Case report / *Prikaz primera*

Pancreas divisum – truly an innocent bystander in acute pancreatitis?

Pankreas divisum – le naključni spremljevalec akutnega pankreatitisa?

Izabela Milanez[1], Samo Plut[2], Jurij Hanžel*[1,2]
[1]*Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia*
[2]*Department of Gastroenterology, University Medical Centre Ljubljana, Ljubljana, Slovenia*
Slovenian Journal of Gastroenterology / Gastroenterolog 2024; 1: 82–87

***Keywords**: pancreas divisum, acute pancreatitis, aetiology of acute pancreatitis, prevalence*

***Ključne besede**: pankreas divisum, akutni pankreatitis, etiologija akutnega pankreatitisa, pogostnost*

ABSTRACT

Pancreas divisum is the commonest congenital malformation of the pancreas. It is caused by failed fusion of dorsal and ventral pancreatic duct. Most patients are asymptomatic. Acute pancreatitis has diverse aetiology. It is mostly caused by gallstones. Causative role of pancreas divisum in aetiology of acute pancreatitis remains unknown. Minority of patients with pancreas divisum develop acute pancreatitis. In any patient with pancreas divisum and acute pancreatitis, other causes of acute pancreatitis must be excluded.

IZVLEČEK

Pankreas divisum je najpogostejša prirojena nepravilnost trebušne slinavke. Nastane zaradi neuspele združitve dorzalnega in ventralnega pankreatičnega voda. Večina obolelih je asimptomatskih. Obstaja več vzrokov nastanka akutnega pankreatitisa. Najpogostejši vzrok so žolčni kamni. Manjšina bolnikov s pankreas divisumom razvije akutni pankreatitis. Pri vsakem bolniku s pankreas divisumom in akutnim pankreatitisom je treba izključiti druge vzroke nastanka akutnega pankreatitisa.

*assist. prof. Jurij Hanžel, MD, PhD
Department of Gastroenterology, University Medical Centre Ljubljana, Japljeva ulica 2, 1000 Ljubljana, Slovenia
E-mail: jurij.hanzel@kclj.si

 Received: 1/17/2024; Review: 1/25/2024; Accepted for publication: 2/6/2024

INTRODUCTION

Pancreas divisum (PD) is the commonest congenital malformation of the pancreas. It is caused by the failed fusion of the dorsal (Santorini) and ventral (Wirsung) pancreatic ducts during the seventh week of embryonic development. Most patients are asymptomatic (1). Several articles estimate different prevalence of PD patients (2.9–18 %) (1–3). The causative role of PD in the development of acute pancreatitis has not yet been definitively clarified. Only a small proportion of patients with PD develop acute pancreatitis (2, 3).

CASE PRESENTATIONS

CLINICAL CASE 1: WHEN PANCREAS DIVISUM IS THE MOST LIKELY CAUSE OF ACUTE PANCREATITIS

In March 2023, a 50-year-old woman was admitted with acute pancreatitis of unknown aetiology.

History and examination: the patient described spasmodic pain 10/10, based on visual analogue scale, radiating in lumbar region. There were no deviations in clinical status with the exceptions of blood pressure 105/70 mmHg and pain in the lower abdominal quadrant and under left costal arch upon superficial palpation. Patient reports no alcohol consumption.

Current medications: ciclesonide as needed.

Laboratory findings: liver tests, calcium and triglycerides within normal range.

Imaging: abdominal ultrasound did not show unequivocal stones in the gallbladder, narrow bile ducts, homogenous pancreas.

We excluded alcoholic, biliary, hyperlipemic, hypercalcemic and with IgG4-related aetiology of acute pancreatitis.

The patient was discharged from the hospital. She was evaluated at the emergency department due to recurrent acute pancreatitis in May and July. She underwent magnetic resonance cholangiopancreatography which showed PD with dilated main pancreatic duct and no convincing abnormalities of the biliary system.

Diagnostic and therapeutic interventions: with recurrent episodes and in the absence of other causes of acute pancreatitis besides PD, the patient underwent endoscopic retrograde cholangiopancreatography in July.

The course of endoscopic retrograde cholangiopancreatography: during procedure we reached major papilla (Figure 1A). We cannulated the bile duct, which was normal. Then we visualised Wirsung's duct (Figure 1B). After having located the minor pailla (Figure 1C), we performed a needle-knife incision and entered Santorini's duct. A sphincterotomy was performed and the opening was dilated to 6 mm (Figure 1D). Contrast agent was completely drained

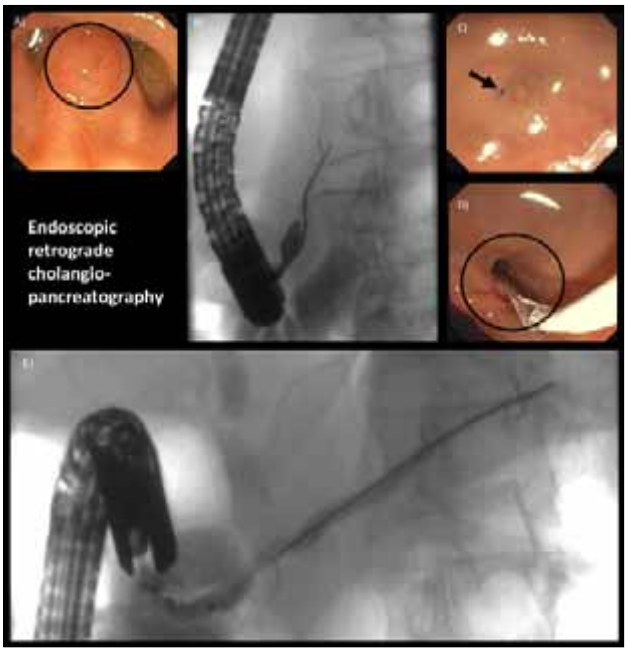

Figure 1. Diagnostic and therapeutic procedures of endoscopic retrograde cholangiopancreatography. A) location of papilla major (circled) between two diverticula. B) Cannulation of papilla major and visualization of Wirsung duct with contrast agent – re-evidence of pancreas divisum. C) Location and appearance of papilla minor (arrow) before dilatation. D) Papilla minor (circled) after dilatation. E) Cannulation of papilla minor and visualization of Santorini duct with contrast agent

from the Santorini duct (Figure 1E). The patient has had no complications during and after the procedure and no recurrences of pancreatitis up to 6 months after the procedure.

CLINICAL CASE 2: WHEN PANCREAS DIVISUM IS NOT THE MOST LIKELY CAUSE OF ACUTE PANCREATITIS

In July 2017, a 31-year-old patient came to the clinic due to chronic pain in the right upper abdominal quadrant.

History and examination: the patient described two years of low-grade pain under right costal arch. Occasionally there are acute exacerbations with sharp pain, which intensifies with movement, coughing, sneezing and occasionally even with a very gentle touch.

Previous interventions: cholecystectomy.

Laboratory findings: We recorded abnormal liver tests (elevated transaminases and mildly elevated gamma glutamyl transferase) during acute exacerbations with sharp pain.

Imaging: there was no evidence of gallstones on abdominal ultrasound or magnetic resonance cholangiopancreatography.

In February 2019, a patient came to the clinic due to recurrent acute pancreatitis. Last episode of emergency visit to the clinic because of pain was in December 2018. We excluded potential choledocholithiasis with endoscopic ultrasound and magnetic resonance cholangiopancreatography. Endoscopic retrograde cholangiopancreatography attempt was painful and unsuccessful at an outside hospital. Due to suspicion of recurrent microcholedocholithiasis we prescribed ursodeoxycholic acid 2x500mg daily. In August 2019, the patient underwent magnetic resonance cholangiopancreatography again, which showed signs of complete PD without chronic pancreatitis. In December 2019, the patient still had no problems. We found excellent clinical improvement after initiation of ursodeoxycholic acid treatment. We concluded that the patient experienced resurrect acute pancreatitis most likely due to recurrent microcholedocholithiasis and less likely due to PD. Considering the development of events, we estimated that sphincterotomy of the minor papilla would only pose an unnecessary risk of complications.

COMPARISON OF KEY DATA FROM BOTH CLINICAL CASE REPORTS

We conducted a comparison of essential data from both clinical case reports, presenting the findings in Table 1. The main differences between the two cases were observed in laboratory findings and the approach to treating recurrent acute pancreatitis. In Clinical Case Report 1, liver tests were within normal range during acute pancreatitis episodes, and the treatment for recurrent acute pancreatitis involved sphincterotomy of papilla minor. In contrast, Clinical Case Report 2 exhibited elevated transaminases and gamma glutamyl transferase during acute pancreatitis episodes. The treatment for recurrent acute pancreatitis in this case involved administration of ursodeoxycholic acid at a dosage 2x500 mg along with a bile diet.

DISCUSSION

Pancreas divisum is the most common congenital malformation of pancreas. Patients with this malformation are mostly asymptomatic (1). In this malformation, the ducts do not fuse completely, thus the drainage of pancreatic exocrine secretions into duodenum is through papilla minor (2). Pancreas divisum leads to acute pancreatitis in minority of patients (1). Accordingly, some studies suggest that some patients with pancreas divisum are more susceptible to developing acute pancreatis (4). It is believed that factors for developing acute pancreatitis in pancreas divisum are relative obstruction of outflow at the minor papilla and the presence of underlying genetic abnormalities associated with pancreatitis ((4–10, 3, 11–16, 1, 17–20).

Table 1. Difference and similarities between two represented clinical cases. Clinical case 1 represents patient when pancreas divisum is most likely the cause of acute pancreatitis. Clinical case 2 represents patient when pancreas divisum is not most likely the cause of acute pancreatitis

	CLINICAL CASE 1	CLINICAL CASE 2
HISTORY	recurrent acute pancreatitis	recurrent acute pancreatitis
LIVER TESTS	within normal range	elevated transaminases and gamma glutamyl transferase
ABDOMEN ULTRASOUND	microcholedocholithiasis	cholecystectomy
DIAGNOSIS OF PANCREAS DIVISUM	magnetic resonance cholangiopancreatography	magnetic resonance cholangiopancreatography
TREATMENT	sphincterotomy of papilla minor with endoscopic retrograde cholangiopancreatography	ursodeoxycholic acid 2x 500 mg, bile diet
PATIENT OUTCOME	without another episode of acute pancreatitis until present day	without another episode of acute pancreatitis until present day

OBSTRUCTION OUTFLOW AS POTENTIAL THEORY IN PATHOGENESIS OF DEVELOPING PANCREATITIS IN PATIENTS WITH PANCREAS DIVISUM

Relative obstruction because of papilla minor stenosis or spasm may lead to pancreas divisum related recurrent acute pancreatitis (3–5). Considering that relative obstruction of outflow at the minor papilla might be the cause of acute pancreatitis, endoscopic treatment such as minor papilla sphincterotomy or stenting may contribute to treatment success in patients with pancreas divisum (3, 7–10). Numerous studies support this hypothesis by portraying the advantages of papilla minor dilatation, resulting in reduced occurrence of acute pancreatitis episodes in patients with pancreas divisum (5, 6, 11–15). Furthermore, certain studies indicate that 44–72% of patients with pancreas divisum and recurrent acute pancreatitis may experience improvement following sphincterotomy and/or stenting of papilla minor (12–16). Variation in clinical success rates reflect different outcome measures used. Strict objective outcome measures exhibited lower success rate compared to subjective measurement like self-reported pain (1, 12–15). Those relatively good clinical outcomes after sphincterotomy were mainly based on patients with recurrent acute pancreatitis, while patients with chronic pancreatitis were less likely to benefit from this type of procedure. It is believed that the pain in patients with chronic pancreatitis is more likely to be multifactorial, and not based on ductal hypertension alone, but also on neuropathy of intrapancreatic nerves and central sensitization. That is why endoscopic therapy may not be as clinically successful in patients with pancreas divisum and chronic pancreatitis compared to patients with pancreas divisum and recurrent acute pancreatitis (11). In addition, patients with chronic upper abdominal pain and no history of pancreatitis improved only about 30% of the time after sphincterotomy of papilla minor (15).

However papilla minor cannulation and sphincterotomy are not without risk of adverse events such as post-endoscopic retrograde cholangiopancreatography pancreatitis, haemorrhage, perforation, cholecystitis and cardiorespiratory complications (11, 20). Patients with pancreas divisum who underwent cannulation of dorsal duct had higher risk for endoscopic retrograde cholangiopancreatography pancreatitis (20). De Jong et al also emphasized the need for careful reflection whether patients with pancreas divisum and recurrent acute pancreatitis would benefit from endoscopic therapy at all. In their study nearly 20% of patients with recurrent acute pancreatitis progressed

to chronic pancreatitis during follow-up despite endoscopic therapy. The theory of recurrent acute pancreatitis progressing to chronic pancreatitis may offer a justification for early endoscopic treatment of recurrent acute pancreatitis in symptomatic patients with pancreas divisum (11). This study also reports a high rate of post-endoscopic retrograde cholangiopancreatography pancreatitis which is consistent with literature (11, 21, 22). The risk of this complication is supposedly higher in patients with pancreas divisum who undergo endoscopic retrograde cholangiopancreatography compared to patients with other indications for endoscopic retrograde cholangiopancreatography. Considering the risks, it is crucial to assess the risk to benefit ratio for patients with pancreas divisum undergoing endoscopic retrograde cholangiopancreatography (21, 22).

Another reason for refraining from recommending endoscopic retrograde cholangiopancreatography to patients is the observation that the dilatation of the Santorini duct, as measured in imaging studies before endoscopic retrograde cholangiopancreatography, did not show a significant association with clinical success. This discovery raises doubts about whether increased ductal outflow is the main pathogenetic mechanism for symptoms in pancreas divisum patients (11).

GENE MUTATIONS THAT MAY CONTRIBUTE TO DEVELOPMENT OF PANCREATITIS IN PATIENTS WITH PANCREAS DIVISUM

Other factors that may contribute to development of pancreatitis in patients with pancreas divisum are gene mutations (3, 16–19). Factor increasing susceptibility to developing acute pancreatitis in patients with pancreas divisum is the presence of rs12338 polymorphism in the cathepsin B gene. The presence of this specific polymorphism is associated with a higher incidence of acute pancreatitis in patients with pancreas divisum than in patients without pancreas divisum ($p < 0.0001$) (3). Another gene mutation to be considered as a causative role in developing pancreatitis in patients with pancreas divisum is gene mutation in cystic fibrosis transmembrane receptor (16). These mutations were found significantly more often in divisum patients with pancreatitis (22%) than in divisum patients without pancreatitis (0%) (16). It is believed that in case of this mutation, pancreatic secretions are more viscous, which may contribute to ductal obstruction (17). Other reported gene mutations that may contribute to pancreatitis in patients with pancreas divisum include PRSS1 (cationic trypsinogen) mutation and polymorphisms of the monocyte chemoattractant protein 1 gene (MCP-1) (18, 19).

CONCLUSIONS

In conclusion, pancreas divisum with contributing factors can potentially lead to development of acute pancreatitis, however other causes of acute pancreatitis must be ruled out – as shown in two represented clinical cases. The key difference between represented clinical cases were elevated transaminases during acute exacerbations of pain.

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