# Acanthosis nigricans in the setting of severe pulmonary disease exacerbated by COVID-19 infection

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## INTRODUCTION

Acanthosis nigricans classically presents with symmetric hyperpigmented velvet-textured flexural and intertriginous plaques often occurring in patients with underlying insulin resistance. Involvement of the lips and oral mucosa is rare and may be suggestive of malignant acanthosis nigricans, which is considered a paraneoplastic syndrome associated with an underlying malignancy, most commonly gastrointestinal or lung cancer.[1] Malignant acanthosis nigricans has a more rapid onset, characterized by ridged, velvet-like plaques involving the palms.[2,3] In endocrinopathy-associated acanthosis nigricans, increased insulin resistance and circulating growth factors induce epidermal proliferation and are thought to contribute to the clinical findings. In the context of malignancy, tumor-associated growth factors may be implicated. Non-malignancy–associated acanthosis nigricans with tripe palms, so named because of the skin changes resembling bovine tripe or stomach, is rare. Here we report a case of acanthosis nigricans in a patient hospitalized for severe pulmonary complications of COVID-19.

*Abbreviation used:*

ILD: interstitial lung disease

## CASE REPORT

A 57-year-old man with history of treated latent tuberculosis, pulmonary coccidioidomycosis, cigarette tobacco use, and no history of diabetes mellitus, was admitted for hypoxic respiratory failure. The patient was diagnosed with severe COVID-19 pneumonia complicated by acute respiratory distress syndrome with acute hyperbaric and hypoxemic respiratory failure requiring intubation, extracorporeal membrane oxygenation, then tracheostomy, and placement on the lung transplantation list. Dermatology was consulted for new-onset progressive skin thickening and dark discoloration on the hands, dorsal aspect of the ankles, and feet, which had developed over the previous month, coinciding with worsening COVID-19 infection. Examination showed well-demarcated hyperpigmented velvety plaques of the dorsal aspects of the hands, fingers (Fig 1), and ankles, and hyperkeratosis of the palms and soles. Removal with isopropyl alcohol was attempted to exclude terra firma-forme dermatosis; however, this was unsuccessful.

Skin biopsy of the dorsal aspect of the hand demonstrated epidermal papillomatosis and hyperkeratosis (Fig 2), findings compatible with acanthosis nigricans.

Findings of acanthosis nigricans were initially concerning for paraneoplastic syndrome and prompted malignancy workup, including computed tomography imaging of the chest, abdomen, pelvis, esophagogastroduodenoscopy, and colonoscopy, all of which were unremarkable. The patient's hemoglobin A1c prior to hospitalization was 5.6%. The

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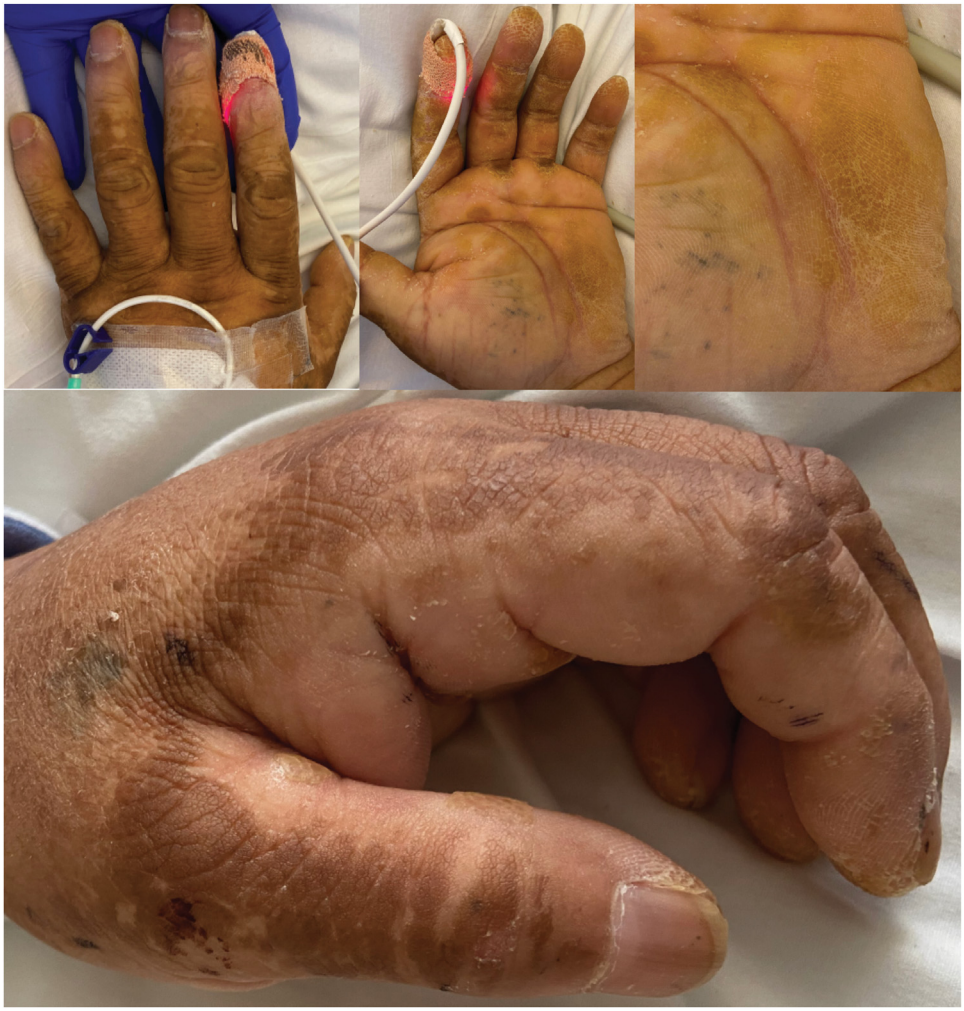

**Fig 1.** Clinical photographs of hands on initial examination. Well-demarcated hyperpigmented plaques on the dorsal aspects of the fingers and hand with focal hyperkeratosis of the palmar aspects of the hand and fingers.

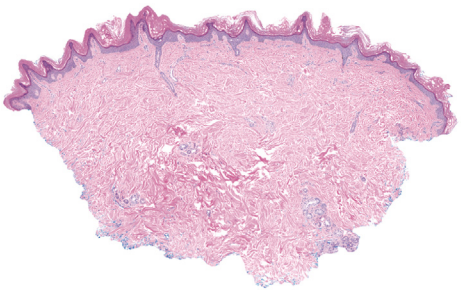

**Fig 2.** Hematoxylin-eosin–stained skin biopsy of the dorsal aspect of the left thumb (original magnification: ×2). The biopsy showed epidermal papillomatosis and hyperkeratosis, with subtle foci of epidermal atrophy overlying the papillomatous dermal papillae.

patient was ultimately able to receive his bilateral lung transplant and underwent tracheostomy tube decannulation. Within 3 months after his lung transplant, the patient reported resolution of his skin thickening and dark discoloration (Fig 3).

## DISCUSSION

Non-malignancy–associated acanthosis nigricans with tripe palms is rare, presenting in 8 out of 87 patients with tripe palms according to a review.[3] Of the remaining 79 malignancy–associated tripe palm cases, gastric cancer was found to be the most common cancer for patients with tripe palms and acanthosis nigricans, whereas lung cancer was the most common for patients with tripe palms without acanthosis nigricans. Conditions identified in the 8 patients without malignancy included chronic bronchitis, bullous pemphigoid, diabetes, and psoriasis,[3] none of which were identified in our patient. Since then, a case of non-malignancy–associated acanthosis

**Fig 3.** Clinical photographs of hands following lung transplant. Resolution of hyperpigmentation and hyperkeratosis of both hands and fingers.

nigricans with tripe palms was also reported in a patient with underlying fibrotic interstitial lung disease (ILD).[4] Interestingly, although acanthosis nigricans is often refractory to treatment, our patient and the patient described in the case report by Danesh et al[4] both noted resolution of skin findings following lung transplantation.

The pathophysiology in endocrine and malignancy—associated acanthosis nigricans is thought to involve epidermal growth factors, including insulin-like growth factor and tumor growth factor-$\alpha$.[5] Acanthosis nigricans in the setting of insulin resistance is also associated with increased adipose tissue expression of tumor necrosis factor-$\alpha$.[6] In contrast, the pathophysiology of acanthosis nigricans associated with ILD has not been well-established. Although platelet-derived growth factor has not been traditionally associated with acanthosis nigricans, it is known to be elevated in patients with ILD and acts as a potent mitogen for mesenchymal stem cell proliferation,[7] including differentiation into epithelial cells, indicating a theoretical mechanism leading to acanthosis nigricans. Additionally, growth factor receptor-signaling pathways (including epidermal growth factor receptor and platelet-derived growth factor receptor) have been found to be activated upon SARS-CoV-2 infection.[8] Elevation of proinflammatory cytokine tumor necrosis factor-$\alpha$ levels has also been demonstrated in patients with COVID-19, in particular in the cytokine release syndrome.[9,10]

In this case, given the negative malignancy workup, the lacking history of diabetes mellitus, and the rapid onset of skin findings coinciding with COVID-19—induced respiratory failure, we propose that the acanthosis nigricans was most likely associated with this patient's acute on chronic pulmonary disease. His computed tomography chest imaging on transfer to our hospital demonstrated subpleural reticulations and traction bronchiectasis, which was thought to be due to either ILD in the setting of COVID-19 respiratory failure or a more chronic fibrosing ILD. Of note, the patient had a history of latent tuberculosis and pulmonary coccidioidomycosis, which, in addition to tobacco use, may have predisposed our patient to severe COVID-19 hypoxic respiratory failure. We hypothesize that activation of growth factor receptor-signaling pathways in the setting of severe lung disease may have contributed to the cutaneous presentation in our patient, suggesting a potential link between development of acanthosis nigricans and the underlying pathophysiology of COVID-19 and ILD.

To our knowledge, new-onset acanthosis nigricans developing in the setting of severe COVID-19 with associated ILD has not been previously reported. New-onset acanthosis nigricans may indicate an underlying malignancy or ILD, and in the appropriate clinical context, further workup for a contributing cause should be considered.

**Conflicts of interest**

None disclosed.

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