Treatment of scleromyxedema and the dermatoneuro syndrome with intravenous immunoglobulin

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Scleromyxedema is a rare disease characterized by extensive mucin deposition with fibrosis, and is associated with a monoclonal gammopathy. Currently there is no consensus on optimal treatment of this potentially fatal disease because of the lack of randomized controlled trials and limited number of case reports. At the time of this writing, 24 cases were published reporting clinical improvement of scleromyxedema with intravenous immunoglobulin. Herein we report a case showing dramatic improvement of scleromyxedema symptoms, both cutaneous and extracutaneous (including the dermatoneuro syndrome), and review the use of intravenous immunoglobulin in the treatment of scleromyxedema. This is a single case. The rarity of scleromyxedema, especially the dermatoneuro syndrome, impedes large trials. In conclusion, increasing evidence supports intravenous immunoglobulin as an effective and relatively safe treatment for both cutaneous and extracutaneous manifestations of scleromyxedema, including the dermatoneuro syndrome. (10.1016/j.jaad.2008.11.013.)

Scleromyxedema or generalized lichen myxedematosus is a rare disease involving extensive mucin deposition, fibrosis, and a monoclonal gammopathy (usually IgGκ light chains). The disease affects both men and women equally and is typically seen in middle-aged adults (30-80 years).1,2 Four diagnostic criteria help delineate scleromyxedema from other nongeneralized forms of lichen myxedematosus: (1) a generalized papular and sclerodermoid eruption; (2) mucin deposition, fibroblast proliferation, and fibrosis; (3) monoclonal gammopathy; and (4) the absence of thyroid disease.3 Histologically, scleromyxedema is characterized by a diffuse deposition of mucin in the papillary and midreticular dermis, increased collagen deposition, and proliferation of irregularly arranged fibroblasts.5

Arbanaire used:
CNS: central nervous system
IV: intravenous
IVIG: intravenous immunoglobulin

The natural course of scleromyxedema is unpredictable. The typical clinical presentation includes a widespread symmetric eruption of 2- to 3-mm waxy, firm papules on the hands, forearms, face, neck, upper aspect of trunk, and thighs.2 Skin may become shiny and stiff, resembling scleroderma, with associated sclerodactyly, and decreased mobility of the mouth and joints.3 In severe cases, infiltration may produce leonine-like facies.4 In addition to cutaneous findings, other organ systems may be affected in scleromyxedema. Musculoskeletal involvement is one of the most common extracutaneous manifestations with up to 90% of patients reporting arthralgia, myalgia, or muscle weakness, which may be associated with elevation of muscle enzymes and inflammatory electromyographic findings.5,6 Gastrointestinal symptoms such as dysphagia and reflux are also common (60%-70% of patients).5,6 Lung involvement may present with either a restrictive or obstructive pattern and may be associated with pulmonary hypertension.7 Involvement of the central nervous system (CNS) is less common (10% of patients),8-12 and can range from mild confusion to fatal encephalopathy.7 A rare manifestation of CNS involvement is the so-called dermatoneuro syndrome, which consists of fever, coma, and seizures with a flu-like prodrome.13
PATIENT PRESENTATION

A 39-year-old Caucasian woman presented initially with a burning pruritus of her right cheek. Over the course of a year this progressed to involve both cheeks, then her upper trunk and extremities, with an eruption of tiny waxy monomorphic papules. The skin over her face, neck, arms, and upper aspect of trunk appeared pebbled with nearly confluent monomorphic yellowish papules (1-mm each), giving the overall impression of thickened, firm skin, with a waxy texture (Fig 1). She had decreased range of motion of her fingers and wrists and a positive doughnut sign over several proximal interphalangeal joints (induration surrounding centrally depressed skin of the knuckles when the fingers are extended). She had no history of renal disease or failure requiring dialysis. Her thyroid function tests produced normal results. Serum protein electrophoresis revealed an IgG bicalonal gammopathy. Bone marrow biopsy specimen was normocellular with a lambda light chain-restricted plasmacytosis (5%-10% of bone-marrow cellularity) and no evidence of frank myeloma. Skin punch biopsy specimen from the upper aspect of the back revealed fibroblast proliferation and copious mucin deposition between thickened collagen bundles (Fig 2).

The patient was given a diagnosis of scleromyxedema and a 6-month course of high-dose nonlyophilized intravenous (IV) immunoglobulin (IVIG) (2 g/kg divided over 5 d/mo) was started. Before each infusion she was pretreated with ibuprofen, acetaminophen, and diphenhydramine. The only adverse effects reported by the patient throughout her IVIG therapy included some shortness of breath and headache lasting for 3 days after each infusion.

After completing 4 cycles of treatment, the patient reported significant symptom improvement with increased range of motion and softening of her cheeks, arms, upper aspect of her back, and chest.

After completing 6 cycles of monthly IVIG infusions, a second punch biopsy specimen was taken directly adjacent to the original biopsy site on the upper aspect of the back. Corresponding to the patient’s clinical improvement (Fig 3), the histologic pattern showed only very scant mucin and mild fibroblastic proliferation in the papillary dermis (Fig 4). The patient then began maintenance therapy with IVIG infusions spaced out to every 2 months.

After a 3-month lapse in her maintenance IVIG therapy, the patient presented to her local emergency department with a 5-day history of flu-like symptoms including fever, fatigue, dizziness, cough, and myalgias. She was given azithromycin and albuterol before being sent home. Several hours later, she developed the new onset of multiple generalized tonic-clonic seizures. She was brought to the hospital in a comatose state with no response to painful stimuli. Before this episode, she had shown no evidence of CNS dysfunction. She underwent a full neurologic workup, including a lumbar puncture, which only showed a slight protein elevation; an electroencephalogram, which revealed no seizure focus and was consistent with toxic or metabolic encephalopathy; and magnetic resonance...
imaging, which revealed normal findings. A complete blood cell count and metabolic panel revealed normal findings and a urine drug screen produced negative results.

The patient was admitted to the intensive care department where she developed high fever (104°F), rigidity, and trismus. She was treated with dantrolene, dexamethasone, naloxone, and physostigmine, all without improvement. After another generalized tonic-clonic seizure episode, the patient became hypoxic and required intubation. She subsequently developed an aspiration pneumonia and was treated with piperacillin/tazobactam. The patient completed a 5-day course of IVIG (400 mg/kg/d) in addition to the continued 10 mg/d of IV dexamethasone. She experienced no further seizures and her encephalopathy improved steadily. After spending 13 days in the hospital, the patient was discharged home with only mild cognitive impairment.

It was believed that this episode was most consistent with the dermatoneuro syndrome, because of the classic presentation (triad of fever, coma, and seizures, with a flu-like prodrome) combined with the lack of other plausible causes for her symptoms, and her dramatic and sustained response to IVIG. The decision was made to keep the patient on regular IVIG maintenance therapy (2 g/kg divided over 3 d/mo). She has maintained full cognitive function since then and has had no further seizures or any other CNS symptoms.

DISCUSSION

The exact pathophysiology of scleromyxedema remains unclear. Paraprotein levels do not correlate with extent or progression of the disease.7 Furthermore, although serum isolated from patients with scleromyxedema does enhance fibroblast proliferation in vitro, purified paraproteins (IgG) from the same patients do not stimulate fibroblasts.14 This suggests that an as-of-yet-unknown factor in the patient’s serum is stimulating fibroblasts to deposit excessive amounts of mucin and collagen in the skin and other tissues.11 Alternatively, Kulczycki et al15 theorize that acidic mucin deposition by fibroblasts is the primary abnormality that then triggers a monoclonal gammopathy.

Currently, there is no unified approach to the treatment of scleromyxedema because of the lack of randomized trials, limited number of case reports, and incomplete understanding of the disease pathophysiology. Multiple modalities have been used with variable success including melphalan,2 interferon alfa,16 autologous stem cell transplantation,17-19 thalidomide,20-25 high-dose dexamethasone,20,27 cyclophosphamide,28 plasmapheresis,29 and IVIG.5,11 Short-term use of melphalan appears to be beneficial, however, long-term use is associated with significant toxicity including hematologic malignancies and septic complications.2 Thalidomide has also been shown to improve symptoms of scleromyxedema, but the teratogenicity and risk of potentially irreversible peripheral neuropathy limit its use.20,23,30
An increasing body of evidence supports IVIG as a safe and effective therapy for scleromyxedema. IVIG has a favorable side effect profile compared with other treatment regimens. At the time of this writing, 24 cases were published showing clinical improvement of scleromyxedema treated with IVIG. In the majority of studies, patients were treated with high-dose IVIG (2 g/kg/mo), although improvement has been reported with doses as low as 0.5 g/kg/mo. Furthermore, it appears that some patients require maintenance IVIG therapy to control symptoms whereas others only need a few infusions to achieve a sustained remission. A recent study published in Medicine is, to date, the largest case series (N = 8) of patients with scleromyxedema treated with high-dose IVIG with long-term follow-up. All patients in the study had a complete or partial response with IVIG therapy with only mild, self-limited side effects.

The association of scleromyxedema with neurologic abnormalities is well known, and symptoms may vary from mild dizziness and confusion to life-threatening encephalopathy with coma and seizures. The pathophysiology behind CNS manifestations of scleromyxedema remains unclear. It has been hypothesized that paraproteinemia leads to hyperviscosity of the blood and an increase in leukocyte aggregation, which may lead to sludging of the CNS microcirculation and encephalopathy.

The term “dermatoneuro” syndrome describes the association of fever, coma, and seizures with a flu-like prodrome. It is a rare manifestation of scleromyxedema with only 10 documented cases. Typically, dermatoneuro syndrome has been treated with intensive care monitoring, plasmapheresis, or combinations of these treatments with variable outcomes. Improved mental status has been observed in patients treated with plasmapheresis alone and patients given combined treatment with both plasmapheresis and steroids. Treatment with IV steroids alone resulted in normalized mental status in one patient and no improvement in another patient who rapidly deteriorated and ultimately died.

Our patient’s symptoms were most consistent with dermatoneuro syndrome and readily responded to a combination of IVIG and corticosteroid, despite an initial lack of response to IV corticosteroid alone. Although there are many reports of scleromyxedema-induced CNS dysfunction responding favorably to IVIG, we believe this to be the first documented case of dermatoneuro syndrome successfully treated with IVIG. Our patient developed CNS dysfunction after a 3-month lapse in her maintenance IVIG therapy. The temporal relationship between the decreased amount of IVIG therapy and the onset of neurologic symptoms has been reported in other cases and suggests that a sudden decrease in IVIG levels may precipitate a neurologic event in a subset of patients.

Adverse events associated with IVIG therapy can be mild, severe, or potentially fatal. The majority of adverse effects are mild and include headache, nausea, low-grade fever, arthralgias, anxiety, flushing, and urticaria. Other rare and more serious adverse effects of IVIG infusion include anaphylaxis, aseptic meningitis, acute renal failure, stroke, myocardial infarction, deep venous thrombosis, and pulmonary embolism. Pretreatment with acetaminophen, nonsteroidal anti-inflammatory drugs, and diphenhydramine is thought to be effective in preventing fever, headache, and urticaria, respectively.

The mechanism by which IVIG improves symptoms of scleromyxedema remains unclear. It is hypothesized that IVIG reduces fibrosis by blocking the as-yet-unknown circulating factor that stimulates fibroblasts. The mode of action of IVIG is complex and may involve multiple pathways including: expression/function of Fc receptors, complement cascade, cytokine networks, cell growth, and differentiation of T cells, B cells, and antigen-presenting cells. In mice with bleomycin-induced pulmonary fibrosis, IVIG works to decrease fibrosis by down-regulating collagen-I levels. IVIG also interferes with profibrotic cytokine pathways by inhibiting interleukin-1 generation and by down-regulating transforming growth factor-β1 production.

In summary, increasing evidence points toward IVIG as an effective and relatively safe treatment for both cutaneous and extracutaneous manifestations of scleromyxedema, including the dermatoneuro syndrome. Our patient showed a significant clinical and histologic improvement with IVIG therapy. According to our literature review, this is the 25th case showing clinical improvement of scleromyxedema with IVIG therapy and the first reported case of dermatoneuro syndrome treated successfully with IVIG. To evaluate the true efficacy and appropriate use of IVIG, randomized controlled trials would be helpful, although in such a rare disease this presents a challenge.

REFERENCES


