

Case scenario

A 54-year-old Chinese woman with a history of alcoholic cirrhosis and hypersplenism presented in 2003 with bilateral peri-orbital, malar, and glabellar swelling (Fig 1). She had a history of milder glabellar swelling 7 years ago. An incisional biopsy of the lesion taken at that time showed granulomatous inflammation. She subsequently failed to attend for follow-up. She came back when she discovered the lesions had enlarged and progressed to her lower eyelids and cheeks.

Her physical examination revealed that the mass arose from the subcutaneous tissue and was attached to the skin. The mass was firm in consistency and had an irregular surface that prevented her from wearing glasses.

She also had a normochromic normocytic anaemia and an erythrocyte sedimentation rate elevated to 83 mm/hour. Her liver function was mildly

abnormal with a thrombocytopenia consistent with cirrhosis and splenomegaly. Her lipid profile and other immunological studies, including a bone marrow trephine, were normal. What is the possible diagnosis?

Progress

Complete excision of the lesions in the underlying orbicularis oculi muscles with full-thickness skin graft coverage was performed. Pathological examination indicated that the lesions were necrobiotic xanthogranulomas (NXG). She recovered well and at the 1-year follow-up there was no evidence of recurrence (Fig 2).

Discussion

Necrobiotic xanthogranuloma is a rare chronic granulomatous condition of unknown aetiology first described in 1980.¹ It can be associated with paraproteinaemia and less frequently with lymphoreticular malignancies, hyperlipidaemia, cryoglobulinaemia, and low C-1 esterase inhibitor. It occurs with equal frequency in middle-aged to elderly men and women.

Clinically, the disease usually presents as yellow-orange or violet papules, plaques, or nodules that progressively enlarge. They vary in size from tiny nodules to involvement of the whole eyelid. They primarily involve

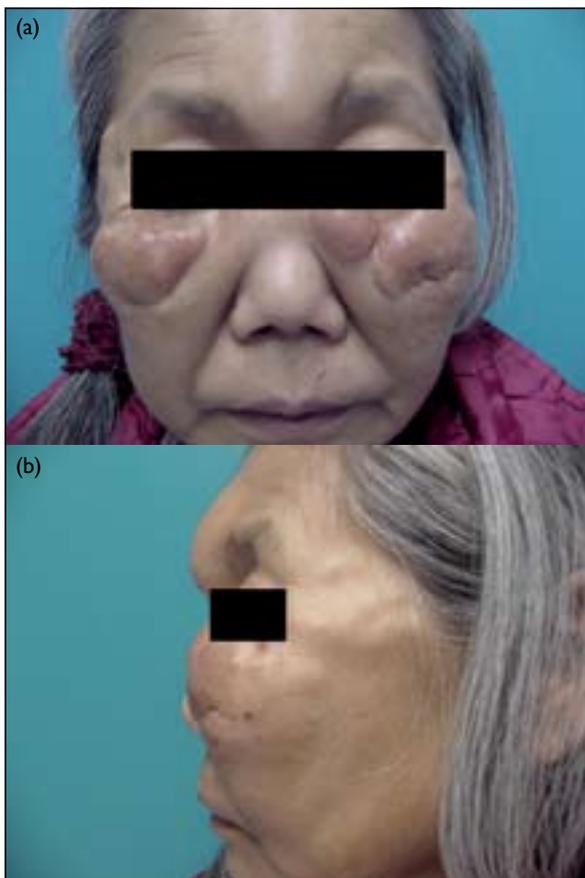


FIG 1. A 54-year-old Chinese woman presents with bilateral peri-orbital, malar, and glabellar swelling



FIG 2. The patient has recovered well and has no evidence of recurrence at the 1-year follow-up

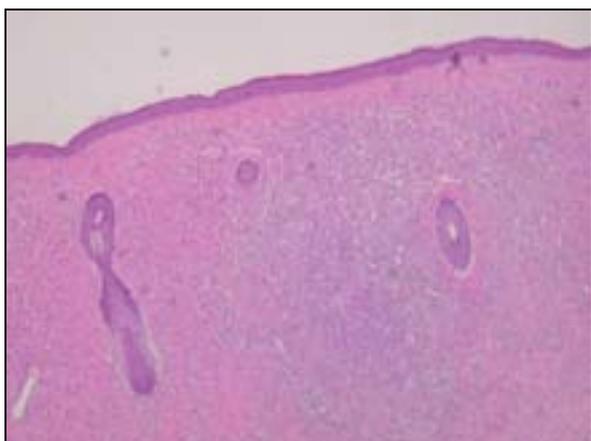


FIG 3. Infiltrate in dermis consisting of macrophages, plasma cells and small lymphocytes (H&E, x20)

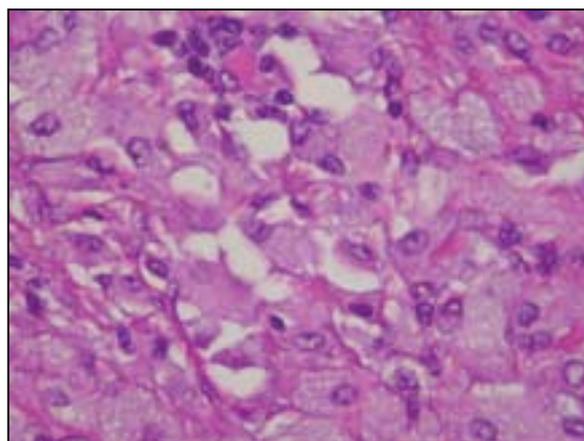


FIG 5. Xanthomatous macrophages with lipid rich foamy cytoplasm (H&E, x400)

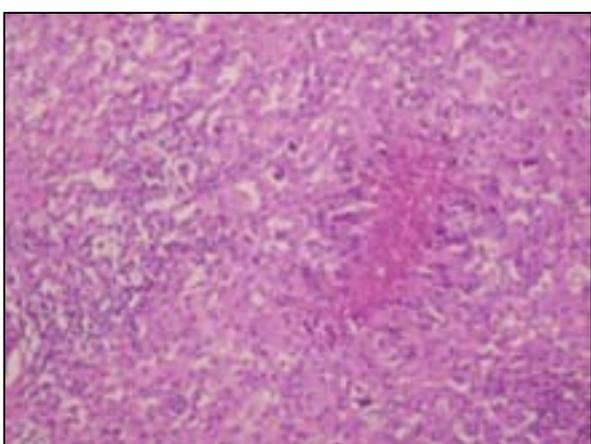


FIG 4. Necrobiotic focus, rimmed by macrophages and lymphoplasmacytic cells (H&E, x100)

the peri-orbital region with bilateral eyelid involvement in 90% of cases. They can also appear at other sites including the trunk and extremities.² The lesions are usually asymptomatic but can ulcerate. Clinical differential diagnoses including orbital xanthogranulomas (XG), Erdheim-Chester disease (ECD), and juvenile XG should also be considered. The peri-orbital plaques of orbital XG and ECD are usually symmetrical but those seen in ECD tend to be locally invasive. However, the peri-orbital lesions in juvenile XG and NXG are usually asymmetrical and tend to involve other parts of the body including the trunk. The ulceration seen in NXG makes these lesions more locally destructive.³

A histological examination of the lesions found an orthokeratotic epidermis and a dense granulomatous reaction with areas of severe necrobiosis. The granuloma was composed of numerous multinucleated bizarre foreign body cells, Touton giant cells, foam histiocytes,

epithelioid cells, and some lymphocytes, which resembled germinal centres (Figs 3-5).¹ Necrobiosis lipoidica, granuloma annulare, subcutaneous rheumatoid nodules, and pseudorheumatoid nodules share similar histopathological findings with NXG in that all show focal areas of collagen degeneration and granuloma formation.² Histologically, necrobiosis lipoidica usually has extensive hyaline necrobiosis and foreign body giant cells. Atypical and Touton giant cells are more common in NXG. Stellate areas of collagen necrosis surrounded by palisading epithelioid histiocytes and scattered multinucleated giant cells, together with a positive stain for connective tissue mucin in the necrotic area suggests a diagnosis of rheumatoid and pseudorheumatoid nodules. These can be distinguished by their different clinical presentations; pseudorheumatoid nodules are not related to systemic disease, including rheumatoid arthritis or rheumatoid fever.³

The possible pathogenesis of NXG is an intracellular accumulation of lipoprotein-derived lipids. In one paper, affected patients' monocytes showed a three-fold enhancement of acetyl low-density lipoprotein uptake compared with controls. However, there was no significant difference in the expression of the CD36 protein and the mRNA levels of scavenger receptor-class A (SR-A). The phagocytic ability was enhanced 1.5 fold. These findings suggest that the activated monocytes may have degraded the modified low-density lipoprotein via a pathway other than CD36 or SR-A.⁴

In 80% of cases, NXG is associated with paraproteinaemia such as monoclonal gammopathy or cryoglobulinaemia. In 10% of cases, it develops into multiple myeloma. It can also involve other organs including the myocardium, larynx, lung, intestine, and ovaries.⁵

Treatment includes chemotherapy with chlorambucil, melphalan, azathioprine, methotrexate,

cyclophosphamide, and nitrogen mustard together with corticosteroids or as monotherapy. Surgical removal with skin grafting, radiotherapy, local corticosteroid injection, pulsed high-dose oral dexamethasone, plasmapheresis, alpha interferon or carbon dioxide laser therapy⁶ have also been documented.

In conclusion, NXG is a chronic and progressive disease of unknown cause; the prognosis is uncertain and there is no definite treatment of choice for its management.

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