India K. Poetzscher
Department of Dermatology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Nikolai Klebanov, MD
Department of Dermatology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Shinjita Das, MD, MPH
Department of Dermatology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Widespread skin-thickening and hyperpigmentation

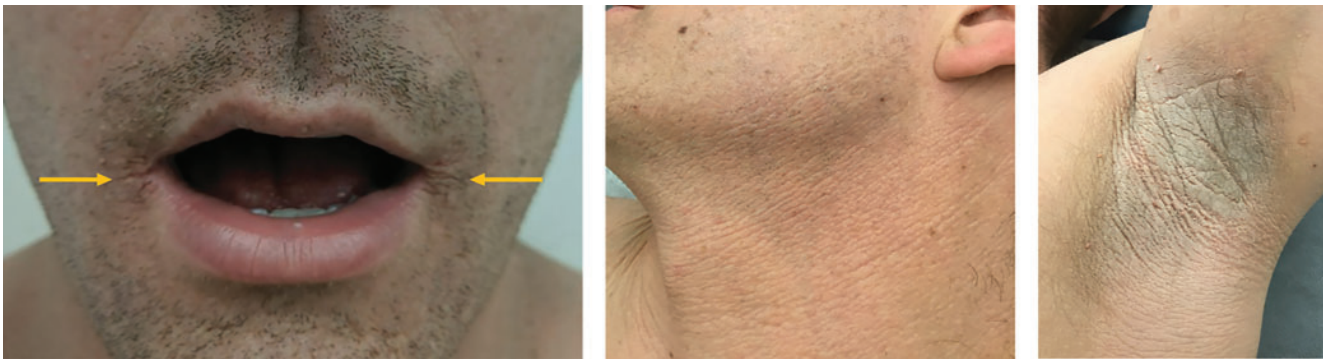

Figure 1. Plaques of acanthosis nigricans on areas of the lips, left neck, and left axilla at initial consultation.

A 37-year-old white male presented with skin-thickening and hyperpigmentation, the onset of which correlated with an increasingly sedentary lifestyle. He noted a subjective decrease in muscle density and a 40-pound weight gain in the decade following active military duty. His height was 6'1" (185.4 cm) and body mass index 32.3 kg/m^2.

At presentation, the patient had extensive velvety hyperpigmented plaques on the forehead, corners of the lips, neck, axillae, trunk (including areolae), extremities, and groin, amounting to approximately 10% to 15% of the body surface area (**Figure 1**).

Clinical features and skin-shave biopsy (showing epidermal papillomatosis) at initial presentation supported the diagnosis of acanthosis nigricans. The distribution and body surface area involvement prompted an initial laboratory workup, with a complete blood cell count, lipid panel, renal panel, and endocrine panel, all of which were normal. Multiple management strategies were attempted, including metformin, isotretinoin, topical theapies (steroids and calcineurin inhibitors), and weight loss. The patient initially experienced mild improvement in visual appearance and pruritus from weight loss and tacrolimus ointment. Though he felt systemically well, his acanthosis nigricans progressively worsened over the next 2 to 3 years (**Figure 2**). This prompted a cancer screening workup (**Table 1**),[1] but to date no major abnormalities have been identified except gradual elevation over 2 years of the total cholesterol level of 202 mg/dL.

PATHOPHYSIOLOGY AND CLINICAL VARIANTS

Acanthosis nigricans classically presents in skin folds (eg, neck, axillae) with symmetrically distributed hyperpigmented plaques with a velvety or verrucous texture.[2] It is more common in Native Americans and African Americans.[2] The precise pathophysiology of acanthosis nigricans is unknown but attributed to insulin-mediated stimulation of keratinocytes and fibroblasts via insulin-like growth factor receptors and epidermal growth factor receptors.[2,3]

doi:10.3949/ccjm.89a.21099

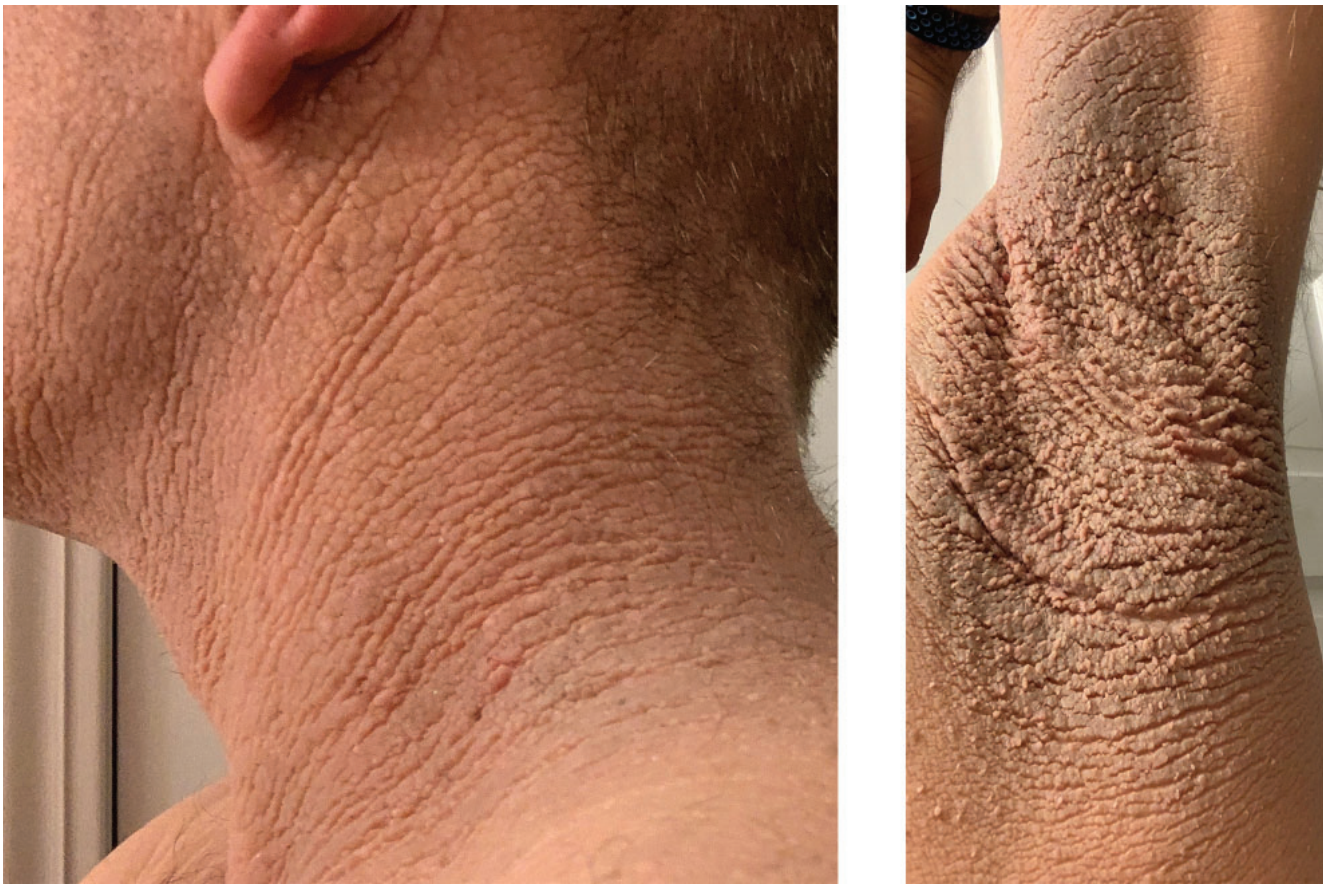

Figure 2. Severe disease progression after 2 years.

Common causes of acanthosis nigricans include obesity, medications, and endocrine abnormalities, with rarer cases due to paraneoplastic phenomenon or a familial trait via germline fibroblast growth factor receptor 3 mutations.[2–4] Obesity-associated acanthosis nigricans can present together with insulin resistance, high body mass index, diabetes, metabolic syndrome, or polycystic ovarian syndrome. Medications associated with acanthosis nigricans include nicotinic acid (niacin), oral corticosteroids, oral contraceptives, methyltestosterone.[2] The paraneoplastic form is most often seen with gastric adenocarcinoma, though other causes have also been identified.[2]

Acanthosis nigricans with abrupt features such as severe and rapid onset, atypical sites (eg, palms or mucosa), widespread distribution at any age, or new onset in patients over age 40 should prompt evaluation for malignancy.[2] A thorough history and physical examination followed by judicious use of laboratory and other investigations should help determine the underlying cause of acanthosis nigricans.

DIFFERENTIAL DIAGNOSIS OF SKIN-THICKENING AND HYPERPIGMENTATION

Other notable conditions can present with skin-thickening or hyperpigmentation:

- Confluent and reticulated papillomatosis is more diffuse with a net-like appearance
- Terra firma-forme dermatosis easily wipes off with rubbing alcohol
- Hemochromatosis, Addison disease, and erythema dyschromicum perstans (ashy dermatosis) all present with flat hyperpigmentation only, without skin-thickening
- Pemphigus vegetans is a rare form of pemphigus with warty (verrucous) ulcerated plaques.

MANAGEMENT

Acanthosis nigricans is first treated by addressing underlying causes with diet and exercise and oral metformin in obesity-associated acanthosis nigricans, surgery or chemotherapy for paraneoplastic

acanthosis nigricans, and removal of the offending agent in drug-induced acanthosis nigricans.[2–6] Skin treatments can help with the cosmetic appearance of plaques. Topical keratolytics (retinoids, salicylic acid, ammonium lactate, chemical peels) may help soften the appearance of acanthosis nigricans but carry a risk of skin irritation. Systemic isotretinoin may be considered in consultation with a dermatologist.

TAKE-HOME POINTS

While patients with milder acanthosis nigricans will not necessarily require a workup for malignancy, close clinical monitoring is recommended as the condition can be the first sign of diabetes or malignancy.[6] Because approximately 17% of malignant acanthosis nigricans appears prior to tumor diagnosis, progression to severe acanthosis nigricans in this patient was the rationale for a more extensive clinical investigation.[5–7]

TABLE 1
Cancer screening workup for acanthosis nigricans with suspicious features[a]

Age-appropriate cancer screening[b]
- Mammography (ages 50–74)[c]
- Cervical cancer screening (ages 21–65)[c]
- Colorectal cancer screening (ages 45–75)
- Lung cancer screening (ages 50–80, with smoking history)

Focused laboratory studies
- Alpha-fetoprotein tumor marker (reference range 0.0–10.0 ng/mL)
- Cancer antigen 19-9 (reference range 1.2–5 U/mL)
- Carcinoembryonic antigen (reference range 0.0–5.0 ng/mL)
- Lactate dehydrogenase (reference range 110–220 U/L)

Imaging/visualization
- Colonoscopy, endoscopy
- Renal and gallbladder ultrasonography
- Consider computed tomography of abdomen and pelvis
- Consider referral to gastroenterology

[a] Screening for intra-abdominal adenocarcinoma in most cases, but also gastric, ovarian, endometrial, uterine/cervical, breast, liver, lung, pancreas, colorectal.
[b] Based on US Preventive Services Task Force guidelines for patients at average risk. See reference 1.
[c] Not performed in our male patient.

DISCLOSURES

Dr. Das has disclosed ownership interest (stock, stock ownership in a publicly owned company) in Bristol-Myers Squibb and Crisper Therapeutics, and work as advisor for Skin Analytics. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

REFERENCES

1. **Department of Health and Human Services.** US Preventive Services Task Force. A & B Recommendations. https://www.uspreventiveservicestaskforce.org/uspstf/recommendation-topics/uspstf-a-and-b-recommendations. Accessed August 18, 2022.
2. **Phiske MM.** An approach to acanthosis nigricans. Indian Dermatol Online J 2014; 5(3):239–249. doi:10.4103/2229-5178.137765
3. **Fukuchi K, Tatsuno K, Matsushita K, Kubo A, Ito T, Tokura Y.** Familial acanthosis nigricans with p.K650T FGFR3 mutation. J Dermatol 2018; 45(2):207–210. doi:10.1111/1346-8138.14107
4. **Torley D, Bellus GA, Munro CS.** Genes, growth factors and acanthosis nigricans. Br J Dermatol 2002; 147(6):1096–1101. doi:10.1046/j.1365-2133.2002.05150.x
5. **Talsania N, Harwood CA, Piras D, Cerio R.** Paraneoplastic acanthosis nigricans: the importance of exhaustive and repeated malignancy screening. Dermatol Online J 2010; 16(8):8. pmid:20804685
6. **Popa ML, Popa AC, Tanase C, Gheorghisan-Galateanu AA.** Acanthosis nigricans: to be or not to be afraid. Oncol Lett 2019; 17(5):4133–4138. doi:10.3892/ol.2018.9736
7. **Krawczyk M, Mykała-Cieśla J, Kołodziej-Jaskuła A.** Acanthosis nigricans as a paraneoplastic syndrome. Case reports and review of literature. Pol Arch Med Wewn 2009; 119(3):180–183. pmid:19514649

Address: *Shinjita Das, MD, MPH, Department of Dermatology, Massachusetts General Hospital, Harvard Medical School, 50 Staniford Street, #292, Boston, MA 02114; sdas4@mgh.harvard.edu*