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Elizabeth Schoenberg  
*Thomas Jefferson University*

Kathleen P. McGuinn  
*Thomas Jefferson University*

Deirdre Connolly  
*Thomas Jefferson University*

Sherry Yang  
*Thomas Jefferson University*

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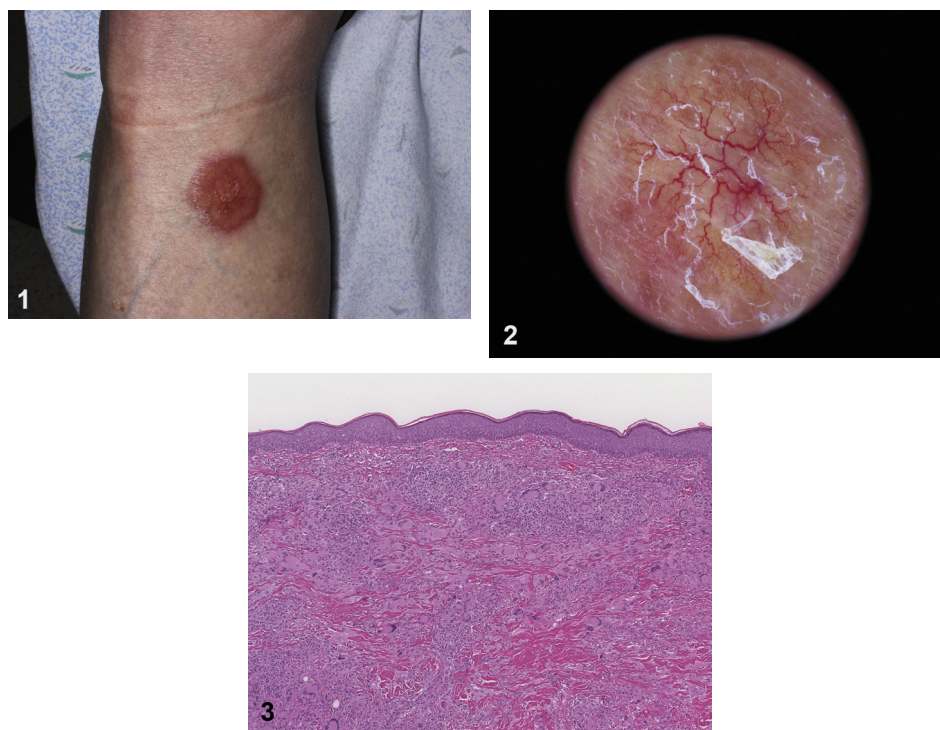
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## An atypical presentation of a rare disease



Elizabeth Schoenberg, BA, Kathleen P. McGuinn, MD, Deirdre Connolly, MD, and Sherry Yang, MD  
*Philadelphia, Pennsylvania*

**Key Words:** monoclonal gammopathy of undetermined significance; necrobiotic xanthogranuloma.



### HISTORY

A 76-year-old white woman presented for evaluation of asymptomatic skin lesions on her right shin, right buttock, and left arm. All lesions initially underwent slow growth and plateaued and then remained stable in size. A complete review of systems revealed normal results. She had 3 well-demarcated erythematous round plaques ranging from 1.5 to 3 cm, all with a central depression, yellow hue, and prominent telangiectasias (Figs 1 and 2). An excisional biopsy was performed. Histologically, there were palisading granulomas within the papillary and reticular dermis, predominantly composed of a histiocytic cell population with multiple large giant cells (S100<sup>+</sup>; Fig 3).

From the Department of Dermatology and Cutaneous Biology,  
Thomas Jefferson University.

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Correspondence to: Elizabeth Schoenberg, BA, Department of  
Dermatology and Cutaneous Biology, Thomas Jefferson  
University Hospital, 833 Chestnut Street, Suite 740,  
Philadelphia, PA, 19107. E-mail: [Elizabeth.Schoenberg@jefferson.edu](mailto:Elizabeth.Schoenberg@jefferson.edu).

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**Question 1: What is the diagnosis?**

- A. Xanthelasma
- B. Necrobiotic xanthogranuloma (NXG)
- C. Necrobiosis lipoidica (NL)
- D. Sarcoidosis
- E. Xanthoma disseminatum (XD)

**Answers:**

**A.** Xanthelasma — Incorrect. Xanthelasmas are noninflammatory soft yellow-orange cholesterol-containing lesions usually present on the eyelids. Histologically, xanthelasmas contain foam cells in the papillary dermis.

**B.** NXG — Correct. NXG usually presents with multiple asymptomatic lesions. Lesions of NXG typically first appear on the trunk or extremities in 60% to 70% of patients, then eventually progress to characteristic periorbital involvement in 80% to 85% of cases. Patients commonly present with an indurated papule, nodule, or plaque with a yellowish hue sometimes with telangiectasias, atrophy, or ulceration. Histologically, palisading granulomas are usually seen in the dermis. The granulomas often contain lipidized histiocytes (foam cells), giant cells, plasma cells, and cholesterol clefts.

**C.** NL — Incorrect. NL presents as an evolving lesion beginning with red to brown papules or plaques progressing into an atrophic, telangiectatic, yellow lesion. NL and NXG share similar features microscopically including hyalinized collagen within the necrobiotic area. However, NXG often displays Touton cells and atypical giant cells and may be distinguished histologically by cholesterol clefts within the granuloma. NL displays lipids altering with collagen bundles causing a layering of hyalinized collagen described as a wedding cake appearance.<sup>1</sup>

**D.** Sarcoidosis — Incorrect. Cutaneous sarcoid often presents with bilaterally symmetrical red-brown-colored lesions. The hallmark on pathology is the presence of naked tubercles meaning the presence of epithelioid cell granulomas without prominent lymphocytes, plasma cells, or caseation.

**E.** XD — Incorrect. XD manifests with an eruption of hundreds of yellow, red, or brown papules that tend to cluster. The lesions are often symmetrical and affect the face, trunk, and intertriginous areas of the extremities.

**Question 2: Which of the following is associated with NXG?**

- A. Diabetes mellitus
- B. Lung disease
- C. Multiple myeloma or monoclonal gammopathy of undetermined significance (MGUS)
- D. Diabetes insipidus (DI)
- E. Hyperlipidemia

**Answers:**

**A.** Diabetes mellitus — Incorrect. NL has been classically associated with diabetes mellitus. The reported prevalence of diabetes mellitus in patients with NL ranges from 11% to 65%.<sup>2</sup>

**B.** Lung disease — Incorrect. Ninety percent of patients with sarcoidosis suffer from lung involvement causing granulomatous inflammation in any part of the lung and may ultimately cause the patient to suffer from bronchiectasis.

**C.** Multiple myeloma or MGUS — Correct. The etiology of the NXG is unclear; however, up to 80% of patients can have associated monoclonal gammopathies, most commonly IgG- $\kappa$ ; this can precede or follow the onset of cutaneous lesions by many years.<sup>3</sup> In this patient, serum protein electrophoresis was significant for an elevated serum monoclonal protein at 0.34 g/dL (normal range,  $\leq 0$ ). Immunofixation identified a monoclonal protein band composed of IgG- $\lambda$ . MGUS was subsequently diagnosed.

**D.** DI — Incorrect. DI is associated with XD in approximately 40% of cases.<sup>4</sup> However, DI is usually mild in these patients and is amenable to treatment with vasopressin.<sup>4</sup>

**E.** Hyperlipidemia — Incorrect. Hyperlipidemia has been associated with xanthelasmas in about 50% of patients.<sup>5</sup>

**Question 3: Which of the following would NOT be an appropriate treatment option for this patient?**

- A. Observation
- B. Alkylating chemotherapeutic agents
- C. Corticosteroids
- D. Intravenous immunoglobulin
- E. Antimetabolites (methotrexate or azathioprine)

**Answers:**

**A.** Observation – Incorrect. Observation is an appropriate option for patients with NXG. Our patient was referred to hematology-oncology for further workup. The patient elected to be closely monitored in lieu of pursuing treatment, as her lesions remained stable in size, and her MGUS had not progressed.

**B.** Alkylating chemotherapeutic agents – Incorrect. Alkylating chemotherapeutic agents are the most common systemic treatment for NXG, especially Chlorambucil, which is used in low doses for patients with associated paraproteinemia.<sup>6</sup>

**C.** Corticosteroids – Incorrect. Topical steroids may be used for small NXG areas, and intralesional injections have been used with mixed results. Systemic corticosteroids as monotherapy display a high relapse rate after discontinuation. Systemic corticosteroids may be used in combination with alkylating agents.<sup>6</sup>

**D.** Intravenous Immunoglobulin – Incorrect. Intravenous immunoglobulin has shown rapid remission in patients with NXG and an underlying hematologic disorder.<sup>6</sup> If other treatment modalities fail, intravenous immunoglobulin may be considered.<sup>6</sup>

**E.** Antimetabolites (methotrexate or azathioprine) – Correct. The use of antimetabolites has not proven to be an effective treatment option. Antimetabolites have not been studied since the

1980s and at the time had only produced a partial remission of symptoms. Ultimately, a patient who received both methotrexate and azathioprine actually experienced additional lesions.<sup>6</sup> Antimetabolites have not been included in recent treatment regimens.

**Abbreviations used:**

DI: diabetes insipidus

MGUS: monoclonal gammopathy of undetermined significance

NL: necrobiosis lipoidica

NXG: necrobiotic xanthogranuloma

XD: xanthoma disseminatum

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