

DR STEPHANIE SUE-YEE LEE (Orcid ID : 0000-0002-2456-4375)

DR JESSICA SPRAGUE (Orcid ID : 0000-0001-5511-9058)

DR JENNIFER MANCUSO (Orcid ID : 0000-0001-8899-3657)

Article type : Brief Report

Title: Atypical Keratosis Pilaris-like Lesions in a Patient with Bethlem Myopathy

Authors: Stephanie S. Lee, MD^{1,2}; Brian Hinds, MD¹; Jessica Sprague, MD^{1,2}; Victoria Barrio, MD^{1,2}; Jennifer Brescoll Mancuso, MD^{1,3}

Institutional affiliations:

¹Department of Dermatology, University of California, San Diego, San Diego, CA, 92122

²Division of Pediatric and Adolescent Dermatology, Rady Children's Hospital, San Diego, CA, 92123

³Department of Dermatology, University of Michigan, Ann Arbor, MI, 48109

Corresponding Author: Stephanie Lee, MD

Address: 3020 Children's Way, Mail Code 5092, San Diego, CA, 92123

Phone: 858-966-6795, Fax: 858-966-4040, E-mail: slee7@rchsd.org

Keywords: connective tissue disorders; skin signs of systemic disease; Bethlem myopathy; collagen diseases; muscular dystrophies

Word count: 565

Figure count: 2

Reference count: 5

Acknowledgements: No acknowledgements.

Conflict of interest: All authors have no conflicts of interest.

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/PDE.14862](https://doi.org/10.1111/PDE.14862)

This article is protected by copyright. All rights reserved

Consent statement: N/A

Abstract: Bethlem myopathy is a collagen VI-related myopathy. Collagen VI is primarily associated with the extracellular matrix of skeletal muscle, but is also found in the skin, blood vessels, and other organs. Dermatologic findings described for Bethlem myopathy include follicular hyperkeratosis and abnormal scar formation, although clinical and histopathologic photographs remain elusive in the literature. We present a case of atypical keratosis pilaris-like follicular lesions in a patient with Bethlem myopathy and provide histopathologic correlation to better characterize the development of skin lesions in this rare neuromuscular disease.

Brief Report:

A 15-year-old obese, non-ambulatory male with a history of Bethlem myopathy presented with multiple non-healing lesions on his legs. There was no history of trauma or excoriations. He was initially followed by wound care and treated with cephalexin and triple antibiotic ointment with minimal improvement.

Physical examination revealed multiple, violaceous to brown, crusted 1-2 cm nodules on his lower legs. In addition, there was a background of many follicular-based, violaceous to brown 1-3 mm hyperkeratotic papules on the legs with mild alopecia in the affected areas (Figure 1). He had non-pitting edema of his lower extremities with subtle brawny discoloration.

Punch biopsies were taken of two lesions, one of a crusted nodule and one of a smaller follicular-based papule. The histopathology of the smaller lesion demonstrated perifollicular fibrosis and hemorrhage with follicular plugging, on the spectrum of keratosis pilaris (KP) (Figure 2A). The histopathology of the larger crusted lesion demonstrated a proliferation of focal slit-like blood vessels amidst dermal fibrosis and hemosiderosis, with immunohistochemistry demonstrating negative LANA (HHV8) and ERG labeling of endothelial cell nuclei and positive CD31 staining of the endothelium (Figure 2B-D). This was felt to be consistent with a reactive acroangiodermatitis-like fibrosing reaction secondary to follicular rupture. Additionally, tissue

culture was performed from a larger crusted nodule for bacteria, fungus and atypical mycobacterium, and resulted only with less than 1+ *Corynebacterium* species, which was thought to be a contaminant. Vitamin A and C levels were normal. The patient subsequently spontaneously developed multiple, similar, new ulcerated, crusted nodules arising from the smaller follicular-based papules.

Discussion:

Bethlem myopathy is a collagen VI-related disorder, characterized by progressive proximal muscle weakness and primarily distal joint contractures.¹ Collagen VI is an extracellular matrix protein critical in maintaining the integrity and function of muscles and the skin. Genetic mutation of collagen VI and collagen VI-related myopathies have been associated with follicular hyperkeratosis and abnormal scar formation.²

The differential diagnosis of our patient's lesions included infection, namely, deep fungal or atypical mycobacterial infection, vitamin deficiency, cutaneous vasculitis and perforating dermatosis. With clinicopathologic correlation, it was concluded that our patient had follicular hyperkeratosis with an atypical KP-like appearance, as well as nodular lesions with hemorrhage and fibrosis. The latter may reflect inflammation secondary to follicular rupture of the atypical KP-like lesions with acroangiokeratitis-like features, possibly due to the predilection for stasis-like alteration in the lower extremities secondary to muscle atrophy and the patient's underlying Bethlem myopathy. Acroangiokeratitis is a benign angioproliferative disorder typically of the lower extremities that is seen in chronic venous insufficiency, paralyzed legs, and amputations. It is interesting to note that collagen VI chains are found around blood vessels, which may possibly play a role in the pathogenesis of such lesions.³

While KP-like lesions are well described in the Bethlem myopathy literature, the etiology has not been elucidated and there are sparse clinical or microscopic photographs available.^{4,5} The atypical crusted, nodular lesions arising from the KP-like lesions in our patient have not yet been described in literature. We postulate that the histopathologic finding of a reactive acroangiokeratitis-like fibrosing reaction may reflect predisposition to microvascular disease in the setting of a non-ambulatory patient with a collagen IV-related myopathy and stasis.

We recommended liberal moisturization and keratolytics and wound care for the non-healing lesions, including aggressive management of venous stasis. The patient, however, has continued to spontaneously develop new crusted ulcerations from the pre-existing KP-like papules.

References:

1. Lampe AK, Flanigan KM, Bushby KM, Hicks D. Collagen Type VI-Related Disorders. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews*®. Seattle (WA): University of Washington, Seattle; June 25, 2004.
2. Bönnemann CG. The collagen VI-related myopathies: muscle meets its matrix. *Nat Rev Neurol*. 2011;7(7):379-390. Published 2011 Jun 21. doi:10.1038/nrneurol.2011.81
3. Sabatelli P, Gara SK, Grumati P, et al. Expression of the collagen VI $\alpha 5$ and $\alpha 6$ chains in normal human skin and in skin of patients with collagen VI-related myopathies. *J Invest Dermatol*. 2011;131(1):99-107. doi:10.1038/jid.2010.284
4. Briñas L, Richard P, Quijano-Roy S, et al. Early onset collagen VI myopathies: Genetic and clinical correlations. *Ann Neurol*. 2010;68(4):511-520. doi:10.1002/ana.22087
5. Saroja AO, Naik KR, Nalini A, Gayathri N. Bethlem myopathy: An autosomal dominant myopathy with flexion contractures, keloids, and follicular hyperkeratosis. *Ann Indian Acad Neurol*. 2013;16(4):712-715. doi:10.4103/0972-2327.120453

Figure Legends:

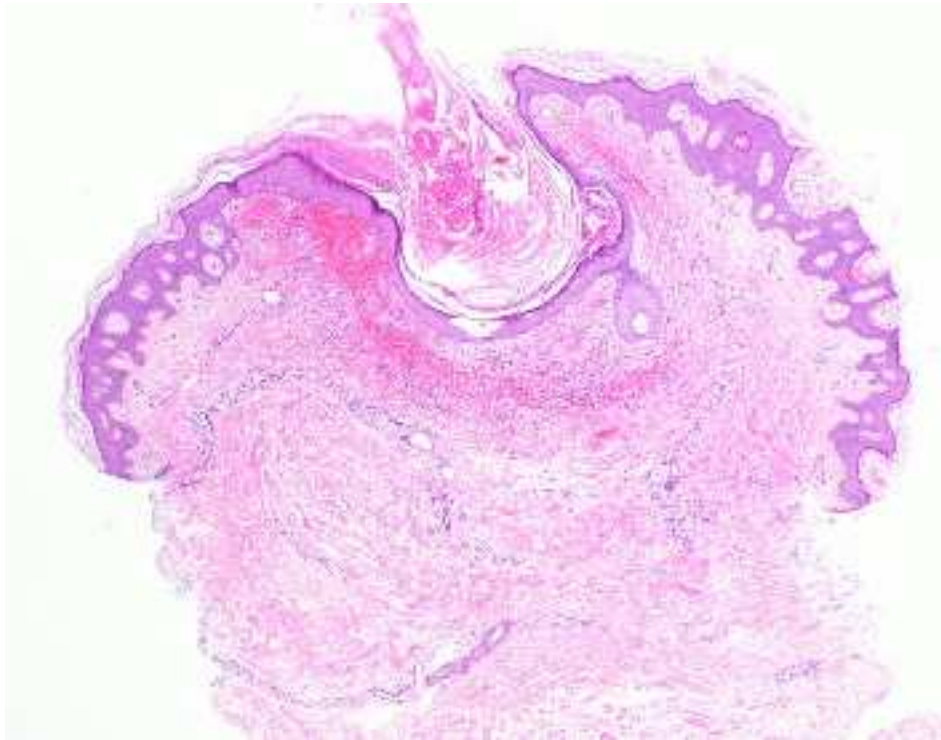
Figure 1. Lower leg with violaceous to brown, crusted nodules with a background of follicular-based, violaceous to brown 1-3 mm hyperkeratotic papules on the legs with mild alopecia of the affected areas.

Figure 2. A. Histopathology (40x) of smaller peri-follicular hyperkeratotic papule revealing epidermal hyperkeratosis and a keratin plug in the hair follicle. B-D: Histopathology of larger crusted nodule. B: Hematoxylin and eosin (H&E, 40x) staining of the larger crusted lesion. C: Immunohistochemistry (40x) demonstrated positive staining of CD31 of endothelial cells. D:

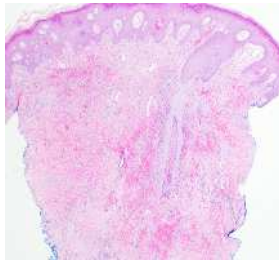
H&E stain (100x) of the larger crusted lesion, demonstrating a proliferation of focal slit-like blood vessels amidst dermal fibrosis and hemosiderosis.



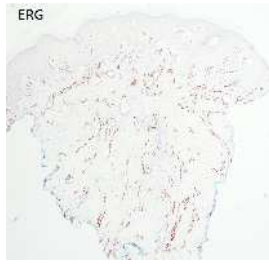
pde_14862_f1.tif



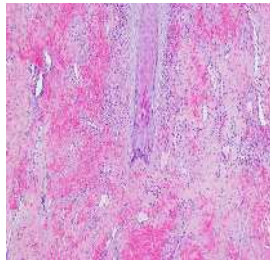
pde_14862_f2a.tif



pde_14862_f2b.tif



pde_14862_f2c.tif



pde_14862_f2d.tif