# The prevalence of dermatologic manifestations related to chronic hepatitis C virus infection in a study from a single center in Turkey

E. Dervis and K. Serez

ABSTRACT

**Background:** Chronic hepatitis C virus (HCV) infection may be associated with many dermatologic manifestations. The aim of this study was to determine the prevalence of dermatologic manifestations related to chronic HCV infection in Turkey.

**Materials and methods:** 70 patients with chronic HCV infection and 70 healthy volunteers were investigated. They were carefully questioned and skin, mucosa, hair and nails were systematically examined. Laboratory tests for the serum levels of aspartate aminotransferase, alanine aminotransferase, γ glutamyl transpeptidase, bilirubine and rheumatoid factor were done in all of them.

**Results:** The only symptom which was more frequent in patients with chronic HCV infection was generalized pruritus (13 cases, 18.57%). It was observed in three cases of the control group (4.28%), the difference being statistically significant (p:0.01). In the group of patients with chronic HCV infection, three patients were diagnosed as leukocytoclastic vasculitis and three as lichen planus (4.28%). Neither leukocytoclastic vasculitis nor lichen planus was observed in the control group.

**Conclusion:** In our patients, an association between HCV infection and pruritus was found. The patients with unexplained pruritus should be investigated for HCV infection. Leukocytoclastic vasculitis and lichen planus were not observed frequently enough to reach statistical significance (p:0.24).

KEY WORDS

**HCV infection, skin manifestations, pruritus, lichen planus, leukocytoclastic vasculitis**

## Introduction

The hepatitis C virus (HCV) is a single-stranded RNA flavivirus that replicates in hepatocytes and peripheral blood mononuclear cells. Transmission of HCV is primarily by blood or blood products (1). The people at high risk for HCV infection are intravenous drug users, organ transplant and hemodialysis patients, people who snort cocaine with shared straws, and health care workers who are at risk for needle-stick and other exposures (2). The hepatic damage from HCV occurs by viral replication within liver hepatocytes. Many extrahepatic diseases and manifestations have been associated with HCV infection. In most cases, the details of pathogen-

esis of these disorders remain uncertain. The virus replicates also within lymphoid cells potentially resulting in the extrahepatic manifestations. Another theory suggests that circulating immune complexes composed of HCV antigens and antibodies deposit in 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 autoantibodies reacting with tissue antigens (1). Chronic HCV infection may be associated with various dermatologic manifestations such as porphyria cutanea tarda (PCT), leukocytoclastic vasculitis, lichen planus (LP), polyarteritis nodosa, pruritus, prurigo nodularis, urticaria and others (1-4). The commonly reported dermatological manifestations in chronic HCV infection are mixed cryoglobulinemia with leukocytoclastic vasculitis and PCT. However, the prevalence of skin manifestations varies from one geographic area to another (2).

The aim of this study was to determine the prevalence of dermatologic manifestations related to chronic HCV infection in our area.

## Materials and methods

Seventy patients with chronic HCV infection (45 females, 25 males) followed up at the Hepatology Outpatient Clinic of Haseki Hospital (Istanbul) were recruited into the study. Chronic HCV infection was diagnosed by the presence of anti-HCV antibodies and HCV-RNA in all the patients' sera. The sera were tested for HCV antibodies by the enzyme-linked immunosorbent assay (ELISA, Innotest, HCV-AbIV, Innogenetics, Belgium). In each anti-HCV positive case, reverse transcriptase-polymerase chain reaction (RT-PCR) was performed to detect HCV-RNA (Cobas Amplicor HCV 2.0, Roche Diagnostic Systems, Bunchburg, NJ, USA). Laboratory tests for the serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ glutamyl transpeptidase (γ-GT), bilirubine and rheumatoid factor (RF) were done in all the patients. Cryoglobulins and the levels of complement were analyzed in patients who had positive serologic tests for RF. Thirty-seven patients (52.85%) with chronic liver disease underwent a liver biopsy. Each liver biopsy was graded for necrotic and inflammatory activity and the stage of fibrosis (scores 0-4), as previously described by Scheuer (5). They were questioned for alcohol or drug abuse, a previous blood transfusion, surgery and hepatitis. Demographic data concerning the patients included in the study were noted and a careful examination of skin, oral mucosa, hair and nails was performed.

Patients with co-existent liver diseases (co-infection with hepatitis B virus, alcoholic liver diseases, drug-induced liver diseases, autoimmune liver diseases), human immunodeficiency virus infection) and those who were receiving treatment with antivirals and/or immunomodulatory agents were excluded.

The control group was recruited from the check-up center of the Haseki Hospital: 70 healthy volunteers compatible by age and sex who were serologically anti-HCV, HBV surface antigen and anti-HIV negative, were investigated for serum levels of ALT, AST, γ-GT, bilirubine and RF.

The informed consent was obtained from all of the patients and healthy controls. Comparisons between the groups were performed with the $X^2$ or Fisher's exact test. The level of significance was $p< 0.05$.

## Results

The mean age of patients was 54.14 ± 12.13 years (range 23-76). 17 had a history of previous surgery, 11 had received blood transfusions, four patients had dental procedures, two underwent hemodialysis for chronic renal failure, and one patient had a history of intravenous drug abuse. In 35 of 70 cases, the route of transmission was not ascertained. 70 healthy volunteers (40 females, 30 males) without any hepatic diseases were assigned to the control group, their mean age was 51.66 ± 12.14 years (range:24-75). The serum levels of ALT and AST were normal in 15 of the 70 chronic HCV infected patients (21,42%). Fifty-five patients (78.57%) showed mild to severe elevations of the serum transaminases. In all the healthy controls, the serum levels of hepatic transaminases were normal. The difference between two groups was statistically significant ($p<0.001$). RF was positive (>20 IU/ml) in four of 70 patients (5.71%) and in none of the control group. In one serum from the RF positive patients, cryoglobulinemia and altered complement levels were detected. Liver biopsies were performed in 37 of the 70 chronically HCV infected patients: in 11 the stage 1 fibrosis, in 10 the stage 2 fibrosis, in 10 the stage 3 fibrosis, and in 6 cases the stage 4 fibrosis was noted.

The main dermatological manifestations observed in both groups are detailed in Table 1. The only symptom which was significantly increased in patients with chronic HCV infection was generalized pruritus in 13 cases (18.57%), while it was observed in only three controls (4.28%), making the difference between the two groups statistically significant ($p<0.01$). Among the 13 patients with pruritus, six had dry skin, and two excoriated papules, the skin in the remaining five was normal. (Table 2). In one of 13 patients with pruritus, a moderate cholestasis was present. Among the three controls with pruritus one had dry skin, while in two the skin was appearing normal.

In three cases of the chronic HCV infection group (4.28%) palpable purpura was observed on their lower extremities. Histopathology revealed a cutaneous leukocytoclastic vasculitis. In one of these, RF was posi-

**Table 1. Dermatological manifestations in patients with chronic HCV infection and in healthy volunteers.**

| Dermatological manifestations | Number of HCV negative patients | Number of HCV positive patients | Statistical differences ($X^2$ or Fisher) |
|---|---|---|---|
| Pruritus | 3 | 13 | p:0.01 |
| Leukocytoclastic vasculitis | - | 3 | p:0.24 |
| Lichen planus | - | 3 | p:0.24 |
| Livedo reticularis | - | 1 | p:1.0 |
| Vitiligo | - | 1 | p:1.0 |
| Cherry angioma | - | 1 | p:1.0 |
| Psoriasis vulgaris | 1 | - | p:1.0 |
| Folliculitis | 1 | - | p:1.0 |
| Chronic urticaria | 1 | 1 | |
| Recurrent aphthous stomatitis | 1 | 1 | |
| Tinea pedis | 3 | 3 | |

tive, the complement levels were low and cryoglobulinemia was detected (Table 3). No palpable purpura was noted in the control group. One of the 70 patients (1.42%) displayed livedo reticularis on her lower extremities.

Cutaneous and mucosal manifestations indicative of LP confirmed by histopathological examination were noted in three patients (4.28%). The LP lasted at least one year, two of them had a mucocutaneous manifestation, while one had a non-erosive LP of oral mucosa. No LP was observed in the control group.

The prevalence of psoriasis vulgaris, cherry angiomas, vitiligo, livedo reticularis without vasculitis, folliculitis was similar in the two groups (Table 1). Chronic urticaria, tinea pedis, recurrent aphthous stomatitis and further conditions were equally distributed in the two groups (Table 1).

Thirty-seven patients with chronic HCV infection underwent a liver biopsy. In 16 of these (43.24%) various skin manifestations were observed, while 21 had no skin symptoms (56.75%). Skin manifestations (especially pruritus) were found more often in patients with severe fibrosis and cirrhosis (stages 3 and 4). A mild fibrosis (stage 1) was found more frequently in patients without skin manifestations compared to patients with skin symptoms (p:0.023).

## *Discussion*

The association of HCV infection with various cutaneous diseases has been already discussed (6-13). The prevalence of cutaneous diseases among HCV-positive patients was however rarely reported (14-17). The purpose of this study was to evaluate the frequency of skin changes among HCV-RNA positive patients.

In several studies, a possible link between pruritus and HCV infection was mentioned (6,16,18). 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. For example, the HCV rate in patients with pruritus was 0.7% in a study from France (6) while in another French study, pruritus was found in 15% of HCV positive patients (16). The HCV rate in patients with prurigo in a study from Japan was

**Table 2. Liver examinations in patients with generalized pruritus.**

| Age | Sex* | ALT** (U/L) | AST** (U/L) | Skin | Liver biopsy Stage of fibrosis |
|---|---|---|---|---|---|
| 55 | F | 270 | 250 | xerosis | 4 |
| 75 | M | 67 | 78 | xerosis | not done |
| 48 | F | 29 | 29 | xerosis | not done |
| 72 | M | 61 | 56 | normal | 3 |
| 63 | M | 166 | 124 | xerosis | 4 |
| 47 | F | 90 | 82 | normal | 3 |
| 58 | F | 151 | 98 | xerosis | 2 |
| 57 | F | 108 | 72 | normal | 4 |
| 76 | M | 26 | 34 | excoriated papules | 4 |
| 55 | F | 91 | 97 | excoriated papules | 2 |
| 72 | M | 80 | 95 | xerosis | 1 |
| 55 | F | 39 | 52 | normal | 4 |
| 60 | M | 65 | 68 | normal | 3 |

** F-female; M-male*
*** normal 5-40 U/L*

**Table 3. Patients with palpable purpura.**

| Age | Sex | ALT (U/L) | AST (U/L) | Additional findings | Liver biopsy |
|---|---|---|---|---|---|
| 45 | F | 134 | 121 | RF:↑80 IU/ml (positive>20IU/ml)<br>C3:↓80.10mg/dl (N:101-186mg/dl)<br>C4:↓5.11mg/dl (N:16-47mg/dl)<br>Cryoglobulins: positive | grade 2 fibrosis |
| 59 | M | 76 | 86 | RF: negative | grade 2 fibrosis |
| 70 | F | 16 | 47 | RF: negative | not done |

**Table 4. Patients with lichen planus.**

| Age | Sex | ALT (U/L) | AST (U/L) | localization of the lesions | Liver biopsy |
|---|---|---|---|---|---|
| 65 | F | 38 | 35 | buccal mucosa and palms and soles | grade 2 fibrosis |
| 71 | F | 90 | 82 | buccal mucosa and body | not done |
| 60 | F | 80 | 60 | buccal mucosa | grade 3 fibrosis |

39%, where the prevalence of HCV infection in the general population is high (7). Compared to healthy controls, in our study chronic generalized pruritus was found more frequently (18.57%), the difference being statistically significant ($p<0.01$). Pruritus was associated with nonspecific excoriations, excoriated papules or xerosis, but no dermatoses usually provoking itch, were noted. However, only one of the 13 patients with pruritus had cholestasis. Since most of the patients had normal γ-GT and bilirubine levels, pruritus can not be explained by cholestasis. In five of 13 patients with pruritus (38.46%) stage 4 fibrosis was observed (probable or definite cirrhosis). Such finding suggests an increased incidence of cirrhosis in patients with pruritus.

Several authors reported an association between leukocytoclastic vasculitis and HCV infection, the deposition immune complex in the vessels being a possible cause (1) Cutaneous vasculitis was identified in 10 of 408 HCV infected patients in one study (14) and in 12 of 611 in another study (15). In a study from our country, anti HCV antibodies were detected in 2 of 25 patients with leukocytoclastic vasculitis (19). In the present study, three of 70 patients with chronic HCV infection (4.28%) had palpable purpura affecting the lower extremities that revealed leukocytoclastic vasculitis on biopsy, while there was no vasculitis case among the controls. According to Karlsberg et al (14), positive serologic tests for HCV antibody and RF in patients with palpable purpura confirm the diagnosis of HCV-induced mixed cryoglobulinemia. In one serum of our patients with vasculitis, RF was positive and cryoglobulinemia was detected, but the type of cryoglobulinemia was not determined.

Several cases of concomitant LP and HCV infection have been reported (11-13). Hepatitis C virus infection seems to be found more frequently in patients with generalized LP, and with mucosal LP, particularly the chronic erosive variant (1). The mechanism of HCV-induced lichen planus is unknown, but is possibly related to the viral replication in lymphocytes (1). Results of epidemiological studies are still controversial. The incidence of HCV infected patients with LP varies from one country to country, from 0% in England to 62% in Japan (20,21). In our country studies revealed a prevalence of HCV infection among patients with LP, ranging from 5 to 12.9 % (17,22-24). The prevalence of LP in the studied patients was higher than that in the control group but the difference was not statistically significant.

Some epidemiological data suggest an association between HCV infection and PCT. In a systematic review, mean prevalence of HCV infection calculated from 2167 patients from 50 studies was 47% (25). We did not observe a case of PCT among our patients. The differences in the observed association between skin manifestations and HCV infection may be due to different genetic and environmental factors and probably also to different laboratory techniques. Viruses may play a potential pathogenic role as triggers for various skin manifestation, especially in genetically susceptible persons.

## *Conclusion*

In our Turkish patients, we found a strong association between HCV infection and pruritus. Patients presenting with persistent generalized pruritus who have

no apparent primary cutaneous disorders should be tested routinely for HCV infection. These findings emphasize that multicenter studies including large number of patients and healthy controls from different ethnic and genetic backgrounds are needed, provided that a standardized approach in selecting patients and standardized laboratory techniques are used.

## REFERENCES


1. Jackson JM. Hepatitis C and the skin. Dermatol Clin 2002; 20: 449-58.

2. Bonkovsky HL, Mehta S. Hepatitis C: A review and update. J Am Acad Dermatol 2001; 44: 159-79.

3. Doutre MS. Hepatitis C virus-related skin diseases. Arch Dermatol 1999;135:1401-3.

4. Matitic M. Hepatitis C virus infection: the dermatological perspective. Acta Dermatoven APA 2003;12: 19-27.

5. Scheuer PJ. Classification of chronic viral hepatitis: a need for reassessment. J Hepatol 1991; 13: 372-4.

6. Cribier B, Santinelli F, Schmitt C, Stoll-Keller F, Grosshans E. Should patients with pruritus be tested for hepatitis C virus infection? A case-controlled study. Br J Dermatol 2000; 142: 1234-64.

7. Kanazawa K, Yaoita H, Tsuda F, Murata K, Okamoto H. Association of prurigo with hepatitis C virus infection. Arch Dermatol 1995; 131: 852-3.

8. Kanazawa K, Yaoita H, Tsuda F, Okamoto H. Hepatitis C virus infection in patients with urticaria. J Am Acad Dermatol 1996; 35: 195-8.

9. Cribier BJ, Santinelli F, Schmitt C, Stoll-Keller F, Grosshans E. Chronic urticaria is not significantly associated with Hepatitis C or Hepatitis G infection. Arch Dermatol 1999; 135: 1335-9.

10. Soufir N, Descamps V, Crickx B, Thibault V, Cosnes A, Becherel PA, et al. Hepatitis C virus infection in cutaneous polyarteritis nodosa: a retrospective study of 16 cases. Arch Dermatol 1999; 135: 1001-2.

11. Cribier B, Garnier C, Laustriat D, Heid E. Lichen planus and hepatitis C virus infection: An epidemiologic study. J Am Acad Dermatol 1994; 31: 1070-2.

12. Sanchez-Perez J, De Castro M, Buezo GF. Fernandez Herrera J, Borque MJ, Garcia-Diez A. Lichen planus and hepatitis C virus: Prevalence and clinical presentation of patients with lichen planus and hepatitis C virus infection. Br J Dermatol 1996; 134: 715-9.

13. Dupin N, Chosidow O, Lunel F, Fretz C, Szpirglas H, Frances C. Oral lichen planus and hepatitis C virus infection: A fortuitous association? Arch Dermatol 1997; 133: 1052-3.

14. Karlsberg 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.

15. Daoud MS, el-Azhary RA, Gibson LE, Lutz ME, Daoud S. Chronic hepatitis C, cryoglobulinemia, and cutaneous necrotizing vasculitis. J Am Acad Dermatol 1996; 34: 219-23.

16. Cribier B, Samain F, Vetter D, Heid E, Grosshans E. Systematic cutenous examination in hepatitis C virus infected patients. Acta Derm Venereol (Stockh) 1998: 78: 355-7.

17. Engin B, Oguz O, Mert A, Ozaras R, Tabak F, Sentürk H. Prevalence of oral lichen planus in a group of hepatitis C patients. J Dermatol 2002; 29: 459-60.

18. Fisher DA, Wright TL. Pruritus as a symptom of hepatitis C. J Am Acad Dermatol 1994; 30: 629-32.

19. Gungor E, Cirit A, Alli N, Karakayali G, Gur G, Artuz F. Prevalence of hepatitis C virus antibodies and cryoglobulinemia in patients with leukocytoclastic vasculitis. Dermatology 1999; 198: 26-8.

20. Ingafou M, Porter SR, Scully C, Teo CG. No evidence of HCV infection or liver disease in British patients with oral lichen planus. Int J Oral Maxillofac Surg 1998; 27: 65-6.

21. Nagao Y, Sata M, Tanikawa K, Itoh K, Kameyama T. Lichen planus and hepatitis C virus in the Northern Kyushu region of Japan. Eur J Clin Invest 1995; 25: 910-4.

22. Erkek E, Bozdogan O, Olutt AI. Hepatitis C virus infection prevalence in lichen planus: examination of lesional 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: 540-4.

23. Kirtak N, Inaloz HS, Ozgoztasi O, Erbagci Z. The prevalence of hepatitis C virus infection in patients with lichen planus in Gaziantep region of Turkey. Eur J Epidemiol 2000; 16: 1159-61.

24. Denli YG, Durdu M, Karakas M. Diabetes and hepatitis frequency in 140 lichen planus cases in Çukurova region. J Dermatol 2004; 31(4): 293-8.

25. Gisbert JP, Garcia-Buey L, Pajares JM, Moreno-Otero R. Prevalence of hepatitis C virus infection in porphyria cutanea tarda: systematic review and meta-analysis. J Hepatol 2003; 39: 620-7.

**AUTHORS' ADDRESSES**

*Emine Dervis MD, Department of Dermatology, Haseki State Hospital, Sarigöl Laleli Cad. No:3/3, Gaziosmanpasa, Istanbul, Turkey*
*Corresponding author. E-mail: eminedervis @hotmail.com*
*Kemal Serez MD, Department of Internal Medicine, same address*