

Cutaneous manifestations in chronic hepatitis C patients: A prospective study from Egypt

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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 extra-hepatic manifestations, many of which are cutaneous.

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

Patients and methods: Four hundred twenty three HCV positive patients from the outpatient and inpatient departments of Mansoura University Hospital, Mansoura University, Egypt were enrolled and evaluated for cutaneous manifestations. All the relevant data regarding history, clinical examination and investigations were recorded and analyzed.

Results: Among all 423 cases cutaneous manifestations were present among 252 (58.3%) patient. Pruritus was the most common dermatological feature seen in 18.44% followed by palmar erythema 12.53% and lichen planus 8.51%. Other cutaneous features were hyperpigmentation, cutaneous vasculitis, photosensitivity and urticaria. Pruritus, Schamberg's disease and photosensitivity were more common in patients with antiviral therapy.

Conclusion: HCV is associated with various dermatological disorders especially generalized persistent pruritus. Further epidemiological studies are essential to determine the real prevalence of various dermatoses in the course of HCV infection with or without antiviral therapy.

KEYWORDS: hepatitis C, cutaneous manifestations, Egypt

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 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,² lichen planus and porphyria cutanea tarda.³ Other manifestations include generalized pruritus, acute and chronic urticaria, polyarteritis nodosa, acral necrolytic erythema, erythema multiforme, Sjogren's syndrome, pigmented purpuric derma-

tos, nodular prurigo and Behcet's disease.³ 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 Muehrcke's lines have also been observed in HCV infection.⁴ Dermatological manifestations have also been seen with antiviral therapy for HCV.⁵ The cutaneous features are not only a cause of morbidity, but 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

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in curing the cutaneous disease for example, cryoglobulinemia.⁶ Also, early diagnosis can help prevent further transmission of the disease. The aim of this study is to assess the spectrum of cutaneous manifestations in patients of HCV in Egypt.

PATIENTS AND METHODS

This descriptive study was conducted in the outpatient clinics of Mansoura University Hospital, Mansoura University, Egypt. Anti-HCV positive patients of all ages and both sexes were examined. A total of 423 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 Performa and later analyzed. Frequencies of various cutaneous manifestations were determined. Descriptive statistics were calculated using SPSS program 10.0. 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 $p < 0.05$.

RESULTS

Among the 423 patients, 252 (58.3%) were males and 180 (41.7%) were females, with male to female ratio of 1.4:1. The overall age ranged from 16-75 years. Maximum number of patients were in the age groups between 30-59 years. The mean age of the patients was 41.37 years (± 12.58). Out of 423 patients in the study, cutaneous manifestations were present among 271 patients (64.07%). These cases presented with one or more skin disease. Sixty four patients (15.13%) had received, or were on antiviral therapy. The regimen used was a combination of 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

Table 1 Main dermatological manifestations (n=423)

Dermatological manifestations	N (%)
Pruritus	78 (18.44)
Palmar erythema	53 (12.53)
Lichen planus	36 (8.51)
Cutaneous lesions only	19 (4.49)
Cutaneous & oral lesions	8 (1.89)
Oral lesions only	9 (2.13)
Clubbing	29 (6.62)
Leuconychia	28 (6.55)
Jaundice	25 (5.91)
Aphthous ulcers	21 (4.96)
Cutaneous vasculitis	18 (4.26)
Spider naevi	17 (4.02)
Purpura	14 (3.31)
Photosensitivity	13 (3.07)
Telangiectasia	11 (2.60)
Urticaria	10 (2.36)
Pigmented purpuric dermatosis	8 (1.89)
Beau's lines	5 (1.18)
Porphyria cutanea tarda	4 (0.96)
Prurigo	3 (0.71)
Acral necrolytic erythema	3 (0.71)
Psoriasis	3 (0.71)
Splinter haemorrhages	1 (0.24)

most common dermatological feature seen in 78 patients (18.44%). It was generalized with exco-riations over limbs and trunk. This was followed by palmar erythema seen in 53 patients (12.53%). Lichen planus was present in 36 (8.51%) patients. The patients presented with cutaneous lesions of various sized pruritic papules and plaques mostly over the extremities. Out of these 36 patients, 19 patients (4.49%) had cutaneous lesions only, and 8 patients (1.89%) had cutaneous as well as oral lesions. Oral lichen planus alone was present in 9 patients (2.13%). 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 31 patients (7.33%). It was a generalized hyperpigmentation not associated with any specific skin lesions. Jaundice was present in 25 patients (5.91%). Aphthous ulcers were found in 21 patients (4.96%). Cutaneous vasculitis was seen in 18 (4.26%) 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, porphyria cutanea tarda, prurigo, Raynaud's phenomenon, Acral necrolytic erythema and various nail changes.

On comparing, the cutaneous features between the patients who had received the treatment with those who were not treated for HCV. It was noted that pruritus, schamberg's disease and photosensitivity were more common in the patients on or who had taken antiviral therapy. The difference was statistically significant only for pruritus while it was non significant (NS) in photosensitivity and schamberg's disease due to small number of patients (Table 2).

Table 2 Comparison of dermatological features in patients with and without antiviral therapy (n=423)

Dermatological findings	With therapy N=64 (15.13%)	Without therapy N=359 (84.87%)	P value
Pruritus	29/64 (45.3%)	49/359 (13.64%)	<0.001
Photosensitivity	4/64 (6.25%)	9/359 (2.5%)	NS
*P. P. D.	6/64 (9.37%)	2/359 (0.55%)	NS

*Pigmented purpuric dermatosis

NS: Not Significant

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 been done on extrahepatic manifestations including cutaneous features. Most of the currently available studies have looked for HCV infection in patients of particular dermatoses. In the present study cutaneous manifestations were studied in 423 patients of hepatitis C infection. The demographic data revealed an almost equal gender distribution. Epidemiological studies have revealed that HCV infection is uncommon in age groups younger than 20 years and prevalent in persons older than 40 years.⁷ Our results show only 4 patients of less than 20 years with a frequency of 0.95%, 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 64.07%. In a previous prospective study conducted in France by Cacoub et al⁸ the frequency reported was 17%. The difference in this study could be due to our genetic, racial and environmental differences as well as different inclusion criteria used in the two

studies. Pruritus with non-specific excoriations was the most common finding with a frequency of 18.44% (Table 1). Cacoub et al,⁸ who reported pruritus in 15% of cases of HCV had concluded that it is one of the most common extrahepatic manifestations of HCV infection. Chronic hepatitis C may be associated with pruritus to the extent that some authorities believe that patients with unexplained pruritus should be investigated for HCV infection.⁹

The relationship between LP and HCV is debatable and several studies have been conducted. A retrospective study by Beard et al¹⁰ reported 70% frequency of HCV in patients of LP. Epidemiological studies by Mahboob et al¹¹ on patients of LP have reported an association 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 8.51%. This difference in frequency could be due to our detection of LP in HCV patients, rather than HCV detection in LP patients. Hepatitis C virus infection seems to be more frequently seen in patients with generalized LP, and with mucosal LP, particularly the chronic erosive variant.¹² The mechanism of HCV induced lichen planus is unknown, but is possibly related to the viral replication in lymphocytes.¹²

Cutaneous vasculitis has been associated with HCV infection. Karlsberg et al¹³ did a systematic dermatological evaluation of 408 patients with hepatitis C and vasculitis was found in 10 (3%) of 408 HCV infected patients. In the present study, our findings are almost similar, as 4.26% of patients with chronic HCV infection had palpable purpura affecting the lower extremities that revealed leukocytoclastic vasculitis on skin biopsy. In a comparative study on essential mixed cryo-

globulinemia in HCV infected vs. non infected patients, 21% of HCV infected patients presented with cutaneous features of palpable purpura.¹⁴ Palpable purpura was a feature seen in all our cases of cutaneous vasculitis. According to Karlsberg et al,¹³ positive serologic tests for HCV antibody and RF in patients with palpable purpura confirm the diagnosis of HCV-induced mixed cryoglobulinemia. There is a strong association between type II and type III mixed cryoglobulinemia and HCV infection. The initial observation was by Pascual et al¹⁵ in 1990, who found anti HCV antibodies in patients with type II cryoglobulinemia. Chronic urticaria is believed to be associated with HCV infection but some researchers do not agree. Cribier et al¹⁶ performed a case-control study and concluded that the association was not significant. Chronic urticaria was seen in 10 of our cases with a frequency of 2.36%. Some epidemiological data suggest an association between HCV infection and PCT. Porphyria cutanea tarda was seen in only 4 of our cases though it is frequently associated with HCV infection. In a systematic review, mean prevalence of HCV infection calculated from 2167 patients from 50 studies was 47%.¹⁷ Cacoub et al reported that the highest rates of porphyria cutanea were in patients with HCV-related liver cirrhosis, suggesting that cirrhosis may play a role in its development.⁸

We found only 3 cases of nodular prurigo. They had compensated liver disease and were not on interferon (INF) therapy. Nodular prurigo is associated with chronic HCV infection and responded to antiviral therapy.¹⁸

Necrolytic acral erythema is a rare, but pathognomonic, manifestation of HCV. We reported 3 cases of Chronic acral necrolytic erythema. The lesions were hyperkeratotic plaques with erosions

and peripheral erythema preferring the acral parts of the legs. These lesions provide unusually specific markers for HCV infection. The symptomatology of acral necrolytic erythema includes pruritis 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.¹⁹ Psoriasis affected 0.71% of our patients. Both genetic and environmental influences have a critical role in psoriasis. The environmental risk factors include trauma, infection, medicines and immunological factors.²⁰ Spider naevi and telangiectasias were seen in patients. These are examples of less specific findings in end stage liver disease with cirrhosis.

Antiviral therapy has been shown to result in cutaneous side effects.^{2,21,22} 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, progressive pigmented purpuric dermatitis (Schamberg's disease) and photosensitivity were more common in patients with antiviral therapy as compared to the patients without antiviral therapy, but the difference was statistically significant only for pruritus. Dessoukey *et al*²³ reported from United Arab Emirates that among 10 patients with pigmented purpuric dermatosis, five patients with positive hepatitis C and two positive for hepatitis B antibodies. These patients were young (average age 42 years), and they did not have manifestations of stasis and venous insufficiency nor a history of medication intake to explain the pathogenesis of the disease.

CONCLUSION

HCV is associated with various dermatological

disorders. In our study patients, we found a strong association between HCV infection and pruritis, so patients presenting with persistent generalized pruritus who have no apparent primary cutaneous disorders should be tested routinely for HCV infection. Epidemiological studies are essential to determine the real prevalence of other dermatoses in the course of HCV infection with or without antiviral therapy.

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