Eur J Dermatol 2003; 13: 302–4

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Article accepted 14/02/2003

Porphyria cutanea tarda, dermatomyositis and non-Hodgkin lymphoma in virus C infection

Virus C infection has been associated with a broad spectrum of extrahepatic diseases such as essential mixed cryoglobulinemia, membranous glomerulonephritis, vasculitis, rheumatoid arthritis and lupus erythematosus. The etiologic role of virus C has also been observed in some neoplasms such as non-Hodgkin's lymphoma and the monoclonal gammapathies. Many studies also support the link between this virus and porphyria cutanea tarda (PCT). Isolated cases suggest a relationship with dermatomyositis. Herein, we report the coexistence of PCT, non-Hodgkin's lymphoma and dermatomyositis in the same patient affected with virus C infection which has never previously been described.

Key words: porphyria cutanea tarda, dermatomyositis, lymphoma, virus C

Case report

A 57-year-old male patient, without known risk factors, was affected with chronic hepatitis C virus (HCV) infection for five years under treatment with IFN-alpha 3×10^6 IU three times a week for two years. He also presented a two-year history of non-Hodgkin's lymphoplasmocytoid lymphoma stage IV A (axillar and cervical lymphadenopathies, liver and splenic infiltration), treated with CHOP (cyclophosphamide, adriamicin, vincristine and prednisone) chemotherapy with complete remission for one year. He consulted with crops of blister-like lesions on the back of the hands and arms *(Fig. 1)*, and hypertrichosis in both malar regions during the previous month. A concentration of 8930 micrograms/24 hours uroporphyrins (0-40 micrograms/24 h) was detected in urine with normal coproporphyrin and porphobilinogen concentrations which confirmed the suspected diagnosis of porphyria cutanea tarda (PCT). Ferritin levels were 1270 ng/ml (70-435 ng/ml). One month later the patient presented with a cervical bultoma diagnosed as recurrence of his lymphoma after lymph node biopsy. At the same time, the patient presented asymptomatic maculo-erythematous lesions on the back of the interphalangeal, metacarpophalangeal and elbow joints (Gottron's sign) *(Fig. 2)*, a poikilodermic plaque on the scalp *(Fig. 3)*, palpebral violaceous erythema and periungual telangiectasias that had developed in the previous weeks. In addition, the patient complained of intense muscular weakness in the scapular and pelvic muscles and also dysphagia for liquids. These clinical manifestations were associated with abnormal muscular enzyme tests; slightly raised creatin phosphokinase (CPK): 139 (0-130), liver function tests: AST 52 (1-25) and ALT 66 (1-29), with normal LDH and aldolase levels and the presence of antinuclear antibodies (ANA) at a titer of 1/80 with negative extractable nuclear

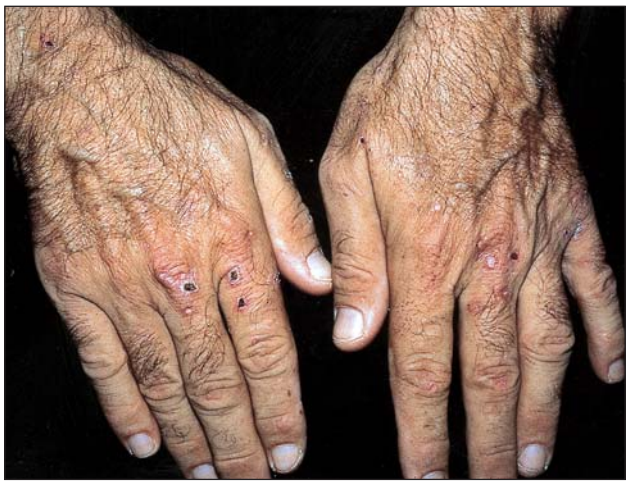

Figure 1. *Multiple crusts and millium cysts on the back of the hands.*

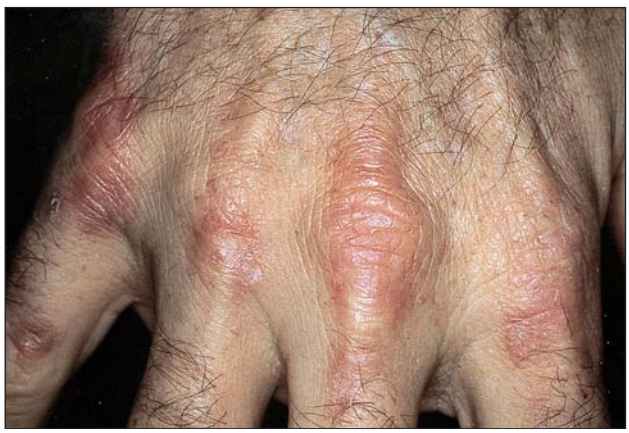

Figure 2. *Gottron's sign on the back of the metacarpophalangeal joints.*

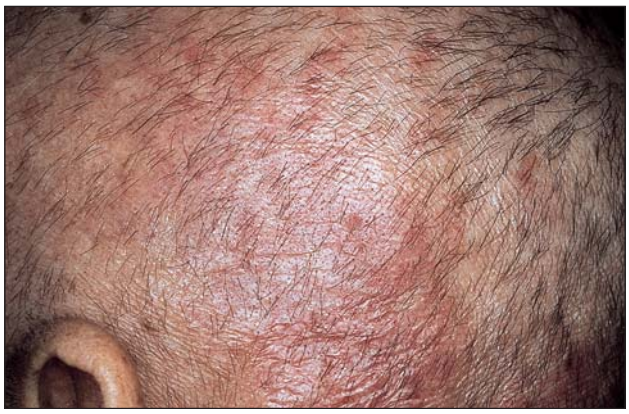

Figure 3. *Poikilodermic plaque located on the scalp.*

antibodies (ENA). A skin biopsy from the hand lesions showed epidermal necrosis with the presence of a subepidermal bulla infiltrated by neutrophils, capillary trombosis and an inflammatory infiltrate in the dermis composed of neutrophils and eosinophils. Direct immunofluorescence showed linear deposition of IgG, IgA, C3 and C1q along the basal membrane and around vessels. All these findings suggested the diagnosis of dermatomyositis. The patient refused further diagnostic tests. After starting chemotherapy with CHOP, partial remission (50% reduction of the cervical mass) of the lymphoma was achieved, with a recovery of the muscular strength, disappearance of the skin lesions and improvement of some analytic parameters: reduction of uroporphyrins (1767 micrograms/24 hours), normalization of CPK with persistence of ANA (1/80) and raised AST and ALT.

Infection by HCV is a frequent cause of post-transfusion hepatitis and the commonest cause of chronic viral hepatitis. Chronic HCV, leads to the appearance of cirrhosis and hepatocellular carcinoma and may encourage the development of a sustained immune response *(Table I)* [1], by stimulating the lymphocytes, with the appearance of a wide range of autoimmune diseases *(Table II).* The association between virus C and certain extrahepatic diseases has been strongly demonstrated, whereas in other cases this relationship is weaker *(Table II)* [2].

The simultaneous presence in one patient with chronic HCV of B cell lymphoma, PCT and dermatomyositis has never been described before. In this case, HCV could be considered the causal factor of all three pathologies, each of which has individually been associated with this virus in the literature. Regarding PCT, the association with HCV is well known [3]. In southern Europe, 70-90% of patients with porphyria have HCV. There are two hypotheses about the way this virus may trigger porphyria: by the increase in oxidative stress in the hepatocytes (the most important mechanism), or by the development of autoantibodies which inhibit uroporphyrinogen decarboxylase [2]. Other factors are probably implicated. Regarding lymphoma, a prevalence of 20-40% of virus C antibodies has been found in patients with low grade B lymphoma, above all if these are associated with cryoglobulinemia or if they are gastrointestinal MALT (mucosal associated lymphoid tumors). This association can be explained by a maintained proliferation of B cells by the virus, with the development of monoclonality [2]. Perhaps the weakest association of HCV is with dermatomyositis/polymyositis which has not properly been demonstrated [4, 5].

None the less, the lymphoma might be the triggering factor for porphyria and dermatomyositis in this case. This hypothesis would be supported by the appearance of the two diseases when the lymphoma recurred, and by the clinical and analytical improvement when chemotherapy was given, without receiving any other specific treatment for these two diseases. Many studies associate dermatomyositis with neoplasms [6], and some suggest a possible relationship between PCT and certain extrahepatic tumors [7], including lymphoma [8]. Some authors even recommend a full clinical check for lymphomas in patients with PCT [7].

Besides, the appearance of PCT together with autoimmune diseases has also been described, particularly with

Table I. *Serologic findings associated with virus hepatitis C infection*

Antinuclear antibodies
Anticardiolipin antibodies
Antithyroid antibodies
Anti-smooth muscle antibodies
Anti-liver/kidney/microsomal antibodies
Rheumatoid factor

Table II. *Extrahepatic diseases or manifestations associated with virus hepatitis C infection*

Autoimmune	Non autoimmune
Mixed Cryoglobulinemia*	Mucosal-associated lymphoid tumors (MALT)
Autoimmune thyroiditis*	Non-Hodgkin B-cell lymphoma +
Membranoproliferative glomerulonephritis +	Porphyria cutanea tarda
Lichen planus	Plasmocytoma
Erythema multiforme +	Pruritus
Autoimmune thrombocytopenic purpura	Necrolytic acral erythema
Lymphocytic syaloadenitis (Sjögren's like) +	
Urticaria +	
Rheumatoid arthritis +	
Mooren's corneal ulcer	
Leukocytoclastic vasculitis +	
Antiphospholipid syndrome	
Erythema nodosum +	
Dermatomyositis/polymyositis	
Vitiligo	
Behçet's syndrome	
Polyarteritis nodosa	
Systemic lupus erythematosus	
Canities	
Hyde's prurigo nodularis	

* Documented or highly probable association [14]
\+ Frequently related to mixed cryoglobulinemia [14]

systemic lupus erythematosus [9], but also with hemolytic anemia, sclerodermia and in a single case with dermatomyositis [10].

Lastly, IFN treatment, that was started two years before the appearance of the PCT, might be responsible for the development of PCT and dermatomyositis. Previous reports have suggested these associations [11, 12] and some authors recommend that patients treated with IFN should be monitored for signs and symptoms of autoimmunity [13]. For this reason the use of IFN-alpha in the treatment of autoimmune diseases associated with HCV is controversial [1]. Treatment with corticosteroids, azathioprine and cyclophosphamid has proved effective, although the viremia persists or may worsen [1].

In conclusion, we consider that the clinical manifestations secondary to HCV infection are taking on increasing importance for the dermatologist, and it is therefore vital to gain a better understanding of this issue. In this case, we show the simultaneous presence of dermatomyositis and PCT associated with HCV infection, lymphoma and/or IFN treatment. We believe that only the description of similar cases will enable us to shed more light on the etiologic role played by virus C infection, IFN and/or lymphoma, together or singly, in the simultaneous occurrence of these diseases. ■

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