Skin manifestations of chronic hepatitis C virus infection in Cairo, Egypt

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المظاهر الجلدية للعدوى بفيروس التهاب الكبد سي المزمن في القاهرة، مصر

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الخلاصة: قيَّم الباحثون المظاهر الجلدية للعدوى بفيروس التهاب الكبد سي المزمن وارتباطها بحالة الكبد؛ ووجدوا لدى دراسة 155 مريضاً مصاباً بذلك في القاهرة، بمصر أن 71 مريضاً (45.8٪) لديهم مظاهر جلدية، هي: الحكة دون أذيات جلدية واضحة 21.3٪، اندفاعات فرفرية مصطبغة 5.2٪، وقرحات قلاعية وحزاز مسطح 3.9٪، والتهاب أوعية بتكسّر الكريات البيض 2.6٪، وصدفيّة 1.9٪، وتينية مبرقشة 1.3٪، وحالات أخرى 5.8٪. فيما ترافق الكبد الضامر وضخامة الطحال والاستسقاء بشكل يُعْتَدّ به إحصائياً مع وجود الأذيات الجلدية، فكان الاختطار النسبي لها في الكبد الضامر 8.0 وفي ضخامة الطحال 2.7 وفي الاستسقاء 1.8؛ كما ارتبط ضمور الكبد ارتباطاً يُعْتَدّ به إحصائياً مع الحكّة وكان الاختطار النسبي 2.1، ولم يكن هناك أي ارتباط للجنس مع أي من الأذيات الجلدية.

ABSTRACT We assessed the dermatological manifestations associated with chronic hepatitis C virus (HCV) infection and their association with liver status. Of 155 patients with chronic HCV infection in Cairo, Egypt, 71 (45.8%) had dermatological manifestations: pruritus without evident skin lesions (21.3%), pigmented purpuric eruption (5.2%), aphthous ulcer and lichen planus (3.9% each), leukocytoclastic vasculitis (2.6%), psoriasis (1.9%), tinea versicolor (1.3%) and other conditions (5.8%). Shrunken liver, splenomegaly and ascites were significantly associated with the presence of skin lesions (relative risk 8.0, 2.7 and 1.8 respectively), and shrunken liver was significantly associated with pruritus (relative risk 2.1). Sex was not associated with any of the skin lesions.

Manifestations cutanées de l'infection chronique par le virus de l'hépatite C au Caire (Égypte)

RÉSUMÉ Nous avons passé en revue les manifestations dermatologiques liées à l'infection chronique par le virus de l'hépatite C (VHC) et leur rapport avec l'état hépatique. Sur 155 patients atteints de cette infection au Caire (Égypte), 71 (45,8 %) présentaient des manifestations dermatologiques : prurit sans lésions cutanées évidentes (21,3 %), éruption purpurique pigmentée (5,2 %), ulcère aphteux et lichen plan (3,9 % chacun), vascularite leucocytoclasique (2,6 %), psoriasis (1,9 %), pityriasis versicolor (1,3 %) et autres affections (5,8 %). L'atrophie hépatique, la splénomégalie et l'ascite étaient significativement associées à la présence de lésions cutanées (risque relatif : respectivement 8,0, 2,7 et 1,8) et l'atrophie hépatique seule était significativement associée au prurit (risque relatif : 2,1). Le sexe n'était associé à aucune des lésions cutanées.

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Introduction

Hepatitis C virus (HCV) infection is often asymptomatic, but numerous extrahepatic disorders, especially dermatological diseases, have been recognized in association with HCV infection [*1–8*]. Cutaneous lesions are a major presenting feature in some patients with HCV infection and can lead to the discovery of occult HCV infection [*8*]. The skin diseases frequently associated with HCV include cutaneous necrotizing vasculitis, mixed cryoglobulinaemia, porphyria cutanea tarda and lichen planus, but other skin disorders, such as pruritus, urticaria, erythema multiforme and nodosum, may also be linked to HCV [*2*]. The prevalence of skin manifestations varies from one geographic area to another, probably due to differences in viral, genetic or environmental factors [*3*].

In most cases, the pathogenesis of these disorders remains uncertain. Replication of the virus in lymphoid cells may cause extrahepatic manifestations. Another theory suggests that circulating immune complexes composed of HCV antigens and antibodies deposit in tissues and initiate an inflammatory cascade. Other possible mechanisms are local formation of immune complexes induced by viral antigens, or a local tissue inflammation induced by autoantibodies reacting with tissue antigens [4].

The aim of this study in Egypt was to detect the dermatological manifestations associated with chronic HCV infection and their association with liver status.

Methods

Sample

The study was conducted on all 155 patients with chronic HCV infection attending the Medical Services Unit of the National Research Centre, Cairo, Egypt from June 2005 to March 2006. Patients with coexisting liver disease (due to hepatitis B, autoimmune disease or alcohol abuse), diabetes mellitus, renal impairment or malignancy and those who were receiving treatment with antivirals and/or immunomodulatory agents were excluded from the study. Informed consent was obtained from every patient and the study was approved by the ethical committee of the National Research Centre.

HCV was diagnosed by: elevated alanine transaminase (ALT) level greater than twice the upper limit of normal for more than 6 months duration; and positive anti-HCV antibodies detected using IgG 3rd-generation commercial enzyme-linked immunosorbent assay (ELISA kit, Sorin Biomedical, Italy).

Data collection

All patients were examined clinically by a hepatologist, internist and dermatologist. The clinical examination included general examinations such as patient's mental state, build, pulse rate, respiratory rate, body temperature, blood pressure, and noting signs of liver cell failure such as pallor, jaundice, palmar erythema, fetor hepaticus and flapping tremor. Chest and heart examinations were done. Abdominal examination was done to detect cases of enlarged liver or spleen and presence of ascites as complications of liver cirrhosis. Abdominal ultrasound was available for only 84 patients as the other patients did not return for the appointment.

All patients had the following investigations (reference values): red blood cells (for males: 4.5–6.4 × $10^3/cm^3$; for females: 3.8–5.6 × $10^3/cm^3$); haemoglobin (males: 13–18 g/dL; females:11.5–16.5 g/dL); total leukocyte count (4–11 × $10^3/cm^3$); platelets count (150–400 × $10^3/cm^3$), fasting blood sugar (70–115 mg/dL), ALT (0–35 IU/mL), aspartate aminotransferase (AST) (0–45 IU/mL), total serum bilirubin (0.2–1 mg/dL),

albumin (3.5–5.2 g/dL), prothrombin concentration (75%–100%) and schistosomal antibody. Previous *Schistosoma* infection was documented by history and schistosomal antibody in the serum ≥ 1/32 U/L.

Due to cost constraints HCV-RNA by polymerase chain reaction (PCR) was done for only 115 patients and was positive for all of them. Peripheral blood cell isolation, RNA extraction and reverse-transcription nested PCR was carried out as described by El Awady et al. [*5*].

Statistical analysis

Data are presented as mean and standard deviation (SD) and percentage. The data were analysed by *Epi-Info*, version 6.2, and by *SPSS PC+*, version 7.5. The following tests of significance were used: analysis of variance (ANOVA) test between more than 2 means, *t*-test between means to analyse differences between means and *t*-test between percentages to analyse percentage difference. Relative risk (RR) and 95% confidence intervals (CI) were calculated to determine the risk and incidence of occurrence of the clinical and laboratory parameters. $P < 0.05$ was considered significant.

Results

The study sample comprised 155 patients; 104 men and 51 women, age range 27–75 years [mean 46.95 (SD 11.13) years].

Biochemical profile of patients with and without dermatological manifestations

Dermatological examination of all 155 patients with HCV revealed that 71 (45.8%) had dermatological manifestations. The most common was pruritus, with no evident skin lesions, in 33 patients (21.3% of the total; 46.5% of skin manifestations). Evident dermatological lesions were present in 38 patients (24.5% of the total; 53.5% of skin manifestations); these were in the form of pigmented purpuric eruption in 8 patients (5.2%); aphthous ulcer and lichen planus in 6 patients each (3.9%); leukocytoclastic vasculitis in 4 patients (2.6%); psoriasis in 3 patients (1.9%); tinea versicolor in 2 patients (1.3%); vasculitis, melasma, localized neurodermatitis, pseudofolliculitis, pitiriasis rosea, chronic eczema, urticaria, scabies and stasis eczema were present in 1 patient each (0.6%). No patient had more than 1 lesion.

Table 1 shows the difference in biochemical tests and viral load between the patients with pruritus, patients with evident skin lesions other than pruritus and patients free of skin lesions. Schistosoma infection was detected in 45 patients. Although the mean values of serum bilirubin and AST were highest among HCV patients with evident skin manifestations other than pruritus, thee differences were not significant. Mean values of serum albumin and prothrombin concentration were lowest among HCV patients with evident skin manifestations other than pruritus, but again this was not significant.

Association of clinical signs with dermatological manifestations

Abdominal ultrasound of 84 patients revealed that 11 patients had normal-sized "bright" liver, 47 had hepatomegaly and 26 had shrunken liver. There were 46 patients diagnosed with splenomegaly and 36 with normal size spleen (2 had had a splenectomy). Ascites was present in 11 patients and absent in 73.

Risk analysis among this subgroup of patients showed that among those free of dermatological manifestations, shrunken liver, splenomegaly and ascites were significantly associated with skin lesions (RR 8.0, 95% CI: 1.2–50.9; RR 2.7, 95% CI: 1.4–5.3;

Table 1 **Biochemical tests and viral load in patients with chronic hepatitis C virus (HCV) infection with pruritus, evident skin manifestations other than pruritus and without skin manifestations**

Test	HCV patients with pruritus (*n* = 33)	HCV patients with evident skin manifestations other than pruritus (*n* = 38)	HCV patients without skin manifestations (*n* = 84)	*P*-value
	Mean (SD)	Mean (SD)	Mean (SD)	
Serum bilirubin (mg/dL)	0.94 (0.44)	1.18 (0.73)	1.14 (0.66)	0.76
ALT (IU/L)	52.91 (45.64)	51.58 (26.05)	53.80 (38.51)	0.98
AST (IU/L)	64.64 (41.4)	74.54 (41.57	59.32 (34.84)	0.45
Serum albumin (g/dL)	3.86 (0.62)	3.71 (0.65)	3.85 (0.66)	0.87
Prothrombin concentration[a] (%)	72.25 (16.56)	69.17 (25.70)	83.75 (14.12)	0.09
Viral load[b] (copies/mL)	217.5 (77.5)	368.6 (342.7)	295.9 (230.5)	0.46

[a]As a percentage of prothrombin time compared to pooled plasma from healthy controls.
[b]Viral load was only established for 115 patients.
SD = standard deviation; ALT = alanine transaminase; AST = aspartate aminotransferase.

and RR 1.8, 95% CI: 1.2–2.9 respectively) (Table 2). There was no sex predilection for the dermatological manifestations. There were no differences with regard to the risk of developing dermatological manifestations between patients with and without schistosomiasis. There was no significant difference as regards liver biochemical tests or viral load between patients with and without dermatological manifestations

Patients with shrunken liver had significantly higher risk of pruritus than those with

Table 2 **Association of liver abnormalities, spleen abnormalities and ascites with skin manifestations in patients with chronic hepatitis C virus (HCV) infection**

Variable	HCV patients with skin manifestations (*n* = 37)		HCV patients without skin manifestations (*n* = 47)[a]		RR	95% CI	*P*-value
	No.	%	No.	%			
Liver							
Normal size	1	2.7	10	21.3			
Hepatomegaly	17	45.9	30	63.8	4.0	0.6–26.8	0.14
Shrunken	19	51.4	7	14.9	8.0	1.2–50.9	0.0004
Spleen							
Normal size	8	21.6	28	59.6			
Splenomegaly	28	75.7	18	38.3	2.7	1.4–5.3	0.0005
Ascites							
Absent	29	78.4	44	93.6			
Present	8	21.6	3	6.4	1.8	1.2–2.9	0.005

[a]1 patient without skin manifestations had had a splenectomy.
RR = relative risk; CI = confidence interval.

hepatomegaly (RR 2.1, 95% CI: 1.2–3.9). Splenomegaly was significantly associated with pruritus (RR 3.3, 95% CI: 1.4–7.9), but the association of ascites with pruritus was not significant (RR 1.6, 95% CI: 0.7–3.9) (Table 3). Males had nearly 2 times greater risk of pruritus than females, but the association was not significant (RR 1.8, 95% CI: 0.8–4.1). There was no significant difference in the mean level of serum bilirubin between patients with pruritus [mean 0.94 (SD 0.44) mg/dL] and patients free from skin lesions [mean 1.14 (SD 0.66) mg/dL].

There was no significant association of hepatomegaly with evident dermatological lesions other than pruritus compared with patients without skin manifestations (RR 1.6, 95% CI: 0.2–12.1). However, shrunken liver was significantly associated with evident dermatological lesions other than pruritus (RR 5.9, 95% CI: 0.9–40.3). Splenomegaly and ascites had nearly 4 times the risk of skin manifestations (RR 3.7, 95% CI: 1.1–12.1 and RR 3.7, 95% CI: 1.7–8.2 respectively) (Table 4).

Discussion

Chronic HCV infection is associated with various dermatological manifestations [*1,9*]. Paoletti et al. reported a 12.5% prevalence of clinical dermatoses in HCV-infected patients [*10*]. We found skin manifestations in 45.8% of HCV-infected patients. The rates in our study are higher than in other studies, probably owing to the different HCV genotype in our population; distribution of HCV genotypes varies according to region [*11*].

Pruritus with no evident skin lesions was the most prevalent skin manifestation in our study, and there was a significant positive association of hepatomegaly, shrunken liver or splenomegaly with pruritus. The RR of pruritus was higher in patients with shrunken liver compared with patients with hepatomegaly, and in patients with splenomegaly compared with patients with normal size spleen. Our result agrees with Cacoub et al., who reported pruritus in 15% of cases of HCV and concluded that it is one of the most common extrahepatic manifes-

Table 3 **Association of liver and spleen abnormalities and ascites with pruritus in patients with chronic hepatitis C virus (HCV) infection**

Variable	HCV patients with pruritus (n = 23)		HCV patients without skin manifestations (n = 47)[a]		RR	95% CI	*P*-value
	No.	%	No.	%			
Liver							
Normal size	0	0.0	10	21.3			
Hepatomegaly	12	52.2	30	63.8			
Shrunken	11	47.8	7	14.9	2.1	1.2–3.9	0.001
Spleen							
Normal size	5	21.7	28	59.6			
Splenomegaly	18	78.3	18	38.3	3.3	1.4–7.9	0.002
Ascites							
Absent	20	87.0	44	93.6			
Present	3	13.0	3	6.4	1.6	0.7–3.9	0.38

[a]1 patient without skin manifestations had had a splenectomy.
RR = relative risk; CI = confidence interval.

Table 4 **Association of liver abnormalities, spleen abnormalities and ascites with evident skin manifestations in patients with chronic hepatitis C virus (HCV) infection**

Variable	HCV patients with evident skin manifestations other than pruritus (*n* = 14)		HCV patients without skin manifestations (*n* = 47)[a]		RR	95% CI	*P*-value
	No.	%	No.	%			
Liver							
Normal size	1	7.1	10	21.3			
Hepatomegaly	5	35.7	30	63.8	1.6	0.2–12.1	0.99
Shrunken	8	57.1	7	14.9	5.9	0.9–40.3	0.03
Spleen							
Normal size	3	21.4	28	59.6			
Splenomegaly	10	71.4	18	38.3	3.7	1.1–12.1	0.01
Ascites							
Absent	9	64.3	44	93.6			
Present	5	35.7	3	6.4	3.7	1.7–8.2	0.01

[a] *1 patient without skin manifestations had had a splenectomy.*
RR = relative risk; CI = confidence interval.

tations of HCV infection [*7*]. In contrast, Paoletti et al. found pruritus in only about 1% of HCV-infected patients [*10*]. The precise mechanism of itch in liver diseases remains unclear, although the presence of bile salts in the skin, histamine and alternative liver metabolites have been proposed as explanations [*12*].

Pigmented purpura (Gougerot–Blum disease) in the form of lichenoid papules in association with brown pigmented lesions is a sign of capillaritis in HCV-infected patients [*13*]. We found pigmented purpuric eruption in 5.2% of our patients. The histopathology of this type of capillaritis reveals narrowing of the lumen with perivascular T-lymphocytic infiltrate, suggesting a cell-mediated immune reaction [*14*].

Our data revealed lichen planus in 3.9% of HCV-infected patients. The prevalence of HCV infection in patients with lichen planus shows wide variation from 3.8% in France [*15*] to 62% in Japan [*16*]. This variation is probably due to genetic differences in different geographic regions. Although the etiology of HCV-induced lichen planus is unknown, it is probably related to viral replication in lymphocytes [*1*]. The coexistence of the 2 conditions is more than coincidental, and it is appropriate to screen all patients with lichen planus for HCV infection [*17*].

Leukocytoclastic vasculitis was found in 2.6% of our patients, which is consistent with the finding of Hartmann et al. who reported leukocytoclastic vasculitis of the skin in 2% of HCV-infected patients [*18*]. They suggested that immune stimulation of T-cell clones in HCV infection produces monoclonal macroglobulins with coaffinity to a constituent of HCV and IgG. Potential antigens of relevance include bacteria, viruses, drugs and other chemicals. Immune complexes have a role in HBV- and HCV-induced vasculitis and in cryoglobulinaemic vasculitis [*19*].

Psoriasis affected 1.9% of our patients. Taglione et al. described HCV-infected

patients with psoriasis [*20*]. Both genetic and environmental influences have a critical role in psoriasis. The environmental risk factors include trauma, infection, medicines and immunological factors. There is considerable evidence that T-lymphocytes have an important role in the development of psoriasis [*21*].

Our data showed urticaria among 0.6% of patients with HCV infection. The prevalence of chronic urticaria varies from 1% to 5% in the general population [*22*]. Doutre et al. described acute and chronic urticaria in various skin diseases with HCV infection [*23*]. However Cribier et al. showed that, at least in Europe, HCV rates in cases of chronic urticaria are similar to those of the general population [*24*]. In patients with HCV, urticaria tends to last longer than the typical few hours, is associated with worse liver status and leaves a brown stain [*25*].

Several studies reported an association between HCV and porphyria cutanea tarda. In a systematic review, the mean prevalence of HCV infection calculated from 2167 patients from 50 studies was 47% [*26*]. However, we did not observe any case of porphyria cutanea tarda in our HCV patients. Porphyria cutanea tarda is the most common form of porphyria and is caused by reduced activity of uroporphyrinogen decarboxylase. The enzymatic defect is essential but not sufficient for the clinical manifestations [*27*]. Recently, mutations in the gene associated with hereditary haemochromatosis have been associated with sporadic and familial porphyria cutanea tarda, suggesting that inheritance of haemochromatosis alleles may be a susceptible factor for the development of the disease [*28*]. This may explain the absence of porphyria cutanea tarda in our patients.

Other dermatologic lesions—aphthous ulcer, tinea versicolor, scabies, melasma, localized neurodermatitis, pseudofolliculitis, pityriasis rosea, eczema and stasis eczema—were each present in 1 patient in our study. We did not find any correlation between these lesions and chronic HCV in other studies, so we do not know if this is a chance association or if HCV may predispose to these lesions. Further studies with a larger number of HCV patients are recommended to evaluate the relationship.

Conclusion

HCV is associated with various dermatological disorders and patients with liver cirrhosis are at higher risk of developing lesions. In those with pruritus, HCV infection should be sought routinely as it is the most common dermatological manifestation in infected patients and the risk of development occurs early in the course of the disease. Epidemiological studies are essential to determine the real prevalence of other dermatoses in the course of HCV infection.

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Hepatitis C

Hepatitis C virus (HCV) is a major cause of acute hepatitis and chronic liver disease, including cirrhosis and liver cancer. Globally, an estimated 170 million persons are chronically infected with HCV and 3 to 4 million persons are newly infected each year. HCV is spread primarily by direct contact with human blood. The major causes of HCV infection worldwide are use of unscreened blood transfusions, and re-use of needles and syringes that have not been adequately sterilized.

No vaccine is currently available to prevent hepatitis C and treatment for chronic hepatitis C is too costly for most persons in developing countries to afford. Thus, from a global perspective, the greatest impact on hepatitis C disease burden will likely be achieved by focusing efforts on reducing the risk of HCV transmission from nosocomial exposures (e.g. blood transfusions, unsafe injection practices) and high-risk behaviours (e.g. injection drug use).

Source: WHO Fact sheet No. 164