Case Report

Treatment of Cryoglobulinemia Associated Peripheral Neuropathy with Rituximab

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ABSTRACT. We describe a man with hepatitis C virus related cryoglobulinemic vasculitis that was resistant to combination treatment of prednisolone, interferon-α, and ribavirin, and that went into remission after treatment with rituximab. (J Rheumatol 2006;33:1197–8)

Key Indexing Terms:
CRYOGLOBULINEMIA HEPATITIS C VIRUS PERIPHERAL NEUROPATHY
RITUXIMAB INTERFERON-α RIBAVIRIN

We describe a man with hepatitis C virus related cryoglobulinemic vasculitis resistant to combination treatment of prednisolone, interferon-α, and ribavirin, which went into remission after treatment with rituximab.

CASE REPORT

A 54-year-old man presented in September 2002 with a 3-week history of diarrhea, weight loss, and arthralgia, and a 3-month history of bilateral hand swelling. Examination revealed purple discoloration of his hands with soft tissue swellings and a vasculitic rash on his legs. Extensive investigations revealed normal colonoscopy, hand radiography, and renal and liver function; and negative serology for celiac disease, autoimmune hepatitis, antineutrophilic cytoplasmic antibody, antinuclear antibody, and extractable nuclear antibody. The significant abnormalities were leukocytosis (white blood cell count 18.3×10^9/l; normal range $4–11 \times 10^9$/l), elevated C-reactive protein (54 mg/l; normal < 6 mg/l), erythrocyte sedimentation rate (38 mm/h; normal range 2–15 mm/h), positive rheumatoid factor (RF), cryoglobulin (monoclonal IgM, kappa subtype, 0.18 g/l), and hepatitis C antibody. His history included alcohol abuse, hepatitis C infection from a needlestick injury, and porphyria cutanea tarda previously treated with venesections. Empirical treatment with prednisolone and ciprofloxacin were initiated. Further investigations confirmed perivascular inflammatory infiltrate on skin biopsy and elevated hepatitis C viral load (genotype 1a). He was treated for 6 months with interferon-α (IFN-α) at 3 million units 3 times weekly and ribavirin 800 mg daily. This was complicated by flu-like symptoms, but resulted in partial improvement of his clinical symptoms as well as disappearance of cryoglobulin from the serum. In August 2003 he had a flare of cutaneous vasculitis and new onset mesenteric vasculitis, at a time when his cryoglobulinemia had recurred (0.12 g/l). This resulted in bowel ischemia with perforation and fecal peritonitis, requiring total colectomy with ileostomy. Serum viscosity screen was normal and electrocardiography excluded atrial fibrillation. Subsequently therapy was changed to pegylated IFN-α 180 μg weekly with ribavirin 1 g daily, and prednisolone dose was escalated from 12.5 mg to 37.5 mg daily. This resulted in rapid improvement of his vasculitic lesions, but was complicated by development of cushingoid body habitus, hypertension, and diabetes mellitus, as well as an increase in the hepatitis C viral load from 220,000 to > 500,000 IU/ml despite 6 months of antiviral therapy. In February 2004, he re-presented with synovitis, purpura, necrotic right leg ulcer, right wrist drop, and burning sensation in both hands and feet. Nerve conduction studies revealed bilateral sensorimotor peripheral neuropathy, with a sural nerve biopsy showing complete loss of myelinated nerve fibers. Blood tests revealed depressed complement concentrations, persistently positive RF, and re-emergence of cryoglobulin (Table 1). Antiviral therapy was stopped, and 4 infusions of rituximab 375 mg/m^2 were given over 2 months. This resulted in resolution of his right wrist drop initially, followed by all other clinical features, which allowed gradual tapering of prednisolone. He remained free of vasculitic symptoms for 15 months after rituximab treatment, but was hospitalized in May 2004 due to rapid atrial fibrillation and acute pulmonary edema associated with ischemic heart disease. In September 2005 he was readmitted with vasculitic lesions in his hands and feet and septic arthritis and osteomyelitis of the right great toe, which required longterm intravenous antibiotic treatment and amputation of the right great toe and distal first metatarsal bone.

DISCUSSION

Cryoglobulins are cold-precipitable proteins consisting of 2 or more immunoglobulin isotypes, whereas cryoglobulinemic vasculitis is a chronic, immune complex mediated disease affecting predominantly small vessels and is associated with vascular, renal, and neurological manifestations[1]. The association of 80%–90% of cases of mixed cryoglobulinemia (MC) with chronic hepatitis C virus (HCV) infection has become apparent since the availability of serological markers for HCV infection, but only a few patients will evolve into cryoglobulinemic vasculitis.

Limited data are available regarding the treatment of HCV related cryoglobulinemic vasculitis, as the majority of patients with autoimmune or extrahepatic manifestations were excluded from multicenter trials. Corticosteroids, IFN-α, ribavirin, immunosuppressive agents, and plasmapheresis have been trialed with variable success[2]. IFN-α treatment for 6 months produced significant clinical improvement in 60% of cases of MC but its efficacy is closely associated with inhibition of HCV replication[3]. Reduction of HCV RNA in responsive patients usually precedes decline of cryocrit; however, the improvement is generally temporary and more than 85% of responders have a relapse within 6 months post treatment.

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Table 1. Patient's laboratory measures before and after rituximab treatment (normal values).

	Jan 2003	Aug 2003	Dec 2003	Feb 2004	June 2004	Dec 2004
CRP, mg/l (< 6)	11	191	ND	9	7	8
RF, IU/ml (< 20)	102	55	74	116	ND	ND
C3, g/l (0.60–1.2)	1.08	0.43	ND	0.63	0.90	ND
C4, g/l (0.12–0.35)	0.06	0.11	ND	0.03	0.15	ND
Albumin, g/l (31–44)	36	31	32	30	36	37
Bilirubin, μmol/l (< 20)	8	16	8	5	6	7
ALP, units/l (30–110)	133	101	126	81	105	106
GGTP, units/l (< 60)	95	32	200	148	277	265
ALT, units/l (< 50)	14	34	30	28	40	41
AST, units/l (< 40)	18	52	52	47	25	32
Cryoglobulins	Positive (0.18 g/l)	Positive	Negative	Positive (0.18 g/l)	Negative	Negative

CRP: C-reactive protein, RF: rheumatoid factor, ALP: alkaline phosphatase, GGTP: gamma glutamyl transpeptidase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, ND: not done.

Combination treatment of ribavirin and IFN-α for 14–20 months has greater efficacy than IFN-α monotherapy[4], but patients infected with genotype 1 showed a trend toward lower clinical and virologic responses. In addition, IFN-α frequently delays healing of active skin ulcers and may worsen peripheral neuropathy[1,2]. Our patient was infected with genotype 1a HCV that failed to respond to both standard and pegylated interferon with ribavirin, as evident by persistently positive HCV RNA. Further, he had a relapse of MC with peripheral neuropathy and worsening cutaneous vasculitis, accompanied by known side effects of prednisolone, necessitating alternative treatment with rituximab.

Rituximab is a chimeric monoclonal antibody against the CD20 antigen, a transmembrane protein expressed on all lineages of B cells. It is highly effective for *in vivo* B cell depletion, resulting in undetectable peripheral B lymphocytes after a single infusion, which then recover 6 to 9 months later[5]. Rituximab was originally approved for the treatment of non-Hodgkin's lymphoma, but its therapeutic use has been extended to other types of lymphoma, leukemia, and several other hematological disorders including idiopathic thrombocytopenic purpura[6].

MC is a consequence of clonal B cell expansions in bone marrow and liver in the presence of chronic HCV infection. A controlled study showed that weekly rituximab infusion at 375 mg/m^2 over 1 month had a clinical and biologic benefit in 20 patients with MC and HCV-positive chronic active liver disease who were resistant to IFN-α therapy[5]. Rituximab produced complete clinical response in 80% of patients, as evidenced by disappearance of purpura, arthralgia, weakness, and peripheral neuropathy, with decline of cryocrit as well as reduction of RF and anti-HCV antibody titers. About 75% of responders remained in remission 12 months after discontinuation of rituximab. Another controlled study using rituximab in type II MC refractory to antiviral or immunosuppressive agents also supports its efficacy and safety[7,8]. Interestingly, rituximab also resulted in dramatic healing of leg ulcers in 3 of 5 patients. Further, the percentage of CD20-positive cells dropped to less than 1% after the first infusion. However, the HCV RNA level increased to twice the baseline levels in responders, whereas it remained the same in nonresponders[5], suggesting the need for further study to explore combination treatment of rituximab with antiviral therapy.

This is the second case report to show that rituximab can induce remission of cryoglobulinemic vasculitis with chronic HCV infection resistant to combination treatment of IFN-α and ribavirin, suggesting the need for further randomized control study in this rare condition. However, our study has also demonstrated again the known resistance of HCV genotype I to antiviral therapy, and the inevitable flare of mixed cryoglobulinemia in the absence of clearance of HCV despite an initial good response to rituximab therapy.

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