Dermatologic Manifestations of Chronic Hepatitis C Infection

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KEYWORDS

• Hepatitis C • Extrahepatic manifestation • Dermatologic manifestation
• Cryoglobulinemia • Porphyria • Lichen planus

KEY POINTS

- HCV infection is associated with several dermatologic diseases, such as symptomatic mixed cryoglobulinemia, lichen planus, porphyria cutanea tarda, and necrolytic acral erythema.
- Most of the dermatologic manifestations may be caused by immune complexes.
- In the interferon and ribavirin era, treatment was associated with dermatologic side effects.
- The new generation of interferon-free and ribavirin-free anti-HCV regimens is devoid of dermatologic side effects.

INTRODUCTION

Chronic hepatitis C virus (HCV) infection is a global health problem and causes significant liver disease among infected patients. It is estimated that millions of people worldwide carry HCV antibodies with higher prevalence in Asia, the Middle East, and North Africa.[1] In the United States, the estimated prevalence of HCV infection is around 1.3% in the general population, but the rate is 3.2% in individuals who are born between 1945 and 1965.[2] HCV is a multifaceted disease and associated with not only liver disease, but also with multiple extrahepatic manifestations, including

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kidney, eyes, musculoskeletal system, skin, nervous system, and immune system involvement.[3]

Chronic HCV infection has been linked to multiple dermatologic conditions, such as mixed cryoglobulinemia (MC), porphyria cutanea tarda (PCT), lichen planus (LP), and necrolytic acral erythema.[4,5] Also, there are some anecdotal associations with psoriasis and prurigo.[5] This article provides the reader the basic mechanisms and clinical features of these clinical conditions, and the management of these dermatologic manifestations.

MIXED CRYOGLOBULINEMIA

MC is one of the common extrahepatic manifestations of chronic HCV infection. In addition to its association with rheumatologic diseases and lymphoma, MC can cause dermatologic manifestation manifested by a rash, usually in the lower extremities. In this context, MC is responsible for small vessel vasculitis caused by the precipitation and deposition of immune complexes in the small vessels at temperatures lower than 37°C.[6]

Based on the composition of the precipitated immune complex, three different immunochemical types of cryoglobulins have been described. Type 1 cryoglobulins consist of pure monoclonal components and are most often caused by underlying multiple myeloma or Waldenström macroglobulinemia.[7] Type 2 is a mixture of monoclonal IgM and polyclonal IgG, and is most often seen in patients with chronic HCV infection, although infection with hepatitis B virus and Epstein-Barr virus were also implicated in some cases. Type 3, in which both IgG an IgM rheumatoid factor are polyclonal, is usually seen in some patients with HCV infection and chronic autoimmune diseases, such as systemic lupus erythematosus.[8] In patients with HCV with MC, type 2 cryoglobulins with rheumatoid factor activity are involved in more than half of the cases, whereas type 3 cryoglobulins account for nearly 40% of MC, and these cryoprecipitates are rich in HCV-RNA.[9,10]

Among all causes of MC, HCV infection accounts for 95% of all cases.[11] However, among patients with chronic HCV infection, the rate of detectable cryoglobulins is around 25% to 50%, albeit the rate of symptomatic patients is lower at 10% to 30%.[12,13] In fact, the gap in these ratios may be attributed to the varying degree of underlying liver disease, the differences in the rates of fibrosis, and the duration of the infection.[14] It has also been shown that the risk of significant cryoglobulinemia increases with the severity of underlying liver disease.[15]

The three most common symptoms of patients with MC are palpable purpura, arthralgia, and weakness, which were named as the core symptoms of cryoglobulinemia by Meltzer and Franklin in 1966.[16,17] The intravascular precipitation of immunoglobulins in lower temperatures causes reversible mechanical obstruction primarily in the small vessels of skin, kidneys, liver, and peripheral nerves and lead to Raynaud phenomenon and immune-complex mediated vasculitis. Among these patients, skin is the most frequently affected organ and palpable purpura is the most common symptom, although chronic ulcers may also occur.[18] The obstructive immune complexes may also cause pruritus, urticaria, and leukocytoclastic vasculitis.[19]

MC is typically diagnosed with history, clinical manifestations, and detecting hypocomplementemia, especially low C4, and cryoglobulins in the laboratory.[20] HCV seropositivity also supports the diagnosis of MC. Rheumatoid factor is almost always positive in patients with MC. Other markers of chronic inflammation can also be present, including elevated erythrocyte sedimentation rate, C-reactive protein, or normocytic anemia.[21] Furthermore, the purpuric skin lesion can be biopsied and pathologic

diagnosis of leukocytoclastic vasculitis can be made. In the affected small blood vessels, cryoglobulins, and immune complexes are shown in the vessel walls.[22]

In summary, MC is an immune-complex mediated small vessel disease affecting mostly skin, but also kidneys, liver, and nervous system, and manifests with palpable purpura, weakness, and arthralgia. Treatment of underlying HCV can suppress the manifestations of vasculitis but immunosuppressive treatment with rituximab may be required, and plasma exchange in some patients.[23–25]

LICHEN PLANUS

LP is an uncommon disease of the stratified squamous epithelium, and may affect various body parts involving skin, oral cavity, genitalia, scalp, and even nails and esophagus.[26] The classic LP lesions are usually pruritic, polygonal, purple papules or plaques.[4] The size of the violaceous, flat-topped lesions may vary from pinpoint to larger than a centimeter.[27]

LP often develops between the ages of 30 and 60 and is seen in less than 1% of the general population.[28,29] The disease does not show any preference for sex and there is no strong racial predilection.[28,30] LP lesions are most commonly seen on the flexor aspects of wrists, forearms, and extensor aspects of hands, ankles, shins, and also genital area.[5] There are more than a dozen different clinical variants of LP; annular LP is common in the genital area; inverse type is usually seen in the intertriginous sites, such as axilla and inframammary area; and atrophic LP is often seen in the legs.[31] New lesions may develop in previously unaffected areas after scratching and trauma, which is known as Koebner phenomenon, also seen in patients with psoriasis. Although LP lesions rarely scars and they are usually self-limited, oral LP lesions more frequently become chronic and considered as premalignant lesions.[32]

The cause of LP is not known; however, it has been proposed that an immune mechanism directed by activated $CD8^+$ T cells against basal keratinocytes plays a major role in the pathophysiology of the disease.[33] Certain types of cytokines, such as tumor necrosis factor-α, interferon-γ, and interleukin-6 and -8, may also play a role in the pathogenesis of LP in patients with HCV infection.[34] During the era of interferon, several studies reported development or worsening of LP lesions during treatment with interferon.[35]

Although the cause and effect relationship has not been clearly shown for HCV infection and LP, previous studies evidently found statistically significant associations between chronic HCV infection and LP.[36–38] A meta-analysis by Shengyuan and colleagues[27] with 70 studies from five continents revealed that the presence of HCV may be used as a predictive marker for certain types of LP, because there was a significant risk for development of LP in patients with HCV infection. This meta-analysis also reported that compared with control subjects, patients with LP had higher HCV prevalence rates with an odds ratio of 5.4. Furthermore, a systematic review by Lodi and colleagues[37] found that compared with control group, the prevalence of LP was 4.8 times higher in patients with HCV. It is estimated that among patients with LP, the prevalence of HCV ranges from 4% in Europe to 24% in the Middle East and it is hypothesized that the difference in these rates was caused by genetic factors, such as different human leukocyte antigen types and the difference in most common HCV genotype in those geographic areas.[39,40] Although there is no definitive screening recommendations for HCV in patients with LP, likely because of the variability in the prevalence of HCV in different parts of the world, screening is an option where the association between two entities is stronger.[41]

The diagnosis of LP mostly relies on the combination of history and physical examination findings. The entire cutaneous surface should be examined, including external genitalia and oral cavity. However, in case of uncertainty, a punch or shave biopsy reaching to mid-dermis level is useful for diagnosis.[42] The characteristic histopathologic finding of LP is saw-tooth pattern of epidermal hyperplasia; thickening of the granular cell layer; vacuolization of the basal layer; apoptotic keratinocytes called Civatte bodies; and an intense infiltration of dermal-epidermal junction, mainly with T cells.[42]

Cutaneous LP is mostly self-limited and may resolve spontaneously. In cases where treatment is required, high-potency corticosteroids are usually the first line of treatment.[42–44]

In patients with HCV, the response of the LP lesion to interferon treatment is controversial, because there are studies reporting both improvement and exacerbation of symptoms with interferon treatment.[45] Similarly, a meta-analysis by Petti and colleagues[46] showed that treatment of HCV infection with anti-HCV medications does not necessarily lead to regression of LP lesions. Interferon-free direct-acting antiviral treatment is a new standard treatment of HCV, albeit the data about the effectiveness of these regimens in patients with HCV and LP are not available.

In conclusion, LP is a disease of the stratified squamous epithelium involving the skin and orogenital mucosa with unknown cause and can be seen in subjects with chronic HCV infection. It is characterized by pruritic, purple, plaques and papules and is diagnosed clinically or with a biopsy. Treatment of LP with interferon-based regimens did not show satisfactory results; however, newly developed direct-acting antivirals are an option for HCV-associated LP.

PORPHYRIA CUTANEA TARDA

The porphyrias are inherited or acquired metabolic disorders caused by reduced activity of enzymes in heme and porphyrin synthesis.[47] PCT, which is also called symptomatic porphyria, is the most common form of these disorders and caused by significant deficiency of hepatic uroporphyrinogen decarboxylase (UROD).[48,49] It is a rare disease of adults and the prevalence of PCT in the United States is estimated to be 1 in 25,000. Although both sexes are equally susceptible to the disease, because of the risk factors, such as alcohol abuse and HCV infection, PCT is seen more commonly in men.[50,51]

There are different types of PCT; type 1 is also called the sporadic form and accounts for nearly 80% of all PCT cases. There is no UROD mutation in this type and enzymatic deficiency is limited to liver. Type 2 is a familial form and UROD mutation is inherited in an autosomal-dominant fashion. Type 2 accounts for nearly 20% of all PCT cases and there is decreased enzymatic activity in all tissues.[52]

The enzymatic deficiency lies in the core of the pathogenesis of PCT. UROD is the fifth enzyme in the heme synthetic pathway and catalyzes the decarboxylation of uroporphyrinogen to coproporphyrinogen.[53] Clinical manifestations of PCT are seen when hepatic UROD activity goes lower than 20% of normal. Accumulation of porphyrinogens leads to formation of uroporphyrin and hepatocarboxyl porphyrins, and the conversion continues with the help of different enzymes and modifications by intestinal bacteria. Finally, porphyrins are transported from liver to skin and lead to phototoxicity.[54] When exposed to light with 400-nm wavelength, these phototoxic porphyrins release photons and cause production of reactive oxygen species, which damage membranes, lipids, and proteins.[55]

The association between HCV and PCT is strong and a meta-analysis by Gisbert and colleagues[56] revealed about 50% of patients with PCT have HCV and this rate

goes up to greater than 70% in southern Europe. In the United States, HCV prevalence in patients with PCT was estimated to be around 66%.[5] Although the exact mechanism through which HCV unmasks the enzymatic deficiency has not been clearly shown, the possible mechanism may include HCV-induced production of reactive oxygen species, which down-regulates hepcidin and cause hepatic iron overload, rather than a direct effect on the enzymatic pathway.[57,58]

The clinical manifestations of PCT are variable and include blistering skin lesions, subepidermal bullae, erosions, milia, hypertrichosis, alopecia, onycholysis, and hypopigmentation.[59] The sun-exposed areas, such as back of the hand, forearm, face, neck, and feet, are more prone to photo damage. Skin lesions may be painful and scarring of the lesions may progress to contractions and calcifications that resemble systemic scleroderma.[60] Because two most common risk factors for PCT are HCV infection and alcohol abuse, hepatocyte injury and transaminase elevations are common in PCT.[61,62] It was also reported that patients with PCT have increased risk for developing cirrhosis and hepatocellular carcinoma.[63]

The diagnosis of PCT is typically suspected on clinical grounds and relies on laboratory testing to detect elevated levels of porphyrins. The first step for diagnosis in a patients with symptomatic PCT is to check total plasma, serum, or spot urine porphyrins.[54] Patients with symptomatic PCT have markedly elevated urinary uroporphyrin and hepatocarboxyl porphyrin. Another useful tool for diagnosis is the plasma porphyrin fluorescent assay, which has a characteristic peak at 620 nm.[54] In subjects with PCT, screening for HCV is important.

The standard treatment of PCT consists of phlebotomy and/or low-dose hydroxychloroquine.[5] It is also important to minimize the risk factors, such as alcohol consumption, estrogen use, iron supplementation, and smoking.[64,65] Additionally, controlling the sun exposure is recommended, with customization of clothing. In familial inheritance cases, genetic counseling is exceptionally important. In patients with HCV, presence of PCT is an indication for treatment of HCV. Historically, treatment with interferon regimens was associated with low response and PCT was reported to be independently associated with insufficient viral response to interferon treatment.[66] In contrast, combining interferon therapy with iron reduction was more beneficial treatment in patients with HCV infection.[67] Finally, despite scarcity of data, treatment of PCT with direct-acting antivirals seems to be more effective than interferon-based regimens.[68]

In summary, PCT is a disease of heme and porphyrin metabolism, caused by decreased activity of UROD enzyme, and manifests with blistering skin lesions. HCV is highly associated with PCT and should be screened when the diagnosis of PCT is made. Although interferon-based treatment regimens show unpredictable response, new direct-acting antivirals have much more promising results in the treatment of HCV-associated PCT.

OTHER DERMATOLOGIC ENTITIES

Psoriasis

Psoriasis is a common, chronic, immune-mediated skin disorder that manifests itself with well-demarcated erythematous plaques with silver scale. Psoriasis is associated with an up-regulated systemic inflammation and overproduction of inflammatory markers, such as tumor necrosis factor-α, interferon-γ, or interleukin-17.[69] The disease does not have a gender predilection and global prevalence ranges between 1% and 8%.[70]

A few hospital-based clinical studies and observational studies have reported an association between HCV infection and psoriasis. Two relatively old studies from Japan

revealed an increased prevalence of anti-HCV antibody among patients with psoriasis compared with the general population.[71,72] A new study by Chun and colleagues[73] reported that HCV infection may up-regulate the inflammatory cytokines and may increase susceptibility to developing psoriasis. However, based on a population-based database study by Kanada and colleagues[74] psoriasis does not seem to be associated with an increased risk of HCV. Additional prospective studies are needed to support the role of HCV in the pathogenesis of psoriasis and whether psoriasis is a true dermatologic manifestation of HCV infection. Nevertheless, in patients with psoriasis, screening for HCV is performed before starting systemic immunosuppressive treatment.[75]

Necrolytic Acral Erythema

Necrolytic acral erythema is a rare, psoriasis-like dermatologic disorder characterized by pruritic, sharply marginated, erythematous to hypopigmented plaques with variable scale on the lower extremities.[76] The histopathologic appearance resembles psoriasis because keratinocyte necrosis, papillomatosis, and psoriasiform changes are usually detected. In a study by Abdallah and colleagues[77] in Egypt, among 30 patients with necrolytic acral erythema, all of them were found to be positive for HCV. There are other studies and case-reports linking this rare dermatologic disease to HCV, and to zinc deficiency.[78] Topical and systemic corticosteroids have been used as the first-line treatment. Additionally, sustained HCV viral eradication seems to improve the skin lesions.[79]

Pruritus

Rather than a dermatologic disease, pruritus is a common symptom in some patients with HCV infection and may be caused in part from cholestasis.[40,57] Nearly 15% of all patients with chronic HCV suffer from pruritus, making it one of their most common dermatologic complaints. Patients with chronic HCV may present either with generalized pruritus on apparently normal skin, or with pruritus with secondary skin findings, such as excoriations and lichenification. The latter is typical for prurigo nodularis and lichen simplex chronicus, both of which are associated with higher HCV prevalence.[80]

Pruritus should be carefully evaluated during HCV treatment, because it may either be secondary to treatment, or to one of the previously mentioned dermatologic manifestations. Interferon and ribavirin regimens were associated with new onset of significant pruritus in more than 10% of patients.[4] In this context, ribavirin was the most important culprit responsible for rash and pruritus. However, the rate of pruritus and rash became much more frequent with first-generation protease inhibitors, between 40% and 60%.[81] In fact, a small number of these patients developed rashes resembling Stevens-Johnson syndrome and was one of the reasons for discontinuation of these regimens. With the advent of new anti-HCV regimens free of interferon and ribavirin, rash and pruritus are no longer important complications of HCV treatment.

SUMMARY

Chronic HCV infection is a systemic disease and associated with various types of extrahepatic manifestations, one of which is dermatologic involvement. Although a myriad of dermatologic diseases have been linked to chronic HCV infection, the evidence is weak except for the association of HCV with MC, LP, PCT, and necrolytic acral erythema. Although the efficacy of interferon-based treatment was low and interferon and ribavirin caused dermatologic complications, viral eradication with the new regimens seems to be high and these regimens are well tolerated. Nevertheless, more

data are needed to establish the efficacy of these regimens in the context of dermatologic manifestation of HCV.

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