Cutaneous Manifestations of Common Liver Diseases

Sunil Dogra, Rashmi Jindal

Department of Dermatology, Venereology and Leprology, Postgraduate Institute of Medical Education and Research, Chandigarh – 160012, India

Skin functions as a window to our overall health and a number of systemic diseases result in various cutaneous changes. Knowledge of these manifestations helps in suspecting an underlying systemic illness. Cutaneous abnormalities are quite common in patients with liver diseases and this article aims to focus on these dermatoses. Cutaneous manifestations seen in patients with liver disease though common are nonspecific. They can also be seen in patients without liver diseases and generally do not indicate about a specific underlying hepatic disorder. The presence of a constellation of signs and symptoms is more useful in pointing toward an underlying hepatobiliary condition. The commonest symptom in patients with liver disease is pruritus which is often protracted and disabling. Other common features include spider angiomas, palmar erythema, paper money skin, xanthelasmas, pigmentary changes, and nutritional deficiencies. In this article, first the common cutaneous manifestations that may be associated with liver disorders are discussed and then common liver diseases with their specific cutaneous findings are discussed. Cutaneous abnormalities may be the first clue to the underlying liver disease. Identifying them is crucial for early diagnosis and better management. (J Clin Exp Hepatol 2011;1:177–184)

Hepatobiliary diseases are commonly associated with changes in skin, nails and hair. These changes are, however, generally nonspecific as they do not point toward a specific diagnosis and can be present in diseases not affecting the hepatobiliary system. At times, a combination of cutaneous signs and symptoms may give a clue to the underlying disease. For instance, the presence of pigmentation, jaundice, and xanthomas suggests the underlying diagnosis of primary biliary cirrhosis (PBC).[1] Data on the incidence of cutaneous changes in patients with chronic liver diseases are limited. In patients of cirrhosis, palmar erythema has been reported to be present in 23%, spider angiomas in 33% and triad of palmar erythema, spider angiomas and white nails is seen in 21% patients.[2,3] For better understanding, first the skin conditions that may represent the underlying liver disease and then the common liver diseases with their typical cutaneous manifestations are discussed.

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Address for correspondence: Sunil Dogra, Associate Professor, Department of Dermatology, Venereology and Leprology, Postgraduate Institute of Medical Education and Research, Chandigarh – 160012, India
E-mail: sundogra@hotmail.com
Abbreviations: ALD: alcoholic liver disease; HBeAg: hepatitis B 'e' antigen; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; LPA: lysophosphatidic acid; PAN: polyarteritis nodosa; PBC: primary biliary cirrhosis; PCT: porphyria cutanea tarda
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SKIN CHANGES THAT MAY REPRESENT LIVER DISEASE

Pruritus

Pruritus is the commonest and at times the most distressing symptom of hepatobiliary diseases. It can be transient and mild or persistent and severe. Conditions associated with cholestasis such as primary sclerosing cholangitis and obstructive gallstone disease commonly present with pruritus where it tends to be generalized but worse on hands and feet.[4] The pathophysiological basis of pruritus in liver diseases is incompletely understood. Historically, the accumulation of bile salts, bile acids, and bilirubin has been considered to be responsible for cholestatic pruritus. Improvement of pruritus with the use of bile acid chelating resins and the disappearance of pruritus after dilating major bile duct stenosis in patients with longstanding intractable cholestatic pruritus are evidences to support the causative role of these substances.[5,6] However, not all patients with elevated levels of bile salts or acids manifest pruritus and also many patients do not respond to bile acid chelating resins.[7] Further concentration of bile salts seems unrelated to the intensity of pruritus.[6,8] Bile salts possibly play a complex role in mediating cholestatic pruritus by interacting with other pruritogens. A number of potential pruritogens including endogenous opioids, histamine, tryptase, and substance P have been investigated. Dramatic improvement in cholestatic pruritus with the use of μ-receptor antagonist naltrexone strongly supports the role of endogenous opioids in the pathogenesis of cholestatic pruritus; however, no correlation has been found between the intensity of itch and opioid levels.[9] Recently,

lysophosphatidic acid (LPA) has been identified as a major pruritogen. It is produced from lysophosphatidylcholine by the action of enzyme autotaxin. In a study done by Kremer et al,[10] the levels of autotaxin and LPA were markedly increased in cholestatic patients with pruritus when compared with those without pruritus. Also, autotaxin activity significantly correlated with the intensity of pruritus; while that of serum bile salts, histamine, substance P, and μ-opioids failed to do so.[10] Pruritus of cholestasis does not get relieved by scratching and usually no visible skin lesions other than excoriations are seen. Sometimes, patients can develop lichenified plaques and prurigo nodular is like lesions. Pruritus of liver diseases is quite resistant to therapy. Bile acid resins like cholestyramine form the first line of therapy. Other treatment options include selective serotonin re-uptake inhibitors, plasmapheresis, and opioid antagonists (naloxone). Rifampicin has also shown good results in some studies by promoting metabolism of endogenous pruritogens.[11,12] A treatment algorithm usually followed in patients with pruritus of chronic liver disease is depicted in Figure 1.[13] Intractable itch in patients of chronic liver disease could be an indication of liver transplant in rare situation even if not associated with liver failure.[14]

Jaundice

Jaundice is a manifestation of hyperbilirubinemia and becomes clinically evident when the serum level of bilirubin exceeds 2.5 or 3.0 mg/dL. The color of the skin depends on the severity of hyperbilirubinemia and ranges from yellow to brown in mild to severe hyperbilirubinemia, respectively.[15,16] Whether, the excess bilirubin is conjugated or unconjugated gives a clue as to whether the cause is hepatic, prehepatic, or posthepatic. Green-colored sweat or green discoloration of gingiva can also occur in patients with jaundice.[17]

Vascular Signs

Spider Angioma

These are collection of dilated blood vessels near the skin surface. Spider angiomas are composed of a central feeding arteriole surrounded by radiating tortuous capillaries. Blanching of lesion when pressure is applied over central arteriole is the hallmark sign. Most common site of occurrence is the trunk and face. Their presence in patients with alcoholic liver disease (ALD) indicates the associated risk of esophageal varices.[18] Further, their presence in increased number acts as a clinical marker of hepatopulmonary syndrome.[19] Elevated estrogen levels are considered to be pathogenic in their development as observed in cirrhosis, pregnancy, and during estrogen replacement therapy.[20] Their presence in adults should prompt to investigate for underlying liver disease. Spontaneous regression with improvement in hepatic status or after liver transplant has been observed.[21] For cosmetic purpose, these can be treated with laser therapy.

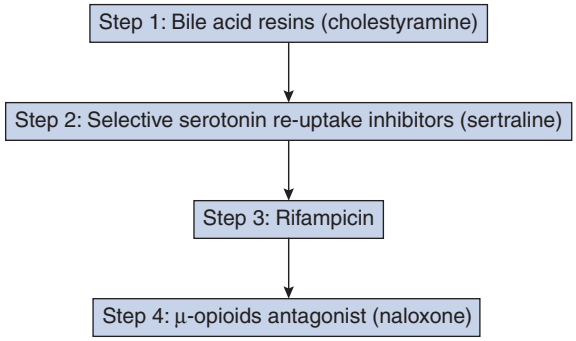

Figure 1 Treatment algorithm for patients with pruritus of chronic liver disease.

Palmar Erythema

Palmar erythema or liver palms can present as generalized redness of palms, dorsum of hands, fingertips, and nail bed. At times, it is localized only to hypothenar eminence. Similar changes can be seen over soles. Erythema blanches on the pressure and flushes synchronously with pulse rate.[18] Patient may complain of throbbing and tingling sensation. Exact pathogenesis of this mechanism is not known, but prostacyclins and nitric oxide are thought to play some role.[22,23] The disturbed androgen balance in patients with ALD leads to local vasodilatation presenting as erythema. Patients of cirrhosis may have accompanied muscle atrophy of thenar and hypothenar eminence which appear to be myogenic in origin and not related to hormonal fators.[18]

Paper Money Skin

Patients with cirrhosis have many randomly scattered thin superficial capillaries over the upper trunk in association with spider angiomas. This resembles the silk threads in American dollar bills and hence is named dollar paper markings or paper money skin.[24]

Other Vascular Changes

Other vascular changes include corkscrew scleral vessels and caput medusae. Patients can also have purpuric lesions, epistaxis, and gingival bleeding either due to vascular fragility or due to acquired clotting factor deficiency.[20] Sometimes, small irregularly shaped hypopigmented patches are seen over arms and legs. These are considered to be due to venous stasis and are known as Bier spots. Their characteristic feature is that they disappear when pressure is applied or when the affected limb is raised from dependent position.[25]

Xanthelasma

Liver diseases can result in various forms of secondary dyslipoproteinemias.[26] Most common are hypertriglyceridemia

and low levels of high-density lipoproteins. Cutaneous manifestation is in the form of xanthelasmas which present as soft, yellowish asymptomatic plaques especially over the eyelids. The PBC is especially known to be associated with hypercholesterolemia and presents as planar, tuberous, and tendinous xanthomas.[27]

Pigmentary Changes

Patients with chronic liver disease often have a muddy gray colored hyperpigmentation predominantly over sun-exposed areas. It may be blotchy or diffuse, at times exaggerated in perioral, periocular areas, and palmar creases. Men often have increased areolar pigmentation in association with testicular atrophy and gynecomastia. Patients with hemochromatosis commonly develop metallic brown discoloration of the skin due to increased melanin production secondary to the cutaneous deposition of hemosiderin, known as bronze diabetes.[29]

Hair and Nail Changes

Patients with chronic liver disease may develop thinning of hair and hair loss. Nail changes in cirrhosis includes clubbing, thickening of nails, longitudinal ridging, white bands (Muehrke's bands), and brittle nails.[29,30] Those with advanced cirrhosis can present with Terry's nails characterized by a ground glass opacity of nail plate which turns powdery white at its proximal end.[31] Bluish discoloration of lunulae occurs in patients with Wilson's disease known as *Azure lunulae*. Splinter hemorrhages and hypertrophic osteopathy can also occur in cirrhosis.[1]

Hormonal Changes

In patients with chronic liver disease, there can be loss of forearm, axillary and pubic hair in both sexes. Men experience a decrease in the growth rate of facial hair and development of female pubic hair pattern along with the loss of libido, testicular atrophy, and oligospermia. Striae distensae can also develop in patients with cirrhosis. Those with chronic alcoholism develop a pseudo-Cushing's syndrome with truncal obesity, moon facies, and proximal muscle wasting.[18]

Nutritional Deficiencies

A number of hepatic diseases predominantly those causing steatorrhea result in the malabsorption of proteins, carbohydrates, minerals, trace elements, and vitamins. Further hypovitaminosis also results from decreased hepatic storage and failure of liver to convert vitamins to metabolically active forms. Also, vitamins are essential to repair the damaged cells and to produce new hepatocytes. Patients with hepatocellular disease including ALD have deficiency predominantly of vitamin B-complex and folic acid, while those with biliary obstruction have deficiency of fat-soluble vitamins (A, D, E, and K).[32] Deficiency of these vitamins leads to changes in skin, nails, hair, and mucosae (Table 1). Deficiency of iron and zinc also commonly present in patients with chronic liver disease. Iron deficiency manifests as angular stomatitis, glossitis, brittle nails, and alopecia. Zinc deficiency can result in the development of dermatitis lesions over body and erosions over genital, perianal, and perioral areas.

Table 1 Mucocutaneous manifestations of vitamin deficiencies in patients with chronic liver diseases.

Vitamin deficiency	Mucocutaneous manifestation
Vitamin A	• Xerosis • Deep skin fissures (dermomalacia) • Follicular hyperkeratosis (phrynoderma) • Xerophthalmia
Vitamin D	• Alopecia
Vitamin E	• Follicular hyperkeratosis
Vitamin K	• Purpura • Ecchymosis • Gingival bleeding
Vitamin C	• Follicular hyperkeratosis • Perifollicular hemorrhages • Stomatitis, epistaxis, bleeding gums (scurvy)
Vitamin B_2 (riboflavin)	• Seborrheic dermatitis • Stomatitis, gingivitis • Conjunctivitis, corneal vascularization
Vitamin B_6 (pyridoxine)	• Seborrheic dermatitis • Photodermatitis • Glossitis, cheilitis
Vitamin B_{12} (cyanocobalamin)	• Hyperpigmentation of flexures, knuckles, palms, and fingers • Pigmented streaks over nails • Enlarged red tongue
Vitamin B_3 (niacin)	• Pellagra (dermatitis, dementia, and diarrhea)
Biotin	• Alopecia • Eczema around nose and mouth • Conjunctivitis
Folic acid	• Gray brown pigmentation on sun-exposed areas • Cheilitis • Glossitis • Mucosal erosions

LIVER DISEASES WITH THEIR TYPICAL CUTANEOUS MANIFESTATIONS

Viral Hepatitis

Hepatitis A Virus

This is generally a transient infection and does not lead to chronic liver disease. The cutaneous manifestations include jaundice, urticaria, and exanthema which are present in a minority of cases.[33] In its relapsing variant, itching, purpura, and small vessel vasculitis can be seen.[34]

Hepatitis B Virus

This is transmitted parenterally and sexually. It may be associated with the presence of other sexually transmitted diseases and include a variety of cutaneous findings.

Urticaria and Angioedema: Serum sickness like syndrome occurs in around 10% patients of acute HBV infection in the preicteric phase.[18] This may range from a mild erythema to a severe illness characterized by fever, malaise, and arthralgia. Circulating immune complexes are considered to be pathogenic.[35] Histopathology reveals small vessel vasculitis with direct immunofluorescence positive for IgG, IgM, C_3, and hepatitis B surface antigen (HBsAg). Erythema multiforme and erythema nodosum like lesions can also be present. These cutaneous changes many a times precede the onset of other features of liver disease.[1]

Polyarteritis Nodosa: Hepatitis B virus infection is present in around 20% patients of polyarteritis nodosa (PAN). The frequency of HBV infection in patients with PAN has considerably declined over the past two decades.[1] About 7–8% patients of acute HBV infection develop PAN and in most of them anti-neutrophil cytoplasmic antibody is negative unlike the classical PAN. Antigen–antibody complexes possibly involving hepatitis Be antigen (HBeAg) are thought to be pathogenic.[36] Management of HBV-associated PAN includes short-term steroid therapy along with anti-virals and plasmapheresis.[37]

Cryoglobulinemic Vasculitis: Cryoglobulins are detectable in 15% patients with HBV infection and this is generally asymptomatic.[1]

Gianotti Crosti Syndrome (Papular Acrodermatitis of Childhood): It is characterized by small umbilicated papules predominantly affecting the extremities, buttocks, and cheeks. It has now been described in association with a number of other viral infections but was initially linked to HBV infection and vaccination. Lesions resolve spontaneously over 6–8 weeks and therefore management is only symptomatic.[1]

Other Skin Lesions: Pyoderma gangrenosum, dermatomyositis, and lichen planus have all been reported to be associated with HBV infection.[38,39] There are few case reports of the development of urticaria, lichen planus, Gianotti Crosti syndrome, and granuloma annulare with HBV vaccination.[40]

Hepatitis C Virus

This is predominantly transmitted parenterally and 75% of patients develop chronic hepatitis.

Cryoglobulinemia: Majority (70%) of type II cryoglobulinemia (polyclonal IgG and monoclonal IgM rheumatoid factor) and a minority of type III cryoglobulinemias (polyclonal IgG and polyclonal IgM rheumatoid factor) are HCV-associated. Common presenting features include small vessel vasculitis affecting the lower extremities, acrocyanosis, livedo reticularis, glomerulonephritis, arthralgia, hepatosplenomegaly, and hypocomplementemia.[41,42] Studies have demonstrated the presence of HCV-RNA in organs affected in cryoglobulinemia mainly the skin and kidneys. All patients with mixed cryoglobulinemia complicating HCV infection should receive anti-virals as first-line therapy.[43]

Polyarteritis Nodosa: A small percentage of patients (30%) with PAN have preceding history of HCV infection.[44] This subgroup is more commonly associated with hypocomplementemia.

Porphyria Cutanea Tarda: This is characterized by blistering leading to scarring and hyperpigmentation predominantly over sun-exposed areas and facial hypertrichosis. There are wide variations in the prevalence of HCV-seropositivity in patients of porphyria cutanea tarda (PCT) ranging from 10% to 90% depending on the geography.[45] Other common associations of PCT are ALD and hemochromatosis. All patients of PCT should be screened for the presence of HCV infection and if positive require interferons for management in addition to regular iron removal.[3]

Necrolytic Acral Erythema: This has been recently described as a specific cutaneous feature of HCV infection.[46] It presents with well-defined acral dusky discoloration with blistering progressing to erythrokeratoderma clinically resembling necrolytic migratory erythema and pseudoglucagonoma.[47] Positive HCV serology with normal glucagon levels help in arriving at the diagnosis. Its development has also been linked to acquired zinc deficiency secondary to chronic liver disease but it needs further confirmation.[1] Resolution of lesions has been seen in patients with interferon-based regimens.[48]

Red Finger Syndrome: This is due to capillary dilatation resulting in erythema. Earlier description of this syndrome was in patients with concomitant HIV and HCV infections.[49]

Lichen Planus: Lichen planus has been found to be positively associated with chronic liver diseases including PBC, chronic active hepatitis, and cirrhosis of unknown cause.[50,51] Studies have both supported and refuted the claims of association between lichen planus and HCV infection.[50–56] A recent meta-analysis has reported that there is significantly higher risk of lichen planus patients being HCV-seropositive.[57] Thus, all patients of lichen planus should ideally be screened for HCV-seropositivity.

Other Skin Diseases: Autoimmune thrombocytopenic purpura, Behcet's disease, vitiligo, and Sjogren's syndrome are some of the autoimmune disorders associated with HCV-seropositivity.[1]

Other Hepatitis Viruses: Hepatitis D virus infection can cause cutaneous features similar to that of HBV infection. Hepatitis F, G, and E viruses causes infections which are generally mild and are rarely associated with dermatological manifestations.[1]

Primary Biliary Cirrhosis

It is an autoimmune disorder predominantly affecting women. Presence of concomitant autoimmune disorders is common including Sjogren's syndrome, CREST syndrome, morphea, and lichen planus.[58–62] Typical clinical picture is of a middle-aged lady with jaundice and pruritus, showing features suggestive of cholestasis on liver function tests and the presence of anti-mitochondrial antibodies. Fifty percent patients of PBC present with pruritus as the initial and predominant feature resulting in excoriations and also post-inflammatory hyperpigmentation. Butterfly sign characterized by normal looking skin over the upper back and surrounding hyperpigmentation is frequently observed.[63,64] This is because of the inability of the patient to scratch the upper back. Secondary hyperlipidemia presenting with xanthelasma palpebrarum, palmar crease, tuberous, and tendinous xanthomas is also a hallmark manifestation.[1] A recent series of 49 PBC patients has reported fungal infections to be the commonest cutaneous manifestation (31.5%); followed by neoplastic lesions (18.4%), dermatitis-urticaria (15.7%), and pigmentary changes (12.4%).[65]

Hemochromatosis

It is a multi-system disorder resulting in the deposition of iron in tissues and organs including liver, pancreas, heart, pituitary, and other endocrine organs. Predominant clinical features include skin pigmentation, diabetes, hepatic cirrhosis, and cardiac failure.[66,67] Apart from the presence of stigmata of chronic liver disease, two characteristic cutaneous abnormalities are seen which include hyperpigmentation and ichthyosiform changes.[68] Hyperpigmentation which is more marked over sun-exposed areas is an early sign of hemochromatosis and acts as a surrogate marker of iron deposition in other organs. It has a grayish or bronze hue and hence named bronze diabetes. Deposition of iron in skin stimulates melanocytes resulting in enhanced melanin production; this is further aggravated by sun exposure. Another important cutaneous change seen is the development of fish like dry scales known as ichthyosis usually in association with koilonychia of nail plate. The exact pathogenesis of this disorder remains unclear.[20] Therapies that lower serum iron levels reverse the cutaneous manifestations; however, skin pigmentation takes a long time to resolve.[22,69]

Cirrhosis Including Alcoholic Cirrhosis

Chronic alcoholism is recognized as one of the common causes of cirrhosis, resulting in end-stage liver disease. Defective synthesis of clotting factors due to cirrhosis leads to bleeding disorders. Cutaneous changes are commonly associated with cirrhosis and are of significant diagnostic value. Spider angiomas, palmar erythema, and Dupuytren's contracture are seen in around 72% of patients with alcoholic cirrhosis.[20] Most distinct lesions of alcoholic cirrhosis include paper money skin and Dupuytren's contracture. These skin changes also help in diagnosis and staging of liver cirrhosis.[70,71] Other than these, alcoholic cirrhosis patients are also found to be more prone to develop disseminated superficial porokeratosis which resolve completely with the improvement of liver function.[72,73] Acquired zinc deficiency in patients of ALD can present as crackled and reticulate eczema over the trunk and extensor of extremities. Also, there can be crusted erosions over the perianal and genital areas, cheilitis, hair loss, and transverse (Beau's) lines over nails.[1] Apart from specific dermatological manifestations of chronic liver disease, patients of chronic alcoholism can present with a number of associated diseases having cutaneous changes (Table 2).[74]

Hepatic Neoplasm

Skin changes are rarely seen in patients with hepatocellular carcinoma (HCC). Cutaneous metastasis presenting as single or multiple firm, painless, reddish-blue nodules

Table 2 Cutaneous manifestations of chronic alcoholism.

Chronic alcoholism-associated diseases with cutaneous abnormalities	Cutaneous diseases aggravated by alcohol
1. Marasmus • Dry wrinkled skin	1. Psoriasis
2. Kwashiorkor: • Scaling and fissuring over flexures • Alternating bands of dark and light hair (flag sign)	2. Rosacea
3. Vitamin deficiencies (Table 1)	3. Discoid eczema
4. Hypogonadism • Reduced facial hair growth	
5. Hyperestrogenemia • Loss of body hair • Spider angiomas • Gynecomastia	
6. Pseudo-Cushing's syndrome • Abdominal striae • Moon facies, buffalo hump, truncal obesity	
7. Porphyria cutanea tarda	
8. Pancreatitis • Subcutaneous fat necrosis • Cullen's sign, Grey Turner sign	
9. Dupuytren's contracture	

are seen in only 1–5% cases.[75,76] Hepatocellular carcinoma can be associated with a PCT-like presentation and there is also a case report of dermatomyositis in a patient of HCC with HBV infection.[77,78] Pityriasis rotunda presenting as round to oval patches of dry ichthyotic skin has been found to be more common in patients with HCC.[79] Hemangioendothelioma, leiomyosarcoma, and sarcomatoid carcinoma are other hepatic tumors which can present with cutaneous metastasis.[80–82]

Alagille Syndrome

It is a hereditary and developmental liver disease characterized by chronic cholestasis, peculiar facies, cardiovascular abnormalities, and vertebral arch defects.[83] The syndromic form has autosomal dominant inheritance and the non-syndromic form is associated with α_1-anti-trypsin deficiency and viral infections (rubella, cytomegalovirus, and HBV). Specific cutaneous manifestations include jaundice, xanthomas, and pruritus. Xanthomas are seen in 29% cases and are widespread involving palmar and plantar creases, inguinal area, popliteal fosse, elbows, and knees. Xanthomas are the result of chronic cholestasis and hypercholesterolemia and tend to improve following liver transplant.[84]

In conclusion, patients with liver diseases can present with a number of cutaneous manifestations. These at times are quite specific and thus help in identifying the underlying disorder. Thorough knowledge of these cutaneous changes is essential both for dermatologists and for hepatologists, so as to make a timely diagnosis aiding in prompt intervention.

CONFLICTS OF INTEREST

None.

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