

Review Article

Hepatitis C: the dermatologic profile

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Abstract

The hepatitis C virus (HCV) is a major public health problem all over the world with a global prevalence of 3%. It is responsible for 70% of cases of chronic hepatitis, the major cause of cirrhosis and the most common cause of hepatocellular carcinoma. The current treatment of chronic hepatitis C is the combination of interferon alpha and ribavirin with the sustained treatment response range of 56-82%.

Chronic hepatitis C is associated with a plethora of extrahepatic manifestations including dermatological disorders e.g. mixed cryoglobulinemia, porphyria cutanea tarda, lichen planus, pruritus and other less common conditions. The current review focuses on the dermatologic perspective of HCV infection highlighting the need of screening patients of different dermatoses for HCV in order to prevent the development of terminal, life-threatening consequences and further transmission of HCV.

Key words

Hepatitis C, skin manifestations, dermatologic profile

Introduction

Hepatitis C virus (HCV) was first identified in 1989 as the causative agent of most cases of posttransfusional and sporadic non-A, non-B hepatitis. According to WHO statistics, the global prevalence of HCV is 3.1% (lower in Europe ~1.03% and Americas ~1.7%) and highest in Africa ~5.3%.¹ In East Mediterranean Region (including Pakistan), the prevalence is ~4.6%.¹

In industrialised countries, HCV accounts for 20% of cases of acute hepatitis, 70% of cases of chronic hepatitis, 40% of cases of end-stage cirrhosis, 60% of cases of

hepatocellular carcinoma and 30% of liver transplants.^{2,3} However, the future burden of hepatitis C is going to multiply geometrically in future. One of the most important actions to prevent the uncontrolled damage is early diagnosing that leads to effective follow up and treatment. Cutaneous manifestations may be the first signs of HCV infection which can help in starting early treatment of this condition.

Hepatitis C virus

Hepatitis C virus (HCV) is a small (50 nm), single-stranded RNA virus with a lipoid envelope (**Figure 1**). It belongs to the family *Flaviviridae* and genus *hepacivirus*. The virion contains a positive single-stranded RNA genome of 9.5 kilobases which consists of many structural genes (C, E1 and E2) that encode for HCV core and envelope glycoprotein, while the nonstructural genes

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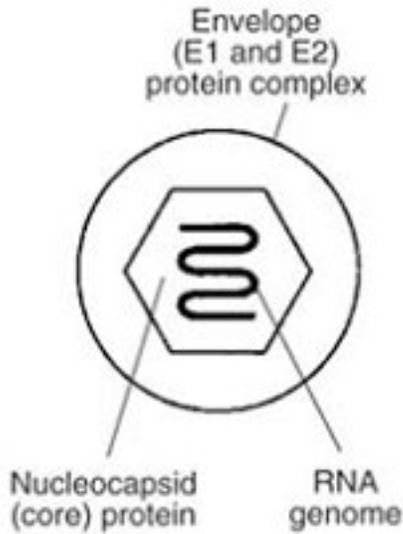


Figure 1 Structure of hepatitis C virus

(NS2, NS3, NS4 and NS5) encode for enzymes involved in virus replication.^{2,3,4}

There are at least 6 genotypes (possibly 12 or more) and more than 50 subtypes of HCV with the genotypes 1, 2, and 3 distributed world-wide (70-80% prevalence of genotype 1 in most Western countries), genotypes 4 and 5 distributed predominantly in Africa and genotype 6 found primarily in Asia.^{2,3,4}

Pathogenesis

Hepatitis C virus infection leads to viral persistence and chronic hepatitis in a very high proportion of infected by an immune escape mechanism despite broad activation of potent humoral and cellular immunological responses to viral proteins (**Figure 2**).⁵ These responses may be thwarted by the high rate of mutations, which leads to the generation of a highly variable mixture of closely related genomes

that persist and continuously evolve in infected individuals. HCV appears to be minimally cytopathic, therefore the immune response against HCV plays a central role in HCV pathogenesis.³ Liver damage in chronic hepatitis C is mostly due to host immune-mediated responses, including cytokine secretion by CD4+ cells and T lymphocytes induced cell death through direct cell-to-cell interactions and cytosine secretion. Moreover, patients with HCV infection frequently have autoimmune diseases and circulating tissue-specific and non-specific autoantibodies.⁶

Epidemiology in Pakistan

Local data reveal prevalence rate from 6-20%.⁶ In a recent study by Idrees *et al.*, of the total 6817 serum samples tested from healthy subjects in Punjab, 998 (14.63%) were positive for anti-HCV antibodies.⁷ HCV-RNA was detected in 494 (49.50%) anti-HCV-positive samples. The prevalence of anti-HCV antibodies was significantly higher in males (15.09%) than in females (12.3%).

Prevalence of HCV may be different in different regions and various groups of the same community. Hospital-based studies revealed prevalence rates of 2.45% (Rawalpindi),⁸ 4.06% (Multan),⁹ 5% (Buner, NWFP),¹⁰ 5.31% (Islamabad) [42],¹¹ 4-6% (Karachi),¹² 9% (Mardan),¹³ 20.89% (Faisalabad),¹⁴ and 25.7% (Northern Areas).¹⁶

Similarly, different groups may show

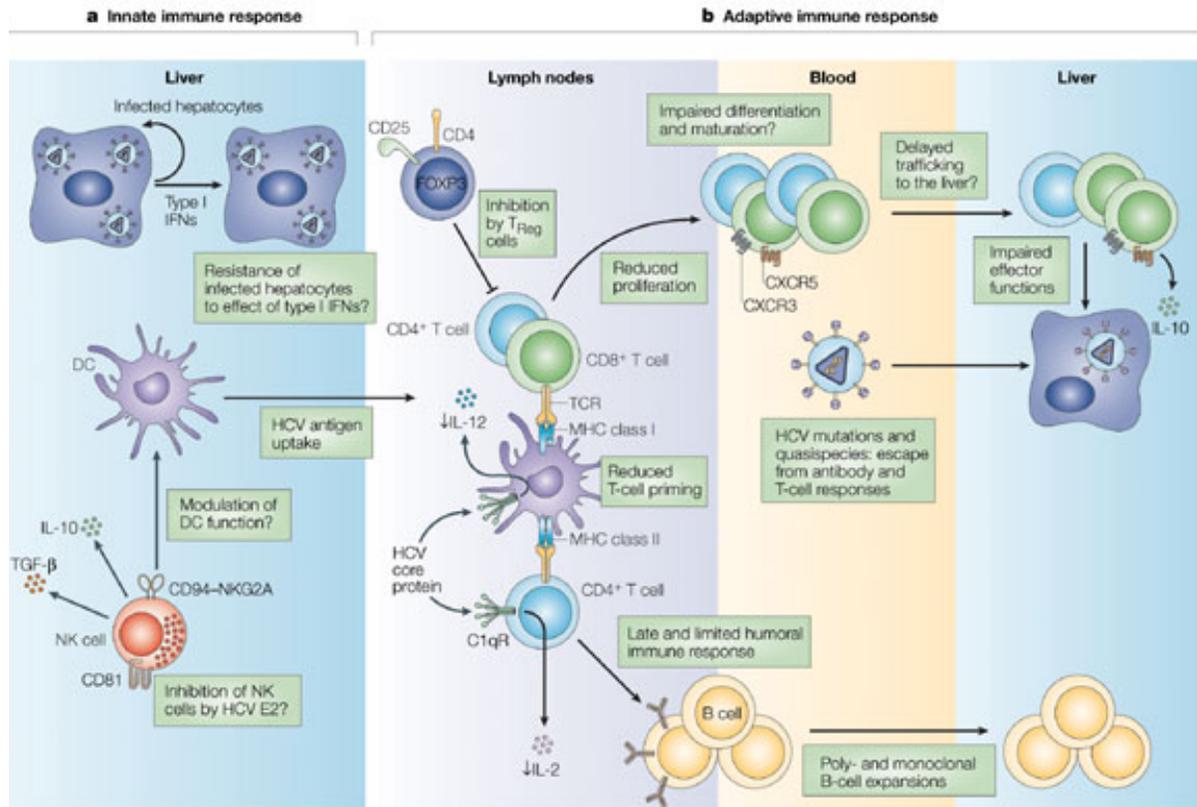


Figure 1 Interactions between HCV infection and immune system of body [5].

different prevalence rates. In a study conducted in thalassemia patients at Karachi incidence of HCV positivity was found to be 46%.¹⁷ In gynecological and obstetric patients rates of 7%¹⁸ and 18.2%¹⁹ were reported.

In Pakistan, the most common HCV genotype is type 3a.²⁰ Of 3351 serum samples tested, type-specific PCR positivity was 94%. 8.35% patients were infected with HCV genotype 1a, 3.01% with 1b, 0.15% with 1c, 7.52% with 2a, 0.80% with 2b, 0.09% with 2c, 49.05% with 3a, 17.66% with 3b, 0.75% with 3c, 2% with 4, 0.18% with 5a, 0.12% with 6a and 4.80% patients were infected with mixed infection.

Transmission and risk groups

HCV primarily spreads through contact with infected blood. High-risk groups include recipients of multiple or repeated blood transfusions or blood products, intravenous drug abusers, prisoners, hemodialysis patients, healthcare workers exposed to needle stick and sharps injuries. In about 50% of infected patients (so-called 'sporadic' cases) have no obvious risk factor.^{2,3,4}

According to another review approximately 10 million people have been infected with HCV in Pakistan.²¹ The majority of patients have acquired their infection through unsafe injections, reuse of syringes and needles and community barber shops used for face and

armpit shaving. More than two-thirds of HCV patients were 40 to 50 years old.²¹

Diagnosis and treatment

Diagnosis of hepatitis C is based on serological assays and HCV RNA. A screening enzyme-linked immunosorbent assay (ELISA) and a confirmatory recombinant immunoblot assay) which detect HCV-specific antibodies (anti-HCV) are used initially. Serological assays are used for screening and epidemiological surveillance. Active infection is confirmed by the presence of viral genome, detected by a qualitative polymerase chain reaction (PCR). The quantitative PCR test is used to monitor disease activity and response to treatment.^{2,3,4}

Currently, the combination of interferon alpha and nucleoside analogue ribavirin is recommended.^{3,4} Recently, significantly increased response rates as compared to conventional interferon alpha, polyetilenglycol (PEG)-conjugated interferon alpha shows significantly better response.²² Several factors determine the treatment response. The sustained virological response to the combination treatment including PEG interferon alpha has been achieved in 42-46% of genotype 1 patients and in 76-82% of genotypes 2 and 3 patients.

Side effects of interferon alpha are numerous and severe and require discontinuation of therapy in 2-10% of patients. The early side effects involve the inconvenience of subcutaneous administration of the medicine three times (or once) weekly for 6-12 months.²²

Prognosis

Patients with anti-HCV-positive, HCC have a significantly worse prognosis compared to patients with HbsAg-positive or alcohol-related liver cancer, as tumors tend to be multifocal and are often diagnosed late, It is particularly important, therefore, that anti-HCV-positive patients with significant underlying liver disease (especially cirrhosis) should undergo regular screening for signs of HCC and by liver ultrasonography and serum α -fetoprotein determinations.^{2,3}

Skin manifestations of HCV

CHC infection is associated with many extrahepatic manifestations in joints, kidneys, muscles, neural and gastrointestinal tissues, and skin.⁷ A long list of dermatological disorders are seen in CHC infection (**Table 1**)

Different studies report different frequencies of various dermatoses. Azafar *et al.* noticed skin manifestations in 54% of their patients and generalized pruritus was the most common finding seen in 15.9% patients.²³ A study from Turkey revealed pruritus to be most frequent symptom seen in 18.57% of patients.²⁴ Other dermatoses included leukocytoclastic vasculitis and lichen planus seen in 4.28% each. Paoletti *et al.*²⁵ from Italy reported 12 of their 96 patients (12.5%) presented with skin disorders in progress of chronic virus C hepatitis. 5 cases of leukocytoclastic vasculitis (LCV) by mixed cryoglobulinemia, 1 case of pruritus, 2 cases of oral lichen planus (OLP), 2 cases of alopecia areata, 1 case of urticaria and 1 case of psoriasis.

Pathogenesis of cutaneous manifestations

The exact mechanisms underlying the extrahepatic manifestations of HCV infection are not fully elucidated but following hypotheses are forwarded to explain this phenomenon.

1. Immune stimulation by HCV

Chronic infection by HCV causes persistent stimulation of both humoral and cellular immunity. HCV acts as a superantigen, bypassing the MHC class II-dependent antigen presentation by antigen presenting cells to TH cells, and initiates a broad-based immunological response causing monoclonal and polyclonal expansion of B cells and T cells. A number of pathogenic antibodies and T cells are produced against self-antigens which have a pivotal role in the causation of many extrahepatic manifestations. In contrast, it is reported that hypervariable region (HVR-1) of envelope protein E2 acts as a T-cell receptor antagonist and suppresses CD4⁺ lymphocytes response and consequent lower expression of IFN- γ and interleukin 12.⁶

2. Pathogenic mimicry

HCV particles have been demonstrated in many tissues including oral LP lesions. Because of their structural resemblance to the normal tissue antigens, many specific antibodies and T cells directed against HCV antigens cross-react with normal tissue antigens and initiate the disease process.

Consequent to these mechanisms, diseases with autoimmune-based pathogenesis may appear for the first time or are aggravated e.g. psoriasis, lichen planus etc.

Dermatologic manifestations of HCV can be classified according to the underlying pathogenic mechanisms (**Table 1**).

A. Diseases due to abnormal B cell immunoglobulin production or deposition

1. Mixed cryoglobulinemia According to the data from Western communities, mixed cryoglobulinemia (MC), type II or type III, is seen in 50% of patients with chronic hepatitis C. Clinically, MC is characterized by systemic vasculitis with variable manifestations. Patients with MC had cirrhosis more often and had a longer history of hepatitis than those without cryoglobulinemia.

The cause of MC is supposed to be the chronic stimulation of the immune system by HCV. The antigen-antibody complexes of viral particles and anti-HCV antibodies initiate the process of vasculitis. An alternative mechanism may be that HCV-specific antibodies or T-cells bind to endothelial cells containing HCV may initiate the process. The treatment for chronic hepatitis C leads to the great improvement in the manifestations of cryoglobulinemia. It is advised to screen the patients with mixed cryoglobulinemia for the presence of anti-HCV.²⁻⁶

2. Antiphospholipid syndrome is a serious multisystemic illness resulting from pathologic production of the anticardiolipin and lupus anticoagulant. Severe coagulopathies in the eye, the brain, the

Table 5 Skin manifestations of hepatitis C according to their frequency and involved mechanisms [2-6].

According to frequency	According to involved mechanism
<p><i>A. Well accepted manifestations</i></p> <ul style="list-style-type: none"> • Pruritus • Mixed cryoglobulinemia • Necrolytic acral erythema <p><i>B. Frequently associated conditions</i></p> <ul style="list-style-type: none"> • Porphyria cutanea tarda • Lichen planus • Polyarteritis nodosa <p><i>C. Case reports or reports of series</i></p> <ul style="list-style-type: none"> • Psoriasis • Vitiligo • Dermatomyositis • Erythema multiforme • Erythema nodosum • Bechet's syndrome • Pyoderma gangrenosum 	<p><i>A. Abnormal B-cell/immunoglobulin production and/or deposition</i></p> <ul style="list-style-type: none"> • Cryoglobulinemia • Antiphospholipid syndrome • Leukocytoclastic vasculitis • B-cell lymphoma • MALT syndromes (mucosal-associated lymphoid tumors) • Plasmacytoma <p><i>B. Autoimmune</i></p> <ul style="list-style-type: none"> • Pruritus • Prurigo nodularis • Lichen planus • Necrolytic acral erythema • Polyarteritis nodosa • Urticaria • Behçet's syndrome • Mooren's corneal ulcer • Sialoadenitis • Thyroiditis • Thrombocytopenia • Psoriasis • Vitiligo, canities • Dermatomyositis • Erythema multiforme • Erythema nodosum • Pyoderma gangrenosum • Erythema dyschromicum perstans • Disseminated superficial actinic porokeratosis • Generalized granuloma annulare <p><i>C. Unknown mechanism</i></p> <ul style="list-style-type: none"> • Porphyria cutanea tarda • Arteriovenous hemangiomas • Unilateral nevoid telangiectasia • Verrucous carcinoma of tongue <p><i>D. Cutaneous changes due to organ failure</i></p> <ul style="list-style-type: none"> • Liver failure and thyroid failure <p><i>E. Cutaneous manifestations due to treatment of HCV</i></p> <ul style="list-style-type: none"> • Interferon or ribavirin therapy

kidney, and large vessels result in symptomatology referable to vascular destruction or bleeding in these organs. In skin, these manifest as purpura, ecchymoses, livedo reticularis, ulcers, nodules etc.³

3. Non-Hodgkin B-cell lymphoma (NHLB) and mucosal-associated lymphoid tumours (MALT) syndrome 20-40% patients of non-Hodgkin B-cell lymphoma have anti-HCV antibodies. NHLB presents like other lymphomas, with lymphoidal masses, gut associated masses, and symptoms of

cryoglobulinemia with palpable purpura and ulcers of the lower legs. Antigen-driven B-cell proliferation from chronic stimulation is the proposed mechanism. A multicenter study showed HCV infection in 172 NHL cases (3.60%) as compared to 169 (2.70%) controls.²⁶

B. Autoimmune diseases in association with HCV

Pruritus and prurigo Pruritus is one of the most common symptoms, occurring in 15% of patients. Dervis and Serez reported pruritus to be the most common feature of HCV seen in 18.57%.²⁴ A local study revealed a figure of 15.9%.²³ Another study of HCV infection with pruritus showed that nonspecific lesions of xerosis, prurigo and keratosis pilaris in two thirds of patients.²⁵ Sometimes pruritus might be due to another dermatosis e.g. urticaria, lichen planus or eczema.

Lichen planus Both mucosal and cutaneous lichen planus have been reported to occur in settings of chronic HCV infection. The reported prevalence of HCV infection in patients with LP shows wide variations, from 3.8% in France²⁷ to 62% in Japan.²⁸ It has been reported that 2.4% to 8% of patients with chronic HCV-related liver disease had oral LP.²⁹ Shahid from Faisalabad reported association between LP and HCV.³⁰ In contrast, other researchers did not find a difference in prevalence of HCV between erosive and nonerosive forms of LP.^{27,31,32}

The etiology of HCV-associated lichen planus is unknown. It may be hypothesised that HCV-specific T cells react against the product of a host gene termed GOR which

shares several amino acids with the core gene product of HCV.³³ It is assumed that although HCV is not the primary cause of LP *per se*, it may play a pathogenic role by triggering LP in genetically susceptible HCV-infected patients.

The treatment with interferon alpha more often than not results in the eruption or aggravation of lesions. Lichen planus may therefore have a different clinical behaviour in patients with HCV infection and/or interferon treatment, hypothesising a role of HCV and/or interferon in the modulation of host/immune response.

Acral necrolytic erythema The symptomatology of acral necrolytic erythema includes pruritus associated with recurrent, erythematous, papular eruptions with blisters and erosions on the dorsal aspects of the feet and ankles. Pain is common with variable-sized erosions. Chronic lesions are hyperkeratotic plaques with erosions and peripheral erythema preferring the acral parts of the legs. These lesions provide unusually specific markers for HCV infection.^{34,35}

Polyarteritis nodosa Although hepatitis B infection is more frequently associated with polyarteritis nodosa, HCV can be occasionally the underlying cause.

Leukocytoclastic vasculitis This is another occasional presentation of vasculitis occurring in association with CHC.

Behcet's syndrome Behcet's syndrome can be a rare manifestation of CHC.

Urticaria and urticarial vasculitis In addition to urticarial vasculitis, chronic

urticaria can be seen in association with HCV. Although many studies refute this association,³⁶ a Japanese study³⁷ and local data^{38,39} reported a significantly higher occurrence of anti-HCV antibodies in patients of chronic urticaria.

Sialadenitis It may present as xerostomia but not with xerophthalmia. Similarly anti-Ro and anti-La antibodies are not positive.⁴⁰

Vitiligo and canities HCV can be a rare cause of failure of melanogenesis of skin and hair resulting in vitiligo or canities.

Erythema nodosum It can occasionally occur in the setting of CHC.

Erythema multiforme HCV infection is just one of many possible causes of EM.

Autoimmune thrombocytopenia Symptoms of low platelet counts occur with petechiae and purpura. Ecchymosis occurs without symptoms.

C. Diseases due to unknown mechanisms

In certain conditions like porphyria cutanea tarda (PCT) the causation is unexplained. In patients with PCT, 70% are HCV positive. PCT is the most common form of porphyria which results from the deficiency of hepatic uroporphyrinogen decarboxylase. HCV probably acts as a non-specific factor that reveals the deficit of uroporphyrinogen decarboxylase in a genetically determined individual. Increased porphyrin in the skin triggers a phototoxic reaction and consequently stimulates collagen synthesis, which may result in sclerodermoid lesions in some patients.⁴¹ A strong association (50-90%) has been demonstrated between

sporadic PCT cases and HCV infection in patients from the Mediterranean basin, Japan and the United States.^{42,43}

D. Tertiary dermatologic disorders

These are nonspecific disorders manifesting as a result of organ failure or disease of the skin associated with organ diseases.

- **Liver failure in CHC infection** This results from cirrhosis, autoimmune hepatitis, cholangitis, and HCC. Symptoms of liver failure are identical to those due to other causes. Amongst 371 patients with HCV, Azafar *et al.*²⁴ reported palmar erythema, leukonychia, jaundice, spider nevi in 11.59%, 7.55%, 5.93%, 4.04%, respectively.
- **Thyroid failure** Consequent to autoimmune thyroiditis, thyroid failure can occur and symptoms of hypothyroidism e.g. thickened, coarse and dry skin, alopecia etc. may be noted.

E. Dermatologic manifestations associated with interferon alfa and ribavirin therapy for HCV infection

Alopecia, pigmentary changes (generalized and lingual), pruritus and hypertrichosis of eyelids and eyebrows are common.⁴⁴ Infrequent changes include erosive oral lichen planus, epidermolytic hyperkeratosis, capillaritis, lichen myxedematosus and psoriasis. Azfar *et al.*²⁴ reported Schamberg's disease and photosensitivity in patients on antiviral therapy more frequently than those without treatment.

F. Other infrequent associations

There are anecdotal reports of certain dermatoses.

- Erythema dyschromicum perstans
- Disseminated superficial actinic porokeratosis⁴⁵
- Papuloerythroderma⁴⁶
- Generalized granuloma annulare⁴⁷
- Arteriovenous hemangiomas
- Verrucous carcinoma of tongue
- Psoriasis
- Unilateral nevoid teleangiectasia
- Pyoderma gangrenosum
- Scleromyxedema^{48,49}
- Epidermolysis bullosa acquisita⁵⁰
- Others

Conclusion

The list of HCV-associated skin disorders is likely to grow in future. Considering the diversity of dermatoses associated with HCV infection, a clinician should be highly vigilant while examining patients presenting with aforementioned skin disorders. Anti-HCV screening may reveal underlying asymptomatic HCV infection which is a potentially curable disease.

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