Case Report

Necrobiotic xanthogranuloma: Highlighting the role of clinicopathologic correlation in an atypical presentation

Camille Gorena, BA, BS[1a], Evan Baird, MD[2], Janine Malone, MD[2], Courtney R. Schadt, MD[2]

[1] University of Louisville School of Medicine, Louisville, KY, USA, [2] Division of Dermatology, University of Louisville, Louisville, KY, USA

Keywords: granulomatous, histopathology, necrobiotic xanthogranuloma

Dermatology Online Journal

Vol. 32, Issue 1, 2026

Abstract

Necrobiotic xanthogranuloma (NXG) is a rare, chronic non–Langerhans cell histiocytosis that clinically manifests as yellow to orange papules or nodules, most commonly involving the periorbital region. Histopathologic features include necrobiotic collagen, multinucleated giant cells (including Touton and Langhans types), granulomatous inflammation with xanthomatous histiocytes, extracellular lipid, and occasionally lymphoid follicles and plasma cells. NXG has a well-documented association with monoclonal gammopathies and extracutaneous malignancies, although the underlying pathogenic mechanisms remain poorly understood. We report the case of a 72-year-old woman presenting with erythematous plaques on the abdomen and extremities. Despite the absence of classic facial involvement and an initial nondiagnostic skin biopsy, further evaluation revealed a clonal plasma cell disorder classified as borderline between monoclonal gammopathy of undetermined significance and smoldering multiple myeloma. A subsequent biopsy demonstrated diagnostic features of NXG. This case underscores the importance of integrating clinical findings with histopathologic evaluation to achieve an accurate diagnosis.

Introduction

Necrobiotic xanthogranuloma (NXG) is a rare, progressive non–Langerhans cell histiocytosis. Clinically, it presents predominantly with granulomatous cutaneous lesions, although extracutaneous necrotizing granulomatous involvement may occur. Lesions typically manifest as yellow to orange papules or nodules, most commonly in the periorbital region. Histopathologic findings characteristically demonstrate a necrobiotic granulomatous dermatitis with degenerated collagen surrounded by granulomatous inflammation, multinucleated giant cells (some with bizarre features, including numerous nuclei), cholesterol clefts, and lymphoid follicles.[1] Plasma cells are commonly present within lesions and, despite the frequent association with an underlying plasma cell dyscrasia, typically show polytypic immunohistochemical staining for kappa and lambda light chains. Approximately 80% of patients with NXG have an associated paraproteinemia, most commonly IgGκ.[2] Cutaneous lesions resembling NXG often lead to detection of underlying paraproteinemia, as their presentation frequently prompts evaluation of serum protein studies and bone marrow examination.[3,4]

Proposed diagnostic criteria include yellow to orange cutaneous lesions and characteristic histopathologic findings as major criteria. Minor criteria include the presence of an associated paraproteinemia or lymphoproliferative disorder and periorbital lesion distribution. In the absence of a foreign body, infection, or other identifiable cause, both major criteria and at least one minor criterion are required for diagnosis.[5] When applied to 859 cases of NXG and its mimics (including Erdheim-Chester disease, granuloma annulare, and necrobiosis lipoidica), these criteria demonstrated greater than 90% sensitivity and specificity.[6] We present a unique case of NXG lacking facial involvement and definitive histopathologic features on the initial biopsy, thereby failing to meet established diagnostic criteria. This case highlights the importance of maintaining a high index of suspicion and emphasizing clinicopathologic correlation in atypical presentations to prompt further investigation and avoid delayed or inaccurate diagnosis.

Case Synopsis

A 72-year-old woman presented with a 2-year history of cutaneous lesions involving the extremities and ab-

a Corresponding Author: Camille Gorena, BA, BS, University of Louisville School of Medicine, 500 S Preston St, Louisville, KY 40202, Tel: 859-552-7215, Email: chgore01@louisville.edu

domen. Her medical history was notable for diabetes mellitus, prior hernia repair, and a resected gastrointestinal stromal tumor. Physical examination revealed multiple red-brown to mildly erythematous dermal plaques and nodules on the arms (Figure 1A), upper thigh, and abdomen (Figure 1B). Two lesions were biopsied, yielding a broad differential diagnosis of granulomatous dermatitis, including granuloma annulare, necrobiosis lipoidica, and NXG. Although the biopsy specimens did not demonstrate histopathologic features fully diagnostic of NXG, the clinical and histologic findings prompted further evaluation, including serum protein electrophoresis (SPEP) and immunofixation electrophoresis (IFE).

SPEP revealed an IgG monoclonal protein with lambda light chain restriction. Light chain quantification showed a normal free lambda light chain level with a mildly elevated kappa light chain level, prompting subsequent bone marrow biopsy and skeletal survey. Bone marrow biopsy demonstrated a 45% cellular marrow with a 10% population of monoclonal plasma cells harboring t(11;14). Increased complement consumption was also noted. The skeletal survey was negative. Given the plasma cell burden at the upper limit of monoclonal gammopathy of undetermined significance (MGUS) and the lower limit of smoldering multiple myeloma (SMM), in the absence of multiple myeloma–defining events (including hypercalcemia, renal failure, anemia, lytic bone lesions, or myeloma-defining biomarkers), the patient was classified as having a plasma cell dyscrasia borderline between MGUS and SMM.

The patient was treated with intralesional triamcinolone acetonide (10 mg/mL), resulting in a modest reduction in lesion size; however, new lesions continued to develop. Repeat SPEP and IFE demonstrated an increased IgG lambda M-spike (1.55 g/dL), new-onset neutropenia (absolute neutrophil count, 540), and a kappa/lambda ratio of 0.87. Given evidence of worsening gammopathy, oncology recommended repeat cutaneous biopsy.

Histopathologic examination revealed nodular and interstitial lymphohistiocytic inflammation involving the dermis and superficial subcutis (Figure 2A). Scattered collections of histiocytes with xanthomatous change were present, along with numerous bizarre multinucleated giant cells, including Touton and Langhans types (Figure 2B). Histiocytes surrounded zones of hypocellular necrobiotic collagen containing extracellular lipid deposits (Figure 2C). These findings were diagnostic of NXG.

The patient received 3 cycles of daratumumab, lenalidomide, and dexamethasone, resulting in only a modest reduction in paraprotein levels, which remained above 1 g/dL. Following the first cycle, she experienced an acute exacerbation of an NXG lesion on the anterior leg, which subsequently began to resolve. Given the suboptimal hematologic response, treatment was escalated to a quadruplet regimen with the addition of bortezomib, with the goal of improved control of both cutaneous disease and paraproteinemia.

Case Discussion

NXG was first described in 1980 by Kossard and Winkelmann,[7] who distinguished it from normolipemic and hyperlipemic plane xanthomas. Of the 8 patients included in their original series, 6 had an associated IgG monoclonal gammopathy, with 2 meeting criteria for multiple myeloma. The association between NXG and monoclonal gammopathy, particularly IgG paraproteinemia, is well established. Our patient's presentation, classified as borderline between MGUS and SMM and characterized by t(11;14), further supports this association. The t(11;14) translocation juxtaposes the cyclin D1 gene with the immunoglobulin heavy chain locus and is present in approximately 15% to 20% of multiple myeloma cases.[8]

Periorbital or other facial involvement occurs in approximately 75% to 80% of patients with NXG, although additional sites of involvement may include the trunk and extremities, as well as extracutaneous organs such as the eye, gastrointestinal tract, and liver.[7] Our patient lacked typical periorbital involvement, with lesions confined to the trunk and extremities. The initial biopsy yielded a broad differential diagnosis of granulomatous dermatitis, including NXG, prompting further evaluation given the known association with monoclonal gammopathy.

The pathogenesis of NXG remains incompletely understood. Monoclonal immunoglobulins are hypothesized to play a central role, supported by evidence of complement consumption that may result from immune complex formation. Similar mechanisms have been proposed in related disorders, including normolipemic and hyperlipidemic xanthomas, in which monoclonal immunoglobulin autoantibody activity has been identified.[9] In our patient, oncologic evaluation noted increased complement consumption as the disease progressed, further supporting this proposed immunologic mechanism. Genetic analysis in 3 patients with NXG identified variants in ABCG5 and ABCG8, which encode heterodimeric transporters essential for reverse cholesterol transport and sterol clearance. Additionally, complete knockout of ABCG5 has been shown to increase chemokine and adhesion molecule expression, potentially facilitating monocyte recruitment to the skin and subsequent cholesterol accumulation.[10]

Treatment of NXG remains challenging owing to its rarity and the absence of standardized therapeutic guidelines. Management has traditionally focused on treating the underlying hematologic disorder when present, as improvement or resolution of paraproteinemia has frequently been associated with clinical improvement of cutaneous disease.[11] Recent recommendations suggest initial therapy with topical or systemic glucocorticoids. In cases of inadequate response, steroid-sparing agents such as chlorambucil may be used, with intravenous immunoglobulin (IVIG) considered for refractory disease.[12] Steinhelfer et al[13] demonstrated that IVIG was

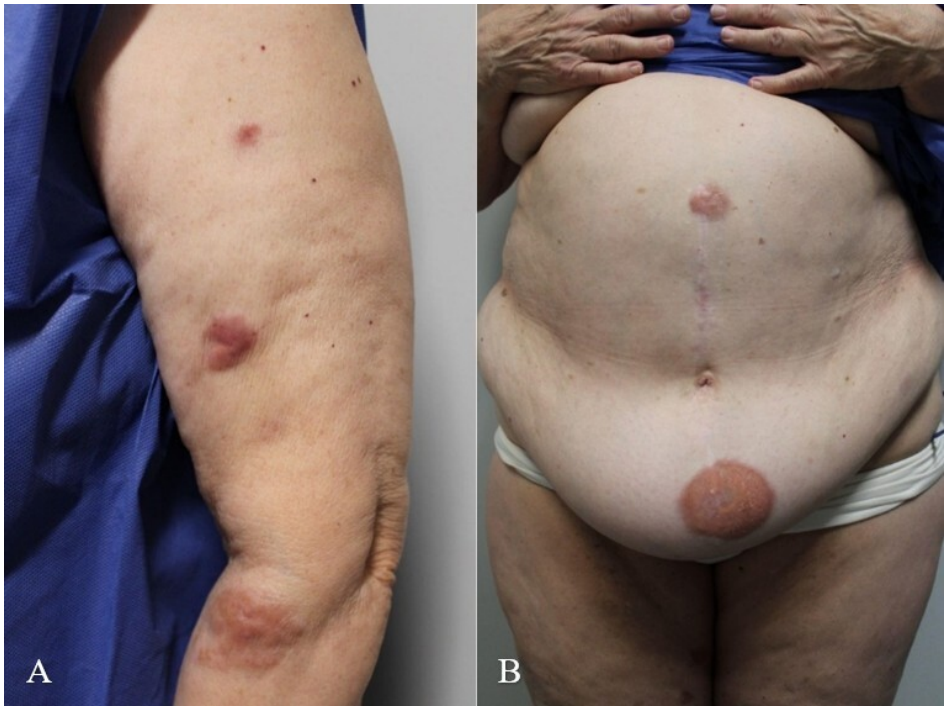

Figure 1. ***(A)*** *Erythematous red-brown plaques on the left anterior arm.* ***(B)*** *Yellow to erythematous plaques on the abdomen.*

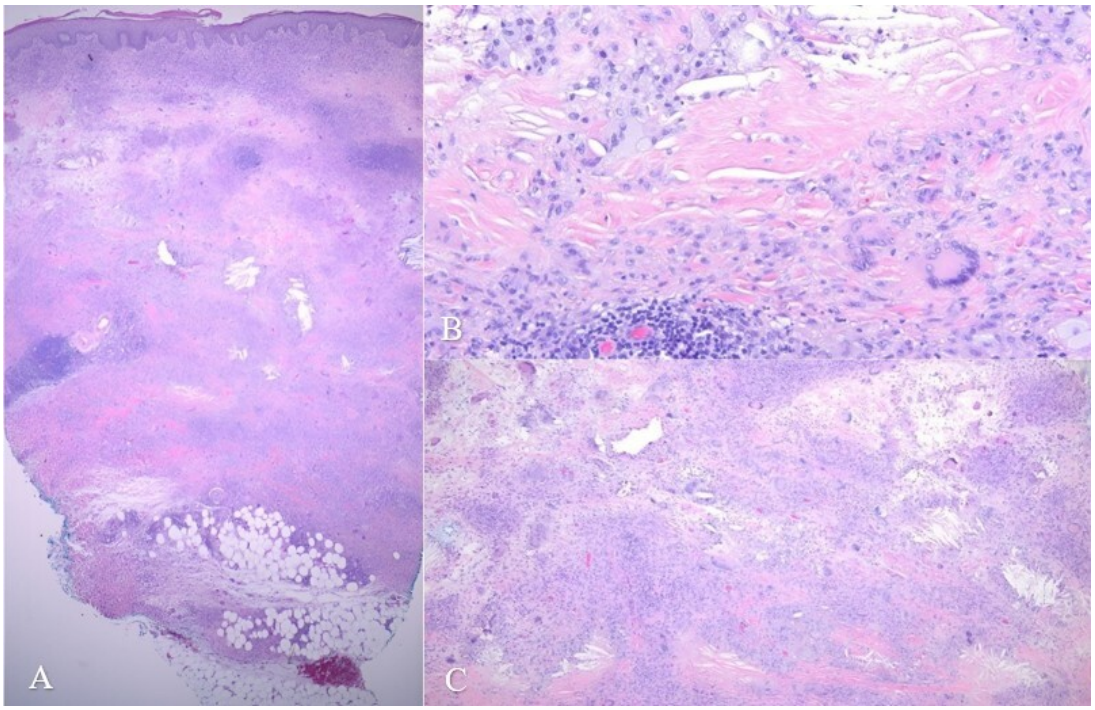

Figure 2. ***(A)*** *Pandermal and subcutaneous infiltrate with alternating hypocellular zones of degenerated collagen and hypercellular inflammatory zones (hematoxylin-eosin, original magnification ×20).* ***(B)*** *Necrobiotic collagen containing cholesterol clefts rimmed by xanthomatous histiocytic inflammation, including a Touton giant cell with multiple nuclei, and lymphoplasmacytic inflammation (hematoxylin-eosin, original magnification ×200).* ***(C)*** *Nodular and interstitial histiocytic inflammation with scattered hypocellular zones of necrobiotic collagen containing extracellular lipid (cholesterol clefts) (hematoxylin-eosin, original magnification ×40).*

the most effective therapy, with complete response observed in 27% of patients and partial response in 54%. Lenalidomide, with or without corticosteroids, was identified as the next most effective treatment option.

Conclusion

We present a patient whose diagnosis of NXG was delayed owing to the absence of major and minor diagnostic criteria at initial evaluation. Her atypical presentation lacked the major criterion of a skin biopsy demonstrating histopathologic features of NXG, as well as both minor criteria of classic periorbital lesions and paraproteinemia. This case underscores the critical role of clinicopathologic correlation in diagnosing NXG, particularly when facial involvement and diagnostic histopathologic features are absent. A high index of clinical suspicion is essential for atypical presentations. Serial biopsies and evaluation with SPEP and immunofixation may be valuable when necrobiotic granulomatous dermatitis presents atypically. Early recognition and interdisciplinary management are crucial to improving patient outcomes, as untreated underlying conditions such as multiple myeloma can be associated with substantial morbidity and mortality.

Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. Fernández-Herrera J, Pedraz J. Necrobiotic xanthogranuloma. *Semin Cutan Med Surg*. 2007;26:108-113. doi:10.1016/j.sder.2007.02.008. PMID:17544963

2. Hilal T, DiCaudo DJ, Connolly SM, Reeder CB. Necrobiotic xanthogranuloma: a 30-year single-center experience. *Ann Hematol*. 2018;97:1471-1479. doi:10.1007/s00277-018-3301-1. PMID:29568990

3. Bhadresha S, Cuthill K, Salisbury J, et al. A case of ulcerated nodules in association with a monoclonal gammopathy. *JAAD Case Rep*. 2024;54:82-84. doi:10.1016/j.jdcr.2024.07.019. PMID:39687065

4. Conforti C, Zalaudek I. Necrobiotic xanthogranuloma as sign of monoclonal gammopathy. *Dermatol Pract Concept*. 2022;12:e2022131. doi:10.5826/dpc.1204a131. PMID:36534574

5. Nelson CA, Zhong CS, Hashemi DA, et al. A multicenter cross-sectional study and systematic review of necrobiotic xanthogranuloma with proposed diagnostic criteria. *JAMA Dermatol*. 2020;156:270-279. doi:10.1001/jamadermatol.2019.4221. PMID:31940000

6. Bassir F, Valido K, Maciejewski KR, Damsky W, Nelson CA. Validation of the delphi consensus diagnostic criteria for necrobiotic xanthogranuloma. *JAMA Dermatol*. 2024;160:1361-1362. doi:10.1001/jamadermatol.2024.3198. PMID:39356540

7. Kossard S, Winkelmann RK. Necrobiotic xanthogranuloma with paraproteinemia. *J Am Acad Dermatol*. 1980;3:257-270. doi:10.1016/s0190-9622(80)80189-7. PMID:7451693

8. Puertas B, González-Calle V, Sobejano-Fuertes E, et al. Multiple myeloma with t(11;14): impact of novel agents on outcome. *Blood Cancer J*. 2023;13:40. doi:10.1038/s41408-023-00807-9. PMID:36935422

9. Szalat R, Pirault J, Fermand JP, et al. Physiopathology of necrobiotic xanthogranuloma with monoclonal gammopathy. *J Intern Med*. 2014;276:269-284. doi:10.1111/joim.12195. PMID:24428816

10. Chen PY, Tang ZL, Hong YY, et al. Genetic aspects of necrobiotic xanthogranuloma. *JAMA Dermatol*. 2024;160:1125-1128. doi:10.1001/jamadermatol.2024.2921. PMID:39230882

11. Claveau JS, Wetter DA, Kumar S. Cutaneous manifestations of monoclonal gammopathy. *Blood Cancer J*. 2022;12:58. doi:10.1038/s41408-022-00661-1. PMID:35411042

12. Hansen I, Ghandili S, Abeck F, Booken N, Schneider SW. Therapy of necrobiotic xanthogranuloma - case series and review of the literature. *J Dtsch Dermatol Ges*. 2023;21:1315-1318. doi:10.1111/ddg.15195. PMID:37811744

13. Steinhelfer L, Kühnel T, Jägle H, et al. Systemic therapy of necrobiotic xanthogranuloma: a systematic review. *Orphanet J Rare Dis*. 2022;17:132. doi:10.1186/s13023-022-02291-z. PMID:35331271