Hyperpigmented Flexural Plaques, Hypohidrosis, and Hypotrichosis

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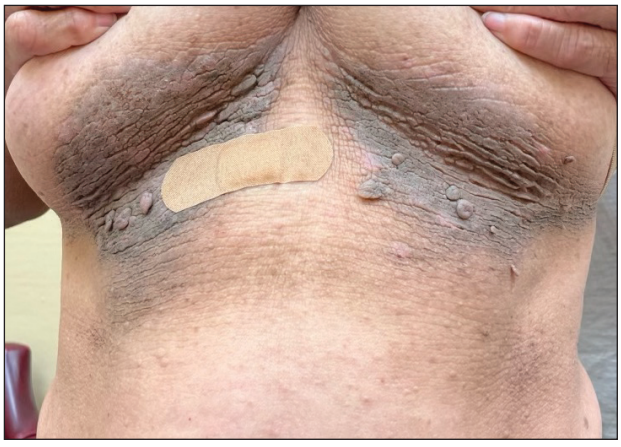

A 61-year-old woman with a history of hypohidrosis and deafness presented with a pruritic rash on the neck and antecubital fossae of several years' duration. Prior treatment with topical corticosteroids failed to resolve the rash. Physical examination revealed thick, velvety, hyperpigmented plaques on the inframammary folds, axillae, groin, posterior neck, and antecubital fossae with lichenification of the latter 2 areas. Many pedunculated papules were seen on the face, chest, shoulders, and trunk, as well as diffuse hair thinning, particularly of the frontal and vertex scalp. Eyebrows, eyelashes, and axillary hair were absent. Two 5-mm punch biopsies of the antecubital fossa and inframammary fold were obtained for histopathologic analysis.

WHAT'S YOUR **DIAGNOSIS?**

a. confluent and reticulated papillomatosis
b. cutaneous paraneoplastic syndrome
c. *FGFR* (fibroblast growth factor receptor) mutation
d. HAIR-AN (hyperandrogenism, insulin resistance, and acanthosis nigricans) syndrome
e. Lelis syndrome

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The authors report no conflict of interest.
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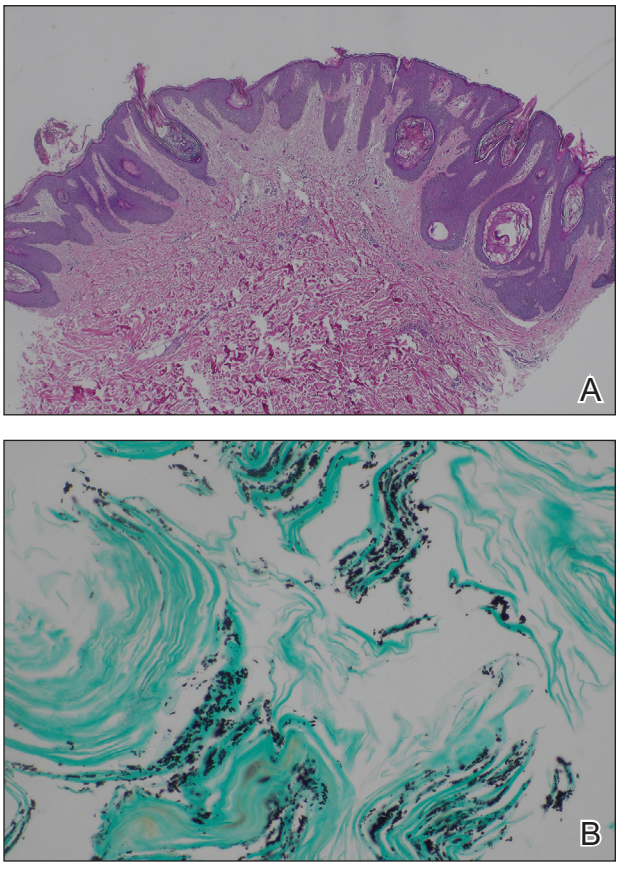
THE **DIAGNOSIS:** Lelis Syndrome

Histopathology revealed spongiotic dermatitis with marked acanthosis and hyperkeratosis (Figure, A) with fungal colonization of the stratum corneum (Figure, B). Our patient was diagnosed with Lelis syndrome (also referred to as ectodermal dysplasia with acanthosis nigricans syndrome), a rare condition with hypotrichosis and hypohidrosis resulting from ectodermal dysplasia.[1,2] The pruritic rash was diagnosed as chronic dermatitis due to fungal colonization in the setting of acanthosis nigricans. The fungal infection was treated with a 4-week course of oral fluconazole 200 mg/wk, ketoconazole cream 2% twice daily, and discontinuation of topical steroids, resulting in the thinning of the plaques on the neck and antecubital fossae as well as resolution of the pruritus. Following antifungal treatment, our patient was started on tazarotene cream 0.1% for acanthosis nigricans.

Ectodermal dysplasias are inherited disorders with abnormalities of the skin, hair, sweat glands, nails, teeth, and sometimes internal organs.[3] Patients with Lelis syndrome may have other manifestations of ectodermal dysplasia in addition to hypohidrosis and hypotrichosis, including deafness and abnormal dentition,[1,3] as seen in our patient. Intellectual disability has been described in many types of ectodermal dysplasia, including Lelis syndrome, but the association may be obscured by neurologic damage after repeat episodes of hyperthermia in infancy due to anhidrosis or hypohidrosis.[4]

When evaluating the differential diagnoses, the presence of hypotrichosis and hypohidrosis indicating ectodermal dysplasia is key. Confluent and reticulated papillomatosis presents with hyperkeratosis, papillomatosis, and focal acanthosis on histopathology. It can present on the neck and antecubital fossae; however, it is not associated with hypohidrosis and hypotrichosis.[5] Although activating fibroblast growth factor receptor, *FGFR*, mutations have been implicated in the development of acanthosis nigricans in a variety of syndromes, these diagnoses are associated with abnormalities in skeletal development such as craniosynostosis and short stature; hypotrichosis and hypohidrosis are not seen.[6,7] HAIR-AN (hyperandrogenism, insulin resistance, and acanthosis nigricans) syndrome typically presents in the prepubertal period with obesity and insulin resistance; acanthosis nigricans and alopecia can occur due to insulin resistance and hyperandrogenism, but concurrent clitoromegaly and hirsutism are common.[6] Sudden onset of extensive acanthosis nigricans also is among the paraneoplastic dermatoses; it has been associated with multiple malignancies, but in these cases, hypotrichosis and hypohidrosis are not observed. Adenocarcinomas are the most common neoplasms associated with paraneoplastic acanthosis nigricans, which occurs through growth factor secretion by tumor cells stimulating hyperkeratosis and papillomatosis.[6]



A, Histopathology revealed a spongiotic and acanthotic epidermis with papillomatous architecture and intermittent wedge-shaped hyperkeratosis (H&E, original magnification ×40). B, Grocott-Gomori methenamine-silver staining showed numerous fungal elements in the stratum corneum (original magnification ×400).

Lelis syndrome is rare, and our case is unique because the patient had severe manifestations of acanthosis nigricans and hypotrichosis. Because the inheritance pattern and specific genetics of the condition have not been fully elucidated, the diagnosis primarily is clinical.[1,8] Diagnosis may be complicated by the variety of other signs that can accompany acanthosis nigricans, hypohidrosis, and hypotrichosis.[1,2] The condition also may alter or obscure presentation of other dermatologic conditions, as in our case.

Although there is no cure for Lelis syndrome, one case report described treatment with acitretin that resulted in marked improvement of the patient's hyperkeratosis and acanthosis nigricans.[9] Due to a lack of health insurance coverage of acitretin, our patient was started on tazarotene cream 0.1% for acanthosis nigricans. General

treatment of ectodermal dysplasia primarily consists of multidisciplinary symptom management, including careful monitoring of temperature and heat intolerance as well as provision of dental prosthetics.[4,10] For ectodermal dysplasias caused by identified genetic mutations, prenatal interventions targeting gene pathways offer potentially curative treatment.[10] However, for Lelis syndrome, along with many other disorders of ectodermal dysplasia, mitigation of signs and symptoms remains the primary treatment objective. Despite its rarity, increased awareness of Lelis syndrome is important to increase knowledge of ectodermal dysplasia syndromes and allow for the investigation of potential treatment options.

REFERENCES

1. Steiner CE, Cintra ML, Marques-de-Faria AP. Ectodermal dysplasia with acanthosis nigricans (Lelis syndrome). *Am J Med Genet*. 2002;113:381-384. doi:10.1002/ajmg.b.10787
2. Lelis J. Autosomal recessive ectodermal dysplasia. *Cutis*. 1992; 49:435-437.
3. Itin PH, Fistarol SK. Ectodermal dysplasias. *Am J Med Genet C Semin Med Genet*. 2004;131C:45-51. doi:10.1002/ajmg.c.30033
4. Blüschke G, Nüsken KD, Schneider H. Prevalence and prevention of severe complications of hypohidrotic ectodermal dysplasia in infancy. *Early Hum Dev*. 2010;86:397-399. doi:10.1016/j.earlhumdev.2010.04.008
5. Le C, Bedocs PM. Confluent and reticulated papillomatosis. *StatPearls*. StatPearls Publishing; 2022. http://www.ncbi.nlm.nih.gov/books/NBK459130/
6. Das A, Datta D, Kassir M, et al. Acanthosis nigricans: a review. *J Cosmet Dermatol*. 2020;19:1857-1865. doi:10.1111/jocd.13544
7. Torley D, Bellus GA, Munro CS. Genes, growth factors and acanthosis nigricans. *Br J Dermatol*. 2002;147:1096-1101. doi:10.1046/j.1365-2133.2002.05150.x
8. van Steensel MAM, van der Hout AH. Lelis syndrome may be a manifestation of hypohidrotic ectodermal dysplasia. *Am J Med Genet A*. 2009;149A:1612-1613. doi:10.1002/ajmg.a.32945
9. Yoshimura AM, Neves Ferreira Velho PE, Ferreira Magalhães R, et al. Lelis' syndrome: treatment with acitretin. *Int J Dermatol*. 2008;47: 1330-1331. doi:10.1111/j.1365-4632.2008.03874.x
10. Schneider H. Ectodermal dysplasias: new perspectives on the treatment of so far immedicable genetic disorders. *Front Genet*. 2022;13:1000744. doi:10.3389/fgene.2022.1000744