

Hepatitis C in dermatology

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ABSTRACT

Hepatitis C is a serious public health problem all over the world. It is caused by a single stranded RNA virus. Most acute infections are subclinical, but in 75% of individuals, infection leads to a chronic hepatitis, which in some cases can progress to cirrhosis and occasionally development of hepatoma. It has wide range of dermatological manifestations. This review article deals with the overview of epidemiology, pathogenesis, clinical manifestations, management and prevention.

Key words: Hepatitis; Epiphenomenon; Interleukins; Interferon

INTRODUCTION

Hepatitis C is a serious public health problem all over the world. So far, it has been reported to infect around 170 million people worldwide. Hepatitis C virus is a linear, single-strand, positive-sense, 9600-nucleotide RNA virus, the genome of which is similar in organization to that of flaviviruses and pestiviruses; HCV is the only member of the genus *Hepacivirus* in the family Flaviviridae. The virus replicates in hepatocytes and blood mononuclear cells. Most acute infections are subclinical, but in 75% of individuals, infection leads to a chronic hepatitis, which in some cases can progress to cirrhosis and occasionally development of hepatoma. A variety of conditions ranging from endocrinopathies to different skin diseases have been described in HCV infections [1-7].

EPIDEMIOLOGY

Prevalence

Around 170-200 million infected individuals worldwide, 3-5 million in the USA. An estimated 10-30% of all those who are infected may develop major liver damage in the 15-30 years following contracting the infection. The prevalence of hepatitis C is lowest in Northern European countries, including Great Britain, Germany and France in which the prevalence of HCV antibodies in blood

donors averages less than 1% for the regions whereas in the U.S, it is approximately 2.5%. Higher rates have been reported in Southeast Asian countries, including India (1.5%), Malaysia (2.3%), and the Philippines (2.3%) [1-7].

Race

Race and ethnicity do not relate to hepatitis C virus (HCV). HCV infection is associated with lower economic status, less education and groups other than whites [1-7].

Sex

No sex preponderance occurs with hepatitis C virus (HCV) infection. Sex differences were not significant [1-7].

Age

About 65% of individuals positive for hepatitis C virus (HCV) antibodies are aged 30-49 years. Younger age at infection often relates to lesser consequences of the infection [1-7].

Transmission

The virus is being transmitted by [1-8]:

1. Blood transfusion,

How to cite this article: Zonunsanga. Hepatitis C in dermatology. Our Dermatol Online. 2015;6(4):466-470.

Submission: 06.11.2014; **Acceptance:** 06.04.2015

DOI: 10.7241/ourd.20154.127

2. Percutaneous routes, such as injection drug use.
3. Occupational exposure to blood and the likelihood of infection is increased in hemodialysis units.
4. It can be transmitted sexually
5. Perinatally

About 10–15% of patients with acute hepatitis C report having potential sexual sources of infection. The chances of sexual and perinatal transmission have been estimated to be 5%. Breast-feeding does not seem to increase the risk of HCV infection between an infected mother and her infant. Health workers are more likely to acquire HCV infection through accidental needle punctures, the efficiency of which is 3%. Infection of household contacts is rare as well [1-8].

High-risk groups [2,3,5-9]:

1. Persons who have used injection drugs or those who have used illicit drugs by non injection routes
2. Persons with HIV infection
3. Hemophiliacs treated with clotting factor concentrates
4. Hemodialysis patients
5. Persons with unexplained elevations of aminotransferase levels
6. Transfusion or transplantation recipients
7. Children born to women with hepatitis C
8. Health care, public safety and emergency medical personnel following needle injury or mucosal exposure to HCV-contaminated blood
9. Sexual partners of persons with hepatitis C infection.

PATHOGENESIS

Different factors such as viral, genetic or environmental may be responsible for cutaneous disorders associated with HCV infection. In most cases, the mechanisms through which HCV may trigger or exacerbate skin manifestations remain unclear and require further examinations.

The pathomechanism of various dermatologic manifestations of HCV can be classified into the following main types [1,8-11]:

- 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 by interfering with host T-cell function due to down-regulating interleukin 2 and interferon gamma function and up-regulating interleukin-10. 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.
- 4) Neoplastic dermatologic manifestations are another category of extrahepatic findings. Local carcinogenic functions of HCV, effect on the p53 system, immune-dysregulation and malignant transformation were considered in the etiology of the conditions. HCV core protein may affect cancer transformation directly through an effect on a promoter gene expression. The core protein is a multifunctional protein with the capacity to bind to the so-called death domain of tumor necrosis factor receptor 1 (TNFR1) and the intracellular portion of lymphotoxin-beta receptor. The portion of TNFR1 active in apoptosis and anti apoptosis signaling pathway is the death domain affected by HCV.
- 5) Dermatologic manifestations are associated with treatments of HCV infection, especially interferon, e.g. IFN-induced vitiligo.

CLINICAL FEATURES

The incubation period ranges from 15–160 days (mean, 7 weeks) [3-7]. Constitutional symptoms of anorexia, nausea and vomiting, fatigue, malaise, arthralgias, myalgias, headache, photophobia, pharyngitis, cough and coryza may precede the onset of jaundice by 1–2 weeks. The nausea, vomiting and anorexia are frequently associated with alterations in olfaction and taste [3-12].

The main dermatological findings seen in most of the studies are Pruritus and prurigo, Palmar erythema, Clubbing, Hyperpigmentation, Lichen planus (Cutaneous, Oral), Leuconychia, Jaundice, Aphthous ulcers, Cutaneous vasculitis, Spider naevi, Purpura, Photosensitivity, Telangiectasia, Urticaria, Acral necrolytic erythema, Schamberg's disease, Psoriasis, Beau's lines, Porphyria cutanea tarda, Prurigo, Raynaud's phenomenon, Splinter haemorrhages, Behçet syndrome, Canities (HCV

causes sudden disruption of the melanizing function of follicles), Erythema dyschromicum perstans, any signs and symptoms of hypo- and hyperthyroidism (Immune thyroiditis is the most common extrahepatic manifestation of chronic hepatitis C infection) [3-12].

Hepatitis C is also associated with erythema nodosum, erythema multiforme, erythema induratum, autoimmune thrombocytopenia, Porokeratosis (disseminated superficial type, believed to be related to immunomodulation of the TP53 gene), Granuloma annulare, symmetric polyarthritis, scarring alopecia, Hypertrichosis of the temples, pigmentary changes, scarring, sclerodermatous changes, chloracne, ulcerations, dystrophic calcifications, sarcoidosis, Non Hodgkin's lymphoma, MALT syndrome and hepatoma [4-12].

HCV infection has been associated with several eye disorders. Keratoconjunctivitis sicca (dry eyes) is part of SS. A few cases of Mooren's ulcers have been reported. Mooren's ulcer is a rapidly progressive, painful ulceration of the cornea [5-12].

Interferon-induced dermatological diseases

Vitiligo is an autoimmune disease in which melanocytes in the skin are destroyed, with resulting depigmentation in affected areas. Although it has no specific association with liver disease, it has been linked to treatments for hepatitis C such as interferons. Interferon-induced vitiligo often completely resolves when interferon is stopped. Typical findings include aggregations of irregularly shaped white patches in a focal or segmental pattern.

Other skin conditions includes capillaritis and worsening of lichen myxedematous.

INVESTIGATIONS

Blood

Neutropenia and lymphopenia are transient and are followed by a relative lymphocytosis. Atypical lymphocytes (varying between 2 and 20%) are common during the acute phase [3,4].

Measurement of the prothrombin time (PT) is important in patients with acute viral hepatitis, for a prolonged value may reflect a severe hepatic synthetic defect, signify extensive hepatocellular necrosis and indicate a worse prognosis [3,4,6,8-12].

Blood sugar should be checked as prolonged nausea and vomiting, inadequate carbohydrate intake, and poor hepatic glycogen reserves may contribute to hypoglycaemia [3,4,6,8-12].

Stool and urine examination may be done as mild and transient steatorrhea as well as slight microscopic hematuria and minimal proteinuria are seen in some patients [3,4,6,8-12].

Liver function test

The serum aminotransferases aspartate aminotransferase (AST) and ALT (previously designated SGOT and SGPT) show a variable increase during the prodromal phase of acute viral hepatitis and precede the rise in bilirubin level. The acute level of these enzymes, however, does not correlate well with the degree of liver cell damage. A diffuse but mild elevation of the gamma globulin is common during acute viral hepatitis.

Jaundice is usually visible in the sclera or skin when the serum bilirubin value is $>43 \text{ mol/L}$ (2.5 mg/dL).

Serum alkaline phosphatase may be normal or only mildly elevated, while a fall in serum albumin is uncommon [3,4,6,8-12].

Serology

Serum IgG and IgM levels are elevated in about one-third of patients during the acute phase of viral hepatitis, but the serum IgM level is elevated more characteristically during acute hepatitis A. During the acute phase of viral hepatitis, antibodies to smooth muscle and other cell constituents may be present and low titers of rheumatoid factor, nuclear antibody and heterophil antibody can also be found occasionally. The antibodies to LKM may be positive.

A specific serologic diagnosis of hepatitis C can be made by demonstrating the presence in serum of anti-HCV which can be detected in acute hepatitis C during the initial phase. This may not be detectable in 5–10% of patients with acute hepatitis C as well as after recovery. In patients with chronic hepatitis C, anti-HCV is detectable in $>95\%$ of cases. Assays for HCV RNA by PCR is the most sensitive tests for HCV infection and represent the "gold standard" in establishing the diagnosis. However, it is not a reliable marker of disease severity or prognosis but is helpful in predicting relative responsiveness to antiviral therapy.

TREATMENT

In typical cases of acute hepatitis C, recovery is rare. Progression to chronic hepatitis is the rule and meta-analyses of small clinical trials suggest that antiviral therapy with interferon alfa monotherapy (3 million units SC three times a week) is beneficial, reducing the rate of chronicity considerably by inducing sustained responses in 30–70% of patients [13-15]. Although treatment of acute hepatitis C is recommended, the optimum regimen, duration of therapy and time to initiate therapy remain to be determined. Many authorities now opt for a 24-week course (beginning within 2–3 months after onset) of the best regimen identified for the treatment of chronic hepatitis C, long-acting pegylated interferon plus the nucleoside analogue ribavirin (1000 – 2000 mg PO), although the value of adding ribavirin has not been demonstrated [13-15].

PREVENTION

IG is ineffective in preventing hepatitis C and is no longer recommended for post exposure prophylaxis in cases of perinatal, needle stick or sexual exposure. Prevention of transfusion-associated hepatitis C has been accomplished by the following successively introduced measures: exclusion of commercial blood donors and reliance on a volunteer blood supply; screening donor blood with anti-HBc; exclusion of blood donors in high-risk groups for AIDS and the introduction of anti-HIV screening tests; and serologic and virologic screening tests for HCV infection [1,2,5-8,13-15].

In the absence of active or passive immunization, prevention of hepatitis C includes behavior changes and precautions to limit exposures to infected persons.

Anti-HCV testing is recommended for:

- anyone who received a blood transfusion or a transplanted organ before the introduction of second-generation screening tests in 1992,
- those who ever used injection drugs (or took other illicit drugs by non injection routes),
- chronically hemodialyzed patients,
- persons with clotting disorders who received clotting factors made before 1987 from pooled blood products,
- persons with elevated aminotransferase levels,

- health workers exposed to HCV-positive blood or contaminated needles,
- persons with HIV infection,
- health care and public safety personnel following a needle-stick or other non percutaneous exposure to HCV-infected material,
- sexual partners of persons with hepatitis C,
- children born to HCV-positive mothers.

For stable, monogamous sexual partners, sexual transmission of hepatitis C is unlikely and sexual barrier precautions are not necessary. For persons with multiple sexual partners or with sexually transmitted diseases, use of protection is recommended [1,2,5-8,13-15].

A person with hepatitis C should avoid sharing such items as razors, toothbrushes and nail clippers with sexual partners and family members. No special precautions are recommended for babies born to mothers with hepatitis C, and breast-feeding does not have to be restricted [1,2,5-8,13-15].

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Source of Support: Nil, **Conflict of Interest:** None declared.