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Systematic Cutaneous Examination in Hepatitis C Virus Infected Patients

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The purpose of this study was to evaluate the frequency of skin changes among 100 patients from the Hepatogastroenterology Department of the University Hospital, Strasbourg, France who were hepatitis C virus-positive (HCV) and HIV-negative. Their clinical data were compared to those of 50 HCV-, and HIV-negative patients from the same Department, who suffered from various liver diseases.

Psoriasis, rosacea, seborrheic dermatitis, cherry angiomas, spider nevus and skin cancers were noted in similar proportions in the two groups. In 15% of HCV-positive patients vs. 4% of controls, chronic pruritus was noted ($p < 0.05$). In 9 HCV-positive patients, pruritus was not related to itching dermatosis, and only 2 of these patients had mild cholestasis. Four cases of lichen planus vs. 0 in the control group were recorded. The virological data of patients with pruritus or lichen planus were not different than those of the rest of the group. Our findings indicate that systematic skin check-up in HCV-positive patients is valuable.

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The hepatitis C virus (HCV) was discovered in 1989 (1) and is classified as belonging to the *Flaviviridae* family. It is mainly transmitted by blood percutaneous exposure or by blood transfusion. Since the first serologic tests for the detection of HCV became available in 1990, many dermatologic patients have been tested. Various cutaneous diseases associated with HCV infection have been described. It is now established that HCV is the major cause of "essential" mixed cryoglobulinemia (2). It has also been demonstrated that more than 60% of patients with sporadic porphyria cutanea tarda are HCV-positive in Italy, Spain and France (3). Nevertheless, the link between HCV infection and the development of porphyria seems to be indirect (4). The association between HCV and lichen planus is more controversial, since epidemiological studies have shown contradictory results (5, 6, 7). It is possible that some cases of lichen, especially erosive lichen planus (8), could be related to HCV infection, but the physiopathology of this association remains unexplored. Urticaria, prurigo, psoriasis, erythema nodosum and other skin diseases associated with HCV have been described (9, 10). The majority of previously published studies have included patients suffering from cutaneous diseases and have analysed the prevalence of HCV-positivity. There have been very few attempts to study the prevalence of cutaneous changes in large groups of HCV-infected patients. In one study, clinical data from 611 HCV-positive patients of the Mayo Clinic were retrospectively reviewed in order to find cases of cutaneous vasculitis (11).

The purpose of the present study was to evaluate the frequency of skin changes related to HCV infection by standardized cutaneous examination of 100 patients chronically infected by HCV. Since cutaneous signs observed in HCV-infected patients could be related to causes other than the viral infection. Fifty HCV-negative patients with various liver diseases were also examined.

PATIENTS AND METHODS

One hundred consecutive inpatients infected by HCV (60 men, mean age 46 ± 16 years, and 40 women, mean age 51 ± 13 years) were examined by the same dermatologist in the Hepatogastroenterology Department of the University Hospital, Strasbourg. The patients were included on the basis of positive ELISA for HCV (i.e. two different strongly positive 2nd or 3rd generation ELISA). All patients coinfected by HIV were excluded from the study. Hepatitis B virus (HBV) serologic tests were also performed in all patients. We included only HBV-negative patients or patients having only HBs antibodies without circulating HBV DNA. The mode of transmission of HCV was blood transfusion in 48% of cases and intravenous drug use in 18%. In 3% of cases, the HCV transmission was probably occupational (nurses) and a sexual transmission was suspected in a 29-year-old woman. In 30% of cases the route of transmission was unknown.

The majority of patients were hospitalized for evaluation of positive serology (liver biopsy) or for follow-up. Among the HCV-positive group, only 20 patients had an alcohol consumption level higher than 40 g/day. The alanine-amino-transferase (ALAT) serum level was normal in 34% of patients, and was higher than twice the upper normal limit in 33% of cases. Seventy-three patients had a liver biopsy, 40 of which showed a Knodell score < 6 (mild to moderate activity) and 30 of which were ≥ 6 (intermediate to high activity). In 3 cases, the Knodell score could not be determined because of the size of the biopsy, but fibrosis was noted in 1 case. Among the 27 patients who did not have a liver biopsy, 21 were considered to have cirrhosis on the basis of clinical and biological changes.

Ten patients (10%) of the HCV-positive group had an hepatocellular carcinoma (HCC). The mean age of the patients with HCC was 68 years. Most of patients with severe cirrhosis or HCC were hospitalized for symptomatic treatment of their hepatic disease. A cryoglobulin type II or type III was present in 12% of cases, and rheumatoid factors were present in 35% of patients. The presence of HCV RNA in the serum was investigated by reverse transcription followed by genomic amplification (RT-PCR) that was done in duplicate. The results of RT-PCR showed the presence of HCV RNA in 81% of patients.

During the same period of time, 50 other inpatients (32 men, mean age 52 ± 12 years, and 18 women, mean age 50.5 ± 11 years) were also examined by the same investigator in the same Hepatogastroenterology Department. All were HCV-, HBV- and HIV-negative. The alcohol intake was higher than 40 g/day in 50% of this group. Among these patients, 16 had liver cirrhosis and 5 had HCC developed on severe cirrhosis. The other patients had chronic hepatitis caused by excessive alcohol intake, acute ethanolic hepatitis, or liver metastasis.

All 150 patients were carefully questioned about urticaria, photosensitivity, fatigue and pruritus. Skin, mucosa, hair and nails were systematically examined. In case of specific skin changes, biopsies were performed.

Statistical comparisons were made by χ^2 test, with Yates' correction when necessary.

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Table I. *Main general and cutaneous symptoms among 100 HCV-positive patients and 50 HCV-negative patients from the same Hepatogastroenterology Department*

	HCV-positive (%) ($n=100$)	HCV-negative (%) ($n=50$)	Comparison (χ^2)
Pruritus	15	4	$p<0.05$
Raynaud's syndrome	7	6	ns
Sicca syndrome	4	2	ns
Xerosis	21	16	ns
Palmar erythema	24	28	ns
Nevus araneus	28	32	ns
Cherry angiomas	49	52	ns
Purpura	6	6	ns
Lichen planus	4	0	ns
Vitiligo	2	2	ns
Psoriasis	4	4	ns
Rosacea	10	16	ns
Acne	2	4	ns
Seborrheic dermatitis	4	6	ns
Actinic keratoses	1	4	ns
Basal cell carcinoma	3	2	ns
Fatigue	38	38	ns

RESULTS

The main dermatological symptoms observed in both groups are detailed in Table I. The purpura noted in the two groups of patients consisted of non-infiltrated small lesions of the inferior limbs due to edema or to chronic venous insufficiency. Histopathological examination of biopsy samples showed only extravasated erythrocytes. We did not observe any cutaneous leucocytoclastic vasculitis. None of our 150 patients had photosensitivity, and no case of porphyria cutanea tarda could be recorded. Urticaria was never observed and none of these patients had urticaria in their past medical history. The frequency of common dermatoses and fatigue was similar in the two groups of patients.

Lichen planus was noted in four patients of the HCV-positive group and in none of the HCV-negative patients. Due to the low number of patients presenting the disease, this difference was not statistically significant. In two cases, there were only oral lesions of lichen, confirmed by histopathological examination. One patient had mucocutaneous lichen planus, and the fourth patient presented cutaneous lesions only. All 4 patients had circulating HCV RNA in their serum (Table II).

The only symptom which was significantly more frequent in the HCV-positive group was pruritus in 15 cases. Among the 15 patients, 2 had macular amyloidosis, 1 had lichen simplex chronicus and a past history of atopic dermatitis, 1 was receiving hemodialysis for chronic renal failure, 1 had mucocutaneous lichen planus and 1 had extensive seborrheic dermatitis. The remaining 9 patients had pruritus despite normal cutaneous examination. A mild cholestasis was present in 2 of them (Table II). Among the 2 HCV-negative patients with pruritus, one had only occasional attacks of pruritus related to agarophoby and the second patient had severe cholestasis due to cirrhosis. The course of the HCV disease, the demographic data, the biological and histological liver data and the virological findings in patients with pruritus were not different from those of the whole group. Chronic pruritus without cutaneous changes or cholestasis was therefore noted in 7 patients of the HCV-positive group and in none of the controls. No other cause of pruritus could be demonstrated in these patients. Laboratory investigations of patients with pruritus or lichen planus are detailed in Table II.

DISCUSSION

Evidence of the association of HCV infection with various cutaneous diseases has been published in many series of patients during the period 1991 – 1997 (9, 10). The other face of the problem was rarely studied: what is the prevalence of cutaneous diseases among unselected HCV-positive patients? In their retrospective analysis of 611 patients with chronic HCV infection, Daoud et al. (11) noted 12 cases of leucocytoclastic vasculitis, and 2 of urticaria. The prevalence of all other cutaneous changes in HCV-infected patients is unknown.

In this prospective study, we examined a group of 100 patients who had similar demographic and virological data to those of the largest cohort of patients published in France (12).

Table II. *Laboratory investigations*

	Sex	Age	PCR	Knodell	ALAT*	ASAT*	Bilirubine*
Patients with lichen planus							
9	M	27	+	2	1.5N	N	N
34	M	50	+	5	2.8N	1.5N	N
51	M	57	+	5	3.4N	2.1N	N
83	F	58	+	5	4.6N	2.2N	1.5N
Patients with pruritus unrelated to dermatologic condition							
3	F	27	+	2	1.5N	N	N
16	M	59	+	ND	1.4N	2.3N	N
21	M	75	+	ND	3N	1.5N	N
26	M	55	+	11	1.7N	1.6N	N
29	M	72	+	7	3.3N	4.8N	1.2N
41	F	24	+	4	1.4	N	N
49	F	54	+	10	8N	5.2N	1.2N
55	F	52	+	1	N	N	N
71	F	53	+	ND	N	1.1N	N

* N: within normal range (ALAT: 8 – 38 UI/L, ASAT: 9 – 29 UI/L, bilirubine: <20.5 μmol/L.).

We did not observe any case of porphyria, urticaria or vasculitis, although cryoglobulinemia or a rheumatoid factor were found in a large proportion of our patients. Positive rheumatoid factors could be a marker of cryoglobulinemia (13), but this should be interpreted with caution. Our data confirm that only a minority of HCV-positive patients have symptomatic cryoglobulinemia. Only a few cases of urticaria associated with HCV infection have been published (11, 14, 15), but in a recent study of 50 consecutive English patients with chronic urticaria, none had the antibody to HCV (16).

We found 9% of patients with pruritus unrelated to a dermatological cause. A possible link between pruritus and HCV infection was emphasized in several studies. Fischer & Wright (17) first reported 4 HCV-positive patients with intense and chronic pruritus. In a series of 978 consecutive patients presenting at a Japanese dermatology clinic, 11 of 28 patients with evidence of prurigo proved to be HCV-positive (38%), vs. 5% of 950 controls (18). In a retrospective French study, 27 patients were specifically investigated for chronic pruritus, among a pool of 1060 HCV-positive patients (19). The estimated prevalence of pruritus was therefore 2.5%, but it is probably underestimated, because all patients were not systematically examined by a dermatologist. Pruritus is frequently observed in liver disease associated with severe cholestasis. Seven of our patients with pruritus had no cholestasis, and no other cause could be evidenced. Only 2 of them had a major increase in transaminase levels. The physiopathology of pruritus associated with HCV-infection is unknown. The role of dry skin, treatments or other factors than HCV itself has been emphasized by Dega et al. (19). Since many of our patients had had blood transfusions or were intravenous drug users, factors other than HCV cannot be ruled out. The cost-effectiveness of routine HCV-testing in patients presenting with pruritus of unknown origin is under investigation.

The link between lichen planus and HCV infection is controversial. Two controlled French studies failed to demonstrate a link between HCV and lichen planus (7, 20), whereas in Japan (8), Florida (5) and Germany (21), the prevalence of HCV among patients with lichen planus was much higher than in control groups. It is likely that the prevalence of HCV infection in the French population is too low to yield significant differences between lichen patients and controls. In the present study, 4 of 100 patients had lichen planus, which is probably more than we would expect among 100 random consecutive patients. Two other French studies (20, 22) found a prevalence of lichen planus of 5% among 61 HCV-positive patients and 2.8% among 105 patients. The highest prevalences of HCV infection in patients with lichen planus, prurigo and urticaria were described in Northern Italy and in Japan, where the prevalence of HCV infection in the general population is high. The heterogeneity of HCV epidemiology world-wide makes it impossible to extrapolate the data from one country to another. The interpretation of prevalence data therefore requires carefully selected control groups, especially when patients are recruited in Dermatology Departments. Large prospective and controlled studies are needed for definitive conclusions. It should also be pointed out that physiopathological data that could reinforce these epidemiological links are lacking. Our hypothesis is that HCV is not the real *cause* of cutaneous diseases, but is rather a triggering factor. In conclusion, our study suggests that skin check-up in HCV-infected patients is valuable, since 13% of our patients had either pruritus or lichen planus.

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