Successful Treatment of Necrobiotic Xanthogranuloma With Intravenous Immunoglobulin

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Necrobiotic xanthogranuloma (NXG) is a rare systemic disease first described by Kossard and Winkelmann1 in 1980, and about 100 cases have been reported since then.2-5 It is clinically characterized by indurated yellowish to red-orange or brown papules or nodules that grow into larger and in some cases very extensive plaques covering the face (especially with periorbital distribution), trunk, and extremities. Lesions are nearly always asymptomatic, but secondarily they may become ulcerated. Moreover, pathologic changes in internal organs have been documented, including giant-cell myocardial disease.6,7 Because involvement of the heart seems to be relatively frequent, routine echocardiography and dynamic cardiac imaging are recommended in all patients. Necrobiotic xanthogranuloma also may involve other organs including the lung, larynx, pharynx, skeletal muscle, kidney, spleen, ovary, and intestine.6,10

Histopathologically, NXG is characterized by a granulomatous inflammation in the dermis extending into the subcutaneous fat. Dense infiltrates of macrophages with some foreign body–type giant cells and foamy macrophages are accompanied by areas of degenerated collagen and a moderate lymphocytic infiltrate in some cases with plasma cells. Mucin deposition or cholesterol clefts can be found. The underlying pathogenesis of the disease remains unknown, although in up to 80% of the patients, an association with paraproteinemia, especially monoclonal IgG-κ proteinemia, can be found.1-5 Less often, bone marrow examination shows multiple myeloma.

No first-line NXG therapy has been established. The recommended therapies of corticosteroids (intranasal and/or systemic), alkylating agents (such as cyclophosphamide, melphalan, or chlorambucil), interferon alfa, antimetabolites, antimicrobial treatment, and plasmapheresis have shown inconsistent success.1,2,11-15 To our knowledge, this is the first report of successful treatment of NXG with intravenous immunoglobulin (IVIg).

REPORT OF CASES

CASE 1

Patient 1 was a 55-year-old woman first seen in 2008 with a 9-year history of progressive, erythematous, brownish, sharply demarked, indurated plaques with elevated erythematosus margins involving her face, neck (Figure 1A), extensive parts of her trunk, and large areas of her extremities. Protein electrophoresis revealed an elevated γ-globulin fraction of 13% of total serum protein with a positive extravagradient. Paraproteinemia had been present for more than 9 years. No plasmacytoma was found by urinalysis or bone marrow biopsy. Monoclonal gammopathy IgG-κ of undetermined significance was diagnosed.

Several biopsy specimens of cutaneous lesions revealed dense dermal infiltrates with macrophages, a few scattered lymphocytes, and some increase in mucin. Slight collagen degeneration was also present. The subcutis was not involved, and foamy macrophages and cholesterol clefts were missing. Although scleromyxedema was considered initially, histologically, the number of macrophages favored a diagnosis of NXG, as did the stereotypical clinical manifestations.

Previous ineffective treatments performed at other institutions included topical steroids, psoralen–UV-A with high-dose UV-A1 (administered repeatedly for several weeks), chloroquine (dose and duration not known), hydroxychloroquine (200-400 mg/d for 3 months), cyclosporine A (150 mg/d for 3 months), acetretin (25-30 mg/d for several months), and ceftriaxone (2 g/d for 21 days). In addition, 8 cycles of extracorporeal photopheresis at 4-week intervals were administered without any improvement.

The patient was then treated with IVIg, 0.5 g/kg/d, for 4 consecutive days at 4-week intervals. After the first cycle, the lesions stopped growing, and a softening of the involved skin was noted. During further treatment with IVIg, the plaques continuously decreased in thickness (shown clinically and via ultrasonography of the skin) and in duration and became paler (Figure 1B). After the fourth IVIg cycle and almost complete regression of the lesions in most sites, we increased the treatment intervals to 6 weeks, and improvement continued. After 6 cycles of IVIg therapy, biopsy specimens from the residual pale erythematosus area revealed a complete resolution of infiltrates. The level of free λ light chains in the serum did not decrease during the treatment (readings included 105, 133, and 170 mg/L) (normal range, <26.3 mg/L). At last follow-up, 11 IVIg cycles had been completed, and the interval between cycles had been extended to 8 weeks.
CASE 2

Patient 2 was a 69-year-old woman with a 5-year diagnosis of NXG and concomitant IgG-k monoclonal gammopathy of undetermined significance. However, she reported having increasing numbers of skin lesions for more than 25 years. The patient was seen with slowly but continuously progressive, asymptomatic, yellow to brownish, sharply demarcated plaques with elevated erythematous margins on her face, left upper arm (Figure 2A), right forearm, thighs, and trunk. The largest lesion, on her left hip, measured 60 x 80 cm.

The patient was treated over the decades with intravenous and oral prednisolone (long-term treatment with intermittent doses between 10 and 15 mg/d), clofazimine (100 mg/d for about 3 months), UV-A1 (10 cycles at high dose), diamino-diphenyl sulfone (dapsone) (100 mg/d for 5 months), minocycline (100 mg/d for several months), interferon alfa-2a (3 Mio IU subcutaneously 3 times a week for 3 months), and mycophenolate mofetil (500 mg/d for several months), all without clinically significant effect. Four years before we first saw her, hematologic examination at another institution revealed multiple myeloma. She underwent 4 cycles of chemotherapy with melphalan (0.25 mg/kg) and prednisolone treatment (50 mg/d for 4 days every 4 weeks), but the skin lesions remained unaffected (although the serum levels of paraproteins decreased).4

Finally, the patient was administered 0.5 g/kg/d of IVIg for 4 consecutive days every 4 weeks. The elevated margins of the skin lesions, induration, and erythematous color decreased substantially after 2 cycles and continued improving with successive cycles (Figures 2B). Some hyperpigmentation remained, especially on the face and lower extremities. The therapeutic interval was extended to 10 weeks, with further remission.

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**Figure 1.** Our patient before (A) and after (B) intravenous immunoglobulin (IVIg) therapy. A, Erythematous, brownish, sharply demarcated, indurated plaques on the face showing elevated erythematous margins. B, Substantial clinical improvement seen after 4 cycles of IVIg treatment.

**Figure 2.** Our patient before (A) and after (B) intravenous immunoglobulin (IVIg) therapy. A, Yellow to brownish sharply demarcated plaques with elevated erythematous margins on the upper extremities. B, Elevated margins of the skin lesions, induration, and erythematous color decreased substantially after 6 cycles of IVIg treatment.
At last follow-up, it was decided that the interval would be extended to 12 weeks, to be followed by treatment intermission if remission was stabilized. A total of 10 cycles of IVIg treatment were administered. The level of free κ light chains in the serum was normal (readings included 12.9, 14.9, and 15.4 mg/L) (normal range, <26.3 mg/L). However, an initially increased level of total κ light chains (18.1 g/L) had normalized already within the first months of treatment (10.5 g/L) (normal range, <12.8 g/L).

A biopsy specimen obtained in 2004 showed a dermal infiltrate of epithelioid macrophages with foreign body–type giant cells, xanthomatized macrophages, and many foam cells together with dermal collagen degeneration extending into the subcutis (Figure 3). Admixed were a few lymphocytes, neutrophilic granulocytes, and plasma cells. A biopsy specimen obtained from a residual upper-arm lesion after the fifth IVIg treatment cycle showed almost complete resolution of the infiltrates.

**COMMENT**

Treatment of NXG is difficult. To our knowledge, a universally effective treatment has never been reported. Corticosteroids (intraleisonal and/or systemic), alkylating agents (eg, cyclophosphamide, melphalan, chlorambucil), antimetabolites, plasmapheresis, and antimicrobial treatment have all been reported to have inconsistent and often unsatisfying outcomes.1,2,11-15 In our 2 cases, many of the known treatments, including extracorporeal photopheresis, were administered without success.

Successful IVIg treatment of paraproteinemia-associated dermatoses, such as scleromyxedema, has been reported.16-18 In our patients, IVIg showed a striking therapeutic effect on NXG. Given the association of NXG with IgG-monoclonal gammopathy (more often IgG-κ than IgG-λ) and with multiple myeloma, it is believed that elevated paraprotein levels play an important role in the pathogenesis of NXG because they might be autoantibodies that stimulate fibroblast proliferation and dermal macrophage deposition. It has also been suggested that the paraproteins cause a giant-cell inflammatory response after being complexed with lipids and deposited in the skin.19 Matsuura and colleagues20 hypothesized that activated monocytes accumulate lipids and are deposited in the skin, thereby eliciting a giant-cell foreign-body response. Others assume that the paraprotein has functional features of a lipoprotein, which may bind to lipoprotein receptors of the macrophages and thereby induce xanthoma formation.21 Finally, an infectious cause has been proposed, based on the discovery of spirochetes in NXG lesions.22

At present, we can only speculate about the molecular mechanisms of IVIg on the improvement of lesions in NXG. However, data from other immune disease models may give us some ideas. With regard to inflammation, immunoglobulins exhibit a dual function. Pathogenic antibodies induce a reaction by activating the complement cascade and the stimulatory Fc receptors on immune cells and by inducing cross-talk between complement and Fc receptors on macrophages.23,24 Phagocytosis, mediated by the Fc receptor, has been blocked by IVIg.25 Moreover, the inhibitory FcγRIIB receptor is modulated from a small subpopulation of the IVIg preparation that contains a specific sialic acid glycoform, resulting in decreased release of proinflammatory cytokines.26-27 The current theories of IVIg-mediated effects include (1) neutralization of pathogenic antibodies by idiotypic or anti-idiotypic antibodies, (2) modulation of expression and function of Fc receptors, (3) change in cytokine network, (4) modulation of B- and T-cell activation, (5) change in Fas apoptotic pathway, (6) effects on dendritic cells and macrophages, and (7) interference with activation of complement.28-30

While IVIg therapy is expensive, it is generally well tolerated, and its adverse effects are rare and easily managed. While some concerns about IVIg adverse events have been raised, mainly acute renal failure and thrombembolic events, long-term IVIg therapy has been found in several studies to be safe and well tolerated by most patients.31,32 The main adverse event during the loading dose period is headache. The annual rate of any adverse event during the IVIg maintenance period found in a large study was 4.4% during the first year, and this trended...
downward with every passing year of treatment without any serious event.31 In general, life-threatening reactions to IVIg are very rare.33 Of the possible pharmacologic predictors, including dose, IgG concentration, IgA level, pH, glycine content, sugar content, sodium content, and osmolality, only IgA level was found to be significantly associated with adverse events.32 The skin lesions in our patients improved dramatically. Therefore, our findings suggest that IVIg can be a successful option in the treatment of this rare and severe disease.

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REFERENCES


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