Frequency of Cutaneous Manifestations in Patients of Hepatitis C Virus Infection

Ambreen Rauf,1 Shahbaz Aman,2 Muhammad Nadeem,3 Atif Hasnain Kazmi4

Abstract

Objective: To determine the frequency of cutaneous manifestations of hepatitis C infection in patients presenting in a tertiary care hospital.

Study Design: Descriptive study.

Place and Duration of Study: Department of Dermatology, King Edward Medical University / Mayo Hospital, Lahore, from 1st January, 2009 to 30th June, 2009.

Methodology: A descriptive (observational) study was conducted in the hepatitis C virus (HCV) infected patients, attending the Skin Department during a period of six months. The patients were diagnosed as HCV positive by enzyme-linked immunosorbent assay (ELISA) and/or polymerase chain reaction (PCR). A thorough medical history was taken and a detailed cutaneous examination was carried out in every patient.

Results: A total of 180 patients were enrolled. Out of them, 95 (52.8%) were males and 85 (47.2%) females. Most of the patients were in the age group of 21 – 30 years. Thirty five (19.4%) patients were taking treatment of hepatitis C. Pruritus was the most common dermatological feature seen in 33.8%, followed by lichen planus in 27.2%. Less common manifestations noted were urticaria (7.8%), vitiligo (5.6%), mixed cryoglobulinemia (4.4%), erythema nodosum (2.8%), erythema multiforme (2.2%), porphyria cutanea tarda (1.1%) and necrolytic acral erythema (1.1%). The signs of chronic liver disease (palmar erythema, jaundice, spider naevi, telangiectasia, leukonychia) were found in 13.8% of patients.

Conclusion: Hepatitis C virus infection is associated with a number of extra-hepatic cutaneous manifestations which may help to identify the silent cases of this grave disease.

Key words: Hepatitis C Virus, Cutaneous manifestations, Pruritus, Lichen planus.

Introduction

Hepatitis C virus is an RNA virus, a member of Flaviviridae.1 Hepatitis C virus infection is a common and major source of slowly progressive liver disease.1,2 Almost 170 million people worldwide have HCV infection which represents 3% of the world population.2 In Pakistan, according to one report, 10 million people...
have been infected with HCV. Although, acute hepatitis C infection is uncommon, majority of patients with this disorder develop chronic hepatitis and hepatocellular carcinoma resulting in severe morbidity in 20 – 30% of infected persons. Early recognition of this infection may alert practitioners to the need for viral testing and appropriate counseling of patients.

Cutaneous features may be the only and earliest signs in this disease. Previously reported most common cutaneous manifestations of HCV are lichen planus, necrolytic acral erythema (NAE), urticaria, mixed cryoglobulinaemia (MC), vitiligo, prurigo nodularis, pruritus, erythema multiforme and erythema nodosum etc. The pathogenesis of skin disorders remains uncertain but it is assumed that the virus replicates within lymphoid cells, potentially resulting in the extrahepatic manifestations. Another theory suggests that circulating immune complexes composed of HCV antigens and antibodies deposit in the tissues and cause initiation of an inflammatory cascade. Other possible mechanisms are a local formation of immune complexes induced by viral antigens, or a local tissue inflammation induced by auto-antibodies reacting with tissue antigens.

Identification of silent cases by cutaneous findings can help in control of this infection. The present study was therefore, aimed to see the frequency of cutaneous manifestations in patients of hepatitis C reporting to the Department of Dermatology, Mayo Hospital, Lahore.

Material and Methods

The study was conducted in the out – and inpatient Department of Dermatology, King Edward Medical University / Mayo Hospital, Lahore and the study protocol was approved by the institutional ethical and research committee. A total of 180 patients with either sex and any age, diagnosed as hepatitis C virus (HCV) positive by ELISA and / or PCR, with any degree of severity or duration of liver disease but having some skin manifestations, were included in our study. All the patients were included, either getting or not getting the treatment for this disease (interferon alpha and ribavirin). Patients with co-existing major systemic diseases like diabetes mellitus, liver disease due to any other viral etiology or any other cause and chronic renal failure, were excluded from the study. Pregnant females and patients suffering from any other skin disease were also omitted from our study.

Written informed consent was taken from all the patients and their identity was kept confidential. Demographic data and a detailed cutaneous examination with full morphological description of the lesions were recorded in a predesigned proforma. Necessary investigations like skin biopsy, serum cryoglobulins, liver function tests, blood sugar profile, abdominal ultrasonography etc., for confirmation of skin lesions, were carried out accordingly. Frequencies of various cutaneous manifestations were noted.

The data were entered into SPSS version 11 and were analyzed. Study variables included age, sex and skin problems like lichen planus, porphyria cutanea tarda, pruritus and cryoglobulinaemia. Mean and standard deviation were used for age. Frequencies and percentages for different variables were calculated. The effect modifiers like age, gender and treatment (with and without) for HCV infection were noted. Frequencies of cutaneous findings were also seen in patients on or with history of antiviral therapy. The statistical analysis was done by using Chi-square test for comparison of cutaneous manifestations with respect to gender and a p-value of < 0.05 was considered significant.

Results

It was a descriptive study. A total of 180 patients, diagnosed as hepatitis C virus positive, were examined for cutaneous manifestations. There were 95 (52.8%) males and 85 (47.2%) females, with male to female ratio of 1.1:1. Thirty Five (19.4%) patients were taking antiviral therapy, a combination of interferon alpha and ribavirin, while 145 (80.6%) patients were not taking any treatment. The age range noted was 18 – 60 years with a mean of 36.1 ± 11.9 years. There were 11 (6.1%) patients in the age range of 18 – 20 years, 66 (36.7%) in 21 – 30 years, 41 (22.8%) in 31 – 40 years, 37 (20.6%) in 41-50 years and 25 (13.9%) patients in 51 – 60 years. So, a majority of patients were in the age group of 21 – 30 years.

The frequency of different cutaneous disorders noted in these cases is shown in Table 1. Pruritus was the most common cutaneous manifestation seen in 61 (33.9%) patients. It was generalized with excoriations and of a mild to moderate intensity. Lichen planus was seen in 49 (27.2%) cases. Out of these, 09 patients had only the oral lesions, 16 patients had only the cutaneous involvement while 24 patients presented with both oral and cutaneous lesions. Skin lesions were violaceous, pruritic papules and plaques of different sizes.
Table 1: Cutaneous manifestations in Hepatitis C infection (n = 180).

<table>
<thead>
<tr>
<th>Cutaneous Manifestations</th>
<th>No.</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>61</td>
<td>33.9</td>
</tr>
<tr>
<td>Lichen planus</td>
<td>49</td>
<td>27.2</td>
</tr>
<tr>
<td>Urticaria</td>
<td>14</td>
<td>7.8</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>10</td>
<td>5.6</td>
</tr>
<tr>
<td>Mixed cryoglobulinaemia</td>
<td>8</td>
<td>4.4</td>
</tr>
<tr>
<td>Erythema nodosum</td>
<td>5</td>
<td>2.8</td>
</tr>
<tr>
<td>Erythema multiforme</td>
<td>4</td>
<td>2.2</td>
</tr>
<tr>
<td>Necrolytic acral erythema</td>
<td>2</td>
<td>1.1</td>
</tr>
<tr>
<td>Porphyria cutanea tarda</td>
<td>2</td>
<td>1.1</td>
</tr>
<tr>
<td>Signs of CLD</td>
<td>25</td>
<td>13.9</td>
</tr>
</tbody>
</table>

CLD = Chronic liver disease

Table 2: Comparison of cutaneous manifestations with sex (n = 180).

<table>
<thead>
<tr>
<th>Cutaneous Manifestations</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lichen planus</td>
<td>29</td>
<td>20</td>
</tr>
<tr>
<td>Pruritus</td>
<td>23</td>
<td>38</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Urticaria</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Mixed cryoglobulinaemia</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Necrolytic acral erythema</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Erythema multiforme</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Prophyria cutanea tarda</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Erythema nodosum</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Signs of CLD</td>
<td>15</td>
<td>10</td>
</tr>
</tbody>
</table>

CLD = Chronic liver disease

Discussion

HCV is probably the most common cause of chronic liver disease in the Western world as well as Pakistan.2,7 Dermatological findings constitute an important proportion of extrahepatic signs related to HCV infection.3,8 Present study reveals that the infection is more commonly seen in the age group from 21 years onwards similar to other studies,3,7,9,10 suggesting that the risk increase with increasing age possibly due to greater exposure to the risk factors.1,5,7 The present study showed a greater number of males as compared to females which is again similar to various other studies9,10 while a study by Adees et al. confirmed it by showing a significantly higher prevalence of anti-HCV antibodies in males than females.11 This can also be attributed to the fact that, in our community, males are at a higher risk due to greater exposure to trauma in daily activities, sexual contact, blood transfusions and intravenous drug abuse.1,3,7

The most common finding in our study was pruritus as noted in earlier studies.5,9 However, the percentage varies in all the studies.5,9 The precise mechanism of pruritus remains unclear, although HCV with moderate to severe fibrosis may result in low-grade cholestasis with pruritus.5,6 The high percentage of pruritus noted in our cases may be due to xerosis or as an adverse event of interferon alpha and ribavirin therapy which is in accordance with other studies.9,12,13

Lichen planus (LP) was the next common finding seen.
in our cases similar to other studies, reflecting a significant co-association between LP & HCV.\textsuperscript{3,9,10,14-17} However, the prevalence of HCV infection in patients of LP shows wide variations from 3.8% in France to 62% in Japan.\textsuperscript{1} This is probably due to the genetic differences and geographic variations in HCV prevalence worldwide.\textsuperscript{16,17} The high percentage of LP noted in our study may be explained on the basis of above mentioned differences and it can also be caused by the antiviral therapy as reported previously.\textsuperscript{1,12,13} The association of LP and HCV suggests that such patients should have an assessment of liver function for early detection and prevention of possible liver damage.

Urticaria was seen among 7.8% of the patients, while variable figures (both high and low percentage) are reported in most of other studies.\textsuperscript{5,9,10,18,19} The reason for variable seropositivity in different populations might be due to the difference in HCV genotypes prevalent in every community as various genotypes differ in their immunologic potential.\textsuperscript{1,7} Mixed cryoglobulinemia (MC) was recorded in 8 (4.4%) cases which is less in contrast to other studies.\textsuperscript{1,10,20} The cause of MC is supposed to be the chronic stimulation of the immune system by HCV.\textsuperscript{1} These patients show cutaneous features of leukocytoclastic vasculitis (LCV), Raynaud’s phenomenon and livedo reticularis. Our study showed LCV in 2.2% of patients which is almost consistent with the finding of some studies\textsuperscript{9,21} while few other studies noticed vasculitis in a higher percentage (10%) of HCV patients.\textsuperscript{1,10} The antigen – antibody complexes of viral particles and anti-HCV antibodies initiate the process of vasculitis.\textsuperscript{1,3} Few of our patients also had a history of Raynaud’s phenomenon but did not manifest livedo reticularis as seen in other studies.\textsuperscript{5,6}

Vitiligo, erythema nodosum and erythema multiforme were also found in our study similar to most of the previous reports.\textsuperscript{3,6} Hepatitis C may induce autoimmune disorders through persistent antigenic stimulation.\textsuperscript{1,3} Two patients of necrolytic acral erythema (NAE) were found in our study in contrast to some international studies in which more cases of NAE were identified related to this infection.\textsuperscript{22,23} Further studies are required in this regard to clarify the matter.

In the present study, we found porphyria cutanea tarda (PCT) in 1.1% of cases which is comparable to a study by Azfar \textit{et al}.\textsuperscript{9} The low percentage of PCT in both the studies may be because of the rarity of this disease in our society while several foreign studies have reported an association between HCV and PCT with a percentage of 47 to 50.\textsuperscript{3,5,24} The low percentage of PCT in the present study may also be correlated with genetic variations and a limited use of alcohol in our society which are the important factors involved in the pathogenesis of disease.\textsuperscript{3} HCV infection increases oxidative stress within hepatocytes and does so to a greater extent than for other chronic viral infections.\textsuperscript{6} The formation of autoantibodies that inhibit uroporphyrinogen decarboxylase, may contribute to its causation.\textsuperscript{6}

Palmar erythema, jaundice, leukonychia, spider naevi and telangiectasia were seen in a comparable manner to the study by Azfar \textit{et al}.\textsuperscript{9} These are the signs of decompensated cirrhosis depending on the severity of chronic liver disease in different studies.\textsuperscript{1} We did not observe any patient of prurigo nodularis, autoimmune thrombocytopenic purpura, alopecia, canities, pityriasis rubra pilaris, psoriasis, Behcet’s syndrome, Sjogren’s syndrome and Schamberg’s disease in association with HCV infection as seen in other reports.\textsuperscript{1,3,6,9}

Antiviral therapy has many cutaneous adverse effects.\textsuperscript{1,9} Three of our patients with erythema multiforme gave a history of this eruption after starting the antiviral treatment. It may be correlated to the side effect of the therapy which is in accordance with other studies.\textsuperscript{1,12,13} Dermatological manifestations like mixed cryoglobulinemia and necrolytic acral erythema showed some kind of improvement in patients on interferon alpha and ribavirin treatment similar to other studies.\textsuperscript{1,8,23} However, specifically designed studies, with a long term follow-up period, are required in this regard to see the exact role of antiviral therapy in persistence or disappearance of cutaneous manifestations associated with HCV infection.

**Conclusion**

Hepatitis C virus infection is associated with a number of extra – hepatic manifestations, many of which are cutaneous and can help to identify the silent cases of this serious disease. However, multi – centre studies including large number of patients are needed to attain more knowledge and to elucidate further problems related to HCV infection in our society.

**References**