Necrobiotic Xanthogranuloma With Scleroderma

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GOAL

To understand the presentation and treatment of necrobiotic xanthogranuloma (NXG)

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Explain the laboratory and histopathology results in NXG.
2. Discuss the theoretical pathogenesis of NXG.
3. Describe the treatment options for NXG.

CME Test on page 317.

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Dr. Russo reports no conflict of interest. The author reports off-label use of the following medications: extracorporeal photophoresis, cyclophosphamide, methotrexate, nitrogen mustard, adrenocorticotropic hormone, azathioprine, radiation therapy, plasmapheresis, hydroxychloroquine, thalidomide, and etretinate. Dr. Fisher reports no conflict of interest.

I report the case of a 68-year-old man who presented with necrobiotic xanthogranuloma (NXG) with concomitant scleroderma, along with the presence of cryoglobulins and cryofibrinogen in the blood. Autoamputation of the distal fingers and parts of the ears also occurred, over time, with exposure to cold temperatures. This is an interesting constellation of findings in this rare disorder that raises questions concerning its pathogenesis. A review of the literature is included.

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Necrobiotic xanthogranuloma (NXG) is a histiocytic disorder often associated with immunoglobulin G (IgG) paraproteinemia and various other systemic laboratory findings.[1] Its distinctive cutaneous lesions show some similarities to both xanthomatous and necrobiotic processes. The orange-yellow of NXG lesions is similar to the color of classic xanthoma, while the

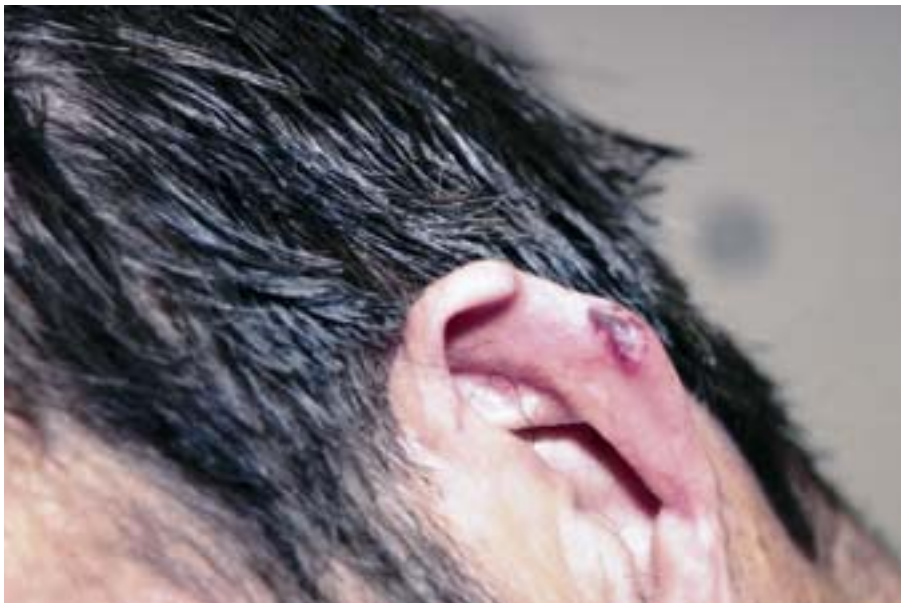

Figure 1. Cold temperature–induced necrosis and autoamputation of a portion of the ear.

atrophy and telangiectasia seen in NXG give the lesions an appearance that is somewhat similar to that of necrobiosis lipoidica.[2] Before NXG was recognized as a distinct disease entity, histologic examination often labeled NXG lesions as "atypical necrobiosis lipoidica."[1]

Case Report

A 68-year-old man presented in June 2000 with multiple, large, firm, orange-yellow indurated plaques distributed over various areas of his body. He stated that the plaques had begun in 1973 on his upper back. He first sought treatment in 1976 at the age of 44 years, when he began to have progressive Raynaud phenomenon and increasing sclerodactyly of the fingers and hands. At that time, results from antinuclear antibody (ANA) and cryoglobulin tests were within reference range, but in 1977, results from a bone marrow biopsy revealed an IgG paraproteinemia λ type that showed decreased iron stores only. In 1982, the patient's fingers had begun to tighten distally and, on radiography, to thin distally, with a penciling effect. Laboratory studies yielded the following values: erythrocyte sedimentation rate (ESR), 48 mm/h; triglyceride, 207 mg/dL; and cholesterol, 244 mg/dL. A biopsy of the bone marrow now showed 10% plasma cells, but those findings were not diagnostic of multiple myeloma. The results from a skin biopsy and workup to rule out Hansen disease were negative, with no definitive diagnosis made.

In 1983, laboratory results were positive for cryoglobulins, and the patient underwent plasmapheresis for 3 months, with some improvement in his fingers and hands but no improvement in his indurated skin plaques. Later, he was given a trial of prednisone without improvement in his skin plaques. At that time, his IgG paraproteinemia was 1.08 gm/dL. By 1988, ulceration and necrosis of his fingers bilaterally on exposure to cold temperatures (resulting in autoamputation of their distal parts) began to appear.

In 1990, as more orange-yellow plaques became visible on his arms, legs, and anterior trunk, a biopsy of one of the arm lesions was performed, and because necrobiotic areas in the dermis were found, the results were interpreted as necrobiosis lipoidica. In 1993, a biopsy of the original plaque on his upper back showed areas of necrobiosis—with scattered giant cells and areas of xanthomatous changes—and the condition was diagnosed as NXG. The patient underwent treatment with extracorporeal photophoresis for 3 months but reported no real benefit in his skin lesions.

In June 2000, examination revealed cold temperature–induced necrosis and autoamputation of areas of his ears (Figure 1), which the patient stated had occurred episodically since 1997. Examination of the skin showed large, hard, indurated, orange-yellow xanthomatous plaques, with areas of necrosis on the upper back, upper chest, abdomen, arms (Figure 2), and both lower legs. His hands showed severe sclerosis with contractures, and autoamputation of the right distal portions of the fingers. Furthermore, surgical amputation of the left distal fingers had been performed in 1997 because of gangrene and failure to autoamputate (Figure 3).

A biopsy of a relatively new plaque on his abdomen revealed large areas of necrobiosis, with

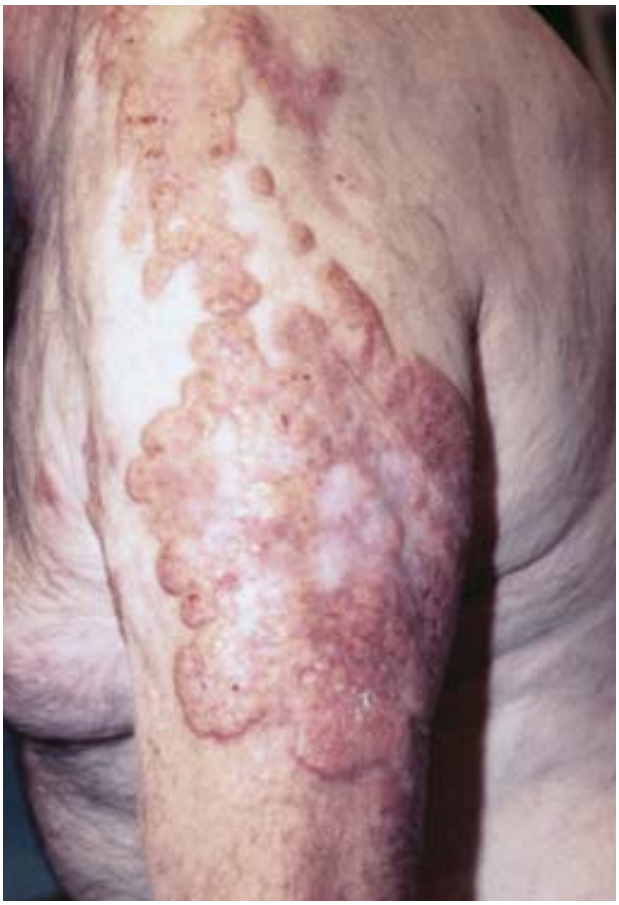

Figure 2. Orange-yellow xanthomatous and sclerotic plaques of necrobiotic xanthogranuloma on the arm.

palisading foamy histiocytes, scattered multinucleated giant cells, and cholesterol clefts (Figure 4). Laboratory results were positive for cryoglobulins and cryofibrinogen. Other laboratory results were as follows: ESR, 92 mm/h; cholesterol, 260 mg/dL; triglyceride, 192 mg/dL; C3, 154 mg/dL (reference range, 88–201); and C4, 14.2 mg/dL (reference range, 16–47). Results from ANA and Scl-70 testing were both normal. A bone marrow biopsy was performed and again interpreted as negative, with no signs of multiple myeloma. Complete blood count showed decreased white blood cells (3700/μL), along with decreased hemoglobin and hematocrit levels, 11.3 g/dL and 33.8%, respectively. The patient's IgG paraproteinemia was now 2130 mg/dL. Echocardiography showed no abnormalities. The patient elected not to undergo any systemic therapy at that time.

Comment

NXG is a rare condition, first described in 1980 by Kossard and Winkelman.[1] It features orange-yellow to red-purple plaques and nodules on the skin. NXG lesions can be characterized by telangiectasia, atrophy, and scarring.[2] The location of the lesions is often in the periorbital areas but can occur on the trunk and extremities, as well. In an excellent 1992 review of more than 48 cases, Mehregan and Winkelman[3] noted that the periorbital region was the most frequently involved area, followed by the trunk, other areas of the face, and extremities. A case of NXG with involvement of the lacrimal gland and episclera only, without skin lesions, has been documented.[4] When lesions are periorbital, they are often bilateral and symmetric and produce a wide range of symptoms, such as pain and blurred vision.[3] Ulceration and pain are not uncommon features of NXG lesions. The incidence of ulceration has been reported as 42% to 43%.[2,5] Lesions also have been noted in old surgical scar sites.[5] In 3 large series, the age of onset ranged from 53 to 56 years.[2,5] The youngest reported case in the literature is that of an 18-year-old woman.[6]

There have been many laboratory abnormalities reported in patients with NXG. The most characteristic finding is a paraproteinemia, usually of the IgG type.[3] IgA paraproteinemia has been reported as well but much less frequently.[7,8] In one large series, 77% of patients with NXG had an IgG paraproteinemia, with 10 of those 26 patients with paraproteinemia also having an associated multiple myeloma, plasma cell dyscrasia, or lymphoreticular disorder.[5] Another series demonstrated a 73% frequency of IgG paraproteinemia in NXG patients, with 2 of those 16 patients with paraproteinemia also having an associated multiple myeloma.[2] Other frequently reported abnormalities include elevated ESR, decreased CH50, decreased C3 and C4 levels, anemia, and leukopenia. To our knowledge, cryoglobulinemia has been reported in 8 prior cases, as well as in the patient described herein. There has been one prior report of cryofibrinogenemia, which also was present in our patient.[9] Elevated serum lipid and glucose levels have been noted occasionally[10-12]; our patient also had an elevated serum lipid level.

Systemic disorders associated with NXG are mainly malignancies of the hematologic or lymphoproliferative type, in particular multiple myeloma.[5] Mehregan and Winkelman[3] have commented that plasmacytosis of the bone marrow is frequent in patients with NXG, but the occurrence of multiple myeloma is still a relatively rare finding. Besides multiple myeloma, chronic lymphocytic leukemia has occurred in one patient with NXG.[5] Recently, amyloidosis of the liver has been reported in one NXG patient.[13] Involvement of internal organs with NXG lesions has been reported occasionally but is

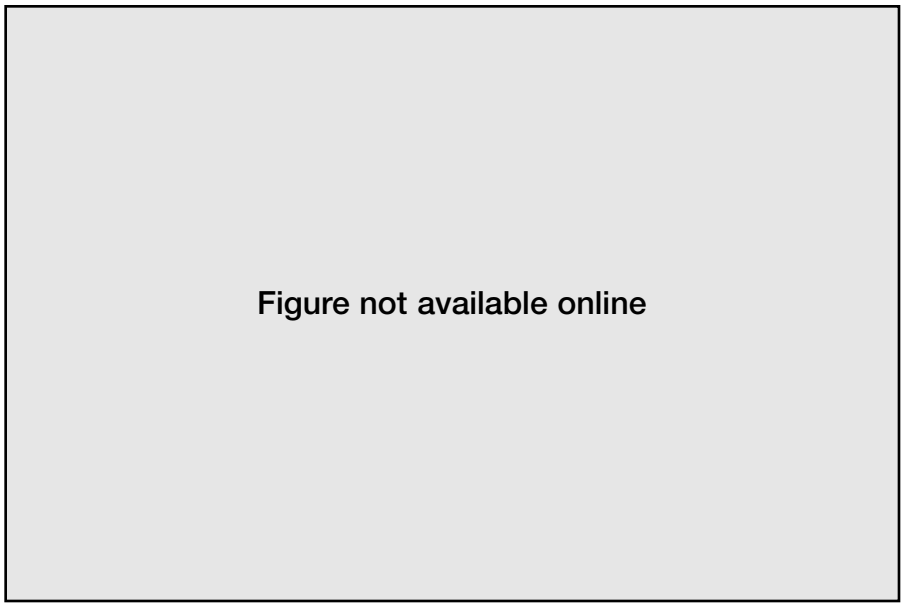

Figure 3. Sclerotic hands with autoamputation of the distal right fingers and surgical amputation of the distal left fingers.

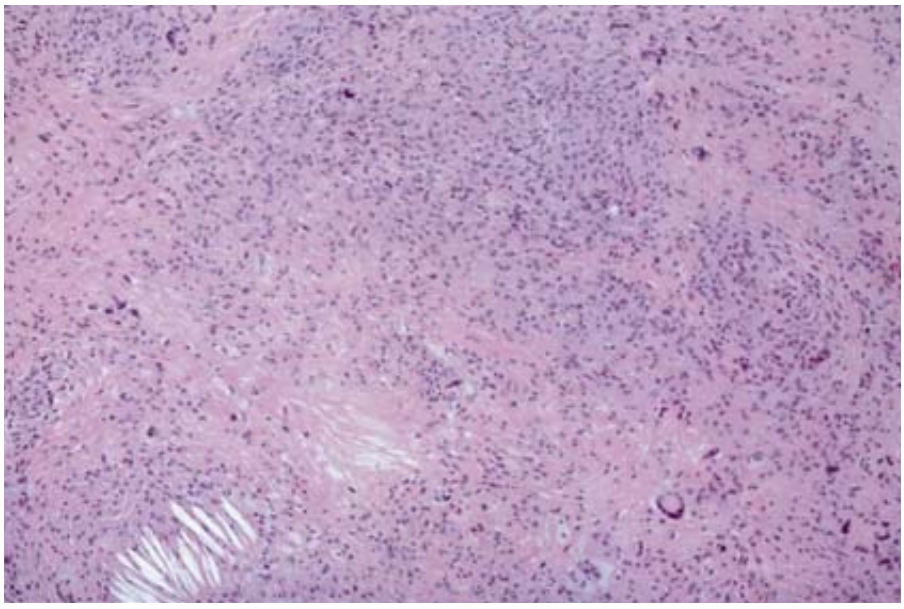

Figure 4. Areas of necrobiosis with palisading foamy histiocytes, scattered multinucleated giant cells, and cholesterol clefts (H&E, original magnification ×10).

probably underreported. Based on their findings, Umbert and Winkelman[11] have recommended that a search for cardiac involvement be undertaken in NXG patients. Echocardiography and dynamic cardiac imaging are recommended.

Histopathologic findings in NXG are usually distinctive.[14] Zones of necrobiosis and fibrosis are seen in the dermis and subcutaneous tissues, with xanthogranulomatous palisading. Characteristically, there are numerous bizarre giant cells of either the Touton or foreign body type.[15] Cholesterol clefts occur in the necrobiotic areas in one third of biopsies, and one half of biopsies show lymphoid nodules, usually found around the areas that have lots of plasma cells.[14] There have been cases of NXG wherein giant cells have been sparse with no cholesterol clefts.[7,15] Leukocytoclasis has been reported only rarely.[7,15] Kossard et al[15] have pointed out that NXG cases that are poor in lipid and giant cells are analogous histologically to the early presentation of juvenile xanthogranuloma, in which Touton giant cells and xanthomatisation are absent. In addition, amyloid deposits in NXG skin lesions have been reported in one patient who also had amyloidosis of the liver.[13] A recent ultrastructural study of an apparent mild case of NXG

demonstrated that the dermal histiocytes were not of the Langerhans cell type.[16]

The pathogenesis of NXG is still unknown. One theory proposes that increased serum IgG complexed with lipid may be deposited in the skin, eliciting a foreign body giant cell reaction that gives the histopathologic changes seen.[17] Another theory proposes that the paraprotein has functional features like a lipoprotein and that the paraprotein binds to lipoprotein receptors in histiocytes, thus stimulating xanthoma formation.[18] These hypotheses do not explain how the lesions occur in NXG cases in which there is no paraproteinemia. An excellent study of one patient with NXG with severe hypocholesterolemia (1.69 mmol/L) demonstrated that the patient's peripheral monocytes were activated and contained a 3-fold increase in cholesterol ester and greatly enhanced low-density lipoprotein uptake capability.[19] The patient also had increased serum levels of macrophage colony-stimulating factor (M-CSF). The authors proposed that the increased M-CSF activated the patient's monocytes to then uptake large amounts of tissue lipid, leading to xanthoma formation and resulting in serum hypocholesterolemia. Although this appears to be a promising finding, there have been cases of NXG in which the patients had increased serum lipids, such as the patient described in this case report.

Our patient also had scleroderma, which was manifested as severe sclerosis of his hands, Raynaud phenomenon, and ulceration and gangrene of portions of his ears and fingers due to cold temperature exposure. Cryoglobulinemia and cryofibrinogenemia, which exacerbate vascular hypersensitivity to cold temperatures, also were present in our patient and contributed to the eventual development of gangrene in certain areas. Recently, the case was reported of a woman with a long-standing history of linear morphea of one arm who developed a single lesion of NXG within the area of morphea.[20] The authors suggest that because there had been earlier reports[21,22] proposing and suggesting ischemia as a cause for morphea and NXG lesions, vascular damage and ischemia could explain the coexistence of NXG and morphea in their patient. Because our patient had such severe systemic ischemic changes—as evidenced by the multiple foci of gangrenous autoamputation that occurred over various areas of his body—it is possible that ischemia may be an initiating factor in both NXG and scleroderma.

An excellent study by Ugurlu et al[5] has followed the long-term course of 26 patients with NXG. At 15 years, overall survival was 90%, with 100% survival at 10 years after the appearance of skin lesions. More important, the time to development of malignancy (multiple myeloma, plasma cell dyscrasia, or lymphoproliferative disease) ranged from 8 years before skin lesions appeared to 11 years after.[5] In the series of NXG patients studied by Mehregan and Winkelman,[3] the multiple myeloma that developed in some patients also showed a relatively benign course. The skin lesions of NXG usually follow a course of slow progression.[3,5]

There is no one curative therapy for NXG; however, there are several treatment modalities that can be used, with varying degrees of success. A combination of chlorambucil or melphalan with oral corticosteroids is one of the most commonly used therapies for NXG.[3,23] Interferon alfa-2b is another treatment that has shown good results.[24,25] Cyclophosphamide, methotrexate, nitrogen mustard, adrenocorticotropic hormone, systemic corticosteroids, intralesional corticosteroids, azathioprine, and radiation therapy all have been used with varying degrees of success.[3,23,26] Plasmapheresis with hydroxychloroquine has been shown to treat ulcerative NXG lesions successfully, thus preventing the formation of new ulcers.[27] Plasmapheresis also has helped decrease the paraproteinemia associated with NXG.[27] Extracorporeal photophoresis was used in our patient, but there was no appreciable change in his NXG lesions. It should be noted that the patient received photophoresis for only 3 months, and this may not have been long enough to produce any significant clinical effects. Thalidomide and etretinate have been somewhat successful in treating ulcers from NXG.[28] The xanthomatous lesions of NXG, however, are not treated successfully with thalidomide or etretinate.[28] Surgical excision of NXG lesions usually results in relatively rapid recurrence.[5] Notwithstanding, there is a report of surgical excision of a single NXG lesion that had not recurred by the one-year follow-up.[20]

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