Review article / *Pregledni članek*

Skin manifestations of common liver diseases

Kožne manifestacije pogostih jetrnih bolezni

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ABSTRACT

Both acute and chronic liver diseases can manifest skin changes, which can be the first clue of underlying liver disease. Common signs and symptoms like jaundice and pruritus indicate general conditions like cirrhosis, while other manifestations indicate specific disorders like viral hepatitis or hemochromatosis. It is crucial to note that these cutaneous findings might be indicative of underlying liver disease and often occur in the setting of hepatic dysfunction. This review highlights key skin-related manifestations associated with common liver diseases.

IZVLEČEK

Bolezni jeter velikokrat spremljajo pridružene spremembe na koži. Srbež in zlatenica sta dva izmed najpogostejših simptomov in znakov, ki ju najdemo pri bolnikih s kronično jetrno boleznijo kot je jetrna ciroza. Pozorni smo na tudi na druge kožne spremembe, ki spremljajo redkejše jetrne bolezni, na primer okužbo z virusnim hepatitisom ali hemokromatozo. V prispevku predstavljamo ključne najdbe na koži, ki so prisotne pri različnih jetrnih obolenjih in nas lahko prvenstveno usmerijo k iskanju do sedaj neopredeljene jetrne bolezni.

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INTRODUCTION

The liver is the second largest organ in the human body after the skin. Numerous signs of liver disease manifest themselves on the skin. These cutaneous manifestations can help recognise and diagnose a serious underlying liver condition. Many hepatobiliary diseases are commonly associated with changes in skin, nails and hair. They can be broadly divided into general cutaneous signs and symptoms that may manifest in cirrhosis like jaundice, pruritus, spider angioma, palmar erythema, caput medusae, xanthomas and other, more specific cutaneous signs that are associated with distinct liver diseases like primary biliary cholangitis, viral hepatitis B, hepatitis C and hemochromatosis among others.

This review article describes the most prevalent general cutaneous manifestations of chronic liver disease and skin manifestations of various liver diseases.

GENERAL SKIN MANIFESTATIONS OF CHRONIC LIVER DISEASE

Jaundice

Jaundice, also known as icterus, manifests as a yellow to brown tint on the skin, sclera, and mucous membranes, attributed to elevated bilirubin levels in the body, typically becoming apparent when these levels surpass two to three times the normal range (1). This discolouration reflects the severity of hyperbilirubinemia, with the depth of colour indicating the extent of the condition. Essential to diagnosing jaundice is identifying whether the bilirubin is conjugated or unconjugated, which helps pinpoint the underlying cause as prehepatic, intrahepatic, or posthepatic (2, 3). Notably, jaundice serves as a prominent indicator of liver disease and requires careful evaluation to address the impaired excretion or obstruction causing bilirubin build-up.

Pruritus

Pruritus is often the most common and distressing symptom in patients with liver disease and is predominantly seen in those suffering from conditions linked to cholestasis, such as primary biliary cholangitis and obstructive jaundice of benign or malign origin (4). It is defined as an unpleasant sensation that causes a scratching response due to various itch mediators acting on nerve endings in the skin, notably influenced by the accumulation of bile acids, endogenous opioids, lysophosphatidic acid (LPA), and autotaxin (ATX) activity (5, 6). Despite the presence of cholestasis, the intensity of pruritus does not always correlate with serum bile acid levels, and treatments like bile acid resins, while commonly used, do not uniformly alleviate the symptoms (7). Emerging evidence points towards LPA and ATX as significant contributors to cholestatic pruritus, with their levels showing a more direct correlation with itch intensity (4, 8).

The management of cholestatic pruritus involves a variety of approaches. Cholestyramine remains the first-line treatment, with rifampicin, sertraline, and opioid antagonists like naltrexone and naloxone also being used, albeit cautiously due to potential side effects (9, 10). Additionally, non-pharmacological treatments such as narrowband ultraviolet B therapy and plasmapheresis can also be used in the alleviation of the symptoms (10, 11).

Spider Angioma

Spider angiomas (SA), also known as spider naevus or spider telangiectasia (Figure 1), are characterised by a central arteriole with radiating small vessels and are found in 10% to 15% of healthy children and notably, in 33% of patients with liver cirrhosis (1, 12). Being approximately 1 to 10 mm in size, these vascular lesions predominantly appear in areas with venous drainage into the superior vena cava, like the face, neck, and upper trunk. Although rare in mucous membranes, severe cases involving bleeding or multiple lesions have been reported (13). SAs can be a

sign of severe liver conditions, including alcoholic liver disease and hepatopulmonary syndrome, where their presence correlates with the severity of liver dysfunction (14). Elevated levels of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) have been recognised as independent predictors of spider nevi in cirrhotic patients (15). Treatment of liver disease often leads to the resolution of SAs, which can also be treated with laser therapy for cosmetic purposes (16). The presence of SAs in adults, especially when numerous, can indicate underlying liver disease and necessitates further investigation.

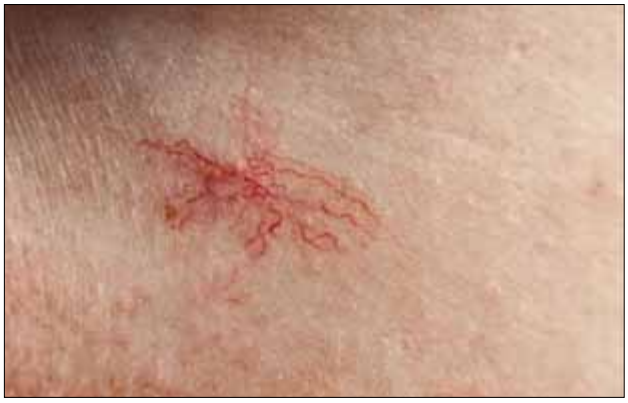

Figure 1. Spider angioma

Paper Money Skin

Paper money skin is closely related to spider angiomas and features diffuse, thin capillary plaques, most commonly found on the patient's trunk. Characterised by numerous slender blood vessels dispersed across the skin, this condition becomes better visible under diascopic examination (17). It is notably present in patients with liver cirrhosis, where these capillaries, along with spider angiomas, create a pattern on the upper trunk reminiscent of the design seen in paper currency, leading to its descriptive name (18).

Palmar Erythema

Palmar erythema (Figure 2), also known as liver palms, manifests as a reddish discolouration across the palms, fingertips, and sometimes soles, often blanching under pressure and pulsating with the heartbeat (19). Though its exact cause remains unclear, factors like prostacyclins, nitric oxide, and hormonal imbalances, particularly in patients with alcoholic liver disease (ALD), are believed to contribute to its occurrence through local vasodilation (19) as well as systemic hemodynamic differences in advanced disease, characterised by splanchnic and peripheral vasodilation, hyperdynamic circulation and localised differences in peripheral circulation between the upper and lower limbs. While palmar erythema is prominently associated with liver cirrhosis - observed in around 23% of cases - it is not exclusive to liver disorders that can arise in various other conditions including pregnancy, rheumatoid arthritis, and certain infections, as well as from the use of specific medications (19, 20). This condition, characterised by non-tender, symmetric redness, especially on the thenar and hypothenar eminences, may also be influenced by abnormal serum oestradiol levels and changes in peripheral circulation in cirrhosis patients. Additionally, palmar erythema's presence and severity can relate to the underlying liver disease's progression, with temperature abnormalities and response to cold also indicating disease severity (19, 21).

Figure 2. Palmar erythema

Caput medusae

Severe portal hypertension can lead to collateral blood flow pathways forming, manifesting as prominent, twisted abdominal varicose veins extending from the umbilicus upwards to connect with systemic circula-

tion. This condition, known as caput medusa (Figure 3), draws its name from its resemblance to the snake-entwined hair of the mythological figure Medusa. Unlike the blood flow pattern observed in inferior vena cava obstruction, where blood is directed towards the head, in caput medusae, the blood moves towards the legs. This phenomenon highlights the distinctive vascular responses associated with advanced portal hypertension (1, 22).

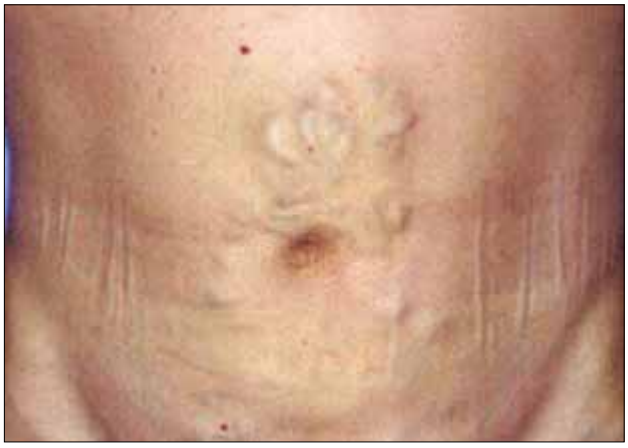

Figure 3. Caput medusae

Xanthomas

Xanthomas (Figure 4) are characterised by yellow-orange papules or plaques, particularly around the eyes resulting from lipid deposits within dermal macrophages. These lesions are frequently associated with cholestatic liver diseases like primary biliary cholangitis (PBC), where they manifest due to abnormalities in cholesterol metabolism and secondary lipid disorders (23). Elevated total cholesterol levels, common in PBC patients, contribute to xanthoma development, with an estimated 15% to 50% of PBC patients exhibiting xanthomas. A specific form, xanthelasmas, are planar xanthomas on the eyelids and are observed in about 5–10% of PBC cases (24). While liver diseases may induce secondary dyslipoproteinemias, leading to manifestations like hypertriglyceridemia and decreased high-density lipoproteins, xanthomas, including xanthelasmas, generally regress with the treatment of the underlying lipid imbalance (25, 26).

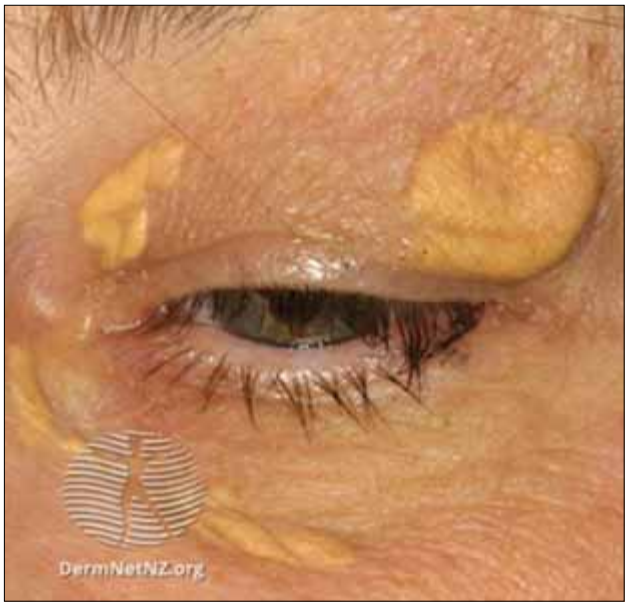

Figure 4. Xanthelasma around the eye

Hair changes

Hair changes in liver disease often indicate hormonal imbalances, manifesting as loss or thinning of axillary and pubic hair or adoption of a female pattern of hair distribution in men. These changes are frequently accompanied by other signs of hormonal alteration such as gynecomastia and testicular atrophy. Chronic alcohol abuse is associated with cutaneous signs such as hair alterations, linking liver dysfunction to major changes in body hair (27, 28), as well as an indication of malnutrition caused by alcoholism.

Nail changes

Nail changes in liver disease include clubbing (Figure 5), thickening, longitudinal ridging, the appearance of white bands known as Muehrcke's lines, and brittleness. Terry's nails, a condition characterised by a white, ground glass appearance of the nail plate with a dark band at the tip, are particularly associated with liver cirrhosis but also with systemic diseases like type 2 diabetes, heart failure and chronic renal failure (29, 30). The absence of the lunula and bluish discolouration of the lunulae, the latter known as Azure lunulae (Figures 6 and 7) in Wilson's disease, along with splinter haemorrhages and hypertrophic osteopathy, are among other nail changes which indicate liver dysfunction.

Picture 5. Clubbing of the nails

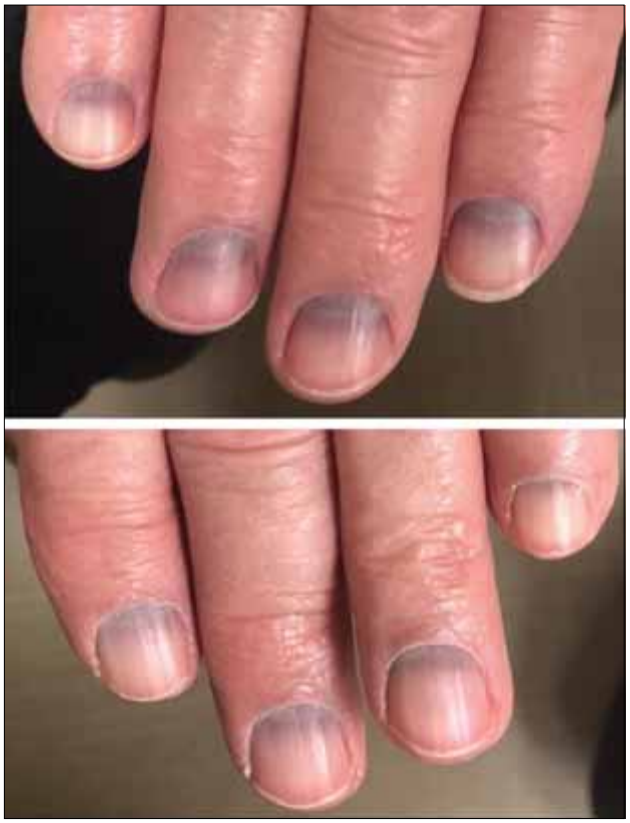

Figure 6 and 7. Bluish discoloration of the lunulae (Azure lunulae)

These alterations may reflect decreased vascularity and increased connective tissue production in the nail bed, underscoring the need for comprehensive evaluation in patients with such symptoms (31–33).

Pigmentary Changes

In patients with primary biliary cholangitis (PBC) and other chronic liver diseases, particularly those related to chronic alcoholism, diffuse, muddy hyperpigmentation and localised, blotchy darkening are often observed. Such pigmentation is notably more intense in areas like the areolae, around the mouth and eyes, and along palmar creases. Moreover, lesions resembling guttate hypomelanosis; sometimes centred around a spider angioma, may appear on less exposed body parts like the buttocks, trunk, and limbs, likely due to vasoconstriction rather than changes in pigmentation (17, 34).

SKIN MANIFESTATIONS OF SPECIFIC LIVER DISEASES

Viral Hepatitis

Viral Hepatitis B

Hepatitis B virus (HBV) infection exhibits a broad spectrum of skin manifestations, ranging from serum sickness-like disease affecting 20–30% of acute HBV patients to polyarteritis nodosa (PAN) in 7–8% of cases (35). These symptoms typically precede clinical liver disease, with serum sickness-like symptoms resolving as HBV antigens are cleared. HBV-associated PAN, distinguished by immune-complex deposition poses a risk through gastrointestinal involvement, with first-line treatments including steroids, antivirals, and plasma exchange (35).

Acute urticaria is a common early sign of HBV, linked to immune complex deposition, potentially leading to systemic symptoms such as arthritis and headaches (22, 36). Hepatitis B can also trigger porphyria cutanea tarda, a metabolic condition causing blisters and fragile skin in sun-exposed areas, increasing hepatocellular carcinoma risk (22, 37). Additionally, HBV is known to cause Gianotti-Crosti syndrome, a papular eruption commonly seen in viral infections, and other skin lesions such as pyoderma gangrenosum and lic-

hen planus, underlining the diverse dermatological impact of this infection (22, 38).

Viral Hepatitis C

Hepatitis C virus (HCV) infection leads to chronic disease in approximately 70% of patients, manifesting through various cutaneous symptoms. Unique to HCV is necrolytic acral erythema (NAE), presenting as papulosquamous eruptions primarily located on the feet (*Figure* 8). Treatment involves direct-acting antivirals, interferon and/or ribavirin treatment. According to the literature, some patients have been responsive to oral zinc supplementation in several cases (39). Moreover, HCV is linked to a range of skin disorders like sarcoidosis, Sjogren syndrome, and vitiligo (40–42). Essential mixed cryoglobulinemia, porphyria cutanea tarda (PCT), and lichen planus have strong associations with chronic hepatitis C, necessitating HCV testing in affected patients (22).

Cryoglobulinemic vasculitis, resulting from HCV-related cryoglobulins, manifests through purpura and ulcers and is treated with antiviral therapy (43). Lichen planus, an autoimmune condition potentially triggered by HCV, appears as violaceous papules or white mucosal lesions. Because of the significant correlation between HCV and oral lichen planus, it is reasonable that patients with this condition are screened for HCV (44).

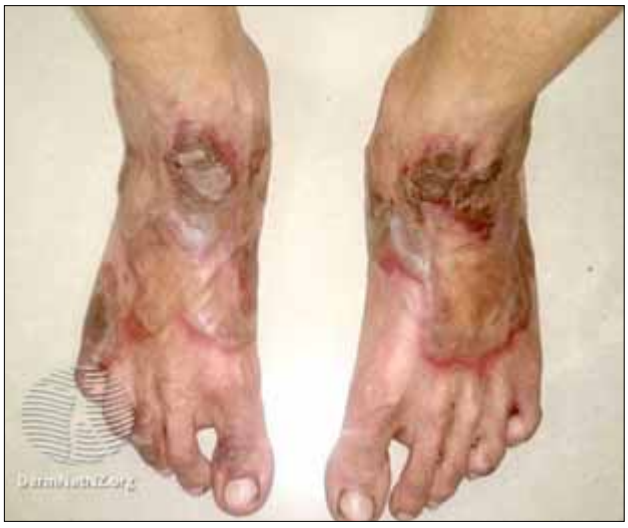

Figure 8. Necrolytic acral erythema

Primary biliary cholangitis

Primary Biliary Cholangitis (PBC) is an autoimmune liver disease mainly affecting middle-aged women and is often associated with other autoimmune conditions such as Sjogren's syndrome and morphea (45). Symptoms include jaundice and intense itching, with liver function tests indicating cholestasis and anti-mitochondrial antibodies often detected. Pruritus, sometimes the initial symptom in 50% of patients, can lead to skin excoriations and post-inflammatory hyperpigmentation, notably with the 'butterfly sign' of unscratched skin on the upper back due to the physical inability to reach this area (46). Secondary hyperlipidaemia, manifesting as xanthelasma and various xanthomas, is another common feature.

A study of 49 PBC patients highlighted fungal infections, including tinea pedis and onychomycosis, as the most prevalent skin manifestations, followed by neoplastic lesions, dermatitis-urticaria, and pigmentary changes (47).

Hemochromatosis

Hemochromatosis is a disorder associated with deposits of excess iron that can cause multiple organ dysfunction, traditionally called '*bronze diabetes*' due to the discolouration of the skin and related impairment of the pancreas. Primary hemochromatosis is an autosomal recessive hereditary iron overload disorder which predominantly affects males and is among the most common genetic conditions in white populations. Hereditary hemochromatosis occurs in homozygotes with a mutation of the hemochromatosis gene (HFE) protein. It may present itself with distinct symptoms such as skin pigmentation, diabetes, cirrhosis, and cardiac failure (48). The hyperpigmentation, especially pronounced in sun-exposed areas, is an early sign of iron deposition, with bronze or grey hue due to increased melanin production. Ichthyosiform changes, resembling fish-like scales, and nail abnormalities are also notable. Systemic effects, including skin changes, are reversible with phlebotomy, which can reduce pigmentation over time (27, 49–51), however, pre-

existing end-organ damage is rarely reversed by phlebotomy.

CONCLUSION

In conclusion, liver diseases often manifest themselves through different skin changes, either related to cirrhosis or specific liver diseases. A clinician must be able to recognise these signs and symptoms, as the cutaneous manifestations can often represent the first clue in diagnosing an underlying hepatobiliary condition.

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