A Dramatic Response to Intravenous Immunoglobulin in a Patient with Mixed Cryoglobulinemia

Ofer Almog MD, Tatiana Berlin MD, Pnina Rotman-Pikielny MD and Yair Levy MD

Department of Medicine E, Meir Medical Center, Kfar Saba, and Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

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Cryoglobulins are immunoglobulins that precipitate when cooled to less than 37°C and dissolve when rewarmed. Mixed cryoglobulinemia type II is an autoimmune disorder comprised of circulating cryoglobulins of both polyclonal IgG and a monoclonal IgM rheumatoid factor that are directed against the IgG.

Type II MC causes small vessel vasculitis. The clinical manifestations of type II MC include skin (60–100%), peripheral nerve (20–90%), arthralgia/arthritis (20–90%), renal (33–55%) and gastrointestinal involvement (< 20%) [1]. Other common features are fatigue and Raynaud's syndrome.

Infection with hepatitis C virus is responsible for up to 90% of all type II MC cases. Because of its major etiological role in type II MC, eradication of HCV by antiviral medications is a main treatment goal for this disorder. Another goal of treatment is symptom related and targets the autoimmune process. While no treatment is required for asymptomatic patients, low dose steroids are administered to patients with mild to moderate cryoglobulinemic syndromes such as purpura, arthralgia, or peripheral sensory neuropathy. With severe manifestations of MC including cryoglobulinemic nephropathy, skin ulcers, sensory motor neuropathy, and widespread vasculitis, high dose steroids with or without cyclophosphamide should be administered. A promising new treatment for MC, which has not yet been studied in large-scale clinical trials, is intravenous immunoglobulin therapy.

We describe the successful case of a female patient with mixed cryoglobulinemia related to non-hepatitis C, who demonstrated a dramatic response to IVIG after high dose steroids and cyclophosphamide provided only partial relief.

Ig = immunoglobulin
MC = mixed cryoglobulinemia
HCV = hepatitis C virus

PATIENT DESCRIPTION

In 1996, a 34 year old woman presented with purpuric rash and epigastric abdominal pain. No diagnosis was made at the time, and she was discharged on a 3 month course of low dose steroids with full relief of her symptoms.

In 2001, the patient's purpura recurred with the addition of arthralgia. Blood analysis for immunoglobulins provided the diagnosis of mixed cryoglobulinemia. While testing negative for HCV antibodies, her cytomegalovirus IgM antibodies were positive. An elevated C-reactive protein and erythrocyte sedimentation rate were also noted. The patient was treated with low dose prednisone augmented later by azathioprine, leading to remission.

In 2002, the patient presented with purpura on her limbs, deterioration of her kidney function, and hematuria. Her creatinine levels rose from 0.8 to 1.2 mg/dl with proteinuria of 1 g per 24 hours. A kidney biopsy revealed focal glomerulonephritis. In addition, the patient had epigastric pain. A gastroscopy revealed non-specific acute gastritis without signs of vasculitis.

IVIG = intravenous immunoglobulin G

A 6 month course of cyclophosphamide therapy was initiated, combined with high dose prednisone. Each attempt at tapering the steroids was followed by reappearance of purpura, abdominal pain, and urinary sediment. The high dose steroid treatment took its toll with manifestations of osteoporosis, myopathy, and water retention.

In 2003, the patient presented with myalgia and right arm weakness, as well as purpura on her limbs. An electromyogram revealed neural damage indicative of mononeuritis multiplex of the ulnar nerve. Because these new symptoms appeared while she was receiving a high dose of steroids, a clinical decision was made to initiate IVIG treatment (2 g/kg body weight).

The response to this new treatment was dramatic. After only one course of IVIG, the disease went into full remission, including disappearance of abdominal pain, arthralgia, purpura, and kidney dysfunction. Cumulatively, the patient received 10 monthly courses of IVIG. One year after the last course of IVIG she remained in remission, receiving only low dose prednisone (5 mg on alternate days).

COMMENT

IVIG has come into increasing use in patients with autoimmune and systemic inflammatory diseases [2]. Of special

interest is the favorable effect of IVIG in vasculitic peripheral neuropathy. Our group has demonstrated the beneficial effect of IVIG in autoimmune diseases in open-label clinical studies [3,4]. We described six patients with various autoimmune/inflammatory diseases (Sjögren's syndrome, systemic lupus erythematosus, vaccination-induced vasculitis, Churg-Strauss vasculitis, sarcoidosis), all with vasculitic peripheral neuropathy. The patients were treated with high dose IVIG (2 g/kg body weight) and followed for 1–5 years after this treatment. In four patients – those with Sjögren's syndrome, Churg-Strauss vasculitis, SLE, and vaccination-induced vasculitis – the neuropathy resolved after IVIG treatment. Thus, we believe that IVIG may be beneficial in cases of resistant vasculitic peripheral neuropathy and that IVIG should probably be considered as either a sole or an adjuvant treatment for patients with contraindications to conventional treatment, or alternatively, for patients in whom conventional treatment has failed.

The use of IVIG in MC type II has been reported without favorable effect. In two case reports the IVIG treatment led to cryoglobulinemia (cryoglobulinemic vasculitis) [5]; while in another report, IVIG therapy, which was started simultaneously with steroids as first therapy in a male patient with cryoglobulinemic polyneuropathy, had a beneficial effect.

The precise mechanism of action of IVIG in the treatment of autoimmune diseases and vasculitides is still largely unknown. A few possibilities have been suggested including anti-idiotype antibodies, down-regulation of autoantibody synthesis, inhibition of complement-mediated tissue damage, blockade of Fc receptors on phagocytic cells, inhibition of complement activation, down-regulation of T and B cell function, anti-cytokine effect, neutralization and enhanced clearance of endogenous pathogenic autoantibodies, and neutralization of bacterial toxins and super-antigens.

IVIG therapy is usually safer than immunosuppressive agents but still has possible adverse effects. These consist of skin rash, headache, arthralgia, anaphylactic hypersensitivity (especially in IgA-deficient patients), renal dysfunction, and possibly thrombotic events.

To the best of our knowledge our report is the first to describe a patient with MC type II whose dermatologic, nephrologic, gastrointestinal and neurologic symptoms were resolved almost completely with IVIG therapy and for a prolonged period. It is important to note that the patient had failed to respond to conventional treatment, which included cyclophosphamide and high dose steroids. We conclude that IVIG therapy may be a reasonable treatment in MC, especially when other modes of therapy have failed.

SLE = systemic lupus erythematosus

Correspondence:
Dr. Y. Levy
Dept. of Medicine E, Meir Medical Center, Kfar Saba 44821 Israel
Phone: (972-9) 747-2592
Fax: (972-9) 744-0085
email: yairlevi@post.tau.ac.il

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