Response of Dystrophic Calcification to Intravenous Immunoglobulin

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF A CASE

A 56-year-old woman with an 8-year history of CREST syndrome, a variant of scleroderma, presented with increasing calcium deposits that were causing inflammation and swelling of the index finger of her left hand (Figure 1), as well as Raynaud phenomenon, telangiectasia, and mild sclerosis of her fingers. She had intense pain and extreme morbidity and was severely handicapped in her office job. A barium swallow test revealed moderate esophageal dysmotility, and a computed tomographic scan demonstrated mild pulmonary fibrosis. Spirometry revealed normal values, particularly for carbon monoxide diffusing capacity and inspiratory vital capacity. There was no evidence of pulmonary hypertension, cardiac or renal manifestations, or systemic metabolic abnormalities in calcium regulation. Serologic tests were positive for antinuclear antibodies and anti–Scl-70 antibodies. Long-term treatment with D-penicillamine (30 weeks), warfarin sodium (13 weeks), and extracorporeal shock wave lithotripsy did not result in any improvement in the cutaneous calcifications or inflammation. The plastic surgeons refused to consider a surgical approach because of the risk of protracted and complicated wound healing.

THERAPEUTIC CHALLENGE

Dystrophic calcification is known as a condition that is difficult to treat. Various therapies have been tried. Pharmacological approaches include warfarin, colchicine, probenecid, bisphosphonates, and diltiazem, all of which have been used with variable success.1,2 In selected cases, patients may benefit from the surgical removal of larger lesions.2 In cases involving small superficial lesions, treatment with carbon dioxide laser therapy may be helpful.3 Recently, reports of treatment with extracorporeal shock wave lithotripsy have been published.4 However, to date, no reliable treatment has been established, and most treatment efforts have been fruitless and frustrating.

SOLUTION

Years ago, we observed the resolution of large dystrophic calcifications in a patient with dermatomyositis who was treated with intravenous (IV) immunoglobulin. Therefore, we decided to initiate therapy with IV immunoglobulin in this case. According to established treatment regimens in autoimmune diseases,5–7 we administered IV immunoglobulin at a dosage of 2 g/d in a 4-day protocol once a month. After 2 cycles, the patient’s pain and in-

Figure 1. Pretreatment photographs show debilitating swelling of the left index finger as well as large, severely painful calcifications and inflammation (A), particularly involving the left index finger (B).
flammation subsided. After 3 more courses, she was free of symptoms and was able to use her left hand without impairment (Figure 2). Her Rodnan skin score improved from 12 points before treatment to 9 points after treatment. The IV immunoglobulin therapy was well tolerated, without adverse effects. Some new lesions began to develop 6 months after the therapy was discontinued.

**COMMENT**

Dystrophic calcification occurs in the presence of normal calcium metabolism, presumably in sites of trauma such as elbows, knees, and fingers. Extrusion of calcium causes extreme inflammation, with pain, morbidity, secondary infection, and ulceration. It is often found in scleroderma, systemic lupus erythematosus, and dermatomyositis, especially in juvenile dermatomyositis. The mechanisms that lead to cutaneous calcification in connective tissue diseases are poorly understood, but tissue damage, hypovascularity, and hypoxia have been suggested to play a role in its development.1 Furthermore, it has been proposed that increased levels of the calcium-binding amino acid and γ-carboxylglutamic acid can promote calcification.9,10 Also, activated macrophages are thought to play a central role in the development of dystrophic calcification.11

Numerous mechanisms have been postulated to explain the effects of IV immunoglobulin therapy. They include passive inhibitory effects such as competition of IgG monomers with autoantibodies in the occupancy of Fc receptors, resulting in a faster clearance of pathogenetic antibodies; blockage of the immune activation by pathogenetic immunocomplexes; and binding of complement factors.12,13 Recent studies focus more intensively on macrophages as targets of IV immunoglobulin therapy. Siragam et al14 and Bruhns et al15 proposed that an interaction of IV immunoglobulin with dendritic cells or sensor macrophages could result in the suppression of effector macrophages. Also, Park-Min et al16 demonstrated that IV immunoglobulin therapy may suppress the expression of the interferon gamma receptor in macrophages and thereby inhibit interferon gamma–mediated macrophage activation.

Kaneko et al17 showed that the anti-inflammatory effect of IV immunoglobulin depends on the sialylation of the Fc core polysaccharide, whereas nonsialylated IgG antibodies mediate proinflammatory activities. This leads to the most interesting hypothesis, ie, that the anti-inflammatory effect of IV immunoglobulin is nothing but the manifestation of a physiologic anti-inflammatory response to IgG antibodies produced in times of health.12 Yet we could not find a precise explanation as to how IV immunoglobulin may induce a resolution of calcium deposits. On the other hand, we did not find any evidence for spontaneous resolution of such extensive calcifications. We hypothesize that the impressive effect we saw in our patient was based mainly on anti-inflammatory effects, possibly owing to suppression of activated macrophages.

The clinical use of immunoglobulin for the treatment of immunodeficiencies and autoimmune disorders has increased rapidly in the last decades. Today, IV immunoglobulin is used to treat idiopathic thrombocytopenic purpura, Kawasaki disease, Guillain-Barré syndrome, myasthenia gravis, and other therapy-refractory chronic autoimmune diseases. Dermatomyositis and systemic lupus erythematosus were the first autoimmune diseases with skin involvement to be successfully treated with IV immunoglobulin.

Systemic sclerosis represents an autoimmune disease in which the skin and other organs undergo damage by excessive deposition of collagen and other matrix proteins. In an uncontrolled trial, Levy et al7 reported a decrease in the Rodnan skin score after treatment with IV immunoglobulin. The improvement in the Rodnan skin score in our patient corroborates their experience. However, our patient had CREST syndrome and was mainly impaired by debilitating dystrophic calcinosis that had been refractory to several therapies. Intravenous immunoglobulin as a single agent resulted in a remarkable reduction of the inflammation, tissue damage, and firm masses of the left index finger. This expensive treatment may be warranted to avoid serious complications and functional impairment in selected patients with cutaneous calcifications.
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