

Original Article

Cutaneous manifestations in patients of hepatitis C

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Abstract *Background* Hepatitis C is a major public health problem, infecting 170 million people worldwide. It is associated with a number of extrahepatic manifestations, many of which are cutaneous.

Objective The purpose of the study was to determine the nature and frequency of dermatological manifestations in hepatitis C virus (HCV) positive patients.

Patients and methods 371 HCV positive patients from the outpatient and inpatient departments of Jinnah hospital, Lahore were enrolled and evaluated for cutaneous manifestations. All the relevant data regarding history, clinical examination and investigations were recorded and analyzed.

Results Among all 371 cases cutaneous manifestations were present among 54%. Pruritus was the most common dermatological feature seen in 15.90% followed by palmar erythema 11.59% and lichen planus 7.82%. Less common features were hyperpigmentation, cutaneous vasculitis, photosensitivity and urticaria. Pruritus, Schamberg's disease and photosensitivity were significantly more common in patients with antiviral therapy.

Key words

Hepatitis C, cutaneous, manifestation

Introduction

Hepatitis C is a serious public health problem all over the world. Since its discovery in 1989 it has infected 170 million people worldwide.¹ Its prevalence is less than 3% in most developed countries, while in Pakistan it is 4-7%.²

A number of extrahepatic manifestations have been associated with hepatitis C;

involving the muscles, bones, neural and gastrointestinal tissue as well as the skin. Frequently associated dermatological manifestations are mixed cryoglobulinemia,³ lichen planus and porphyria cutanea tarda.⁴ Other manifestations include generalized pruritus, acute and chronic urticaria, polyarteritis nodosa, acral necrolytic erythema, erythema multiforme, Sjogren's syndrome, pigmented purpuric dermatoses, nodular prurigo and Behcet's disease.⁴ Cutaneous manifestations in chronic liver disease (CLD) due to any other cause such as jaundice, palmar erythema, spider nevi and nail changes like leuconychia and

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Muehrcke's lines have also been observed in HCV infection.⁵ Dermatological manifestations have also been seen with antiviral therapy for HCV.⁶

The cutaneous features are not only themselves a cause of morbidity, but they can also provide an indirect clue for the underlying disease. Such an observation leads to early detection and initiation of therapy. Accurate and timely diagnosis of HCV is critical to prevent the life threatening complications. Antiviral therapy for HCV may be effective in curing the cutaneous disease for example, cryoglobulinemia.⁷ Moreover, such identification can help prevent further transmission of the disease.

Studies regarding dermatological manifestations associated with HCV have been conducted overseas, but in Pakistan, at present, no comprehensive studies have been published. The studies that have been conducted in Pakistan have focused mainly on the prevalence of HCV in certain specific dermatoses like lichen planus, chronic urticaria etc. To our knowledge, this is the first study of its kind assessing spectrum of cutaneous manifestations in patients of HCV in Pakistan.

Patients and methods

This descriptive study was conducted in the outpatient and inpatient departments of Jinnah hospital, Lahore. Hepatitis C patients of all ages and both sexes were examined. A total of 371 anti-HCV positive patients were enrolled. All patients with HCV, confirmed by serological markers, ELISA and/or PCR were included in the study. Patients with any degree of severity or duration of liver

disease and with or without clinical features of cirrhosis of liver were considered.

Anti-HCV positive patients who were also positive for hepatitis B antigen or had suspicion of liver disease due to any other viral etiology or any other cause were excluded from the study. Concurrent presence of hepatitis C developing in known cases of other chronic systemic diseases, such as diabetes mellitus, chronic renal disease, autoimmune/rheumatologic diseases, were also excluded.

Patients fulfilling the inclusion and exclusion criteria were subjected to detailed history, clinical examination and relevant investigations. The data were recorded in a comprehensive proforma and later analyzed. Frequencies of various cutaneous manifestations were determined. Frequencies of cutaneous features were also compared in patients on or with history of antiviral therapy with those without history of antiviral therapy. Chi square test was applied to assess significance at $p \leq 0.05$.

Results

Among all 371 cases, 195 (53%) were males and 176 (47%) were females, with male to female ratio of 1.1:1. The overall age ranged from 18-79 years. Maximum numbers of patients were in the age groups between 30-59 years. The mean age of the patients was 45.67 years (S.D±13.61)

Out of 371 patients in the study, cutaneous manifestations were present among 200 cases (54%). These cases presented with one or more skin feature. Forty patients (10.78%) had received or were on antiviral therapy, which was a combination of

Table 2 Main dermatological manifestations (n=371)

<i>Dermatological manifestations</i>	<i>N (%)</i>
Pruritus	59 (15.90)
Palmar erythema	43 (11.59)
Clubbing	32 (8.63)
Hyperpigmentation	23 (6.19)
Lichen planus	
Cutaneous	29 (7.82)
Oral	12 (3.23)
Leuconychia	28 (7.55)
Jaundice	22 (5.93)
Aphthous ulcers	17 (4.58)
Cutaneous vasculitis	16 (4.31)
Spider naevi	15 (4.04)
Purpura	13 (3.50)
Photosensitivity	11 (2.96)
Telangiectasia	10 (2.70)
Urticaria	9 (2.43)
Schamberg's disease	7 (1.89)
Psoriasis	3 (0.81)
Beau's lines	3 (0.81)
Porphyria cutanea tarda	2 (0.54)
Prurigo	2 (0.54)
Raynaud's phenomenon	2 (0.54)
Splinter haemorrhages	1 (0.27)

interferon and ribavirin. None of the patients were on interferon therapy alone or on ribavirin therapy only. All the patients were on supportive/symptomatic therapy.

The various dermatological features and their frequencies observed are shown in **Table 1**. Pruritus was the most common dermatological feature seen in 59 patients (15.9%). It was generalized with excoriations over limbs and trunk. This was followed by palmar erythema seen in 43 patients (11.59%). Lichen planus was present in 29 (7.82%) patients. The patients presented with cutaneous lesions of various sized pruritic papules and plaques mostly over the extremities. Out of these 29 patients, 13 patients had cutaneous lesions only and 4 patients had cutaneous as well as oral lesions. Oral lichen planus alone was present in 12 patients (2.34%). In some

cases there were whitish streaks over the oral mucosa, while in others painful erosive lesions were seen over the tongue. Hyperpigmentation was seen in 23 patients (6.19%). It was a generalized hyperpigmentation not associated with any specific skin lesions. Jaundice was present in 22 patients (5.93%). Aphthous ulcers were found in 17 patients. (4.58%) Cutaneous vasculitis was seen in 16 (4.31%) patients. The patients presented with erythema, palpable purpura, plaques, erosions and ulcers over the feet and lower legs.

Other cutaneous features observed were spider naevi, purpura, photosensitivity, telangiectasia, urticaria, Schamberg's disease, psoriasis, porphyria cutanea tarda, prurigo, Raynaud's phenomenon and various nail changes.

When cutaneous features between patients with or without antiviral therapy were compared, pruritus, Schamberg's disease and photosensitivity were more common in the patients on or who had taken antiviral therapy. The difference was statistically significant in photosensitivity while it was highly significant in pruritus and Schamberg's disease (**Table 2**).

Discussion

Hepatitis C is the most common cause of chronic viral liver disease. The first hepatitis C antibody test was made available in 1989, prior to that unexplained cases of chronic hepatitis were labeled as non-A and non-B hepatitis. Various studies have also been done on extrahepatic manifestations including cutaneous features. Most of the

Table 3 Comparison of dermatological features in patients with and without antiviral therapy (n=371)

Dermatological findings		With antiviral therapy n=40 (10.78%)	Without antiviral therapy n=331 (89%)	P value
Pruritus (n=59)	+	19 (32%)	40 (68%)	<0.001
	-	21	291	
Schamberg's disease (n=7)	+	5 (71%)	2 (29%)	<0.001*
	-	35	329	
Photosensitivity (n=11)	+	3 (27%)	8 (73%)	<0.05*
	-	37	323	

*Yates Corrected value

currently available studies have looked for HCV infection in patients of particular dermatoses. In the present study cutaneous manifestations were studied in 371 patients of hepatitis C infection.

The demographic data revealed an almost equal gender distribution. A study carried out by Umar *et al.*² in Pakistan showed a similar male to female ratio. Epidemiological studies have revealed that HCV infection is uncommon in age groups younger than 20 years and prevalent in persons older than 40 years.⁸ Our results show only 3 patients of less than 20 years with a frequency of 0.81%, hence an almost similar scenario but we found the infection also common in the age range of 30-59 years. This may indicate that in our region younger persons are becoming a victim to the disease.

The frequency of cutaneous manifestations in HCV patients was found to be 54%. In a previous prospective study conducted in France by Cacoub *et al.* have reported a frequency of 17%.⁹ The difference in this study could be due to our genetic, racial and environmental differences as well as different inclusion criteria.

Pruritus with non-specific excoriations was the most common finding with a frequency of 15.90% (**Table 1**). Several etiologies can

be considered. Pruritus could be a direct effect of HCV, it could be related to INF therapy, or cholestasis alone could be the cause.¹⁰

Palmar erythema was present in a significant number of cases in the present study but a comparative study is required to assess the association with HCV infection as compared to other causes of CLD.

The relationship between LP and HCV is debatable and several studies have been conducted. A retrospective study by Beaird *et al.*¹¹ reported 70% frequency of HCV in patients of LP. Another case-control study on 340 LP patients revealed 55% frequency.¹² Epidemiological studies by Tameez-ud-Deen *et al.*¹³ on patients of LP have reported an association of 32.7% while Mahboob *et al.*¹⁴ have reported a frequency of 23.5%. All these studies were conducted on patients of LP while in our study HCV positive patients were examined for features of LP. We found a frequency of 7.82%. This difference in frequency could be due to our detection of LP in HCV patients rather than HCV detection in LP patients.

A generalized hyperpigmentation was seen in 23 (6%) of cases. All other causes of hyperpigmentation were ruled out. Our finding could not be supported by any further references. Jaundice was found in 22

(5.93%) of our patients.

Cutaneous vasculitis has been associated with HCV infection. Karlsberg *et al.*¹⁵ did a systematic dermatological evaluation of 408 patients with hepatitis C and vasculitis was found in 10 (3%) patients. Our findings of 4% vasculitis are almost similar. In a comparative study on essential mixed cryoglobulinemia in HCV infected vs. non infected patients, 21% of HCV infected patients presented with cutaneous features of palpable purpura.¹⁶ Palpable purpura was a feature seen in all our cases of cutaneous vasculitis. Cryoglobulins are immunoglobulins that undergo reversible precipitation at low temperatures. They consist of IgG and IgM polyclonal rheumatoid factors. There is a strong association between type II and type III mixed cryoglobulinemia and HCV infection. The initial observation was by Pascual *et al.* in 1990 who found anti HCV antibodies in patients with type II cryoglobulinemia.¹⁷

Spider naevi and telangiectasias were seen in patients. These are examples of less specific findings in end stage liver disease with cirrhosis. Chronic urticaria is believed to be associated with HCV infection but some researchers do not agree. Cribier *et al.*¹⁸ performed a case-control study and concluded that the association was not significant. chronic urticaria was seen in 9 of our cases with a frequency of 3.84% (**Table 2**). Study in Pakistan on patients of chronic urticaria by Ahmed *et al.* showed a frequency of 13.16% cases positive for anti-HCV antibodies.¹⁹ Deranged liver function tests were seen in only 2 patients. Hence there maybe a significant association but further studies are necessary to establish or refute the link.

Porphyria cutanea tarda was seen in only 2 of our cases though it is frequently associated with HCV infection.²⁰ Nodular prurigo is associated with chronic HCV infection and responded to antiviral therapy has been seen.²¹ We found only 2 cases, they had compensated liver disease and were not on interferon (INF) therapy.

Antiviral therapy has been shown to result in cutaneous side effects.^{6,22,23} However, it is difficult to differentiate between cutaneous adverse reactions due to antiviral therapy and cutaneous manifestations of HCV itself. In the present study many cutaneous features were found in both groups but pruritus, Schamberg's disease and photosensitivity were more common in patients with antiviral therapy as compared to the patients without antiviral therapy (**Table 2**). Specifically designed further follow up studies are required in this regard.

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