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# Periorbital necrobiotic xanthogranuloma resolved with three years of systemic lenalidomide treatment

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ABSTRACT

*Purpose:* To describe a case report of the successful management of necrobiotic xanthogranuloma (NXG), a rare periorbital disease.

*Observations:* A 61-year-old patient presented with bilateral upper and lower lid lesions which were initially misdiagnosed as xanthelasmas and later confirmed to be NXG. Further investigation also uncovered a diagnosis of multiple myeloma. The patient was started on a lenalidomide treatment for his multiple myeloma, specifically chosen by a coalition of Hematology/Oncology, Dermatology, Internal Medicine and Oculoplastics, to simultaneously treat his NXG. His periocular lesions were monitored for response without additional intervention. It was initially difficult to determine if the patient's periocular involvement was improving due to conflicting concurrent ulceration and decreased height of the lesions. At 18 months, improvement became apparent. After three years of treatment, the patient's periocular lesions had clinically disappeared. Follow-up with the patient confirmed that there had been no return of either the NXG or multiple myeloma three years after treatment cessation.

*Conclusions and Importance:* This case contributes to the existing literature by documenting complete resolution of NXG after three years of lenalidomide treatment, which is a much longer treatment duration than typically described in the literature. These observations alert treating physicians that a longer treatment interval may be needed to address NXG.

## 1. Introduction

Necrobiotic xanthogranuloma (NXG) is a rare dermal condition with unknown etiopathogenesis and is commonly associated with paraproteinemia. The disease most typically affects the periocular region but may also present on other areas of the body, including the trunk, extremities, and other areas of the face.[1–3] This report highlights the treatment of a 61-year-old male with xantholomatous periocular lesions that had been present for over one year prior to the eventual diagnosis of NXG.

## 2. Case report

The patient (61-year-old male) was referred for evaluation and management of bilateral upper and lower lid lesions that were originally diagnosed as xanthelasmas. Examination revealed thickened yellow and beige plaques on all four lids that had some features consistent with cholesterol xanthelasmas and a yellowish-pink elevated area on his left lateral canthal region (Fig. 1A). At that time, the clinicians consulted to evaluate his eyelids were unaware of his systemic gammopathy. The location and appearance of the left lateral canthal lesion did not align with the typical presentation of cholesterol xanthelasmas, so a portion of this atypical lesion was excised and biopsied (the remaining lid lesions were left untreated because they were too large to remove without skin grafting). Histopathologic examination showed a florid histiocytic proliferation in association with broad zones of necrobiosis and cholesterol clefting (Fig. 2A), with numerous multinucleated giant cells (Fig. 2B) and Touton-type giant cells (Fig. 2C). Immunohistochemical stains showed the giant cells to be strongly and diffusely positive for CD163 and negative for CD34, desmin, p63, S100 protein, smooth muscle actin,

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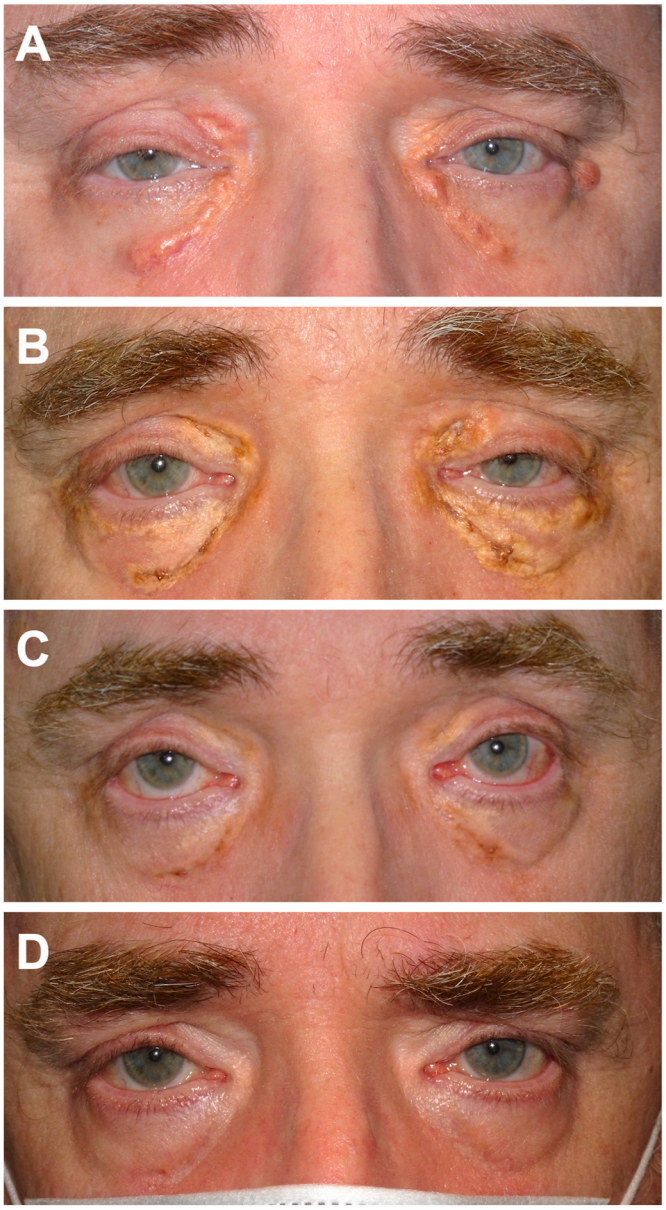


**Fig. 1.** Progression of periocular necrobiotic xanthogranuloma with lenalidomide treatment
**A.** Thickened yellow periorbital lesions on all four lids of a 61-year-old male initially diagnosed as xanthelasmas but later revealed to be necrobiotic xanthogranuloma (NXG) by incisional biopsy of the atypical lesion on left lateral canthus. **B.** Concurrent ulceration and decrease in thickness of periorbital NXG lesions after six months of systemic lenalidomide for multiple myeloma. **C.** Greatly decreased size of lesions, with some areas of ulceration and crusting remaining, after 18 months of lenalidomide treatment. **D.** Full resolution of periorbital lesions after three years of treatment. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

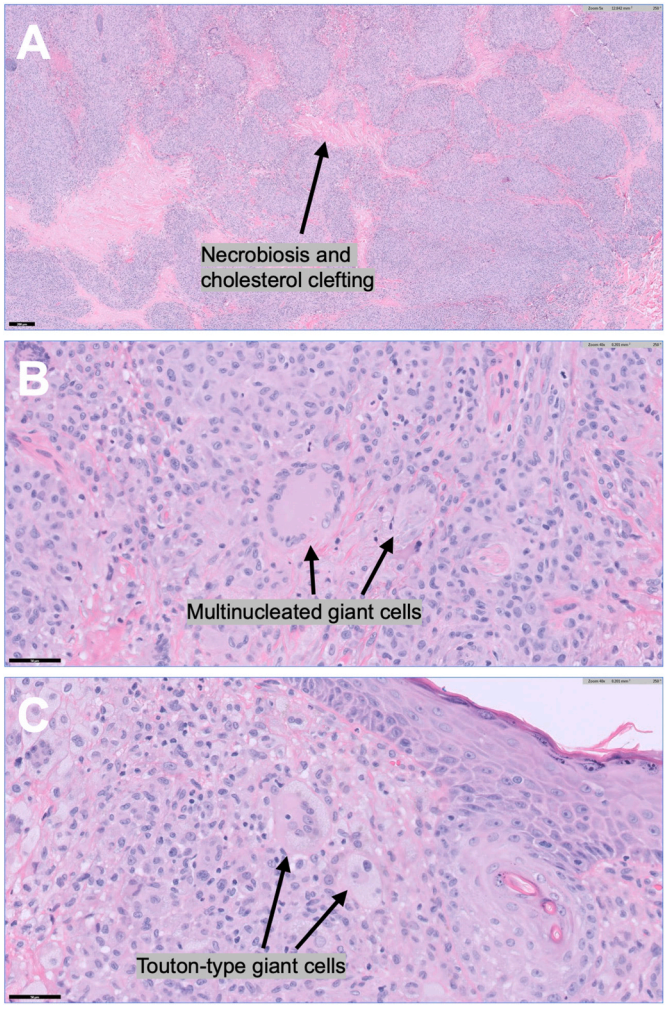


**Fig. 2.** Histopathological images of a periocular necrobiotic xanthogranuloma partially excised from a 61-year-old male
**A.** Hematoxylin an eosin staining of a partially excised necrobiotic xanthogranuloma from a 61-year-old male patient showed a florid histiocytic proliferation in association with broad zones of necrobiosis and cholesterol clefting (10x magnification; Scale bar - 200μm). **B.** Multinucleated giant cells were present (40x magnification; Scale bar - 50μm) **C.** Touton-type giant cells were present containing a wreath of nuclei and peripheral foamy cytoplasm (40x magnification; Scale bar - 50μm).

and MNF116. These findings were consistent with NXG.

Based on the available literature, considerations of surgical and systemic treatment options were undertaken (i.e., surgical excision, corticosteroids, alkylating agents, antimetabolites, antimicrobials, and others).[4,5] Discussion with the patient's primary care provider uncovered a prior diagnosis of IgG kappa monoclonal gammopathy. In response to the NXG diagnosis, the patient's hematologist ordered a bone marrow aspirate and biopsy, which revealed a diagnosis of multiple myeloma. After a discussion by the involved physicians, the patient was started on a lenalidomide treatment (15 mg QD 21 days on, seven days off) along with a corticosteroid (5 mg prednisone QD) for his multiple myeloma. The treating physician elected to monitor the condition of the patients' periocular lesions with no other direct intervention because treatment for systemic disease with lenalidomide was a documented treatment option for NXG.

Over the course of three years of systemic treatment with lenalidomide, the lesions on the patient's lids initially worsened and then slowly improved. After 6-months of his systemic treatment, the lesions looked slightly less thick and inflamed but covered a wider area of his eyelids and had areas of ulceration (Fig. 1B). Surgical intervention was contemplated but not invoked because of the ulceration and concerns about the impact on healing. Due to decreased elevation of the lesions, it wasn't clear if the ulceration was an atrophic response to treatment, or part of the course of NXG. After 18 months of treatment, the lesions had greatly decreased, with some areas of ulceration and crusting as the soft tissue induration slowly improved (Fig. 1C). After three years of treatment, the lesions had clinically disappeared (Fig. 1D). The patient's treatment was stopped after three years based on his negative systemic

testing for multiple myeloma and resolution of the NXG. The patient has been off medication and systemically stable for three years without recurrence of the eyelid lesions or the gammopathy at the time of publication of this case report.

## 3. Discussion

NXG is a rare granulomatous disease without clearly defined treatment guidelines. The exact pathogenesis of the disease is unknown. All cases involve cutaneous involvement, often with ulceration, scarring, atrophy, and telangiectasias present within the lesions as the disease progresses.[1,4,6,7] The disease is often accompanied by paraproteinemia, multiple organ involvement, and increased risk for hematologic and lymphoproliferative malignant disorders, and thus, treatment of systemic aspects of the disease with various agents (i.e., corticosteroids, IVIG, lenalidomide, cyclophosphamide, chlorambucil, thalidomide, melphalan) has been the most common therapeutic plan. Surgical removal, while sometimes successful, is not a first-line treatment option due to reports of recurrence of skin lesions following attempted surgical excision.[5]

In a 2022 systemic review of 175 patients diagnosed with NXG, Steinhelfer et al. reported that 55 % had paraproteinemia, the most common being multiple myeloma (7 %).[6] The three most promising treatments for resolution of the disease in the aforementioned review were IVIG (21 total patients, 37 % complete resolution, 54 % partial resolution), corticosteroids alone (45 total patients, 11 % complete resolution, 20 % partial resolution), and lenalidomide treatment with or without corticosteroids (22 total patients, 18 % complete resolution, 32 % partial resolution).[6] Prospective, comparative, randomized control trials would be required to determine the best therapeutic approach for NXG and develop clear treatment guidelines, though the limited number of available cases makes this an unrealistic expectation. Thus, the suggested duration for systemic treatment, such as lenalidomide, has yet to be determined. The literature reviewed by the authors revealed treatment with lenalidomide typically lasting 3–18 months.[6,8–12]

Our patient had many aspects of the typical presentation of NXG, including periorbital lesions and associated multiple myeloma. Notably, during the time interval where lenalidomide treatment was typically discontinued in the reviewed literature (3–18 months), the initial effects on our patient's periocular lesions were ambiguous and no clear improvement was seen until the later stages. Three years of lenalidomide treatment was required for full resolution of the periocular lesions. It is unclear whether the initial ulceration of the periocular lesions was a response to the treatment or if the natural course of the NXG, progressing to characteristic ulcerations. Since the patient's paraproteinemia resolved concurrently with the disappearance of the NXG, it's also not clear if the resolution of the paraproteinemia was responsible for the involution of the NXG rather than the lenalidomide being directly responsible for the change in the NXG lesions.

## 4. Conclusion

This case adds to the existing literature by documenting full resolution of NXG by a longer regimen of lenalidomide treatment than reported in the reviewed literature, with follow-up three years after cessation of treatment to confirm no disease recurrence. The necessary duration of treatment (three years) to see our patient's full recovery may also encourage persistence with systemic treatment, even in the case of an initially worsening periocular involvement.

## CRediT authorship contribution statement

**Llwyatt K. Hofer:** Writing – review & editing, Writing – original draft, Conceptualization. **Kaila A. Buckley:** Writing – review & editing, Formal analysis, Data curation. **Jill A. Foster:** Writing – review & editing, Formal analysis, Conceptualization.

## Patient consent

Written consent was obtained from the patient regarding the publication of this case report and the associated images. Documentation has been retained by the authors.

## Claims of priority

After conducting a literature review on 6/2/24 utilizing PubMed and Google Scholar using key word (Necrobiotic xanthogranuloma, lenalidomide), we did not find any prior reports of lenalidomide treatment being continued for three years or longer and the resulting impact on the necrobiotic xanthogranuloma.

## Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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