Hepatitis C mixed cryoglobulinemia with undetectable viral load: A case series

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Key words: hepatitis C mixed cryoglobulinemia vasculitis; undetectable viral load.

INTRODUCTION

Mixed cryoglobulinemic vasculitis is caused by circulating cold-precipitable immunoglobulins, or cryoglobulins, composed of monoclonal (type II) or polyclonal (type III) IgM directed against a polyclonal IgG. It causes palpable purpura and has long been associated with hepatitis C virus (HCV) infection. The initial theory regarding the new antiviral medications, which have been so successful in treating hepatitis C, was that once the HCV was treated, the mixed cryoglobulinemic vasculitis would also resolve. Although initial studies confirmed this theory, later studies found that the vasculitis is persistent in some patients despite successful HCV treatment. Vasculitis occurred within months after treatment of HCV infection in most cases in the literature, but we present 3 cases of mixed cryoglobulinemic vasculitis months to years after successful HCV treatment and negative viral load and a review of the current literature.

Abbreviations used:

DAA: direct-acting antiretrovirals
HCV: hepatitis C virus
LCV: leukocytoclastic vasculitis

REPORT OF CASES

Case 1

A 54-year-old man with history of hepatitis C treated with peginterferon α-2a, ribavirin, and telaprevir with undetectable viral load since 2012, presented in February 2016 with a rash on his legs for 6 weeks. He presented with a similar rash annually for about 4 years, which was diagnosed as vasculitis and successfully treated with prednisone each time. Physical examination showed erythematous nonblanching papules and patches on his lower legs and medial thighs (Fig 1). Punch biopsy results were consistent with leukocytoclastic vasculitis (LCV), and direct immunofluorescence showed an IgM-mediated vascular inflammatory process. Laboratory values showed positive rheumatoid factor and cryoglobulins. His HCV viral load was undetectable. He was given 2 prednisone tapers followed by 2 infusions of 1 g of rituximab separated by 2 weeks with gradual improvement. Four months after his last rituximab infusion, the patient had another flare of cutaneous vasculitis and was treated with a prednisone taper and 2 additional rituximab infusions. His skin remained clear at last follow-up.

Case 2

A 51-year-old white man with a 1-year history of LCV presented with positive type II cryoglobulins and HCV viral load of 1.9 million IU/mL in December 2009. Over the next 2 years, he was admitted for renal failure multiple times owing to cryoglobulinemia, treated with plasmapheresis, intravenous immunoglobulin, and rituximab. His HCV was treated with peginterferon α-2a and ribavirin twice, with telaprevir added on the second round, completed in 2012.

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Funding sources: None.

Conflicts of interest: Dr Caster receives research support from Mallinckrodt pharmaceuticals and support from the National Institutes of Health 1K08DK102542-01A1. The rest of the authors have no conflicts to disclose.

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JAAD Case Reports 2018;4:684-7.
2352-5126

https://doi.org/10.1016/j.jdcr.2018.04.004

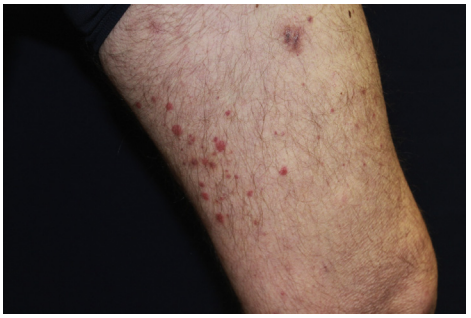

Fig 1. Mixed cryoglobulinemic vasculitis. Patient 1: physical examination found erythematous nonblanching papules and patches on lower legs and medial thighs.

All subsequent measurements of HCV viral load showed undetectable levels. However, he continued to have admissions for acute kidney injury, fevers, and rash associated with positive serum cryoglobulins whenever attempts were made to reduce plasmapheresis treatments to fewer than once a week. He was started on cyclophosphamide and corticosteroids in June 2013 in addition to continuation of weekly plasmapheresis, in an attempt to reduce cryoglobulin production. He was subsequently treated with azathioprine, cyclophosphamide, mycophenolate mofetil, and finally rituximab in 2015. This treatment led to a brief remission of symptoms, but rituximab was required again after a relapse in May 2016. Rituximab has improved clinical symptoms, but the patient remains plasmapheresis dependent.

Case 3

A 60-year-old white woman with a history of LCV manifested as livedo reticularis, mixed cryoglobulinemia (MC), and HCV treated with ribavirin and peginterferon α-2a presented in 2015 with livedo reticularis, increased creatinine, and proteinuria. Her HCV viral load had been undetectable since treatment was completed in 2009 and remained undetectable during this acute flare of MC. A kidney biopsy found membranoproliferative glomerulonephritis with features suggestive of cryoglobulinemic glomerulonephritis (Fig 2). Kidney electron micrograph showed granular to coarsely granular subendothelial and mesangial deposits, suggestive but not diagnostic for cryoglobulinemia (Fig 3). She was treated with corticosteroids and 4 doses of 500 mg of rituximab weekly, after which the rash resolved, and rheumatoid factor, complement levels, and urine protein returned to normal. Ten months later, she remained asymptomatic, and laboratory evaluation for cryoglobulinemia was negative (See Table I for a summary of these cases in addition to a summary of cases in the literature.).

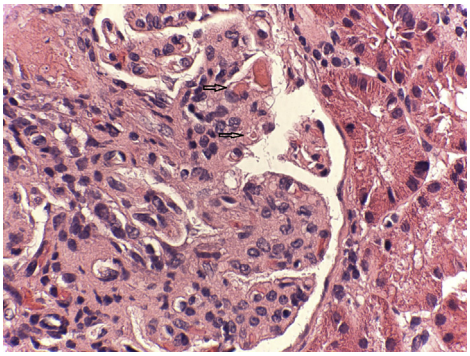

Fig 2. Cryoglobulinemic glomerulonephritis. Patient 3: kidney biopsy found membranoproliferative glomerulonephritis with cryoglobin plugs/hyaline thrombi (*arrows*), suggestive of cryoglobulinemic glomerulonephritis. (Hematoxylin-eosin stain; original magnification: ×60.)

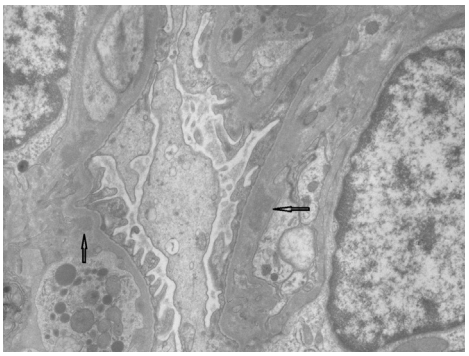

Fig 3. Cryoglobulinemia. Patient 3: electron microscopy. Kidney electron micrograph shows granular to coarsely granular subendothelial and mesangial deposits (*arrows*) suggestive of but not diagnostic for cryoglobulinemia.

DISCUSSION

With the advent of direct-acting antiretrovirals (DAA) for hepatitis C infection, many patients who would have otherwise had chronic hepatitis C and the long-term sequela have had sustained viral response and clinical remission of disease. Direct-acting antiretrovirals are molecules that target specific nonstructural proteins of the virus and result in disruption of viral replication and infection. The first DAAs for hepatitis C were protease inhibitors, telaprevir and boceprevir, usually used in conjunction with peginterferon and ribavirin.[1] These are rarely used now because of the introduction of more potent and better-tolerated DAAs, which can be used without interferon, and, in many cases, ribavirin.

MC is an autoimmune disorder associated with hepatitis C that has significant morbidity and mortality.[2] Historically, renal involvement is found to be the