CME CREDIT

EDUCATIONAL OBJECTIVE: Readers will be familiar with common skin signs of liver disease

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Recognizing and treating cutaneous signs of liver disease

ABSTRACT

Cutaneous changes may be the first clue that a patient has liver disease. Recognizing these signs is crucial to diagnosing liver conditions early. Here we describe the spectrum of skin manifestations that may be found in various liver diseases.

KEY POINTS

Pruritus due to liver disease is particularly resistant to therapy. Cholestyramine (Questran) 4 g/day, gradually increased to 24 g/day, is one option. If the pruritus does not respond or the patient cannot tolerate cholestyramine, rifampin (Rifadin) can be tried.

Spider angiomas, Bier spots, and "paper-money" skin are all superficial vascular problems that may be related to liver disease.

Cutaneous lesions often accompany alcoholic cirrhosis and have been detected in up to 43% of people with chronic alcoholism. The combination of spider angiomas, palmar erythema, and Dupuytren contracture is common in alcoholic cirrhosis.

Although porphyria cutanea tarda is associated with liver disease in general, recent studies show that patients with hepatitis C are at particularly high risk.

doi:10.3949/ccjm.76A.08113

Dysfunction in the body's second largest organ, the liver, often yields changes in the body's largest organ, the skin. If we can recognize these manifestations early, we are better able to promptly diagnose and treat the underlying liver disease, as well as the skin lesions.

The liver has many jobs: synthesizing proteins such as clotting factors, complements, and albumin; neutralizing toxins; and metabolizing lipids and carbohydrates. Insults to the liver can compromise any of these functions, affecting visceral organs, joints, gastrointestinal tissues, and the skin. Dermatologic signs of specific liver diseases include alopecia and vitiligo associated with autoimmune hepatitis, and xanthelasma in chronic cholestatic liver disease.

This article reviews the important cutaneous manifestations of specific liver diseases. We focus first on skin conditions that may represent liver disease, and then we discuss several major liver diseases and their typical cutaneous manifestations.

JAUNDICE AND HYPERBILIRUBINEMIA

Jaundice, the cardinal sign of hyperbilirubinemia, is usually recognizable when serum bilirubin levels exceed 2.5 or 3.0 mg/dL. The color of the skin typically reflects the severity of the bilirubin elevation.[1,2] Jaundice due to mild hyperbilirubinemia tends to be yellowish, while that due to severe hyperbilirubinemia tends to be brownish (**FIGURE 1**).

Establishing whether the excess bilirubin is conjugated or unconjugated gives a clue as to whether the cause is prehepatic, intrahepatic, or posthepatic.[3–8] One of the liver's main func-

FIGURE 1. Characteristic yellowish discoloration of the sclera in the eye of a patient with end-stage liver disease.

tions is to conjugate bilirubin into a secretable form. Prehepatic causes of jaundice include hemolysis and ineffective erythropoiesis, both of which lead to higher levels of circulating unconjugated bilirubin.[4] Intrahepatic causes of jaundice can lead to both unconjugated and conjugated hyperbilirubinemia.[4,8] Posthepatic causes such as bile duct obstruction primarily result in conjugated hyperbilirubinemia.[4]

Skin color typically reflects the severity of the jaundice

PRURITUS AND PRURIGO NODULARIS

Pruritus can be multifactorial or the result of a specific dermatologic or systemic condition.[9] A thorough history and physical examination are warranted to rule out hepatic or systemic causes of itching.[10]

The liver neutralizes toxins and filters bile salts. If its function is impaired, these materials can accumulate in the body, and deposition in the skin causes irritation and itching.[11,12] In cholestatic liver disorders such as primary sclerosing cholangitis and obstructive gallstone disease, pruritus tends to be generalized, but worse on the hands and feet.[13]

Although the severity of pruritus is not directly associated with the level of bile salts and toxic substances, lowering bile salt levels can mitigate symptoms.[11]

Treatment. Pruritus due to liver disease is particularly resistant to therapy.

In a strategy described by Mela et al for managing pruritus in chronic liver disease,[14] the initial treatment is the anion exchange resin cholestyramine (Questran) at a starting dose of 4 g/day, gradually increased to 24 g/day in two doses at mealtimes.

If the pruritus does not respond adequately to cholestyramine or the patient cannot tolerate the drug, then the antituberculosis drug rifampin (Rifadin) can be tried. Rifampin promotes metabolism of endogenous pruritogens and has been effective against cholestatic pruritus when started at 150 mg/day and increased up to 600 mg/day, depending on the clinical response.[14]

Third-line drug therapies include opioid antagonists such as naltrexone (ReVia) and nalmefene (Revex).[14,15]

Plasmapheresis can be considered if drug therapy fails.[16] Experimental therapies include albumin dialysis using the molecular adsorbent recirculating system (a form of artificial liver support), antioxidant treatment, and bright-light therapy.[15] Liver transplantation, when appropriate, also resolves cholestatic pruritus.[14]

Prurigo nodularis

Prurigo nodularis, distinguished by firm, crusty nodules, is associated with viral infections (eg, hepatitis C, human immunodeficiency virus), bacterial infections, and kidney dysfunction.[17,18] The lesions are intensely pruritic and often lead to persistent scratching, excoriation, and, ultimately, diffuse scarring.[19]

Treatment. Although the exact cause of prurigo nodularis is not known and no cure exists, corticosteroid or antihistamine ointments control the symptoms in most patients with hepatitis.[19] Low doses of thalidomide (Thalomid), a tumor necrosis factor antagonist, have also been used safely and effectively.[18,19]

SUPERFICIAL VASCULAR SIGNS

Spider angiomas

Spider angiomas, or spider nevi, are collections of dilated blood vessels near the surface of the skin.[20] They appear as slightly raised, small, reddish spots from which fine lines radiate outward, giving them a spider-like appearance (**FIGURE 2**).[21,22]

Spider angiomas can occur anywhere on the body, but they occur most often on the face and the trunk.[21,23] A key feature is that

they disappear when pressure is applied and reappear when pressure is removed.[23,24] Biopsy is rarely necessary for diagnosis.

These lesions occur with elevated estrogen levels, such as in cirrhosis, during estrogen therapy, or during pregnancy.[25–28] Although spider angiomas are common in pregnant women and in children, adults with spider angiomas deserve a workup for liver dysfunction.[29]

Given their innocuous nature and asymptomatic course, spider angiomas themselves require no medical treatment.

Bier spots

Bier spots are small, irregularly shaped, hypopigmented patches on the arms and legs. They are likely due to venous stasis associated with functional damage to the small vessels of the skin.[30]

Since Bier spots are a sign of liver disease, they must be distinguished from true pigmentation disorders. A key distinguishing feature is that Bier spots disappear when pressure is applied. Also, raising the affected limb from a dependent position causes the hypopigmented macules of Bier spots to disappear, which is not the case in true pigmentation disorders.[10,30]

Paper-money skin

Paper-money skin (or "dollar-paper" markings) describes the condition in which the upper trunk is covered with many randomly scattered, needle-thin superficial capillaries. It often occurs in association with spider angiomas. The name comes from the resemblance the thread-like capillaries have to the finely chopped silk threads in American dollar bills.[10,31] The condition is commonly seen in patients with alcoholic cirrhosis and may improve with hemodialysis.[31]

PALMAR ERYTHEMA

Palmar erythema is a florid, crimson coloration of the palms of the hands and the fingertips. It can occur anywhere on the palm and fingers but is most common on the hypothenar eminence. It can occur in a number of liver conditions but most often with cirrhosis.[32] Hepatic compromise, as seen in alcoholic liver disease, disrupts the body's androgen balance, causing local vasodilation and erythema.[32,33] Although the exact mechanism remains unknown, research suggests that prostacyclins and nitric oxide play a role, as both are increased in liver disease.[32,33]

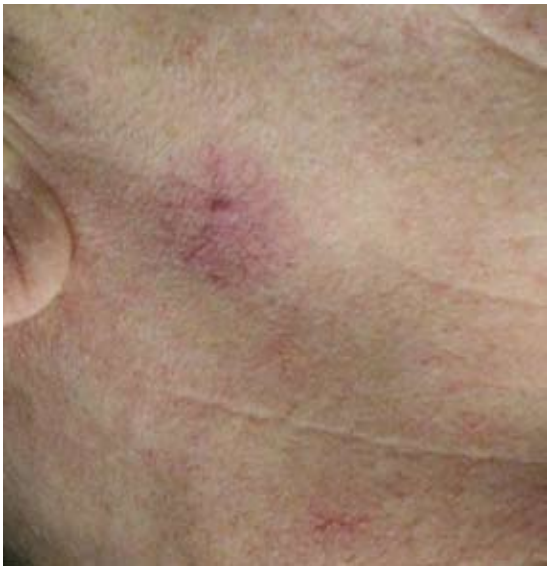

FIGURE 2. Spider angiomas on the neck of an elderly patient with liver failure. Note the characteristic central vessel and symmetrically radiating thin branches.

XANTHELASMA

Eyelid xanthelasma indicates high cholesterol, a sign of cholestatic liver disease

Xanthelasma—a localized cholesterol deposit beneath the skin and especially beneath the eyelids—is a common manifestation of hypercholesterolemia. Xanthelasma often presents as a painless, yellowish, soft plaque with well-defined borders,[34] which may enlarge over the course of weeks.

Several liver diseases can lead to various forms of secondary dyslipoproteinemia.[35] The most common dyslipoproteinemias in liver disease are hypertriglyceridemia and low levels of high-density lipoprotein cholesterol, and both of these often accompany fatty liver disease.[36] Hypercholesterolemia is a common feature of primary biliary cirrhosis and other forms of cholestatic liver disease.[37] Studies suggest that the total plasma cholesterol level is elevated in as many as 50% of patients with compromised liver function.[38]

Treatment. The underlying hyperlipidemia is treated with cholesterol-lowering drugs. Laser treatment and surgical excision have proven efficacious in treating the lesions.[39]

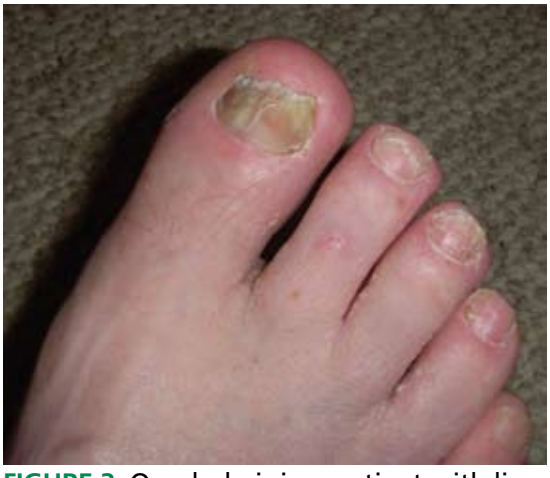

FIGURE 3. Onycholysis in a patient with liver disease exhibiting characteristic separation of the nail plate distally.

OTHER CUTANEOUS FINDINGS IN LIVER DISEASE

Bleeding and bruising. Liver disease can cause hypersplenism and thrombocytopenia, in addition to a decrease in clotting factors. These may present with a myriad of cutaneous symptoms, including purpura, bleeding gums, and easy bruising and bleeding, even from minor trauma.[40–42]

Hyperpigmentation of the skin may accompany hemochromatosis, alcoholic liver disease, and cirrhosis.[43–45]

Hair and nail loss. Patients with hepatocellular dysfunction may develop hair-thinning or hair loss and nail changes such as clubbing, leukonychia (whitening), or onycholysis, affecting the nails of the hands and feet (FIGURE 3).[46,47]

"Terry's nails," in which the proximal two-thirds of the nail plate turns powdery white with a ground-glass opacity, may develop in patients with advanced cirrhosis.[48]

ALCOHOLIC CIRRHOSIS AND THE SKIN

Paper-money skin and Dupuytren contracture may signal alcoholic cirrhosis

The cutaneous changes associated with alcoholic cirrhosis are more widely recognized than those due to other forms of liver dysfunction. In the United States, approximately 3 million people have alcoholic cirrhosis, the second-leading reason for liver transplantation.[49,50]

As the body's main site of alcohol metabolism, the liver is the organ most affected by excessive alcohol intake, which can lead to end-stage liver disease secondary to alcoholic cirrhosis.[41,51] The characteristic feature of cirrhosis is advanced fibrous scarring of parenchymal tissue and the formation of regenerative nodules with increased resistance to blood flow throughout the organ.[41,52] The insufficient blood flow damages vital structures in the liver and compromises liver function. For example, liver cirrhosis leads to defective hepatic synthesis of clotting factors and results in bleeding disorders.

Cutaneous lesions often accompany alcoholic cirrhosis and have been detected in up to 43% of people with chronic alcoholism.[53] Skin changes in alcoholic cirrhosis can be of great diagnostic value. The combined prevalence of spider angiomas, palmar erythema, and Dupuytren contracture in alcoholic cirrhosis was found to be 72%. Paper-money skin and Dupuytren contracture are more distinct lesions for alcoholic cirrhosis.[31] Recognizing these skin changes contributes to the diagnosis and staging of liver cirrhosis.[51,52]

Dupuytren contracture

Dupuytren contracture is characterized by progressive fibrosis and thickening of tendons in the palmar fascia, the connective tissue that lies beneath the skin of the palms.[54] Over time, as fibrotic involvement expands across the fascia, rampant stiffness of the joints ensues, sometimes to a point where the fingers cannot fully flex or extend.[54]

Although the exact cause of Dupuytren contracture is unknown, it appears to be associated with excess alcohol consumption and can be found in patients with alcoholic cirrhosis.[54,55] These patients often present with painless stiffness of the fingers, curling of fingers, and loss of motion in involved fingers.[54] Surgery in the form of limited fasciectomy has been curative in such patients.[54]

Disseminated superficial porokeratosis

Porokeratosis is a keratinization disorder of clonal origin that presents as a linear configuration of white scaly papules that coalesce into plaques throughout the body.[56] Although it most commonly afflicts fair-skinned people, patients with alcoholic cirrhosis have a

much greater susceptibility than the general population.[57,58]

A recent study[58] documented that the lesions completely resolved when liver function improved, thus underlining the relationship between the two conditions. Since immunosuppression has been linked to eruption of the lesion, the fact that both humoral and cell-mediated immune responses are impaired in alcoholic liver disease provides another dimension to the association between porokeratosis and alcoholic cirrhosis.[58]

These lesions can transform into squamous cell carcinoma.[59] The risk of widespread metastases in squamous cell carcinoma highlights the importance of dermatologic consultation in such patients.[59]

HEPATITIS C AND THE SKIN

Extrahepatic manifestations have been documented in up to 74% of people with hepatitis C virus infection.[60] In addition to parasthesias, arthralgias, and myalgias, hepatitis C has a significant association with porphyria cutanea tarda, lichen planus, vitiligo, sialadenitis, urticarial vasculitis, corneal ulcers, xerosis, pruritus, and prurigo nodularis.[60–64] Although the primary causative agents of sialadenitis are bacteria, viruses such as hepatitis C have been implicated as a cause of chronic sialadenitis with associated xerostomia.[65]

Patients with hepatitis C being treated with interferons also present with cutaneous manifestations such as hyperkeratosis and vasculitis.[63]

Porphyria cutanea tarda

Porphyria cutanea tarda is the most common of the porphyrias, disorders distinguished by deficiencies or defects in one or more of the enzymes responsible for hepatic production of heme.[66] If these enzymes are impaired, heme precursors such as porphyrins accumulate.[66]

Porphyria cutanea tarda results from a deficiency of the hepatic enzyme uroporphyrin decarboxylase. In the absence of this enzyme, shortwave visible light activates uroporphyrin deposited in the skin, resulting in a photochemical reaction that generates reactive oxygen species that lead to the characteristic skin blistering.

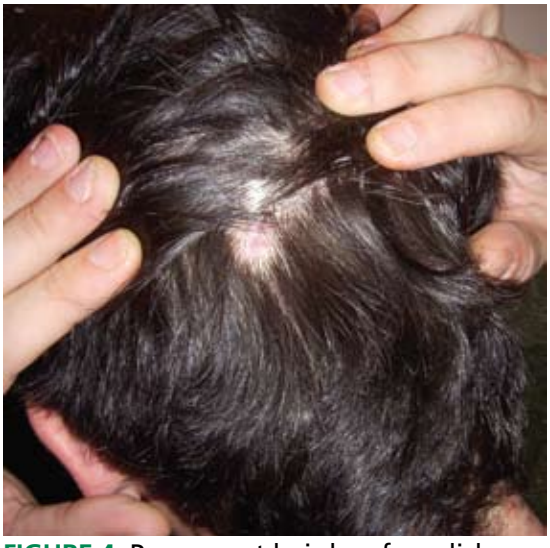

FIGURE 4. Permanent hair loss from lichen planopilaris in a patient with chronic hepatitis C virus infection.

Although porphyria cutanea tarda is associated with liver disease in general, recent studies confirm that patients with hepatitis C are at particularly high risk.[67] Those with the disorder often present with skin photosensitivity.[68] Many develop blisters on sun-exposed skin, including the dorsal aspects of the hands and forearms and on the neck and face. Chronic porphyria cutanea tarda can lead to scarring, alopecia, and skin ulceration.[69] As the blisters heal, keratin-filled milial cysts may develop in the areas of ulceration.

Porokeratosis can transform into squamous cell carcinoma

The condition is also commonly associated with melasma-like hyperpigmentation and hypertrichosis in sun-exposed areas of the head and neck. People of Northern European ancestry may be more at risk than the general population because of a presumed genetic susceptibility.[70]

Treatment. Because many patients with porphyria cutanea tarda have iron overload, they need to restrict foods rich in iron and to avoid alcohol.[71,72] Severe cases may necessitate iron removal via phlebotomy or antimalarial therapy. Patients with porphyria cutanea tarda induced by hepatitis C should have their bodily iron stores depleted before starting antiviral therapy.[60]

Lichen planus

Lichen planus is a chronic pruritic, papular condition that often presents clinically with

the "five P's": pruritic, planar, polygonal, purple papules. It can occur throughout the body but typically affects the wrists and ankles, causing mild to severe itching in most affected people.[73] In about 50% of patients, the lesions resolve within 6 months, and in 85% they subside within 18 months.[74]

Lichen planopilaris is a subset of lichen planus that causes scaling and atrophy of the scalp and permanent hair loss (**FIGURE 4**).[73]

Interferon-induced vitiligo

Vitiligo is an autoimmune disease in which melanocytes in the skin are destroyed, with resulting depigmentation in affected areas.[75] Although it has no specific association with liver disease, it has been linked to treatments for hepatitis C such as interferons.[76] Interferon-induced vitiligo often completely resolves when interferon is stopped.[77]

Typical findings include aggregations of irregularly shaped white patches in a focal or segmental pattern.[78] The diagnosis is based on the medical history, physical examination, and sometimes skin biopsy.

HEMOCHROMATOSIS

Hemochromatosis or "bronze diabetes" is a devastating multisystem disease with a relentless course. It is among the most common genetic disorders of metabolism, and results in deposition of iron in tissues and organs throughout the body, including the liver, usually in patients ages 30 to 40.

As iron stores increase in tissues and organs, multiorgan failure and associated complications may ensue. In addition, surplus iron stores can also result in widespread bronze discoloration of skin exposed to the sun. Hemochromatosis also results in loss of body hair, ichthyosiform alterations, and koilonychia.[79]

Treatments that lower serum iron levels can reverse the cutaneous manifestations of the disorder and minimize the risk of organ failure.

Since the condition is inherited in an autosomal-recessive pattern, family members of patients should consider being screened.[80]

Hyperpigmentation in hemochromatosis

Hyperpigmentation is an early sign of hemochromatosis, affecting up to 90% of patients. Usually, sun-exposed areas of the body are the most prone and take on a grayish or brownish-bronze hue.[81] Cutaneous iron deposits injure vital skin structures, initiating a process that culminates in enhanced melanin production by melanocytes.[82] Exposure to ultraviolet light may have synergistic effects with iron, hastening the process of hyperpigmentation. As a result of this synergistic effect, many patients with hemochromatosis notice tanning with minimal sun exposure.

Although organ function can improve immediately with phlebotomy to reduce iron stores, skin hyperpigmentation does not immediately resolve.[81,82]

Ichthyosiform alterations in hemochromatosis

Ichthyosiform changes, in which the skin takes on the appearance of fish scales,[83] can be seen in patients with hemochromatosis.[80] Affected areas typically become extremely dry. Treatment includes topical hydrating creams and ointments. Avoiding sunlight is paramount, as sunlight exposure may exacerbate the condition.[83]

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