Case Report

Rituximab Treatment for Resistant Antiphospholipid Syndrome

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ABSTRACT. Antiphospholipid syndrome (APS) and catastrophic antiphospholipid syndrome (CAPS) can be challenging to treat. As they are rare, clinicians are not often exposed to these complex diseases. For the patient resistant to standard treatments new therapeutic directions can be perplexing, especially in the context of ongoing thromboses and bleeding episodes. We describe 3 patients, 2 with APS and one with CAPS, resistant to conventional medications, who responded to treatment with rituximab, an anti-CD20 monoclonal antibody. Since rituximab infusion, all the patients have had stable platelet counts and no further episodes of bleeding or thromboses. (J Rheumatol 2006;33:355–7)

Key Indexing Terms:
ANTICARDIOLIPIN ANTIBODIES
CATASTROPHIC ANTICARDIOLIPIN ANTIBODIES
RITUXIMAB
DEEP VEIN THROMBOSIS
THROMBOCYTOPENIA
ANTIPHOSPHOLIPID SYNDROME

Clinical features of antiphospholipid syndrome (APS) include recurrent arterial or venous thromboses, pregnancy morbidity, and the presence of antiphospholipid antibodies, most commonly anticardiolipin (ACL), lupus anticoagulant antibodies (LAC), and/or anti-ß$_2$-glycoprotein I antibodies[1]. Catastrophic antiphospholipid syndrome (CAPS), which represents fewer than 1% of all patients with APS, is an exaggerated form of APS resulting in multiorgan failure[2].

Treatment of APS and CAPS can be challenging. Oral anticoagulants, corticosteroids, plasma exchange, intravenous immunoglobulins (IVIG), and cyclophosphamide are the most commonly used agents. Yet these therapies are not always effective and novel approaches need to be investigated in resistant cases.

Rituximab is a genetically engineered chimeric murine/human anti-CD20 monoclonal antibody cell-surface protein believed to function in B cell cycle initiation and differentiation. The CD20 antigen represents an ideal target for immunotherapy of B cell lymphomas and B cell-mediated autoimmune diseases like idiopathic thrombocytopenic purpura (ITP), rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE)[3-5]. It is highly effective in depleting circulating B cells for several months[6,7]. In APS and CAPS the possibility of eliminating autoreactive B cells remains intriguing.

There are several mechanisms in which B cell involvement is key in the immunopathogenesis of autoimmune diseases. B cells may function as antigen-presenting cells and provide important costimulatory signals required for CD4+ T cell clonal expansion and effector functions. Also, T cell activation is a critical component of the immune system for which B cells may be activators. Finally, B cells may secrete proinflammatory cytokines; thus in APS and CAPS the potential to eliminate autoreactive B cell clones is also intriguing.

We describe 2 patients with APS and one with CAPS[8], resistant to standard treatments, responding to rituximab.

CASE REPORTS

Case 1. A 34-year-old man had presented 12 years earlier with lower extremity deep vein thrombosis and thrombocytopenia. He was diagnosed with ITP, and was given warfarin and prednisone 1 mg/kg and had a splenectomy. ACL IgG was elevated (23 GPL) and a Russell viper venom test was positive for LAC even though he was taking high-dose corticosteroids. He was also diagnosed with APS. Despite treatment, the platelet count remained low at $10 \times 10^3/\mu$l. Plasmapheresis, IVIG, cyclophosphamide, vincristine, pulse dexamethasone, and azathioprine were tried, but were ineffective. He developed additional thromboses in the superior vena cava, upper extremity, and external jugular vein. Rituximab 375 mg/m^2 once weekly for 4 weeks was initiated. The platelet count rose after infusion and has remained at $324 \times 10^3/\mu$l 14 months later. He has had no further episodes of thromboses or thrombocytopenia while continuing warfarin.

Case 2. A 54-year-old man was diagnosed in 1996 with ITP refractory to corticosteroids, but initially responsive to vincristine. In 2001, he relapsed, reporting bruising and gum bleeding. The platelet count was $< 10 \times 10^3/\mu$l. Danasol, IVIG, and cyclophosphamide were tried and were ineffective. Laboratory investigations revealed hemoglobin 8.7 g/dl, positive IgG

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Coombs' test, positive ACL IgG (38 GPL), and positive LAC Exner test with confirmation by Russell viper venom test. He was diagnosed with Evans's syndrome and APS. Vincristine was reinstituted, but was ineffective. He then had a myocardial infarction. Rituximab 375 mg/m^2 once weekly for 4 weeks was started. At the fourth infusion, the platelet count was $28 \times 10^3/\mu$l, 2 weeks later it was $140 \times 10^3/\mu$l. Forty-one months later the platelet count remains above $150 \times 10^3/\mu$l. He has had no further episodes of bleeding or thromboses.

Case 3. A 27-year-old nulliparous woman presented with intractable abdominal pain. Exploratory laparotomy revealed hepatic hemorrhages and microthrombi. She also developed additional thrombi in the right internal jugular, subclavian, and axillary veins, along with Budd-Chiari syndrome (Figures 1–3). Laboratory values included a platelet count of $68 \times 10^3/\mu$l, partial thromboplastin time 78.8 s due to LAC, and ACL IgG 89 GPL. She was diagnosed with CAPS. Treatment with heparin and methylprednisolone 1 mg/kg/day was ineffective. Despite prednisone therapy, platelets decreased to $42 \times 10^3/\mu$l. Rituximab 375 mg/m^2 once weekly for 4 weeks was started. One week after infusion of rituximab, the platelet count increased to $117 \times 10^3/\mu$l. Twenty months later, the platelet count has remained at $384 \times 10^3/\mu$l, with no further episodes of thromboses or thrombocytopenia.

Two patients with APS and one patient with CAPS, resistant to conventional treatment, responded to rituximab. The presence of associated thrombocytopenia complicated necessary anticoagulant therapy. For more than one year since the rituximab infusion, these patients have had stable platelet counts, no further arterial or venous thromboses, and no evidence of bleeding. All 3 patients are now in clinical remission.

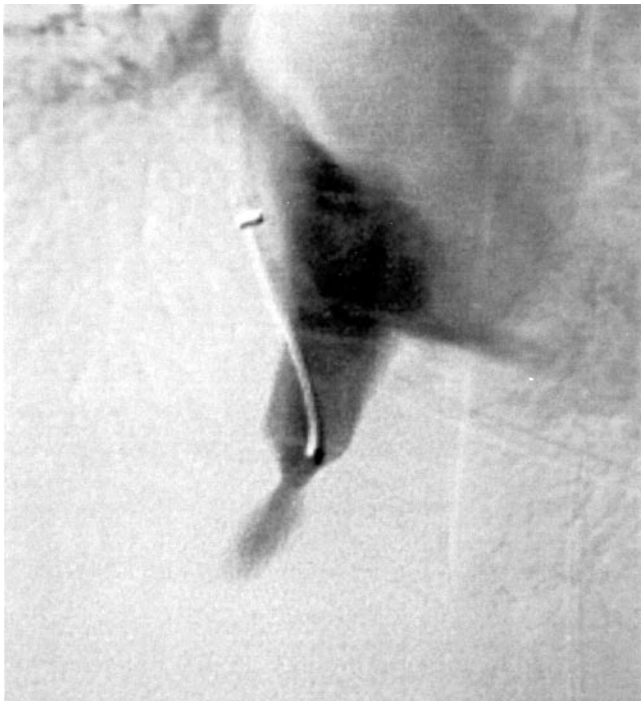

Figure 2. An inferior venogram showing severe stenosis in the intrahepatic portion of the inferior vena cava.

DISCUSSION

B cells may be key contributors in the immunogenesis of APS and CAPS, with the mechanism of action of rituximab in these hematological disorders occurring through depletion of the pathologic B cells. These cells may either act as antigen-presenting cells that initiate inflammation by the production of cytokines, or have a direct influence on T cells[9,10]. The depletion of these immunologic B cells may decrease or even halt the continuing cascade of inflammatory mediators signaling thrombocytopenia, bleeding, and/or thrombosis.

Therefore, depletion of peripheral B cells with an anti-CD20 antibody in patients with autoimmune diseases might reduce disease activity. In a randomized, double-blind, controlled study of 161 patients with active RA despite methotrexate (MTX) treatment, 2 infusions of rituximab, alone or in combination with cyclophosphamide or continued MTX, provided symptomatic improvement in disease activity at 24, 48, and 102 weeks[11].

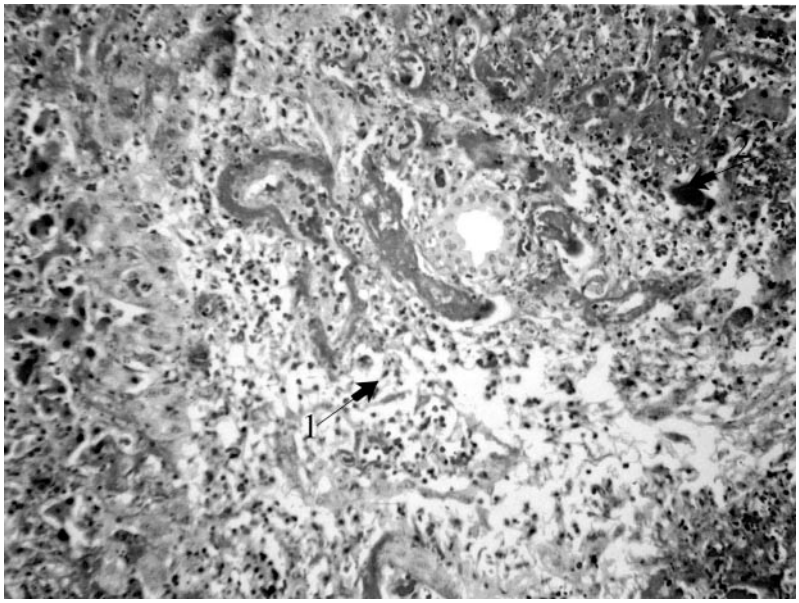

Figure 1. Liver biopsy reveals thrombosed vessels (1) and focal area of hemorrhage (2).

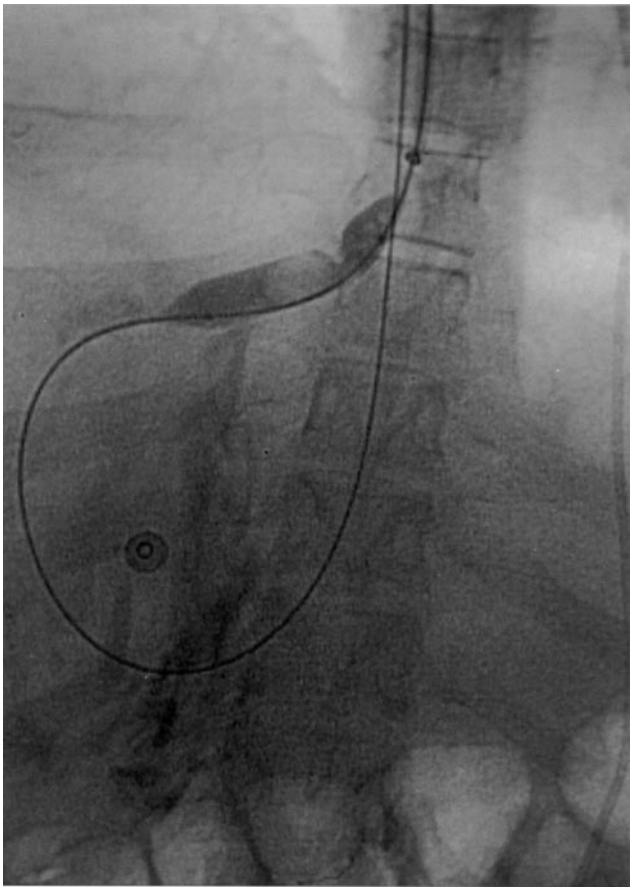

Figure 3. Hepatic venogram shows severe stenosis of the right hepatic vein at its origin to the inferior vena cava.

In our series of 3 patients, we used rituximab 375 mg/m^2 once weekly for 4 weeks. In previous studies, rituximab has been used in a similar fashion, with doses ranging between 200 and 375 mg/m^2 once weekly for 4 weeks[13]. Other treatment protocols have included either one or two 300–375 mg/m^2 infusions once every 2 weeks for 4 weeks. Finally, a few studies have treated patients with only one infusion of rituximab 1000 mg or two 750 mg infusions alone or in combination with prednisolone, MTX, or cyclophosphamide. Similar therapy has been used in patients with RA and SLE as well as others[12,14].

This is the first report of successful treatment with B cell depletion. Consequently, rituximab may be an effective adjuvant treatment method combined with warfarin in resistant APS and CAPS[15]. The potential of B cell depletion with rituximab in APS and CAPS appears promising. This novel therapeutic approach warrants further investigation.

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