Case Report

Remission of refractory hepatitis C-negative cryoglobulinaemic vasculitis after rituximab and infliximab

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Keywords: cryoglobulinaemia; glomerulonephritis; infliximab; rituximab; tumour necrosis factor; vasculitis

Introduction

Cryoglobulinaemia is an immune complex-mediated disease characterized by immunoglobulins that precipitate in the cold, and is usually associated with inflammatory manifestations. Three types of cryoglobulinaemia are recognized according to the cryoprecipitated immunoglobulins. In type I, a monoclonal immunoglobulin is identified. In types II and IIIa, two classes of immunoglobulins are present: a polyclonal IgG and an IgM with rheumatoid factor activity, the latter either monoclonal in type II or polyclonal in type III. Type II cryoglobulinaemia is often associated with hepatitis C virus (HCV) infection but also occurs with non-Hodgkin’s lymphoma or without obvious cause. Conventional treatment is not standardized, but in the absence of viral infection typically involves corticosteroids, immunosuppressives and plasma exchange [1].

B-cell depletion with the chimeric monoclonal antibody rituximab, a treatment for B-cell lymphoma, is also under investigation for autoimmune disease [2], especially those associated with circulating autoantibodies, such as rheumatoid arthritis [3], systemic lupus erythematosus and vasculitis. By depleting B cells, rituximab has the potential to reduce the development of plasma cells, thereby limiting cryoglobulin production. As a separate therapeutic mechanism, blockade of tumour necrosis factor (TNF) appears to be effective in antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis, rheumatoid arthritis, where TNF plays a central role in endothelial activation, inflammatory cell recruitment and vascular injury [4]. TNF inhibition may thus also be an effective therapy for cryoglobulinaemic vasculitis.

We report a case of HCV-negative type II cryoglobulinaemia with severe multisystem disease, refractory to conventional agents but in whom rituximab led to falls in cryoglobulin levels and partial disease control, and subsequent infliximab therapy led to full remission.

Case

A 48-year-old woman with a 6 month history of relapsing rash, abdominal pain and peripheral oedema was admitted to hospital for further investigation. Physical examination showed bilateral oedema up to the lower abdomen and hypertension (blood pressure 180/108 mmHg), while the chest X-ray confirmed bilateral pleural effusions and an enlarged cardiac silhouette. Abnormal laboratory results included platelets 91 × 10⁹/l, serum creatinine 124 μmol/l, proteinuria 1.2 g/24 h, haematuria and hypoalbuminaemia (28 g/l). Cryoglobulins were positive, with a cryocrit of 6% containing IgG at 1.1 g/l and a monoclonal IgM band at 1.3 g/l, elevated rheumatoid factor, 455 IU/ml and hypocomplementaemia (C3, 0.61 g/l, normal range 0.80–2.14 g/l; C4, 0.01 g/l, normal range 0.13–0.60 g/l). Viral screening was negative for hepatitis B and C by serology and polymerase chain reaction (PCR). A kidney biopsy was performed which revealed endocapillary proliferation, mesangial interpositioning and luminal thrombi within the capillary wall; immunofluorescent stains were strongly positive for IgM and IgG and moderately so for C3 and C1q. A diagnosis of HCV-negative cryoglobulinaemic vasculitis with glomerulonephritis was made and treatment commenced with intravenous (i.v.) methyprednisolone (1 g/day for 3 days), oral prednisolone (60 mg for 3 days and 40 mg thereafter) and a single dose of i.v. cyclophosphamide (12 mg/kg). Two weeks later,
because of gradual deterioration of renal function (serum creatinine, 221 μmol/l; urine protein 6 g/24 h) and a falling haemoglobulin (6.9 g/dl), the patient underwent plasma exchange (60 ml/kg/day for 5 days). The subsequent course was complicated by severe influenza A pneumonia and secondary *Staphylococcus aureus* and fungal infections leading to respiratory failure, requiring intensive care and dialysis.

Despite further plasma exchange, vasculitis, renal failure and recurrent bacterial sepsis persisted while left ventricular failure with a dilated cardiomyopathy was noted. She then received monoclonal anti-CD20

![Fig. 1.](https://academic.oup.com/ndt/article-abstract/20/1/213/1818538)

(a) Serum creatinine and proteinuria after diagnosis (the dotted line indicates the upper limit of the normal range for serum creatinine). (b) Rheumatoid factor and cryocrit after diagnosis. (c) Complement C3 and C4 after diagnosis (the dotted line indicates the lower limit of the normal range for C3, 0.8 g/l; and C4, 0.13 g/l). (d) Levels of circulating T cells (CD3-positive, normal range 0.70–2.10 × 10^9) and B cells (CD19-positive, normal range 0.10–0.50 × 10^9) after B cell depletion (Cy = cyclophosphamide; PE = plasma exchange; IVIg = i.v. immunoglobulin).
antibody, rituximab (Roche, UK), 375 mg/m² as four, weekly, infusions with oral prednisolone (15 mg/day). This led to depletion of circulating B cells. Her purpura remitted, proteinuria declined and renal function returned to normal (Figure 1a). Her cryocrit and rheumatoid factor fell and complement levels rose. The patient was then discharged from hospital (Figure 1).

However, a day later, she had a major gastrointestinal haemorrhage, with a mesenteric arteriogram identifying a site of bleeding in the distal ileum. Two laparotomies for recurrent haemorrhage were required, with a right hemicolecctomy and partial ileac resection. The bowel histopathology demonstrated a necrotizing vasculitis compatible with cryoglobulinaemic vasculitis. She was treated with sequential plasma exchange and high dose i.v. immunoglobulins. Continued falls in haemoglobin indicated ongoing intestinal vasculitis and she received the anti-TNF monoclonal antibody infliximab (single dose 5 mg/kg). This led to stability in the haemoglobin; the patient was discharged home again and began an uneventful recovery.

Four months after the initial course of rituximab and due to persistent positive cryoglobulinaemia (cryocrit 2%), increased rheumatoid factor (206 IU/ml) and low complement (C3, 0.92 g/l; C4, 0.04 g/l) a second course of rituximab 1000 mg 2 weeks apart, was administered. At last review, 10 months after the first course of rituximab, the patient was normotensive with normal renal function and negative cryoglobulins, while current medication consisted of lisinopril, carvedilol, bumetonide and prednisolone 5 mg/day.

**Discussion**

**Type II mixed essential cryoglobulinaemia** is the result of monoclonal IgM paraprotein with rheumatoid activity binding to polyclonal IgG in the circulation causing immune complexes, complement activation, vasculitis and glomerulonephritis. Common clinical manifestations include purpuric and necrotizing skin lesions, acroparaesthesia, Raynaud’s phenomenon, neuritis, arthralgia, fever, hepatosplenomegaly and nephrotic syndrome. **Type II cryoglobulinaemia** is associated with chronic hepatitis C infection in almost 90% of cases. In our patient, diagnosis of HCV-negative type II mixed essential cryoglobulinaemia was based on presentation of nephrotic syndrome, immunological markers of cryoglobulins, and a renal biopsy, which confirmed deposits of IgM and IgG in capillary walls. There was no evidence of underlying malignancy.

Conventional treatment of HCV-negative cryoglobulinaemia would include the combination of steroids and cytotoxic agents. Induction therapy with pulse methylprednisolone followed by long-term oral prednisolone and cyclophosphamide is often beneficial. Plasma exchange is also used to reduce the level of circulating cryoglobulins. These approaches were complicated in our case by intercurrent infections that made the use of alternative cytotoxics, such as chlorambucil, contra-indicated. In addition, conventional agents are often ineffective, so there is an obvious need for novel, safer treatments.

A rationale for B-cell depletion is based on the possibility that IgM rheumatoid factor-producing plasma cells are CD20 positive or, more probably, that continued cryoglobulin production requires plasma cell replenishment from the B-cell pool. The development of the chimeric human–mouse monoclonal anti-CD20 antibody, rituximab, enables the possibility that IgM rheumatoid factor-producing plasma cells are CD20 positive or, more probably, that continued cryoglobulin production requires plasma cell replenishment from the B-cell pool. Its efficacy has been proven in treating lymphomas and recently in various autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus [2].

Previous experience of rituximab in cryoglobulinaemia is limited. Sansonno *et al.* [5] has reported the use of rituximab in 20 HCV-positive patients, 80% of whom showed remission of clinical signs and laboratory features (Table 1). Zaja *et al.* [6] has reported results from three HCV-negative patients with mixed cryoglobulinaemia who responded to rituximab and two HCV-positive patients with renal involvement with a good response in one. There have been two reports of single cases of cryoglobulinaemia with renal failure that showed clinical and serological improvement [7,8].

In this case, rituximab was effective in controlling cutaneous and renal disease and led to a major fall in cryoglobulins, but gastrointestinal vasculitis persisted. In view of the inflammatory nature of the vasculitis

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on biopsy, and the probable dependence of this on inflammatory cytokines, we chose to use the anti-TNF antibody, infliximab, which previously has been shown to have potential for the control of vasculitis in studies of ANCA-associated vasculitis [4]. Two previous reports of three cases of HCV-positive cryoglobulinaemia found either only a transient response or no response to infliximab [9,10]. Ours is the first report of a clinically useful response to infliximab in HCV-negative cryoglobulinaemia. Following infliximab, there was no further evidence of gastrointestinal bleeding and our patient’s recovery continued uneventfully. Additional study of the role of infliximab for the rapid control of cryoglobulinaemic vasculitis is warranted, but it may need to be combined with strategies to reduce cryoglobulin levels, as in this case.

In conclusion, even though there is frequently a good clinical response to rituximab, the serological response often is incomplete, with cryoglobulins remaining detectable and ongoing evidence of complement activation. Our case also highlights the differential response of different organ manifestations to this treatment, and the need for additional interventions, such as infliximab, to achieve full clinical remission. Repeated courses of rituximab appear desirable to control immunological markers and maintain remission, but it is not known how effective this will be in the longer term. There is a need for improved understanding of the therapeutic mechanism of rituximab in cryoglobulinaemia, for prospective clinical trials and perhaps for the investigation of the role of other B-cell-depleting monoclonal antibodies, such as anti-CD19 or anti-CD22.

Acknowledgements. The authors are grateful to Stella Burns for supervising rituximab and infliximab therapy and for data collection.

References

Conflict of interest statement. M. Koukoulaki, S. C. Abeygunasekara and K. G. C. Smith have no conflict of interest. D. R. W. Jayne has received grant support from Roche (UK) and Schering-Plough.

Acknowledgements. The authors are grateful to Stella Burns for supervising rituximab and infliximab therapy and for data collection.

Received for publication: 20.7.04
Accepted in revised form: 30.9.04