

Cutaneous manifestations of hepatitis C in the era of new antiviral agents

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Abstract

The association of chronic hepatitis C virus (HCV) infection with a wide spectrum of cutaneous manifestations has been widely reported in the literature, with varying strength of epidemiological association. Skin diseases which are certainly related with chronic HCV infection due to a strong epidemiological and pathogenetic association are mixed cryoglobulinemia, lichen planus and porphyria cutanea tarda. Chronic pruritus and necrolytic acral erythema are conditions that may share a possible association with HCV infection, while several immune-mediated inflammatory skin conditions, such as psoriasis, chronic urticaria and vitiligo, have been only anecdotally reported in the setting of chronic HCV infection. Traditional interferon-based treatment regimens for HCV infection are associated with substantial toxicity and a high-risk of immune-related adverse events, while the advent of new direct-acting antivirals with sustained virological response and improved tolerability will open the door for all-oral, interferon-free regimens. In the new era of these direct acting antivirals there will be hopefully a renewed interest in extra-hepatic manifestations of HCV infection. The aim of the present paper is to review the main cutaneous HCV-related disorders - mixed cryoglobulinemia, lichen planus, porphyria cutanea tarda and chronic pruritus - and to discuss the potential impact of new antiviral treatments on the course of these extra-hepatic manifestations of chronic HCV infection.

Key words: Chronic liver disease; Hepatitis C virus; Interferon-free agents; Extra-hepatic manifestation; Skin diseases; Mixed cryoglobulinemia; Lichen planus

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Core tip: It is known that the association of hepatitis C virus (HCV) infection with a wide spectrum of cutaneous manifestations has been widely reported in the literature. In the new era of direct acting antivirals there will be hopefully a renewed interest in the diagnosis and treatment of extra-hepatic manifestations of HCV infection. The aim of the present paper is to review the main cutaneous HCV-related disorders and to discuss the potential impact of new antiviral treatments on the course of these extra-hepatic manifestations of chronic HCV infection in order to help all the clinicians dealing with patients undergoing antiviral treatment.

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INTRODUCTION

Hepatitis C virus (HCV) is known to induce both hepatic and extra-hepatic manifestations. Chronic HCV infection is now considered a systemic disease with multi-organ involvement. The association of chronic HCV infection with a wide spectrum of cutaneous manifestations has been widely reported in the literature, with varying strength of epidemiological association. In registry-based studies, about 17% of HCV patients present at least one skin manifestation, which can be directly or indirectly induced by chronic HCV infection^[1]. In Table 1, the cutaneous extra-hepatic manifestations (cEHMs) are summarized according to the quality of epidemiological and pathogenetic relationship with chronic HCV-infection.

The recognition of cEHMs is important for the clinician for several reasons. First, to ensure early diagnosis by routine HCV-testing in patients with higher risk of infection than the general population; Second, some of these manifestations may improve after effective antiviral treatment without or in combination with skin-targeted therapy; Third, cEHMs may identify a difficult-to treat patient subset, requiring a tailored antiviral regimen as well as multidisciplinary care.

Skin disease which are certainly related with chronic HCV infection are mixed cryoglobulinemia (MC), lichen planus (LP) and porphyria cutanea tarda (PCT). In these disorders testing for HCV infection is recommended, in the light of the strong epidemiological and pathogenetic association. Psoriasis, chronic pruritus and necrolytic acral erythema are conditions sharing a possible association with HCV infection, although they lack definitive epidemiological and experimental evidence to support universal screening for HCV. Moreover, other immune-mediated inflammatory skin conditions, such as chronic urticaria and vitiligo, have been anecdotally reported in the setting of chronic HCV infection in retrospective

studies and case-series. The complex interplay between the cutaneous immune system and the HCV-induced immune response in a genetically predisposed individual can induce or change the course of inflammatory skin conditions. For example, chronic HCV infection is a major infectious comorbidity complicating the therapeutic management of psoriasis, which is increasingly based on systemic immune-modulating agents, such as methotrexate, cyclosporine and TNF-alpha inhibitors.

Thus, the nature of HCV extra-hepatic manifestations requires a multidisciplinary approach, in order to ensure a correct diagnosis and optimize therapeutic interventions.

Traditional interferon (IFN)-based treatment regimens for HCV infection were associated with substantial toxicity and a high-risk of immune-related adverse events. These included a plethora of IFN-induced manifestations and the induction or worsening of immune-mediated, inflammatory skin conditions, such as psoriasis, eczema, lichenoid eruptions, pruritus and alopecia areata. IFN-related cutaneous adverse events have to be differentiated clinically from true, primary cEHMs of HCV infection.

In 2011, boceprevir and telaprevir were licensed for use in HCV as new first wave, first-generation direct-acting antivirals (DAAs), still to be administered in combination with IFN and ribavirin. To overcome this limit, in 2014 three new HCV DAAs (Sofosbuvir, Simeprevir and Daclatasvir) have been licensed worldwide for use as IFN-free, a major achievement in the field of hepatology^[2]. For the first time in three decades the availability of new direct-acting antivirals with sustained virological response and improved tolerability will open the door for all-oral, IFN-free regimens. Nevertheless, these new treatment regimens have to be tested in real-life clinical scenarios, such as difficult to treat patient subsets with advanced fibrotic disease and/or substantial comorbidity. In the new era of these direct acting antivirals there will be hopefully a renewed interest in extra-hepatic manifestations of HCV infection.

The aim of the present paper is to review the main cutaneous HCV-related disorders - MC, LP, PCT and chronic pruritus - and to discuss the potential impact of new antiviral treatments on the course of these extra-hepatic manifestations of chronic HCV infection.

MIXED CRYOGLOBULINEMIA - CUTANEOUS MANIFESTATIONS

Skin is the most frequently involved organ of MC-related vascular inflammation in chronic HCV-infected patients and clinical manifestations include palpable purpura (21%) with or without livedo, Raynaud phenomenon (15%), pruritus (8%), urticaria (6%) and leg ulcers. Leucocytoclastic small vessel vasculitis is the main histological correlate of cutaneous lesions^[3].

Systemic vasculitis involving the kidneys, heart and central nervous system characterizes the severe forms

Table 1 Classification of cutaneous extrahepatic manifestations of chronic hepatitis C virus infection

Cutaneous conditions with defined epidemiological and/or pathogenetic association
Mixed cryoglobulinemia
Lichen planus
Porphyria cutanea tarda
Cutaneous conditions with possible association
Pruritus (prurigo nodularis/lichen simplex cronicus)
Necrolytic acral erythema
Cutaneous conditions with anecdotal association
Psoriasis
Chronic urticaria
Vitiligo
Erythema multiforme
Erythema nodosum
Pyoderma gangrenosum

of MC disease, with increased risk of death due to end-organ complications, progression of liver disease and lymphoma. In severe MC disease, cutaneous lesions comprise hemorrhagic ulcers and skin necrosis, due to immune-complex deposition in small-to medium sized blood vessel with complement activation^[4].

In patients with mild- to moderate symptomatic HCV-related MC, an optimal antiviral treatment is warranted in order to attain a sustained virological response and cutaneous improvement. Treatment goals in MC patients are clinical remission of MC-related organ manifestations, clearance of cryoglobulins, in addition to sustained virological responses, while limiting the use of immune-modulating agents with risk of liver toxicity. In the majority of MC patients, there is a good correlation of SVR and clinical response, with remission of end-organ manifestations and symptoms. Other useful laboratory response markers are clearance of cryoglobulins, complement levels (C3, C4, CH50 activity) and rheumatoid factor activity. On the other hand, patients who relapse after initial HCV antiviral treatment frequently develop a clinical relapse of MC disease^[5].

Combination antiviral therapy with pegylated IFN/ribavirin yields a SVR in almost 52% of patients with symptomatic MC disease, as recently shown in a meta-analysis of ten clinical studies^[6]. Triple antiviral therapy with Peg-IFN-alpha/ribavirin and a first-generation protease inhibitor (telaprevir or boceprevir) in severe HCV-associated MC vasculitis determined a complete clinical response of MC and SVR in 66.7% of treated patients of an open-label cohort study. In the same study, the improvement of clinical responses was at the costs of a higher rate of serious adverse events (46.6%), mostly haematological ones, in comparison to dual antiviral regimens^[7]. Antiviral treatment with second-generation protease inhibitors could have a potential impact on the course of HCV-associated symptomatic MC, due to an improved tolerability profile and high efficacy. Preliminary clinical experience with sofosbuvir in dual or triple antiviral regimens for symptomatic MC highlighted the need for longer treatment durations (>

12 wk), especially in the background of advanced liver fibrosis, in order to obtain clearance of cryoglobulins and long-lasting clinical remission^[8,9].

In severe MC vasculitis with advanced renal and liver involvement, the addition of immune-modulating agents is crucial for targeting the B-cell clonal autoimmune responses and clonal expansions in the blood and liver. Rituximab, an anti-CD20 monoclonal antibody, proved to be safe and superior to conventional immunosuppressive agents (glucocorticoids, azathioprine or cyclophosphamide) in the treatment of severe HCV-associated MC vasculitis^[10]. Rituximab has been used successfully in monotherapy, or in combination or sequential treatment strategies with Peg-IFN-alpha/ribavirin, optimizing treatment outcomes in patients with severe MC disease^[11,12]. Symptomatic moderate-to severe MC thus identifies a distinct subset of difficult-to treat HCV patients, who require a tailored treatment approach, combining new generation antivirals and immune-modulating agents. Furthermore, symptomatic MC patients are at increased risk of haematological adverse events during IFN-based regimens and could clearly profit from new all-oral treatment strategies. Considering the under-representation of these patients in registrative trials there is a need for large, prospective, multi-center studies, assessing the impact of new direct acting antivirals on the natural history of HCV-associated MC vasculitis syndrome.

LP

LP is an inflammatory disorder involving the skin and the oro-genital mucous membranes. It is the prototypical disease belonging to the spectrum of lichenoid tissue reactions (LTRs), which are characterized by an interface-dermatitis histological pattern, with a T-cell mediated autoimmune attack on basal keratinocytes. It can affect the skin and its appendages (hair and nails) as well the mucosal surfaces of the genitalia, oesophagus, urinary tract, high respiratory tract and the eyes, with organ-specific clinical phenotypes (Figure 1A). Oral lichen planus (OLP) (Figure 1B) is the most studied clinical phenotype of LP in the setting of chronic HCV infection, with the erosive form being the most severe and recurrent clinical variant^[13].

The association between LP and chronic HCV infection has been described in several epidemiological studies, with conflicting results depending on study design and country-specific prevalence of HCV burden. In hyperendemic regions such as Egypt, Japan and Southern Europe the rate of association can be as high as 35%, whereas it can decline to 0.5% in the low-incidence countries of Northern Europe. Two recent meta-analysis of published studies support the association between chronic HCV infection and LP. Patients with LP have a five-fold greater risk of HCV-infection (OR 5.4; 95%CI: 3.5-8.3) compared to control subjects. Conversely, the odds ratio for a diagnosis of LP among patients with HCV is 2.5 (95%CI: 2.0-3.1)^[14]. This association

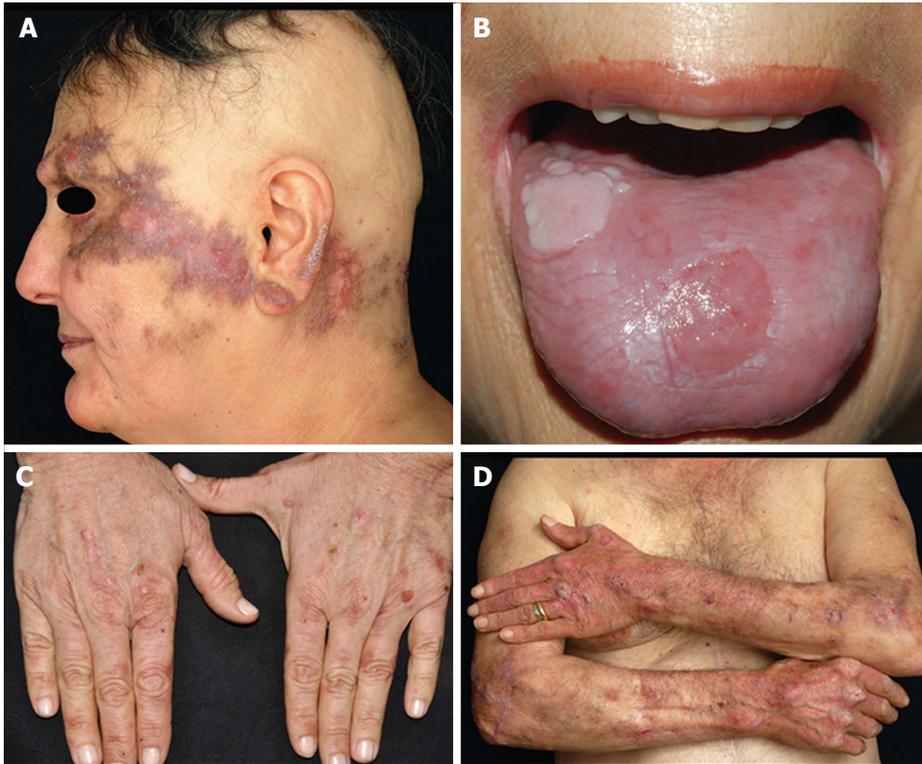


Figure 1 Cutaneous extra-hepatic manifestations of chronic hepatitis C virus infection. A: Cutaneous Lichen planus with inflammatory hyperpigmentation and cicatricial alopecia; B: Erosive oral lichen planus; C: Porphyria cutanea tarda, with typical involvement of sun-exposed acral skin; D: Chronic pruritus with secondary nodular scratch lesions, or prurigo nodularis.

proved to be not significant in the isolated cutaneous LP subtype. In summary, the variability in the association between HCV and LP can only be partially explained by a geographic effect and differences in study design, with genetic factors (HLA-DR-associations), age and IFN-based treatments also playing a role. Several authors agree to routinely check for HCV infection in patients with a clinically and histologically-confirmed diagnosis of LP disease^[15,16].

The current pathogenetic hypothesis regard LP as a T-cell mediated autoimmune reaction to a viral protein or to a self-epitope shared by the virus and presented by basal keratinocytes, which are attacked by cytotoxic CD8⁺ T cells. The immune dysregulation in LTRs is characterized by the subepithelial infiltration of CD8⁺ cytotoxic T-cells, natural killer-cells, myeloid and plasmacytoid dendritic cells releasing Th1-cytokines, such as tumor necrosis factor (TNF)-alpha and IFN-gamma^[17]. Type- I IFNs (IFN-alpha and beta), produced by plasmacytoid dendritic cells, promote the epithelial expression of MxA protein and the recruitment of cytotoxic T-lymphocytes *via* CXCR-3/IP-10 CXCL-10 interactions. This cellular immune reaction pattern is common to many disease states, such as viral infections and cutaneous lupus erythematosus. Supposed trigger factors of lichenoid inflammation are viral antigens, cross-reactive autoantigens or xenobiotics (drugs, chemicals), which are presented by basal keratinocytes to immune cells^[18]. Experimental data strongly suggest that HCV may be involved in the pathogenesis of OLP,

inducing a cellular immune response directed against HCV antigens and basal cell epithelial damage. The presence of HCV-RNA in mucosal and cutaneous lesions has been demonstrated by polymerase chain reaction-based techniques in several studies, suggesting a tissue-compartmentalization of HCV, albeit with low levels of viral replication. Other studies did not replicate these findings^[19,20].

Pilli *et al*^[21] further demonstrated the presence of HCV-antigen specific CD4 and CD8 T-cells in the lesional cell-infiltrate of HCV⁺ OLP patients, with higher frequency and IFN-gamma production than the clones in the peripheral blood. Whether the cytotoxic T-cell response may be directed against viral antigens presented by basal keratinocytes or simply induced by the local Th1-biased cytokine milieu is still under debate.

In HCV-infected patients, mucosal LP more frequently runs a chronic persistent course, with higher prevalence of erosive-ulcerative lesions and extensive disease, compared to non-infected LP patients. Treatment outcomes in patients with OLP associated with chronic HCV infection are often unsatisfactory compared to patients suffering from idiopathic disease. In addition, the evolution of oral lesions is often fluctuating, with repeated periods of relapse according to the degree of liver function decompensation, although some authors have found no correlation between the severity of LP disease and HCV-viral load or liver disease parameters^[22,23]. IFN-based treatment regimens may negatively influence established LP or induce the onset

of lichenoid lesions, as type- I IFNs are a major driver of lichenoid inflammation^[24]. Accordingly, there is a relative contraindication for IFN-based antiviral treatment in patients with concomitant LP and chronic-active HCV infection.

In this patient subset, a new therapeutic strategy with IFN-free regimens (Sofosbuvir, Simeprevir and/or Daclatasvir according to genotype) should be taken into account, optimizing treatment outcomes for both liver and extra-hepatic involvement. As yet, there are no published reports on the impact of IFN-free regimens on the clinical course of LP.

In patients with stable liver disease and symptomatic muco-cutaneous LP, treatment should be aimed at suppressing lichenoid-tissue inflammation with immune-modulating agents, while reducing the risk of HCV replication or liver-toxicity. Treatment of LP is based on a step-wise approach with the use of topical and/or systemic immune-modulating agents, depending on disease's course (acute vs chronic), extent (localized vs multifocal disease) and impact on patient's quality of life^[25]. Systemic treatment of LP should be restricted to severe mucosal or generalized-cutaneous disease, and includes different drugs, such as retinoids (acitretin), steroids and immunosuppressive agents (methotrexate, cyclosporine), albeit with a lack of high-quality evidence and clinical guidelines^[26]. In HCV-infected patients, systemic treatment of LP needs to be tailored on a case-by case basis, with strict monitoring of liver-function and HCV-replication parameters. As systemic steroids carry a substantial risk of reactivating HCV replication, treatment with alternative systemic agents should be preferred. Cyclosporine A has been successfully used for the treatment of severe, mucosal LP and its safety in HCV-infected patients has been reported in the setting of transplantation and autoimmune diseases^[27]. Moreover, in patients with chronic-active HCV infection and concomitant, severe LP the combination of new DAAs and cyclosporine A is possible, with a lower risk of drug interactions compared to first-generation protease-inhibitors^[28].

PCT AND LIVER DISEASE

PCT comprise a group of diseases resulting from an inherited or acquired dysfunction of the uroporphyrinogen decarboxylase enzyme (UROD). PCT is the most frequently occurring type of non-acute porphyria. The acquired, sporadic form of PCT (type I) occur in predisposed individuals with deficient activity of the enzyme in the liver, which is triggered by the exposure to liver toxins (hepatotoxic aromatic hydrocarbons), drugs (alcohol, estrogens), cigarette smoking, dialysis and hepatopatic viruses, with HCV at the forefront^[29].

The epidemiological association of PCT with HCV infection is strong, with increasing rates from Northern Europe, Australia and England (20%) to Southern Europe (70%-90%). When adjusting for geographical variation and variability in study designs the association between

PCT and HCV remains significant, with a reported 50% mean HCV prevalence in PCT patients^[30]. Screening for HCV infection and a comprehensive assessment of liver-function is therefore mandatory in the diagnostic workup of PCT. On the other hand, in patients with active HCV-related hepatic disease routine testing for porphyrin metabolism is not recommended, as there is only a 5% reported prevalence of preclinical or overt PCT in the HCV infected patient population^[31]. Iron overload (hepatic siderosis) is a critical pathogenetic event, disrupting the enzymatic activity of UROD by inducing the formation of an intracellular inhibitor, probably derived from hydroxymethylbilane and/or uroporphyrinogen.

HCV infection is an important trigger of PCT, interacting with other hepatotoxic and genetic susceptibility factors, usually preceding the clinical expression of PCT. HCV increases the production of reactive oxygen species, leading to hepatic down-regulation of hepcidin, the key regulator of iron absorption and metabolism^[32]. This contributes to iron overload in conjunction with other factors, such as genetic predisposition, further decreasing the activity of UROD below the critical threshold for deranged porphyrin metabolism^[33].

The clinical aspects of PCT are characterized by typical cutaneous lesions (vesicles, bullae, erosions and crusting) developing in sun-exposed areas, resulting in scarring, milia and mottled hypo-/hyper-pigmentation (Figure 1C). Other diagnostic clues are photosensitivity, skin fragility, facial hypertrichosis and late-stage sclerodermoid plaques. Laboratory investigations are necessary for diagnosis and differentiation with other cutaneous porphyrias, as previously reviewed. There are no significant differences in the clinical presentation of PCT between HCV positive and HCV-negative cases, but the former present more advanced histological and biochemical liver disease. Genetic studies have described in PCT patients the importance of the mutation profile in the *HFE*-gene, which is linked to hereditary hemochromatosis. Up to two-thirds of PCT patients carries a mutation of the *HFE* gene (H63D or C282Y mutations), and heterozygous carriers are at a higher risk of progression to severe liver disease and fibrosis. *HFE*-genotyping is clinically relevant since PCT patients with homozygosity for C282Y mutation do not respond to chloroquine and should be preferentially treated with phlebotomy^[34]. In a Spanish study, the same mutation was significantly associated with HCV-negative PCT patients, which presented hepatic siderosis. The H63D mutation was reportedly more frequent in HCV⁺ PCT patients, with milder defects in iron haemostasis^[35].

Standard of care for PCT includes photoprotection, anti-malarial drugs (chloroquine) and phlebotomy, the latter to reduce hepatic iron stores. In the setting of chronic HCV infection, effective antiviral treatment may potentially improve clinical and laboratoristic manifestations of PCT, especially when preceded by therapeutic phlebotomy. Since iron is also involved in the progression of HCV-related liver disease, depletion of iron stores by phlebotomy can improve both conditions. In a

clinical study with IFN-based regimens, the presence of PCT was independently associated with an insufficient virological response^[36]. Consequently, effective management of PCT and iron-reduction should precede antiviral therapy, as phlebotomy proved beneficial for treatment outcomes of IFN-based regimens^[37]. On the other hand, occurrence of new-onset PCT has been reported in some cases during IFN/ribavirin therapy^[38]. Indeed, ribavirin is known to induce haemolytic anemia, which further aggravates liver iron excess and progression to clinically manifest PCT in predisposed individuals. For this reason, studies addressing the role of new triple of quadruple-antiviral drug regimens in PCT + HCV⁺ patients in combination with iron-reduction therapy are warranted. In conclusion, PCT + HCV⁺ patients should undergo a comprehensive assessment of iron metabolism, hereditary hemochromatosis, *HFE*-gene mutations and evaluate exposure to hepatotoxic trigger factors in order to optimize therapeutic management.

PSORIASIS

Psoriasis is a common, chronic, immune-mediated inflammatory disease which affects the skin (plaque psoriasis) and/or joints (psoriatic arthritis). As other immune-mediated disorders, such as rheumatoid arthritis and IBDs, psoriasis results from the complex interplay between genetic factors and environmental triggers and has been recently linked to the metabolic syndrome. Moderate-to severe psoriasis and psoriatic arthritis are associated with substantial systemic inflammation and both conditions are driven by the overproduction of Th1-Th17 cytokines [TNF-alpha, IFN-gamma, interleukin (IL)-17, IL-12/23]^[39]. Chronic HCV infection and related liver disease represent one of the many comorbidities affecting psoriasis patients, thus representing a challenge for its clinical management. The epidemiological association between psoriasis and chronic HCV infection has been described mainly by hospital-based clinical studies and observational studies in countries with a heterogeneous burden of HCV and psoriatic disease. An increased risk of HCV infection among patient with moderate-to severe psoriasis and psoriatic arthritis has been reported in Taiwan, Japan and Italy, independently of exposure to interferon-based antiviral regimens, which are a well-known trigger of psoriasis^[40-43]. Other observational studies from Italy and the United States did not confirm these findings, probably due different study-designs and limited sample of psoriatic patients^[44,45]. Recently, a large case-control study further supported the association between psoriasis and HCV infection, reporting a significant odds-ratio of 1.75 (95%CI: 1.37-2.25) in the multivariate analysis. In the same study there is a significant interaction with smoking, a risk factor common to both psoriasis and progression of HCV-related liver disease^[46]. Interestingly, in two hospital-based studies Imafuku *et al.*^[47] described a distinct patient subset with psoriasis and associated chronic HCV infection. These HCV-

infected patients present a *de-novo* onset of psoriasis in higher age, with a significantly lower BMI, compared to HCV negative psoriatic controls, while maintaining a positive correlation with diabetes and hypertension. This evidence supports the role of HCV infection as a trigger factor for psoriatic disease in genetically predisposed individuals^[47]. A potential confounding factor in these studies is the increased monitoring and screening procedures related to moderate-to severe psoriasis, a condition increasingly treated with a wide array of systemic immunomodulating agents. This could account for an increased HCV detection rate in these patients, which are additionally exposed to a significant risk of nonalcoholic fatty liver disease and to potential hepatotoxic drugs, such as methotrexate and retinoids. Thus, additional prospective studies are warranted in order to support the role of psoriasis as a true extrahepatic manifestation of chronic HCV infection and to evaluate the course of psoriatic disease after effective and sustained antiviral response. Screening for HBV and HCV infection is routinely performed before initiating systemic treatment of psoriasis, as a chronic active infection can have a clinical impact on treatment selection^[48]. As yet there are no comprehensive and definitive recommendations addressing the issue of universal screening for HCV infection in the general psoriasis population. Treatment with immunomodulating drugs, such as TNF-alpha antagonists (etanercept, adalimumab, infliximab), has proved safe and effective in controlling psoriatic disease in HCV-positive patients, as reported in several case-series^[49]. Furthermore, the risk of HCV reactivation in patients exposed to TNF-alpha inhibition was considered to be low, as only three cases of HCV-related liver disease occurred in a total of 216 exposed patients^[50]. There is a need for long-term data on the safety of the new biologic agents, with TNF-alpha antagonists and IL-23/12 blockers, in the treatment of moderate-severe plaque psoriasis and psoriatic arthritis with concomitant HCV infection.

PRURITUS AND PRURITIC ERUPTIONS IN CHRONIC HCV INFECTION

Pruritus is a common symptom of hepatic diseases, mainly linked to chronic cholestatic disorders (primary biliary cirrhosis, primary sclerosing cholangitis), where it can run a chronic (> 6 wk duration) and refractory course. Although frequently overlooked by clinicians, in chronic HCV infection pruritus represent the most common extra-hepatic cutaneous manifestation, affecting up to 15% of patients in a large cohort study.

Proper clinical assessment of pruritus in HCV infection is important, as this can be an early, acute and transient symptom of a recent infection or a persistent manifestation of chronic HCV infection, possibly responding to effective antiviral treatment. Chronic pruritus (CP) is now defined as persisting more than 6 wk, involving primarily-diseased, non-inflamed or secondarily diseased

skin. CP is increasingly being recognized as the skin equivalent of pain, because it is associated with a significant impairment of quality of life and is frequently treatment-resistant^[51]. In the setting of chronic HCV infection patients present mainly with two clinical pictures, either with generalized pruritus on apparently non-diseased (normal) skin, or pruritus associated with secondary scratch lesions (papules, nodules, excoriations, lichenification). Chronic scratch lesions are typical of prurigo nodularis (Figure 1D) and lichen simplex cronicus, both pruritic conditions significantly associated with an increased prevalence of HCV infection in case-control studies^[52,53]. In the presence of primary, inflammatory skin changes, pruritus is related to a cutaneous disease, such as psoriasis, LP and urticaria, which are frequently observed in HCV infected patients. Despite the paucity of data on the clinical course reported in previous studies, pruritus associated with chronic HCV infection may recognize multiple pathogenetic factors^[54]. Dry-skin (xerosis) and skin barrier defects, alterations of peripheral pruriception due to neuropeptide imbalance and concomitant cholestasis can all contribute to the genesis of chronic pruritus in HCV infected patients.

Recently the role of autotaxin (lysophospholipase D) and its product lysophosphatidic acid has been discovered in the pathogenesis of pruritus linked to cholestatic liver disease. Patient with cholestatic pruritus present high serum levels of lysophosphatidic acid, a potent neuronal activator, and increased autotaxin activity. Serum autotaxin activity showed a significant correlation to itch intensity, both diminishing after effective therapeutic interventions^[55]. Furthermore, both autotaxin activity and lysophosphatidic acid are increased in chronic HCV infection, showing a strong correlation with liver cirrhosis stage, related complications and prognosis^[56]. Further studies should address the role of autotaxin serum activity and lysophosphatidic acid as mediators linking HCV-related liver fibrosis and non-cholestatic pruritus.

During active antiviral treatment, new-onset of localized or generalized pruritus associated with primary skin lesions has to be carefully approached by the clinician, in order to differentiate dermatological adverse events from true extra-hepatic skin manifestations. Traditional treatment with IFN and ribavirin can induce pruritic skin eruption in 8%-10% of HCV-patients, as well as elicit pre-existent pruritic skin diseases, such as eczema and psoriasis^[57]. First generation protease inhibitors, telaprevir and boceprevir, have also been increasingly associated (41%-61% rate) with adverse cutaneous drug reactions, most commonly grade 1-2 pruritic eczematous eruptions. Telaprevir-associated dermatitis occur more frequently (56% vs 34%) in comparison to IFN/ribavirin treated patients, and is constantly associated with pruritus (95% of cases) and secondary lesions (xerosis, excoriations and lichenification)^[58]. In the case of progressive (grade 2) or severe-generalized (grade 3) pruritic skin eruption treatment telaprevir needs to be discontinued. The risk

of severe cutaneous drug reactions, namely Stevens-Johnson Syndrome and Drug Reaction with Eosinophilia and Systemic Symptoms, has been reported in telaprevir-treated patients and early diagnostic signs (cutaneous pain, mucous membrane involvement, systemic inflammation) should be promptly detected^[59]. Cutaneous adverse reactions represent an emerging issue of dual-and triple antiviral combination therapies and require effective recognition and management, in order to ensure adherence to antiviral treatment.

CONCLUSION

HCV infection is one of the main cause of chronic liver disease worldwide^[60]. In the last decades clinical support for patients with chronic HCV infection has advanced rapidly due to the enhanced understanding of the pathophysiology of the disease and the improvements in therapy and prevention. Unfortunately, HCV infection is not limited to the hepatic involvement but it may lead to extra-hepatic diseases as well, in particular dermatological and mucocutaneous manifestations. In addition, dermatological adverse events are a potential concern during classic (IFN-based) and "new" (DAAs) anti-viral treatment. For this reason a throughout knowledge of cEHMs is mandatory for HCV-treating physicians, in order to deal with both hepatic and extra-hepatic diseases and to correctly address dermatological side effects during treatment. Skin disease which are certainly related with chronic HCV infection due to a strong epidemiological and pathogenetic association are MC, LP and PCT. Necrolytic acral erythema and CP are conditions that may share a possible association with HCV infection, while several immune-mediated inflammatory skin conditions, such as chronic urticaria and vitiligo, have been only anecdotally reported in the setting of chronic HCV infection. Psoriasis has been recently associated with chronic HCV-infection and notably both conditions share a common background of TNF-alpha based chronic systemic inflammation. Some of these conditions may complicate the clinical scenario of HCV infection, thus resulting in difficult-to treat patients, who may require a tailored antiviral regimen as well as multidisciplinary care. This is why the upcoming of new direct acting antivirals will help boost interest in extra-hepatic manifestations of HCV infection. Anyhow these new treatment regimens have to be tested in real-life clinical scenarios, such as patient subsets with advanced fibrotic disease and/or substantial comorbidity. It is possible but yet unproven that the more effective and rapid antiviral response observed with new IFN-free antiviral regimens will improve outcome in these clinical settings, especially when HCV infection is burdened by extra-hepatic manifestations.

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