# Should we routinely check for hepatitis B and C in patients with lichen planus or cutaneous vasculitis?

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## هل ينبغي فحص مرضى الخزاز المسطح أو الالتهاب الوعائي الجلدي روتينياً، بحثاً عن التهاب الكبد (بي) (B) وسي (C)؟

هالة علي إبراهيم ومنال محمد بدور ومنى جمال الدين مرسي وعايدة عبد القادر محمد عبد القادر

**خلاصة:** كان هدف هذه الدراسة تعيين معدل انتشار المستضد السطحي لفيروس التهاب الكبد (بي) وأضداد فيروس التهاب الكبد (سي) في مجموعة مكونة من 43 مريضاً بالخزاز المسطح و19 مريضاً بالالتهاب الوعائي الجلدي، بالمقارنة مع ثلاثين شخصاً شاهداً. وأظهرت النتائج أن 12 مريضاً (27.9%) بالخزاز المسطح كانوا إيجابيين للمستضد السطحي HBs على حين كان 9 مرضى (20.9%) إيجابيين لأضداد فيروس التهاب الكبد (سي). وكان 3 (7%) إيجابيين للإثنين. أما في مرضى الالتهاب الوعائي الجلدي، فقد كان 3 (15.8%) إيجابيين للمستضد السطحي HBs و7 (36.8%) إيجابيين لأضداد فيروس التهاب الكبد (سي)، بينما كان 3 (15.8%) إيجابيين للإثنين. ومن بين المجموعة الشاهدة، وجد أن 8 (26.7%) كانوا إيجابيين للمستضد السطحي HBs على حين كان 3 (10%) إيجابيين لأضداد فيروس التهاب الكبد (سي) وكان واحد (3.3%) إيجابياً للإثنين، ولم تكن هذه القيم ذات أهمية إحصائية.

ABSTRACT The study aimed to determine the prevalence of HBs-Ag and anti-HCV antibodies in a group of 43 patients with lichen planus and 19 patients with cutaneous vasculitis versus 30 controls. The results showed that 12 (27.9%) patients with lichen planus were positive for HBs-Ag, 9 (20.9%) were positive for anti-HCV antibodies and 3 (7%) were positive for both. In cutaneous vasculitis patients, 3 (15.8%) were HBs-Ag-positive, 7 (36.8%) were anti-HCV-positive and 3 (15.8%) were positive for both. In the control group, 8 (26.7%) were HBs-Ag positive, 3 (10%) were anti-HCV-positive and 1 (3.3%) was positive for both. These values were not statistically significant.

**Devrait-on systématiquement rechercher une infection par les virus des hépatites B et C chez les patients présentant un lichen plan ou atteints de vascularite cutanée?**
RESUME Cette étude vise à déterminer la prévalence des antigènes HBs et des anticorps anti-VHC dans un groupe de 43 patients présentant un lichen plan et de 19 patients ayant une vascularite cutanée par rapport à un groupe de 30 témoins. Les résultats ont montré que 12 patients (27,9%) ayant un lichen étaient Ag HBs positifs, 9 (20,9%) étaient positifs pour les anticorps anti-VHC et 3 (7%) étaient les deux. Chez les patients ayant une vascularite cutanée, 3 (15,8%) étaient Ag HBs positifs, 7 (36,8%) étaient positifs pour l'anticorps anti-VHC et 3 (15,8%) étaient les deux. Dans le groupe des témoins, 8 (26,7%) étaient Ag HBs positifs, 3 (10%) étaient positifs pour l'anticorps anti-VHC et 1 (3,3%) était à la fois Ag HBs positif et positif pour l'anticorps anti-VHC. Les valeurs n'étaient pas statistiquement significatives.

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## Introduction

Hepatitis C virus (HCV) accounts for most cases of transfusion-associated hepatitis worldwide. However, over 90% of cases are not related to transfusions. Chronic liver disease develops in 50% of people infected with HCV [*1*]. Viral hepatitis infections have been known to produce various dermatologic conditions in patients who are known to have been infected or are unaware they have been exposed to those viruses. Dermatologic disorders reported to be associated with HCV and/or hepatitis B virus (HBV) infection(s) include: lichen planus (LP), cutaneous vasculitis, mixed cryoglobulinaemia, erythema multiforme, Behcet's syndrome, erythema nodosum and pyoderma gangrenosum [*2,3*].

Patients with LP have an increased prevalence of HBV and HCV infection [*4*]. In such patients, liver abnormalities frequently occur, especially chronic active hepatitis [*5*]. Therefore, HBV is thought to contribute to the development of LP and some authors have reported a relationship between LP and hepatitis B [*6*]. It has also been estimated that HBV-infected patients have at least twice the risk of developing LP than the general population [*5*]. Recently, a few cases of concomitant LP and HCV have been described [*4,7*]. It has also been suggested that LP could be a possible marker of HCV infection, but the link between these diseases has not been clearly established [*6*].

Leukocytoclastic vasculitis is mediated by the deposition of immune complexes in post-capillary venules. HBV has been associated with cryoglobulinaemia, a condition in which immune complexes precipitate at a lowered temperature [*8,9*]. These cryoprecipitates may contain hepatitis B surface antigen (HBs-Ag), anti-hepatitis B surface antibodies or viral particles [*8,9*]. Cryoglobulinaemia may result in purpura, arthropathy, renal disease, Raynaud phenomenon or erythrocyanosis [*8*]. Furthermore, HBV has been directly implicated in small vessel vasculitis because viral particles resembling HBV have been detected in the post-capillary venules of infected people [*9*].

Isolated cases of erythema multiforme [*10*], erythema nodosum [*11*], urticaria [*12*], leukocytoclastic vasculitis [*13*] and other types of cutaneous vasculitis associated with HCV infection have been reported, but they could be fortuitous and no controlled study has ever shown a significant association of these diseases with HCV infection.

Our study aimed to:

- estimate the prevalence of LP and cutaneous vasculitis among patients with skin disorders who were attending the Alexandria Main University Hospital;
- evaluate the prevalence of HBs-Ag and HCV antibodies in a group of patients with various dermatoses;
- determine HBV and HCV coinfection rates in the study population.

## Patients and methods

The study cohort was consecutively selected from patients seen at the Dermatology Department of the Main University Hospital, Faculty of Medicine, Alexandria University, Egypt.

Between April 1996 and May 1997, 43 cases of LP were diagnosed clinically and histologically. Drug-induced lichenoid eruption was not included. The group included 29 females, 12–66 years of age (mean age 41.6 years) and 14 males, 7–65 years of age (mean age 29.1 years).

During the same period, a group of 19 patients with cutaneous vasculitis, diagnosed clinically and pathologically, were also included. They consisted of 14 fe-

males, 19–52 years of age (mean age 37.4 years) and 5 males, 18–55 years of age (mean age 30.8 years).

A group of 30 patients with dermatoses other than LP or cutaneous vasculitis were randomly assigned as controls. They included 13 females, 20–40 years of age (mean age 27.9 years) and 17 males, 18–30 years of age (mean age 23.4 years).

All the patients were asked whether they had viral hepatitis and about the risk factors for liver disease. Patients were asked about injections, surgical operations, tattoos, intravenous drug abuse, transfusions, ear piercing, history of schistosomiasis, diabetes, asthma, renal disease, blood diseases and history of jaundice. Education (illiterate or educated) as a marker of socioeconomic level was also included as a non-parenteral risk factor.

Serum levels of alanine aminotransferase (ALT) were measured to screen for liver disease. Serum was tested for HBs-Ag using Enzygnost HBs-Ag monoclonal II (Behring Diagnostics, Marburg, Germany), and for anti-HCV antibodies using Detect-HCV, version 3 (Biochem Immunosystems). Statistical analysis was performed using *Epi-Info* statistical software package. $\chi^2$ and Fisher exact test were used to test significance and ANOVA was used for post comparison.

## Results

During the study period, a total of 25 385 patients were seen at the outpatient clinic of the Department of Dermatology giving a prevalence of 0.169% for LP and 0.075% for cutaneous vasculitis.

Demographic data, risk factors for HBV and HCV infection and biochemical and virological features of the patients with LP, cutaneous vasculitis and controls are shown in Table 1. Of the 43 patients with LP, 9 (20.9%) had anti-HCV antibodies by enzyme-linked immunosorbent assay (ELISA-3). HBs-Ag was detected in 12 (27.9%) patients, and 3 were positive for both. In the 19 patients with cutaneous vasculitis, 7 (36.8%) had anti-HCV antibodies, 3 (15.8%) had HBs-Ag and all these 3 had both. Anti-HCV antibodies were found in only 3 (10%) of the 30 controls and HBs-Ag was found in 8 (26.7%); 1 was positive for both.

Abnormal liver enzymes were found in 18 (41.9%) of the patients with LP, 7 (36.8%) of the patients with cutaneous vasculitis and 5 (16.7%) of the controls. However, only 5 of the 15 HBs-Ag-positive patients and 6 of the 16 anti-HCV-positive patients had abnormal liver enzymes. None of the patients reported intravenous drug abuse or intravenous infusion of medication. Table 2 shows the virological data of cases of LP and cutaneous vasculitis. Three (3) of the LP patients suffered from the oral erosive variety. None of these had HBs-Ag and only 1 had anti-HCV antibodies. The results of the histopathological examination of the patients with cutaneous vasculitis who were hepatitis-marker positive are shown in Table 3.

## Discussion

In our study, the prevalence of anti-HCV antibodies in patients with cutaneous vasculitis (7/19, 36.8%) and those with LP (9/43, 20.9%) was much higher than in the control patients (3/30, 10.0%). This is comparable with other studies, such as that by Sanchez-Perez et al. [*14*] in 1996 where the prevalence of anti-HCV antibodies in LP patients was also 20%. Our findings are also comparable with a study by Bellman and colleagues who found the prevalence of HCV in patients with LP was 23% compared with

Table 1 **Features of patients with lichen planus (LP), cutaneous vasculitis (CV) and of controls**

| Feature ($n$ = 43) | LP ($n$ = 19) | | CV ($n$ = 30) | | Control | | Statistical significance |
|---|---|---|---|---|---|---|---|
| Age (years) | | | | | | | |
| < 20 | 7 | | 2 | | 4 | | |
| 20–40 | 17 | | 10 | | 26 | | |
| > 40 | 19 | | 7 | | 0 | | |
| Mean age (range) | 37.5 (7–66) | | 35.6 (18–55) | | 25.3 (18–40) | | $F$ = 6.01 $P$ = 0.004* |
| Male/female | 14/29 | | 5/14 | | 17/13 | | |
| | **No.** | **%** | **No.** | **%** | **No.** | **%** | |
| Surgery | 10 | 23.3 | 5 | 26.3 | 1 | 3.3 | $P$ = 0.045* |
| Blood transfusion | 7 | 16.3 | 2 | 10.5 | 1 | 3.3 | $P$ = 0.217 |
| Schistosomiasis | 4 | 9.3 | 0 | 0 | 5 | 16.7 | $P$ = 0.159 |
| Accidental puncture wound | 4 | 9.3 | 5 | 26.3 | – | | $P$ = 0.090 |
| Tattoo | 1 | 2.3 | 0 | 0 | – | | |
| Ear piercing | 19 | 44.2 | 9 | 47.4 | – | | $P$ = 0.816 |
| ALT > 21 U/L | 18 | 41.9 | 7 | 36.8 | 5 | 16.7 | $P$ = 0.071 |
| HBs-Ag | 12 | 27.9 | 3 | 15.8 | 8 | 26.7 | $P$ = 0.578 |
| Anti-HCV | 9 | 20.9 | 7 | 36.8 | 3 | 10.0 | $P$ = 0.077 |

*Significant association – = no data available
HBs-Ag = hepatitis B surface antigen Anti-HCV = antibodies to HCV
ALT = alanine aminotransferase

4.8% in the control patients [*15*]. Other recent studies which evaluated the prevalence of HCV markers in patients with LP gave different results from one area to another, ranging from 4% in eastern France to 38% in Spain [*16,17*]. These data suggest an association between LP and HCV infection.

A fortuitous association between LP and HCV appears unlikely because the prevalence of LP in the population is reported to be less than 1% [*17*]. In our study it was 0.169%, although it was limited to dermatology patients; nonetheless it was still far less than 1%. The reasons for the high prevalence of HCV infection in patients with LP and cutaneous vasculitis are not known. The role of HCV in the development of LP remains unclear. A suggested explanation is a possible alteration in epidermal antigenicity induced by HCV that can interact with activated T cells, which then increase their production of interferon-gamma, which in turn causes keratinocytes to express major histocompatibility antigens (HLA-DR) and to be destroyed by T cells [*14*]. However, the replication of HCV in skin and mucosal LP lesions has not been described.

In our study, 3 of the patients had oral erosive LP but none was seropositive for HBs-Ag and only 1 was positive for anti-HCV antibodies. This finding was also reported in a study of 180 patients with oral erosive LP who did not show significant association with liver dysfunction [*18*] unlike other reports which claim such an association [*14*]. This discrepancy could be be-

Table 2 **Virological data of cases of lichen planus (LP) and cutaneous vasculitis (CV)**

| Feature | Total (*n* = 62) | | HBs-Ag +ve (*n* = 9) | | Anti-HCV +ve (*n* = 10) | | Both +ve (*n* = 6) | | Both –ve (*n* = 37) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % | No. | % | No. | % |
| Age (years) | | | | | | | | | | |
| < 20 | 9 | 14.5 | 2 | 22.2 | 1 | 10.0 | 0 | 0 | 6 | 16.2 |
| 20–40 | 27 | 43.5 | 4 | 44.4 | 2 | 20.0 | 3 | 50.0 | 18 | 48.6 |
| > 40 | 26 | 41.9 | 3 | 33.3 | 7 | 70.0 | 3 | 50.0 | 13 | 35.1 |
| Mean age (range) | 36.9 (7–66) | | 31.3 (7–50) | | 46.9 (19–65) | | 44 (32–55) | | 34.5 (12–66) | |
| Male/female | 19/43 | | 4/5 | | 3/7 | | 2/4 | | 10/27 | |
| Educated | 17 | 27.4 | 4 | 44.4 | 2 | 20.0 | 1 | 16.7 | 10 | 27.0 |
| Surgery | 14 | 22.6 | 1 | 11.1 | 4 | 40.0 | 3 | 50.0 | 6 | 16.2 |
| Blood transfusion | 8 | 12.9 | 0 | 0 | 1 | 10.0 | 2 | 33.3 | 5 | 13.5 |
| Schistosomiasis | 5 | 8.1 | 1 | 11.1 | 1 | 10.0 | 1 | 16.7 | 2 | 5.4 |
| Diabetes | 6 | 9.7 | 1 | 11.1 | 3 | 30.0 | 2 | 33.3 | 0 | 0 |
| Accidental puncture wound | 10 | 16.1 | 2 | 22.2 | 1 1 | 0 | 2 | 33.3 | 5 | 13.5 |
| Tattoo | 1 | 1.6 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2.7 |
| Ear piercing | 27 | 43.5 | 3 | 33.3 | 6 | 60.0 | 3 | 50.0 | 15 | 40.5 |
| ALT > 21 U/L | 25 | 40.3 | 3 | 33.3 | 4 | 40.0 | 2 | 33.3 | 16 | 43.2 |
| LP/CV | 43/19 | | 9/0 | | 6/4 | | 3/3 | | 25/12 | |

F *(of mean ages) = 2.70* P *= 0.053*
*HBs-Ag +ve = positive for hepatitis B surface antigen by ELISA*
*Anti-HCV +ve = positive for antibodies to HCV by ELISA*
*ALT = alanine aminotransferase*

Table 3 **Results of the histopathological examination of the patients with cutaneous vasculitis**

| Histopathological reaction | Anti-HCV-positive (*n* = 7) | | HBs-Ag-positive (*n* = 3) | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Lymphocytic predominance | 3 | 42.9 | 1 | 33.3 |
| Leukocytoclastic vasculitis | 4 | 57.1 | 2 | 66.7 |

cause oral LP pathogenesis in hepatitis C is due to host factors induced by HCV infection rather than direct HCV participation. Similarly, we could not find an association between HBV or HCV infections and certain LP clinical variants or with cutaneous extension of LP lesions.

Cutaneous vasculitis has been reported as the initial manifestation of hepatitis C [*13*] and the activity of vasculitis does not

necessarily correlate with the activity of the patient's hepatitis [*19*]. In our study, 3 (15.8%) patients presenting with cutaneous vasculitis had HBs-Ag and 7 (36.8%) had anti-HCV antibodies. Anti-HCV antibodies were significantly higher than in the control group. However, confirmatory tests, e.g. HBV-DNA and HCV-RNA estimation, could not be carried out because of financial restrictions.

It has been suggested by Pakula et al. [*20*] that cutaneous vasculitis may result from cryoglobulinaemia related to chronic HBV infection. Similarly, the vasculitis in HCV infection is probably the result of cryoglobulins rather than a direct result of virus deposition in the vessel wall. Cryoglobulinaemia could be caused by the aggregation of immune complexes comprising of HCV and anti-HCV antibodies with IgA type rheumatoid factor that lead to cutaneous vasculitis [*21*]. The exact mechanism of vasculitis, however, remains unknown.

In our study, histopathological examination of tissue sections from the patients with cutaneous vasculitis revealed perivascular lymphocytic predominance in 42.9% of the anti-HCV-positive and in 33.3% of the HBs-Ag-positive subjects. Leukocytoclastic vasculitis was evident in 57.1% of the anti-HCV-positive and 66.7% of the HBs-Ag-positive cases. Since both pathological patterns of cutaneous vasculitis have been reported [*20,22*], we can assume that cutaneous vasculitis in patients infected with hepatitis virus evolves through various pathogenetic means.

In 1991, Hearth-Holmes et al. [*13*] proposed that hepatitis C be considered in the differential diagnosis of cutaneous vasculitis. Our study supports their suggestion and we consider that this should also be applied to patients with LP as these may be the dermatologic manifestations associated with HCV infection.

The high incidence of hepatitis B and C coinfection detected in our study (6 out of 62, 9.7%) and those of others [*23*] suggests that there is a common mode of transmission. It could be surgery as 3 of the 6 (50%) had had previous surgery. Another mode could be sexual transmission as all 6 patients were > 20 years old.

A substantial proportion of cases of sporadic hepatitis occur without obvious exposure. Acute hepatitis C is asymptomatic in more than 90% of the cases and usually goes undiagnosed. Although HCV accounts for most cases of transfusion-associated hepatitis, 90% of HCV cases are not connected with transfusion [*3*]. This is certainly the case in our study where only 4 of the 19 (21.2%) anti-HCV-positive patients had a history of transfusion.

There does not appear to be a correlation between HBV and HCV infections and elevated ALT levels as only 9 of the 23 HBs-Ag-positive (39.1%) and 8 of the 19 anti-HCV-positive (42.1%) subjects had elevated ALT levels. This has been reported in other studies where ALT levels were monitored for 6 months and were repeatedly normal in 5 of 50 (10%) volunteer blood donors with HCV infection [*24*]. Current screening methods are certainly more sensitive than elevated ALT levels in identifying HCV infections.

## Conclusions

In this study, we showed that the presence of cutaneous signs of LP or vasculitis should suggest to the dermatologist that a hepatitis virus may be a possible etiological or provocative agent and that such patients should be monitored with liver enzyme assessment for early detection and prevention of possible liver damage.

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## Correction

**Self-efficacy for dietary behaviour concerning heart disease among Alexandria school pupils by G.M. Mounir, I.M. Fatohy and N.H. Mahdy. EMHJ, Vol. 4 No. 3, December 1998, page 464.**

In the heading and footnotes of Table 7, $S_{\bar{x}}$ (B) should read SE (B)