CHRONIC HEPATITIS C INFECTION AND SKIN DISEASES: AN UPDATE

MAZEN S. DAOUD, MD*, SARAH M. DIETRICH, MD*, LAWRENCE E. GIBSON, MD*, SALEH DAOUD, MD. Ph.D.#

Department of Dermatology
*Mayo Clinic, Rochester MN, U.S.A**
AND
Department of Dermatology and Venereology
Damascus University, Damascus Syria#

Hepatitis C virus (HCV) is a lipid-enveloped, single-stranded RNA virus that is believed to be responsible for most cases of post-transfusion hepatitis as well as a large proportion of community acquired non-A non-B hepatitis. At least 60% of patients infected with HCV are infected by contaminated blood products or by intravenous drug abuse and less than 5% of patients are infected via sexual transmission (1). Recombinant immunoblot assay (RIBA) is a sensitive and specific technique that tests the antibody activity against four different HCV proteins (2). Reverse transcription polymerase chain reaction (PCR) detects HCV RNA, an indication of active viral replication. HCV genotyping and HCV RNA quantification will be the futurc tools for diagnosis and follow up after treatment in patients with chronic HCV infection.

This paper will focus on the skin diseases associated with HCV infection.

1. Porphyria cutanea tarda (PCT):

PCT is a rare disorder of porphyrin metabolism characterized by blisters on the exposed areas of the arms, forearms and dorsal hands (Figure 1), skin fragility, facial hypertrichosis and eventual dermal sclerosis. Laboratory findings show increased urinary uroporphyrin and/or increased fecal coproprophyrin excretion. PCT is either sporadic (type 1) when uroporphorinogen decarboxylase is deficient only in the liver, or familial

(type 2) when the enzyme is also deficient in non-hepatic tissues. PCT is exacerbated by toxic factors

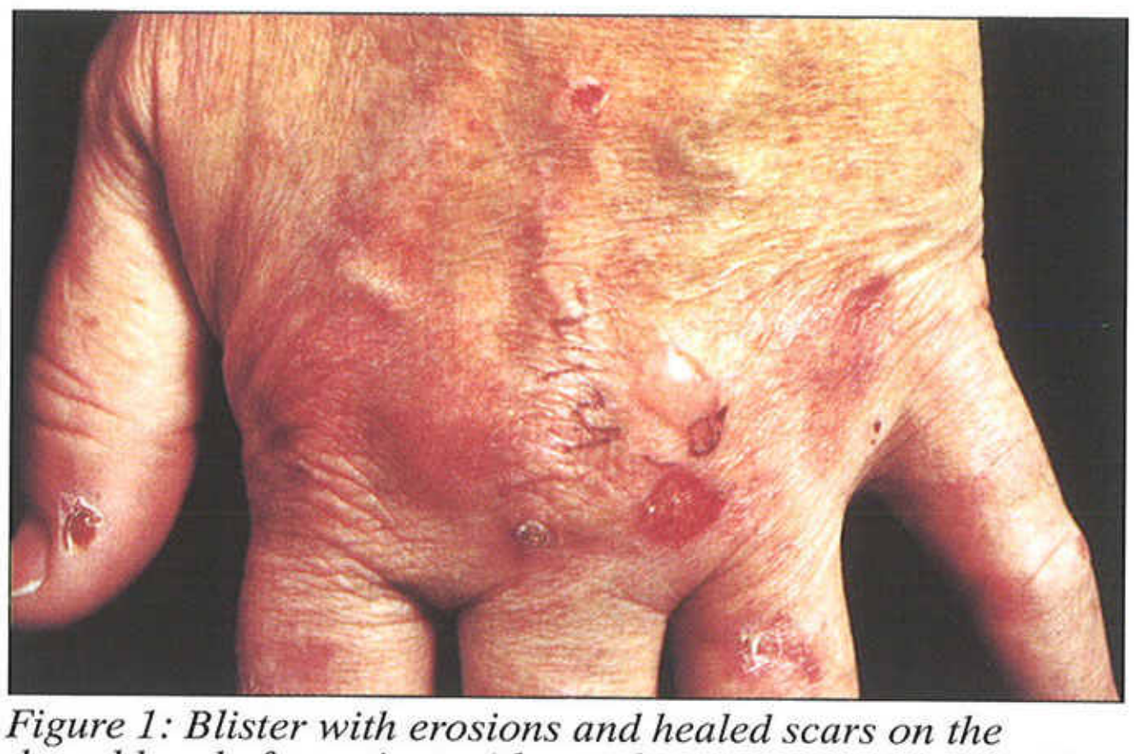

Figure 1: Blister with erosions and healed scars on the dorsal hand of a patient with porphyria cutanea tarda and HCV infection.

such as alcohol, estrogen, and drugs.

Infections, especially those which interfere with liver function, are known to cause exacerbation or initiate clinical disease in patients with PCT by unmasking the underlying porphyrin metabolic abnormality. Viral hepatitis B and/or C are examples of infections known to exacerbate PCT. PCT has recently been associated with chronic hepatitis C virus infection, especially in Europe (3-12) (Table 1).

Recently, we investigated the prevalence of HCV infection in patients with PCT in the United States (13). There were 36 patients (21 women and 15 men, average age 54 years). The diagnosis was established based on elevated uroporphyrins in 24-hour urine porphyrin studies in all 36 patients. No family history of PCT was present in any of these patients. 26 patients (72%) reported a history of alcohol use.

Risk factors for acquiring HCV infection were as follow: Four patients admitted a past history of intravenous drug abuse. Eight patients had a history of blood transfusion prior to the diagnosis of PCT and prior to 1989. Two other patients had a history of tattoo.

Six patients had anti-HCV antibody using a four-antigen RIBA-2. Indeterminate results were obtained in two others. All four patients with a history of IV drug abuse were positive for HCV antibody. None of the eight patients with a history of blood transfusion prior to 1989 were positive for HCV antibody. A history of blood transfusion was not helpful as a screening method to identify patients with HCV-associated PCT.

All patients who tested negative with RIBA-2

Reprint request:
Mazen S. Daoud, MD
Department of Dermatology
Mayo Clinic, 200 First Street, SW
Rochester, MN 55905, U.S.A

Table 1. Prevalence of hepatitis C in porphyria cutanea tarda from various studies around the world.

Reference	country	city	# patients	method	+HCV	(%) positive
3	France	Nice	13	RIBA	10	76%
4	France	Strasbourg	13	RIBA	7	58%
			13	PCR	7	58%
5	Italy	Milan	74	ELISA	56	76%
			74	RIBA	61	82%
			74	PCR	49	66%
6	Japan	Nagasaki	7		5	71%
7	Ireland	Dublin	20	ELISA	2	10%
				PCR	2	10%
8	Australia	Melbourne	112	ELISA	26	23%
9	Czech Republic	Praha	92	ELISA	20	22%
10	Germany	Berlin	106	RIBA	8	8%
			106	PCR	8	8%
11	Spain	Madrid	34	RIBA	21	62%
12	Spain	Madrid	34	RIBA	31	91%
			32	PCR	21	65%

were also negative by PCR. One of the two patients with indeterminate RIBA-2 results had HCV RNA detected by PCR, and the other patient had negative PCR results. The patients with positive RIBA-II were also positive for HCV RNA in the serum by PCR.

Liver enzymes (AST and ALT) are usually elevated during the initial visit when the diagnosis of PCT is made. This elevation varies between several units above normal limits to a 3-fold increase. The degree of elevation usually can not predict patients with HCV infection. Ferritin level is usually elevated, however, there is no clear evidence of hemochromatosis. Only one of the patients with a history of IV drug abuse had a concomitant infection with human immunodeficiency virus and HCV. No evidence for hepatitis B infection was seen.

Cessation of alcohol intake is recommended in all PCT patients with or without HCV infection. Significant improvement in skin lesions associated with a reduction in serum liver enzymes, reduction in ferritin level and reduction of urinary porphyrins was seen in four patients with HCV-associated PCT. Two patients were treated with a-interferon in addition to phlebotomy. One patient discontinued treatment because of financial reasons. The other patient's lesions cleared, and liver enzymes normalized after a few weeks of treatment with 3 million units of interferon a day and phlebotomy of 500 cc of blood a month to keep his hemoglobin around 12.0 to 12.5 g/dL.

Seven of our patients (19%) had evidence of HCV infection. This prevalence is much lower than reported in Southern European countries, however, similar rates are seen in Germany, Ireland, Australia, and Czech Republic. These regional differences in the prevalence of HCV infection in PCT could be related to the differences in HCV genotypes in each of these countries. HCV type 1a is the most common in the United States (62%), followed by type 1b (20%) (14). In Europe, types 2 and 3 are more common than in the U.S. It is possible that a specific genotype, perhaps more common in the Mediterranean countries, may be responsible for the high incidence of HCV-associated PCT. Other cofactor(s) such as genetic predisposition, certain HLA- types, or other concomitant hepatitis virus infection may add to the liver injury and unmask the clinical manifestations of PCT.

In conclusion, HCV is an important cause of liver injury leading to unmasking of underlying porphyrin metabolic abnormalities. However, not all patients with HCV infection develop frank PCT. In a review of 157 patients with documented HCV infection from our institution, only one patient had clear clinical and biochemical evidence of PCT (MSD, unpublished data).

The prevalence of alcohol use in patients with PCT is about 70%, varying between 40% and 70% in other studies (3-12). Alcohol is still the most important agent in precipitating PCT. All patients with

PCT and HCV infection reported alcohol use. It is possible that the additive liver toxicity from HCV and alcohol leads to the clinical manifestations of the disease in some patients. In others, alcohol alone or in combination with other hepatotoxic agents (medications, HIV, or others) is the triggering event.

2. Cryoglobulinemia and cutaneous leukocytoclastic vasculitis:

The association of HCV infection with leukocytoclastic vasculitis (LCV) and essential mixed cryoglobulinemia (EMC) has been well documented. Recently, we reported 12 patients (8 men and 4 women) with this triad (15). The majority of patients present with palpable purpura,

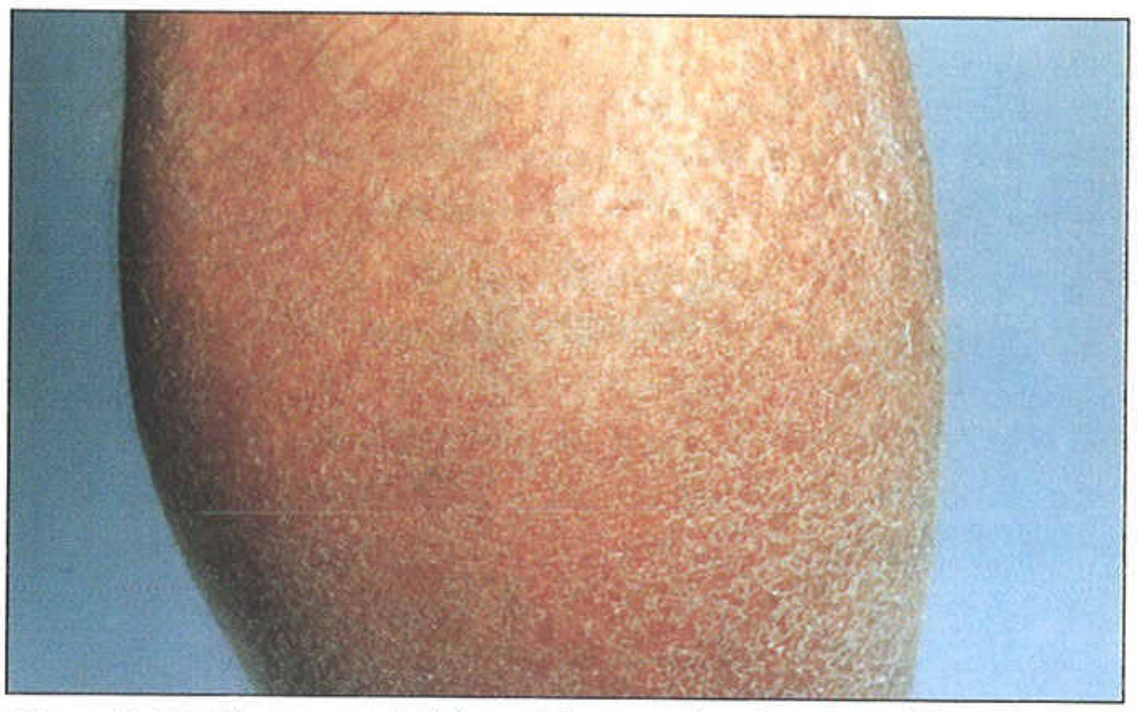

Figure 2. Red brown petechiae with excessive dryness of the skin on both legs of a patient with leukocytoclastic vasculitis, essential mixed cryoglobulinemia and HCV infection.

petechiae (Figure 2), papules and occasionally with ulcers. The lower extremities are the most common location (Figure 3), however, the trunk may be involved. The majority of patients present with a chronic history of recurrent eruptions. The mean duration of vasculitis prior to diagnosis is about 3 years. Intravenous drug abuse and blood transfusion are common risk factors for acquiring HCV infection in these patients. The average duration between the presumed acquisition of HCV and the appearance of skin lesions is quite lengthy and ranges between 10-18 years. Patients often complain of leg swelling, burning pain and paresthesia, and arthralgia.

Laboratory evaluation reveals an elevated liver enzymes and rheumatoid factor in almost all patients. Antinuclear antibody (ANA) is occasionally positive, however, in low titer. Complement studies usually show decreased total complement, however, we

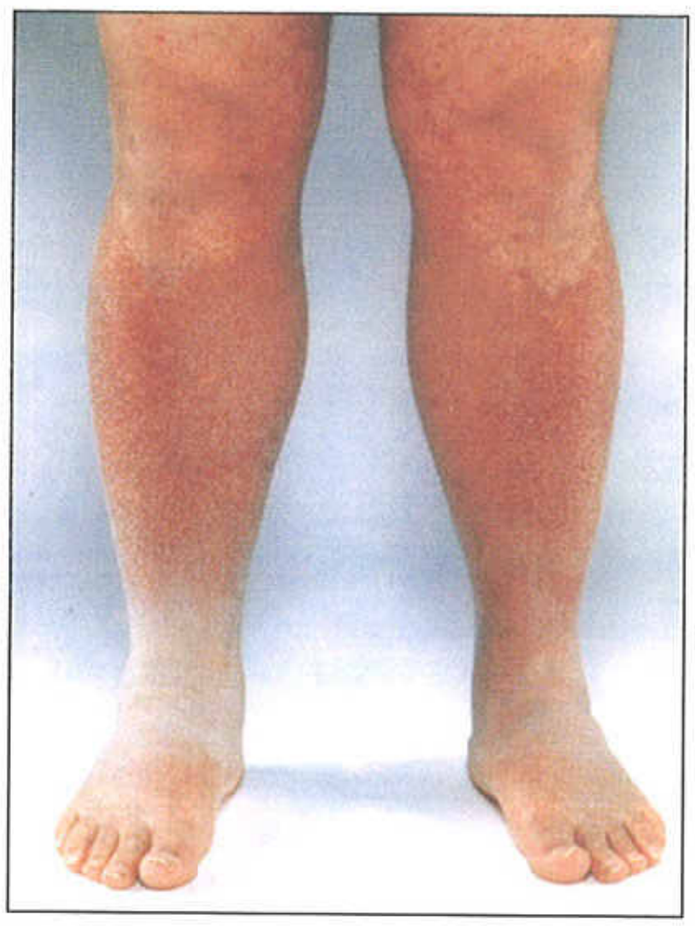

Figure 3. Same patient in Figure 2. Note the subtle symmetrical petechial eruptions that may resemble chronic stasis dermatitis. Discrete purpuric lesions are seen on the medial thighs.

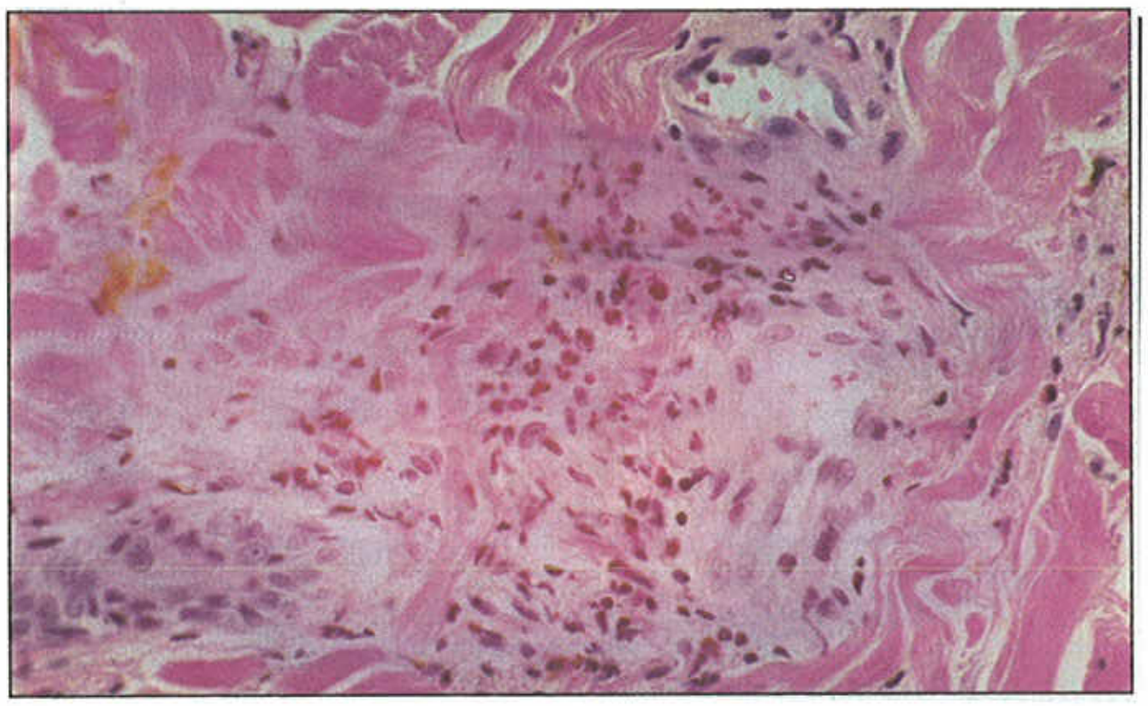

Figure 4. Hyalinized necrosis of blood vessel wall with nuclear dust and extravasation of red blood cells characteristic of leukocytoclastic vasculitis. Note the hemosiderin deposition in the dermis.

have seen a few patients with normal levels. C3 is usually within normal limits and C4 is almost always decreased.

Cryoglobulins are usually present in small amounts of the cryocrits. Immunoelectrophoresis reveals a monoclonal (usually IgM and rarely IgA) component and a polyclonal (usually IgG and rarely IgA or IgM) component. The diagnosis of cryoglobulinemia type II is characteristic.

Skin biopsy usually shows the characteristic changes seen in LCV such as fibrinoid necrosis of blood vessel walls with extravasation of red blood cells (Figure 4). Dermal hemosiderosis is promi-

nent and is caused by recurrent episodes of vasculitis and deposition of hemosiderin in the dermis and dermal macrophages. Nuclear dust is not a common feature. Liver biopsy may reveal a spectrum of changes ranging from mild hepatitis with mild piecemeal necrosis to chronic active hepatitis with cirrhosis.

Treatment with interferon result in prompt disappearance of skin lesions and normalization of cryoglobulinemia. Recurrence is possible after discontinuation of therapy.

In summary, the triad of LCV, EMC and HCV infection is a unique constellation of clinical and laboratory signs that should be recognized so early treatment can be initiated.

3. Leukocytoclastic vasculitis:

Since the description of the above triad we have encountered four patients with cutaneous LCV and chronic hepatitis C virus infection without evidence of cryoglobulinemia. These patients have a similar clinical and biochemical profile to those patients with the complete triad of LCV, EMC and HCV infection. In a review of 139 patients with cutaneous LCV, 15 patients (11%) presented with this triad (16). Two patients presented with cutaneous LCV and viral hepatitis (one with hepatitis B and one with hepatitis C) but no cryoglobulinemia. Similarly, five patients present with LCV and cryoglobulinemia, but without evidence for hepatitis C infection. We consider these cases to represent incomplete forms of the triad. We postulate that adequate follow up may reveal the complete triad of this syndrome.

4. Cutaneous periarteritis nodosa (PAN):

Cutaneous PAN is a well recognized vasculitid that affects medium-sized vessels without systemic involvement distinguishing it from systemic PAN. Hepatitis B virus occurs in 10% to 55%, and HCV infection occurs in 5% to 20% of patients with systemic PAN (17). Cutaneous manifestations of systemic PAN include palpable purpura, livedo retcularis, and occasionally subcutaneous nodules and ulcerations.

There is no convincing evidence in the literature to link HCV infection with cutaneous PAN. Recently we reviewed our experience with 79 patients with cutaneous PAN (18).

HCV antibody was checked in 39 patients and was negative in all except one patient. This patient had typical pathologic findings of cutaneous PAN with inflammation of a medium-sized artery at the deep dermal level. The patient also had cryoglobulinemia (essential mixed type II), elevated rheumatoid factor, and decreased C4. We considered this form of vasculitis to be a subset of the triad of HCV, cryoglobulinemia, and cutaneous vasculitis rather than a subset of cutaneous PAN with HCV infection. We believe that HCV infection is generally not associated with cutaneous PAN.

5. Lichen planus (LP):

The association between liver disease and LP has been a controversial issue for the last two decades. The majority of these studies sought an association between LP and chronic active hepatitis regardless of its cause. Recently, patients with HCV-associated LP were described (2,19,20). Generalized cutaneous LP and mucocutaneous LP were felt to be associated with HCV infection (2). In a study of 78 patients with cutaneous and mucosal LP from Spain, 16 patients (20%) had positive antibodies to HCV. In 13 of these 16 patients, HCV-RNA was detected in the serum by PCR (21). Abnormal liver enzymes were found in all of these 13 patients in contrast to 20% of patients in the control group. Buccal mucosal involvement was seen in 11 of 13 patients. Erosive LP was present in 38% of HCV-associated LP as compared to 12% in LP without HCV infection. The clinical morphology of LP lesions are similar regardless of HCV infection status (Figures 5 and 6).

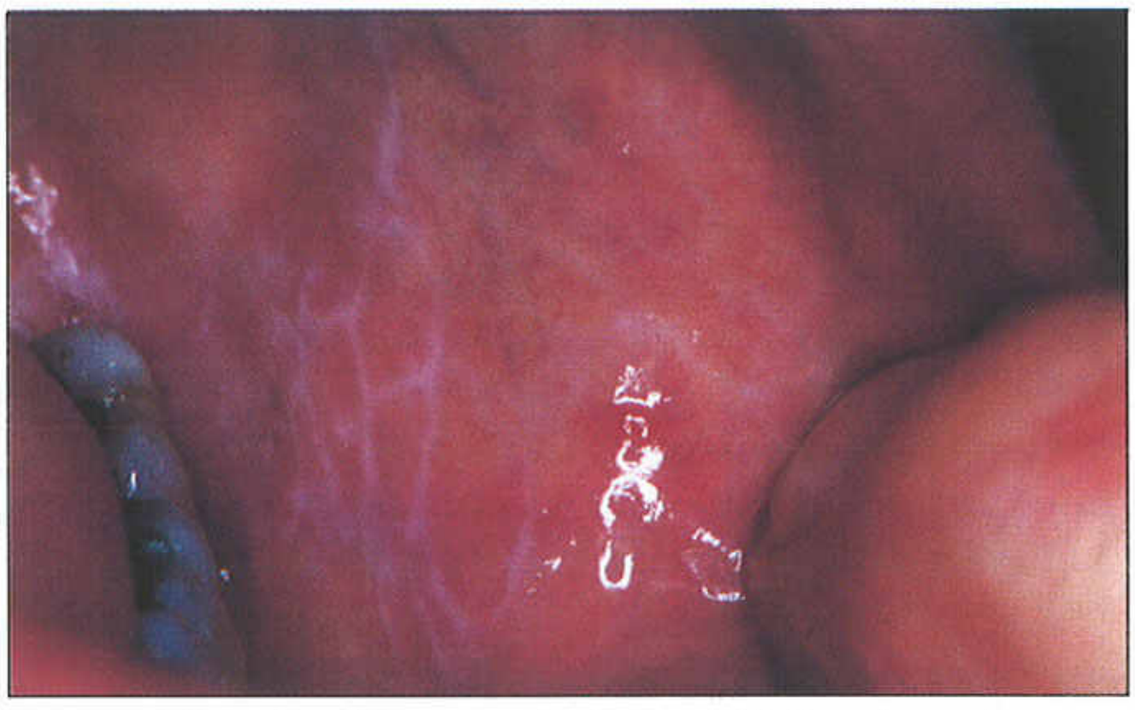

Figure 5. White, lace-like network of mucosal lichen planus in a patient with HCV infection.

Similar results are seen from a similar study in a study from Italy (22). HCV genotypes found in

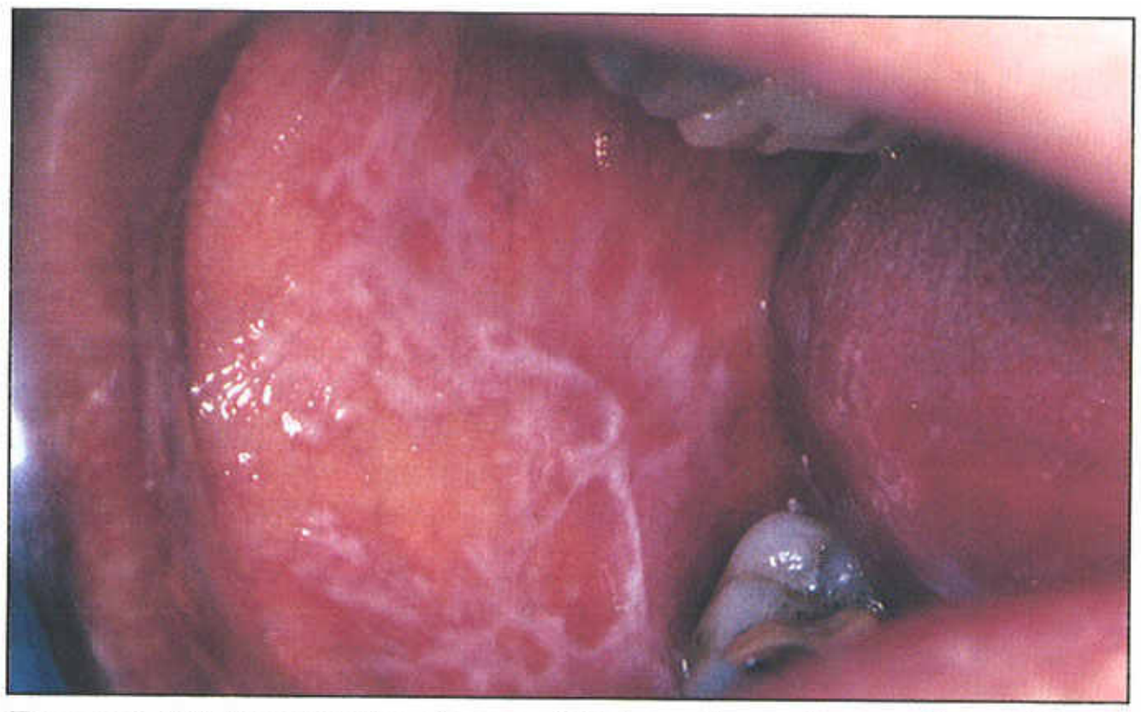

Figure 6. White reticular plaque of lichen planus in a patient with HCV infection.

patients with LP do not differ from those seen in patients with HCV infection without associated LP (23).

The diagnosis of LP is usually made simultaneously with, or occasionally many years after the diagnosis of liver disease. On the other hand, only 5% of patients with chronic HCV infection have LP, however, this is still higher than that seen in the general population (23).

In summary, we agree with Rebora (24) that the etiopathogenetic role of HCV in LP cannot be denied. However, it should be considered that the majority of cases of HCV-associated LP come from the Mediterranean area where the prevalence of HCV infection is higher. In a random survey of 100patients from Italy attending a dermatology clinic (24), eight were anti-HCV antibody positive. 20% of healthy controls in one study from Spain has elevated liver enzymes (21). It seems that patients with erosive LP, mucosal LP, and chronic generalized cutaneous LP are at higher risk. Further case-controlled studies are needed to better define this relationship.

6. Behcet's syndrome:

The association between HCV infection and Behcet's syndrome is controversial. Two studies of more than 235 patients with Behcet's syndrome demonstrated no increase prevalence of HCV infection as compared with the general population (25)

7. Sialoadenitis:

Recent studies have shown an association between HCV infection and sialoadenitis. Labial biopsy was obtained from 22 patients with chronic hepatitis C infection. A mild degree of sialoadenitis was present in 17 patients (77%) (26). The vast majority of these biopsies (15 of 17) showed mild inflammation. In contrast to findings in patients with Sjogren's syndrome, the majority of these patients were male, had negative ANA, had lower frequency of HLA-DR3 and showed mild inflammation on biopsy. In Sjogren's syndrome the majority of patients are female with positive ANA and HLA-DR3 and the lymphocytic inflammation is usually more intense.

It is yet to be proven whether these changes are clinically relevant and whether they are specific for HCV infection. Further studies are needed to confirm this association.

8. Urticaria:

In one recent study (27), 79 Japanese patients with urticaria were evaluated for the presence of serum HCV antibody and serum HCV RNA by PCR analysis. 19 of those 79 patients (24%) had positive antibody to HCV and 17 of them had positive HCV RNA by PCR. The HCV-associated urticaria patients were older and their eruptions lasted longer than patients without HCV infection. Liver enzymes were elevated at presentation in the former group.

To our knowledge this is the only study that shows such a high association between HCV and urticaria. More studies are needed to confirm this association.

9. Gianotti-Crosti syndrome (GCS):

The association between Gianotti-Crosti syndrome (papular acrodermatitis) and hepatitis B infection is well known. There are no reports yet of association between GCS and HCV infection.

Conclusion:

There are a growing number of skin diseases reported with HCV infection. Strong association is seen with cryoglobulinemia with or without cutaneous LCV and a search for HCV infection is mandatory in patients with cryoglobulinemia and LCV. HCV can unmask an underlying porphyrin metabolism abnormality causing clinical PCT. The prevalence of HCV infection in patients with PCT varies around the world. We still recommend a search for

HCV infection in all patients with PCT.

The clinician should maintain a high index of suspicion in patients who present with recent unexplained onset of LP, urticaria, erythema nodosum, sialoadenitis, or papular acrodermatitis (Gianotti-Crosti syndrome). Some of these skin diseases may lead to a rapid detection of HCV infection, which often results in more successful treatment.

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