Review Article

Dermatologic Manifestations of Hepatitis C Infection and the Effect of Interferon Therapy: A Literature Review

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Abstract

The skin could be a main target organ for extrahepatic manifestations in hepatitis C virus- (HCV) infected patients and research data suggest that interferon treatment may be associated with immune-mediated skin lesions. However, case reports propose that the response of dermatologic extrahepatic manifestations to interferon in patients with chronic HCV is greatly different. The objective of this study is to summarize currently available data on dermatologic conditions associated with chronic HCV infection. In addition, we investigate the incidence of the development of immune mediated dermatologic disorders during interferon therapy in these patients.

Keywords: hepatitis C virus, interferon, skin manifestations

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Introduction

Hepatitis C virus (HCV) infection is a widespread disorder that may involve different organs due to its extrahepatic manifestations. A variety of conditions ranging from endocrinopathies to different skin diseases have been described in HCV infections.[1] Different factors such as viral, genetic, or environmental may be responsible for cutaneous disorders associated with HCV infection.[2] In most cases, the mechanisms through which HCV may trigger or exacerbate skin manifestations remain unclear and require further examinations. The various dermatologic manifestations of HCV can be classified into three main types according to a proven or suspected etiology: 1) primary due to direct HCV infection of the skin, lymphocytes, dendritic cells, and blood vessels. This hypothesis has been confirmed by the detection of HCV RNA particles in epidermal cells and skin lesions. 2) Skin manifestations of HCV infection may be an epiphenomenon resulting from the interruption of immune responses. An example would be cryoglobulinemia-induced leukocytoclastic vasculitis. 3) Disruption of HCV-infected organs other than skin may produce nonspecific cutaneous signs due to typical skin responses to that organ. For example, thyroid hormone release in early HCV-linked autoimmune thyroiditis can culminate in skin responses and manifestations.[3–5]

Interferon (IFN), a biological medication used to treat viral hepatitis, has considerable clinical potential to cause different effects on different organs such as the skin. The response of the skin to IFN therapy is unpredictable[6] and the role of IFN in post-treatment persistence of skin manifestations needs to be assessed. A number of skin disorders are autoimmune in nature and immunomodulatory activity[7] of IFN may exacerbate these dermatologic disorders. The issue is further complicated by multiple IFN regimens [i.e., Peginterferon (a longer-acting form of IFN) alone or with ribavirin (RBV)] used in practice. In addition, dermatologic disorders may require prolonged immunosuppressive therapy, which can increase HCV viremia and worsen liver disease.[8]

The aim of the present study is to review the literature concerning the association between HCV infection and various cutaneous manifestations. Another objective is to monitor the role of IFN-based treatment of HCV infection in cutaneous manifestations.

Lichen planus (LP)

Concomitant occurrence of lichen planus (LP) with HCV infection was first described by Mokni et al.[9] Since then, there have been a substantial number of reports on the possible association between LP and chronic hepatitis C (CHC) though the role of HCV in LP remains unclear.[10,11]

Different surveys show the association between HCV and LP to be affected by geographical regions. Given the odds ratio and prevalence figures in different countries, it has been estimated that the prevalence of HCV in patients with LP varies from 4% in Europe to 24% in the Middle East.[10]

The geographic heterogeneity of the association between LP and HCV is difficult to elucidate. It has been hypothesized that differences in genetic factors, such as different human leukocyte antigen types[12] different HCV genotypes,[13] and socioeconomic factors[11] have variable degrees of pathogenetic potential for the development of LP.

Although the mechanism of disease induction by HCV is not known, HCV replication in the oral mucosa and direct contribution to lesion formation, high rate of mutation in HCV and repeated activation of immune cells and immunological pathways may be involved.[10,14]

To date, little attention has been paid to the different effects of interferon-alpha (IFN-α) therapy, with or without RBV for LP. However, many small series and case reports document the impact of IFN on HCV-associated LP.[15,16] The development of *de novo* LP was described in 34 cases. In addition, LP improved in 9 cases, worsened in 7 cases, remained at the same level in 6 cases, and developed *de novo* after discontinuing IFN in 1 case. IFN was interrupted in 4 cases of worsening LP and in 7 cases of *de novo* LP.

Moreover, several case reports have described a relationship between LP and IFN therapy in patients without HCV infection.[17,18]

The mechanisms by which IFN exerts disease-promoting effects have not been adequately defined. IFN-mediated signaling may play important roles in the pathogenesis of the disease. This role

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is supported by the fact that several IFN-inducible proteins such as human myxovirus resistance protein A (whose gene is strictly regulated by IFN-α/β in a dose-dependent manner), IFI27, IRF1, IFTM1, and CXCL9 are upregulated in LP lesions.[19]

It is probable that IFN-α can induce LP lesions by its interference with the cytokine cascade. It has recently been reported that IFN-α increases the gene expression of IL-2Rα which is engaged in IL-2-induced human T-cell proliferation in vitro[20] and that prohibits the natural destruction of the antigen-activated T-cells.[21]

It seems also to be instrumental for development of the Th1 response by inducing the interleukin-12 receptor β2 chain.[22] These effects can participate in lymphocyte accumulation in the inflammatory regions.

Increased keratinocyte expression of HLA DR II molecules and the intercellular adhesion molecule-1 by IFN-γ can contribute to the epidermal migration of the activated Th cells expressing high levels of lymphocyte function associated antigen-1[23] and for their adhesion to keratinocytes. Therefore, we propose that IFN-α promotes Th cell accumulation and their differentiation to the Th1 subset. The increased production of IFN-γ causes migration and adhesion of these cells to the keratinocytes, culminating in cell toxicity.

Mixed cryoglobulinemia (MC)

Cryoglobulins are mostly immunoglobulins that precipitate at temperatures below 37°C and can cause diseases associated with chronic inflammatory disorders and infection.[24]

In the early 1990s, improvement of serologic diagnosis of hepatitis C infection showed a profound association between CHC infection and essential mixed cryoglobulinemia (MC).[25] This observation has been confirmed by subsequent studies which demonstrate that cryoprecipitates are rich in HCV RNA and anti-HCV.[26] The prevalence of HCV infection in essential MC patients differs geographically from 40% to 92% of cases, approaching 90% of cases in the Mediterranean basin.[27]

Conversely, between 25% and 50% of patients with CHC have detectable cryoglobulinemia with 10%–30% having symptoms.[28,29]

The clinical importance of cryoglobulinemia is the consequence of intravascular precipitation of immunoglobulins, which can produce (reversible) mechanical obstruction of small vessels culminating in Raynaud's phenomenon and immune complex–mediated vasculitis, principally in the skin, kidneys, and peripheral nerves.[25] So, dermatologic manifestations are a classic presenting complaint in essential MC.[4] In a new study, researchers found that among 231 rheumatology patients with MC (92% HCV-infected), purpura was associated with poorer survival.[29] In another study, of 62 patients undergoing MC, palpable purpura was the most common dermatological feature seen in 21% followed by Raynaud's phenomenon (15%), pruritus (8%), and urticaria (6%).[30] Leukocytoclastic vasculitis and leg ulcers also have been reported as dermatologic symptoms in MC patients.[30]

Treatment of HCV-MC patients with severe organ involvement remains difficult and various approaches such as corticosteroids and cytotoxic agents have been used to treat MC. Some open trials have investigated the value of antiviral therapies in patients with HCV-associated cryoglobulinemic vasculitis. It seems that antiviral therapy is the first-line treatment[28] and cutaneous manifestations of MC are an early, sensitive indicator of response to IFN in terms of liver disease and viremia.[31]

Antiviral medication has been indicated to reverse bone marrow monoclonal B cell expansion in HCV-MC patients.[32] The rate of sustained virological responses (SVR) varied from 17% to 27% in series where patients have been treated with rIFN-α monotherapy.[33,34] SVR is defined as the clearance of HCV RNA during antiviral therapy which persists at least 6 months after completing an antiviral course.[35] Although this approach provides a satisfactory response rate, additional treatment may be required in MC patients with severe organ involvement and/or without an early virological response.[35] For example, up to 60% of patients treated with Peg-IFN-α/RBV have experienced SVR.[35] On the contrary, RBV monotherapy of MC did not provide any virological response.[36]

In summary, it can be suggested that combination therapy more frequently culminates in SVR and clinical response of MC symptoms than IFN monotherapy.[37] Nonetheless, there has been concern that during or subsequent to IFN therapy, in rare instances, symptoms of MC can arise or worsen.[38]

Porphyria cutanea tarda (PCT)

Porphyria cutanea tarda (PCT) is the most commonly occurring disease of porphyrin metabolism and is due to a marked deficiency of hepatic uroporphyrinogen decarboxylase.[39] As a result of this defect, porphyrin accumulate in the liver and are then transported to the skin where they are photoactivated by long-wave ultraviolet light, producing reactive oxygen species that cause characteristic skin fragility and blistering in sun-exposed areas of the skin.[40]

The prevalence of HCV infection in patients with PCT is high and ranges between 40%–50% depending on the country.[41,42] Nonetheless, the exact mechanism through which HCV unmasks the enzyme deficiency is unclear. HCV does not seem to have any direct effects on porphyrin metabolism, and perhaps HCV induces the disease in genetically predisposed individuals.[43] PCT may be related to HCV-induced hepatic iron overload.[44] In addition the highest rates of PCT in patients with HCV-related liver cirrhosis, suggest that cirrhosis may play a role in disease development.[45] Other risk factors include alcohol use, hereditary hemochromatosis, estrogen therapy, hemodialysis, diabetes mellitus, and myeloproliferative disorders.[46]

The response to IFN-α therapy in PCT is unpredictable with some patients ameliorating, others remaining stationary and others deteriorating. For instance, Fernandez et al.[47] have demonstrated that patients with CHC and PCT rarely responded to IFN-α treatment. While some authors such as Sheikh et al.[48] have described a patient in whom PCT remitted after six months of therapy with IFN-α without any significant reduction in HCV RNA levels. They have proposed that the resolution of dermatological lesions in this patient was due to the immunomodulatory effect of IFN-α.

There are only limited data about the development of PCT during IFN-α therapy.[49,50] In some cases PCT occurred de novo after IFN therapy.[50] These patients were treated with Peg-IFN plus RBV.[50] Another patient who had non-Hodgkin's lymphoma and dermatomyositis received IFN monotherapy. He showed PCT progression after 24 month of therapy, and his PCT cleared after starting chemotherapy.[49] Fortunately, in some instances dermatologic symptoms could be reduced with adjuvant therapy.[50] PCT has also been reported during IFN therapy in patients without HCV infection.[51]

Psoriasis

Some investigators have focused on psoriasis as a dermatologic manifestation of HCV infection. This emphasis has been placed on different types of evidence such as the presence of psoriasis in

HCV-infected patients,[52] detection of anti-HCV antibodies in psoriatic patients[53], and detection of HCV RNA by polymerase chain reaction in the skin lesions of psoriatic patients with HCV infection.[53] It is possible that the presence of HCV in the skin could trigger psoriasis through stimulating inflammatory cells to infiltrate skin lesions.[52] In addition, there have been reports of new onset or reoccurrence of psoriasis in patients with or without previous histories of psoriasis after IFN treatment of CHC.[54,55] Exacerbations of psoriasis have usually occurred between one and six weeks after the beginning of IFN therapy but could happen as long as six months after starting IFN treatment. In the vast majority of patients, psoriasis exacerbation induced by IFN-α and withdrawal of IFN results in psoriasis improvement. The close association among the onset of psoriasis and IFN-α treatment reflects that the drug may act as a triggering agent. The mechanism of an IFN-induced flare up in psoriasis is not well understood but immunomodulatory effects of IFN might be responsible for the activation of T cells toward the skin in this situation.[56]

Vitiligo

Little evidence is available on the role of HCV infection in vitiligo[57–60] and to date, there has been no clear association between HCV infection[58] and this autoimmune disease. Only in one study a significantly greater proportion of HCV-infected patients had vitiligo.[57] In addition, a patient with Porokeratosis of Mibelli was described who suffered from long-standing chronic active hepatitis and rapidly expanding vitiligo.[59] It has been proposed that cell cytotoxicity in vitiligo with inflammatory raised borders may be triggered by HCV infection.[60]

There are limited data regarding vitiligo complications during IFN therapy for CHC. Tomasiewicz et al.[61] have described a case of vitiligo that occurred during the third month of treatment with Peg-IFN and RBV. In this patient, the SVR was the result of a 52-week regimen although hypomelanotic cutaneous lesions persisted. In another patient with chronic active hepatitis C IFN alpha-2a induced vitiligo all skin lesions resolved entirely without requiring therapy after discontinuation of IFN.[62] These cases suggest that vitiligo may be developed during IFN therapy as a side effect. It is possible that IFN-α causes vitiligo through induction of antimelanocyte autoantibodies or activation of cytotoxic T cells.

Alopecia

Evidence suggests that autoimmune alopecia may be one of the cutaneous diseases associated with hepatitis C.[63] For the first time, Shibuya and colleagues described a child with posthepatic aplastic anemia complicated by alopecia totalis. After bone marrow transplant, this patient showed postoperative hair growth.[64] In another study Paoletti et al.[63] found that of 96 HCV-infected patients, two had alopecia areata (AA). Nonetheless, when anti-HCV antibodies were measured in the sera of 45 patients with AA, none were HCV seropositive.[65]

Recent studies have shown that IFN treatment can cause hair loss which may occur all over the body, not just on the head.[66-68] The side effect of IFN therapy is usually noticed in up to 36% of treated patients in pivotal clinical trials[67–69] and it seems that the incidence of alopecia increases with the duration of treatment.[69] It is possible that Peg-IFN induces immunologic modulation (shift from a Th2 immune-driven response to a Th1) and stimulates the synthesis of Th1-cytokines such as IL-1, IL-2, and IFN-γ.[66] In addition Peg-IFN increases cytotoxic T cell activity.[70] These are in accordance with the findings of Hoffmann[71] who has described increased mRNA and protein expression of Th1-cytokines (IFN-γ, IL-2), and IL-1β in skin biopsies from patients with AA.

Sarcoidosis

A relationship between HCV infection and sarcoidosis was first postulated in 1993. Until now, the prevalence of HCV infection has not been estimated in a large series of sarcoidosis patients. However, the number of cases of sarcoidosis associated with HCV reported annually has augmented considerably, whether related or not to antiviral therapy.[72,73] Sarcoidosis is now a well-recognized but uncommon complication of antiviral therapy for HCV infection[74] although the IFN-associated sarcoidosis has also been described without HCV infection.[75] Different studies have indicated that patients with CHC have a higher risk of IFN-induced sarcoidosis.[76] For example, analysis of HCV-infected patients with sarcoidosis has shown that disease to be triggered by antiviral therapy (mainly by IFN) in 75% of cases (60% IFN plus RBV; 15% Peg-IFN).[73] The incidence of sarcoidosis in HCV patients receiving antiviral therapy varies from 0.09% to 0.2%.[72,73] Interestingly, this incidence is still considerably higher than that of sarcoidosis in the general population.[77]

Possible mechanisms of IFN-α in inducing or exacerbating sarcoidosis are as follows: 1) induction and increased expression of MHC class II antigens (required for antigen presenting cell activation) and release of pro-inflammatory cytokines by APC; 2) directly activating and polarizing Th0 and shifting the Th balance towards Th1 immune response; 3) transient activation of $CD4^+$ T cells and expansion of a proinflammatory $CD4^+CD28^-$ T cell subset; and 4) by induction of overproduction of IFN-γ.[78,79]

Briefly, some studies have documented the development of sarcoidosis shortly after treatment with IFN for CHC and propose that HCV-infected patients often have cutaneous and articular involvement. Therefore, special attention to dermatologic signs should be given in the course of IFN therapy because even minimal skin involvement may propose a clue to an early diagnosis of IFN-induced sarcoidosis.[80]

Polyarteritis nodosa (PAN)

Polyarteritis nodosa (PAN) is a rare autoimmune disease that features spontaneous inflammation of the arteries. A few cases of polyarteritis nodosa-like disease have been reported among HCV-infected patients.[81,82]

The clinical sign of PAN-type HCV-associated vasculitis has only been studied in a small group of patients. Patients with PAN-type vasculitis have more severe disease with an increased erythrocyte sedimentation rate and C-reactive protein levels. The most common symptom being multifocal, mainly motor mononeuropathy (present in 90%) and renal insufficiency with hypertension (present in 50%).[81,83] Other characteristics are purpura, cerebral vasculitis, myalgia, arthralgia, and ischemic abdominal pain.[81,83]

The prevalence of anti-HCV antibodies between patients with PAN ranges from 5% to 12%.[84] This model of vasculitis may be associated with MC or with IFN-α therapy.[38] The mechanisms by which HCV-infected patients develop PAN-like vasculitis or cryoglobulinemic vasculitis are unclear. It must be noted that because of differences in clinical and pathological features and therapeutic strategy, PAN-type vasculitis should be distinguished from other types of vasculitis in HCV patients.[81] Moreover, HCV-associated PAN should be considered in the differential diagnosis of necrotiz-

ing fibrinoid arteritis even in a patient with normal liver function test results and in the absence of cryoglobulinemia.[85]

Pruritus

Pruritus is a common presenting complaint in HCV-infected patients and may culminate in part from cholestasis.[86] Up to 15% of patients with HCV infection experience pruritus[83] and the majority of HCV-related pruritus are associated with prurigo, xerosis, or nonspecific excoriations.[86] In a study, HCV RNA was detected in a skin specimen from the biopsy of a skin lesion by the RT PCR method. However, the non-affected skin specimens from the patients were HCV RNA negative.[87]

Another report[88] described a series of patients with prurigo, 39% of whom had anti-HCV antibodies. Anti-HCV prevalence was significantly higher in prurigo patients than in 979 controls (6%). Some scientists hypothesized that pruritus was only rarely a presenting sign of HCV infection.[89]

Nonetheless, identification of pruritus as a sign of hepatitis C is considerable for two reasons: first, pruritus may be the manifesting symptom of HCV, and thus special attention should be paid to any patient suffering from pruritus that is not secondary to a primary skin disorder. Second, pruritus may be the primary manifestation of HCV-infected patients and may be efficiently improved by prudent therapeutic intervention.[90]

Relationship between pruritus and response to IFN in HCV-infected patients has been looked at, but not clearly defined. On the one hand, pruritis has been observed during both monotherapy (6%–13%) and combination therapy with IFN-α plus RBV.[91] On the other hand, few case reports describe resolution of the recently recognized HCV-related prurigo with IFN-α monotherapy.[88,92] Moreover, a favorable effect of IFN-α on prurigo without HCV infection has also shown.[93]

According to Maticic et al.[68] pruritis was significantly more common in successfully and unsuccessfully treated patients as compared with healthy subjects. Therefore, it is possible that the virus itself does not necessarily play a role in pruritus induction.

Other dermatologic disorders

The only dermatologic disease diagnostic for HCV infection is necrolytic acral erythema (NAE)[94] since to date, 100% of reported NAE cases have HCV infection.[95] The signs and symptoms of disease consist of pruritus associated with recurrent, erythematous, papular eruptions with blisters and erosions on the dorsal parts of the feet and ankles. Cases are not responsive to steroids but have shown improvement within weeks with IFN-based therapy, such as IFN together with RBV or oral zinc.[96]

Other cutaneous conditions that may be associated with CHC infection include urticaria[97] Behcet disease,[98] erythema nodosum and erythema multiforme,[99] although the epidemiological and clinical association between HCV and these diseases is not well defined.

Conclusion

The list of HCV-associated skin diseases may progress at a faster rate in the future. Additional studies are necessary to prove or disprove an etiopathogenetic role of HCV in these conditions. In view of the wide range of dermatoses associated with HCV infection, a physician should be highly cautious when examining patients who present with the abovementioned skin disorders. IFN-α has been shown to be beneficial in treatment of patients with CHC. However, skin reactions to the therapeutic use of IFN are unpredictable and some patients have experienced adverse side effects. Side effects associated with IFN therapy represent a major obstacle to adequate treatment for patients with HCV. It is important for the physician to keep these potential side effects in mind and to inform patients when beginning IFN treatment.

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