Clinical Examination: Skin

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Recognition of cutaneous presentations associated with liver disease can provide clues to diagnosis and disease severity. It is important to recognize that these cutaneous findings are not necessarily disease specific and may occur in other clinical settings in the absence of liver disease. To cover this spectrum, I will review skin changes seen with hepatic cirrhosis followed by skin associations with specific liver diseases, including primary biliary cirrhosis, viral hepatitis, hemochromatosis, and Wilson's disease.

CIRRHOSIS

Cirrhosis can lead to many clinical manifestations involving the skin including jaundice, vascular changes, pruritus, and nail changes.¹ Jaundice is the yellowish discoloration of the skin caused by hyperbiliruniemia and usually becomes clinically evident when the serum levels exceed 2 to 3 mg/dL^{2,3} (Fig. 1). This discoloration extends to the mucosal surfaces and is often most evident in the sclera (*icterus*). The mucosal involvement provides distinction from carotemia, which can be more orange-yellow and spares the mucosa and sclera.

Vascular changes can occur because of increased levels of serum estradiol, including palmar erythema and spider angiomas (Figs. 2 and 3). Spider angiomas are named for the radiating vessels from a central area arteriole in the skin and blanch when pressure is applied. The radiating vessels distinguish them from cherry angiomas, which are discrete, well-defined papules. Palmar erythema occurs in 23% of patients with liver cirrhosis, as well as Wilson's disease and hematochromatosis.⁴ These changes are not specific to liver cirrhosis and may be seen in other increased estrogen states such as pregnancy. Other vascular manifestations include dilated veins in the abdominal wall (*caput medusa*) and changes secondary to clotting deficiency and vascular fragility such as purpura. Other hormonal changes can include testicular atrophy, gynecomastia, and striae.

Pruritus can be a severe and therapeutically challenging cutaneous symptom in multiple hepatobiliary diseases. The mechanism for pruritus is related to the accumulation of bile salts and acids, supported by evidence of symptom improvement after treatment with bile acid chelating resins such as cholestyramine.⁵ Scratching of the skin does little to relieve symptoms and leads to secondary changes including erosions, prurigo nodules, and lichenification of the skin.

Abbreviations: PCT, porphyria cutanea tarda.

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FIG 1 Jaundice with lichenification of the skin from chronic pruritis.

Treatment options include phototherapy, sertraline, rifampicin, and naloxone.³

Nail changes in cirrhosis may include clubbing, Terry nails (white nail bed), and Muehrcke nails (transverse white bands) (Figs. 4 and 5).

VIRAL HEPATITIS

Most dermatological findings associated with viral hepatitis, such as small vessel vasculitis and polyarteritis nodosa, may be observed with both hepatitis B and C. Certain diagnoses, such as mixed cryoglobulinemia (types II and III) and lichen planus, are more commonly associated with hepatitis C.⁶

Mixed cryoglobulinemia is a systemic vasculitis that can affect the kidneys and peripheral nervous system, as well as the skin. Immunocomplexes of IgG and IgM deposit along the endothelium leading to cutaneous changes of nonpalpable purpura (Fig. 6). Hepatitis C virus has been identified in affected skin.^{7,8} Diagnosis is confirmed by histopathology showing leukocytoclastic vasculitis and direct immunofluorescence of involved skin showing vascular deposition of IgM and C3.

Lichen planus typically presents with extremely pruritic flat-topped papules on the distal extremities (Fig. 7). The

FIG 2 Palmar erythema.

papules and plaques have a violaceous hue and a whitish “net-like” change on the surface called Wickham striae. Lichen planus can also present on the oral mucosa, often the buccal mucosa, and may be ulcerated or erosive (Fig. 8). Biopsy shows histopathological findings of lichenoid

FIG 3 Spider angioma.

FIG 4 Clubbing.

interface dermatitis. Although most patients with lichen planus do not have hepatitis, there is an increased incidence of hepatitis C with lichen planus especially with erosive oral lichen planus.⁹⁻¹¹

Other cutaneous presentations associated with hepatitis C include necrolytic acral erythema and porphyria cutanea tarda (PCT). Necrolytic acral erythema presents with discoloration at acral sites (especially the feet/lower legs) associated with scale (hyperkeratosis), erosions, or even vesicles. These

FIG 5 Terry nails.

FIG 6 Mixed cryoglobulinemia.

changes can mimic nutritional deficiencies including necrolytic migratory erythema and pseudoglucagonoma.^{2,3} PCT is discussed further in the following section in the discussion of hemochromatosis (Fig. 9).

FIG 7 Lichen planus demonstrating "net-like" whitish change known as Wickham striae.

FIG 8 Oral lichen planus.

Polyarteritis nodosa is a medium vessel vasculitis that can be systemic or restricted to the skin. Cutaneous changes include livedo racemosa (Fig. 10), subcutaneous nodules (Fig. 11), and even cutaneous ulceration or necrosis. Hepatitis B is the most common infectious trigger, accounting for 7% of all cases.^{12,13}

FIG 9 Porphyria cutanea tarda.

FIG 10 Livedo racemosa seen in polyarteritis nodosa.

Hepatitis B is associated with many other nonspecific cutaneous eruptions seen across etiological spectra including urticaria, erythema nodosum, erythema multiforme, and Gianotti-Crosti syndrome (papular acrodermatitis of childhood) (Figs. 12 and 13).

FIG 11 Subcutaneous nodules in polyarteritis nodosa.

FIG 12 Erythema nodosum.

METABOLIC DISEASE: HEMOCHROMATOSIS, PORPHYRIA CUTANEA TARDA, AND WILSON'S DISEASE

In hemochromatosis, the iron overload seen in multiple organ systems is reflected in the skin by a bronze hue known as bronze diabetes (Fig. 14).¹⁴ Although deposition of iron is thought to be the primary cause for pigmentary changes, there can also be a grayish brown coloration caused by activation of melanin production, especially on the face.¹⁵

The iron overload in hemochromatosis can predispose patients to development of PCT. Therefore, PCT can be an important cutaneous presentation that leads to the diagnosis of hemochromatosis.^{16,17} PCT is precipitated by an acquired or hereditary decreased activity of hepatic uroporphyrinogen decarboxylase, and often genetic predisposition plus other factors lead to the clinical presentation.¹⁸ Other risk factors include hepatitis C, HIV, hepatic tumors, alcohol intake, and estrogens.¹⁸

PCT is the most common form of porphyria that presents with vesicles and bullae on sun-exposed areas (often on the dorsal hands), facial hypertrichosis, and sclerodermoid fea-

tures. The vesicular presentation may heal with scarring and milia formation (Fig. 9). Skin biopsy of acute areas can show typical histopathological findings of a subepidermal pauc inflammatory cleft with preservation of the dermal papillae known and “festooning.” However, in resolving nonbullous lesions, the histopathological features may be nonspecific, and diagnostic confirmation with evaluation for elevated urine uroporphyrin levels is more reliable.¹⁹

In Wilson’s disease, the most distinctive cutaneous feature is bluish discoloration of the nail lunulae (*azure lunulae*), which is the most proximal part of the nail next to the nail fold.²⁰ Pretibial hyperpigmentation and ocular changes (Kayser-Fleischer ring) can also be seen, and anetoderma has been reported.²¹

PRIMARY BILIARY CIRRHOSIS AND PRIMARY SCLEROSING CHOLANGITIS

In addition to pruritus and jaundice, melanosis and xanthomas or xanthelasma can occur in primary biliary cirrhosis.^{1,22} Melanosis presents as diffuse or circumscribed brownish gray pigmentation on the skin caused by increased melanin deposition. Xanthomas are

FIG 13 Gianotti-Crosti syndrome.

FIG 14 Bronze hyperpigmentation in hemochromatosis (bronze diabetes).

yellowish papules or plaques that occur with dyslipidemia (Fig. 15). Long-term biliary obstruction leads to elevated serum cholesterol, which can manifest as planar xanthomas (plaques on trunk and extremities), xanthelasma (periorbital papules and plaques), and tuberous xanthomas (nodules).^{1,3}

FIG 15 Xanthelasma.

FIG 16 Pyoderma gangrenosum.

Given the association of primary sclerosing cholangitis with inflammatory bowel disease, especially ulcerative colitis, skin findings may include pyoderma gangrenosum and erythema nodosum. Pyoderma gangrenosum starts as a pustule that ulcerates and has a purple border (Fig. 16). Erythema nodosum consists of tender, nonulcerated, subcutaneous nodules typically on the lower legs (Fig. 12).

SUMMARY

Inspection of the skin and nails and evaluation for symptoms of pruritus are valuable tools in evaluation of liver diseases. In addition to providing clues for the diagnosis of liver diseases, recognition of these dermatological features can provide further reassurance, guidance, and potential treatment of the patient's dermatological concerns and conditions.

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