

CLINICAL REPORT

Cutaneous Manifestations in Patients Positive for Anti-Hepatitis C Virus Antibodies

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Cutaneous diseases can indicate the presence of hepatitis C virus (HCV) infection. The aim of this study was to analyse the frequency of cutaneous findings in HCV infection and HCV RNA positive cases in Turkey. Fifty consecutive patients positive for anti-HCV antibodies, negative controls, and patients positive and negative for HCV RNA were examined for any cutaneous findings that could be associated with HCV infection. The risk of infected patients developing cutaneous finding was higher than for non-infected individuals. Only pruritus showed a statistically significant difference in separate assessment of cutaneous symptoms. There were no differences in cutaneous findings in HCV RNA positive and negative cases. The risk of developing a dermatological finding, especially pruritus, was increased in HCV infection. However, because the number of patients in this study was too low to allow statistical evaluation of the prevalence of dermatological symptoms and diseases, multi-centre studies including large numbers of patients are needed. Key words: hepatitis C virus; hepatitis C virus ribonucleic acid; skin.

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Hepatitis C virus (HCV), which is the major causative microorganism of non-A, non-B hepatitis, and is known to have infected about 3% of the world population and 1% of Turkish people, causes some extrahepatic disorders in addition to liver diseases. A significant proportion of these disorders involve the skin (1–4).

The aim of this study was to investigate the frequency of skin diseases or symptoms in cases positive for anti-HCV antibodies, and determine whether such skin findings have any significance in groups that are positive or negative for HCV RNA.

MATERIALS AND METHODS

The study was performed on 50 consecutive patients positive for anti-HCV antibodies, who were followed up by gastro-

enterology and clinical infection departments of Ministry of Health, Ankara Oncology Hospital between September 2002 and September 2003. Patients found to be infected with hepatitis B virus (HBV) and/or human immunodeficiency virus (HIV), and whose skin findings could be attributed to HCV therapy, were excluded from the study. The control group comprised 50 otherwise healthy individuals with negative anti-HCV antibody results matched for age and gender.

For each patient, gender, age, accompanying illnesses, the time of detection of anti-HCV antibodies, possible means of transmission of HCV, and the onset of skin manifestations were recorded. Physical and dermatological examinations were performed.

Laboratory investigations comprised whole blood count, red blood cell sedimentation rate, fasting blood sugar level, liver and kidney function tests, thyroid function tests, anti-thyroglobulin and anti-mitochondrial antibodies, hepatitis markers, anti-HIV antibodies, venereal disease research laboratory (VDRL), rheumatoid factor, anti-nuclear antibodies (ANA), anti-double-stranded DNA (anti-dsDNA) and cryoglobulin tests. Skin biopsies and pathological examinations were performed when required.

HCV RNA tests were also performed on the sera of anti-HCV antibody positive patients and the skin findings for HCV RNA positive and negative cases were compared.

Statistical evaluation was performed using *t*-test, chi-square test and Fisher's exact test, between both anti-HCV antibody positive and control groups and between positive and negative HCV RNA cases among those infected with HCV. In addition, odd's ratios within 95% safety margin were determined in order to find the level of risk associated with diseases investigated in the study group compared with the control group. The lowest limit of significance was taken as 0.05 in the evaluations.

RESULTS

The study involved a patient group of 50 individuals (age range 23–71 years, mean 51 years) with positive anti-HCV antibody results and a control group of 50 individuals (age range 28–82 years, mean 48 years) with negative anti-HCV antibody results. Both groups comprised 21 men (42%) and 29 women (58%). No statistically significant difference was observed between these 2 groups when comparing for age and gender.

When the possible means of transmission were investigated in the cases positive for anti-HCV antibodies, it was found that 35 patients had a history of dental treatment, 26 had undergone surgical operations, 19 were hospitalized, 13 had received blood transfusions, 4 had had unprotected sexual intercourse, 3 had had invasive treatments, 2 had family members infected with HCV, 2 were using intravenous drugs, 1 was undergoing haemodialysis, and 1 had a history of contaminated

needle pricking. In some cases there was more than one possible cause. Three patients gave no information about the possible route of transmission. The reasons for investigating anti-HCV antibodies were: routine tests in 25 cases (50%), who presented with complaints such as abdominal pain, fatigue and jaundice in 9 (18%), postoperative studies in 7 (14%), investigations of dermatological diseases in 6 (12%), for blood donation in 2 (4%) and having a HCV-infected family member in 1 (2%). The time that patients had been positive for anti-HCV antibodies ranged from being newly diagnosed to 18 years.

The patient group with anti-HCV antibody positive test results and the control group were compared for presence of general dermatological findings. Forty (80%) cases had at least one dermatological finding, whereas only 22 (44%) individuals in the control group had dermatological findings ($p < 0.001$). The risk of developing a dermatological finding was found to be increased 0.196-fold in HCV-infected patients compared with the control group (95% confidence interval (CI) 0.081–0.478).

Skin findings in the patient and control groups are shown in Table I. Pruritus was the most frequent finding in the infected group. Cutaneous necrotizing vasculitis was not seen in the patient group. However, in one patient with urticaria, histopathological findings of leukocytoclastic vasculitis were seen. When the dermatological findings that were observed in the 2 groups were compared, a significant difference was seen only

Table I. Skin manifestations in anti-hepatitis C virus (HCV) antibody positive and negative groups

Cutaneous manifestations	Anti-HCV (+)		Control	
	(n = 50)		(n = 50)	
	n	%	n	%
Pruritus	25	50	6*	12
Xerosis	14	28	6	12
Cutaneous necrotizing vasculitis	0	0	0	0
Mixed cryoglobulinaemia	0	0	0	0
Porphyria cutanea tarda	0	0	0	0
Sicca syndrome	0	0	0	0
Livedo reticularis	1	2	0	0
Raynaud's phenomenon	0	0	0	0
Palmar erythema	4	8	0	0
Nevus araneus (spider angioma)	1	2	1	2
Purpura-petechia-telangiectasia	2	4	0	0
Lichen planus	2	4	0	0
Psoriasis	1	2	1	2
Vitiligo	0	0	0	0
Recurrent aphthous stomatitis	4	8	2	4
Urticaria	2	4	1	2
Cutaneous T-cell lymphoma	1	2	0	0
Cutaneous B-cell lymphoma	0	0	0	0
Skin tag	2	4	5	10
Acne vulgaris	1	2	5	10
Seborrhoeic dermatitis	2	4	3	6
Rosacea	2	4	0	0
Senile angioma	1	2	2	4

* $p < 0.001$.

in pruritus ($p < 0.001$) (odds ratio 0.136). No statistical differences were seen in the other findings.

HCV RNA results were positive in 36 patients with anti-HCV antibody positive results, and negative in 14. Skin findings in HCV RNA positive and negative patients are shown in Table II. No statistical differences were found in skin findings for the patients with positive and negative HCV RNA results.

DISCUSSION

HCV is probably the most common cause of chronic liver disease worldwide (2). The course of HCV infection is subclinical in general, and presents with non-hepatic, rather than hepatic symptoms. Dermatological findings constitute an important proportion of extrahepatic signs related to HCV infection (4). Cacoub et al. (5) performed a multicentre study to examine the skin findings accompanied by HCV in 321 patients with chronic hepatitis C (CHC). A total of 122 (39%) patients presented at least one clinical extrahepatic manifestation and of these, at least one skin finding was observed in 55 (17%). Paoletti et al. (6) found HCV-related skin disorders in 12 (12.5%) of 96 CHC patients. In our study, dermatological findings were observed in 80% of the cases with HCV infection. In addition, HCV infection was diagnosed in 12% of patients in the study group while being investigated for a cutaneous complaint.

Although the details of pathogenesis of these disorders remain uncertain, immune system changes, such

Table II. Comparison of each cutaneous finding according to hepatitis C virus (HCV) RNA positivity

Cutaneous manifestations	HCV RNA (+)		HCV RNA (-)	
	(n = 36)		(n = 14)	
	n	%	n	%
Pruritus	19	53	6	43
Xerosis	13	36	1	7
Cutaneous necrotizing vasculitis	0	0	0	0
Mixed cryoglobulinaemia	0	0	0	0
Porphyria cutanea tarda	0	0	0	0
Sicca syndrome	0	0	0	0
Livedo reticularis	0	0	1	7
Raynaud's phenomenon	0	0	0	0
Palmar erythema	3	8	1	7
Nevus araneus (spider angioma)	1	3	0	0
Purpura-petechia-telangiectasia	1	3	1	7
Lichen planus	0	0	2	14
Psoriasis	1	3	0	0
Vitiligo	0	0	0	0
Recurrent aphthous stomatitis	2	6	2	14
Urticaria	2	6	0	0
Cutaneous T-cell lymphoma	1	3	0	0
Cutaneous B-cell lymphoma	0	0	0	0
Skin tag	1	3	1	7
Acne vulgaris	1	3	0	0
Seborrhoeic dermatitis	2	6	0	0
Rosacea	0	0	2	14
Senile angioma	1	3	0	0

as immune complexes and specific T lymphocytes depositions in organs like skin, and the role of alterations in autoimmune system have been mentioned in the development of some skin lesions (3, 7). In most cases immunological mechanisms arising from the viral-dependent proliferation of monoclonal and polyclonal lymphocytes and extrahepatic tissue invasion by replicating HCV are currently postulated in the aetiopathogenesis of extrahepatic and cutaneous findings (3, 4).

In the study by Cacoub et al. (5) the cutaneous manifestations found were: mouth sicca syndrome (12.5%), ocular sicca syndrome (10%), Raynaud's phenomenon (6.5%), purpura (6.5%), pruritus (6.2%), cutaneous vasculitis (5.9%), symptomatic mixed cryoglobulinaemia (MC) (4.7%), polyarteritis nodosa (PAN) (2.8%), SLE (1.9%), psoriasis (1.9%), porphyria cutanea tarda (PCT) (0.9%), lichen planus (LP) (0.9%), Sjögren's syndrome (0.9%) and mixed connective tissue disorder (0.3%). Pawlotsky et al. (8) found LP in 3 out of 61 cases with CHC, cutaneous vasculitis with high levels of cryoglobulins in 4 cases, autoimmune thrombocytopenic purpura in one and callosities, Raynaud's phenomenon, oesophageal dysfunction, sclerodactyly and telangiectasia syndrome in one each. More recently, Dervis & Serez (9) investigated the prevalence of dermatological manifestations in 70 CHC patients: pruritus (18.6%), leukocytoclastic vasculitis (4.3%) and LP (4.3%) were the most common skin findings. In our study pruritus in 25 (50%) cases was the most frequent skin finding. Other skin findings are shown in Table II. When the skin findings in the cases with HCV were compared with the control group, we observed that only pruritus was statistically different. However, the number of cases in our study is too low to allow for exact biometric evaluation of prevalence differences in the 2 groups. With such a low number of cases, dermatological symptoms and diseases seen by chance may be over-represented in the data. This accounts for differing prevalence rates across publications using a similar statistical approach.

It has been reported recently that cutaneous lesions constitute the major findings at discovery of occult HCV infections in some patients (10). While the correlation between HCV infection and some extrahepatic findings, such as essential mixed cryoglobulinaemia (EMC), PCT, membranoproliferative glomerulonephritis, and high prevalence of autoantibodies was clearly demonstrated, uncertainty continues for other findings (5, 10, 11). However, diseases such as LP, prurigo nodularis, pruritus, PAN, Sjögren's syndrome, psoriasis, urticaria and B-cell lymphoma are frequently seen in cases of HCV infection (3, 11).

Cutaneous necrotizing vasculitis has been associated with CHC and cryoglobulinaemia (4). HCV-related vasculitis may present palpable purpura, urticaria or livedo

reticularis, most of which present as leukocytoclastic vasculitis associated with cryoglobulinaemia (6, 12–14). HCV-anti-HCV antibody immune complexes are believed to activate the complement by cryoprecipitating in vessels, leading to vasculitis (14).

Essential mixed cryoglobulinaemia is believed to develop in long-lasting HCV infection. While both type I and II are observed in CHC, it has been reported that type II is more frequent (3, 15, 16). The percentage of patients with HCV who have circulating cryoglobulins has been reported as between 0% and 59% (8, 17). High levels of anti-HCV antibodies have been shown in the sera of patients with EMC in many studies; this again indicates a pathogenic relationship between EMC and HCV infections (11).

No cases with MC were found in our study. Histopathologically leukocytoclastic vasculitis was revealed in a case with urticaria; however, cryoglobulin was found to be negative. Apart from this case, no other vasculitis patients were recorded. Cryoglobulin was also negative in another patient with livedo reticularis.

Prevalence ratios of HCV infection with accompanying LP reported in the literature are inconsistent; while some studies indicate a relationship, others do not (18–20). Oral localization is the most commonly reported form of LP related to chronic hepatitis (19). Up to 26% of patients with oral LP have chronic liver disease, one-third of whom were infected with HCV (7). Pawlotsky et al. (8) observed LP with a ratio of 5% in patients. Nagao et al. (21) found a LP prevalence of 16.7% in patients. However, in the study of Cribier et al. (22) with 52 patients with LP, out of which 4 had oral localization, HCV prevalence was not found to be higher in LP patients than in patients with other type of dermatosis. In a study from Turkey, the prevalence of HCV infection was not found to be increased in Turkish patients with LP (23). However in another study from Çukurova region co-association of LP with HCV was found to be significant (24). There were 2 (4%) cases with LP in our study. When this value was compared with the control group, it was found to be statistically insignificant.

B-cell lymphoproliferative diseases have also been observed in cases with HCV infection. In particular, B-cell non-Hodgkin's lymphomas has been defined in patients with long-lasting HCV infection related to type II EMC (5, 11, 25–27). We did not find any case with cutaneous B-cell lymphoma in our study. However, in one case with cutaneous T-cell lymphoma (mycosis fungoides) anti-HCV antibody and HCV RNA were found to be positive. As far as we know, there is no reported case of HCV infection accompanying cutaneous T-cell lymphoma in the literature. Since there are reports suggesting the possible roles of viruses such as Epstein-Barr virus and cytomegalovirus in the development of cutaneous T-cell lymphoma, HCV could also have an aetiopathogenic role (28, 29).

Sicca syndrome and cases with PCT accompanying HCV infection have also been reported in the literature. In general, evaluations of HCV prevalence in patients with PAN range from 5% to 31% (11, 30). No patients with Sicca syndrome, PCT or PAN were found in our study.

In the study of Kanazawa et al. (31) pruritus was diagnosed in 28 patients, and positive results for anti-HCV antibody were found in 11 of these 28 patients and positive HCV RNA was found in 8 patients. In a single-centre study from Turkey, similar to the results of our study, the only symptom which was significantly increased was found to be pruritus (9). It has been suggested that pruritus could be related to cholestasis induced by HCV, accumulation of immune complexes in the skin could have a role, or cutaneous tropism could be stimulated through the neuropeptides playing a role in the inter-neuronal communication between neurons and immune system (4, 32, 33). Pruritus was found in 25 (50%) patients in our study group. This ratio was found to be significantly different in the statistical evaluation compared with the ratio of pruritus in the control group ($p < 0.001$).

The aetiopathogenic role of HCV in urticaria remains controversial. There are reports indicating the existence and non-existence of a possible relationship (11, 34). Existence of urticaria in cases with positive anti-HCV antibody in our study had no statistical significance compared with the control group. However, vasculitis was shown histopathologically in one case with urticaria and positive anti-HCV antibody.

Many studies report hepatitis C and psoriasis accompanying each other; some authors suggest that hepatitis C is one of the triggering factors of psoriasis (35–37). There was one case in each of our study and control groups; however this had no statistical significance.

Skin findings such as palmar erythema, nevus araneus, purpura, petechias and acne are related to the damage in the liver rather than HCV infection (38). When our study and control groups were compared in terms of these findings, no statistical significant changes were seen between the groups.

In the literature there are few case reports about the association of HCV infection and other dermatological findings. It has been reported that erythema nodosum, erythema multiforme, prurigo nodularis, necrolytic acral erythema, disseminated superficial porokeratosis, SLE, pityriasis rubra pilaris, graft-versus-host disease, pyoderma gangrenosum, granuloma annulare, pernicious-like lesions, lichenoid and granulomatous interface dermatitis and purpura with follicular localization can be seen (3, 5, 11). In addition, it has also been reported that HCV infection could be related to pseudo-Kaposi's sarcoma, Behçet's disease, vitiligo and malakoplakia (3, 4, 6). Findings such as xerosis, skin tag, seborrhoeic dermatitis and rosacea are mostly found to be coincidental. These findings were observed in our case. However, it is likely that these accomplishments are coincidental.

There are few assessments concerning the cutaneous findings in HCV RNA positive or negative patients in the literature. In the study of Kanazawa et al. (34) there were marked clinical and biochemical differences between the patients with urticaria who had HCV RNA in serum and those who did not. In another study performed on patients with HCV infection and EMC, it was observed that vasculitis had improved with interferon-alpha treatment only in patients whom HCV RNA became negative and no improvement was seen in patients that HCV RNA continued to be positive (39). This finding can be attributed to the continuance of the antigenic stimulus in HCV RNA positive cases. In order to investigate a possible increase in skin findings in HCV RNA positive cases, all the skin findings of the patients with positive and negative HCV RNA were compared with each other; no significant differences were found between the 2 groups. Our findings did not support the results of the studies, however, we believe that further research is necessary to clarify this issue.

In conclusion, the risk of developing any dermatological symptoms and, among these, pruritus in HCV-infected people were found to be increased in comparison with HCV absent individuals. No difference was found in the risk of developing any cutaneous symptoms between HCV RNA positive and negative patients. As far as we know there are no other studies in the literature comparing the skin manifestations between HCV RNA positive or negative patients; in this respect our study is important. However, the number of patients in our series was too low to evaluate statistically the exact prevalence differences in the 2 groups. Multicentre studies including large numbers of patients are therefore needed for further assessments.

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