

Case Report

A Case of Cutaneous Vasculitis with Underlying Hepatitis C and Cryoglobulinaemia

Cheryl Groves, Clare Devereux, Clifford McMillan.

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ABSTRACT

We report a 74 year old lady presenting with cutaneous leukocytoclastic vasculitis. The underlying aetiology was established as chronic hepatitis C infection with associated cryoglobulinaemia. This presented clinically as recurrent cutaneous vasculitic eruptions with absence of any other clinical manifestations. In this case, antiviral treatment to eradicate hepatitis C virus (HCV) was deemed inappropriate given the low necroinflammatory score determined by liver biopsy, absence of other systemic sequelae of cryoglobulinaemia and potential risks of therapy given her age. Currently her cutaneous disease is relatively well controlled with intermittent application of potent topical steroids. This case highlights the need to consider hepatitis C as a potential aetiological factor in all patients with cutaneous vasculitis. We suggest that viral hepatitis screening should be routine in all patients presenting with cutaneous vasculitis.

INTRODUCTION

Cutaneous vasculitis is a common diagnosis encountered in routine dermatology practice. Underlying autoimmune diseases, malignancy, drugs and systemic vasculitis are often found to be aetiological factors. Infections also play a major role including streptococcus, staphylococcus, mycobacterium and hepatitis B or C^{1,2}. We present a case of occult chronic hepatitis C with associated cryoglobulinaemia manifesting as a cutaneous leukocytoclastic vasculitis in an elderly lady.

CASE REPORT

A 74 year old lady presented to dermatology out-patients with



Fig 2. Close up view showing vasculitis

an eight year history of a recurrent tender, non-blanching, palpable, purpuric rash involving her lower limbs (figs 1 and 2). A diagnostic punch biopsy revealed a leukocytoclastic vasculitis. She had no significant medical history and denied systemic upset, recent infections or new medications.



Fig 1. Lower limbs showing vasculitis

Laboratory investigations confirmed normal full blood count, renal, liver and thyroid function with an absence of microscopic haematuria and red cell casts on urinalysis testing. Inflammatory markers, autoimmune screen, double stranded DNA, pANCA and cANCA were all negative and remained so on repeated sampling. Normal anti-streptolysin O

Department of Dermatology, Belfast HSC Trust, Belfast City Hospital Campus, Lisburn Road, Belfast BT9 7AB, United Kingdom

Correspondence to Dr Groves

Cheryl_groves2003@yahoo.com.au

titre, complement and immunoglobulin levels were reported. Chest radiograph was normal. Rheumatoid factor was positive. Chronic hepatitis C virus infection was confirmed by enzyme immunoassay and reverse-transcriptase polymerase chain reaction. The virus was typed by limited sequencing of the 5' non-coding region of the virus and was confirmed as genotype 2. The HCV specific antibody level was abnormally low, in keeping with immune-complex sequestration.

Given the association between hepatitis C infection and type II [mixed] cryoglobulinaemia, the presence of serum cryoglobulins was sought and detected. A diagnosis of hepatitis C related cryoglobulinaemic cutaneous vasculitis was made. Her only risk factor for contraction of hepatitis C was a blood transfusion received in 1954 in the United States following a spontaneous abortion.

She was referred to the regional hepatology unit for further assessment including consideration of hepatitis C eradication therapy. Subsequent liver biopsy revealed changes consistent with chronic hepatitis C infection with a necroinflammatory score of only 1 out of a possible 8 and a modified staging score of 0. Eradication of hepatitis C virus with interferon 2 alpha plus ribavirin was deemed inappropriate in this patient given the low necroinflammatory score on liver biopsy, the absence of other systemic sequelae of cryoglobulinaemia and potential risks of therapy. Intermittent use of potent topical steroids has to date controlled exacerbations of her cutaneous vasculitis and prevented progression to ulceration.

DISCUSSION

At the time of initial presentation to dermatology out-patients there was no reason to have a clinical suspicion of chronic hepatitis C infection in this otherwise healthy elderly woman. A study of hepatitis C in Northern Ireland by McDougall³ described 78% of patients as asymptomatic at the time of diagnosis - a figure substantiated by earlier studies^{3,4}. An increased awareness of HCV infections' cutaneous manifestations may enhance its chances of detection.

Our patient presented with palpable purpura but this is just one such cutaneous indication of underlying hepatitis C infection. Others include livedo reticularis, urticaria, lichen planus, erythema multiforme, erythema nodosum and porphyria cutanea tarda⁵⁻⁸.

Subsequent detection of cryoglobulins in our patient confirmed the underlying pathology responsible for the leukocytoclastic vasculitis. Cryoglobulins are immunoglobulins that precipitate at temperatures below 37°C and re-dissolve with warming. Cryoglobulinaemia can manifest in two ways. Firstly, by precipitation and obstruction of small blood vessels in the peripheries [feet, hands, nose and ears] resulting in cutaneous ischaemia and possible infarction. Secondly, by deposition as immune complexes thereby initiating a leukocytoclastic vasculitis. Depending on the site of deposition, various clinical entities may arise – palpable purpura, arthritis, glomerulonephritis or peripheral neuropathy. Our patients' vasculitis was limited to cutaneous involvement.

Cryoglobulinaemia is classified into three types. Type I consists of a single monoclonal immunoglobulin [Ig], usually a paraprotein, which is associated with haematological

disorders. Type II is characterised by polyclonal IgG rheumatoid factor and monoclonal IgM rheumatoid factor. Polyclonal IgG and IgM rheumatoid factors are found in type III. Types II and III are known as mixed cryoglobulinaemia and can be associated with several conditions. Haematological associations include lymphoma and myeloma. It also exists with autoimmune disorders such as rheumatoid arthritis and systemic lupus. Infections implicated include parasitic, bacterial and viral infections, of which HCV is more common than hepatitis B virus.

Essential mixed cryoglobulinaemia is a term used to describe mixed cryoglobulinaemia occurring without identification of a primary disease. Evidence suggests that HCV infection may well be responsible for a majority of those cases previously defined as 'essential'. Anti-HCV antibodies are found in 70-100% of patients with mixed cryoglobulinaemia¹⁰. Contrastingly, among patients with chronic HCV infection, one third to one half have serological markers of cryoglobulinaemia but the clinical syndrome of mixed cryoglobulinaemia, as manifested in this case, occurs rarely in only 1-2%^{11,12}.

The definitive management of hepatitis C related cryoglobulinaemia is by eradication of the virus with subsequent suppression of the cryoglobulinaemic process. Use of pegylated interferon alpha [IFN-alpha] 2a or 2b in combination with ribavirin has been shown to be effective with sustained virological response [defined as undetectable viraemia 24 weeks after the end of therapy] reported as 76% using 24 weeks of IFN-alpha 2a plus ribavirin and 82% using IFN-alpha 2b plus ribavirin for the genotype group applicable to our patient - genotype 2 or 3^{13,14}.

The decision not to offer IFN-alpha combined with ribavirin therapy to this patient was based on her age, low necroinflammatory score on liver pathology and risk of significant side effects such as myelosuppression, polyarthritis, thyroiditis and peripheral neuropathy. Alternative therapies which have been implemented for cutaneous mixed cryoglobulinaemia are systemic prednisolone, azathioprine, mycophenolate, dapsone or plasmapheresis. More recently, rituximab has been used successfully¹⁵.

Currently, this lady's flares of cutaneous vasculitis are successfully treated to resolution with topical agents only. If, however, the cutaneous features become unresponsive to topical measures or further sequelae of cryoglobulinaemia should develop, further consideration will be given to treatment with pegylated IFN-alpha combined with ribavirin or alternatively a systemic immunosuppressant agent.

In summary, our case report highlights the interesting association between hepatitis C virus, cryoglobulinaemia and leukocytoclastic vasculitis. Heightened awareness of all the cutaneous manifestations of hepatitis C can only serve to increase the diagnostic rate of a notoriously clinically silent infection. Although cutaneous vasculitis is a relatively common clinical presentation, this case emphasises the need to perform full screening investigations to exclude the least prevalent aetiologies and to consider underlying hepatitis C infection, even in those you least suspect.

The authors have no conflict of interest.

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