Chapter

Extrahepatic Manifestations of Hepatitis C Infection

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Abstract

Chronic infection with the hepatitis C virus (HCV) is a major cause of liver disease worldwide and is also responsible for extrahepatic manifestations (EHM) involving many different organs and apparatus: skin, salivary glands, eyes, thyroid, kidneys, peripheral and central nervous system, and immune system. Mixed cryoglobulinemia is the most frequent, best known and strictly HCV-associated EHM. A significant association between HCV and B-cell Non-Hodgkin-Lymphoma is reported although the incidence of lymphoma among HCV-infected patients overall remains low. HCV-infected patients have increased rates of insulin resistance, diabetes, and atherosclerosis, which may lead to increased cardiovascular disorders. The mechanisms causing the extrahepatic effects of HCV infection are likely multifactorial and may include endocrine effects, HCV replication in extrahepatic cells, or a heightened immune reaction with systemic effects. Because of this associations, it is suggested testing for HCV infection the patients with a clinical condition described as linked to hepatitis C. Conversely, patients diagnosed with HCV infection should have evaluation for a possible EHM. EHM of HCV can be considered an established indication for antiviral treatment with direct acting antivirals, even in the absence of overt liver disease. Successful eradication of HCV can improve and in some cases cure EHM of HCV. B cell depleting agents may be considered to be the best biological target option for patients with more severe EHM in combination with the antivirals.

Keywords: HCV, chronic hepatitis C, cryoglobulinemia, B-cell lymphoma, thyroid dysfunction, type 2 diabetes, Sjögren's syndrome, porphyria cutanea tarda, lichen planus, glomerulonephritis, neuropathy, polyarthritis, extrahepatic manifestations

1. Introduction

Persistent infection with hepatitis C virus (HCV) is a leading cause of chronic liver disease, resulting in about 400000 deaths per year. The estimated global HCV prevalence is 1.0%, corresponding to 71 million individuals. Antiviral medicines can cure more than 95% of persons with hepatitis C infection, thereby reducing the risk of death from cirrhosis and liver cancer, but access to diagnosis and treatment is low. There is currently no effective vaccine against hepatitis C; however, research in this area is ongoing [1].

However, these data are underestimated do not taking into account the extrahepatic aspects that make this infection a systemic disease. Early after its discovery, it was shown that HCV is not only hepatotropic but also lymphotropic. It was also shown that several extrahepatic manifestations (EHM) can complicate HCV infection [2–4].

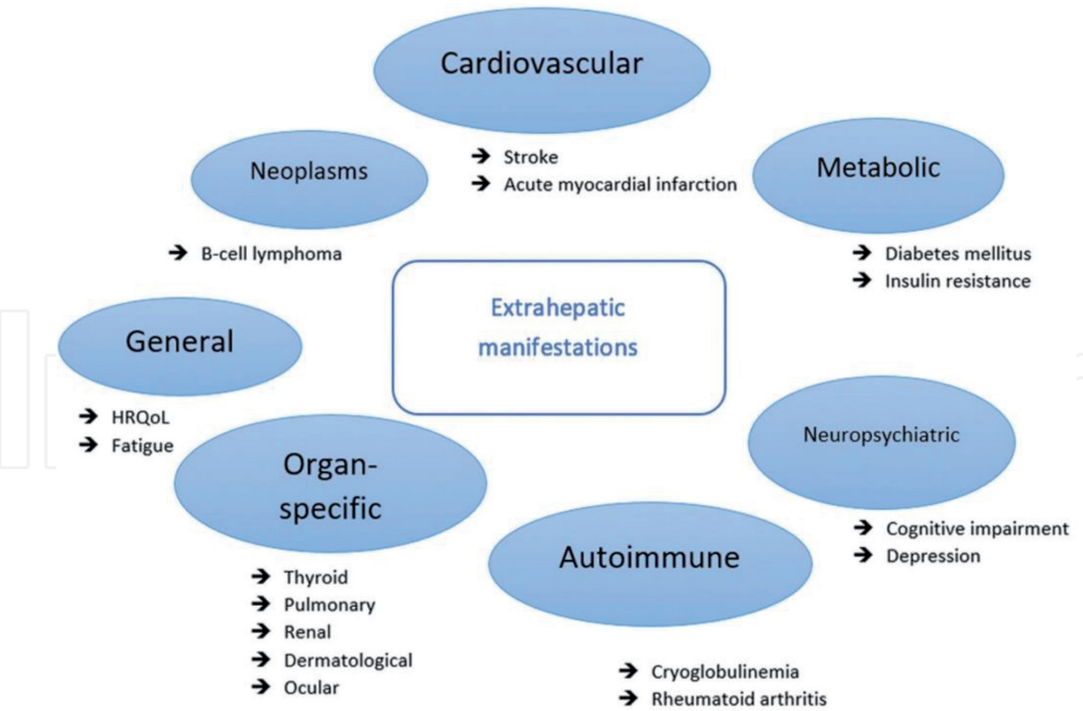

Figure 1.
The spectrum of extrahepatic manifestations of HCV [6].

Moreover, chronic HCV infection has been associated with numerous EHM and diseases, although a direct link is often difficult to establish.

Association should not be confused with causality. The association merely suggests a hypothesis, such as a common cause, but does not offer proof [5].

A causal relationship is easily acceptable if the strength of association is hight. Furthermore, according to the criterion of plausibility, the association ought to be biologically plausible.

The EHM described as linked to HCV hepatitis are numerous:

Mixed cryoglobulinemia (MC), sicca syndrome (SS), Non-Hodgkin Lymphoma (NHL), serum monoclonal gammopathy, thyroid disease, type 2 diabetes mellitus and glucose intolerance, many autoimmune disorders, renal disease, rheumatologic, neurological, cardiovascular and dermatological disorders [6] (**Figure 1**).

Here are described the most clinical important and best studied of these pathological conditions.

2. Biological plausibility and pathophysiology

The pathophysiology of EHM of HCV hepatitis is only in part understood and for some of them unexplained.

The mechanisms causing the extrahepatic effects of HCV infection are likely multifactorial and may include endocrine effects, HCV replication in extrahepatic cells, or a heightened immune reaction with systemic effects.

Due to the fact that HCV has been shown to infect both hepatocytes and lymphocytes, lymphoproliferative diseases such as lymphoma and MC are most closely linked to hepatitis C infection. These conditions are the most studied from the point of view of their pathophysiology. The primary mechanism of injury in cryoglobulinemia is a vasculitis triggered by immune complex deposition.

HCV has been shown to be a lymphotropic virus and associated with several lymphoproliferative disorders, including monoclonal gammopathies in addition to

MC and B-cell NHL. HCV infection of lymphocytes could play a direct role in cellular transformation, specifically in de novo large B-cell lymphoma. HCV infection of two B-cell lines can produce mutations in tumor suppressor and proto-oncogenes which were identified in HCV-associated B-cell lymphomas.

Two particulars although not mutually exclusive models of infection-driven malignant transformation were described.

Direct lymphocyte transformation by lymphotropic transforming viruses (Epstein–Barr virus, human herpesvirus, and human T-lymphotropic virus type) expressing viral oncogenes has been reported. A model of lymphocyte transformation finally leading to clonal expansion as an indirect mechanism of pathogenesis has been proposed. Sustained stimulation of lymphocyte receptors by viral antigens, viral replication in B-cells, and damage of B-cells have been also proposed as mechanisms of pathogenesis.

Expression of HCV viral proteins in B-cells of HCV-infected patients upregulates B-cell receptor signaling. Pro-inflammatory cytokines, such as the interleukins (IL-6, IL-17 and IL-10) and transforming growth factor-beta have also been reported to contribute to aberrant B-cell proliferation.

Glomerular injury in HCV-related glomerulonephritis is primary induced by a deposition of circulating immunocomplexes containing anti-HCV antibodies, HCV antigens and complement factors. Formation and deposition of such immunocomplexes occurs also in absence of cryoglobulins. Formation of glomerular antibodies is a further possible mechanism of HCV-related glomerular injury.

Peripheral nerves of patients with HCV-related peripheral neuropathy may show vasculitic changes involving the vasa nervorum, giving a possible explanation of nerve damage.

Studies have shown that dysthyroidism is mediated by immunological mechanisms rather than by direct HCV infection. The pathogenesis may involve changes in self-antigen expression and sustained stimulation of the immune system by HCV, bystander activation of autoreactive T-cells by cytokine release, infection of the lymphatic cells, chromosomal aberrations and abnormal expression of major histocompatibility complex class II molecules by thyrocytes, or cross-reactivity between viral antigens and thyroidal antigens.

Primary causation of dermatological EHM (apart the cryoglobulinaemic ones) results from direct infection of HCV in the skin, lymphocytes, dendritic antigen-presenting cells, and blood vessels. Secondary causation occurs when HCV infection manifests in the skin due to epiphenomena resulting from the disruption of immune responses [2–4, 6, 7].

The most common extrahepatic findings with which the relationship to HCV infection is more strongly established are cryoglobulinemia, autoimmune disorders (including autoantibodies and SS), porphyria cutanea tarda (PCT), and lichen planus (LP). There also appears to be a clear association with B-cell NHL (particularly in patients with underlying cryoglobulinemia), but the incidence of lymphoma among HCV-infected patients overall remains low.

3. Mixed cryoglobulinemia

MC is the most frequent, best known and strictly HCV-associated EHM (about 90% of MC patients tested positive for HCV antibodies in some studies) [7, 8].

MC may be defined a both autoimmune and B-lymphoproliferative disorder (LPD) that may evolve to a frank malignancy in about 8–10% of cases [9].

The definition of MC refers to the presence of serum Igs that reversibly precipitate at low temperatures (<37°C) and are represented by circulating immune

complex typically consisting of an IgM rheumatoid factor (mono-oligoclonal in type II MC, or polyclonal in type III MC) and polyclonal Ig (most frequently IgG) including anti-HCV antibodies. MC has been generally reported, at least subclinical, in the majority of HCV patients, even if data may widely vary in different geographical areas (from 20 to >50%). Only a minority of MC patients (5 to >30%) shows a symptomatic MC or MC syndrome (usually women aged more than 50 years), but even asymptomatic patients might develop MC in the future [10].

Factors that seem to favor the development of MC are female sex, increasing age, alcohol consumption (> 50 g/day), advanced liver fibrosis and steatosis.

The clinical manifestations of MC are secondary to a systemic vasculitis characterized by the deposition of cryoglobulins in the vessels and can be classified as one of the circulating immune complexes mediated systemic vasculitis involving small and medium-sized blood vessels.

The classic syndrome of MC consists in the triad of purpura, fatigue and arthralgia, but the various involvement of different organs and tissues (mainly skin, joints, renal, peripheral nerves) leads to variable clinical presentation and evolution.

Palpable purpura (leukocytoclastic vasculitis) and petechiae most often affects the legs (**Figure 2**).

Papules, ulcers, and livedo can also occur and can affect any skin site.

Reynaud Syndrome can be present, with or without digital gangrene, in about one third of patients.

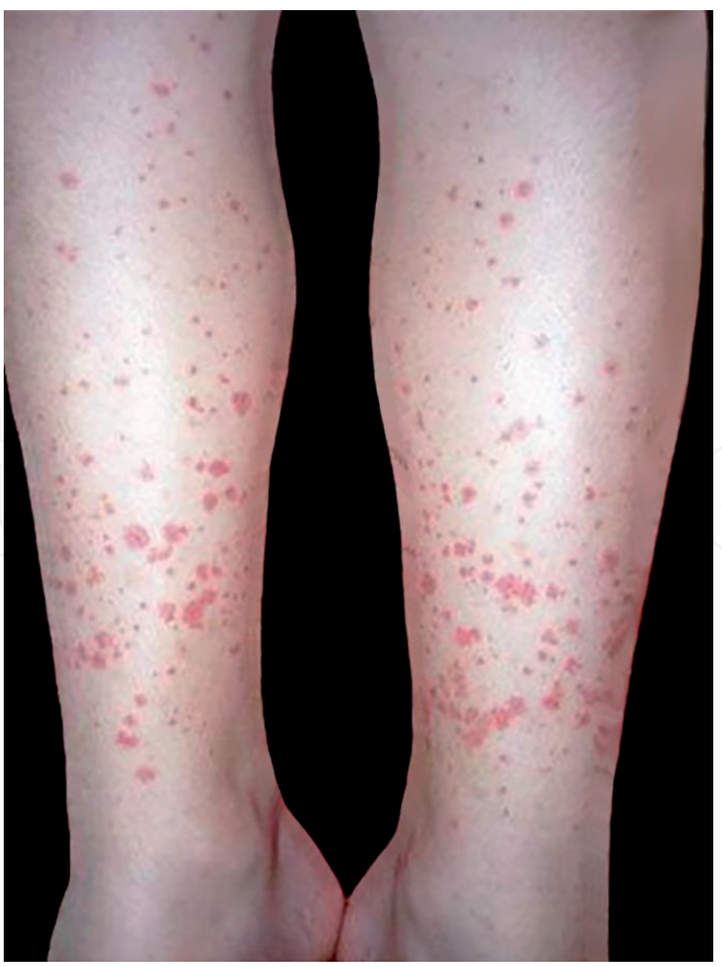

Figure 2.
Cutaneous manifestation of mixed cryoglobulinemia (see text).

Common manifestations of MC are arthralgias (polyarthralgia, but relatively rare is arthritis), renal disease, usually membranoproliferative glomerulonephritis (MPGN), and neurologic disease.

MPGN is characterized in most cases by proteinuria, mild haematuria and mild renal insufficiency. In the worst cases, a severe involvement of the kidney is observed (15% of cases).

The peripheral neuropathy including mixed neuropathies (prevalently sensitive, axonal) is common in MC (80–90% of cases), and also in HCV without MC (see below 9.).

HCV-related peripheral neuropathy is characterized by numbness, burning skin and pruritus.

Central nervous system involvement in patients with HCV-positive MC is rare (see below 9).

4. Sicca syndrome (secondary Sjögren syndrome)

Sjögren syndrome is described as a chronic, slowly progressive autoimmune disease characterized by lymphocytic infiltration of the exocrine glands and B-lymphocyte reactivity resulting in xerostomia and dry eyes. SS, to be differentiated from the primary Sjögren Syndrome, occurs in MC and also in HCV patients without MC [2–4]. In most instances the typical serological and histopathologic findings of Sjögren Syndrome are lacking. SS is more frequently reported in type II than in type III MC [2, 4].

Some studies showed an association between MC in HCV infected patients and severe liver damage [11].

However, discordant data exist. It is common clinical experience, including our own, to find patients with symptomatic HCV-related MC and a mild or moderate liver disease and conversely patients with the most severe form of chronic hepatitis C (advanced fibrosis, compensated and decompensated cirrhosis, hepatocellular carcinoma) without any symptom of MC (even when laboratory testing positive for MC).

5. Non-Hodgkin lymphoma and other hematological disorders

5.1 Non-Hodgkin lymphoma

The very close association between MC and HCV infection leads to the hypothesis that HCV may be involved in the pathogenesis of lymphoma as well.

A significant association between HCV and B-cell NHL was reported and confirmed in the large majority of studies [12].

This association involves different histopathological types of B-cell NHL, the most strictly associated being the lymphoplasmacytic, marginal zone and diffuse large B-cell lymphoma.

Some discordant data suggested the contribution of genetic factors and the incidence of lymphoma among HCV-infected patients overall remains low.

In an observational, prospective, multicenter, case–control study, the prevalence of HCV-antibodies was found of 0.16 among NHL and of 0.085 among controls and non-lymphoid malignancies patients [13].

Although the difference was statistically significant ($P < 0.001$), the odds ratio was 2.049 and its confidence intervals included the equality. NHL features

Feature (overall freq.)	HCV-positive NHL (48)	HCV-negative NHL (252)		
	Bearing feature	Freq. (conf. Int. 95%)	Bearing feature	Freq. (conf. Int. 95%)
Extranodal inv. (0.593)	30	0.625 (0.488–0.762)	148	0.587 (0.526–0.648)
Marrow inv. (0.283)	16	0.333 (0.200–0.466)	69	0.274 (0.219–0.329)
Stomach inv. (0.067)	2	0.042[a]	18	0.071 (0.039–0.103)
Liver inv. (0.030)	4	0.083 (0.005–0.161)	5	0.020 (0.003–0.037)
Cryoglobulinis (0.033)	3	0.063[a]	7	0.028 (0.026–0.030)
Age to 20 (0.007)	0	0	2	0.008[a]
Age 21–40 (0.090)	2	0.042[a]	25	0.099 (0.062–0.136)
Age 41–60 (0.300)	12	0.250 (0.128–0.372)	78	0.310 (0.253–0.367)
Age > 60 (0.603)	34	0.708 (0.579–0.837)	147	0.583 (0.522–0.643)
WF A, B, C[b] (0.286)	14	0.304 (0.071–0.437)	70	0.283 (0.227–0.339)
WF D, E, F[b] (0.248)	10	0.217 (0.098–0.336)	63	0.255 (0.201–0.309)
WF G, H, I, J[b] (0.464)	22	0.478 (0.334–0.622)	114	0.462 (0.400–0.524)
MALT (0.053)	3	0.062[a]	13	0.052 (0.022–0.088)

[a] *Lower confidence limit below.*
[b] *WF classification is available for 293.*

Table 1.
NHL features among HCV-positive and HCV-negative patients [13].

among HCV-positive and HCV-negative patients observed in this study are reported in the **Table 1**.

5.2 Serum monoclonal gammopathy and thrombocytopenia

A serum monoclonal gammopathy (MG), more frequently type IgMk and diagnosed as MG of uncertain significance (MGUS), was frequently observed in HCV patients, in most cases associated with a 2a/c genotype of the virus.

Available data suggest that HCV-related LPD are the result of multiple and cooperating mechanisms and events belonging to three principal categories: an important and sustained activation of the B-cell compartment; an inhibition of B-cell apoptosis; genetic/epigenetic and environmental factors (see also above 2.).

Thrombocytopenia is often observed in patients with chronic HCV hepatitis and sometimes it is disproportionally severe with respect of the stage of fibrosis-cirrhosis.

It is possible recognize as causal factors of thrombocytopenia in HCV chronic hepatitis the following: decrease of hepatic thrombopoietin, direct cytopathic involvement of HCV on megakaryocytes, production of platelets-associated immunoglobulins, hypersplenism.

6. Endocrine pathology and hepatitis C virus infection

6.1 Thyroid disease

The prevalence of thyroid disorders is generally high in HCV-positive patients and most frequently represented by antithyroid peroxidase antibodies

in female subjects. Hypothyroidism has been frequently observed, especially in HCV MC, and an association with papillary thyroid carcinoma was also shown [14].

6.2 Type 2 diabetes mellitus and glucose intolerance

Several studies showed that HCV (especially genotype 3) could lead to the development of type 2 diabetes mellitus, possibly as a result of HCV-induced metabolic disturbances. However, discordant data exist. Insulin resistance was observed in 30–70% of HCV patients [3, 15].

The cause of the association of HCV with diabetes is unknown. In addition, the magnitude of the association may be overestimated because patients with diabetes have more parenteral exposures than the general population, placing them at increased risk for transmission of blood transmitted viruses. Furthermore, not all studies controlled for the presence of cirrhosis, which may be associated with impaired glucose tolerance.

7. Autoimmune and rheumatologic disorders

7.1 Autoantibodies

A number of autoimmune disorders have been associated with chronic HCV infection, including subclinical autoantibody formation, autoimmune thyroid disease, sialadenitis/SS, and autoimmune thrombocytopenic purpura.

Autoantibodies are common in patients with chronic HCV infection. Antinuclear antibodies, antibodies directed against the Fc portion of IgG (rheumatoid factor), anticardiolipin antibodies, smooth muscle antibodies, or antithyroid antibodies are detected in 40 to 65 percent of patients. While antibodies are often present in low titres, do not appear to influence the presentation or course of the infection.

Nevertheless, the presence of autoantibodies may result in diagnostic difficulties.

For example, an HCV-infected patient with arthralgias, arthritis, and rheumatoid factor positivity may be misdiagnosed initially as having rheumatoid arthritis. In this setting, testing for other rheumatoid-arthritis-associated autoantibodies that are observed infrequently in patients with HCV infection, such as anti-citrullinated peptide antibodies (anti-CCP), may be helpful diagnostically.

In other cases, a difficult differential diagnosis between hepatitis C and autoimmune hepatitis can rise. In these cases, the liver biopsy findings are decisive. In rare cases the two disease coexist in the same patient.

Making a precise diagnosis is crucial because the treatment is completely different.

7.2 Rheumatologic disorders

Polyarthralgia is the most common rheumatologic symptom described in HCV-infected patients. HCV arthritis could be part of the MC or be independent. HCV-associated oligoarticular or polyarticular non-erosive arthritis can clinically mimic rheumatoid arthritis, although anti-CCP antibodies and erosive joint changes are generally absent [2].

8. Renal disease

Several renal manifestations have been associated with HCV infection, the most common being MPGN. HCV-associated membranous or proliferative glomerulonephritis or focal segmental glomerulosclerosis have been also described. The strongest association was reported for cryoglobulinaemic MPGN. Microhaematuria and proteinuria are the most frequent clinical findings of MPGN. The presence of a renal involvement is one of the worst prognostic indices in the natural history of MC [16].

9. Neurological disorders

Peripheral neuropathy: see above, in the context of MC. Less frequently, peripheral neuropathy can be present without MC. Peripheral neuropathy can be sensory or sensorimotor.

Symptoms of fatigue and deficits in concentration and working memory are commonly reported in patients with chronic HCV infection. Some studies have suggested neurocognitive impairments associated with HCV, even after controlling for other comorbid conditions, such as substance abuse, affective disorders, and cirrhosis. Functional imaging studies have also identified metabolic changes in the central nervous system in the setting of HCV infection (not ascribable to hepatic encephalopathy) [3].

10. Dermatological manifestations

Apart the dermatological manifestations of MC (see above 3.) the are other dermatological conditions associated with HCV infection deserving to be discussed.

10.1 Lichen planus

Cutaneous LP is characterized by flat-topped, pink to violaceous, pruritic papules with a potentially generalized distribution. The papules appear

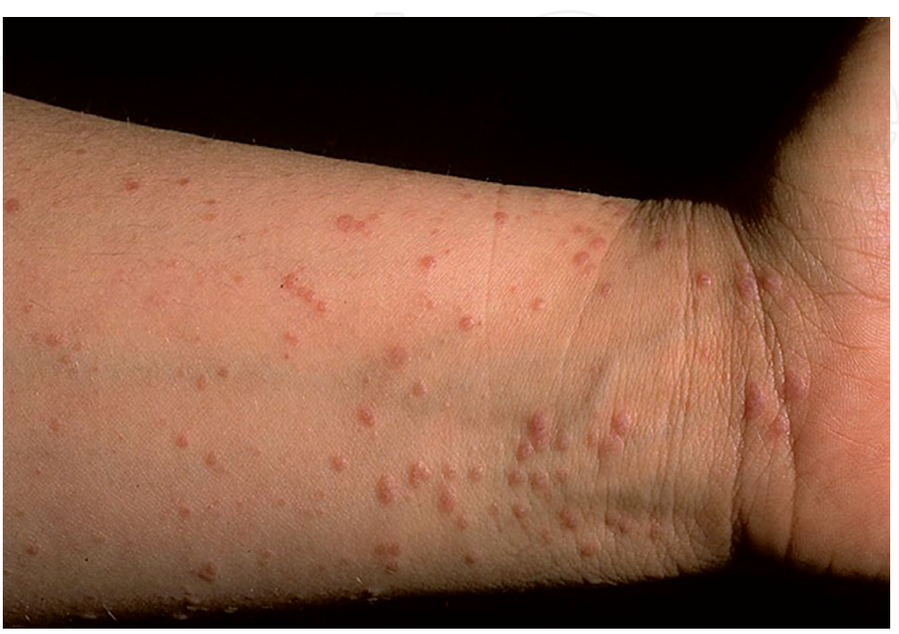

Figure 3.
Typical manifestation of lichen planus of the volar distal forearm and wrist in a hepatitis C patient (see text).

polygonal-shaped, translucent under incident light. They are 2–4 mm in diameter, with irregular margins and a hard-elastic consistency (**Figure 3**). LP can also involve mucus membranes, hair, and nails.

HCV infection has been reported frequently among patients with LP. In some studies, the prevalence of anti-HCV antibodies in patients with LP ranges from 10 to 40%.

Systematic reviews have reported that patients with oral LP planus are approximately two to six times more likely to have reactive anti-HCV antibodies compared with controls, although there is substantial geographical heterogeneity to the findings.

LP can be seen in patients with a variety of liver diseases, particularly advanced liver disease.

There is evidence of a genetic risk for HCV-associated LP. The most commonly used drugs in cutaneous LP are topical and systemic corticosteroids, for their immunosuppressive and anti-inflammatory effects [4, 17, 18].

10.2 Porphyria cutanea tarda

PCT is a disease caused by reduced activity of the enzyme uroporphyrinogen decarboxylase (UROD), causing the subsequent build-up of uroporphyrinogen in the blood and urine. PCT has both sporadic and inherited (autosomal dominant) forms that are indistinguishable clinically. A strong association between the sporadic form of PCT and HCV infection has been demonstrated in multiple studies (an overall prevalence of HCV of 50%). However, there was marked geographic variability; lowest prevalence rates (20 to 30%) were observed in reports from Australia, the Czech Republic, and France, while the highest rates (71 to 85%) were observed in Japan, Italy, and Spain. The prevalence in North America was 66%.

A central factor in the geographic variability appeared to be the baseline rates of HCV infection in the general population.

The skin and the liver are the two main sites affected in sporadic PCT. Skin disease is characterized by photosensitivity and skin fragility, with which exposure

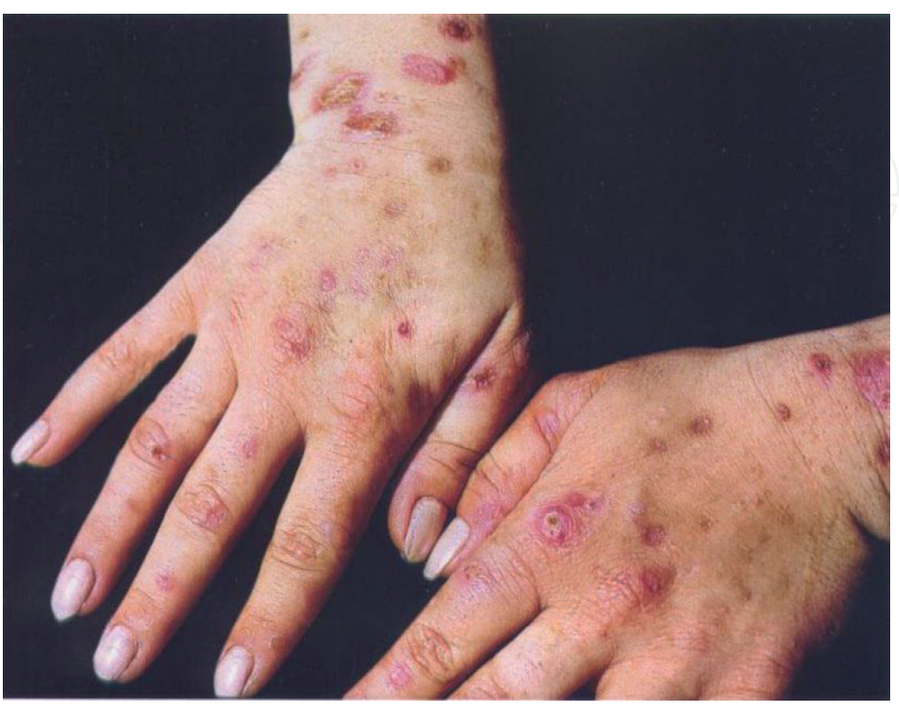

Figure 4.
Typical cutaneous manifestations of porphyria cutanea tarda (see text).

to the sun and/or minor trauma can lead to skin erythema and the development of vesicles and bullae that may become haemorrhagic.

Hyperpigmentation, hypopigmentation, hirsutism, and sclerodermatous changes may develop with the passage of time (**Figure 4**).

Chronic liver disease is common in sporadic PCT. Liver biopsy shows a wide range of changes, including steatosis, mild to severe inflammation, hepatic fibrosis, and cirrhosis. Environmental triggers are thought to be necessary to provoke an attack of PCT. Possible triggers of PCT include polyhalogenated hydrocarbons (such as hexachlorobenzene), oestrogens, but above all, iron overload and alcoholic beverages. The diagnosis of PCT is typically suspected on clinical grounds and is confirmed by the demonstration of markedly elevated urine uroporphyrin levels. The diagnosis can also be made directly by measuring hepatic UROD activity. All patients with PCT should be tested for HCV infection, as well as other potential disease associations, including HIV infection, iron overload, and hemochromatosis (with HFE mutation testing). Careful history of alcohol intake and testing of heavy alcohol intake markers are fundamental.

Management of PCT in patients with HCV infection includes avoiding precipitating factors (such as sun, alcohol, oestrogens, and polyhalogenated hydrocarbons), treating an underlying iron overload state, if present, and treating HCV infection.

PCT often, but not always, improves with clearance of HCV viremia. The currently used pharmacological protocol for PCT include the administration of a half tablet of chloroquine (125 mg) twice a week [19, 20].

11. Cardiovascular and respiratory diseases

Although data from individual cohorts have not been consistent, evidence overall suggests that chronic HCV infection is associated with adverse cardiovascular diseases and outcomes: dilated cardiomyopathy, hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy, myocarditis, and aortic atherosclerosis. These associations are still object of debate. Because cardiovascular diseases are common and multifactorial, it is difficult to determine whether HCV is a major contributing factor in an individual patient [3].

Idiopathic pulmonary fibrosis is a serious condition described in association with HCV infection.

12. Clinical implications and laboratory tests

Because of the associations, it is suggested testing for HCV infection in patients with clinical condition described above and other suspected to be linked to HCV. Anti-HCV antibodies (an inexpensive test) must be checked and if positive, quantitative HCV-RNA, genotype and complete workup of hepatitis C performed.

Conversely, patients diagnosed with chronic HCV infection should have evaluation for EHM at the initial visit and routinely during follow-up. History of an HCV-infected patient should cover rheumatologic symptoms (e.g., arthritis/arthralgias, dry eyes or mouth) and the physical exam should include a skin exam to evaluate for findings of cryoglobulinemia, PCT, and other associated dermatologic features. Superficial lymph node sites must be checked. Abdominal ultrasound is part of the HCV patient evaluation. It is in addiction necessary to perform a chest x-ray with particular attention to the mediastinum.

Laboratory testing should include a complete blood count, an assessment of renal function, evaluation for proteinuria and haematuria, and thyroid function tests. Cryoglobulins and complement levels should be checked if there is evidence of renal disease or other compatible clinical findings. Testing for other EHM should be guided by symptoms or specific physical findings.

Mild serum amylase elevation is a common finding in HCV patients generally without any pancreatic involvement clinically detectable.

13. Treatment of extrahepatic manifestations of HCV infection

13.1 Antiviral treatment

The armamentarium against HCV has been expanded with the availability of molecules able to directly target non-structural proteins that play a key role in HCV replication. These agents, orally administrated for a relatively short period of time (2–3 months) have been called direct acting antivirals (DAA) and target some of the main molecular components of HCV, including NS3/4A protease (first and second-generation protease inhibitors), NS5B polymerase (nucleoside and non-nucleoside analogues) and NS5A protein.

DAA can cure more than 95% of persons with HCV infection, thereby reducing the risk of death from cirrhosis and liver cancer.

Antiviral treatment is recommended for all patients with EHM.

Because of their not negligible rate of contraindications, important side effects, scarce tolerability, low compliance and adherence, length course of treatment, parenteral route of administration, and the insufficient rate of sustained virological response (SVR) obtainable (not more than 60%), the interferon (IFN) based therapies for HCV hepatitis must be considered obsolete.

Moreover, IFN, with its immunological stimulating properties, could be contraindicated and possibly worsen or elicit some EHM (for example thyroid disfunction, autoimmune EHM). A caution attitude could be suggested also in MC, exacerbated in some cases treated with IFN alone (without glucocorticoids).

The antiviral drug ribavirin maintains a very marginal role in this context. Ribavirin common side effects are dermatologic and require caution if used in cutaneous EHM of HCV hepatitis.

DAA-based, IFN-free regimens should be considered the standard antiviral therapeutic approach in HCV-related EHM [21].

At the present, DAA-based, IFN-free regimens should be used following the recommendations for individuals with HCV mono-infection in the current international guidelines.

Detailed assessment of drug–drug interactions is crucial since some medications are contraindicated or not recommended during DAA therapy [22, 23].

The vast majority of studies on the use of antiviral therapies in EHM - HCV diseases have been carried out in patients with MC vasculitis, which is considered the prototype of systemic autoimmune disease associated with HCV, both for their frequency and potential life-threatening involvement. All reported studies show that vasculitic manifestations largely improve after antiviral treatment (even in patients with partial virological responses) and often disappear, especially in patients with SVR.

Treatment of low-grade lymphomas only with DAAs antiviral therapies may be recommended whereas more aggressive lymphomas would require the addition of chemotherapy/rituximab.

IFN-free antiviral regimens might be less effective than IFN-containing regimens in some patients with B cell lymphoma, possibly due to the lack of additional anti-proliferative activity of IFN, while the association of rituximab with DAA regimens could be more effective than isolated antiviral therapies.

At the present there is little data on the response of other EHM to DAAs antiviral therapies for HCV hepatitis.

13.2 Non antiviral treatment of HCV-extrahepatic manifestations

Non-antiviral therapeutic approaches should be evaluated according to the type of EHM and the severity of the clinical presentation. The non-antiviral therapeutic approaches mainly used in EHM patients include glucocorticosteroids, immunosuppressant agents, plasma exchange and biological therapies.

Non-antiviral therapeutic approaches are recommended for moderate and, especially, for severe organ-specific involvements. Patients with moderate to severe vasculitic manifestations may be treated with short-term glucocorticoid regimens to control inflammation rapidly. Regimens of methylprednisolone (0.5–1.0 g/day) for three days followed by prednisone (not exceeding 1 mg/kg/day) may be appropriate in the setting of skin ulceration, sensorimotor neuropathy, glomerulonephritis, and other severe vasculitic manifestations.

For aggressive B cell NHL, the therapy remains based on immunochemotherapy with anthracycline-containing regimens in combination with rituximab as in HCV-negative patients.

Plasma exchange may be added to other therapies, especially in patients with severe/life-threatening cryoglobulinaemic vasculitis. Such intervention is useful in patients with immediately life-threatening involvements and for those with hyperviscosity syndrome. Apheresis techniques should always be used as a complementary therapy in combination with other strategies (antiviral therapies, B cell depleting agents).

B cell depleting agents may currently be considered to be the best biological target option for patients with the more severe EHM, always with a reasonable individualized assessment of the benefits and risks. The most promising non-antiviral therapeutic approach to HCV-related cryoglobulinemia is rituximab.

The use of antiviral therapies in combination with immunosuppressant/biological agents should normally be made sequentially (first, use immunosuppressant/biological agents and, once the major end-organ effects have been controlled, use antiviral therapy), or concomitantly. It seems reasonable to carry out the combination on a case by-case basis [21].

The orally active thrombopoietin-receptor agonist elthrombopag may be used in severe thrombocytopenic HCV patients.

Appropriate local and systemic treatments are needed for cutaneous and ocular EHM of HCV (see above 10.) [18, 20].

14. Prevention of extrahepatic manifestations treating HCV hepatitis with DAAs

In a large population study, it was found that successful DAA treatment resulting in SVR was associated with significant reductions in the future risk of several EHM of HCV, including MC, glomerulonephritis and LP but not NHL or diabetes. The magnitude of risk reductions ranged between 0.23 and 0.61.

SVR was associated with a reduction in risk of PCT, but it was only marginally statistically significant [24].

15. Conclusions

Chronic HCV infection can cause significant EHM and should be considered as a systemic disease rather than a disease affecting only the liver.

EHM of HCV can affect virtually every organ via a variety of mechanisms.

It is important to emphasize that the severity of these disorders does not necessarily correlate with the severity of hepatic disease.

Some investigations have shown that therapy of chronic HCV infection can result in resolution or improvement of extrahepatic diseases linked to HCV and even prevent their onset.

Awareness on the part of the clinician is necessary to recognize these numerous and heterogeneous pathological conditions. This in turn can lead to appropriate screening, early treatment and improved outcomes [4, 6].

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