

# Anthrax vaccine–induced nodules



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## INTRODUCTION

Injection site granulomas secondary to aluminum-containing vaccinations are a well-known, but rare phenomenon. Most previously reported cases were attributed to the influenza and tetanus vaccines.<sup>1,2</sup> Clinical and histologic manifestation often mimics that of a neoplastic process, resulting in a diagnostic challenge for the dermatologist and dermatopathologist. Here we report a new case of anthrax vaccine–induced nodules, which demonstrates a reactive granular histiocytosis pattern. Predominance of aluminum in the biopsy specimen, via scanning electron microscopy with energy dispersive x-ray spectroscopy (SEM/EDX) or ammonium aurin-tricarboxylate stain, can help rule out Langerhans cell histiocytosis (LCH) and cutaneous pseudolymphomas. Dermatologists and dermatopathologists should be cognizant of this entity and reaction pattern, especially in those lesions occurring in anatomic locations prone to receiving vaccinations to avoid mistaking it for a neoplastic process.

## CASE REPORT

A 37-year-old African-American woman presented with a pruritic nodule on the left upper arm that was present for several years. She reported a similar lesion on her right upper arm, which was biopsied a year prior at a different institution. The biopsy report from her right arm rendered a differential diagnosis of LCH versus lymphocytoma cutis; however, the slides were not available for review. Physical examination found a 4-cm poorly demarcated reticulated hyperpigmented patch (Fig 1).

### Abbreviations used:

LCH: Langerhans cell histiocytosis  
 SEM/EDX: scanning electron microscopy with energy dispersive x-ray spectroscopy



**Fig 1.** Left upper arm; 2-cm linear hypertrophic biopsy scar through the center of a 4-cm poorly demarcated reticulated hyperpigmented patch.

Palpation of this area found a poorly circumscribed subcutaneous nodule. On the right arm, a large poorly demarcated reticulated hyperpigmented patch with an underlying subcutaneous nodule and a well-healed biopsy site from a year prior was appreciated. Because of suspicion of a neoplastic

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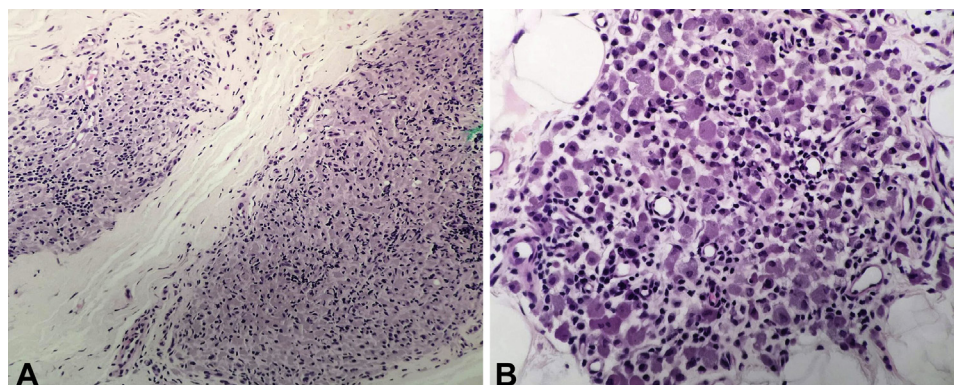
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**Fig 2.** **A**, Aggregates of macrophages with violaceous cytoplasm and admixed chronic inflammatory cells. **B**, Violaceous color and granular nature of the cytoplasm within the histiocytes. (**A** and **B**, Hematoxylin-eosin stain; original magnifications **A**,  $\times 200$  **B**,  $\times 400$ .)

process, an excisional biopsy of the left arm lesion was performed. The clinical differential submitted with the biopsy specimen included LCH, lymphocytoma cutis, dermal hypersensitivity reaction, lymphoma, granulomatous process, and nodular amyloidosis.

On hematoxylin-eosin stain, biopsy of the left upper arm showed multiple pale-to-violaceous inflammatory nodules within the deep subcutis. On closer inspection (**Fig 2, A**) aggregates of macrophages with abundant, violaceous cytoplasm and admixed chronic inflammatory cells were identified. The violaceous color and granular nature of the cytoplasm within the histiocytes is quite striking on  $\times 40$  magnification (**Fig 2, B**). The histologic features were very similar to those seen following postbiopsy excisions when aluminum chloride is used for hemostasis. The initial histologic differential diagnosis included, but was not limited to, infectious etiology, LCH, reactive granular histiocytosis, Erdheim-Chester disease, and granular histiocytosis not otherwise specified. Immunohistochemical and cytochemical analysis of the sample stained positive for CD68 and periodic acid–Schiff, and negative for S-100, CD1a, Grocott methenamine silver, and Fite.

Upon further questioning, the patient reported a history of 9 doses of anthrax vaccine; 6 injections in her left arm and 3 in her right arm as part of her military deployment requirements. Per chart review, this was the only vaccination she had received multiple times in both arms within the last 5 years. Given the vaccination history and these histologic features, tissue blocks were sent for SEM/EDX to further evaluate the granule-containing histiocytes, which showed that they contained aluminum. A diagnosis of aluminum granuloma secondary to repeated anthrax vaccination was rendered. Both nodules were excised,

resulting in complete resolution and no recurrence at 1 year.

## DISCUSSION

Injection site granulomas are a known but uncommon finding. Multiple causative vaccines have been reported in the literature including tetanus (Tetracoq), influenza, hepatitis B and more.<sup>1-5</sup> Although these nodules have been reported in clinical trials with the anthrax vaccine, occurring in 36%, 34%, and 4% of cases with the first, second, and third doses administered, respectively, there is no way to discern what truly caused them.<sup>6</sup> They can present as persistent, pruritic subcutaneous nodules postulated to be the result of a delayed, granulomatous hypersensitivity reaction to aluminum hydroxide-containing vaccines.<sup>2-4</sup> Aluminum, an adjuvant that prolongs the antibody response, is added to many vaccines (**Table I**).<sup>7-9</sup>

In a case series of subcutaneous nodules at vaccine injection sites published by Chong et al,<sup>1</sup> 13 of the cases were located on the upper arm. Although the type of vaccine administered varied, all contained aluminum as an adjuvant. Three cases showed histologic findings comparable to those present in our patient. The key finding is the presence of aggregates of histiocytes with a characteristic abundant violaceous granular cytoplasm. The granulomas contained aluminum ions on dispersive radiograph microanalysis, and excision was shown to be curative in all cases.<sup>1</sup>

A similar phenomenon of collections of granular macrophages can be seen when looking at failed metal-metal grafts.<sup>10</sup> In a case reported by Miller et al,<sup>10</sup> a reactive histiocytic infiltrate was noted incidentally on a lymph node biopsy from a patient with a history of joint arthroplasty, which demonstrated CD68<sup>+</sup> and PAS<sup>+</sup> abundant cytoplasmic

**Table I.** Quantities of aluminum in vaccines

Vaccine	Amount of aluminum
Pneumococcal	0.125 mg/dose
Dtap (Hib)	<0.17-<0.625 mg/dose 0.225 mg/dose
Hib/Hepatitis B	0.225 mg/dose
Hepatitis A	0.225-0.25 mg/dose (pediatrics) 0.45-0.5 mg/dose (adults)
Hepatitis B	0.225-0.5 mg/dose
Hepatitis A/Hepatitis B	0.45 mg/dose
Dtap/inactivated polio/Hepatitis B	<0.85 mg/dose
Dtap/inactivated polio/Hib	0.33 mg/dose
Human papillomavirus	0.225 mg/dose
Anthrax	0.83 mg/dose

Table adapted from the CDC.<sup>9</sup>  
Dtap, Diphtheria-tetanus-acellular pertussis; Hib, haemophilus influenza type B.

granules with minute particles of polarizable intracellular material. Cobalt-chromium and titanium were found with SEM/EDX. The rendered diagnosis was non-Langerhans cell histiocytosis secondary to knee prosthesis.<sup>10</sup>

Distinct injection site granulomas can develop in response to aluminum within different vaccines. Since the diverse mimics of this reaction pattern can include panniculitis, lupus profundus, lymphocytoma cutis, and deep granuloma annulare/rheumatoid nodule, it should be kept in every dermatologist's differential diagnosis when lesions occur within anatomic locations prone to receiving vaccinations, such as the deltoid or buttocks. Further history may need to be elicited to render the correct

diagnosis and avoid mistaking these granulomas for a neoplastic process.

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