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CASE REPORT

Necrobiotic xanthogranuloma with paraproteinemia without periorbital involvement—a case report

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KEYWORDS

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ABSTRACT

Necrobiotic xanthogranuloma is an uncommon granulomatous disease involving the skin and extracutaneous tissues. It is characterized by indurated, yellow-red plaques and nodules, involving primarily the face and less frequently the trunk and extremities. The disease has a strong association with paraproteinemia and other hematologic or lymphoproliferative disorders. Histologically, the dermal part shows xanthogranulomatous change with extensive necrobiosis and many Touton and foreign-body giant cells. Here, we describe a case of a 46-year-old man with a 1-year history of multiple cutaneous lesions over the trunk and thighs. Necrobiotic xanthogranuloma was diagnosed by histology and clinically associated with paraproteinemia. This case is also unusual in that there was no periorbital involvement, which is believed to be a typical feature of this disease.

Introduction

Necrobiotic xanthogranuloma (NXG) is a rare destructive xanthogranulomatous disease classically involving the face, particularly the periorbital region, and the trunk. It has a chronic, progressive clinical course and is typically resistant to treatment. NXG is closely associated with paraproteinemia with a monoclonal gammopathy. Other hematologic or lymphoproliferative diseases may also appear in association with NXG.[1,2] The clinical course is chronic and often progressive. Because of the rarity of this disease, we report a patient with the cutaneous and histological findings of NXG with associated monoclonal gammopathy. The lack of characteristic involvement of the periorbital region in this patient is an unusual feature of this entity.

Case report

A 46-year-old man presented with a 1-year history of annular plaques of various sizes with raised erythematous borders around a depressed center, on the trunk, arms, buttocks, and legs (Figure 1). The patient's face was spared. The lesions began as indurated papulonodules, which slowly enlarged with advancing margins. The lesions were painful and became ulcerated. There were 12 lesions ranging from 2 cm to 5 cm in diameter. Two of them were ulcerated. A skin biopsy was performed on the lesion located on the left thigh.

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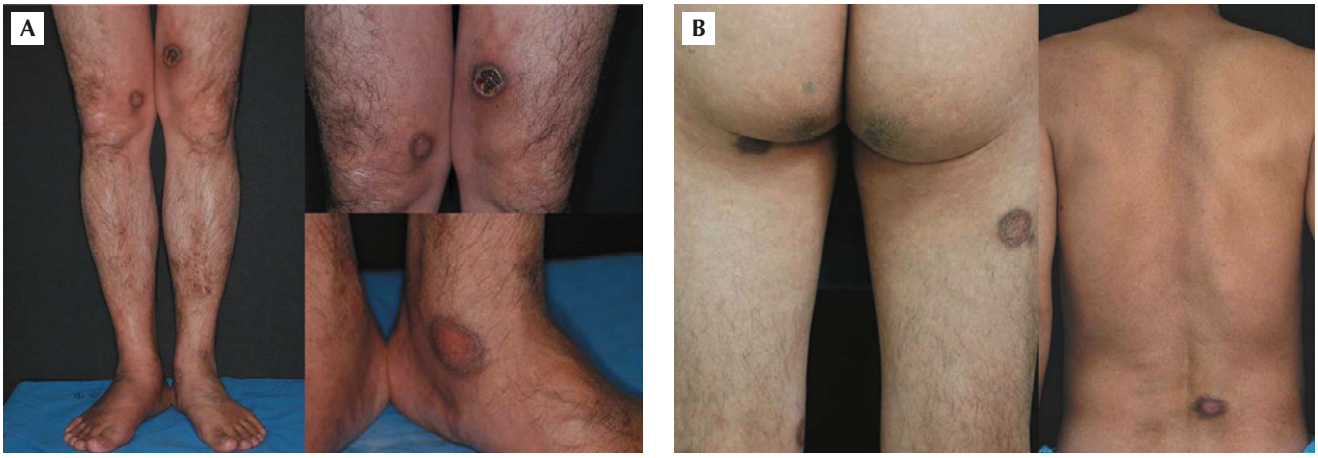

Figure 1 (A,B) Multiple annular plaques with raised erythematous borders and central depressions on trunk, arms, buttock and legs.

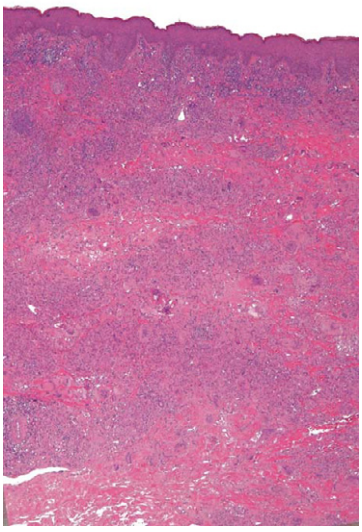

Figure 2 Skin biopsy specimen from the left thigh showed extensive geographic necrobiosis surrounded by histiocytes, many multinucleated giant cells, and lymphocytes throughout the dermis extending into deep subcutis (H&E, original magnification 40×).

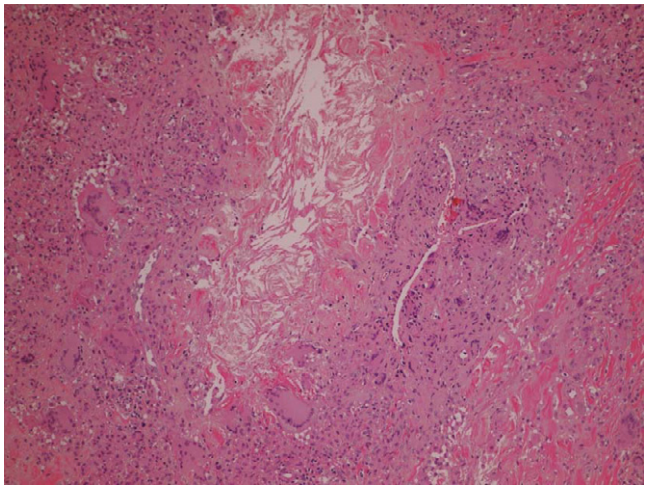

Figure 3 Higher magnification of extensive necrobiosis and dense histiocytic infiltrate with multinucleate giant cells (H&E, original magnification 100×).

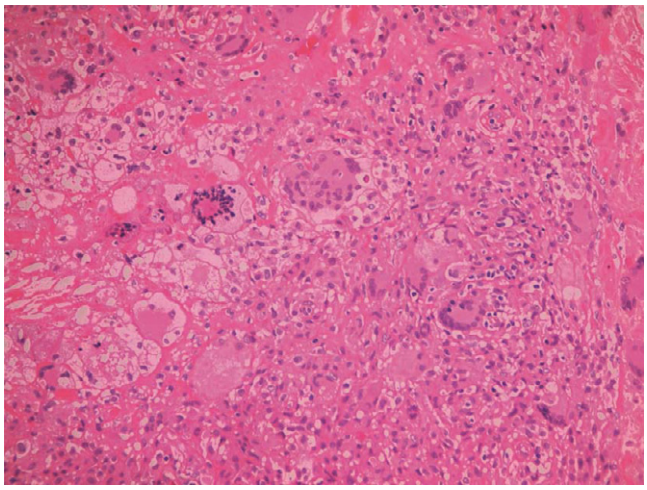

Figure 4 Conspicuous xanthomatous histiocytes were seen in this field (H&E, original magnification 400×).

Histological examination revealed massive palisading granulomatous inflammation around the extensive geographic necrobiosis throughout the dermis extending into deep subcutis (Figure 2). The areas of necrobiosis were surrounded by foamy histiocytes in addition to conspicuous giant cells (Figures 3 and 4), many of which were of the Touton type. Cholesterol clefts were also prominent (Figure 5). A diagnosis of NXG was made.

Laboratory investigation showed that the hemogram, test results for renal and liver function, fasting glucose levels, and lipid profiles were within normal ranges. Serum protein immunoelectrophoresis showed a monoclonal gammopathy of the IgG kappa type (IgG, 3350 mg/L; normal range: 700–1600 mg/L). Bence-Jones proteins were not detected in urine. Examination of the bone marrow showed normal cellularity

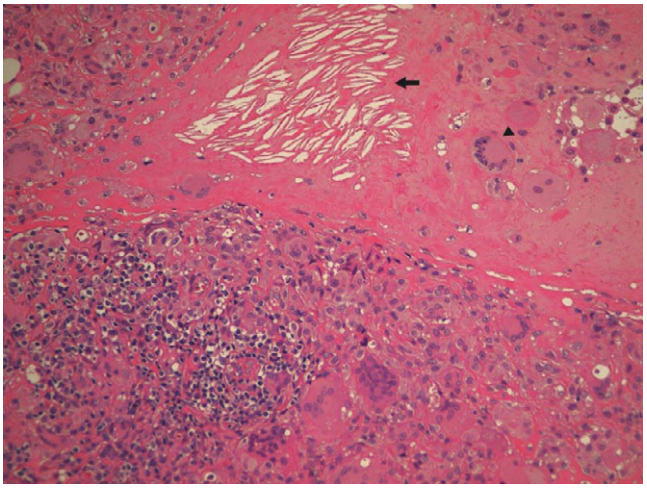

Figure 5 Bands of necrobiosis with cholesterol clefts (arrow) with surrounding Touton giant cells (arrowhead) and foamy histiocytes (H&E, original magnification 400×).

without an increase in the number of plasma cells. An elevated erythrocyte sedimentation rate (73 mm/hr; normal range: 0–15 mm/hr) was noted. Antinuclear antibody was positive at a low titer of 1:80. The C3 level was normal, but C4 levels were below 5.45 mg/L. Test results for rheumatic factor were negative, and cryoglobulin was not detected. Chest and skeletal X-rays were normal. Chest-abdominal-pelvic computed tomography was also negative.

This patient commenced with therapy of prednisolone 40 mg daily for 1 week. The skin lesions showed improvement, concurrent with softening of the lesions, and ulcerative wounds ceased to enlarge. The prednisolone was tapered to the dose of 20 mg daily and used for 2 weeks. Then the condition was controlled with 10 mg prednisolone daily, with gradual improvement of the lesions. The paraprotein level remained unchanged. However, two new lesions on the patient's left thigh appeared after 11 months of follow-up. Medium dose steroid (prednisolone 40 mg) therapy was re-initiated. Clinical condition was continually monitored.

Discussion

NXG was a rare condition and first recognized as a distinct entity by Kossard and Winkelmann in 1980.[1] The characteristic clinical picture is of slowly progressive infiltrating xanthomatous plaques, typically affecting the periorbital region. The face, trunk, arms and upper thighs are also commonly involved. A small number of patients without periorbital involvement have been described.[3–10] We reported another case of NXG in the absence of facial lesions. In reviewing the English literature of NXG patients who had no facial involvement, most patients presented with extensive lesions involving trunk, buttock and four extremities, as did our patient. In these patients, ulcerations occur early and are a prominent feature in most cases. NXG may also involve extracutaneous sites such as lung and heart.[11,12] Thus, routine echography and dynamic cardiac imaging are recommended. Many laboratory abnormalities are associated with NXG. In about 75% of reported cases, protein electrophoresis demonstrated a monoclonal gammopathy, most commonly an IgG kappa light chain,[1,12] as did the patient described here. Laboratory investigation also frequently showed elevated erythrocyte sedimentation rates, and about 50% of patients had leukopenia and hypocomplementemia.[12] Cryoglobulinemia has been found in approximately 40% of cases.[2,12] Some patients also demonstrated positive results for antinuclear antibody and rheumatic factor.[1,4] Serum cholesterol and triglyceride levels do not correlate with the disease, and are usually normal.

The histopathological features of NXG are distinct and observed mainly in the deep dermis and the subcutaneous tissues. NXG is marked by granulomatous inflammation, which is composed of foamy histiocytes, lymphocytes, foreign-body type multinucleated giant cells, and Touton giant cells alternating with collagen necrobiosis. Cholesterol clefts are usually observed within the necrobiotic foci[12,13] and are characteristic of NXG. Our case also displayed cholesterol clefts, which are a helpful clue for the differential diagnosis. Nodular lymphoid aggregates are often reported in association with the granulomas.[13] The major histological differential diagnoses with NXG is necrobiosis lipoidica. The clinical lesions of necrobiotic lipoidica could be confused with NXG, especially when lesions of the latter are present over the pretibial lesions. However, necrobiosis lipoidica is usually not associated with any serum protein abnormalities. The presence of massive necrobiosis associated with numerous cholesterol clefts, foamy histiocytes, bizarre multinucleated giant cells and Touton-type giant cells distinguishes necrobiotic xanthogranuloma from necrobiosis lipoidica.[13] Cholesterol clefts are rarely seen in necrobiosis lipoidica. A review of 331 cases of necrobiosis lipoidica, which extended over a 50-year period, identified only three cases with cholesterol clefts, and all were associated with severe diabetes mellitus.[14]

Given the high frequency of monoclonal gammopathy in patients with NXG, malignancies of the hematologic or lymphoproliferative type should be investigated. The most common associated malignancies are multiple myeloma, plasma cell dyscrasia and lymphoproliferative disease.[12,15] Hematologic disorders may emerge before or after the onset of skin lesions (8 years before onset to at least 11 years after onset).[16] For this reason, patients with NXG require lifelong follow-up care. But low incidence of multiple myeloma in the NXG population was noted ,which has a high incidence of paraproteinemia. In the largest and latest review by Spicknall and Mehregan[12] in 2009, only 3 NXG patients of the 70 reported since 1993 had multiple

myeloma. In the general population, 18% of all patients found to have a paraprotein have multiple myeloma, certainly a much higher percentage than in NXG patients with a paraprotein.[12]

There are many ways to treat NXG but they are often unsuccessful, and recurrences are frequent. Well-established therapeutic schemes are lacking because there have not been any randomized controlled trials. Chemotherapy with low-dose alkylating agents, such as melphan,[1,2] chlorambucil,[2,17,18] and cyclophosphamide[19,20] are the most commonly reported treatments for patients with NXG with or without accompanying plasma cell dyscrasias or multiple myeloma, because of the hypothesis that reduced paraprotein load will improve cutaneous disease. However, these therapies typically achieve incomplete or transient relief and cytotoxic side effects are also associated with potential serious morbidity. In addition, the response of the paraprotein level to different treatment modalities has been variable and is not essential for clinical improvement. Other treatments, such as high-dose corticosteroids, intralesional corticosteroids, interferon alpha-2b, methotrexate, and azathioprine have all been tried with variable success.[12,21,22] Surgical removal of the lesions should be avoided because of the high rates of recurrence at the excision sites. In 2007, Goede et al[23] reported the first case with NXG, who had been blinded by massive periorbital infiltration and was refractory to treatment with high-dose corticosteroid, interferon-alpha, and plasmaphereses, but successfully treated with autologous, peripheral blood stem cell transplantation. In our case, because of the absence of periorbital or systemic involvement and malignant tumor, we elected to treat this patient with steroids. However, relapse of cutaneous lesions was noted after 11 months of follow-up, even under maintenance treatment with prednisolone 10 mg daily. Poor wound healing of ulcerative lesions was also a challenge to treatment in our case.

The pathogenesis of NXG remains poorly understood. Bullock et al[24] first hypothesized that the paraprotein has the functional features of a lipoprotein that binds to the lipoprotein receptors of monocytes, thereby inducing xanthoma formation. Langlois et al[25] suggested that the monoclonal gammopathy may be the initial abnormality, and the xanthogranuloma may arise from secondary proliferation of macrophages bearing receptors for the Fc portion of IgGs. However, instead of the expected monotypic staining, Wood et al[13] found polytypic staining patterns in the inflammatory cells of all 11 NXG skin biopsies. Therefore, the author suggested that the skin lesions in NXG represent reactive inflammation and are possibly not associated with the presence of monoclonal plasma cells or multiple myeloma. Additional studies are warranted.

In summary, NXG is a rare disorder that is associated with lymphoproliferative disorders such as multiple myeloma. It is often misdiagnosed and can be confused both clinically and histologically with other granulomatous and xanthomatous diseases. The prognosis of NXG depends on the severity of disease and the extent of extracutaneous involvement. We presented a patient with the histological and laboratory features of NXG. Unlike most patients with NXG, he did not have periorbital lesions at presentation. Because NXG is associated with a potentially life-threatening systemic disease, its recognition by the physician is important.

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