

## Case Report

# Necrobiotic xanthogranuloma: a report of two fascinating cases

## 漸進性壞死性黃色肉芽腫：兩宗趣味盎然的病例報告

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Necrobiotic xanthogranuloma (NXG) is a rare granulomatous disorder of the skin. It is characterised by indurated nodules and erythematous, yellow plaques mostly affecting the periorbital region. In recent years, NXG has been increasingly associated with paraproteinaemia and haematological disorders, such as multiple myeloma. Hereunder we report two cases with histological and clinical findings of NXG. We believe that case one is the first report case of NXG on a background of hepatitis C and case two is the first case report of extrafacial unilateral NXG to our knowledge.

漸進性壞死性黃色肉芽腫是一種罕見的肉芽腫類皮膚病。其特徵在於硬化結節和紅黃色斑塊，大多影響眼眶週圍。近年來，此病已經越來越多地發現與副蛋白血症和其他血液學疾病如多發性骨髓瘤相關。下文我們報告了兩例漸進性壞死性黃色肉芽腫的組織學和臨床表現。我們相信案例一是此病有著丙型肝炎背景的首宗病例報告；案例二，則是我們所知道此病顏面外單側發病的首宗病例報告。

**Keywords:** Disfigurement, hepatitis C, Necrobiotic xanthogranuloma, systemic involvement, unilateral

**關鍵詞：**毀容、丙型肝炎、漸進性壞死性黃色肉芽腫、全身性累及、單側

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## Introduction

Necrobiotic xanthogranuloma (NXG) is a rare disease, classified by Kossard et al in 1980 as a separate clinical and histopathological entity from normolipaeamic xanthomas. The disease usually presents in the fifth and sixth decades of life and does not have a predilection for men or women. NXG usually affects the skin, however it is considered a systemic disease and has the potential to affect several organs.<sup>1,2</sup> It is often associated with a paraproteinaemia. Its prognosis depends upon the severity of the disease and extracutaneous involvement. Due to the limited data available, no first-line or optimal therapy has been established for NXG and therapeutic recommendations have been developed from anecdotal evidence. We report two cases of NXG with fascinating clinical presentations.

### Case 1

A 57-year-old male patient presented with a three-year history of a yellow-orange reticulated rash affecting the upper chest and back and perioricular region. There was also noticeable lichenoid pigmentation affecting the upper shoulders (Figure 1). He had a medical history of hepatitis C, diagnosed in 1999, which failed to respond to Interferon and Ribavirin combination therapy. He also had a history of insulin dependent Type 2 Diabetes Mellitus and hypertension.

Upon initial review, he had low fasting cholesterol (2.5 mmol/L) and total protein (59 g/L). Triglycerides were on the lower limit of normal (0.7 mmol/L). Additional investigations revealed a trace of oligoclonal gammopathy with IgG-kappa and lambda. Inflammatory markers (WCC, CRP and ESR), C3, C4 and cryoglobulins were within normal limits. Immune serology showed ANA of 1:80 (speckled), but otherwise revealed no abnormalities. Fasting plasma glucose was raised (8.1 mmol/L). Urinalysis was unremarkable.

A provisional diagnosis of NXG was made and punch biopsies were taken from the eyelid and chest. Histopathology of the eyelid (Figure 2a) demonstrated florid xanthogranulomatous inflammation in the dermis with numerous foamy histiocytes and multinucleated giant cells. The appearance was consistent with NXG, despite the lack of appreciable necrobiosis in the inflammatory infiltrate. Histopathology of the chest (Figure 2b) showed foamy histiocytes, lymphocytes and occasional multinucleated giant cells, including Touton giant cells, further consistent with NXG albeit more subtle.

Treatment with neotigason, plaquenil, 200 mg twice daily in combination with narrow Band UVB (nbUVB), intravenous immunoglobulins (IVIg), thalidomide and dapsone were trialled, however all resulted in unacceptable side effects or were ineffective and were ceased. A significant improvement in this patients' NXG lesions was observed after the successful treatment of his Hepatitis C with combination therapy: ombitasvir/paritaprevir/ritonavir.

### Case 2

A 63-year-old female presented in 2006 with a peri-ocular nodule, swelling and inflammation of right eye and epistaxis that started 20 years previously. In 2009, she developed a lesion on the left side of her neck, which was thought to be a lipoma. She progressed to develop hyperpigmented subcutaneous nodules in the left inguinal areas. Subsequently, she developed large brownish plaques with yellow discolouration on her back, left arm, left submammary and left thigh (Figure 3). All of her extrafacial skin lesions were unilateral.

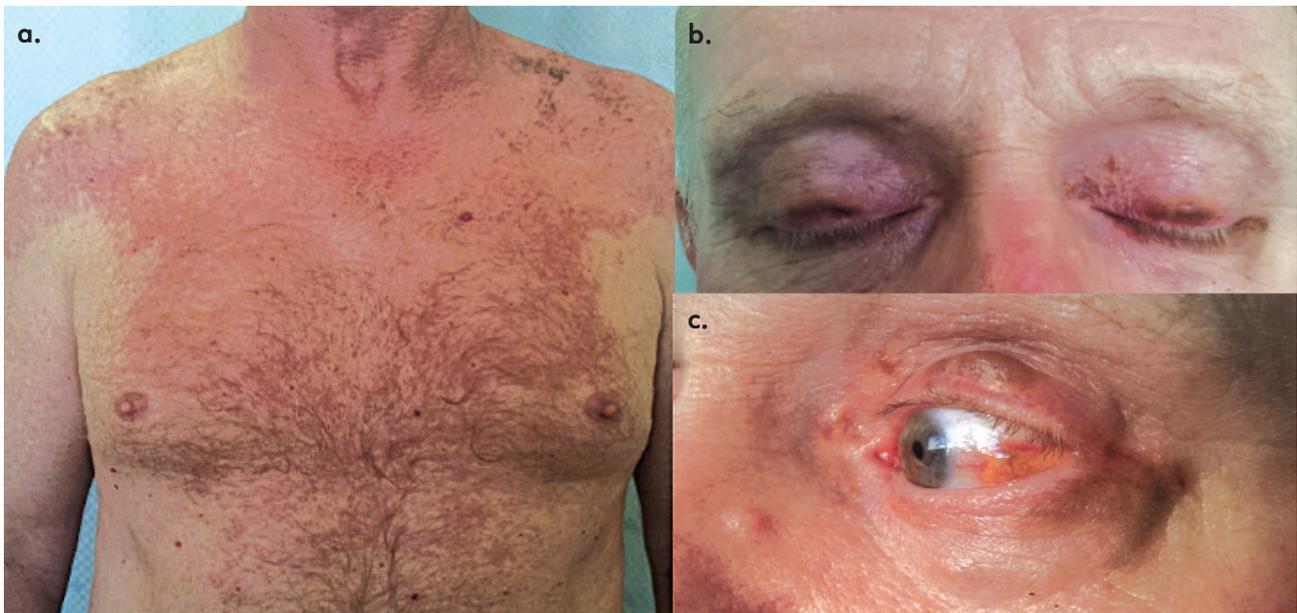
Her other investigations were largely unremarkable, apart from a monoclonal expansion of IgG with a predominance of lambda light chains in the beta gamma region, a

borderline cholesterol of 5.5 mg/L, a mildly raised ESR and CRP and mildly deranged LFT's.

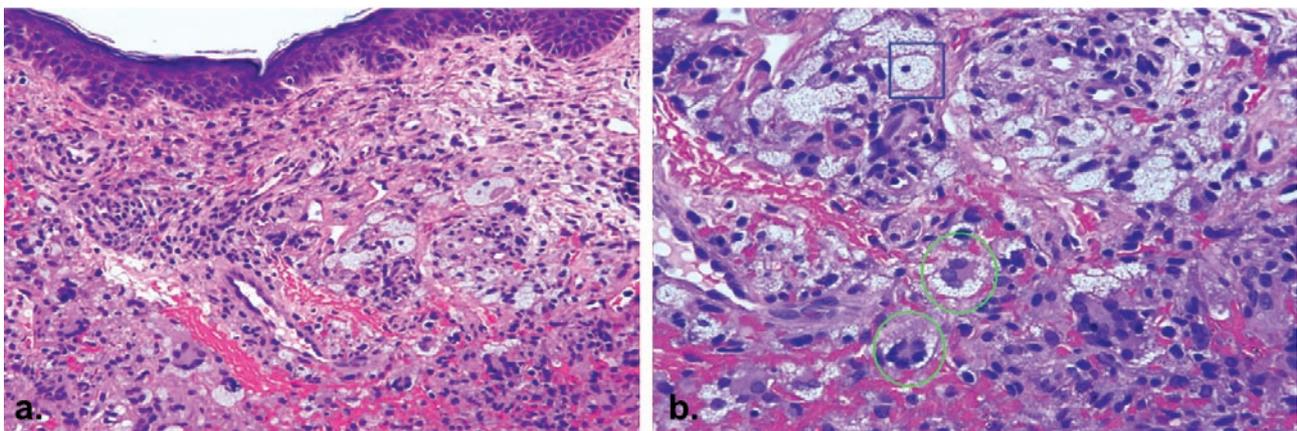
Histopathology of a lesion from her left breast revealed a florid granulomatous inflammation throughout the dermis as well as subcutis, with fibrous thickening of the septa. The infiltrate consisted of prominent giant cells, including

Touton type giant cells, as well as scattered foamy histiocytes. The granulomas were associated with large areas of necrobiotic collagen, cholesterol crystals and fine calcification consistent with NXG (Figure 4).

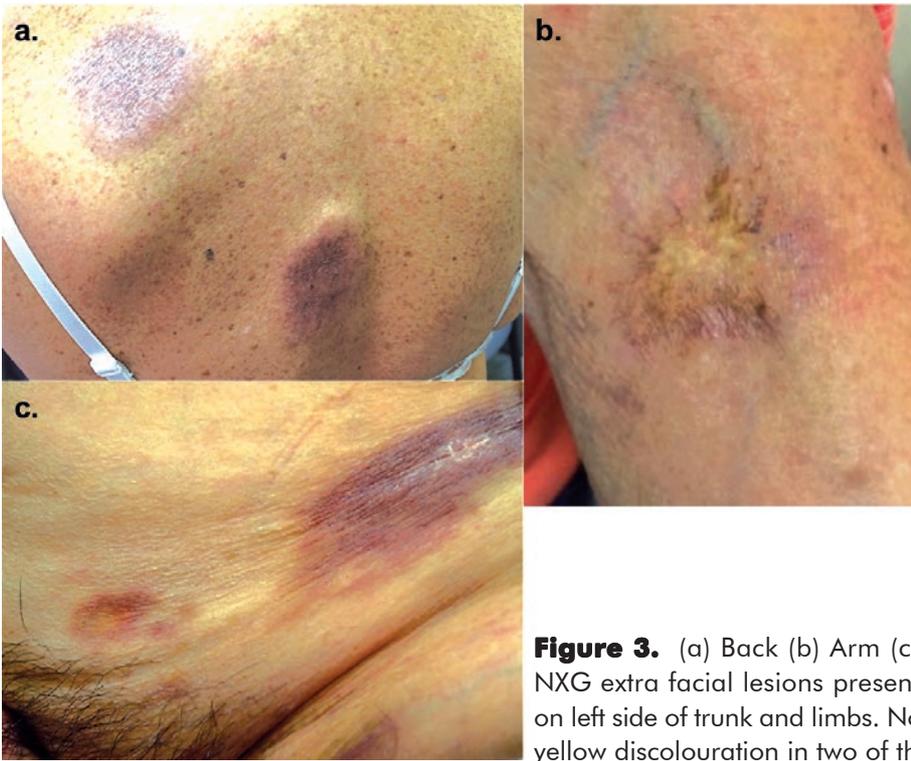
The patient unfortunately continued to suffer from epistaxis and progressive eye symptoms with



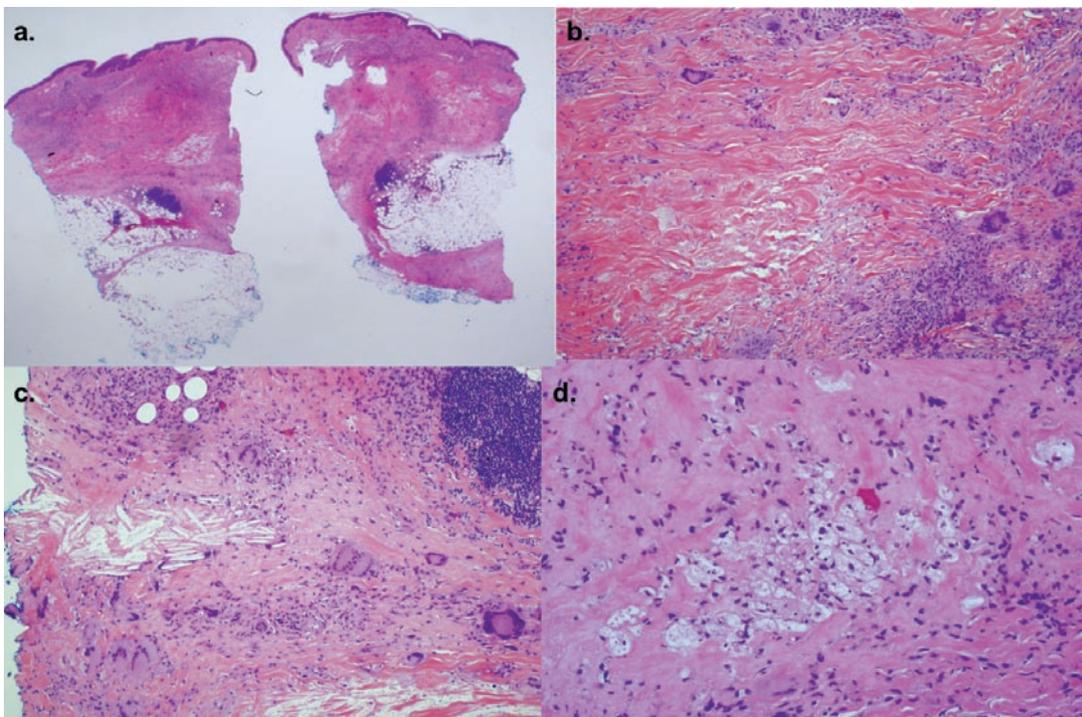
**Figure 1.** (a) Well-demarcated, large erythematous patches with lichenification in an apron-like appearance distributed over the shoulders, and trunk. Areas of hyperpigmentation are present. (b) and (c) Characteristic yellow and brownish indurated nodules and plaques with surface telangiectasia on the upper eyelids. There is lipid accumulation in the lateral canthus and sclera of the eye.



**Figure 2.** (a) Florid xanthogranulomatous inflammation in the dermis. (b) The chronic inflammatory infiltrate is characterised by Touton type multinucleated giant cells (green circles), foamy histiocytes (blue square) and lymphocytes.



**Figure 3.** (a) Back (b) Arm (c) Groin. Typical NXG extra facial lesions presenting unilaterally on left side of trunk and limbs. Note characteristic yellow discoloration in two of the plaques.



**Figure 4.** (a) Punch biopsy of the left breast/chest. (b) and (c) Florid granulomatous inflammation throughout the dermis as well as subcutis, with fibrous thickening of the septa. The infiltrate consists of prominent giant cells, including Touton type giant cells, as well as scattered foamy histiocytes. (d) The granulomas are associated with large areas of necrobiotic collagen, cholesterol crystals and fine calcification.

bilateral inflammation of the cornea. There was a medical history significant for plasma cell dyscrasia, autoimmune hepatitis, osteoarthritis affecting the left knee and monoclonal gammopathy of uncertain significance. She is currently taking 2 mg of chlorambucil daily as an attempt to prevent the development of more serious haematological problems. Prednisolone has also been trialled for her epistaxis and skin lesions with no appreciative benefit. Moreover her episodes of epistaxis are still problematic and impact negatively upon her quality of life. She is also using Prednisolone Forte eye drops for her eye symptoms. Treatment with intralesional corticosteroids has been used successfully in treating several cutaneous plaques. However she has recently developed new plaques.

## Discussion

NXG is characterised by yellow to red-brown indurated papules, nodules or plaques with surface telangiectasia. In particular the macroscopic yellow hue is pathognomonic of xanthodermatoses. This condition can be delineated from other xanthodermatoses from the plaques and subcutaneous nodules subject to atrophy and ulceration in the long term.<sup>3</sup> Clinically, the lesions have a predilection for the periorbital region, but commonly present on the face, trunk and extremities and are cosmetically disfiguring. The periorbital distribution leads to a propensity for conjunctivitis, uveitis and keratitis. The lesions are commonly asymptomatic, however tenderness, pruritis and burning have been described.<sup>4</sup>

This case series highlights two unique presentations of NXG and broadens our understanding of this rare xanthodermatosis. The successful treatment of hepatitis C leading to the healing of NXG lesions in case one and the unilateral appearance of NXG in case two are believed to have never before been reported.

The aetiology of NXG is unknown. However many have been theorised. For example, it has been postulated that paraproteins act as antibodies responding to chronic, autologous antigen. These are thought to act as lipoproteins and bind to histiocytic receptors leading to granuloma formation.<sup>5</sup> Diagnosis is commonly made through histopathological analysis of a cutaneous lesion. Typical histological presentation is of a palisading, granulomatous infiltrate involving the dermis and the subcutis, surrounding areas of degenerated collagen. Inflammatory infiltrate include sheets of macrophages, histiocytes, lymphocytes, Touton and foreign body giant cells. Cholesterol clefts occur within areas of necrobiosis. In close proximity to the granulomas is a hyaline necrobiosis that imparts a lobulated appearance to the tissue.<sup>2</sup>

An IgG kappa monoclonal gammopathy is one of the most characteristic findings, however some cases do not have a paraprotein, and these patients tend to be more difficult to treat. Kossard et al, described six of eight patients with a IgG monoclonal serum paraproteinaemia.<sup>6</sup> Urine electrophoresis for Bence-Jones proteins and light chains and immunoperoxidase stains of paraffin sections for light chains, kappa and lambda may supplement clinical suspicion of underlying malignancy.<sup>7</sup> Interestingly, most cases of NXG have normolipidaemia and some are hypolipidaemic.

The most common haematological disorder associated with paraproteinaemia in NXG patients is monoclonal gammopathy of uncertain significance.<sup>8</sup> Systemic manifestations of NXG have been described, albeit uncommonly. Autopsies in patients with cutaneous disease have revealed cardiac, renal, oesophageal, lung<sup>9</sup> and upper respiratory tract involvement.<sup>4</sup>

Patients should have blood test during their visit, alongside a thorough clinical examination and possibly further investigations if warranted. As the time to develop an associated malignancy can be up to 20 years, it has been recommended that

patients be followed up in 6-12 monthly intervals for the duration of their lifetime to monitor for mucous membrane, lung, myocardial and haematological abnormalities and malignancies.<sup>4,6</sup>

Many patients affected by NXG do not require immediate or extensive treatment. However those with disfiguring cutaneous symptoms or systemic involvement will require systemic therapy.<sup>8</sup> Successful local treatment has been reported with psoralen ultraviolet A treatment, local radiation therapy,<sup>2</sup> and intralesional corticosteroids. Systemic treatment with alkylating agents, such as cyclophosphamide, chlorambucil, melphalan and nitrogen mustards, alone or in combination with oral prednisolone is a common treatment approach. Immunosuppressive treatments such as methotrexate, hydroxychloroquine, dapsone, azathioprine have also been used, often with unsatisfying results unfortunately. Plasmaphoresis and IVIG have been reported as being successful for the treatment of NXG.<sup>10</sup>

## Conclusion

NXG has been more widely reported in the literature since being recognised as a clinical entity in 1980. Yet, it continues to be a medical challenge with an elusive pathogenesis and without definitive therapy. With its distinctive cutaneous lesions, NXG can be disfiguring and demoralising. Of even greater concern is its potential to manifest systemically through malignancy, granulomatous organ infiltration and autoimmune disease. Our

two cases bring to light to the variability of the clinical presentation of NXG and the need for further research into this curious enigma.

## Acknowledgement

We would like to acknowledge the input of Dr. Deshan Sebaratnam for case 1.

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