

Acquired perforating dermatosis in patients with copper deficiency



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INTRODUCTION

Acquired perforating dermatosis (APD) commonly presents as pruritic, dome-shaped nodules or papules that can contain a keratotic plug in their center, favoring the extensor surfaces.¹ It is characterized histologically by transepidermal elimination of substances, including elastic fibers, keratin, and collagen.² Though the exact pathophysiology is unknown, there is an association of APD with renal failure, diabetes, and drugs, including tumor necrosis factor inhibitors. Within APD, elastosis perforans serpiginosa has been reported with penicillamine in Wilson disease, suggesting that copper dysregulation may be involved in its pathophysiology.³ We report 2 cases of patients who presented with APD in the setting of underlying copper deficiency, including 1 whose eruption resolved with copper supplementation.

CASE REPORTS

Case 1

A 47-year-old woman with a history of gastric bypass surgery via duodenal switch, autoimmune gastritis complicated by chronic diarrhea, chronic normocytic anemia, iron deficiency, type 2 diabetes mellitus, and stage 3 chronic kidney disease (CKD) was admitted for candidal esophagitis and subacute bilateral lower extremity weakness. Dermatology was consulted for tender, nonpruritic papules lasting for 1 week. On the bilateral upper and lower extremities, there were 10 to 15 well-defined medium-brown firm hyperkeratotic papules ranging from 3 mm to 6 mm, extending distally to the right dorsal index finger (Fig 1). Punch biopsy of a left arm lesion was suggestive of reactive perforating collagenosis, showing necrobiotic collagen fibers and lymphohistiocytic infiltrate perforating up through

Abbreviations used:

APD: acquired perforating dermatosis
CKD: chronic kidney disease
HS: hidradenitis suppurativa

the epidermis. Trichrome and Verhoeff-Van Gieson stains showed both focal collagen trapping in the epidermis and extensive transepidermal elimination of elastic fibers (Fig 1, B). Laboratory testing revealed a hemoglobin of 7.3 g/dL (mean corpuscular volume, 106 fL), iron of 90 μ g/dL (normal range, 50-212 μ g/dL), creatinine of 1.76 mg/dL (normal range, 0.6-1.3 mg/dL), vitamin B12 of 1102 pg/mL (normal range, 180-933 pg/mL), and folate of 22.9 ng/mL (normal range, \geq 5.9 ng/mL). Her chronic anemia, refractory to iron transfusions, prompted a workup for myelodysplastic syndrome. A previous bone marrow biopsy showed mild myeloid maturation arrest but no blasts and normal flow cytometry. Neurologic examination revealed loss of vibration and decreased bilateral lower extremity strength, and electromyography showed mixed sensory and motor neuropathy. Her refractory anemia, neurologic abnormalities, and multiple malabsorption risks increased suspicion for copper deficiency. Additional testing demonstrated low serum ceruloplasmin (3 mg/dL; normal range, 18-53 mg/dL) and serum copper (7 μ g/dL; normal range, 70-175 μ g/dL). She received intravenous and oral copper supplementation. Her anemia improved, and her neurologic symptoms completely resolved. Her cutaneous lesions were asymptomatic, thus no skin-directed therapy was initiated. Because the patient's cutaneous lesions resolved, she is no longer followed by dermatology but continues to follow up with

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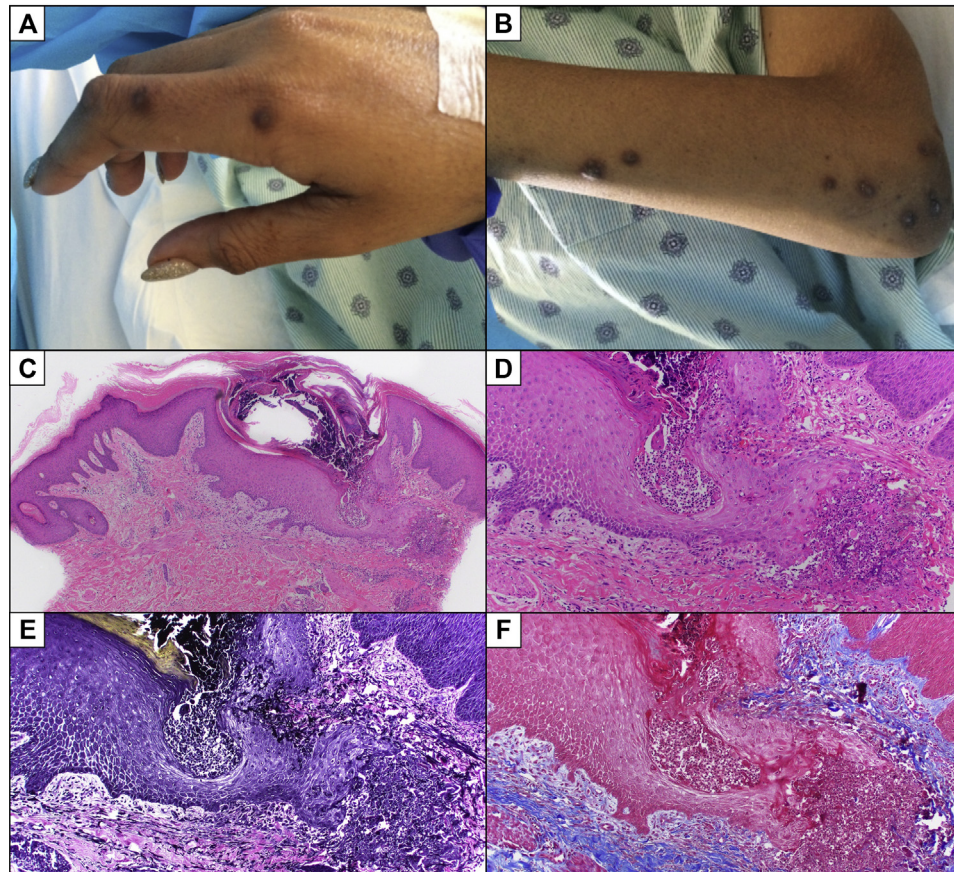


Fig 1. Case 1. **A**, On the dorsal aspect of the second digit on the right hand and **(B)** extensor aspect of the left arm, there were well-defined medium-brown lobulated firm hyperkeratotic papules. **C** and **D**, Hematoxylin-eosin–stained sections of a punch biopsy from the left arm showed necrobiotic collagen, elastic fibers, and a lymphohistiocytic infiltrate demonstrating transepidermal migration through an acanthotic epidermis into a central invagination with overlying keratotic crust. **E**, Verhoeff-Van Gieson and **(F)** Trichrome stains showed extensive transepidermal elimination of elastic fibers and focal collagen trapping. Findings are consistent with reactive perforating dermatosis. (**C** and **D**, Hematoxylin-eosin stain; **E**, Verhoeff-Van Gieson stain; **F**, Trichrome stain; original magnifications: **C**, $\times 4$; **D**, $\times 10$; **E**, $\times 10$; **F**, $\times 10$.)

hematology for her iron deficiency anemia and anemia of CKD.

Case 2

A 44-year-old woman with a history of gastric bypass surgery via duodenal switch, chronic anemia, iron deficiency, and severe hidradenitis suppurativa (HS) was admitted for HS pain and was noted to have an eruption of slightly pruritic papules lasting for 1 month. She had approximately 30 5-mm to 8-mm brown papules with central slightly hyperkeratotic core on her arms and legs (Fig 2). Laboratory testing revealed a white blood cell count of $9.4 \times 10^9/L$, hemoglobin of 7.1 g/dL (mean corpuscular volume, 102 fL), serum iron of 30 $\mu\text{g/dL}$, and otherwise normal basic chemistry. Her medications for HS included clindamycin 1% gel twice daily and

doxycycline 100 mg twice daily, metformin 1500 mg daily, spironolactone 200 mg daily, and zinc gluconate 30 mg 3 times daily. Punch biopsy from an arm lesion was suggestive of reactive perforating dermatosis, with necrobiotic collagen in the superficial dermis transmigrating across the epidermis into a horn-like proliferation of keratotic crust and basophilic debris. Trichrome and Verhoeff-Van Gieson stains showed transepidermal elimination of elastic fibers. Given her anemia, history of malabsorptive bypass surgery, and zinc supplementation, her serum copper level was measured, and it was found to be 28 $\mu\text{g/dL}$ (normal range, 70-175 $\mu\text{g/dL}$). Serum ceruloplasmin was 4 mg/dL (normal range, 18-53 mg/dL). Topical fluocinonide 0.05% ointment twice daily was started for pruritus. Zinc was discontinued, and copper 4 mg daily

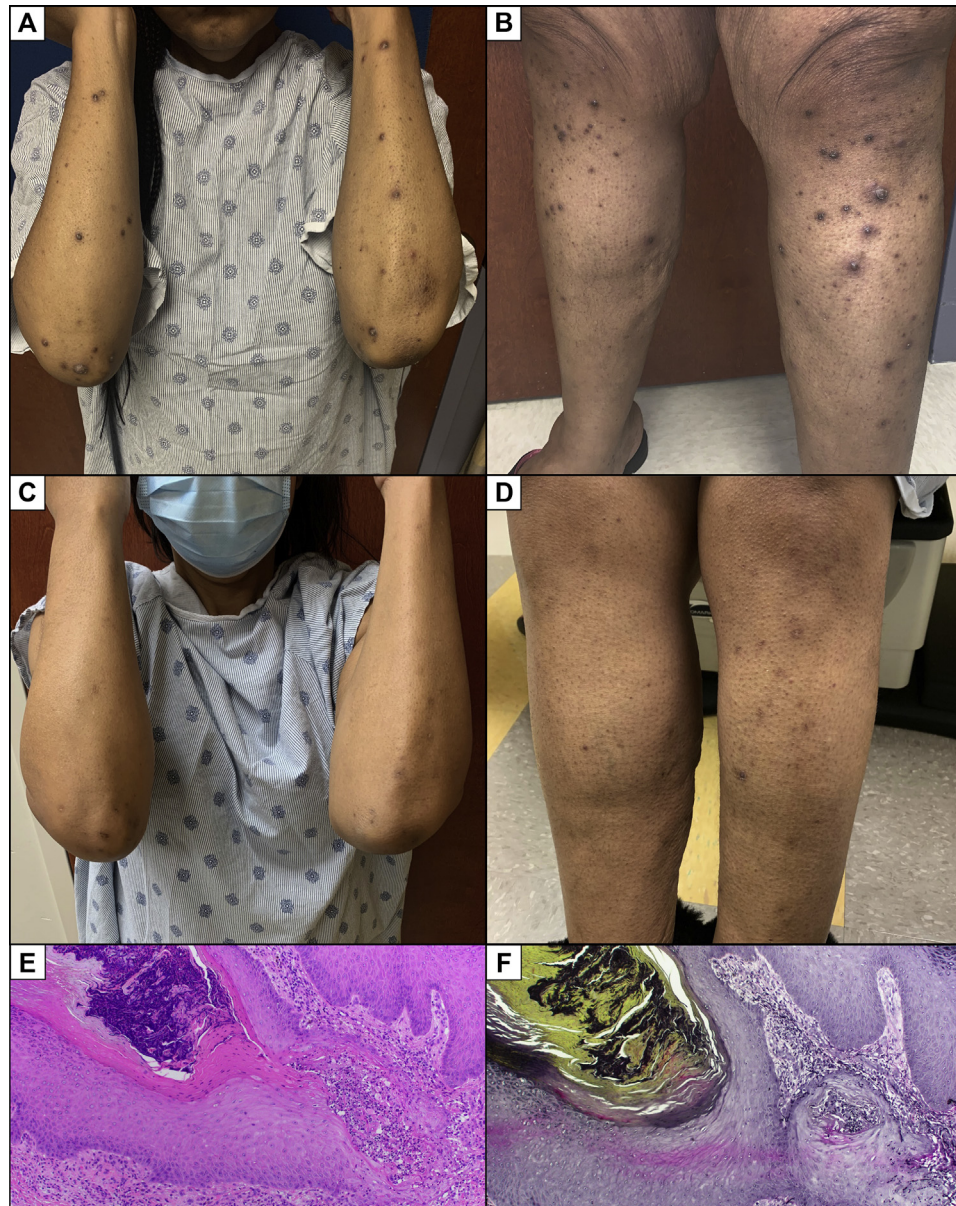


Fig 2. Case 2. **A**, On the extensor aspects of the arms and **(B)** lower portions of legs, there were clusters of 5-mm to 8-mm brown papules with central hyperkeratotic cores. **C** and **D**, Three months after discontinuation of zinc supplementation and resolution of copper deficiency with oral copper supplementation, there was complete resolution, with only residual post-inflammatory hyperpigmentation. **E**, Hematoxylin-eosin–stained sections showed necrobiotic collagen in the superficial dermis transmigrating into an epidermal invagination containing keratotic crust and basophilic debris. **F**, Verhoeff-Van Gieson revealed transmigration of numerous elastic fibers. (**E**, Hematoxylin-eosin stain; **F**, Elastin Von Gieson stain; original magnifications: **E**, $\times 10$; **F**, $\times 10$.)

significantly improved the anemia, and her APD completely resolved 3 months later.

DISCUSSION

Copper deficiency should be considered in select patients with APD, including those who have

received malabsorptive gastric bypass surgery or zinc supplementation.⁴ The majority of copper absorption occurs in the proximal gastrointestinal tract, entering enterocytes via the Ctr1 transporter.⁵ Anatomic modifications in restrictive and malabsorptive weight loss surgery, including gastric sleeve,

Table I. Overview of most common etiologies of copper deficiency, both inherited and acquired

Category	Causes	Mechanism
Hereditary/ inherited	Menkes disease	X-linked recessive disease resulting in impairment of copper transport in the body
Iatrogenic	Penicillamine	Medication that chelates copper, leading to increased excretion in urine
Malabsorption	Gastric bypass surgery	Reduction in surface area or bypass of proximal gastrointestinal tract, the major site of copper absorption in the body
	Zinc supplementation	Excess zinc decreases copper absorption
	Parenteral nutrition, chronic tube feeding, malnutrition	Insufficient dietary intake
	Excessive alcohol consumption	Effect on copper metabolism within the body

Roux-en-Y, and duodenal switch, commonly lead to deficiencies in essential elements, including copper, zinc, iron, selenium, and vitamins A, B, C, D, and K. Zinc supplementation is sometimes used in cases of acne and HS for its wound healing and antiinflammatory properties. Excess zinc upregulates metallothionein production in enterocytes. These enterocytes then slough off into feces, restricting additional zinc absorption. However, because copper has a higher binding affinity than zinc for metallothionein, this also leads to fecal loss of copper.⁴ Other etiologies of copper deficiency have been listed in Table I. Diagnosis of copper deficiency is commonly obtained through measurements of serum copper, ceruloplasmin, and 24-hour urine copper levels.⁵

Copper deficiency can manifest with hematologic and neurologic abnormalities, likely due to the dysfunction of copper-dependent enzymes. Copper deficiency disrupts hematopoiesis, resulting in

microcytic or macrocytic anemia, leukopenia, and can mimic myelodysplastic syndrome. Neuropathy from copper deficiency often mimics vitamin B12 deficiency, and patients present with a spastic gait with loss of vibration and proprioception; however, patients may also present with myeloneuropathy or optic neuropathy. Copper supplementation reverses the hematologic findings, although the degree of improvement of the neurologic deficits may vary.

The association of APD in patients with diabetes mellitus and CKD is well documented in published literature, although the exact pathophysiology of APD is unknown.⁶

Copper has been implicated in the pathogenesis of acquired elastosis perforans serpiginosa due to its association with penicillamine, a copper chelator used in Wilson disease.^{7,8} One proposed mechanism for penicillamine causing elastosis perforans serpiginosa may be indirect inhibition of the copper-dependent enzyme lysyl oxidase that is necessary for cross-linkage of elastic and collagen fibers within the dermis.⁷

Treatment of APD can be difficult. Narrow-band ultraviolet B therapy appears to be most effective in the setting of CKD.⁹ Other reported medical treatments for APD include topical retinoids as well as oral or intralesional corticosteroids. For more severe cases, methotrexate or oral retinoids can be considered.

We described 2 patients presenting with APD who were subsequently diagnosed with acquired copper deficiency. As demonstrated in these cases, copper deficiency may play a crucial role in the pathogenesis of transdermal elimination and should be considered as a reversible etiology of APD in relevant patient populations.

Conflicts of interest

None disclosed.

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