DNA (ctDNA, ang. *circulating tumor DNA*), ki je najbolj preučevan vzorec v tekoči biopsiji raka. Glavni vir ctDNA predstavljajo žive, apoptotične in nekrotične tumorske celice v tumorskem mikrookolju. Delež ctDNA v cfDNA se lahko znatno spreminja in sega od 3 % do 93 %, saj je odvisen od lokacije tumorja, njegove velikosti ter njegove ožiljenosti (17). Poleg tega lahko na koncentracijo ctDNA vplivata tudi jetrna in ledvična funkcija ter zdravljenje. Večji tumorji na splošno proizvajajo več ctDNA kot manjši, vendar pa igrata vlogo tudi vrsta in tip tumorja. Bolniki z napredovano boleznijo imajo praviloma višje ravni ctDNA v primerjavi s pacienti z lokaliziranimi tumorji, pri katerih se ravni ctDNA povečujejo s stopnjo napredovanja bolezni (18). Nedavna študija je pokazala, da se mutacijski odtisi in metilacijski vzorci ctDNA razlikujejo od netumorske frakcije cfDNA (19). V ctDNA večine bolnikov z rakom lahko zaznamo spremembe, kot so točkovne mutacije, variacije v številu kopij genov, spremembe mikrosatelitov in spremembe v metilaciji DNA (20–22). Številne študije so analizirale potencialne označevalce iz vzorcev tkiva in cfDNA in dokazale zaznavo sprememb v obeh vzorcih (19, 23, 24).

Te ugotovitve kažejo, da so rezultati cfDNA primerljivi z rezultati običajnih invazivnih tkivnih biopsij.

METILACIJSKI OZNAČEVALCI V TEKOČINSKI BIOPSIJI

Poiskali smo študije, kjer so uporabili metilacijske označevalce za zaznavo HCC na fragmentih cfDNA ali ctDNA v serumu ali plazmi (Tabela 1).

Izvedene so bile meta-analize, ki so iz velikega števila študij izluščile najboljše kandidate za različno metilirane gene med HCC in normalnimi vzorci. Obsežna meta-analiza, ki je vključila kar 144 študij, je identificirala šest genov (*RASSF1A*, *PCDKN2A*, *CDH1*, *RUNX3*, *GSTP1* in *WIF1*) z največjo razliko v metilaciji serumskih vzorcev bolnikov s HCC in zdravih posameznikov (35). Prav tako je nedavna študija pokazala, da se hipermetilacija specifičnih metilacijskih

Tabela 1. Pregled metilacijskih označevalcev za detekcijo HCC v pekočinski biopsiji. An overview of methylation markers for HCC in liquid biopsy

Metoda	Tip vzorca	Število vzorcev	Tip metilacije	Geni in/ali genske lokacije	Referenca
Bioinformatska analiza in klinična validacija	Plazma ctDNA	1,098 HCC vzorcev in 835 normalnih kontrol	Hipo in hiper	Diagnostični panel: BMPR1A, PSD, ARHGAP25, KLF3, PLAC8, ATXN1, chr6:170, chr6:3, ATAD2, chr8:20 Prognostično prediktivni panel: SH3PXD2A, C11orf9, PPFIA1, chr17:78, SERPINB5, NOTCH3, GRHL2, TMEM8B	[19]
Klinična validacija	Tkivo in cfDNA	127 normalnih in 415 HCC tkivnih vzorcev; 37 kontrolnih in 37 HCC cfDNA vzorcev	Hipo and hiper	Diagnostični panel: chr19:51 (intragenska regija), ALX3, WINT3A, chr1:42 (intragenska regija), GJB6	[23]
Klinična validacija	Plazma cfDNA	237 HCC in 257 kontrolnih vzorcev	Hiper	TBX	[25]
Klinična validacija	cfDNA	135 HCC in 302 kontrolnih vzorcev	Hiper	Diagnostični panel: HOXA1, EMX1, TSPYL5	[26]
Klinična validacija	Tkivo in plazma cfDNA	151 tkivnih in plazemskih vzorcev	Hiper	RGS10, ST8SIA6, RUNX2, VIM	[27]
Klinična validacija	Tkivo in plazma cfDNA	74 HCC in 29 normalnih tkivnih vzorcev; 116 HCC, 81 cirozni in 98 zdravih kontrolnih plazemskih vzorcev	Hiper	Diagnostični panel: HOXA1, EMX1, AK055957, ECE1, PFKP, CLEC11A (normaliziranih na gen B3GALT6)	[24]
Klinična validacija	Plazma cfDNA	289 pacientov	Hiper	SEPT9	[28]
Klinična validacija	Tkivo in plazma cfDNA	116 tkivnih in 326 plazemskih vzorcev	Hiper	SOCS3	[29]
Klinična validacija	Serum cfDNA	80 HCC, 40 cirozni jeter, 40 kronični hepatitis B in 20 zdravih kontrol	Hipo	UBE2Q1	[30]
Klinična validacija	Plazma cfDNA	72 HCC, 37 benignih jetrnih bolezni in 41 zdravih kontrol	Hiper	APC, GSTP1, RASSF1A, SFRP1	[31]

Tabela 1. Nadaljevanje

Metoda	Tip vzorca	Število vzorcev	Tip metilacije	Geni in/ali genske lokacije	Referenca
Klinična validacija	Tkivo in plazma cfDNA	25 tkivnih in 130 plazemskih vzorcev	Hiper	CDKN2B, PCDKN2A	[32]
Klinična validacija	Plazma cfDNA	84 HCC, 26 pacientov s kronično jetrno boleznijo in 84 zdravih kontrol	Hiper	FBLN1, VIM	[33]
Klinična validacija	Tkivo in plazma cfDNA	24 tkivnih in plazemskih vzorcev	Hyper	APC, FHIT, CDKN2B, PCDKN2A, CDH1	[34]
Meta-analiza	144 vključenih študij	2044 HCC in 1371 zdravih serumskih vzorcev	Hipo and hiper	RASSF1A, PCDKN2A, CDH1, RUNX3, GSTP1, WIF1	[35]
Meta-analiza	33 vključenih študij	4113 pacientov	Hiper	RASSF1A	[36]
Literaturni pregled	Plazma ali serum ctDNA	3442 HCC in 2696 zdravih kontrol	Hiper	DBX2, THY1, TGR5, MT1M, MT1G, INK4A, VIM, FBLN1, RGS10, ST8SIA6, RUNX, SEPT9	[37]

mest v HCC pojavi zelo zgodaj v razvoju raka, ta pa ostanejo metilirana tudi v napredovalnih stadijih HCC (38).

Kisiel s sodelavci je izvedel raziskovalno pilotno študijo faze I in faze II, kjer so poskušali odkriti HCC z metilacijskimi označevalci na cfDNA v plazmi (24). Panel s šestimi označevalci (*HOXA1*, *EMX1*, *AK055957*, *ECE1*, *PFKP* in *CLEC11A*), so normalizirali na gen *B3GALT6*, in zaznali HCC z občutljivostjo 95 % in specifičnostjo 92 %. Občutljivost in specifičnost panela narašča z napredovanjem bolezni in presega občutljivost in specifičnost tumorskega označevalca alfa-fetoprotein (AFP). Te in druge študije so potrdile, da je mogoče HCC natančno zaznati s krvnimi preiskavami. Wen in njegova ekipa so razvili novo visoko zmogljivo metodo metilacije DNA MCTA-Seq (ang. *Methylated CpG Tandems Amplification and Sequencing*), ki lahko analizira na tisoče CpG otokov v enem samem vzorcu tekočinske biopsije (27). S to metodo so identificirali štiri gene2ewrr, ki imajo različno stopnjo metilacije v cfDNA bolnikov s HCC v primerjavi z zdravimi bolniki. Občutljivost in specifičnost detekcije HCC v cfDNA z uporabo izbranega klasifikatorja I, ki vsebuje štiri izbrane gene (*RGS10*, *STSIA6*, *RUNX2* in *VIM*) in podpornega klasifikatorja II (15 označevalcev, ki kažejo na čezmerno odmiranje jetrnih celic in povečujejo občutljivost testa) sta bili 94 % in 89 % (27).

Xu s sodelavci je razvil panel z desetimi metilacijskimi označevalci (regije *BMPR1A*, *PSD*, *ARHGAP25*, *KLF3*, *PLAC8*, *ATXN1*, Chr 6:170, Chr 6:3, *ATAD2*, Chr 8:20) za cfDNA, ki je učinkovito razlikoval bolnike s HCC od posameznikov z okužbo z HBV, HCV, zamaščenimi jetri in zdravimi posamezniki. Panel je bil uporabljen za izdelavo diagnostičnega napovednega modela. Poleg tega je bil razvit prognostični model, ki temelji na panelu osmih metilacijski označevalcev v kombinaciji s kliničnimi in demografskimi značilnostmi. Oba panela sta bila boljša od tradicionalnega tumorskega označevalca AFP in predhodno odkritih metilacijskih označevalcev (19). Hlady s sodelavci je ustvaril metilacijski panel s petimi označevalci, ki so uspešno razlikovali bolnike s HCC od bolnikov s cirozo (23).

Pri testiranju izbranih označevalcev za cfDNA se bolje obnesejo tisti, ki so bili identificirani iz cfDNA, kot pa tisti, ki so bili izbrani na podlagi rezultatov

tumorskega tkiva. Nedavno je bil razvit nov visoko zmogljiv krvni test z imenom epiLiver, ki je tumorsko specifičen in je namenjen odkrivanju HCC. Test temelji na metilacijskem profilu cfDNA (38). Test združuje štiri HCC CpG specifična mesta, skupaj z biološkim označevalcem, značilnim za jetrno tkivo. Štirje specifični označevalci za HCC so se izkazali za izjemno učinkovite, saj so zaznali 98 % vzorcev HCC (vsaj eno od štirih izbranih mest CpG je bilo metilirano v tumorskih vzorcih), pri čemer je bila specifičnost 100. Test ima pomembno pomanjkljivost, saj ni specifičen samo za HCC, ampak lahko zazna tudi druge vrste raka. Z dodatkom jetrno specifičnega označevalca je bilo možno razlikovanje primarnih malignih tumorjev jeter od jetrnih metastaz. S kombinacijo označevalcev, ki identificirajo hepatocelularni karcinom (HCC), ter označevalcev, ki lahko prepoznajo izvor tkiva v jetrnih zasevkih, so dosegli občutljivost 84,5 % in specifičnost 95 % pri razločevanju med bolniki s HCC, zdravimi posamezniki ter kroničnimi bolniki s HBV.

ZAKLJUČEK

Naraščajoče število raziskav s področja DNA metilacije izpostavlja njen velik potencial v diagnosticiranju HCC, napovedovanju prognoze, spremljanju bolezni in oceni odziva na zdravljenje. V zadnjih letih so tehnološki napredki omogočili odkrivanje sprememb DNA metilacije ne samo v tkivnih vzorcih, temveč tudi v vzorcih tekočinskih biopsij, ki omogočajo hitro in neinvazivno karakterizacijo tumorja. Raziskave kažejo, da so metilacijski označevalci v cfDNA učinkoviti pri prepoznavanju HCC, kar je bilo podkrepljeno z odkritjem panelov metilacijskih označevalcev. Verjamemo, da bodo metilacijski označevalci v cfDNA dodatno izboljšali občutljivost in specifičnost pri diagnosticiranju HCC ter omogočili boljšo in hitrejšo obravnavo bolnikov s HCC.

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Paneli cirkulirajočih mikroRNA za detekcijo hepatocelularnega karcinoma

Circulating microRNA Panels for Detection of Hepatocellular Carcinoma

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***Ključne besede**: hepatocelični karcinom, serum, plazma, cirkulirajoča mikroRNA*

***Keywords**: hepatocellular carcinoma, serum, plasma, circulating microRNA*

IZVLEČEK

Hepatocelularni karcinom (HCC) je drugi vodilni vzrok smrti zaradi raka na svetu. Visoka stopnja obolevnosti in umrljivosti poudarja nujnost identifikacije učinkovitih bioloških označevalcev, ki bi omogočili zgodnjo diagnozo HCC. Naraščajoče število raziskav o nekodirajočih RNA, vključno z mikroRNA, v povezavi s HCC, kaže na njihovo potencialno uporabnost pri diagnozi HCC. Namen tega pregleda je predstaviti panele miRNA z visoko specifičnostjo in občutljivostjo za odkrivanje HCC iz vzorcev krvi.

ABSTRACT

Hepatocellular carcinoma (HCC) is the second leading cause of cancer death worldwide. The high rate of morbidity and mortality emphasizes the necessity of identifying effective biomarkers that would enable the early diagnosis of HCC. The growing number of studies on non-coding RNAs, including microRNAs, in association with HCC indicates their potential utility in the diagnosis of HCC. This review aims to present miRNA panels with high specificity and sensitivity for the detection of HCC from blood samples.

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UVOD

Hepatocelularni karcinom (HCC) je najpogostejši rak jeter in drugi vodilni vzrok smrti zaradi raka na svetu (1, 2). Ta agresivna oblika raka predstavlja kar 90 % vseh primarnih rakov jeter (3). Običajno se HCC razvije ob prisotnosti ciroze, medtem ko kronični virusni hepatitis, povezan s hepatitisom B (HBV) in C (HCV), poškodbe zaradi alkoholne ali nealkoholne maščobne bolezni jeter, izpostavljenost aflatoksinom ter genetska nagnjenost dodatno spodbujajo proces tumorigeneze (4).

V zadnjem času narašča število raziskav, ki kažejo, da so cirkulirajoče nekodirajoče RNA (ncRNA), vključno z mikroRNA (miRNA), prisotne v telesnih tekočinah, kot so urin, plazma, serum ali slina, lahko koristne kot potencialni diagnostični biooznačevalci (5, 6). Te zunajcelične ncRNA v telesnih tekočinah naj bi se sprostile iz celic po poškodbi ali apoptozi celic, ali pa jih izločajo zunajcelični vezikli, kot so eksosomi (7, 8). Cirkulirajoče ncRNA štejejo za tumorsko specifične zaradi njihove zelo specifične prisotnosti med različnimi tkivi ali boleznimi (9, 10).

Številne raziskave opisujejo vlogo ncRNA pri pojavu in razvoju HCC (11), pri čemer lahko njihovo spremembo v izražanju uporabimo v diagnostične namene (12). V tem prispevku se bomo osredotočili na panele cirkulirajočih miRNA, ki bi bili lahko uporabni za določanje hepatocelularnega karcinoma v krvnih vzorcih.

MikroRNA pri raku

MiRNA so skupina majhnih nekodirajočih RNA, običajno dolgih med 20 in 22 nukleotidov. Te molekule izvirajo iz različnih genomskih virov, vključno z intergenskimi regijami in zaporedji eksonov znotraj nekodirajočih transkripcijskih regij. Pomembno je omeniti, da velik delež, do 60 % znanih miRNA, izvira iz intronskih zaporedij, ki se nahajajo bodisi v genih, ki kodirajo proteine, bodisi v nekodirajočih transkripcijskih regijah. MiRNA se lahko pojavljajo kot posamezni geni ali kot skupki v genomskih regijah. V nekaterih primerih so skupki miRNA sočasno regulirani in prepisani, kar kaže na kompleksne mehanizme regulacije (13). Ocenjujejo, da miRNA v človeškem genomu predstavljajo več kot 3 % vseh genov. Glede na funkcionalnost so miRNA izjemno raznolike in vplivajo na številne vidike regulacije genov. Njihova osrednja funkcija pri sesalcih je predvsem inhibicija translacije preko interakcij s 3'-UTR (neprevedena regija) ciljnih mRNA. V kompleksnem celičnem okolju posamezne miRNA lahko vplivajo na več mRNA tarč, včasih tudi do 200 mRNA tarč za eno miRNA. Prav tako je lahko ena sama mRNA regulirana z več različnimi miRNA (14).

V okviru raziskav raka so miRNA postale ključni regulatorji specifičnih genov. Po svojem delovanju so podobne številnim proteinskim transkripcijskim faktorjem, za katere je znano, da so ključni akterji pri preoblikovanju normalnih celic v maligne. MiRNA vplivajo na različne faze izražanja genov, vključno s transkripcijo, stabilnostjo in translacijo mRNA. Rakave celice kažejo genetske in epigenetske spremembe v primerjavi z nemalignimi celicami, pri čemer imajo miRNA pomembno vlogo pri teh spremembah. Z novimi tehnologijami lahko izvedemo celotno profiliranje genoma, s čimer so odkrili različne značilnosti miRNA, edinstvene za določene vrste raka, kar poudarja diagnostični potencial teh molekul. Kombinacija označevalcev miRNA z drugimi biološkimi označevalci obeta boljšo oceno tveganja za razvoj raka, izboljšanje preventivnih strategij in napovedovanje bolezni. Poleg tega so bili specifični genetski polimorfizmi povezani z nagnjenostjo k razvoju različnih vrst raka. Zato se vse bolj poudarja potreba po združevanju genomskih mutacij z označevalci miRNA, kar omogoča oblikovanje celovitih panelov označevalcev za natančnejšo oceno tveganja in zgodnjo diagnozo v okviru raziskav raka ter v klinični praksi (15–17).

Cirkulirajoče tumorske miRNA

Identifikacija miRNA kot potencialnih označevalcev v serumu ali plazmi je predstavljala pomemben preboj, ki ponuja minimalno invazivno metodo za zgod-

nje odkrivanje raka. Razumevanje značilnosti sekretornih miRNA in njihova uporabnost pri zgodnjem odkrivanju raka sta tako izjemnega pomena (18, 19). V zadnjih letih so miRNA pritegnile veliko pozornost raziskovalcev, ki so prepoznali njihov potencial za diagnozo in prognozo raka. Za sistematičen pregled literature smo izvedli obsežno iskanje na portalu PubMed. Za specifičen tip raka (hepatocelularni rak HCC) smo združili izraze 'miRNA panel' s 'plazma' ali 'serum' ter 'diagnoza'. S tem iskanjem smo identificirali 53 študij, ki smo jih skrbno pregledali in izbrali tiste, ki so uporabljale panele miRNA za odkrivanje HCC ter jih primerjale s normalnimi kontrolami. Med izbranimi študijami smo nato izbrali originalne članke, ki so testirali svoje izbrane panele miRNA na vzorcih človeškega seruma ali plazme ter ovrednotili kombinirane panele izbranih miRNA označevalcev.

Cirkulirajoče miRNA pri hepatocelularnem karcinomu

Panele miRNA smo razvrstili v tri skupine. Prvo skupino sestavlja osem panelov, ki vključujejo izključno miRNA. V drugi skupini so trije paneli, v katerih so miRNA združene z dolgimi nekodirajočimi RNA (lncRNA) in mRNA. Tretjo skupino vključujejo štirje paneli, kjer so bile miRNA kombinirane z α-fetoproteinom (AFP). Omeniti velja, da je bilo več miRNA uporabljenih v več panelih miRNA. Te miRNA so: miR-126, miR-21, miR-122, miR-125b, miR-375, miR-206, miR-192, miR-223, miR-26a in miR-27a (Tabela 1).

Tabela 1. Pregled panelov cirkulirajočih miRNA za odkrivanje HCC

miRNA panel	Tip vzorca	Število vzorcev	Izražanje	Statistika	Referenca
miRNA paneli					
miR-122 miR-192 miR-21 miR-223 miR-26a miR-27a miR-801	plazma	457 HCC, 167 normalnih vzorcev	↑ ↑ ↑ ↓ ↓ ↓ ↓	PPK = 0,941	[20]
miR-206 miR-141-3p miR-433-3p miR-1228-5p miR-199a-5p miR-122-5p miR-192-5p miR-26a-5p	serum	261 HCC, 173 normalnih vzorcev	↑ ↑ ↑ ↑ ↓ ↓ ↓ ↓	PPK = 0,887 (95 % IZ = 0,850–0,918) občutljivost = 85,55 % specifičnost = 73,3 %	[21]
miR-214-5p miR-125b miR-1269 miR-375	serum	224 HCC, 84 normalnih vzorcev	↓ ↓ ↑ ↓	PPK = 0,95 s 95 % IZ občutljivost = 83,2 % specifičnost = 96,9 % točnost = 86,8 %	[22]
miR-27b-3p miR-192-5p	serum	212 HCC, 110 normalnih vzorcev	↑ ↑	PPK = 0,823 (p < 0.0001)	[23]
miR-375 miR-10a miR-122 miR-423	serum	149 HCC, 149 normalnih vzorcev	↑ ↑ ↑ ↑	PPK = 0,995 (95 % IZ = 0,985–1)	[24]

HCC, hepatocelularni karcinom; AFP, α-fetoprotein; PPK, površina pod krivuljo; IZ, interval zaupanja; PNV, pozitivna napovedna vrednost; NNV, negativna napovedna vrednost; ↑ povišano izražanje; ↓ znižano izražanje; SN, standardna napaka

Tabela 1. nadaljevanje

miRNA panel	Tip vzorca	Število vzorcev	Izražanje	Statistika	Referenca
miR-4661-5p miR-4746-5p	eksosomi v serumu	84 HCC, 26 normalnih vzorcev	↑ ↑	PPK = 0,942 (95% IZ = 0.895–0.972) občutljivost = 84,5 % specifičnost = 89,3 % PNV = 88,8 % NNV = 85,2 %	[25]
miR-126 miR-21 miR-30c miR-193b miR-122 miR-222 miR-125b	serum	34 HCC, 25 normalnih vzorcev	↑ ↑ ↑ ↑ ↑ ↑ ↑	PPK = 1,00 SN = 0 p < 0,001	[26]
miR-10b miR-181a miR-106b	serum	27 HCC, 50 normalnih vzorcev	↑ ↓ ↑	PPK = 0,94 (95 % IZ = 0,89–0,99)	[27]
miRNA + lncRNA + mRNA paneli					
miR-16-2 miR-21-5p lncRNA-CTBP mRNA LAMP2	serum	78 HCC, 42 normalnih vzorcev	↑ ↑ ↑ ↑	občutljivost = 79,5 % specifičnost = 100 %	[28]
miR-1262 lncRNA-RP11-513I15.6 mRNA RAB11A	eksosomi v serumu	60 HCC, 18 normalnih vzorcev	↓ ↓ ↓	občutljivost = 100 % specifičnost = 76,7 % PNV = 81,1 % NNV = 100 % točnost = 88,3 %	[29]
miR-4764-5p lncRNA-RP11-156p1.3 mRNA RFTN1	serum	49 HCC, 36 normalnih vzorcev	↓ ↓ ↓	občutljivost = 100 % specifičnost = 76,7 % PPV = 81,1 % NNV = 100 % točnost = 88,3 %	[30]
miRNA + AFP paneli					
miR-122 miR-885-5p miR-29b AFP	serum	192 HCC, 95 normalnih vzorcev	↑ ↑ ↓	PPK = 1	[31]
miR-92-3p miR-107 miR-3126-5p AFP	serum	115 HCC, 40 normalnih vzorcev	↑ ↑ ↓	PPK = 0,988	[32]
miR-125b miR-223 miR-27a miR-26a AFP	serum	90 HCC, 30 normalnih vzorcev	↓ ↓ ↓ ↓	PPK = 0,936 (IZ = 0,878–0,995) občutljivost = 0,907 specifičnost = 0,933	[33]
miR-206 miR-126 AFP	plazma	38 HCC, 20 normalnih kontrol	↑ ↓	PPK = 0,989 (IZ = 0,919–1,000)	[34]

HCC, hepatocelularni karcinom; AFP, α-fetoprotein; PPK, površina pod krivuljo; IZ, interval zaupanja; PNV, pozitivna napovedna vrednost; NNV, negativna napovedna vrednost; ↑ povišano izražanje; ↓ znižano izražanje; SN, standardna napaka

MiRNA paneli

Pri pregledu panelov miRNA za odkrivanje HCC so vsi paneli pokazali visoko diagnostično natančnost z vrednostmi površine pod krivuljo (PPK) od 0,887 do 1,00 (Tabela 1). Vsak panel je bil sestavljen iz dveh do osmih miRNA (20–27). Paneli so bili razviti z različnimi metodologijami. Nekateri so za začetni presejalni postopek uporabili mikromreže (20) ali mreže za izražanje genov (24), drugi pa so uporabili nabore podatkov iz prosto dostopnih zbirk podatkov Gene Expression Omnibus (GEO) ali The Cancer Genome Atlas (TCGA) (25), ali uporabili tehnike sekvenciranja (21). Nekatere študije so v procesu razvoja panela uporabile bolj neposreden pristop (22, 26, 27), medtem ko so druge izbrale večfazno strategijo. Ena študija je uporabila dvofazni pristop (24), druge pa so ga razširile na trifazni pristop (20, 21, 25).

Čeprav so nekateri paneli pokazali visoko vrednost PPK, na primer študiji Ali in sod. (26) ter Jiang in sod. (27), je bila njihova kohorta precej majhna, 34 oziroma 27 primerov HCC. Za pridobitev objektivnejših rezultatov bi bilo potrebno panela dodatno testirati. Zanesljivejši so rezultati študij, ki so uporabile večfazno testiranje na večjih kohortah, kot so študije, ki so jih izvedli Zhou in sod. (20), Tan in sod. (21) ter Zhu in sod. (23).

Panel, ki je bil testiran na največ vzorcih so objavili Zhou in sod., kjer so z uporabo mikromrež preverili 723 miRNA v 137 vzorcih plazme. Panel je bil preizkušen na preskusni skupini, nato pa potrjen z neodvisno skupino, kar zagotavlja visoko diagnostično natančnost tega miRNA panela (20).

MiRNA paneli v kombinaciji z lncRNA in mRNA

V primerjavi s paneli, kjer so vključene izključno miRNA so paneli in so miRNA kombinirali z lncRNA in mRNA, imeli občutljivost od 79,5 % do 100 % in specifičnost od 76,7 % do 100 % (Tabela 1) (28–30). Čeprav so rezultati teh študij obetavni, je vredno omeniti, da temeljijo na relativno majhnem številu vzorcev (49 do 78) v primerjavi s paneli, kjer so vključene izključno miRNA. V študijah, kjer so panele kombinirali z lncRNA in mRNA, so uporabili neposreden pristop brez validacijskih kohort, zato bi za potrditev njihove statistične vrednosti morali biti paneli preverjeni še na neodvisnih kohortah.

MiRNA paneli v kombinaciji z AFP

AFP je eden najpogosteje uporabljenih biooznačevalcev, ki so ga prvič predstavili v šestdesetih letih prejšnjega stoletja, kljub temu pa je njegova občutljivost za diagnosticiranje HCC okoli 60 %, specifičnost pa je še vedno neustrezna (35). V do tretjini primerov HCC ostanejo AFP vrednosti v serumu normalne, poleg tega se lahko zvišanje AFP pojavi tudi pri nekaterih benignih boleznih jeter in drugih tumorjih (npr. tumor zarodnih celic) (36).

AFP je bil vključen v miRNA panele za izboljšanje statistične vrednosti panelov, kar potrjuje visoka vrednost PPK, ki se giblje od 0,936 do 1 (Tabela 1) (31–34). Čeprav nobena panela v kombinaciji z AFP ni imela večfaznega testiranja, je študija, ki jo je izvedel Zekri in sod. imela veliko kohorto 192 primerov HCC, poleg tega je imela njihova panela tudi najboljši statistični potencial (31).

ZAKLJUČEK

HCC je kompleksna bolezen, ki vključuje različne dejavnike tveganja in jo običajno diagnosticiramo, ko je rak v napredovalem stadiju s slabim preživetjem. Pomanjkanje specifičnih diagnostičnih markerjev za HCC predstavlja izziv za zgodnje odkrivanje bolezni in zdravljenje raka. MiRNA so regulatorji izražanja genov in imajo ključno vlogo pri patogenezi HCC. Njihovo izražanje je spremenjeno celo v zelo zgodnjih fazah raka, zato je njihov potencial za detekcijo HCC v zgodnji fazi pomemben.

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Obravnava bolnika s krvavitvijo iz zgornjih prebavil

Management of upper gastrointestinal bleeding

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***Ključne besede**: melena, hemoragični šok, varice, ulkus, ezofagogastroduodenoskopija*

***Keywords**: melena, hemorrhagic shock, varices, ulcer, gastroscopy*

IZVLEČEK

Krvavitev iz zgornjih prebavil ostaja nevarno urgentno stanje s smrtnostjo med 2 in 10 %. Z anamnezo v grobem lahko ločimo, ali gre za varikozno ali nevarikozno krvavitev. Varikozna krvavitev je bolj verjetna pri bolnikih s kronično jetrno boleznijo. Bolniki, ki prejemalo nesteroidne antirevmatike, antitrombotike ali antikoagulanse, ponavadi krvavijo iz peptičnih ulkusov. Obravnava bolnika se začne s hemodinamsko oceno. Nestabilni bolniki najprej prejmejo glukosalinične raztopine. Transfuzija krvi pred urgentno gastroskopijo je indicirana pri vrednostih hemoglobina med 70–80 g/L, pri hudih krvavitvah pa že prej. Bolniki s sumom na varikozno krvavitvijo že na urgenci prejmejo vazoaktivna zdravila (terlipresin ali somatostatin), bolniki z nevarikozno krvavtvijo pa zaviralec protonske črpalke. Pri šokiranih bolnikih in bolnikih v respiracijski insuficienci je prag za intubacijo in namesititev v intezivno enoto nizek. To omogoča varno in učinkovito urgentno endoskopijo in preprečuje zaplete, ki se lahko zgodijo med endoskopijo (aspiracija, poslabšanje hemodinamike, se-

ABSTRACT

Upper gastrointestinal bleeding remains a dangerous emergency condition with a mortality rate between 2 and 10%. Based on patient history we can roughly distinguish whether the bleeding is of varicose or non-varicose ethiology. Varicose bleeding is more likely in patients with chronic liver disease. Patients receiving nonsteroid anti-inflammatory drugs, antithrombotics or anticoagulants usually bleed from peptic ulcers. The first step in the management is hemodynamic assessment. Unstable patients are initially treated with glucosaline solutions. Blood transfusion before emergency gastroscopy is indicated for hemoglobin values between 70–80 g/L, and earlier for severe bleeding. Patients with suspected variceal bleeding should receive vasoactive drugs (terlipressin or somatostatin) in the emergency room, while patients with suspected non-variceal bleeding should be treated with proton pump inhibitors. The threshold for intubation and placement into the intensive care unit should be low as this enables safe and effective emergency endoscopy and prevents complications

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kundarni srčni zastoj). Hemodinamsko nestabilni bolniki potrebujejo urgentno gastroskopijo v roku 6 ur, ostali pa v roku 24 ur. Prisotnost intezivista/anesteziologa ob gastroskopiji preprečuje sekundarne srčne zastoje med posegom in olajša endoskopsko hemostazo. Tako je za učinkovito in varno oskrbo bolnikov s krvavitvijo iz zgornjih prebavil potrebno sodelovanje urgentnega zdravnika, intezivista/anesteziologa in gastroenterologa.

that may occur during endoscopy (aspiration, deterioration of hemodynamics, secondary cardiac arrest). Hemodynamically unstable patients require urgent gastroscopy within 6 hours while in other patients it should be performed within 24 hours. The presence of an intensivist/anesthesiologist during gastroscopy prevents secondary cardiac arrests during the procedure and facilitates endoscopic hemostasis. Thus, for effective and safe care of patients with bleeding from the upper gastrointestinal tract, the cooperation of an emergency physician, an intensivist/anesthesiologist and a gastroenterologist is necessary.

UVOD

Krvavitev iz zgornjih prebavil je pogost vzrok za napotitev v urgentno ambulanto. Hospitalizacija zaradi krvavitev iz zgornjih prebavil je potrebna pri približno 70/100.000 prebivalcev letno. Smrtnost teh krvavitev je med 2–10 %.

V grobem ločimo varikozno in nevarikozno krvavitev. Poglavitna simptoma bolnikov s krvavitvijo iz zgornjih prebavil sta oslabelost ali izguba zavesti, vodilni znak pa bledica kože, sluznic ter odvajanje črnega mazavega blata. Bolniki so lahko popolnoma hemodinamsko stabilni (večina), lahko pa so v hemoragičnem šoku z grozečim sekundarnim srčnim zastojem. Hitra anamneza lahko pri večini bolnikov pomaga ločiti, ali gre pri bolniku za varikozno ali nevarikozno krvavitev že v urgentni ambulanti. Ločevanje med tema dvema tipoma krvavitve je pomembno, saj je obravnava nekoliko drugačna. Bolniki z znano jetrno cirozo večinoma krvavijo iz varic, ne pa vedno. Bolniki, ki prejemajo nesteroidne antirevmatike, antitrombotična ali antikoagulacijska zdravila brez zaščite sluznice z zaviralci protonske črpalke, običajno krvavijo iz peptičnih ulkusov želodca ali dvanajstnika. Bolniki z več internističnimi obolenji, še zlasti bolniki s stenozo aortne zaklopke in bolniki na hemodializi, največkrat krvavijo iz žilnih malformacij v antrumu želodca ali tankem črevesu.

PRISTOP K BOLNIKU S SUMOM NA KRVAVITEV IZ ZGORNJIH PREBAVIL

Ob sumu na krvavitev iz zgornjih prebavil je prvo in najpomembneje oceniti hemodinamsko stanje bolnika, saj je hemodinamska stabilnost osnovno vodilo pri obravnavi bolnika. Velika večina bolnikov bo potrebovala endoskopski pregled zgornjih prebavil – ezofagogastroduodenoskopijo (gastroskopija).

Hemodimanska ocena in stabilizacija:

Izmerimo vitalne funkcije. Ob nizkem krvnem tlaku in/ali povišani srčni frekvenci (nad 100/min) je treba najprej nadomestiti volumen z infuzijami glukosaličnih raztopin. Pred napotitvijo na gastroskopijo naj bo krvni tlak normalen in srčna frekvenca pod 100, saj to večinoma odraža primerno stopnjo hemodinamske stabilnosti za varno gastroskopijo. Pozornost je potrebna pri bolnikih, ki prejemajo beta zaviralce, saj imajo ti bolniki lahko nizko frekvneco kljub hemodinamski nestabilnosti. V mejnih primerih je koristno določiti laktat v krvi, saj tako lažje ocenimo hemodinamsko stabilnost.

Transfuzija krvi

Za transfuzijo krvi pred gastroskopijo se odločimo ob vrednostih hemoglobina pod 70–80 g/L. Kri je treba pridobiti, preveriti in priklopiti pred napotitvijo na gastroskopijo, saj lahko gastroskopija traja tudi eno uro

ali pa bolnik med gastroskopijo postane nestabilen. Kadar gre za zelo hude krvavitve (obilno bruhanje sveže krvi; hemohezija namesto melene; hipotenzija, ki se slabo odzove na tekočine), se za transfuzijo krvi lahko odločimo tudi pri višjih vrednostih hemoglobina, saj lahko izmerjena vrednost hemoglobina še ne odraža dejanskega stanja ali pa pričakujemo, da bi bolnik hitro krvavel.

Uporaba zdravil v urgentni ambulanti pred napotitvijo na gastroskopijo

Pri bolnikih s sumom na ulkusno krvavitev apliciramo bolus zaviralca protonske črpalke, saj to pomaga stabilizirati krvni strdek, ki je morda nastal v vmesnem času oz. nekoliko olajša endoskopsko hemostazo. Dokazov za to je sicer malo. Pri izbranih bolnikih je lahko pred napotitvijo na gastroskopijo koristna enkratna aplikacija prokinetika eritromicina, saj se tako izboljša vidljivost med gastroskopijo.

Bolniki s sumom na varikozno krvavitev (predhodna krvavitev iz varic, sum na jetrno cirozo ali pa je že znana) naj že v urgentni ambulanti prejmejo vazoaktivno zdravilo somatostatin (vsaj bolus, še bolje bolus in kontinuirano infuzijo) ali terlipresin. Bolniki z jetrno cirozo in krvavitvijo naj v urgentni ambulanti prejmejo tudi intravenski antibiotik (običajno amoksicilin s klavulansko kislino ali ceftriakson), saj to pomembno zmanjša umrljivost teh bolnikov znotraj iste hospitalizacije.

Napotitev bolnika na urgentno gastroskopijo

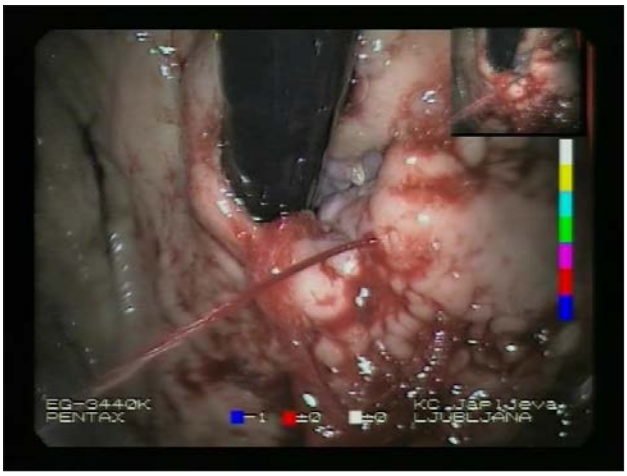
Večina bolnikov s sumom na krvavitev iz zgornjih prebavil potrebuje gastroskopijo. V Zahodni Evropi in ZDA, kjer endoskopijo ne opravljajo v sklopu urgentne obravnave, so poskušali razviti točkovnike, ki bi predvideli, kateri bolniki ne potrebujejo urgentne gastroskopije, pač pa jo lahko odložijo za nekaj dni. Eden takih točkovnikov je točkovnik Glasgow-Blatchford. Bolniki, ki po tem točkovniku dosežejo 0 ali 1 točko, ne potrebujejo urgentne gastroskopije ali hospitalizacije (Tabela 1). Vseeno pa potrebujejo gastroskopijo v roku nekaj dni.

Tabela 1. Točkovnik Glasgow-Blatchford

kriterij	število točk
Sečnina (mmol/L)	
< 6,5	0
6,5–7,9	2
8,0–9,9	3
10,0–24,9	4
> 25	6
Hemoglobin (g/L) - moški	
> 130	0
120–129	1
100–119	3
< 100	6
Hemoglobin (g/L) - ženske	
> 120	0
100–119	1
< 100	6
Sistolični krvni tlak (mm Hg)	
≥ 110	0
100–109	1
90–99	2
< 90	3
Drugi kriteriji	
Frekvenca srca ≥ 100 / minuto	1
Prisotna melena	1
Sinkopa	2
Znana jetrna bolezen	2
Znano srčno popuščanje	2

V splošnem pa velja, da urgentno gastroskopijo opravimo v roku 24 ur. Izjema so bolniki, ki so bili hemodinamsko nestabilni. Pri teh bolnikih je indicirana gastroskopija v roku 6 ur. Urgentno gastroskopijo napravimo šele po hemodinamski stabilizaciji. V koli-

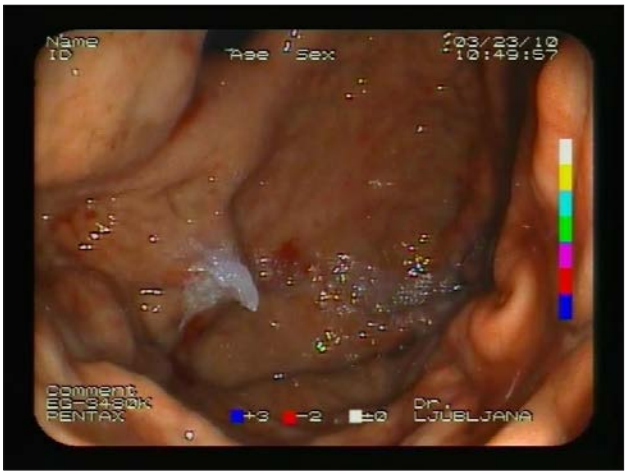
kor je šlo za šokovno stanje (povišan laktat), je priporočljivo, da bolnika sprejmemo v intenzivno enoto. V intenzivni enoti je treba zagotoviti ustrezne venske dostope in invazivno merjenje krvnega tlaka. V primeru respiracijske insuficience ali motnje zavesti, je potrebna intubacija pred urgentno endoskopijo. Namen intubacije je preprečiti poslabšanje respiracijske insuficience med gastroskopijo (zaradi posega in sedacije). Dodaten namen intubacije je tudi preprečevanje aspiracije želodčne vsebine, saj je želodec pogosto poln krvi, pacienti pa se med gastroskopijo napenjajo in ob tem bruhajo. Poleg tega intubacija olajša delo endoskopistu (saj se bolnik ne premika, ne bruha, ne spahuje) in zmanjša trpljenje bolnika.



Slika 1. Krvavitev iz varice kardije želodca
Vidna je aktivna karvavitev iz kardije želodca (endoskop v inverziji)

Endoskopska oskrba krvavitve – urgentna gastroskopija

Z gastroskopijo pregledamo požiralnik, želodec in dvanajstnik. Krvavitev iz varic požiralnika ali kardije želodca najdemo pri do 20 % bolnikov (Slika 1). Pri teh bolnikih opravimo endoskopsko ligacijo (požiralnik) (Slika 2) ali pa v varico vbrizgamo tkivni adheziv/sklerozacijsko sredstvo (Slika 3). Peptični ulkusi želodca in dvanajstnika so najbolj pogosta najdba. Razdelimo jih po Forrestovi klasifikaciji (Tabela 2).

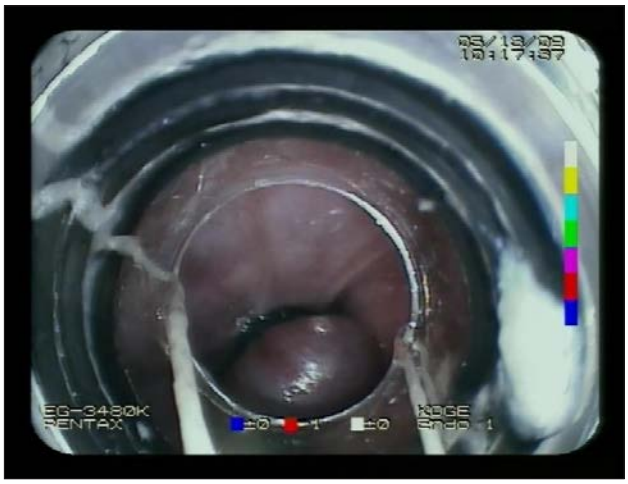


Slika 2. Tkivni adheziv izpolni defekt v varici
Tkivni adheziv endoskopsko vbrizgamo v krvavečo varico. Ta izpolni defekt in ustavi krvavitev. Uporabljamo ga za zaustavljanje krvavitev v želodcu

Endoskopska oskrba ulkusov vključuje injekcijsko terapijo (vbrizgavanje adrenalina in sklerozacijskega sredstva v krvavečo lezijo preko endoskopa) ali me-

Tabela 2. Forrestova klasifikacija peptičnih ulkusov

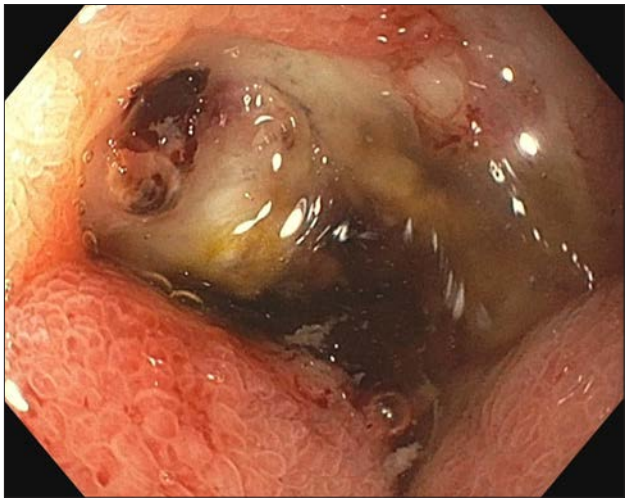
Aktivno krvaveči ulkusi		**Oskrba**
Forrest Ia	brizgajoča krvavitev	endoskopska hemostaza, nato zaviralec protonske črpalke
Forrest Ib	mezenje krvi	endoskopska hemostaza, nato zaviralec protonske črpalke
Znaki nedavne krvavitve		
Forrest IIa	vidna žila	endoskopska hemostaza, nato zaviralec protonske črpalke
Forrest IIb	strdek na ulkusu	odstranitev strdka in nato eventualna endoskopska hemostaza, nato zaviralec protonske črpalke
Forrest IIc	pega v nivoju ulkusa	zaviralec protonske črpalke
Zaključena krvavitev		
Forrest III	ulkus s cistim dnom	zaviralec protonske črpalke



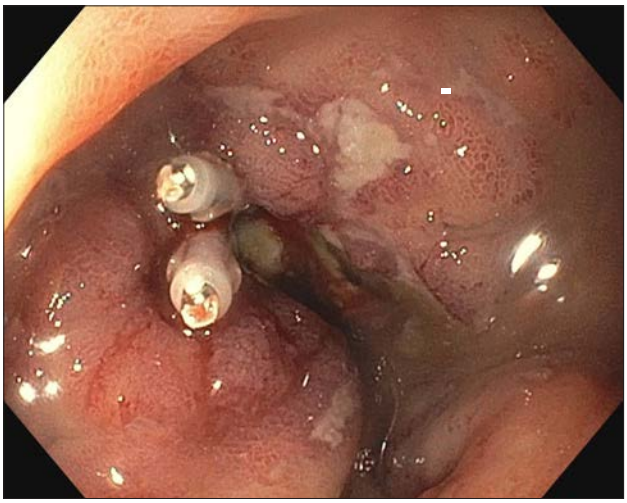
Slika 3. Postavljena elastična ligatura na krvavečo varico v požiralniku
Postavitev elastičnih ligatur je metoda izbora za oskrbo krvavečih varic požiralnika in tudi za eradikacijo varic pri bolnikih, ki so že krvaveli

hansko oskrbo (postavitev sponk ali termično terapijo) (Slika 4 in Slika 5). Kadar endoskopska oskrba ni uspešna, je naslednji korak angiografija z embolizacijo ali pa kirurško zdravljenje.

Krvavitev je lahko tudi posledica tumorjev požiralnika, želodca ali dvanajstnika. Endoskopska oskrba večinoma ni uspešna, zato je tu na mestu predvsem angiografija z embolizacijo ali kirurško zdravljenje. Krvavitev iz žilnih malformacij je pogosta, oskrbimo



Slika 4. Ulkus dvanjstnika Forrest IIa
Ulkus dvanajstnika, ki je nastal ob prejemanju nesteroidnih antirevmatikov ob sočasni okužbi z bakterijo Helycobacter Pylori. Viden je krn žile. Čeprav žila v trenutku endoskopije ne krvavi, je verjetnost ponovne krvavitve zelo visoka, zato je indicirana endoskopska oskrba



Slika 5. Ulkus dvanajstnika Forrest IIa – endoskopska hemostaza z dvema sponkama
Ulkus je bil oskrbljen s postavitvijo dveh mehanskih sponk (ang. clip). Sponki v roku nekaj dni spontano odpadeta. Tak bolnik potrebuje najprej zdravljenje z zaviralci protonske črpalke v kontinuirani infuziji 3 dni, saj alkalno okolje izboljša celjenje. Ob odpustu iz bolnišnice je potrebno tudi zdravljenje okužbe s Helicobacter Pylori ter navodila glede izogibanja uporabe nesteroidnih antirevmatikov

jo z argonsko koagulacijo ali postavitvijo sponke. Pogost vzrok za krvavitev iz požiralnika sta hud ezofagitis ali pa poka Mallory-Weiss. Poka Mallory-Weiss nastane ob bruhanju in napenjanju. V anamnezi je značilen podatek, da je bolnik najprej bruhal nekrvavo vsebino, šele nato se je pojavila sveža kri v izbruhanini. To je drugače kot pri bolnikih, ki bruhajo zaradi dražečega učinka krvi v želodcu ob drugih vzrokih za krvavitev. Redek, a zelo pomemben vzrok, za masivno krvavitev iz zgornjih prebavil (običajno se pokaže kot hemohezija in ne kot melena) je aortoenterična fistula. Ob sumu na aortoenterično fistulo je treba opraviti CT angiografijo. Redki vzroki za krvavitev iz zgornjih prebavil so hematobilija (ob tumorjih je hepatobiliarnega sistema) in Crohnova bolezen.

Oskrba po urgentni endoskopiji

Bolniki, ki so krvaveli iz varic požiralnika, prejemajo 3–5 dni po ustavitvi krvavitve vazoaktivna zdravila (terlipresin ali somatostation, redkeje dandanes oktreotid). V tem obdobju je treba tudi napraviti dolgoročni plan. Krvavitev iz varic je resen zaplet jetrne ciroze, zato je treba razmisliti, če je bolnik kandidat

za presaditev jeter. Po ukinitvi vazoaktivnih zdravil je treba uvesti neselektivni beta zaviralec karvedilol in narediti plan titracije skozi nekaj tednov, saj se tako zmanjša verjetnost ponovnih krvavitev iz varic. Treba je tudi načrtovati kontrolne gastroskopije z namenom eradikacije varic s pomočjo ligacije varic. Endoskopsko ligacijo se izvaja vsake 3 tedne do eradikacije varic.

Bolniki, ki so krvaveli iz peptičnih ulkusov, potrebujejo zaviralec protonske črpalke nekaj tednov. Bolniki, ki so krvaveli iz visokorizičnih peptičnih ulkusov (Forrest Ia, Ib, IIa, IIb), potrebujejo visokodozno zdravljenje z zaviralci protonske črpalke v obliki kontinuirane infuzije, ki naj, če je le mogoče, traja 72 ur. Izključiti je treba okužbo z bakterijo Helycobacter Pylori. Običajno to naredimo med gastroskopijo s pomočjo biopsij sluznice antruma. Če biopsije nismo odvzeli, lahko ugotovimo prisotnost bakterije Helycobacter Pylori s pomočjo določitve v vzorcu blata še med isto hospitalizacijo.

Bolniki, ki so pred krvavitvijo prejemali aspirin zaradi sekundarne preventive, naj z zdravilom nadaljujejo takoj po napravljeni hemostazi. V splošnem indiciramo zgodnjo ponovno uvedbo antitrombotičnih zdravil, saj tako zmanjšamo število trombotičnih dogodkov in smrtnost. Glede antikoagulantne terapije se odločamo individualno za vsakega bolnika po posvetu z ustreznimi specialisti.

ZAKLJUČEK

Krvavitev iz zgornjih prebavil ostaja nevarno urgentno stanje. Obravnava bolnika se začne s hemodinamsko oceno. Po hemodinamski stabilizaciji je treba v roku 24 ur opraviti urgentno gastroskopijo, razen pri zelo ogroženih bolnikih, kjer poseg opravimo znotraj 6 ur. Prisotnost intezivista ali anesteziologa ob posegu preprečuje sekundarne srčne zastoje med posegom in olajša endoskopsko hemostazo. Tako je za učinkovito in varno oskrbo bolnikov s krvavitvijo iz zgornjih prebavil potrebno sodelovanje urgentnega zdravnika, intezivista/anesteziologa in gastroenterologa.

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Pristop k bolniku s sumom na neoplazmo jeter, žolčnega voda in trebušne slinavke

Approach to the patient with suspected neoplasm of liver, bile ducts and pancreas

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***Ključne besede**: incidentalom, neoplazma, cista, karcinom*

***Keywords**: incidentaloma, neoplasm, cyst, carcinoma*

IZVLEČEK

Naključno ugotovljene lezije jeter, žolčnih vodov in trebušne slinavke predstavljajo heterogeno skupino lezij, ki so običajno klinično asimptomatske. Med seboj se razlikujejo glede na videz, etiologijo ter maligni potencial. Kljub temu, da so tovrstne lezije večinoma benigne narave, jih moramo ustrezno prepoznavati in pravilno opredeliti. Njihova incidenca v svetovnem merilu narašča zaradi široke dostopnosti in dobre kvalitete slikovnih preiskav trebuha. Transabdominalni ultrazvok trebuha je po navadi prva slikovna preiskava, ki jo nato, če ne moremo nesporno opredeliti benigne etiologije lezije, nadgradimo s superiornejšimi radiološkimi metodami kot sta računalniška tomografija ali magnetno resonančno slikanje. Pri obravnavi bolnikov z naključno ugotovljenimi lezijami jeter, žolčnega voda in trebušne slinavke namenimo posebno pozornost bolnikom z dejavniki tvegainja za nastanek raka prebavil in zato potrebujejo redno sledenje.

ABSTRACT

Incidentally detected lesions of the liver, bile ducts and pancreas represent a heterogeneous group of lesions that are usually clinically asymptomatic. They differ in terms of appearance, aetiology and their malignant potential. Even though these types of lesions are mostly benign, their proper recognition and correct evaluation are necessary. Their incidence is increasing worldwide due to the wide availability and good quality of abdominal imaging. A transabdominal ultrasound of the abdomen is usually the first imaging examination, which is upgraded with superior radiological methods such as computed tomography or magnetic resonance imaging if the benign aetiology of the lesion cannot be determined beyond doubt. When treating patients with incidentally found lesions of the hepato-pancreato-billiary tract, we pay special attention to patients with risk factors for gastrointestinal cancer and therefore need regular screening.

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UVOD

Asimptomatske lezije jeter, žolčnih vodov in trebušne slinavke predstavljajo heterogeno skupino lezij, ki jih običajno ugotovimo naključno. Njihova prevalenca se je v zadnjih letih pomembno povečala zaradi dostopnosti in kakovosti slikovnih preiskav. Med seboj se razlikujejo po morfoloških značilnostih in etiologiji, čemur sledi pristop k njihovi obravnavi. Zaradi raznolikega malignega potenciala je ključna njihova pravilna opredelitev. Pri obravnavi bolnikov s tovrstnimi lezijami namenimo posebno pozornost bolnikom, ki imajo zaradi svoje osnovne bolezni povišano tveganje za nastanek raka prebavil in potrebujejo redno presejanje.

JETRNE LEZIJE

Asimptomatske jetrne lezije so pogosta naključna najdba radioloških preiskav trebuha (1). Njihova incidenca je v porastu v zadnjem desetletju zaradi široke dostopnosti in kvalitete slikovnih preiskav trebuha, predvsem transabdominalnega ultrazvoka (UZ) in računalniške tomografije (CT) (2). Naključno ugotovljene lezije jeter so pogoste, najdemo jih pri 10 % do 33 % vseh bolnikov, ki so opravili slikovno preiskavo zaradi kakršnih koli, z najdbo tudi nepovezanih vzrokov. Velika večina teh najdb je benigne etiologije (3). V diagnostiki jetrnih lezij je ključno poznavanje bolnikovih pridruženih bolezni, saj te usmerjajo nadaljnjo obravnavo. Večina bolnikov z novoodkritimi jetrnimi lezijami namreč nima simptomov, prav tako tudi klinični pregled po navadi posebnosti ne pokaže (4). Znaki in simptomi bolnikovih težav pa so lahko posledica osnovne jetrne bolezni (na primer jetrne ciroze) ali pa so z lezijo vzročno povezani (na primer razširjena maligna bolezen).

Prepoznava bolnikovih dejavnikov tveganja omogoča ustrezno usmerjanje diagnostičnih postopkov, predvsem v skupinah bolnikov, kjer obstaja velika verjetnost, da je novoodkrita lezija maligne narave (5). K bolnikom z visokim tveganjem prištevamo starejše bolnike, s pridruženimi jetrnimi boleznimi kot so jetrna ciroza, okužba s hepatitisom B in C, primarni sklerozirajoči holangitis, avtoimuni hepatitis ter bolezni jeter kot sta hemokromatoza in Wilsonova bolezen. V anamnezi usmerjeno povprašamo o škodljivem uživanju alkohola ter rabi androgenov, kontraceptivov in anabolikov. Pozorni smo na prisotnost komponent metabolnega sindroma in njemu pridružen nealkoholni steatohepatitis (6). Pri bolnikih, ki so bili zdravljeni ali se zdravijo zaradi raka, pomislimo, da gre za zasevke osnovne bolezni. Bolniki z nizkim tveganjem so običajno mlajši (< 45 let), nimajo družinske obremenitve z rakom, znane jetrne bolezni ali zgoraj naštetih dejavnikov tveganja. V primeru, ko klinična anamneza ni znana in se zdi, da je tveganje za bolnika oziroma maligno naravo novo ugotovljene jetrne lezije nizko, je pomembno jasno navesti, da so morfološke značilnosti lezije skladne z benigno etiologijo, ki ne zahteva nadaljnje opredelitve (1, 3, 7).

Pri diagnostiki jetrnih lezij, ki jih ne moremo enoznačno opredeliti s transabdominalnim ultrazvokom, se poslužimo drugih slikovnih preiskav, predvsem CT abdomna s kontrastnim sredstvom in magnetno resonančnega slikanja (MR). Solidne lezije, večje od 10 mm, katerih benigne etiologije nismo nesporno potrdili, namreč potrebujejo opredelitev s CT ali MR. UZ vodena biopsija lezije je indicirana, kadar slikovne preiskave narave lezije ne pojasnijo (7).

Jetrni hemangiomi so najpogostejši benigni jetrni tumorji. Njihova prevalenca je ocenjena na 0,4 do 20 %, pogostejši so pri ženskah (8). Zelo redko so simptomatski. Zaradi značilnega videza lahko diagnozo postavimo zgolj s slikovnimi preiskavami. Kirurško zdravljenje je potrebno zgolj v redkih primerih in je indicirano le pri velikih, simptomatskih hemangiomih. Glede na priporočila ameriškega in evropskega združenja za gastroenterologijo, sledenje hemangiomov značilnega, nesuspektnega izgleda, ni potrebno (9).

Fokalna nodularna hiperplazija (FNH) predstavlja drugi najpogostejši benigni jetrni tumor s prevalenco med 0,3 in 3 % populacije. FNH se pogosteje pojavlja pri ženskah, navadno med 40. in 60. letom starosti (9). FNH je po navadi naključno ugotovljena, saj le

redko povzroča klinične simptome. Tipične lezije je mogoče jasno prepoznati in opredeliti z uporabo kontrastnih slikovnih preiskav. V nejasnih primerih je za razlikovanje FNH od jetrnega adenoma priporočena jetrna biopsija. Asimptomatske FNH ne potrebujejo zdravljenja. Pri ženskah, ki uporabljajo oralno kontracepcijo je priporočeno spremljanje dinamike velikosti FNH enkrat letno prva tri leta po postavitvi diagnoze (10).

Jetrni adenomi so redki benigni jetrni tumorji. Njihova prevalenca je ocenjena na okoli 0,01 %. Najpogosteje se pojavljajo pri ženskah po 30. letu starosti, zlasti v povezavi z jemanjem oralne kontracepcije in prekomerne telesne teže (9), zato je uporaba oralnih kontraceptivov, maternicnih vsadkov, ki sproščajo hormone in anabolnih steroidov po postavitvi diagnoze kontraindicirana. Zaradi možnosti maligne transformacije ali krvavitve priporočamo resekcijo adenomov, večjih od petih centimetrov. Manjše adenome je smiselno spremljati s CT ali MR vsakih 6–12 mesecev (9, 10).

Jetrne ciste pri ultrazvočni preiskavi trebuha naključno najdemo pri 3–5 % preiskovancev. Enostavne ciste so navadno manjše od 1 cm in asimptomatske (11). Večje ciste lahko povzročajo simptome kot so tiščanje v epigastriju, zgodnja sitost ali neznačilne bolečine v trebuhu. Enostavne ciste je potrebno ločiti od biliarnih cistadenomov in ehinokoknih cist s pomočjo superiornejših slikovnih preiskav kot sta CT in/ali MR jeter. Nadaljnja opredelitev cističnih sprememb s CT je potrebna, kadar imajo zaskrbljujoče znake kot so neenakomerna zadebelitev stene, muralni noduli, septe znotraj ciste, kalcinacije ali drugi vključki. Asimptomatske enostavne ciste ne potrebujejo zdravljenja. Kadar večje ciste povzročajo simptome, je indicirana njihova oskrba, bodisi sklerozacija ali kirurška resekcija (11).

Rak jetrnih celic (*angl. hepatocellular carcinoma, HCC*) je najpogostejši primarni rak jeter. Njegova incidenca zadnja desetletja narašča tako v svetu, kot pri nas. HCC je peti najpogostejši rak in drugi najpogostejši vzrok smrti zaradi raka. Večina, skoraj 90 % bolnikov s HCC ima jetrno cirozo, ob čemer pa se pri bolnikih s kroničnim virusnim hepatitisom B in hemokromatozo HCC lahko pojavi še pred nastopom jetrne ciroze (12). K najpogostejšim vzrokom za nastanek HCC prištevamo okužbo z virusom hepatitisa B in C, prekomerno uživanje alkohola ter izpostavljenost aflatoksinu. Jetrna ciroza je tako najpomembnejši dejavnik tveganja za nastanek HCC, ne glede na etiologijo ciroze, vendar je incidenca HCC višja v primeru posthepatitične jetrne ciroze. Ob epidemiji debelosti in naraščajočo incidenco nealkoholnega steatohepatitisa, postaja omenjena etiologija jetrne bolezni čedalje pomembnejši dejavnik tveganja za nastanek HCC. Pri bolnikih z jetrno cirozo ali drugimi dejavniki tveganja, je indicirano UZ presejanje bolnikov na HCC vsakih 6 mesecev. Pri bolnikih z jetrno cirozo in lezijah, ki so večji od 10 mm ima CT s kontrastnim sredstvom osrednjo vlogo pri postavitvi diagnoze HCC. Ameriško združenje za radiologijo (*American College of Radiology*) je ustvaril sistem LI-RADS (iz angl. Liver Imaging Reporting and Data System), na podlagi katerega, lahko postavimo radiološko diagnozo HCC. Ta upošteva velikost lezije (< 10 mm, 10–19 mm, ≥ 20 mm), obarvanje v arterijski fazi (hiper, izo- ali hipovaskularnost), izgled izplavljanja kontrastnega sredstva, prisotnost obarvane kapsule okoli lezije in rast lezije (minimalno povečanje za 5 mm in ≥ 50 % povečanje premera lezije v ≤ 6 mesecih ali ≥ 100 % povečanje v ≤ 1 letu). Če bolnik nima jetrne ciroze, je za opredelitev lezije potrebna biopsija, enako tudi v primeru vsake jetrne lezije v cirotičnih jetrih z nediagnostičnim izvidom CT in/ali MR s kontrastnim sredstvom. Spremembe v cirotičnih jetrih, manjše od enega centimetra, terjajo spremljanje z uporabo ene izmed slikovnih metod vsake 4 mesece, eno leto (13).

LEZIJE ŽOLČNIKA IN ŽOLČNIH IZVODIL

Dilatacija žolčnega voda. Skupni žolčni vod normalno prečno meri do 6 mm, čemer dodamo 1 mm širine za vsako dekado nad 60. letom starosti (7, 14). Pri asimptomatskih bolnikih po holecistektomiji v preteklosti, z normalnim hepatogramom, menimo,

da je skupni žolčni vod premera do 10 mm še primerno širok (15, 16). V primeru suma na ekstrabiliarno obstrukcijo maligne ali benigne narave se poslužimo endoskopskega ultrazvoka ali MR holangiopankreatikografije (MRCP). Endoskopska retrogradna holangiopankreatografija (ERCP) je terapevtska metoda z namenom razrešitve obstrukcije, ne glede na njeno etiologijo (7).

Polipi žolčnika. Bolnike, pri katerih smo naključno odkrili polip žolčnika, velikosti 10 mm in več, napotimo k abdominalnemu kirurgu za predvideno holecistektomijo (17). Polipi žolčnika, velikosti do 9 mm, potrebujejo spremljanje in sicer prvič čez 6 mesecev, kasneje enkrat letno. Če nimajo dinamike rasti, lahko njihovo sledenje verjetno opustimo po petih letih, saj je verjetnost maligne alteracije nizka (18). Polipi manjši od 5 mm in brez dinamike rasti, imajo glede na izsledke številnih tujih študij praktično nično tveganje za nastanek raka žolčnika. Posebno previdni smo pri bolnikih s primarnim sklerozirajočim holangitisom in polipi žolčnika, kajti ti so bistveno bolj ogroženi za nastanek raka žolčnika in jih zato ultrazvočno spremljamo na 6 mesecev, za holecistektomijo pa se odločimo prej (19).

Zadebelitev stene žolčnika. Normalna debelina stene žolčnika znaša 3 mm. *Adenomiomatoza žolčnika* je pogosta, benigna najdba, ki nastane zaradi proliferacije epitela in/ali gladkih mišičnih vlaken v steni žolčnika (20). Adenomiomatozo ponavadi naključno odkrijemo pri ultrazvočnem pregledu abdomna, za potrditev diagnoze se poslužimo MR, ki je v tem primeru bolj občutljiv in specifičen kot CT (21).

Holangiokarcinom je rak žolčnih vodov, ki razmeroma redka oblika raka, predstavlja manj kot 1 % vseh malignomov ter okvirno 3 % vseh gastrointestinalnih tumorjev (22). Glede na anatomsko lokalizacijo razlikujemo intrahepatični, perihilarni (Klatskinov tumor) in ekstrahepatični holangiokarcinom (23). Intrahepatični holangiokarcinom predstavlja 15 % vseh primarnih intrahepatalnih tumorjev in je za hepatocelularnim karcinomom drugi najpogostejši primarni rak jeter (24). Holangiokarcinom ima na splošno zelo slabo prognozo, z visoko stopnjo ponovitve po operativnem in dopolnilnem kemoterapevtskem zdravljenju. Kljub razvoju kirurških tehnik in novih možnosti sistemskega zdravljenja je petletno preživetje nizko in znaša do 10 % (25).

LEZIJE PANKREASA

Pankreatične cistične neoplazme (PCN) predstavljajo heterogeno skupino cističnih lezij, ki jih običajno ugotovimo naključno. Pri obravnavi in sledenju cističnih lezij pankreasa je ključna pravilna opredelitev, saj se njihov maligni potencial za nastanek raka trebušne slinavke pomembno razlikuje, s tem pa je povezana odločitev glede spremljanja in morebitnega kirurškega posega. V grobem jih lahko razdelimo v dve glavni kategoriji, to so mucinozne in ne-mucinozne neoplazme. Mucinozne neoplame obdaja visokoprizmatski epitelij, ki izloča mucin. Makroskopsko je vsebina mucinoznih cist visoko viskozna, vlecljiva, z značilno povišano koncentracijo tumorskega označevalca karcinoembrionalnega antigena (CEA) nad 192 ng/ml. Nemucinozne neoplazme obdaja kuboidni epitelij, ki mucina in CEA ne izloča (26).

Razlikujemo psevdociste, serozne cistične neoplazme, solidne psevdopapilarne neoplazme, cistične pankreatične nevroendokrine tumorje, mucinozne cistične neoplazme in intraduktalne papilarne mucinozne neoplazme.

Psevdociste so zaplet akutnega pankreatitisa. Nastanejo lahko v parenhimu trebušne slinavke ali ob njej. Sestavljene so iz propadlega tkiva, organizirane nekroze in vnetnih celic ter so pretežno tekočinske vsebine. Obdaja jih fibrozna ovojnica, brez pravega epitelija. Psevdociste nimajo malignega potenciala in zato ti bolniki ne potrebujejo spremljanja (26). Psevdociste lahko postanejo simptomatske zaradi svoje velikosti in pritiska na prileže organe.

Serozne cistične neoplazme, znane tudi pod imenom serozni cistadenom, so skupek številnih mikrocist, ki jih obdaja kuboidni epitelij. Na slikovnih preiskavah je prisoten značilen izgled satovja (angl. *honeycomb*

pattern). Pogosteje se pojavljajo pri ženskem spolu, predvsem med 50. in 70. letom starosti. Serozne cistične neoplazme praktično nimajo malignega potenciala, zato spremljanje ni potrebno. Če zaradi svoje velikosti postanejo simptomatske (bolečina, vzrok pankreatitisa, biliarna ali gastrointestinalna obstrukcija) je indicirano kirurško zdravljenje (26, 27).

Solidne psevdopapilarne neoplazme so delno cistične, delno solidne lezije, ki jih obdaja kuboidni epitel in fibrozna psevdokapsula. Pojavljajo se predvsem pri mlajših bolnicah. Zaradi zmernega malignega potenciala je indicirano kirurško zdravljenje, dolgoročno preživetje pa odlično (26, 27).

Cistični pankreatični nevroendokrini tumorji predstavljajo približno 15 odstotkov vseh nevroendokrinih neoplazem. Vzniknejo predvsem v področju glave trebušne slinavke pri starosti med četrto in šesto dekado. Na slikovnih preiskavah izstopa njihova hipervaskularnost, vendar se za razlikovanje od ostalih vrst PCN velikokrat poslužimo EUZ vodene punkcije lezije. Asimptomatske cistične nevroendokrine neoplazme imajo nižji maligni potencial kot solidne neoplazme in jih zato do velikosti 2 cm le spremljamo (26–28).

Mucinozne cistične neoplazme se pojavljajo pretežno pri bolnicah in sicer v srednjem starostnem obdobju. Na slikovnih preiskavah vidimo makrocistično lezijo, pogosto s kalcinacijami. Lezije, ki so večje od 3 cm oziroma imajo pridružene druge nevarnostne dejavnike, obravnavamo kot visoko rizične za maligno alteracijo (26–28).

Intraduktalne papilarne mucinozne neoplazme (IPMN) so najpogostejša vrsta PCN. Pojavljajo se v vseh segmentih trebušne slinavke, a najpogosteje jih najdemo v področju glave pankreasa, lahko so solitarne ali multiple. Glede na povezavo z pankreatičnim sistemom izvodil razlikujemo IPMN stranskih vodov, IPMN glavnega voda in IPMN mešanega tipa. Vse IPMN imajo maligni potencial, ki pa je odvisen od komunikacije z glavnim pankreatičnim vodom, njegovo dilatacijo, velikostjo lezije, hitrostjo rasti in prisotnostjo muralnih nodulov ali solidne komponente (26–28).

Enotnih smernic za obravnavo in spremljanje PCN ni, obstajajo pa priporočila evropskega združenja (2018), priporočila *American College of Gastroenterology* (2018), priporočila ameriškega združenja za gastoenterologijo (2015), revidirana Fukuoka priporočila (2017) in priporočila ameriškega združenja za radiologijo (2017), ki se razlikujejo glede na intervale spremljanja in obravnavo bolnikov s PCN. Kljub razlikam v priporočilih za sledenje PCN, so ta enotna glede nevarnostnih dejavnikov, ki so: prisotnost muralnega nodula ali solidne komponente, dilatacija glavnega pankreatičnega voda, velikost lezije ≥ 3–4 cm ali pozitiven citološki izvid tanko-igelne endoskopsko ultrazvočno (EUZ) vodene aspiracije vsebine ciste. Druga pomembna merila, ki jih je treba upoštevati, vključujejo hitro rast ciste (≥ 5 mm/leto), povišane ravni serumskega označevalca Ca 19-9, novonastalo sladkorno bolezen in akutni pankreatitis, za katerega domnevamo, da je etiološko povezan s cistično lezijo (27, 28).

Prisotnost zlatenice, intramuralnega nodula (≥ 5 mm) ali solidne komponente v cisti, pozitivni citološki izvid ali dilatiran glavni pankreatični vod ≥ 10 mm predstavljajo jasne indikacije za kirurško resekcijo, saj gre zelo verjetno že za maligno alteracijo PCN in je potrebna predstavitev na multidisciplinarnem konziliju (26, 28).

Priporočila različnih združenj za sledenje pankreatičnih cist temeljijo na velikosti lezije ob njenem odkritju ob predpostavki, da ni prisotnih tveganih ali zaskrbljujočih znakov. Evropske smernice iz leta 2018 predlagajo MRI ali EUZ na 6 mesecev v prvem letu sledenja in nato enkrat letno, ob čemer se svetuje tudi določitev serumskega označevalca Ca 19-9 in klinični pregled. Ameriška priporočila so zaenkrat edina, ki predlagajo opustitev spremljanja v primeru odsotnosti dinamike lezije po petih letih sledenja. Odločitev glede spremljanja PCN mora biti premišljena, upoštevajoč vrsto lezije, starost bolnika, stanje

splošne telesne zmogljivosti, njegove pridružene bolezni ter morebitne klinične posledice (26–28).

Rak trebušne slinavke. V pankreasu lahko vznikne več vrst neoplazem, 85–90 % rakov predstavlja duktalni adenokarcinom, zato pod pojmom rak trebušne slinavke smatramo prav to obliko (29).

Rak trebušne slinavke se najpogosteje pojavi pri starejših bolnikih. Začetna prezentacija je odvisna od lokacije tumorja. Tumorji korpusa in repa trebušne slinavke so navadno diagnosticirani v bolj napredovalih stadijih kot tumorji glave, kjer zaradi pritiska tumorske mase pride do obstrukcije skupnega žolčnega voda in/ali pankreatičnega voda (30). Pri bolnikih s simptomi, kot so hujšanje, bolečine, zlatenica in z UZ ugotovljene spremembe v trebušni slinavki, opravimo CT abdomna s kontrastnim sredstvom. Če gre za resektabilen tumor, histološka potrditev pred operacijo ni potrebna (31). Če je tumor mejno resektabilen oz. najdemo lokalno napredovalo bolezen, je potrebno opraviti EUZ vodeno biopsijo tumorja. Če so že na CT vidni jetrni zasevki, opravimo na njih biopsijo, saj je patološka potrditev diagnoze pogoj za sistemsko kemoterapijo. Potrebno je poudariti, da je perkutana biopsija trebušne slinavke kontraindicirana pri potencialno resektabilnih tumorjih (31).

ZAKLJUČEK

Lezije jeter, žolčnega sistema in trebušne slinavke so pogosta naključna najdba opravljenih slikovnih preiskav trebuha. Pomembna je njihova pravilna opredelitev, pri nadaljnji obravnavi pa je potrebno poznavanje bolnikovih pridruženih stanj in bolezni. Posebno pozornost namenimo bolnikom, ki imajo povišano tveganje za nastanek raka prebavil.

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Epiploični apendagitis – redek vzrok entero-subkutane fistule

Appendagitis epiploica – a rare cause of entero-subcutaneous fistula

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***Ključne besede**: appendagitis epiploica, akutni abdomen, enteo-subkutana fistula, zdravljenje*

***Keywords**: appendagitis epiploica, acute abdomen, enteo-subcutaneus fistule, treatment*

IZVLEČEK

Appendagitis epiploica je redek vzrok akutnega abdomna, ki ga lahko zaradi nizke incidence in nespecifične klinične slike zamenjamo z drugimi pogostejšimi stanji, predvsem akutnim divertikulitisom, apendicitisom ali holecistitisom. Predstavljamo primer 56-letne bolnice z akutno bolečino v desnem zgornjem abdomnu. Ob izključitvi drugih vzrokov smo številnimi radiološkimi modalitetami opredelili diagnozo epiploičnega apendagitisa. V nadaljnem kliničnem poteku se je razvil kasen zaplet omenjene entitete z nastankom entero-subkutane fistule. Bolnico smo zdravili konzervativno. S prikazom primera primera in pregledom literature želimo poudariti, da na epiploični apendagitis pomislimo ob izključitvi drugih, pogostejših vzrokov akutnega abdomna. Z ustrezno diagnozo se namreč lahko izognemo nepotrebnemu kirurškemu zdravljenju.

ABSTRACT

Appendagitis epiploica is a rare cause of acute abdomen and is often misdiagnosed for other more common causes of acute abdomen due to its low incidence and nonspecific clinical presentation. Appendagitis epiploica is commonly mistaken as other more severe causes of acute abdominal pain, such as diverticulitis, acute appendicitis or cholecystitis. We present the case of a 56-year-old patient with acute abdominal pain. After the exclusion of other causes, the diagnosis of appendagitis epiploica was defined using several radiological modalities. In the subsequent clinical course, a late complication developed with the formation of an entero-subcutaneous fistula. The patient was treated conservatively. By presenting the following case report and reviewing the literature, we would like to emphasize that appendagitis epiploica should be included in the differential diagnosis of acute abdominal pain to avoid unnecessary medical and surgical treatment.

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UVOD

Epiploični apendagitis je redek in pogosto spregledan vzrok akutnega abdomna.

Prava incidenca epiploičnega apendagitisa ni znana, ocenjena je na približno 8,8 primerov na milion prebivalcev letno. Omenjena entiteta je opisana pri 2 do 7 % bolnikov, pri katerih je bil sprva postavljen sum na akutni divertikulitis in 0,3 do 1 % bolnikov s sumom na akutni apendicitis (1). Epiploični apendagitis se najpogosteje pojavi pri bolnikih med 30. in 50. letom starosti z mediano starostjo 40 let. Incidenca pri moških je do štirikrat-krat višja kot pri ženskah (1–3). Epiploični apendagitis se lahko pojavi v kateremkoli segmentu kolona, najpogosteje pa prizadane rektosigmoidalni predel črevesa (1, 4, 5). Dejavniki tveganja za nastanek epiploičnega apendagitisa so prekomerna telesna teža in s tem povezan obseg abdominalnega maščevja ter prekomeren telesni napor (1, 5, 6).

OPREDELITEV

Epiploični apendiksi oz. izrastki so sestavljeni iz pedunkuliranega maščobnega tkiva, pritrjenega na površino debelega črevesa, ki se najpogosteje nahaja na tenijah (*taenia libera* in *taenia omentalis*) cekuma in sigmoidnega kolona. Maščobni izrastki so pokriti s serozo, ki jo oskrbujejo ena ali dve arteriji in vena, njihova velikosti znaša med 0,5–5 cm. Epiploični izrastki so prisotni že v otroštvu, povečajo pa se v odrasli dobi, predvsem pri bolnikih s prekomerno telesno težo, kar predstavlja tudi dejavnik tveganja za nastanek zapletov.

Primarni epiploični apendagitis opredeljen je kot ishemični infarkt epiploičnega izrastka, povzročen zaradi torzije in posledične motnje prekrvavitve, kar vodi v ishemijo. Slednja lahko nastane tudi zaradi spontane tromboze centralne vene. Posledično pride do edema, ishemične nekroze in aseptičnega vnetja. Od hitrosti nastanka epiploičnega apendagitisa je odvisna tudi klinična manifestacija. Postopna torzija apendiksov lahko se lahko manifestira s sliko kroničnega vnetja z malo ali nič simptomi, akutna strangulacija povezana z nastankom znakov in simptomov akutnega abdomna.

Sekudarni epiploični apendagitis je odraz širjenja vnetnega procesa iz prileţnih strukur, predvsem divertiklov debela črevesja, slepiča ali žolčnika.

KLINIČNA SLIKA

Klinična slika je nespecifična in po navadi imitira druga pogostejša stanja kot so akutni apedicitis, akutni divertikulis in akutni holecistitis.

Bolniki z epiploičnim apendagitisom najpogosteje zbolijo z akutno ali subakutno bolečino v spodnjem delu trebuha. Bolečina je pri 60–80 % bolnikov lokalizirana v levem abdomnu, ampak je lahko prisotna tudi v desnem spodnjem kvadrantu. Bolečina je pogosto konstantna, topa in dobro lokalizirana (7). Redkejši simptomi so zgodnja sitost, bruhanje, napihnjenost, diareja in povišana telesna temperatura. Ob kliničnem pregledu bolniki po navadi niso prizadeti in nimajo znakov sistemskega vnetnega odgovora. Bolečina je lokalizirana na prizadeto področje, znaki peritonealnega draženja so po navadi odsotni (8). Pri 10–30 % bolnikov lahko zatipamo bolečo rezistenco (9). V laboratorijskih izvidih ne najdemo odstopov, ki bi bolnikove težave pojasnili. Diferencialna krvna slika, sedimentacija in vrednost CRP so po navadi normalni oz. le blago povišani (5–10).

Epiploični apendagitis je velikokrat ugotovimo pri bolnikih, ki opravijo slikovne preiskave zaradi dosedaj neopredeljene bolečine v trebuhu (11, 12, 13). Na diagnozo moramo pomisliti tudi, ko eksploracija trebušne votline ne razkrije katerega od bolj pogostih vzrokov akutne abdominalne bolečine (14).

Pomembno je, da pri obravnavi bolnika z akutno bolečino v trebuhu pomislimo na epiploični apendagitis. Molla s sodelavci je dokazal, da je pri približno 7 odstotkih bolnikov s sumom na akutni divertikulitis šlo dejansko za primarni epiploični apendagitis (15).

Diferencialna diagnoza epiploičnega apendagitisa vključuje številne druge vzroke za nastanek akutne bolečine v spodnjem delu abdomna. Pomislimo na torzijo ovarija, ektopično nosečnost, mesenterični limfadenitis, akutni infarkt omentuma, ledvične kamne ter vnetja v področju male medenice (16).

Transabdominalni ultrazvok trebuha kot prva izmed diagnostičnih preiskav ima omejeno vlogo. Na mestu bolečnosti lahko prikaže dobro omejeno, nestisljivo hiperehogeno lezijo, ki leži v stiku s steno debelega črevesja. Dopplerska preiskava prikaže odsotnost krvnega pretoka v leziji. Okoljne strukture imajo lahko spremenjeno ehogenost zaradi širjenja vnetja v prileţno maščenje in peritonej (15, 17, 18).

Računalniška tomografija abdomna (CT) s kontrastnim sredstvom je preiskava izbora v diagnostičnem algoritmu, s čimer izključimo tudi druge vzroke akutnega abdomna. Preiskava prikaže zamejeno lezijo z značinimi atenuacijski vrednostmi za maščobo, omejeno z hiperdenznim robom, ki je poledica draženja prileţnega visceralnega dela peritoneja (19, 20, Slika 1, 2).

Magnetnoresonančno slikanje (MR) se ne uporablja rutinsko, zaradi boljše resolucije pri pregledu mehkih tkiv lahko poda dodatne informacije pri opredelitvi lezije (20).

ZDRAVLJENJE

Pred razvojem in široko dostopnostjo slikovnih preiskav je bil epiploični apendagitis predvsem domena kirurških strok in ugotovljen med operativno eksploracijo z namenom zdravljenja drugih vzrokov akutnega abdomna. Dandanes omenjeno bolezensko stanje smatramo kot benigno in samoomejujoče, v večini primerov je indicirano konzervativno zdravljenje.

Glede zdravljenja nimamo jasnih priporočil. Dostopnih je le malo podatkov, ki izhajajo iz kliničnih primerov v tuji literaturi. Bolnike zdravimo konzervativno s protibolečinskimi zdravili. Analgetiki iz skupine steroidnih protivnetnih zdravil so terapija izbora, a verjetno ne spremenijo naravnega poteka same bolezni. Antibiotično zdravljenje nima vloge in ga ne predpisujemo. Bolniki večinoma ne potrebujejo hospitalizacije (21, 22, 25).

Do popolne razrešitve brez kirurške intervencije po navadi pride v 3 do 14 dneh (5, 16, 23, 24). Tveganje za ponovitev v literaturi ni bilo opisano, ampak je verjetno zelo nizko. Redko se lahko vneti apendiksi pripnejo na abdominalno steno ali druge visceralne organe in tako predisponirajo k intestinalni obstrukciji in intususcepsiji. Vneti in nekrotični apendiksi lahko redko napredujejo v formacijo abscesa (25, 26). Kirurško zdravljenje je indicirano za bolnike, katerih simptomi se ne izboljšajo po konzervativnem zdravljenju, za tiste z novimi ali hujšimi simptomi (npr. povišana telesna temperatura, progresivna bolečina, navzea, bruhanje, inapetenca) ali zapleti, ki jih ne moremo obvladati nekirurško (npr. intususcepcija, ileus, absces) (27). V tuji literaturi opisanega primera entero-kutane fistule nismo našli.

PRIKAZ PRIMERA

56-letna bolnica s hipotirozo, policističnimi jajčniki, suspektno Crohnovo boleznijo v remisiji brez tozadevne terapije in nedavno prebolelo nezapleteno COVID 19 okužbo je bila napotena v urgentno gastroenterološko ambulanto zaradi akutne bolečine v trebuhu. Dva dneva pred pregledom je zbolela z difuznimi bolečinami po desni strani trebuha, ki so se intenzivirale navkljub analgetični terapiji z paracetamolom in metamizolom. Z izjemo bolečin in prehodnega odvajanja bolj tekočega oblata, drugih težav ni navajala. Povišane telesne temperature ni imela. Šest mesecev pred nastankom težav je opravila gastroskopijo, ki je potrdila kronični gastritis, blag refluksni ezofagitis in hiatalno hernijo, ter koloileoskopijo, ki je prikazala popolno endoskopsko remisijo sluznice debelega in tankega črevesja.

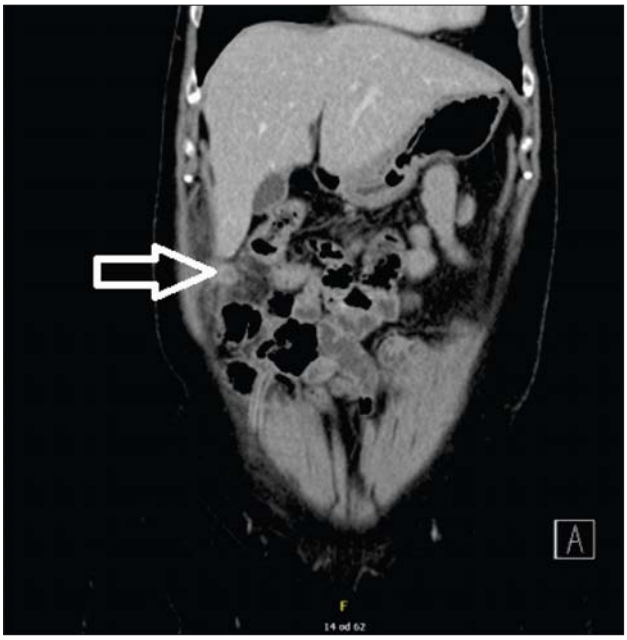
Ob pregledu je bil trebuh izrazito palpatorno boleč v McBurneyevi točki. Posumili smo na akutni apendicitis, zato smo bolnico napotili na urgentni tranabdominalni ultrazvok trebuha, ki je prikazal izrazit

meteorizem in znake draženja ozkočrevesnih vijug v srednjem delu abdomna. Radioloških znakov akutne apendicitisa ali holecistitisa ni bilo videti. V laboratorijskih izvidih ni bilo prisotnih klinično pomembnih odstopov, vnetni kazalci niso bili povišani. Gospo smo odpustili v domačo oskrbo z analgetikom in spazomolitikom ter jo zaradi anamnestičnega podatka o Crohnovi bolezni tankega črevesa napotili na MR enterografijo.

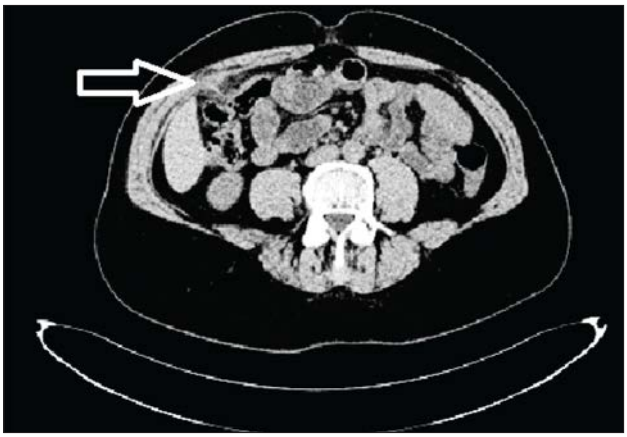
Zaradi vztrajajočih težav je bila gospa tri dni kasneje pregledana v urgentni abdominalni kirurški ambulatni, kjer so ob kliničnem pregledu ponovno ugotavljali palpatorno bolečnost v desnem spodnjem kvadrantu. V laboratorijskih izvidih je izstopala le blago povišana vrednost CRP (25 mg/L). Napotili so jo še nujni pregled pri ginekologu, ki ni ugotavljal akutnega ginekološkega vzroka, in na CT abdomna s kontrastnim sredstvom. Slednjega je opravila 10 dni po pregledu oziroma 15 dni po pričetku bolečine v trebuhu. Slikanje je prikazalo nekoliko strukturno spremenjen omentum desno pred hepatalno fleksuro s 1,3 cm veliko debelorobo in centralno utekočinjeno spremembo tik pod ali v samem peritoneju s hiperdenzno strukturo – po izgledu epiploičnega apendagitisa, in minimalno zadebeljeno steno kratkega segmenta terminalnega ileuma s poudarjenim priležnim žiljem in številnimi pomnoženimi bezgavkami ob ileocekalnem žilju (Slika 1, 2).

Bolničino dokumentacijo smo za tem obravnavali na internistično-kirurškem konziliju, ki je indiciral konzervativno zdravljenje.

Čez 3 tedne je bolnica na mestu predhodne bolečnosti, na desni strani trebuha otipala cca 2 x 2 cm veliko, blago bolečo in premakljivo rezistenco. Opravili smo laboratorijsko kontrolo, kjer ponovno nismo beležili odstopov, in ultrazvok (UZ) trebušne stene, ki je prikazal spremenjeno trebušno steno v premeru cca 4 x 3,5 cm, po izgledu absces s centralno kolikvacijo, ki se v ozkem tračku – fistula – širi preko trebušne stene v podkožje (Slika 3).



Slika 1. CT abdomna s kontrastom: epiploični apendagitis v koronarni ravnini

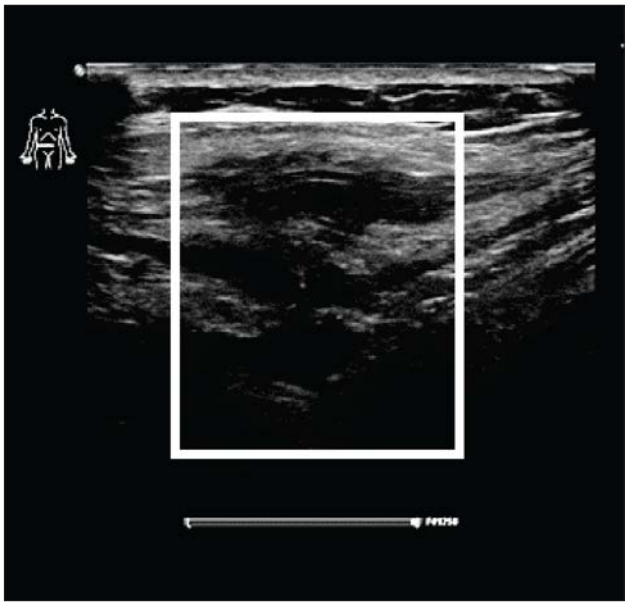


Slika 2. CT abdomna s kontrastom: epiploični apendagitis v aksialni ravnini

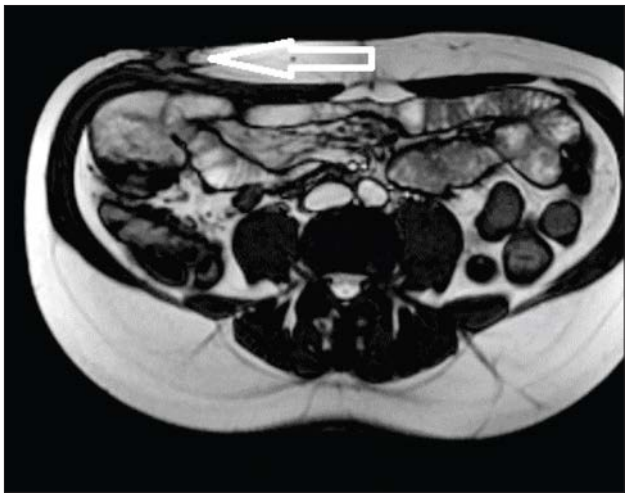
Bolnica je bila ponovno pregledana v urgentni abdominalni kirurški ambulanti, kjer so indicirali nadaljevanje konzervativnega zdravljenja.

Dva meseca po pričetku težav je opravila še magnetno resonančno enterografijo (MR), ki ni prikazala sprememb v sklopu Crohnove bolezni in potrdila delni regres sprememb v sprednji trebušni steni (Slika 4).

Klinično stanje bolnice se progresivno izboljšalo, tipna rezistenca je bila ob kontrolnem pregledu palpatorno komaj zaznavna. Bolničine težave se zaenkrat niso ponovile.



Slika 3. UZ abdomna: širjenje intraabdominalnega abscesa preko trebušne stene v obliki fistule v podkožje



Slika 4. MR enterografija: defekt trebušne stene v regresiji

ZAKLJUČEK

Epiploični apendagitis je redek in zato pogosto spregledan vzrok akutnega abdomna. Klinična slika je nespecifična in ponavadi imitira druga pogostejša stanja kot so akutni apedicitis, akutni divertikulis in akutni holecistitis. Diagnozo postavimo s slikovno preiskavo, najpogosteje s CT abdomna s kontrastnim sredstvom. Bolnike z epiploičnim apendagitisom večinoma zdravimo konzervativno, kirurško zdravljenje je indicirano v primeru zapletov ali ponovitve bolezni.

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Sodobna obravnava bolnikov z akutno jetrno porfirijo

Modern treatment of patients with acute liver porphyria

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***Ključne besede**: porfirije, akutna jetrna porfirija, hemin, givosiran*

***Keywords**: porphyrias, acute hepatic porphyria, hemin, givosiran*

IZVLEČEK

Porfirije so redke presnovne bolezni, ki so posledice motenj v sintezi hema. Glede na glavne klinične manifestacije jih delimo na kožne (fotosenzibilne) porfirije in akutne jetrne porfirije. Akutne jetrne porfirije so posledica čezmerne proizvodnje prekurzorjev porfirina, δ-aminolevulinske kisline in porfobilinogena v jetrih, simptomi pa so posledica poškodbe, predvsem živčnega sistema. Akutna intermitentna porfirija je najpogostejša oblika jetrnih porfirij. Večina bolnikov je ženskega spola, bolezen pa je redka pred puberteto ali po menopavzi. Pred nastopom osrednjih simptomov se pojavijo prodromi, ki lahko trajajo več dni in se najpogosteje kažejo kot utrujenost, nemir, nespečnost in motnje koncentracije, ki jim sledijo postopno vse hujše bolečine v trebuhu, slabost, bruhanje in subtilni nevrološki znaki. Z analizo naključnega vzorca urina na δ-aminolevulinsko kislino in porfobilinogena izključimo ali potrdimo diagnozo akutna jetrna porfirija. Standardno zdra-

ABSTRACT

Porphyrias are rare metabolic disorders caused by defects in heme synthesis. The diseases have been grouped as acute hepatic porphyrias and photocutaneous porphyrias. Acute porphyrias are due to hepatic overproduction of the porphyrin precursors, delta-aminolevulinic acid and porphobilinogen, and the symptoms are caused by injury primarily to the nervous system. Acute intermittent porphyria is the acute type most often encountered in clinical practice. The typical patient with an attack of acute intermittent porphyria is a previously healthy young woman who has had several days of severe fatigue and an inability to concentrate, followed by progressively worsening abdominal pain, nausea, vomiting, and subtle neurologic signs. By analysing a random urine sample for delta-aminolevulinic acid and porphobilinogen, we rule out or confirm the diagnosis of acute hepatic porohyria. Infusion of glucosaline fluids and hemin are

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vljenje akutnih zagonov akutne jetrne porfirije sta infuzija glukosaliničnih tekočin in hemin. Givosiran, interferenčno zdravljenje RNK, zavira izražanje jetrne sintaze δ-aminolevulinske kisline 1 s posledičnim zmanjšanim kopičenjem δ-aminolevulinske kisline in porfobilinogena. Tovrstno zdravljenje pomembno zmanjša potrebo po uporabi hemina in analgetikov ter število akutnih napadov.

standard treatments for acute episodes of acute hepatic porphyria.

Givosiran, an RNA interference therapy, inhibits the expression of hepatic delta-aminolevulinic acid synthase 1 with consequently reduced accumulation of delta-aminolevulinic acid and porphobilinogen. This type of treatment significantly reduces the need to use hemin and analgesics and significantly reduces the number of acute attacks.

UVOD

Porfirije so redke presnovne bolezni, ki jih povzročajo prirojene ali pridobljene encimske motnje v sintezi hema. V poti nastanka hema je udeleženih osem encimov in okvara posameznega encima povzroči eno od osmih porfirij. Glede na glavne klinične manifestacije delimo porfirije na kožne (fotosenzibilne) porfirije in akutne (jetrne) porfirije.

Kožne porfirije nastanejo zaradi čezmernega kopičenja fotosenzibilnih porfirinov v jetrih ali v kostnem mozgu. Poznamo štiri tipe kožnih porfirij: porfirija cutanea tarda (PCT), X-vezana dominantna protoporfirija (XLDPP), kongenitalna eritropoetska porfirija (CEP) in eritropoetska porfirija (EPP) (1, 2).

Akutne jetrne porfirije (*angl.* acute hepatic porphyrias, AHP) nastanejo zaradi čezmernega kopičenja prekurzorjev porfirina, δ-aminolevulinske kisline in porfobilinogena v jetrih. Povzročajo akutne nevrovisceralne simptome, ki zahtevajo pogoste hospitalizacije in pomembno zmanjšajo kakovost življenja. Med akutne jetrne porfirije (AHP) uvrščamo akutno intermitentno porfirijo (AIP), porfirijo zaradi pomanjkanja dehidrataze δ-aminolevulinske kisline, dedno koproporfirijo in variegatno porfirijo. Dedna koproporfirija in variegatna porfirija sta podobno kot kožne porfirije tudi fotosenzibilni (3).

Akutna intermitentna porfirija (AIP)

AIP, najpogostejša vrsta AHP (približno 80 % primerov), je posledica pomanjkanja hidroksimetilbilanske sintaze (porfobilinogen deaminaze), tretjega encima v biosintezni poti hema. V osnovi bolezen nastane zaradi čezmerno izraženega gena sintaze 1 aminolevulinske kisline (ALAS1*)*, ki povzroči povečanje koncentracije nevrotoksičnih intermediatov δ-aminolevulinske kisline (ALA) in porfobilinogena (PBG). Ti se kopičijo v telesu, kar vodi do značilnih znakov in simptomov bolezni (4). Mutacije so avtosomno dominantne. Čeprav moški in ženske enako pogosto podedujejo mutacije, večinoma zbolevajo ženske v rodni dobi. V Evropi in Ameriki je razširjenost (prevalenca) mutacij približno 1/2000 oseb. Akutni napadi se pojavijo pri manj kot 10 % ogrožene populacije zaradi vpliva okoljskih dejavnikov, zdravil, ki inducirajo citokrom P450, prehrane in hormonskih nihanj (5, 6). Razširjenost akutne intermitentne porfirije v Evropi ocenjujejo na 1/75.000, medtem ko je porfirija variegata približno dvakrat redkejša, dedna koproporfirija pa izjemno redka (7).

KLINIČNA SLIKA

Večina bolnikov je ženskega spola, bolezen pa se redko pojavi pred puberteto ali po menopavzi (8). Pred nastopom osrednjih simptomov se pojavijo prodromi, ki lahko trajajo več dni, in se najpogosteje kažejo kot utrujenost, nemir, nespečnost in motnje koncentracije (9), ki jim sledijo postopno vse hujše bolečine v trebuhu, slabost, bruhanje in subtilni nevro-

loški znaki, kot so šibkost ali bolečine v udih, periferna nevropatija, anksioznost, zmedenost in halucinacije. Generalizirane konvulzije se pojavijo pri 20 % bolnikov, nevrološki simptomi pa lahko napredujejo v parezo udov in paralizo dihalnih mišic. Bolniki imajo pogosto dolgotrajno hipertenzijo in/ali kronično ledvično bolezen. Zaradi spremljajočih psihiatričnih simptomov je večje tveganje samomorilnosti.

Ob kliničnem pregledu lahko ugotavljamo tahikardijo, hipertenzijo in potenje (10, 11).

Laboratorijske preiskave ne pokažejo posebnosti, z izjemo hiponatremije in blago patološkega hepatograma.

Pregledna slika trebuha lahko pokaže paralitični ileus. Analgetiki, vključno z opioidi, bistveno ne zmanjšajo bolečine (10).

Diferencialna diagnoza

Zaradi nespecifičnih simptomov AIP pogosto spregledamo in napačno opredelimo kot akutno bolečino v trebuhu, sindrom razdražljivega črevesa, Crohnovo bolezen, endometriozo, dismenorejo, Guillain-Barréjev sindrom, polinevropatijo ali celo fibromialgijo in psihosomatsko bolezen (12).

Bolniki navadno prebolijo le nekaj akutnih epizod, ponavljajoče se akutne napade pa ima manj kot 10 % bolnikov. V večini primerov AIP odkrijemo zelo pozno, lahko celo 15 let od nastopa prvih simptomov. Zaradi akutne hude bolečine v trebuhu imajo bolniki pogosto kirurški poseg. Približno 15 % bolnikov je imelo pred diagnozo AIP kolektomijo, 13 % apendektomijo in kar 18 % histerektomijo (13).

DIAGNOSTICIRANJE

Barva svežega urina pri akutni porfiji ni spremenjena, saj sta δ-aminolevulonska kislina in porfobilinogen brezbarvna. Le če je urin pri sobni temperaturi daljši čas izpostavljen svetlobi, se zaradi porfirinom podobnim pigmentom obarva temno rdečkasto. Pri akutnih porfirijah je koncentracija porfobilinogena v urinu zvišana več kot desetkrat nad normalno vrednostjo. Najdba je specifična in zadošča za uvedbo zdravljenja. 24-urno zbiranje urina med akutno epizodo ni potrebno, saj zadostuje določitev koncentracije porfobilinogena (in kreatinina) v naključnem urinskem vzorcu.

Ob sumu na AHP lahko z analizo naključnega vzorca urina na PBG in ALA izključimo ali potrdimo diagnozo AHP. Optimalni čas za analizo je med napadom, a lahko testiranje ob sumu na AHP opravimo kadar koli. Glede na rezultat biokemijske analize bolezen dodatno potrdimo z genetskim testiranjem (10).

ZDRAVLJENJE

Bolniki z znano AHP se morajo izogibati sprožilnim dejavnikom, kajenju, stresu, alkoholu, posebnim dietam, stradanju, okužbam in določenim zdravilom (Tabela 1). Posebno pozornost moramo posvetiti hormonskim spremembam med menstruacijskim ciklom.

Ob zdravljenju akutne epizode moramo prepoznati in prekiniti uporabo zdravil, ki lahko sprožijo ali poslabšajo bolezen (Tabela 1). Bolniki potrebujejo infuzijo (najbolje 10-odstotne glukoze v 0,45 % NaCl), antiemetik in analgetik ter po potrebi zdravila za obvladovanje krčev.

Za specifično zdravljenje akutne porfirije uporabljamo hemin (Normosang, Orphan Europe), ki inhibira pot sinteze hema in ustavi nastajanje nevrotoksičnih presnovkov. Zdravilo prejmejo bolniki enkrat na dan v odmerku 3–4 mg/kg telesne mase v 30-minutni infuziji. Bolečine in slabost izzvenijo po štirih dneh. Bolnik lahko odide domov, ko ne potrebuje analgetikov in je sposoben zadostnega energijskega vnosa. Učinek zdravljenja s heminom ni takojšen. Hemin ni indiciran za preprečevanje akutnih napadov, kronične bolečine ali za izboljšanje kakovosti življenja. Zaradi večjega tveganja prevelikega odmerjanja železa in nastanka tromboz je preventivno zdravljenje s heminom prepovedano.

Kot zadnja možnost zdravljenja hudih oblik bolezni je do nedavnega bolnikom, odpornim na hemin, preostala le presaditev jeter (10).

V zadnjem letu je tudi v Sloveniji na voljo novo zdravljenje AHP z givosiranom, dvoverižno majhno interferenčno ribonukleinsko kislino (siRNA), ki povzroči razgradnjo ALAS1, informacijske ribonukleinske kisline (mRNK) v hepatocitih, preko interference z RNK, kar povzroči znižanje ALAS1mRNK ter s tem znižanje ravni nevrotoksičnih intermediatov ALA in porfobilinogena PBG v krvnem obtoku, ključnih povzročiteljev napadov in drugih simptomov AHP.

V raziskavi Envision, nadzorovani s placebom, so pri bolnikih z AHP, ki so enkrat na mesec prejemali givosiran v odmerku 2,5 mg/kg, 14 dni po prvem odmerku opazili mediano zmanjšanje vrednosti urinske ALA za 83,7 % in PBG za 75,1 % glede na izhodiščne vrednosti. Največje zmanjšanje ravni ALA in PBG so dosegli pri približno tretjem mesecu, in sicer za 93,8 % pri ALA ter za 94,5 % pri PBG, in se po nadaljnjem zdravljenju ni spremenilo.

Štiriindevetdeset bolnikov z AHP (89 bolnikov z AIP) je šest mesecev enkrat mesečno prejemalo subkutano injekcijo givosirana v odmerku 2,5 mg/kg ali placeba. Med raziskavo je bila dovoljena uporaba hemina za zdravljenje akutnih napadov porfirije. Mediana starosti bolnikov v raziskavi je bila 37,5 leta (19–65 let), 89,4 % je bilo žensk. V skupinah ni bilo razlik glede števila predhodnih akutnih napadov, predhodnega zdravljenja s heminom ter uporabe analgetikov in/ali opioidov.

Givosiran je v primerjavi s placebom zmanjšal število akutnih napadov za 74 % pri vseh vnaprej določenih skupinah, vključno s starostjo, spolom, raso, regijo in izhodiščnim indeksom telesne mase (ITM). Potreba po zdravljenju s heminom se je zmanjšala za 77 %, potreba po uporabi opioidnih zdravil pa za 33 %.

V bolnikovi celoviti oceni sprememb v zdravstvenem stanju (*angl.* patient global impression of change, PGIC) je večji delež bolnikov z AHP, ki so se zdravili

Tabela 1. Varnost zdravil pri bolnikih z akutno porfirijo

Zdravilo	Varnost uporabe
fenitoin	ni varna
barbiturati	ni varna
valproat	ni varna
karbamazepin	ni varna
primidon	ni varna
klonazepam	verjetno ni varna
lorazepam	verjetno varna
gabapentin	verjetno varna
magnezijev sulfat	verjetno varna
propofol	verjetno varna
ketamin	verjetno ni varna
oralni kontraceptivi	ni varna
progestini	ni varna
spironolakton	ni varna
furosemid	verjetno varna
klorpromazin	verjetno varna
ibuprofen	verjetno varna
opiatni analgetiki	verjetno varna
difenhidramin	verjetno varna
litij	verjetno varna
aminoglikozidi	verjetno varna
penicilinski antibiotiki	verjetno varna
sulfonamidi	verjetno ni varna
eritromicin	verjetno ni varna
flukonazol	verjetno ni varna
nitrofurantoin	verjetno ni varna
rifampicin	verjetno ni varna
varfarin	verjetno varna

Opomba: Manj varna zdravila naj bi previdno uporabili le ob odsotnosti manj tveganih načinov zdravljenja, za kratek čas in le za nujno zdravljenje. Podrobnejše zbirke zdravil so dosegljive na: http://porphyriadrugs.com, http://www.porphyriafoundation.com in http://www.drugs-porphyria.org

z givosiranom (61,1 %), od pričetka raziskave ocenil svoje splošno stanje kot 'bistveno izboljšanje' ali 'precejšnje izboljšanje' v primerjavi z bolniki, ki so prejemali placebo (20 %) (13).

NAPOVED IZIDA BOLEZNI IN KAKOVOST ŽIVLJENJA

Pred letom 1980 je bila smrtnost bolnikov z AHP do 25 % (11), a sta zgodnje prepoznanje bolezni in specifično zdravljenje močno izboljšali napoved izida bolezni. Akutna porfirija je povezana z večjim tveganjem kronične ledvične bolezni in okvare jeter, večje pa je tudi tveganje raka jetrnih celic (14).

Nepredvidljivi, akutni in izčrpavajoči napadi so lahko življenjsko nevarni, zato bolniki v obdobju med posameznimi napadi doživljajo izrazit strah in tesnobo ter kronične simptome, ki pomembno vplivajo na vsakodnevno delovanje in kakovost življenja (QoL). Bolniki z AHP se na lestvici QoL uvrščajo na podobno mesto kot bolniki s kroničnimi boleznimi, kot sta ulcerozni kolitis in kronična obstruktivna pljučna bolezen (15).

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Endoskopska papilarna dilatacija z balonom velikega premera – Retrospektivna analiza primerov na Kliničnem oddelku za gastroenterologijo

Endoscopic papillary large balloon dilatation – Retrospective analysis of cases at the Department of Gastroenterology

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Ključne besede: *balonska dilatacija, EPLBD, ERCP, zapleteni žolčni kamni*

Keywords: *balloon dilatation, EPLBD, ERCP, difficult common bile duct stones*

IZVLEČEK

Izhodišče. Endoskopska papilarna dilatacija z balonom velikega premera (EPLBD) je zelo uspešna metoda za odstranjevanje velikih kamnov v žolčevodu. Za odstranitev kamna so občasno potrebne dilatacije na zelo velike premere. Namen naše analize je bil oceniti varnost pri EPLBD zelo velikih premerov (15 mm in več) ter uspešnost posega.

Metode. V retrospektivno analizo smo vključili bolnike z EPLBD premera od 15 do 20 mm, ki so bili obravnavani na Kliničnem oddelku za gastroenterologijo, UKC Ljubljana, med januarjem 2018 do vključno julijem 2023.

ABSTRACT

Background. Endoscopic papillary large balloon dilatation (EPLDB) is a highly successful method for the removal of large bile duct stones. Very large diameter dilatations are occasionally required to remove the stone. The goal of our analysis was to evaluate the safety of EPLBD of very large diameters (15 mm and more) and the success of the procedure.

Methods. In our analysis, we included patients, who underwent EPLBD with a diameter from 15 to 20 mm and were treated in the Department of Gastroenterology, University Medical Centre Ljubljana, between January 2018 and July 2023.

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Rezultati. Retrospektivna analiza je vključevala 41 bolnikov, pri katerih je bilo skupno opravljenih 42 dilatacij z balonom velikega premera. Velikost dilatacijskega balona se je gibala ob 15 do 19 mm. Pri 81 % je prišlo do uspešne odstranitve kamnov ob preiskavi, preostali so za dokončno odstranitev potrebovali ponoven ERCP. Pri nobenem od bolnikov po EPLBD nismo ugotavljali zapletov v smislu pankreatitisa, krvavitve ali perforacije.

Zaključek. Ob ustrezni indikaciji je EPLBD varna in uspešna metoda zdravljenja.

Results. Our retrospective analysis consisted of 41 patients, of whom 42 EPLBD were made. The diameter of the dilatation balloon ranged from 15 to 19 mm. In 81% of the patients, there was a successful extraction of the common bile duct stones, in other cases a second ERCP was needed. No complications in terms of pancreatitis, bleeding or perforation were identified in any of the patients after EPLBD.

Conclusions. EPLBD is a safe and successful method when used for proper indications.

UVOD

Žolčne kamne v žolčniku pogosto najdemo v klinični praksi s prevalenco v razvitih državah 10–15 %. Bolniki lahko ostajajo asimptomatski vse življenje, toda v 10–25 % se lahko pojavijo simptomi kot so biliarne kolike ali komplikacije kot npr. biliarna obstrukcija (1). Endoskopska retrogradna holangiografija (ERCP) je metoda izbora za terapevtsko intervencijo v primeru pasaže kamnov v skupni žolčevod (2). Večina kamnov v skupnem žolčnem vodu je med ERCP odstranjenih z endoskopsko sfinkterotomijo (EST) ter ekstrakcijskim balonom ali košaro, toda 10–15 % kamnov je lahko prevelikih oziroma prezapletenih za uporabo standardnih tehnik (3, 4). Zapleteni žolčni kamni so opredeljeni s premerom več kot 1,5 cm, dodatno pa še glede na število, obliko, samo lokacijo ter anatomske faktorje pacienta, toda popolnoma jasna definicija zaenkrat ni podana (1, 2). Svetovna priporočila pri bolnikih z zapletenimi žolčnimi kamni svetujejo EST, ki ji sledi endoskopska papilarna dilatacija z balonom velikega premera (EPLBD) od 12 do 20 mm. V primeru koagulopatije svetujejo le EPLBD brez EST (1). V večini študij so prikazali uspešnost ter varnost uporabe teh metod (2). Pri obravnavi bolnikov, ki imajo zapletene žolčne kamne, smo v našem centru pri naši analizi želeli predstaviti uporabnost in varnostni profil EPLBD.

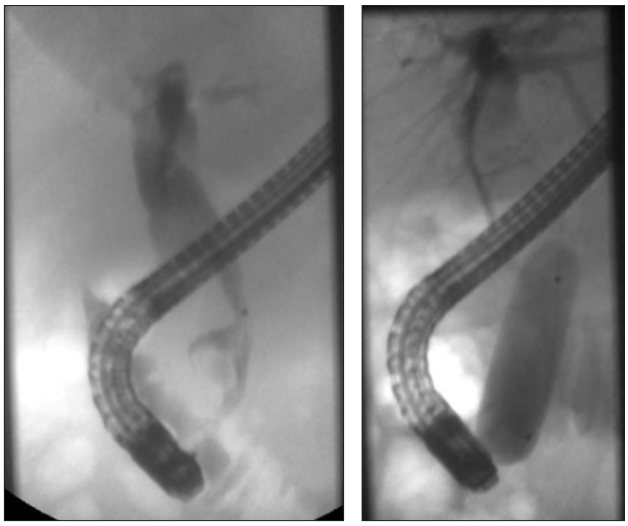
METODE

Opravili smo retrospektivni pregled medicinske dokumentacije bolnikov z opravljeno balonsko dilatacijo papile, ki smo jih obravnavali na Kliničnem oddelku za gastroenterologinjo od januarja 2018 ter vključno julija 2023. V kohorti smo sprva pridobili 144 bolnikov, ki so imeli skupno opravljenih 154 dilatacij. Iz kohorte smo izključili bolnike, ki niso imeli opravljene dilatacije z velikim premerom, ki smo jo opredelili kot dilatacijo 15–20 mm. Končno kohorto je tako predstavljalo 41 bolnikov, pri katerih je bilo opravljenih 42 EPLBD (Slika 1 in Slika 2).

Primaren cilj je bilo analizirati velikosti premera dilatacij, uspešnosti odstranitve žolčnih kamnov iz skupnega žolčnega voda ter morebitnih takojšnjih ali kasnejših zapletov po ERCP. Dodatno smo analizirali, ali so imeli med EPLBD opravljeno tudi EST ter ali so po EPLBD potrebovali ponoven ERCP.

REZULTATI

Analiziranih je bilo 41 bolnikov, od tega 25 žensk (61 %) in 16 moških (39 %). Starost ob opravljenem ERCP se je gibala od 37 do 91 let, povprečna starost je bila 73 let. Pri 40 bolnikih je bil opravljen enkraten poseg z EPLBD, v enem primeru pa je bil poseg opravljen dvakrat. Skupno smo tako analizirali 42 primerov EPLBD.



Slika 1. in Slika 2. ERCP – prikazan primer EPLBD

Razpon premera dilatacijskega balona v naših primerih se je gibal od 15 do 19 mm, predominiral je premer 15 mm (Tabela 1).

Tabela 1. prikaz števila dilatacij glede na premer dilatacijskega balona

Premer dilatacijskega balona	Število dilatacij
15 mm	25
15,5 mm	2
16 mm	2
16,5 mm	1
17 mm	3
18 mm	7
19 mm	2
Skupno	**42**

V 34 primerih (81 %) so bili žolčni kamni po opravljeni dilataciji uspešno odstranjeni. V 14 primerih (33 %) je bil po opravljeni EPLBD potreben ponoven ERCP. Za razrešitev zaostalih žolčnih kamnov v 8 primerih (19 %), v 6 primerih (14 %) pa je bil ponoven ERCP potreben tudi po uspešni ekstrakciji kamnov.

Ob analizi bolnikov, ki so potrebovali ponoven ERCP, kljub prvotni uspešni odstranitvi žolčnih kamnov ob EPLBD, je bil pri dveh bolnikih ugotovljen recidiv žolčnih kamnov v skupnem žolčevodu, pri dveh je bil postavljen sum na recidiv, ki smo ga na ERCP ovrgli. En bolnik je imel zaradi recidivnih žolčnih kamnov v skupnem žolčevodu nadaljnje opravljenih več ERCP in bil v končni fazi predlagan za konstukcijo holedoho-jejunalne anastomoze. Pri enem bolniku pa smo nadaljnje ugotovili stenozo žolčevoda in potrdili adenokarcinom papile Vateri.

V 62 % (26 primerih) so imeli bolniki med ERCP opravljeno tudi EST. V ostalih primerih smo jo opravili že ob predhodnih ERCP.

Ob analizi smo zabeležili le en zaplet in sicer odtrganje košare ob poskusu litotripsije kamna v žolčevodu s potrebo po urgentni holecistektomiji. Zaplet ni bil posledica balonske dilatacije. Ne glede na premer dilatacijskega balona drugih zgodnjih ali poznih zapletov, predvsem v smislu krvavitve, pankreatitisa ali perforacije nismo ugotovili.

RAZPRAVA

EPLBD je metodo, ki so jo prvič opisali Ersoz in sod. leta 2003 za uporabo pri ekstrakciji večjih žolčnih kamnov, ki jih s standardnimi metodami niso mogli odstraniti. Pri endoskopski balonski dilataciji papile uporabljamo balone premera 4–10 mm, medtem ko se pri EPLBD uporabljajo baloni premera 12–20 mm (5–6). EPLBD lahko opravimo po opravljeni dolgi ali kratki endoskopski sfinkterotomiji, toda zaradi možnosti zapletov s krvavitvijo in perforacijo svetujemo krajšo EST. V praksi se mora endoskopist večkrat odločiti za EPLBD že po opravljeni sfinkterotomiji zaradi neuspešne ekstrakcije kamnov. EPLBD z EST je v svetu postala široko uporabljana metoda (1).

Glede na literaturo se podatki o uspešnosti ekstrakcije kamnov ob kombinaciji EST in EPLBD iz skupnega žolčnega voda gibajo med 72,7 % do 100 % (7). V naši analizi smo uspešnost ekstrakcije dosegli v 81 %, kar se sklada s podatki v literaturi.

Kombinacija EST in EPLBD je upoštevajoč literaturo superiorna glede uspešnosti odstranitve velikih kamnov v primerjavi z drugimi intervencijami. Edino

holangioskopija z litotripsijo je pokazala boljše rezultate, toda omejujoč dejavnik na tem mestu je njena dostopnost, cena in dolga učna krivulja (2, 8).

Premer dilatacije je najpomembnejši faktor za uspešnost odstranitve kamnov pri kombinaciji EST z EPLBD. Z večanjem odprtine ampule se težavnost odstranitve kamnov manjša, toda ob tem prihaja do večjega tveganja za zaplete (9, 10). Jasnih kriterijev, za katero velikost dilatacijskega balona se odločiti, nimamo. V večini objavljenih študij se je kot kriterij odločitve glede velikosti uporabil premer distalnega žolčevoda (1).

Več retrospektivnih analiz je prikazalo ugoden varnostni profil kombinacije EST s EPLBD z manj zapleti v primerjavi s preostalimi preiskavami, vključno s perforacijo ter post-ERCP pankreatitisom (2, 4). Tveganje za perforacijo sicer naraste, če uporabimo dilatacijski balon z večjim premerom kot je premer distalnega žolčevoda ter v primeru strikture (1). Tudi naši podatki so prikazali varnost preiskave, saj z izjemo zapleta z odtrganjem košare pri poskusu litotripsije, drugih zapletov, ne glede na premer dilatacije, nismo beležili.

ZAKLJUČKI

EPLBD je varna in učinkovita metoda, ki skupaj z EST predstavlja prvi korak pri obravnavi zapletenih žolčnih kamnov.

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Slovenian Journal of Digestive Diseases / Gastroenterolog

NAVODILA AVTORJEM ZA PRIPRAVO PRISPEVKOV

Slovenian Journal of Digestive Diseases / Gastroenterolog je zunanje recenzirana strokovna revija, ki izhaja tri do štirikrat letno. V reviji so objavljeni raziskovalni članki, prikazi primerov, strokovni članki s področja bolezni prebavil in interne medicine ter nacionalne smernice.

1.0 Splošna načela

Uredništvo sprejema prispevke, ki še niso bili objavljeni in ne bodo objavljeni kje drugje. Izjemoma lahko uredništvo sprejme v objavo že objavljen prispevek, za katerega je koristno, da doseže ciljni krog bralstva (npr. klinične smernice in priporočila), pri čemer morajo avtorji to uredništvu sporočiti ob oddaji prispevka ter zagotoviti pristanek odgovornega urednika revije, kjer je prispevek že bil objavljen.

Raziskovalni članki in prikazi primerov naj bodo napisani **v angleškem jeziku**, pri čemer jih mora obvezno spremljati prevod naslova ter Abstracta in Keywords (kot Izvleček in Ključne besede) v slovenščini. Tujim piscem bomo Abstract in Keywords prevedli v slovenski jezik v uredništvu revije.

Strokovni in pregledni članki in nacionalne smernice naj bodo napisani **v slovenščini**, saj so namenjeni domačim bralcem. V angleščino naj bodo prevedeni samo Izvleček in Ključne besede (kot Abstract in Keywords).

2.0 Oblikovanje prispevka

2.1. Struktura prispevka

Splošna navodila za pisanje naj sledijo navodilom Britanskega medicinskega združenja (BMJ Journal). Navodila najdete na spletnem mestu BMJ Journals na povezavi https://authors.bmj.com/.

Pisava v prispevku naj bo Times New Roman, velikost črk 12 pt, razmik med vrsticami 1,5 in širina robov 2,5 cm. Kraticam se izogibajte. Če so nujne, naj bodo izpisane, ko se prvič pojavijo. [Primer: Kronična vnetna črevesna bolezen (KVČB)].

Priporočamo, da za pisanje prispevka uporabite Wordov dokument **Gastroenterolog–Predloga za prispevek.docx**, ki že vsebuje vse zgoraj navedene nastavitve in hkrati tudi osnovne priporočene stile ter elemente za oblikovanje strukture prispevka. Predloga je dosegljiva tudi na članski spletni strani **Navodila avtorjem** lahko pa za predlogo zaprosite uredništvo revije preko elektronske pošte SloJouDD@gmail.com.

2.2. Prispevke pripravite in oddajte z naslednjimi elementi:

a. Spremni dopis,
b. Naslovna stran,
c. Izvleček,
d. Glavno besedilo,
e. Tabele in slike,
f. Reference,
g. Izjava avtorjev.

a. Spremni dopis

V spremnem dopisu na kratko razložite **temo** vašega prispevka. Tukaj tudi zapišete, če je bilo delo že objavljeno v delni obliki na kakšnem strokovnem srečanju. Pri prispevkih, ki obravnavajo raziskave na ljudeh ali živalih mora biti v poglavju Metode navedeno ustrezno soglasje pristojne komisije oziroma ustanove, da je raziskava etično sprejemljiva v skladu z načeli Helsinške deklaracije oziroma ostalimi pomembnimi dokumenti, ki obravnavajo etičnost biomedicinskih raziskav.

b. Naslovna stran:

Naslovna stran naj vsebuje **slovenski in angleški naslov**. Iz naslova mora biti razvidno glavno sporočilo članka.

Navedite vse **avtorje** s svojimi akademskimi in strokovnimi naslovi ter popoln naslov ustanove od koder posamezen avtor prihaja in kjer je delo nastalo.

Vodilni avtor je postavljen na zadnje mesto in je ločen z besedico 'in' oz. 'and'.

Prvi avtor je praviloma eden, če pa sta dva, naj bosta imeni obeh prvih avtorjev podčrtana. V tem primeru naj bo na naslovni strani tudi dodana opomba 'prva avtorja sta prispevala enakovredno' ('both authors equally contributed').

Korespondenca je praviloma vezana na vodilnega avtorja. Izjemoma je lahko vezana na prvega avtorja. Na naslovni strani naj bo jasno zapisano, na katerega avtorja bo vezana korespondenca (torej kdo bo korespondenčni avtor). Poleg akademskega in strokovnega naslova ter popolnega naslova ustanove od koder korespondenčni avtor prihaja, navedite tudi njegov e-mail naslov, na katerega se lahko avtorji po potrebi obrnejo glede dodatnih vprašanj v zvezi s prispevkom.

c. Izvleček

V izvlečku napišite **glavno sporočilo članka**. Napisano naj bo preprosto, v dobro razumljivem jeziku. Napisano naj bo tako, da ga razume širok krog bralcev.

Raziskovalni članki naj imajo **strukturiran** izvleček.

Ostali članki (prikazi primerov, nacionalne smernice) pa naj imajo **nestrukturiran** izvleček.

– **Navodila za strukturiran izvleček:**

Obsega lahko do 250 besed. Kratice so nezaželene, v podpoglavju Zaključki pa prepovedane. V izvlečku navedite predvsem nove ugotovitve. Izvleček ima naslednja poglavja: Izhodišče (Background), Namen (Aim), Material in metode (Material and Methods), Rezultati (Results), Zaključek (Conclusions), Ključne besede (Keywords).

Izvleček (Abstract) in Ključne besede (Keywords) je potrebno prevesti v slovenščino. Prevod naj bo natančen.

Poglavja strukturiranega izvlečka:

Izhodišče (Background):

Opišite problem, ki ga naslavlja delo. Razložite, kaj je neznano na področju dela. Navedete dileme, ki se jih loti vaše delo.

Namen (Aim):

Opišite namen dela, torej kaj poskušate v svojem članku razjasniti oziroma proučiti in se navezuje neposredno na poglavje Izhodišče.

Material in metode (Material and Methods):

Opišite metode, ki ste jih uporabili v svojem članku. To poglavje naj bo kratko, saj jih natančen bralec lahko prebere kasneje v članku.

Rezultati (Results):

Temu poglavju namenite največ prostora. Podajte rezultate, ki so pomembni za razumevanje glavnega sporočila članka. Rezultate napišite natančno (povprečna vrednost s standardnim odklonom ali intervalom zaupanja, mediana vrednost z interkvartilnim razponom ...). Dodajte vrednosti statistične signifikance oziroma intervala zaupanja.

Zaključek (Conclusions):

Na kratko navedite glavno sporočilo in ugotovitev svojega članka. Napišete samo tiste zaključke, ki izvirajo iz vaših rezultatov. Kratice so v tem delu prepovedane.

Ključne besede (Keywords):

Navedite 4-7 ključnih besed (besed, ki so v naslovu ne uporabite, saj te iskalniki že avtomatsko prepoznajo).

– **Navodila za nestrukturiran izvleček:**

Nestrukturiran izvleček naj vsebuje do 250 besed. Nestrukturiranega izvlečka ne delite na podpoglavja, ampak ga zapišete kot enotno besedilo. V tem kratkem besedilu poskušajte opisati svoje glavne najdbe oz. sporočilo vašega članka.

Izvleček je potrebno prevesti v angleščino.

Na koncu navedete Ključne besede v slovenskem in angleškem jeziku (Keywords).

d. Glavno besedilo:

Glavno besedilo **raziskovalnih člankov** naj **ima naslednja poglavja**: *Uvod (Introduction)*, *Material in metode (Materials and Methods)*, *Rezultati (Results)*, *Razprava (Discussion)*.

Znotraj teh poglavij lahko avtorji po svoji presoji naredijo podpoglavja, če s tem dosežejo večjo preglednost.

Struktura ostalih člankov (prikazi primerov, nacionalne smernice, ...) **ni predpisana** in jo lahko pisec prilagodi po svoji potrebi na način, ki je najbolj primeren za določen članek.

Poglavja raziskovalnega članka:

Uvod (Introduction):

Razložite problem, ki se ga članek loteva. Upoštevajte, da gre za bralce z veliko predhodnega znanja, zato ni potrebno razlagati tistega kar pričakujemo, da naši bralci dobro poznajo. Predstavite zadnja dognanja iz literature in morebitne pomanjkljivosti. Na koncu uvoda v ločenem odstavku razložite kakšen je namen vašega dela.

Material in metode (Materials and Methods):

Natančno opišete metode in proučevane bolnike. Priporočamo delitev v podpoglavja, saj tako močno olajšate branje članka. Opišete statistične metode. Opišete in ustrezno citirate dovoljenja etične komisije. Opišite značilnosti izvedbe raziskave, vzorec ki ga proučujete (npr. randomizacijo, dvojno slepi poskus, navzkrižno testiranje, testiranje s placebom, itd.), standardne vrednosti za teste, časovni odnos (prospektivna, retrospektivna študija).

Rezultati (Results):

Opišite natančno in analizirajte z ustreznimi statističnimi testi. Zaželeno je, da čim več rezultatov prikažete v obliki tabel in slik. Tabele in slike naj, če je le mogoče, ne vsebujejo kratic. Lahko so barvne, saj bodo tako dobro vidne v elektronski obliki. Upoštevajte pa tudi, da bo tiskana verzija črnobela. Tabele in slike smiselno vstavite v besedilo prispevka – oštevilčite jih ločeno po vrstnem redu, na vsako tabelo in sliko se je treba sklicevati v besedilu. Vsaka tabela in slika naj imata naslov v slovenskem in angleškem jeziku.

Razprava (Discussion):

Vsebuje komentarje vseh vaših rezultatov. Svoje rezultate primerjate z literaturo in poskušajte razložiti morebitne razlike med svojimi rezultati in rezultati drugih. V zadnjem odstavku povzamete glavno sporočilo in nakažete nadaljnje poti raziskovanja svojega raziskovalnega problema.

e. Tabele in slike

Tabele in slike naj bodo narejene na tak način, da jih bo bralec razumel brez branja celotnega članka. Če je le mogoče, naj bodo brez kratic. Če so kratice res nujne, naj bodo razložene ob vznožju tabele ali slike.

Tabele (Tables):

Vsaka tabela naj ima svoj naslov, ki ga zapišete nad tabelo. V primeru, da tabela potrebuje opombe, jih zapišete v vznožje tabele. Tabele so vstavljene v besedilo članka in so označene po vrsti, glede na vrstni red pojavljanja v besedilu (slovenski članki: Tabela 1, Tabela 2, ...; angleški članki: Table 1, Table 2, Table 3 ...). Tabele naj bodo oblikovane kot tabele v urejevalniku besedila (npr. preko opcije Insert Table). Lahko jih tudi prenesete iz programa Excel kot tabelo. Pri tem je pomembno, da jih NE prenesete kot sliko, saj jih v tem primeru ne moremo oblikovati. Slovenski članki naj imajo poleg slovenskega naslova tabele tudi angleški prevod naslova tabele (da ga lahko razumejo tujci). Angleški članki ne potrebujejo prevoda naslova tabele v slovenščino.

Slike (Figures):

Slike priložite kot ločene datoteke. Slike naj bodo v formatu visoke resolucije (npr. .jpg ali .tif v resoluciji 300 dpi). V tekstu jasno označite, kje naj se pojavi določena slika. To storite tako, da v oklepaju na želenem mestu v tekstu, navedete zaporedno številko slike (slovenski članki: Slika 1, Slika 2....; angleški članki: Figure 1, Figure 2 ...). Vsaka slika potrebuje besedilo k sliki (naslov in kratko razlago). Besedilo k sliki zapišete v tem poglavju za vsako sliko posebej. Slovenski članki naj imajo poleg slovenskega besedila k sliki tudi angleški prevod besedila k sliki (da ga lahko razumejo tujci). Angleški članki ne potrebujejo prevoda besedila k sliki v slovenščino.

f. Reference:

Vsako navajanje trditve ali dognanj drugih morate podkrepiti z referenco, na katero se v besedilu sklicujte z zaporedno arabsko številko v oklepaju. Za citiranje uporabite stil citiranja Britanskega zdravniškega združenja (ang. BMJ reference style). Natančna navodila in primere citiranja najdete na njihovi spletni strani 'BMJ Author Hub' oz. na naslednji povezavi: https://authors.bmj.com/writing-and-formatting/formatting-your-paper/.

Priporočamo uporabo orodja za citiranje literature (npr.: Zotero, Mendeley, EndNote ...), saj je tako možnost napake manjša. V orodju za citiranje uporabite slog 'BMJ'. Pred oddajo prispevka prosimo preverite še ročno, če so citati v skladu z navodili 'BMJ'. Pri citiranju navedete prve tri avtorje. Če je avtorjev več dodate na koncu 'et al'.

Nekateri primeri pravilnega citiranja (več na spletni strani 'BMJ'):

Članek objavljen v tiskani reviji:

1. Koziol-Mclain J, Brand D, Morgan D, et al. Measuring injury risk factors: question reliability in a statewide sample. Inj Prev 2000; 6:148-50.

Članek objavljen v spletni verziji revije (ki še ni objavljen v tiskani obliki):

2. Dark P, Dunn G, Chadwick P, et al. The clinical diagnostic accuracy of rapid detection of healthcare-associated bloodstream infection in intensive care using multipathogen real-time PCR technology. BMJ Open 2011; 1:e000181. doi: 10.1136/bmjopen-2011-000181.

Članek v suplementu:

3. Mugosa A, Cizmovic M, Lakovic T, et al. Accelerating progress on effective tobacco tax policies in Montenegro. Tobacco Control 2020; 29:s293-s299.

Izvleček:

4. Bricca A, Swithenbank Z, Scott N, et al. 21 Predictors of recruitment in randomised controlled trials of smoking cessation: meta-regression analyses from the IC-SMOKE systematic review project. Abstract competing for the 'doug altman scholarship'. BMJ Evidence-Based Medicine 2019; 24:A52-A53.

Knjiga:

5. Howland J. Preventing Automobile Injury: New Findings From Evaluative Research. Dover, MA: Auburn House Publishing Company 1988:163-96.

Poglavje v knjigi:

6. Nagin D. General deterrence: a review of the empirical evidence. In: Blumstein A, Cohen J, Nagin D, eds. Deterrence and Incapacitation: Estimating the Effects of Criminal Sanctions on Crime Rates. Washington, DC: National Academy of Sciences 1978:95-139.

Elektronski vir:

7. Extraintestinal Complications of IBD. Crohns Colitis Found. https://www.crohnscolitisfoundation.org/what-is-ibd/extraintestinal-complications-ibd (accessed 7 Dec 2022).

g. Izjava avtorjev

Prispevku, namenjenemu za objavo, mora biti priložena 'Izjava avtorjev prispevkov', ki jo najdete na spletni strani Izjava avtorjev ali pa za predlogo zaprosite uredništvo preko elektronske pošte SloJouDD@gmail.com.

Izjavo naj podpišejo vsi avtorji (lastnoročno ali digitalno), izpolnjeno in podpisano izjavo pa priložite članku, ko ga pošiljate uredništvu v recenzijo. Navodila za popolnitev in pošiljanje izjave se nahajajo v predlogi izjave in na spletni strani.

3.0 Oddaja prispevkov

Prispevke pošljite po elektronski pošti na naslov:

SloJouDD@gmail.com

ali na naslov

Uredništvo Slovenian Journal of Digestive Diseases / Gastroenterolog
Japljeva ulica 2, 1000 Ljubljana

Prispevku priložite vse potrebne priloge naštete v navodilih avtorjem.

4.0 Uredniško delo

Odgovorni urednik vsak oddani prispevek pregleda in se odloči o uvrstitvi v uredniški postopek. Prispevke, uvrščene v uredniški postopek, posreduje drugim članom uredniškega odbora, ki poskrbijo za tehnične in slogovne popravke. Popravljen prispevek nato vrnejo avtorjem v pregled. Vsebino prispevka ocenita dva strokovna recenzenta, ki ju avtorji ne poznajo, prav tako strokovna recenzenta nista seznanjena z identiteto avtorjev. Prispevek pregledata tudi lektorja za slovenski in angleški jezik. Po končanem uredniškem delu dobi avtor svoje delo v pregled, odobritev ter upoštevanje popravkov.

Pred objavo avtor dobi po elektronski pošti v vpogled tudi delovno pdf datoteko s prelomom oblikovanega članka (krtačni odtis), vendar na tej stopnji upoštevamo samo popravke tiskovnih napak in pa opozorila na morebiti manjkajoče ali neustrezno postavljene slike ali tabele ali neustrezne sklice na elemente, vsebovane v prispevku. Končna verzija članka lahko oblikovno nekoliko odstopa zaradi morebitne dodatne prilagoditve prelomu.

Odgovor z morebitnimi pripombami je potrebno vrniti v dveh dneh, sicer razumemo, kot da se avtor s popravki in prelomom prispevka strinja.

Slovenian Journal of Digestive Diseases / Gastroenterolog

INSTRUCTIONS TO AUTHORS FOR THE PREPARATION OF PAPERS

Slovenian Journal of Digestive Diseases / Gastroenterolog is an externally peer-reviewed professional journal that is published three to four times a year. The journal publishes research articles, case reports, and professional articles in the field of gastrointestinal diseases and internal medicine, as well as national guidelines.

1.0 General principles

The editors accept contributions that have not yet been published and will not be published elsewhere. Exceptionally, the editors may accept for publication an already published article for which it is useful to reach the target readership (e. g. clinical guidelines and recommendations), whereby the authors must inform the editors of this when submitting the article and ensure the agreement of the editor-in-chief of the journal where the article has already been published.

Research articles and case reports should be written **in English** and must be accompanied by a translation of the title of the article, Abstract and Keywords (such as Izvleček and Ključne besede) in Slovenian. For foreign writers, the Abstract and Keywords will be translated into Slovenian by the editorial office of the magazine.

Professional and overview articles and national guidelines should be written **in Slovenian**, as they are intended for domestic readers. Only the Abstract and Keywords should be translated into English (as Abstract and Keywords).

2.0 Designing the contribution

2.1. Structure of the contribution

General guidelines for writing should follow the guidelines of the British Medical Association (BMJ Journal). Instructions can be found on the BMJ Journals website at https://authors.bmj.com/. The font in the paper should be Times New Roman, font size of 12 pt, line spacing of 1.5 and margin width of 2.5 cm. Avoid abbreviations. If they are necessary, they should be listed when they first appear. [Example: Chronic Inflammatory Bowel Disease (IBD)]. We recommend that you use the document 'Gastroenterolog - Article template.docx' to write the paper, which already contains all the settings mentioned above and the basic recommended styles for creating the document, as well as all the required elements of the paper's structure. The template is available on the website with the Instruction to Authors or you can request a template from the editors via email at SloJouDD@gmail.com.

2.2. Prepare and submit contributions with the following items:

a. Accompanying letter,
b. Cover, home page,
c. Extract,
d. The main text,
e. Tables and figures,
f. References,
g. Authors' statement.

a. Accompanying letter

Briefly explain **the topic** of your paper in the cover letter. You also write here if the work has already been published in partial form at a professional meeting. In the case of contributions dealing with research on humans or animals, the appropriate consent of the competent committee or institution must be stated in the chapter Methods, that the research is ethically acceptable by the principles of the Declaration of Helsinki or other important documents dealing with the ethics of biomedical research.

b. Cover/The Title page

The Cover/Title page should contain a **Slovenian and English title**. The main message of the article should be evident from the title. List all **authors** with their academic and professional titles and the full address of the institution where each author comes from and where the work was created. The **leading author** is placed last and is separated by the word 'and'. As a rule, the **first author** is one, but if there are two, the names of both first authors should be underlined. In this case, the note 'both authors equally contributed' should also be added to the title page. As a rule, **correspondence** is bound to the lead author. Exceptionally, it can be linked to the first author. The title page should clearly state to which author the correspondence will be attached (i. e. who will be the corresponding author). In addition to the academic and professional title and the full address of the institution from which the corresponding author comes, also indicate his e-mail address, to which the authors can contact, if necessary, regarding additional questions related to the contribution.

c. Extract

Write the **main message of the article** in the abstract. It should be written simply, in well-understood language. It should be written in such a way that it can be understood by a wide range of readers. Research articles should have a structured abstract. Other articles (case reports, national guidelines) should have an unstructured abstract.

– Instructions for structured extract:

It can contain up to 250 words. Abbreviations are undesirable and prohibited in the Conclusions subsection. In the subsection Abstract, mention only the new findings. The Abstract has the following chapters: Background, Aim, Material and Methods, Results, Conclusions, and Keywords. The Abstract and Keywords must be translated into Slovenian. The translation should be accurate.

Structured extract chapters:

Background:
Describe the problem the work addresses. Explain what is unknown in the field of work. You list the dilemmas your work tackles.

Aim:
Describe the purpose of the work, i. e. what you are trying to clarify or examine in your article and it is directly linked to the Background chapter.

Material and Methods:
Describe the methods you used in your article. This chapter should be kept short, as the careful reader can read them later in the article.

Results:
Give this chapter the most space. Give results that are relevant to understanding the main message of the article. Write the results exactly (average value with standard deviation or confidence interval, median value with interquartile range ...). Add statistical significance or confidence interval values.

Conclusions:
Briefly state the main message and conclusion of your article. You write only those conclusions that come from your results. Abbreviations are prohibited in this section.

Keywords:
Enter 4-7 keywords (do not use words that are in the title, as search engines already automatically recognize them).

– Instructions for unstructured extract:

The unstructured abstract should contain up to 250 words. Do not divide the unstructured extract into subsections; write it as a unified text. In this short text, try to describe your main findings or the message of your article. The abstract must be translated into Slovenian. In the end, you list keywords in English and Slovenian.

d. Main text:

The main text of **research articles** should **have the following chapters**: Introduction, Materials and Methods, Results, and Discussion. The authors can create subchapters within these chapters at their judgement if this achieves greater transparency.

The structure of other articles (case studies, national guidelines, etc.) **is not prescribed** and the writer can adapt it according to their needs in the way that is most suitable for a specific article.

Research paper chapters:

Introduction:

Explain the problem the article is addressing. Note that this is for readers with a lot of prior knowledge, so there is no need to explain what we expect our readers to know well. Present the latest findings from the literature and any shortcomings. At the end of the introduction, in a separate paragraph, explain the purpose of your work.

Materials and Methods:

You describe in detail the methods and the patients studied. We recommend dividing the article into sub-chapters, as this makes the article much easier to read. Describe statistical methods. You describe and properly cite the permissions of the ethics committee. Describe the characteristics of the research design, the sample you are studying (e. g. randomization, double-blind trial, cross-over testing, placebo testing, etc.), standard values for tests, and temporal relationship (prospective, retrospective study).

Results:

Describe accurately and analyse with appropriate statistical tests. It is desirable to display as many results as possible in the form of tables and figures. Tables and figures should, if possible, not contain abbreviations. They can be in colour, as they will be so easily visible in electronic form. Also, note that the printed version will be black and white. Insert tables and figures in the text of the paper in a meaningful way – number them separately in order, each table and figure must be referred to in the text. Each table and figure should have a title in Slovenian and English.

Discussion:

Contains comments on all your results. Compare your results with the literature and try to explain any differences between your results and those of others. In the last paragraph, you summarize the main message and indicate further ways of exploring your research problem.

e. Tables and figures

Tables and figures should be made in such a way that the reader can understand them without reading the entire article. If possible, they should be without abbreviations. If abbreviations are really necessary, they should be explained at the foot of the table or figure.

Tables:

Each table should have its title, which you write above the table. If the table needs notes, write them at the foot of the table. Tables are inserted into the text of the article and are marked by type, according to the order of appearance in the text (Slovene articles: Tabela 1, Tabela 2, ...; English articles: Table 1, Table 2, Table 3 ...). Tables should be formatted as tables in a text editor (e. g. via the Insert Table option). You can also download them from Excel as a table. It is important that you DO NOT download them as an image, as in this case, we cannot format them. In addition to the Slovenian table title, Slovenian articles should also have an English translation of the table title (so that foreigners can understand it). English articles do not need a translation of the title of the table into Slovenian.

Figures:

Attach images as separate files. Images should be in high resolution format (e. g. .jpg or .tif in 300 dpi resolution). In the text, indicate where a particular image should appear. You do this by stating the serial number of the image in parentheses at the desired place in the text (Slovene articles: Slika 1, Slika 2 ...; English articles: Figure 1, Figure 2 ...). Each image needs a caption (title and brief description). Write the text for each picture in this chapter for each picture separately. In addition to the Slovenian text accompanying the picture, Slovenian articles should also have an English translation of the text accompanying the picture (so that foreigners can understand it). English articles do not need a translation of the text accompanying the picture into Slovenian.

f. References:

Any citation of the claim or findings of others must be supported by a reference, which is referred to in the text by a sequential Arabic number in parentheses. For citations, use the BMJ reference style. Detailed instructions and citation examples can be found on their 'BMJ Author Hub' website at the following link: https://authors.bmj.com/writing-and-formatting/formatting-your-paper/. We recommend using a literature citation tool (e.g.: Zotero, Mendeley, EndNote ...), as this way the possibility of error is smaller. Use the BMJ style in the citation tool. Before submitting the paper, please check manually if the citations are by the BMJ instructions. When citing, please cite the first three authors. Add 'et al.' at the end if there are more authors.

Some examples of correct citations (more on the BMJ website):

Article published in a printed magazine:

1. Koziol-Mclain J, Brand D, Morgan D, et al. Measuring injury risk factors: question reliability in a statewide sample. Inj Prev 2000; 6:148-50.

Article published in the online version of the magazine (which has not yet been published in print):

2. Dark P, Dunn G, Chadwick P, et al. The clinical diagnostic accuracy of rapid detection of healthcare-associated bloodstream infection in intensive care using multi-pathogen real-time PCR technology. BMJ Open 2011; 1:e000181. doi: 10.1136/bmjopen-2011-000181.

Article in the supplement:

3. Mugosa A, Cizmovic M, Lakovic T, et al. Accelerating progress on effective tobacco tax policies in Montenegro. Tobacco Control 2020; 29:s293-s299.

Extract:

4. Bricca A, Swithenbank Z, Scott N, et al. 21 Predictors of recruitment in randomized controlled trials of smoking cessation: meta-regression analysis from the IC-SMOKE systematic review project. Abstract competing for the 'Doug Altman scholarship'. BMJ Evidence-Based Medicine 2019; 24: A52-A53.

Book:

5. Howland J. Preventing Automobile Injury: New Findings from Evaluative Research. Dover, MA: Auburn House Publishing Company 1988:163-96.

Book Chapter:

6. Nagin D. General deterrence: a review of the empirical evidence. In: Blumstein A, Cohen J, Nagin D, eds. Deterrence and Incapacitation: Estimating the Effects of Criminal Sanctions on Crime Rates. Washington, DC: National Academy of Sciences 1978:95-139.

Electronic resource:

7. Extraintestinal Complications of IBD. Crohn's Colitis Found. https://www.crohnscolitisfoundation.org/what-is-ibd/extraintestinal-complications-ibd (accessed 7 Dec 2022).

g. Authors' statement

The contribution intended for publication must be accompanied by the 'Statement of the authors of the contribution', which can be found on the website Declaration of Authors or you can ask the editors for a template via email SloJouDD@gmail.com. The statement should be signed by all authors (by hand or digitally), and the completed and signed statement should be attached to the article when you send it to the editors for review. Instructions for completing and sending the declaration can be found in the declaration template and on the website.

3.0 Submission of contributions

Send contributions by e-mail to:

SloJouDD@gmail.com

or to the address:

Slovenian Journal of Digestive Diseases / Gastroenterolog editorial office, Japljeva ulica 2, 1000 Ljubljana, Slovenia.

Attach all the necessary attachments listed in the instructions to the authors of the paper.

4.0 Editorial work

The editor-in-chief reviews each submitted contribution and decides on inclusion in the editorial process. Contributions included in the editorial process are forwarded to other members of the editorial board, who take care of technical and stylistic corrections. The revised paper is then returned to the authors for review. The content of the paper is evaluated by two expert reviewers who are unknown to the authors, and the expert reviewers are also not aware of the identity of the authors. The contribution is also reviewed by proofreaders for the Slovenian and English languages. After finishing the editorial work, the author gets his work reviewed, approved and corrections taken into account. Before publication, the author also receives a working pdf file with a break of the designed article (brush print) by e-mail, but at this stage, we only take into account corrections of typographical errors and warnings about possible missing or inappropriately placed images or tables or inappropriate references to elements contained in the paper. The final version of the article may deviate slightly due to possible additional adjustments to the fold. The answer with any comments must be returned within two days, otherwise, it will be understood that the author agrees with the corrections and breaks in the paper.