

## Original Article

# Frequency of various cutaneous disorders in chronic hepatitis C virus infection

Amer Ejaz, Riaz Ahmed\*, Imran Fazal\*\*, Muhammad Tahir\*

Consultant dermatologist, Combined Military Hospital, Kharian Cantonment

\*Department of Medicine, Combined Military Hospital, Kharian Cantonment

\*\* Department of Cardiology, Combined Military Hospital, Kharian Cantonment

**Abstract** *Background* Silent chronic hepatitis C (HCV) infection is endemic in our society. Several different cutaneous manifestations have been studied with it. Understanding these may help in early diagnosis of HCV disease.

*Objective* To determine the types and frequency of various cutaneous disorders in chronic hepatitis C virus infection.

*Patients and methods* This cross sectional study was conducted at the medical department of Combined Military Hospital, Kharian cantonment, Pakistan. Patients of chronic hepatitis C confirmed by serological markers, ELISA, and positive PCR were enrolled from outpatient department. Detailed history taking and relevant systemic examination was carried out. All enrolled patients were specifically examined by a dermatologist to diagnose or rule out the presence of skin disease. Biochemical profile including complete blood count, platelet count, cryoglobulins, and antibodies against nucleus, neutrophil cytoplasm, cardiolipin, and smooth muscle were done. All this information was entered into a specially designed pro forma. All data was analyzed using SPSS Program 10.0. Descriptive statistics were calculated for the study variables.

*Results* One hundred patients were enrolled during the study period. 47% patients with chronic HCV infection were found to have at least one dermatological disease. Cryoglobulinemia was the commonest finding followed by lichen planus and chronic urticaria. Manifestations with lesser frequency included vitiligo, xerostomia, and purpura.

*Conclusion* Dermatological diseases are fairly common in patients with chronic HCV infection and can help to identify the silent cases.

### *Key words*

Chronic hepatitis C, skin manifestations, lichen planus, urticaria, vitiligo.

## Introduction

Chronic hepatitis C (HCV) infection is a major public health problem around the world with an estimated global prevalence of 3%.<sup>1</sup> Prevalence in Pakistan has variably been estimated to be between 3.3% to 13.5%.<sup>2,3,4</sup> However, most

studies done in Pakistan lack population-based epidemiological work and representation across the country.<sup>5</sup> Therefore we need to have large scale population based epidemiological work to elucidate the true prevalence in our population.

HCV infection is associated with a host of extrahepatic manifestations many of which are seen by a dermatologist and help in early diagnosis of the disease.<sup>6</sup> Cutaneous manifestations of chronic HCV infection are divided into three groups. Often associated are

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### Address for correspondence

Dr. Amer Ejaz,  
Combined Military Hospital,  
Kharian Cantonment  
Email: amer\_ejaz@yahoo.com

livedo reticularis, cutaneous vasculitis (leukocytoclastic), porphyria cutanea tarda, and mixed cryoglobulinemia. Associated are pruritus, urticaria, lichen planus, polyarteritis nodosa, and Sjogren's syndrome. Uncommonly associated are vitiligo, psoriasis, erythema nodosum, erythema multiforme, pyoderma gangrenosum, Behcet's syndrome, granuloma annulare, and porokeratosis.<sup>7</sup>

The silent epidemic of chronic HCV infection is spreading fast in our country.<sup>8</sup> Early diagnosis and identification of silent cases, as well as carriers, is imperative in control of this disease. Cutaneous manifestations in such patients can help in this regard. There is paucity of literature from our country delineating this feature of HCV infection. This study was therefore planned to observe and understand the frequency of skin diseases found in patients suffering from chronic HCV infection.

### **Patients and methods**

This study was conducted at the medical department of Combined Military Hospital, Kharian, from January 2008 to December 2008. The study was approved by the research and ethics committee of the hospital. Written informed consent was obtained from all the participating patients.

During the study period all adult patients of either sex who were known patients of chronic hepatitis C, confirmed by serological markers, ELISA, and/or positive PCR for more than six months were included in the study on the basis of non-probability convenience sampling. Patients who had a known history of diabetes mellitus, coexistent hepatitis B infection, chronic renal failure, or rheumatologic disease were excluded from the study.

Biochemical profile of each patient included complete blood count and platelet count. Thrombocytopenia was defined as platelet level below  $110.10^9/L$ . Anti nuclear antibodies, anti smooth muscle antibodies, antineutrophil cytoplasm antibodies, and anticardiolipin antibodies were detected by indirect immunofluorescence. Cryoglobulins were detected by the Winfield method.

Patients were interviewed by the investigator and data regarding demographic profile, duration of disease, and presence of associated medical illness were collected. Patients were examined by dermatologist to identify and diagnose the skin disease.

Data were recorded in a specially designed pro forma. All data were analyzed using statistical package SPSS 10.0. Descriptive statistics were used. Mean±standard deviation was calculated for age. Frequencies and percentages for variables were calculated.

### **Results**

One hundred patients were enrolled in the study. Out of 100, 72% were male and 28 % were female, male to female ratio was 2.6:1. Age range was 20 to 51 years (mean 30 years, standard deviation  $\pm 4.0$ ). Ninety seven percent patients were receiving antiviral treatment with interferon-alpha 2b and ribavirin while in 3% treatment was not yet started. Forty seven percent had at least one manifestation while 53% were free of skin disease at the time of examination.

Cryoglobulinemia was the most common manifestation, a total of 14% as shown in **Table 1**. Both lichen planus and chronic urticaria were both next most common manifestation in our

**Table 1** frequency of skin manifestations in HCV patients (n=100)

Clinical manifestation	N (%)
Cryoglobulinemia	14 (14.0)
Lichen planus	9 (9.0)
Chronic urticaria	9 (9.0)
Vitiligo	6 (6.0)
Xerostomia	4 (4.0)
Purpura	2 (2.0)
Sialadenitis	2 (2.0)
Vasculitis	1 (1.0)
None	53 (53.0)
Total	100 (100.0)

study i.e. 9%. The third most common was vitiligo, seen in 6% of the patients. Four patients had xerostomia (4%). Purpura and sialadenitis each were noted in 2% of the patients. Vasculitis was seen in 1% of patients.

### Discussion

Our study represented a small group of patients and cannot be applied to whole population. Nevertheless as very little research work has been carried out in the country on the subject, this study provides hypothesis for the future researcher.

Demographic profile of patients in our study reveals a preponderance of males which in our opinion is not true representation of chronic HCV infection in our population. For one, the sample size in our study is too small and it is hospital based study. Current data from Pakistan shows a somewhat equal male to female ratio.<sup>9,10</sup> However, we believe larger population based studies should be carried out in different regions of our country to assess the true demographic profile of this disease.

Studies carried out in different centers of the world show that up to 40% to 74% of the patients of chronic HCV infection may have one manifestation in the course of disease.<sup>11</sup> Our

study revealed that 47% of the our patients had at least one cutaneous manifestation which is in concordance with earlier literature. One of the studies reveals that HCV-RNA was detected in skin lesions not found in normal cell and that lymphotropism and antigen-antibody complexes may be implicated in the causation of these lesions.<sup>12</sup> Other studies done in Pakistan show data in concordance with our results.<sup>9,10</sup>

Cryoglobulins are found in many patients with chronic HCV infection and can present as leukocytoclastic type of cutaneous vasculitis. Studies reveal 19% to 50% occurrence of cryoglobulins in patients with chronic hepatitis C.<sup>13,14</sup> Our study shows cryoglobulinemia in 14% of patients but only one patient with overt cutaneous vasculitis was seen. One Pakistani study shows cutaneous vasculitis in 4.3% of patients but the researchers did not carry out cryoglobulins levels.<sup>9</sup> This lower percentage of cryoglobulins levels found in our study may be due to early course of disease, small population sample or may show a different disease behavior in our patients. Larger studies in this regard should clarify the matter.

The association of lichen planus with chronic HCV infection is at best questionable.<sup>15,16</sup> An age and gender matched controlled study has found no statistically significant difference in the development of lichen planus in their patients.<sup>16</sup> Some workers have isolated HCV RNA from lesional skin in patients with LP and chronic HCV infection and an HCV related product has been postulated as a possible antigen in LP.<sup>17</sup> However, patients from northern Europe (including the UK), USA and Nepal have shown no association between LP and HCV infection.<sup>18</sup> Our study shows a 6% chance of developing lichen planus in patients with chronic HCV infection. Our results are in concordance with earlier Pakistani studies.<sup>9,10</sup>

Pruritus and urticaria are well recognized associations of hepatitis C.<sup>19,20</sup> The prevalence of pruritus in HCV infected patients varies from one country to another, and the epidemiology of HCV differs substantially between countries, it is therefore difficult to compare the results.<sup>21</sup> Pruritus was associated with nonspecific excoriations, excoriated papules or xerosis, but no dermatoses usually provoking itch, were noted. Pruritus and urticaria are examples of less specific clues to underlying HCV infection in the appropriate setting (e.g. post-transfusion, organ transplantation, surgery, intravenous drug use, injury of the nasal mucosa from snorting cocaine through shared straws). Chronic urticaria and pruritus were second most frequent manifestation in our study (6%). Another Pakistani study found pruritus to be the commonest presentation (15.9%) while urticaria was found in 2.4% patients.<sup>9</sup> Larger studies need to be done on Pakistani population to truly validate the results.

Xerostomia was found in 4% of patients in our study. This is significantly lower than a French study finding that 57% of HCV-associated chronic liver disease patients exhibited a grade 3 or 4 sialadenitis. Further data show that up to 80% of HCV-infected individuals may have some salivary or lachrymal abnormality, frequently represented by histological signs of mild sialadenitis, whereas clinical evidence of dry mouth and dry eyes is often absent (but may be underevaluated).<sup>22</sup> The lower frequency in our study may be due to geographical factors, small study sample or using hyposalivation as the only marker of sicca syndrome.

Several aspects and limitations of this study should be considered. Firstly, our study represents a small portion of the diseased population, the frequencies and the clinical patterns thus noted may be verified on a large

scale before applying the data to a community, secondly our study does not take into account the duration of disease, stage of the disease and relation of dermatological manifestations to predict the course and prognosis of HCV infection. However, not much work has been done on the subject in Pakistan and larger, preferably community based studies should be done to better understand the problem.

## Conclusion

This study shows that dermatological conditions are very common in patients with chronic HCV infection and when confronted with a suspected skin lesion, the dermatologist should be aware of the silent epidemic.

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### Authors Declaration

Authors are requested to send a letter of undertaking signed by all authors along with the submitted manuscript that:

The material or similar material has not been and will not be submitted to or published in any other publication before its appearance in the *Journal of Pakistan Association of Dermatologists*.