JAMA Dermatology Clinicopathological Challenge

Painful Ulcerative Lesions on Bilateral Lower Extremities

Kevin X. Liu, DPhil; Adam B. Raff, MD, PhD; Margaret S. Lee, MD, PhD

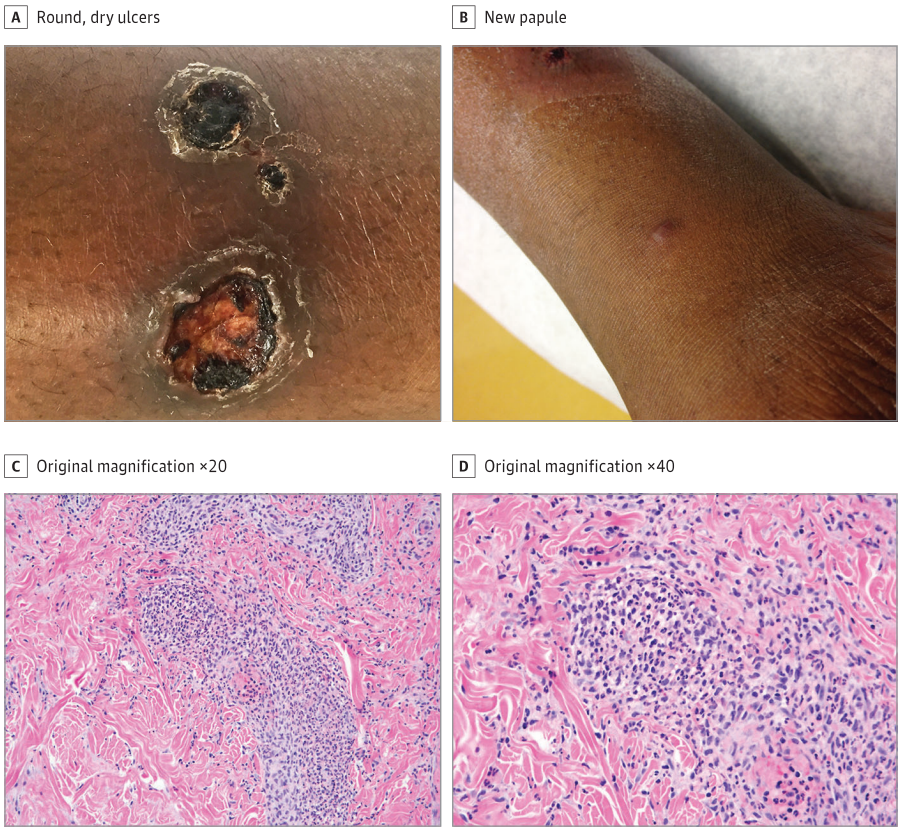

Figure. A, Discrete, round, dry ulcers with central eschar and raised borders on left lateral lower leg. B, A new, 4-mm intact papule on right medial lower leg. C and D, Histopathological images from punch biopsy specimen of the papule, hematoxylin-eosin.

A young black woman with a history of Graves disease presented with painful lesions on both legs. She reported chills, bilateral lower extremity swelling, and several small, painful, "pimple-like bumps" appearing on her bilateral lower legs, which ulcerated several days later. The ulcers progressed despite a recent course of trimethoprim-sulfamethoxazole for cultures growing methicillin-sensitive *Staphylococcus aureus*. The patient's medications included methimazole and atenolol, which she had been taking since her diagnosis of Graves disease 1 year prior. She had not taken other over-the-counter medications or supplements. Physical examination of her bilateral lower extremities revealed pitting edema and multiple discrete, round, dry ulcers, most with central eschars, dusky gray borders, and collarettes of scale (**Figure**, A). Results from the initial laboratory workup revealed elevated levels of C-reactive protein and increased erythrocyte sedimentation rate. A punch biopsy specimen of an ulcer edge demonstrated a mid- and deep dermal marked lymphohistiocytic infiltrate with neutrophils and focal abscess, suggesting a nonspecific infection. The patient was initially treated with cephalexin, mupirocin, and conservative wound care, but the eruption later worsened, with new lesions appearing on her right leg. During follow-up, an intact 4-mm papular lesion was identified on her lower right leg (Figure, B). No pathergy at the previous punch biopsy site was observed. A biopsy of the new intact papule was performed (Figure, C and D).

WHAT IS YOUR DIAGNOSIS?

A. Polyarteritis nodosa

B. Methimazole-induced vasculitis

C. Ecthyma

D. Pyoderma gangrenosum

Diagnosis

B. Methimazole-induced vasculitis

Microscopic Findings and Clinical Course

The biopsy specimen of the closed papule revealed an intraepidermal and dermal perivascular neutrophilic infiltrate with marked papillary dermal edema, necrosis of vessel walls, and focal fibrinoid necrosis (Figure, C and D). Special stains performed with periodic acid–Schiff–diastase, Grocott methenamine silver, Brown-Brenn, and acid-fast Bacillus were all negative for organisms. Additional laboratory tests revealed normal C3 and C4 complement levels, ANA titer 1:80 (reference range, <1:40), perinuclear anti-neutrophil cytoplasmic antibody (P-ANCA) titer of 1:20 (reference range, <1:20), anti-myeloperoxidase (MPO) titer of 141 U (reference range, <2.8 U), and anti-Sjögren-syndrome-related antigen A (anti-SSA/Ro antibodies) level of 120 U (reference range, 0-40 U).

In collaboration with rheumatology and endocrinology colleagues, methimazole was withdrawn, and the patient's ulcers healed rapidly on a prednisone taper and methotrexate. Her thyrotoxicosis remained suppressed under immunotherapy, and she later received radioiodine therapy for her Graves disease.

Discussion

Methimazole and propylthiouracil are thionamide antithyroid medications.[1] Owing to its simpler dosing regimen and more rapid antithyroid effect, methimazole is often the drug of choice for Graves disease.[2] Methimazole prescriptions in the United States have increased from 158 000 in 1991 to 1.36 million in 2008.[2] In parallel, reports of methimazole-associated vasculitis have increased, with clinical manifestations ranging from cutaneous ulcers to pulmonary hemorrhage.[3-9]

The incidence of ANCA-positive propylthiouracil-associated vasculitis is reportedly 39.2 times higher than in patients receiving methimazole.[3] Hydralazine, minocycline, and propylthiouracil are commonly prescribed medications known to cause positive ANA, P-ANCA, and MPO-ANCA test results, and vasculitic skin, kidney, and lung disease.[1,10] Cutaneous lesions include maculopapules, vesicles, purpura, bullae, and ulcers on the lower extremities, with hemorrhage and/or necrosis.[1,4-10] Clinicians should exclude more common causes of these skin lesions, including infections, neoplasms, and primary vasculitides, and must be aware that drug-induced vasculitis can occur after several years on a medication.[1] One should perform an ANCA test and obtain a skin biopsy specimen for histologic evidence of vasculitis.[1] A positive ANCA test result with multi-antigenicity helps differentiate drug-associated vasculitis from primary vasculitides.[1]

Propylthiouracil alters the structure and oxidation activity of MPO and interacts with MPO to produce harmful reactive metabolites that lead to autoinflammatory processes.[1] Methimazole does not inhibit oxidation activity of MPO, and no other cause has been identified, so the pathophysiology of methimazole-associated vasculitis remains unknown.[1]

Treatment recommendations for drug-associated vasculitis include withdrawal of the offending drug and immunosuppressive therapy for severe cases.[1,4-10] The duration of immunosuppression is usually shorter than that needed for primary ANCA-positive vasculitides.[1,10] This case illustrates the importance of close communication between specialists in the prompt diagnosis and management of potentially serious medication reactions. Furthermore, with the growing use of methimazole as a first-line treatment for Graves disease, physicians need to be aware that methimazole can cause vasculitis, even months or years after therapy is begun.[3,10]

ARTICLE INFORMATION

Author Affiliations: Harvard Medical School, Boston, Massachusetts (Liu); Department of Dermatology, Massachusetts General Hospital, Harvard Medical School, Boston (Raff); Department of Dermatology, Boston University School of Medicine, Boston, Massachusetts (Lee).

Corresponding Author: Margaret S. Lee, MD, PhD, Department of Dermatology, Boston University School of Medicine, 609 Albany St, Boston, MA 02118 (margaret.lee@bmc.org).

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