

Frequency of Cutaneous Manifestations in Patients of Hepatitis C Virus Infection

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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.

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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.¹ 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.³ 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.² 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.^{1,4-6} The pathogenesis of skin disorders remains uncertain but it is assumed that the virus replicates within lymphoid cells, potentially resulting in the extrahepatic manifestations.⁵ Another theory suggests that circulating immune complexes composed of HCV antigens and antibodies deposit in the tissues and cause initiation of an inflammatory cascade.^{1,5} 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.^{1,5}

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).

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

CLD = Chronic liver disease

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

Cutaneous Manifestations		Sex	
		Male	Female
Lichen planus	49	29	20
Pruritus	61	23	38
Vitiligo	10	8	2
Urticaria	14	7	7
Mixed cryoglobulinaemia	08	6	2
Necrolytic acral erythema	02	2	0
Erythema multiforme	04	2	2
Prophyria cutanea tarda	02	2	0
Erythema nodosum	05	1	4
Signs of CLD	25	15	10

CLD = Chronic liver disease

on flexor and extensor aspects of extremities and trunk. Oral lesions included both the whitish streaks and erosive lesions on buccal mucosa as well as gums. Other cutaneous findings noted were urticaria in 14 (7.8%) patients followed by mixed cryoglobulinaemia in 8 (4.4%), vitiligo in 10 (5.6%), erythema nodosum in 5 (2.8%), erythema multiforme in 4 (2.2%), porphy-

ria cutanea tarda in 2 (1.1%) and necrolytic acral erythema in 2 (1.1%) cases. The patients of mixed cryoglobulinaemia presented signs of leukocytoclastic vasculitis (LCV), Raynaud’s phenomenon and livedo reticularis. The signs of chronic liver disease included palmar erythema, spider naevi, jaundice, telangiectasia and leukonychia in 25 (13.9%) patients. Blackish – brown hyperpigmentation was seen in a few cases including those of PCT or as a feature of chronic liver disease, mostly on the face and limbs.

The comparison of different cutaneous disorders in both male and female patients in our study is shown in (Table 2) but it was found to be statistically insignificant ($p > 0.05$). Three of our patients with erythema multiforme had given the history of this eruption after starting antiviral treatment while patients with mixed cryoglobulinemia and necrolytic acral erythema showed some kind of improvement in cutaneous eruptions after getting this therapy.

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 studies^{9,10} 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.^{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.¹ This is probably due to the genetic differences and geographic variations in HCV prevalence worldwide.^{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.^{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.^{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.^{1,7} Mixed cryoglobulinemia (MC) was recorded in 8 (4.4%) cases which is less in contrast to other studies.^{1,3,10,20} The cause of MC is supposed to be the chronic stimulation of the immune system by HCV.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^{9,21} while few other studies noticed vasculitis in a higher percentage (10%) of HCV patients.^{1,10} The antigen – antibody complexes of viral particles and anti-HCV antibodies initiate the process of vasculitis.^{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.^{5,6}

Vitiligo, erythema nodosum and erythema multiforme were also found in our study similar to most of the previous reports.^{3,6} Hepatitis C may induce autoimmune disorders through persistent antigenic stimulation.^{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.^{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 *et al.*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.^{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.³ HCV infection increases oxidative stress within hepatocytes and does so to a greater extent than for other chronic viral infections.⁶ The formation of autoantibodies that inhibit uroporphyrinogen decarboxylase, may contribute to its causation.⁶

Palmar erythema, jaundice, leukonychia, spider naevi and telangiectasia were seen in a comparable manner to the study by Azfar *et al.*⁹ These are the signs of decompensated cirrhosis depending on the severity of chronic liver disease in different studies.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.^{1,3,6,9}

Antiviral therapy has many cutaneous adverse effects.^{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.^{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.^{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

1. Muzaffar F, Hussain I, Haroon TS. Hepatitis C: the dermatologic profile. *J Pak Assoc Dermatol* 2008; **18**: 171-81.

2. Chung CM, Nunley JR. Overview of hepatitis C and skin. *Dermatol Nurs* 2006; **18** (5): 425-30.
3. Schwartz RA, Birnkrant AP. Cutaneous manifestations of hepatitis C. [Internet] *Online CME from Medscape* Jun 2010. Available from: <http://emedicine.medscape.com/article/1134161-overview>
4. Kochhar AM, Reddy BSN. Cutaneous manifestations of hepatitis B and C virus infections. *Int J Dermatol* 2003; **48** (2): 73-6.
5. Dervis E, Serez K. The prevalence of dermatologic manifestations related to chronic hepatitis C virus infection in a study from a single center in Turkey. *Acta Dermatoven APA* 2005; **14**: 93-8.
6. Aman S, Haroon TS. Skin and Hepatitis C. *J Coll Physicians Surg Pak* 2001; **11** (10): 601-2.
7. Umar M, Bushra HT, Shuaib A, Anwar A, Shah NH. Spectrum of chronic liver disease due to hepatitis "C" virus infection. *J Coll Physicians Surg Pak* 2000; **10** (10): 380-3.
8. Bonkovsky HL, Mehta S. Hepatitis C: A review and update. *J Am Acad Dermatol* 2001; **44**: 159-79.
9. Azfar NA, Zaman T, Rashid T, Jahangir M. Cutaneous manifestations in patients of hepatitis C. *J Pak Assoc Dermatol* 2008; **18**: 138-43.
10. Ejaz A, Ahmad R, Fazal I, Tahir M. Frequency of various cutaneous disorders in chronic hepatitis C virus infection. *J Pak Assoc Dermatol* 2010; **20**: 10-4.
11. Idrees M, Lal A, Naseem M, Khalid M. High prevalence of hepatitis C virus infection in the largest province of Pakistan. *J Dig Dis* 2008; **9**: 95-103.
12. Aamir S, Ullah Z, Iqbal Z, Khan AA, Yaqub F, Malik K. Cutaneous manifestations of interferon alfa and ribavirin for hepatitis C. *J Pak Assoc Dermatol* 2008; **18**: 14-20.
13. Fortune BE, Francis S, Forman LM. Hepatitis C virus therapy – related skin manifestations. *Gastroenterol Hepatol* 2010; **6** (5): 326-8.
14. Beaird LM, Kabloon N, Franco J, Fairley JA. Screening of HCV in lichen planus patients. *J Am Acad Dermatol* 2001; **44**: 311-2.
15. Erkek E, Bozdogan O, Olut AI. Hepatitis C virus infection prevalence in lichen planus, examination of regional and normal skin of hepatitis C virus infected patients with lichen planus for the presence of hepatitis C virus RNA. *Clin Exp Dermatol* 2001; **26** (6): 540-4.
16. Lodi G, Giulian M, Majorana A, Sardella A, Bez C, Demarosi F, et al. Lichen planus and hepatitis C virus: a multicentre study of patients with oral lesions and a systemic review. *Br J Dermatol* 2004; **151**: 1172-81.
17. Al Robae AA, Al Zolibani AA. Oral lichen planus and hepatitis C virus. *Acta Dermatoven APA* 2006; **15**: 14-19.
18. Ahmed I, Wahid Z, Ahmed Z. Chronic urticaria: frequency of anti-HCV antibodies. *J Pak Assoc Dermatol* 2003; **13**: 178-83.
19. Malik LM, Mufti S, Saeed S, Ahmed S, Hussain I. Hepatitis C seropositivity in patients with acute and chronic urticaria. *J Pak Assoc Dermatol* 2008; **18**: 144-8.
20. Agnello V, de Rosa FG. Extrahepatic disease manifestations of HCV infection: some current issues. *J Hepatol* 2004; **40**: 341-52.
21. Karlisberg PL, Lee WM, Casey DL, Cockerell CJ, Cruz PD. Cutaneous vasculitis and rheumatoid factor positivity as presenting signs of hepatitis C virus induced mixed cryoglobulinemia. *Arch Dermatol* 1995; **131**: 1119-23.
22. Abdallah MA, Ghozzi MY, Monib HA, Hafez AM, Hiatt KM, Smoller BR, et al. Necrolytic acral erythema: a cutaneous sign of hepatitis C virus infection. *J Am Acad Dermatol* 2005; **53** (2): 247-51.
23. El-Ghandour TM, Sakr MA, El-Sebai H, El-Gammal TF, El-Sayed MH. Necrolytic acral erythema in Egyptian patients with hepatitis C virus infection. *J Gastroenterol Hepatol* 2006; **21** (7): 1200-6.
24. Gisbert JP, Garcia-Buey L, Pajares JM, Moreno-Otero R. Prevalence of hepatitis C virus infection in porphyria cutanea tarda: systemic review and meta – analysis. *J Hepatol* 2003; **39** (4): 620-7.