

# Reversible acral and mucosal hyperpigmentation in a patient with B12 deficiency secondary to polyglandular autoimmune syndrome type II

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Ishan Asokan<sup>1\*</sup> , Rachel Wheatley<sup>2</sup>, Jenna Lullo<sup>2</sup>,  
Meiling Yuen<sup>2</sup> and Jan Smogorzewski<sup>2</sup>

## Abstract

Reversible cutaneous hyperpigmentation often occurs in the setting of nutritional deficiencies and protein energy malnourishment, with atypical presentations arising from autoimmune disease. Here, we present a 52-year-old female with hypertension, type I diabetes, and Hashimoto's thyroiditis, under the diagnosis of polyglandular autoimmune syndrome type II, referred for evaluation of asymptomatic hyperpigmentation of the palms, soles, hard palate, and tongue for 6 months. The patient underwent a significant work-up, including esophagogastroduodenoscopy, which revealed hypertrophic gastropathy as well as evidence of acquired B12 deficiency secondary to pernicious anemia. The patient was initiated on B12 supplementation, with eventual resolution of mucocutaneous findings.

## Keywords

B12 deficiency, hyperpigmentation, polyglandular autoimmune syndrome type II

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## Introduction

Nutritional deficiencies, such as cobalamin (vitamin B12), can manifest in hematologic, psychiatric, gastrointestinal, and cardiovascular changes. Cutaneous findings unique to B12 deficiency include hyperpigmentation, vitiligo, angular stomatitis, and hair changes.<sup>1</sup> B12 deficiencies usually result from malabsorption, warranting initial repletion with intramuscular injections. Here, we present a case of a 52-year-old female with polyglandular autoimmune syndrome (PGAS) type II who developed new-onset hyperpigmentation for 6 months secondary to pernicious anemia.

## Case

A 52-year-old female with hypertension, type 1 diabetes mellitus, Hashimoto's thyroiditis, and pernicious anemia, under the umbrella diagnosis of PGAS type II, was referred to Dermatology for evaluation of asymptomatic hyperpigmentation of the palms, soles, hard palate, and tongue for 6 months (Figure 1(a) and (c)). Dermoscopy was not performed on the mucocutaneous lesions. The patient denied personal or family history of irregular hyperpigmentation

and denied any itching or pain associated with the lesions. Review of systems was notable for fatigue, without associated fevers, chills, joint pain, swelling, numbness, or sensory loss. Medications prior to onset of hyperpigmentation included long-acting insulin, atorvastatin, and iron supplementation. Initial differential included Laugier–Hunziker syndrome, Addison's disease, Peutz–Jeghers syndrome, or an acquired or drug-induced nutritional deficiency.

Laboratory investigations demonstrated a chronic macrocytic anemia with pancytopenia, with an unremarkable infectious work-up. Hemoglobin on admission was 5.6 g/dL (12.0–15.5 g/dL), which decreased from a baseline of 10.7 g/dL

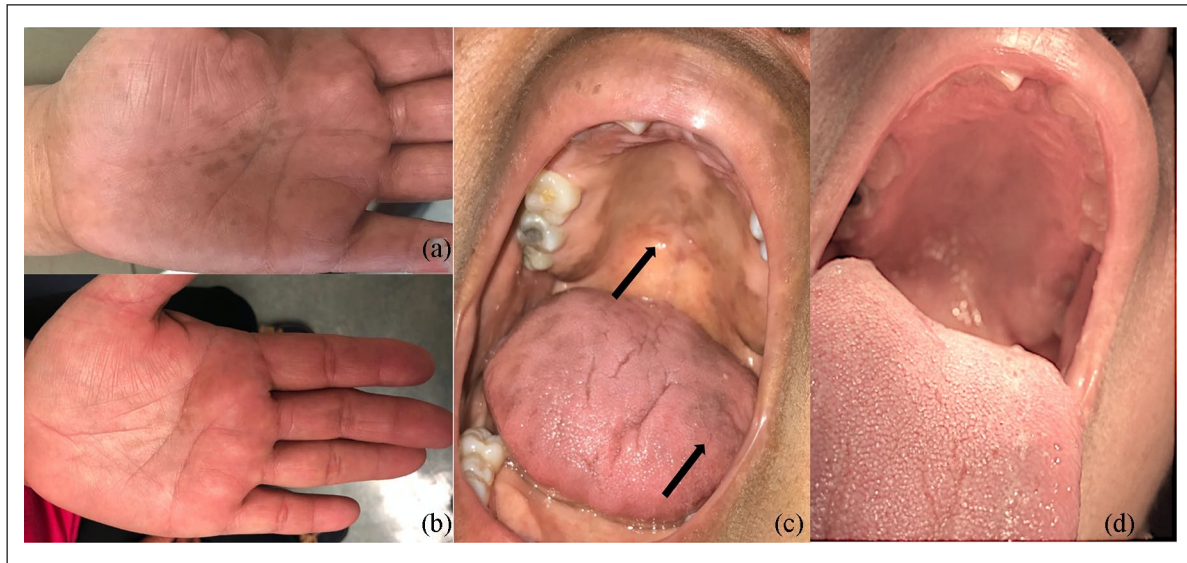
<sup>1</sup>Department of Medicine, UCLA Medical Center, Los Angeles, CA, USA  
<sup>2</sup>Division of Dermatology, Harbor-UCLA Medical Center, Torrance, CA, USA

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### Corresponding Author:

Jan Smogorzewski, Division of Dermatology, Harbor-UCLA Medical Center, 1000 W Carson Street, Torrance, CA 90502, USA.  
Email: jsmogorzewski@dhs.lacounty.gov





**Figure 1.** (a) Right palm with numerous faint tan-brown hyperpigmented macules ranging from 2 to 7 mm on central palm and scattered faint tan-brown hyperpigmented macules between finger spaces bilaterally. (b) Evidence of improvement in hyperpigmentation on palm after vitamin B12 supplementation. (c) Palate and tongue with faint tan-brown hyperpigmented macules. (d) Evidence of improvement in hyperpigmentation on tongue and palate 6 months later.

with lactate dehydrogenase (LDH) elevation to 1669 U/L (normal <280 U/L), and peripheral blood smear revealed hemolysis. Following transfusion, the patient underwent endoscopy showing antral mucosal glandular hyperplasia and atypia, as well as gastric nodules. Anemia work-up confirmed vitamin B12 deficiency, that is, <50 pg/mL (normal, 190–900 pg/mL). In addition, homocysteine and methylmalonic acid (MMA) levels were elevated to 113.3  $\mu\text{mol/L}$  (normal, <15  $\mu\text{mol/L}$ ) and 38.980  $\mu\text{mol/L}$  (normal, 0.00–0.40  $\mu\text{mol/L}$ ), respectively, with confirmation of serum intrinsic factor and parietal cell antibodies. This led to the diagnosis of pernicious anemia secondary to vitamin B12 deficiency. The patient was initiated 1000  $\mu\text{g}$  of vitamin B12 intramuscular injections daily for 1 week with transition to maintenance oral therapy for 6 months. At that time, her B12 level increased to 844 pg/mL, and there was significant improvement in hyperpigmentation (Figure 1(b) and (d)).

## Discussion

Hyperpigmentation secondary to protein energy malnutrition, zinc deficiency, and niacin deficiency (pellagra) is primarily reported in low-income countries.<sup>2</sup> Mechanistically, melanocyte recruitment is often confined to the dorsum of the hands and feet, with interphalangeal joint involvement in patients with severe disease.<sup>3</sup> Our patient's atypical mucosal involvement mirrors prior cases attributable to dietary deficiencies.<sup>4</sup>

Although the precise mechanism is unknown, B12 deficiency is theorized to increase pigmentation either through increased production of melanin or through disordered transport of melanin to keratinocytes. B12 deficiency leads to a decrease in intracellular glutathione levels, which normally

inhibit tyrosinase activity, thus increasing melanogenesis.<sup>5</sup> Alternatively, B12-mediated interruptions in melanin transfer between melanocytes and keratinocytes result in pigment incontinence and atypical pigmentation patterns, typically involving buccal and palmar creases.<sup>6</sup> Diffuse skin hyperpigmentation has been seen in patients with B12 deficiencies, though rarely reported.<sup>4</sup> The skin manifestations of disease precede many of the typically paired neurologic and hematologic sequelae, specifically macrocytic anemia, associated with acquired B12 deficiency, highlighting the importance of early recognition by dermatologists.

Patients with PGAS type II may develop Addison's disease, type 1 diabetes, and autoimmune thyroiditis. In Addison's disease, the mechanism of increased hyperpigmentation occurs following increased synthesis and cleavage of pro-opiomelanocortin (POMC) into expressed alpha-melanocyte-stimulating hormone ( $\alpha$ -MSH), typically occurring as intraoral pigmentation followed by generalized hyperpigmentation.<sup>7</sup> However, aside from the referenced autoimmune conditions associated with PGAS, patients can develop pernicious anemia and simulate localized hyperpigmentation as seen in our patient.<sup>8</sup> For this reason, B12 deficiency may be overlooked as a reversible cause for hyperpigmentation in a patient otherwise at risk of  $\alpha$ -MSH-mediated melanogenesis and should be considered in patients with localized cutaneous and mucosal hyperpigmentation. In addition, patients who have undergone gastrectomy for malignancy present with similar patterns of disease, thereby signaling the importance of identifying acquired B12 deficiencies.

Skin findings may precede symptomatic, irreversible neurologic sequelae as well as severe anemia.<sup>9</sup> Other cases of B12 deficiencies showcased increased angiogenesis as another

skin-related manifestation, possibly in the setting of B12-mediated vascular endothelial growth factor (VEGF) activity in implicated areas.<sup>10</sup>

In summary, it is important to consider multiple etiologies in patients with acquired versus inherited cutaneous hyperpigmentation syndromes. Clinical assessment of symptoms in conjunction with the geographic distribution of hyperpigmentation should guide decision to pursue B12 deficiency as a cause for atypical hyperpigmentation.

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### ORCID iD

Ishan Asokan  <https://orcid.org/0000-0003-4602-0114>

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