Cutaneous Manifestations of Chronic Liver Disease

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KEYWORDS

• Cutaneous manifestations • Liver disease • Cirrhosis • Pruritus • Jaundice

KEY POINTS

- Although chronic liver disease can be caused by multiple different etiologies, cutaneous physical examination findings seen in patients with chronic liver disease are often nonspecific.
- Pruritus, jaundice, and spider angiomas are common skin findings seen in many patients with hepatic dysfunction.
- Specific cutaneous signs of chronic liver disease are commonly seen in the setting of untreated hepatitis.

INTRODUCTION

There are many cutaneous manifestations of liver disease. Recognition of various skin associations of liver disease can not only help guide diagnosis but may help with management of the underlying liver disease as well. Cutaneous manifestations can be divided into general cutaneous signs and symptoms that may manifest in cirrhosis, and other, more specific cutaneous signs that are associated with distinct chronic liver diseases. General cutaneous signs include pruritus, jaundice, xanthomas, spider angiomas, palmar erythema, hair loss, and nail changes. Liver diseases with more specific cutaneous signs that are reviewed here include primary biliary cholangitis, hepatitis B, hepatitis C, hemochromatosis, and alcoholic liver disease.

GENERAL CUTANEOUS SIGNS OF HEPATIC DISEASE

Pruritus

Pruritus is defined as an unpleasant sensation that prompts a response to scratch.[1] Overall, it is the most common skin-related complaint and the most common cutaneous manifestation of liver disease. In patients with liver disease, pruritus is often associated with cholestasis in conditions like primary biliary cholangitis, primary

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sclerosing cholangitis, obstructive choledocholithiasis, carcinoma of the bile duct, and chronic viral hepatitis.

The sensation of itch is primarily mediated by unmyelinated C-fibers with nerve endings in the epidermis. Various itch mediators act on these nerve endings and transmit the sensation of itch through the ascending spinothalamic nerve tract, resulting in the perception of itch. There are various itch mediators in the skin, and several are thought to play a role in liver disease, including bile acids, endogenous opioids, lysophosphatidic acid, and autotaxin.[2,3] Bile acids (BAs) accumulate in patients with liver disease resulting in cholestasis. It is known that injection of bile acids into the skin of healthy individuals produces the sensation of itch.[4] However, pruritus does not always happen in all patients with cholestatic liver disease; thus, implying that BA levels do not always correlate with intensity of pruritus. In addition, BA resins do not always successfully diminish itch in patients with cholestasis.[5] Nevertheless, BA resins remain a mainstay of therapy in cholestatic patients. Although some studies have demonstrated that endogenous opioids also may play a role mediating itch, the relationship between endogenous opioids and itch intensity has not been fully elucidated.[6] Lysophosphatidic acid (LPA), a phospholipid produced by the enzyme autotaxin (ATX), is another endogenous molecule that has been found to play a significant role in cholestatic pruritus.[6,7] Unlike endogenous opioids, serum LPA levels and ATX activity does correlate with intensity of pruritus.

Pruritus has a significant impact on patient-reported quality of life and is often the reason patients seek medical care.[8] Currently, cholestyramine, an anion exchange resin, is the only medication approved by the Food and Drug Administration for cholestatic pruritus.[9] There are several additional agents that have been studied as treatment for cholestatic pruritus. A meta-analysis of five prospective randomized clinical trials showed that rifampicin is effective in treating cholestatic pruritus as well. However, administration for longer than 2 weeks is not recommended because of side effects including potential hepatotoxicity.[10] Sertraline, a serotonin reuptake inhibitor, has also shown to be moderately effective in cholestatic pruritus.[11] Because sertraline is metabolized by the liver caution should be used when administering this agent in patients with liver disease. The fourth line of therapy is opioid antagonists. Both μ-opioid receptor antagonists, naltrexone and naloxone, have been effective in treating cholestatic pruritus; however, they should be avoided in patients with acute liver injury or severe liver insufficiency.[12–14] Further research investigating LPA antagonists and ATX blockers as future therapeutic agents is still required. Additional nonpharmacological treatments may be used in combination with these oral therapies or as second-line treatments if the usual oral therapies fail. These include narrowband ultraviolet B therapy (nbUVB), plasmapheresis, nasobiliary drainage, albumin dialysis, and biliary diversion procedures. Of these, nbUVB therapy is commonly used in the dermatologic setting to treat itch and inflammatory disorders of the skin. The antipruritic effect of phototherapy may be due to an alteration of cytokine release, depletion of Langerhans cells, chemical modification of pruritogens in the skin, and the reduction of skin sensitivity to pruritogens.[15]

Nevus Araneus

Nevus araneus, commonly known as a spider angioma, is a cutaneous vascular manifestation that can be seen in 10% to 15% of healthy individuals. However, when multiple spider angiomas are seen, they can be a manifestation of liver disease, especially alcoholic cirrhosis and hepatopulmonary syndrome.[16,17] Spider angiomas are so named because they consist of an ascending spiraling arteriole, ending in the superficial epidermis, with numerous branching capillaries radiating peripherally in the

papillary dermis, revealing the configuration of a spider.[18] They are classically nonpalpable, blanching lesions approximately 1 to 10 mm in size, usually dispersed over the face, chest, arms, and hands. However, atypical lesions have been described in conjunction with liver disease, including larger spider angiomas, papillary spider angiomas, and mucocutaneous spider angiomas.[19–21] Spider angiomas are dilations of preexisting arterioles in the skin, thought to be mediated by various factors including increased estrogen levels, increased vascular endothelial growth factor, basic fibroblastic growth factor, and even substance P.[22,23] Spider angiomas tend to resolve as the underlying liver disease is treated.

Palmar Erythema

Palmar erythema refers to a nontender, blanching, symmetric redness of both palms, and sometimes soles. Erythema is most commonly seen on the thenar and hypothenar eminences of the palmar surface.[24] Although palmar erythema can be seen in many clinical states, palmar erythema of hepatic disease should not be confused with physiologic erythema of the palms, which often presents over the entire palm due to positioning, temperature, or pressure. Palmar erythema seen in hepatic disease has been observed to be caused by increased free estrogen levels, which leads to vasodilation of surface capillaries in the hands.[24]

Xanthomas

Xanthomas are yellow-orange papules or plaques that form around the eyes due to the deposition of lipids in the dermis, specifically macrophages. They can develop due to either a primary or secondary lipid disorder, but in the setting of hepatic disease, xanthomas are most commonly seen secondary to primary biliary cholangitis (PBC).[25,26] Total cholesterol is often elevated in PBC[27], and abnormal cholesterol metabolism in hepatic disease contributes to formation of xanthomas. It is thought that approximately 15% to 50% of patients with PBC have xanthomas[25]. Xanthelasmas, or plane xanthomas of the eyelids, are believed to occur in approximatley 5-10% of patients with PBC.[28] Xanthomas tend to regress with treatment of the underlying hyperlipidemia.

Jaundice

Jaundice refers to a yellow to brown discoloration of the skin and/or mucous membranes secondary to hyperbilirubinemia, often exceeding the range of 2.5 to 3.0 mg/dL. The color change often corresponds to the level of bilirubin with mild hyperbilirubinemia causing mild yellow color change all the way to brown, indicating more severe hyperbilirubinemia.[29] When present, it is important to establish the cause of jaundice, including conjugated or unconjugated and prehepatic, intrahepatic, or posthepatic.[30]

CUTANEOUS PATTERNS SEEN IN SPECIFIC HEPATIC DISEASES

Primary Biliary Cholangitis

PBC is an autoimmune disease leading to the progressive destruction of the small bile ducts of the liver. In 50% of patients, the presenting symptom is pruritus. Pruritus when accompanied by jaundice, hyperpigmentation, and xanthomas is specific for PBC.[31] However, PBC can present with a variety of other cutaneous manifestations. In a prospective case control study looking at dermatologic manifestations in 49 patients with PBC, a total of 330 different skin disorders were identified and more than one-third of these patients presented initially with a cutaneous finding of PBC. The most common cutaneous presentation of PBC in this cohort was fungal infections

including tinea pedis and onychomycosis. Pruritus and xerosis (dry skin) were found in 69.3% of patients.[32] In addition, because PBC is an autoimmune disorder, it can be seen in conjunction with other autoimmune disorders that affect the skin, including Sjögren syndrome, and morphea.[33–35]

Hepatitis B

Hepatitis B is a chronic liver infection caused by the hepatitis B virus. The infection is often divided into the pre-icteric (prodromal) phase and the icteric phase. Urticarial lesions are common during the prodromal phase and are thought to be due to immune-complex deposition.[36] Urticaria is characterized as the development of wheals (itchy edematous papules or plaques in the superficial dermis, that typically develop acutely within 24 hours) and/or angioedema (more painful swelling that occurs deeper in the dermis and subcutaneous/submucosal tissue lasting longer than 24 hours).[1]

Hepatitis B infection can also present with various types of vasculitides, including small vessel vasculitis, urticarial vasculitis, and polyarteritis nodosa.[37] Small vessel vasculitis refers to immune-complex deposition in the dermal post-capillary venules, leading to cutaneous presentations with palpable purpura, erythematous papules, or hemorrhagic vesicles that range in size from 1 mm to several centimeters.[1] Urticarial vasculitis is a variant of small vessel vasculitis that presents with urticarial lesions rather than erythematous or purpuric lesions.

Polyarteritis nodosa (PAN), a type of medium-sized vasculitis, is most commonly associated with hepatitis B. In fact, approximately 7% to 8% of patients with hepatitis B have concomitant PAN.[38–40] PAN usually occurs approximately 6 months into a hepatitis B infection, likely due to immune-complex deposition. Interestingly, the treatment for hepatitis B–associated PAN is antiviral agents combined with plasma exchanges.[40]

In addition to vasculitis, metabolic disorders like porphyria cutanea tarda (PCT) also may be seen with hepatitis B. Porphyrias are metabolic disorders that arise from either inherited or acquired deficiencies in 1 of 8 heme synthesis enzymes. The disorder manifests on the skin as blisters, erosions, milia, or fragile skin in sun-exposed areas of the body, classically the dorsal hands. Of the various types of porphyrias, PCT is most commonly seen in hepatitis infections.[41] Although the exact etiology of this relationship is not clear yet, activation of the host immune system and complement system with heightened autoimmune phenomenon are thought to be contributing factors.[41,42] It is also important to mention that patients with PCT and chronic active hepatitis have an increased risk of developing hepatocellular carcinoma.[43]

Finally, hepatitis B infections have also been known to trigger a type of dermatitis called acrodermatitis papulosa, or Gianotti-Crosti syndrome. This is a symmetric, popular eruption on the face, extremities, and buttocks associated most commonly with viral infections.[44] Although it is more common to see Gianotti-Crosti syndrome in childhood, it has been reported several times in adults associated with concomitant hepatitis B infection.[45,46]

Hepatitis C

Although recent advances in hepatitis C treatment often cure patients of the infection, patients who do not receive or who fail treatment can go on to develop chronic infection, which is associated with multiple cutaneous manifestations. Some skin findings associated with chronic hepatitis C infection are also seen in patients with hepatitis B infection, including small vessel vasculitis, urticarial vasculitis, and PCT. Other cutaneous manifestations, such as cryoglobulinemia, necrolytic acral erythema, sarcoidosis, and lichen planus, are more specific to hepatitis C infection.

Cryoglobulinemia refers to the presence of cryoglobulins, or immunoglobulins with the ability to precipitate at temperatures less than 37 °C in the blood.[47] The presence of cryoglobulins in the blood leads to a systemic inflammatory syndrome that includes cryoglobulinemic vasculitis with cutaneous manifestations. Predisposing conditions for this type of vasculitis include hepatitis C infection.[48] In fact, approximately 80% of mixed cryoglobulinemia is secondary to hepatitis C virus (HCV) infection.[49] Cutaneous manifestations of this type of vasculitis include purpura, ulcers usually on distal extremities, livedo reticularis, and urticarial lesions. The treatment for cryoglobulinemia depends on the underlying cause. For hepatitis C–related cryoglobulinemia, treatment with direct-acting antiviral therapy is essential.[47]

Another common cutaneous manifestation seen in patients with hepatitis C is necrolytic acral erythema (NAE). NAE is even thought to be a cutaneous marker for hepatitis C infection.[50,51] Clinically, NAE presents as painful and/or pruritic well-circumscribed dark violet to black-colored plaques with hyperkeratosis on mostly acral skin. Although it can present clinically similar to necrolytic migratory erythema, positive HCV serology with normal glucagon levels can help make the diagnosis.[52] Treatment of NAE is also very closely related to treatment with hepatitis C. Several reports have shown resolution of NAE with interferon alfa and ribavirin.[53,54] Oral zinc, even in patients with normal zinc serum levels, has also shown to be effective, as it may enhance the effects of hepatitis C treatment.[55–57]

Lichen planus (LP) is a chronic autoimmune, inflammatory disorder that affects both the skin and mucous membranes. Its exact etiology is unknown; however, infectious triggers, especially hepatitis C, are known to be associated with LP. It is clinically characterized as having shiny, flat-topped, violaceous, polygonal-shaped papules up to a centimeter in size.[58] However, in the mouth, it manifests most commonly on the buccal mucosa as reticular white plaques, white papules, or atrophic erosions.[59] Many studies have shown a significant association between LP and HCV, more specifically erosive oral LP.[59] The prevalence of hepatitis C in patients with oral LP is high, and longstanding HCV infection has been observed to be a risk factor in development of oral LP.[60,61] A meta-analysis also showed significant association between oral LP and HCV, suggesting that it is reasonable to screen for hepatitis C in patients with oral LP. Of note, isolated cutaneous LP has not been shown to be significantly associated with HCV.[58]

Hemochromatosis

Hemochromatosis, and the state of iron overload it describes, is most commonly caused by an inherited disorder affecting iron transportation. Whereas PBC is most commonly seen in female individuals, 90% of patients with diagnosed with hemochromatosis are male.[31] Hereditary hemochromatosis is one of the most common genetic disorders in white individuals and often clinically manifests in those with underlying comorbid inflammatory liver conditions such as hepatic steatosis, alcoholic liver disease, and hepatitis.[62–64] In addition to nonspecific cutaneous stigmata associated with comorbid hepatic disease, one of the most commonly seen cutaneous findings in patients with excess iron deposition in the skin is hyperpigmentation.

Hyperpigmentation is the presenting symptom in one-third of patients with hemochromatosis and is usually generalized, yet prominence can be noted on exposed skin.[65] Skin often appears slate gray (due to dermal iron) or brown (due to increased melanin production).[66,67] In a minority of patients, the mucous membranes and conjunctiva are also affected. This hyperpigmentation is reflected in the description of hemochromatosis as “bronze diabetes.”

Unlike most other causes of chronic liver disease, most systemic dysfunction due to iron deposition can be effectively treated. Phlebotomy usually reverses damage done

to many organ systems, including the skin, and phlebotomy often leads to lightning of the skin.[62,67]

Cirrhosis and Alcohol Cirrhosis

Cirrhosis refers to the histology findings of hepatic nodules, fibrosis, and loss of functional hepatocytes that occurs in the setting of chronic liver disease.[67] Four of the most common liver diseases that lead to cirrhosis include alcoholic liver disease, chronic viral hepatitis, hemochromatosis, and nonalcoholic liver disease.[67,68]

Cutaneous manifestations of cirrhosis affect the skin, nails, and hair. Alterations in vascular physiology lead to the appearance of palmar erythema, spider angiomas, and paper money skin. Paper money skin is a rarer variant of spider angiomas that appear as diffuse, thin plaques of superficial capillaries usually on the trunk. These lesions blanch with diascopy and the wiry thin vessels resemble the silk threads seen on dollar bills in the United States.[69] Caput medusa describes the dilated and tortuous abdominal veins that occur due to portal hypertension.

Nail changes seen in the setting of cirrhosis include those caused by defects to the nail bed, such as Muerhcke lines and Terry nails. Muerhcke lines are characterized by double transverse lines that disappear when pressure is applied. These paired lines are due to decreased serum albumin and abnormal nail bed vasculature.[64,67] In Terry nails, the proximal two-thirds of the nail appears white with sparing of the distal nail that appears as a band of normal pink or brown color.[31,66,67] Clubbing, in which the angle between the proximal nail fold and nail plate is greater than 180°, is often seen in patients with pulmonary hypertension.[1] Although Terry nails are classically associated with cirrhosis, the nail findings in patients with cirrhosis are nonspecific and can be seen in a variety of other systemic conditions.

Diffuse thinning or loss of pubic and axillary hair or the development of female distribution of pubic hair is often seen in the setting of hyperestrinism. Cutaneous manifestations of liver disease are seen in nearly half of chronic alcoholics.[66,70] Nearly three-fourths of patients with alcohol cirrhosis have spider angiomas, palmar erythema, and Dupuytren contracture.[70]

SUMMARY

Ultimately, there are many cutaneous manifestations of liver disease. In some instances, cutaneous signs may be a marker of liver disease (ie, NAE) or may even be related to underlying severity of liver disease. In other cases, cutaneous signs may be more nonspecific (ie, pruritus, spider angiomas). Ultimately cutaneous manifestations are important to both recognize and treat. Recognition of these skin findings may aid in earlier diagnosis and management of chronic liver diseases, and treatment of cutaneous signs helps render a more complete approach to patient care.

DISCLOSURE

The authors have nothing to disclose.

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