

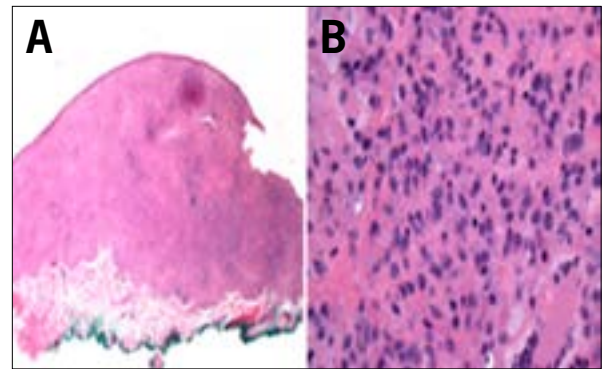
# Periorbital Necrobiotic Xanthogranuloma Treated Successfully With Novel Multiple Myeloma Therapy

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## Case Report

A 46-year-old woman with a medical history of a multinodular goiter presented to the department of dermatology with extensive yellow papules and nodules surrounding both eyelids that had developed over the past 3 years. A skin biopsy was done that showed chronic granulomatous dermal inflammation and foreign body giant reaction consistent with juvenile xanthogranuloma after ruling out a ruptured chalazion. She was subsequently referred to our institute for a comprehensive dermatology evaluation and underwent a repeat biopsy of the skin of the right lateral canthus, which resulted in a diagnosis of necrobiotic xanthogranuloma (NXG, Figure 1). Given its association with underlying plasma cell dyscrasias, a workup was undertaken. The complete blood count (CBC) revealed a white blood count (WBC) of  $2.93 \times 10^3/\mu\text{L}$ , absolute neutrophil count (ANC) of 950 cells/ $\mu\text{L}$ , and hemoglobin level of 16.6 g/dL. The chemistry panel showed plasma protein of 8.6 g/dL, plasma albumin of 4.3 g/dL, creatinine of 0.86 mg/dL, and calcium of 9.2 mg/dL. The serum protein electrophoresis (SPEP) test showed an M-spike in the  $\gamma$  region of 1.64 g/dL, and the serum immunofixation electrophoresis (IFE) test showed IgG  $\kappa$ . Urine protein electrophoresis (UPEP) was negative for Bence-Jones protein.  $\beta_2$  microglobulin was 2.58 mg/dL. Quantitative immunoglobulin testing revealed an elevated IgG of 2180 mg/dL (normal, 751-1560 mg/dL). A bone marrow biopsy revealed plasma cell dyscrasia with hypercellular marrow (60%) and an atypical plasma cell population of 7% of the bone marrow space. Immunohistochemical staining revealed a subset of plasma cells that



**Figure 1.** A, Hematoxylin and Eosin [H&E] stain demonstrating dense infiltrate of inflammatory cells in the dermis. B, H&E stain showing characteristic extracellular lipid and cholesterol clefts in acellular necrobiotic debris.

A is  $\times 20$  (original magnification) and B is  $\times 400$  (original magnification).

were positive for BCL-1, CD123, and CD 117-C-KIT. A definite clonal plasma cell population was not detected by immunohistochemical stains for  $\kappa$  and  $\lambda$  light chains on the bone marrow sample, presumably because any small clonal proliferation was obscured by more numerous benign background polytypic plasma cells. However, flow cytometry showed a small population of  $\kappa$ -restricted plasma cells. A skeletal survey was negative for any lytic lesions.

Hematologic studies and bone marrow findings were consistent with monoclonal gammopathy of unknown significance (MGUS). Owing to pain associated with the skin lesions and cosmetic concerns, therapy was initiated with lenalidomide (Revlimid, Celgene) 25 mg orally daily for 3 weeks given on a 28-day cycle. After adjusting the lenalidomide dose for neutropenia at the second cycle, dexamethasone 40 mg on days 1, 8, and 15 of a 28-day cycle was added in the third cycle. The patient completed 5 cycles by August

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**Figure 2.** Skin appearance prior to treatment with lenalidomide and dexamethasone (A), and after treatment (B).

2012, with M-spike improving to 1.04 g/dL. The dermatologic evaluation following the addition of dexamethasone to the third cycle revealed near-complete resolution of bilateral superior eyelid papules, as well as right lateral and left medial canthus nodules.

Owing to worsening neutropenia, lenalidomide and dexamethasone were discontinued after the fifth cycle. However, the patient's lesions recurred, and we reinstated therapy within 3 months of discontinuation of lenalidomide with a combination of thalidomide 100 mg and dexamethasone 20 mg a day for 4 days every 2 weeks. At this time, there was an M-spike of 1.22 g/dL and the IgG was 1930 mg/dL. A dramatic dermatologic response (Figures 2A and 2B) and decrease in gammopathy (M-spike, 1.08 g/dL; IgG, 1680 mg/dL) was seen after 3 months of therapy, which the patient continued with good tolerance.

## Discussion

NXG is a chronic and progressive non-Langerhans histiocytosis,<sup>1</sup> with a prevalence slightly higher in women than in men and a reported mean age of onset in the sixth decade of life.<sup>2</sup> It is primarily a cutaneous disorder with a proclivity for periorbital involvement (>70% of cases), followed by involvement of the trunk and extremities, with more than 1 site being involved in more than 90% of cases.<sup>2</sup> The disease is characterized by indurated, violaceous yellow-red nodules or plaques in the dermis or subdermal tissues<sup>3</sup> and may show signs of ulceration, telangiectasis, and atrophy.<sup>4,5</sup> Extracutaneous lesions, reported in order of decreasing frequency, include involvement of the lung, heart, oral cavity, orbit, liver, spleen, medulla, genitalia, mastoid, facial nerve, and kidney.<sup>2</sup> These findings are often asymptomatic and evasive, with diagnosis confirmed only in postmortem biopsy.<sup>6</sup>

NXG typically demonstrates a histologic mix of inflammatory cells, with histiocyte predominance and areas of necrobiosis. The amount of xanthomatous change

is variable and may be inconspicuous. Touton-type giant cells with peripheral cytoplasmic xanthomatous change are a classic finding, but foreign body giant cells are also frequent. The presence of extracellular lipid is an important feature, and cholesterol clefts may be seen. Changes can involve both the dermis and subcutaneous tissue.

The association between NXG and hematologic malignancies has been described in the literature. The most commonly described association is plasma cell dyscrasia, such as monoclonal gammopathy of unknown significance (MGUS), with up to 80% of patients having IgG gammopathy with either  $\kappa$  (71% reported) or  $\lambda$  (28% reported) light chain, with infrequent association with IgA and IgM gammopathy.<sup>2</sup> The association with multiple myeloma has been reported in 20 cases.<sup>2</sup>

Other associations include non-Hodgkin lymphoma, chronic lymphocytic leukemia,<sup>7</sup> Hodgkin lymphoma,<sup>8</sup> lymphoplasmacytic lymphoma,<sup>9</sup> Waldenström's macroglobulinemia,<sup>10</sup> amyloidosis,<sup>11</sup> and myelodysplastic syndrome.<sup>12</sup> The cutaneous lesions may either precede or follow development of malignancy, with nearly all cases favoring the former.<sup>13</sup> Reportedly, hypocomplementemia is the most common laboratory abnormality, followed by leukopenia, cryoglobulinemia, and hyperlipidemia.<sup>2</sup>

Various treatment modalities have been employed, with variable dermatologic responses seen with immunomodulatory drugs, immunosuppressive agents, alkylating agents, corticosteroids, high-dose therapy, and autologous stem cell transplantation.<sup>5,14</sup> Such strategies could be used in addition to local therapy, including local steroid injection, surgery, or carbon dioxide laser treatment. The correlation between dermatologic response and gammopathy has been reported, with inconsistent results.<sup>2</sup>

Surgical excision of periorbital lesions has been associated with a high rate of recurrence, stimulation of lesional activity, and scar formation with resultant eyelid retraction; therefore, avoidance of surgery has been recommended.<sup>15,16</sup>

The efficacy of intralesional injection with triamcinolone acetonide has been reported in 2 patients with small volume periorbital disease.<sup>12</sup> One of the 2 patients had underlying MGUS and was treated with 9 injections of triamcinolone. The patient had improvement in symptoms of nodularity, discoloration, and diplopia, but not in proptosis or pain; the other reported case did not mention any correlation with underlying paraproteinemia.

Interestingly, lenalidomide resulted in a response at 3 months and no recurrence at a 12-month follow-up in 1 reported case.<sup>16</sup>

Thalidomide use has been reported in 3 cases.<sup>17</sup> In the first case, no improvement in xanthomatous lesions was reported with thalidomide 200 mg/day; however, associated skin ulcer did improve.<sup>18</sup> The second case was a patient with scleritis who was treated with an unknown

dose and duration.<sup>19</sup> The third patient was treated with thalidomide for 24 months and dexamethasone for 9 months, with documented remission at a follow-up of more than 3 years.<sup>17</sup>

The xanthomatous lesions of the patients reported to have received an immunomodulatory drug in combination with dexamethasone responded notably well in all cases. This demonstrates that these drugs could potentially be promising in maintaining long periods without symptoms and conserving skin integrity.<sup>2</sup>

The length of systemic treatment has not been defined. In the case series mentioned using lenalidomide and thalidomide, duration of treatment was 3 and 24 months, respectively.<sup>20</sup>

These drugs, incorporated either in standard-dose regimens or in high-dose protocol with autologous transplantation, are appropriate for patients with NXG and associated overt multiple myeloma. In contrast, treatment should be proposed in patients with MGUS if progression of underlying gammopathy is evident or if extracutaneous localization or cosmetically disfiguring lesions exist, as in our patient.

The skin lesions in our patient improved dramatically with a combination of immunomodulatory therapy with corticosteroids, which is congruent with the results attained in previously reported cases.

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## Commentary

### Immunomodulatory Drugs for the Treatment of Periorbital Necrobiotic Xanthogranuloma

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Immunomodulatory drugs (IMiDs) are novel agents used in the treatment of some hematologic malignancies, including multiple myeloma (MM). The introduction of these agents has led to significant improvements in the overall survival and quality of life of multiple myeloma patients.<sup>1</sup> IMiDs have a wide spectrum of effects on the immune system, including downregulation of tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), a highly pleiotropic cytokine produced primarily by monocytes and macrophages, which plays a central role in the host protective immune response to infections.<sup>2</sup> IMiDs also downregulate IL-1 $\alpha$  and IL-6, increase production of IL-10 from mononuclear cells, enhance natural killer (NK) cell activity, and modify cytokine production and T-cell activity.<sup>2</sup>

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Ghani and associates<sup>3</sup> reported the successful use of the immunomodulatory drugs thalidomide and lenalidomide (Revlimid, Celgene), in the treatment of a patient with periorbital necrobiotic xanthogranuloma (NXG) who was noted to have IgG  $\kappa$  monoclonal gammopathy. NXG is a rare and progressive granulomatous disorder that is most common in the periorbital area. NXG was first described in 1980 by Kossard and Winkelmann in a case series of 8 patients with multiple xanthomatous plaques and subcutaneous nodules with xanthogranulomatosis and necrobiosis on histologic examination.<sup>4</sup> All of the patients were noted to have monoclonal gammopathy with predominantly IgG  $\kappa$  (6 of the 8 patients). A larger review of 48 patients with NXG noted that 32 of them had monoclonal gammopathy.<sup>5</sup> It was also reported that low complement levels, anemia, and leukopenia are frequently associated with NXG. The pathogenesis of NXG remains unclear. Theories regarding pathogenesis include deposition of immunoglobulins and lipid complexes with a foreign body giant-cell reaction and monocyte activation with intracellular lipid accumulation.<sup>6</sup>

Treating patients with NXG has been challenging, as there are no established treatment guidelines. Surgical excision has been attempted with some success, but it proposes the risk of cosmetic disfigurement.<sup>7</sup> Other employed treatment modalities available are corticosteroids,<sup>8</sup> chlorambucil,<sup>9</sup> melphalan,<sup>10</sup> intravenous immunoglobulin,<sup>11</sup> interferon  $\alpha$ -2b,<sup>12</sup> plasmapheresis,<sup>13</sup> and autologous stem cell transplant.<sup>14</sup>

Thalidomide activity was first reported as a potential treatment for relapsed MM patients in 1999,<sup>15</sup> but it was later noted to be associated with considerable toxicity.<sup>16</sup> Lenalidomide, an analogue of thalidomide, was developed to have greater anti-MM activity and improved tolerability compared with thalidomide, with a lower risk of thrombosis and neuropathy.<sup>17,18</sup> A case report of thalidomide in combination with dexamethasone was reported earlier in the treatment of an NXG patient with monoclonal gammopathy who achieved a complete resolution of skin lesions and a sustained response for more than 3 years after treatment.<sup>19</sup>

The case report by Ghani and associates shows a good response to treatment with IMiDs and corticosteroids in a patient with periorbital NXG associated with monoclonal gammopathy. Based on this case report and similar earlier case reports, immunomodulatory drugs for the treatment

of NXG may be the new treatment of choice, as they can be both effective and less toxic than other treatment options. Given the rarity of NXG, conducting a clinical trial to test the duration and effectiveness of such treatments is a challenge. Accordingly, this signifies the importance of these case reports to help establish a treatment approach in the meantime.

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