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# An Edematous and Ulcerative Eruption With Nasolabial Sparing in an Older Woman

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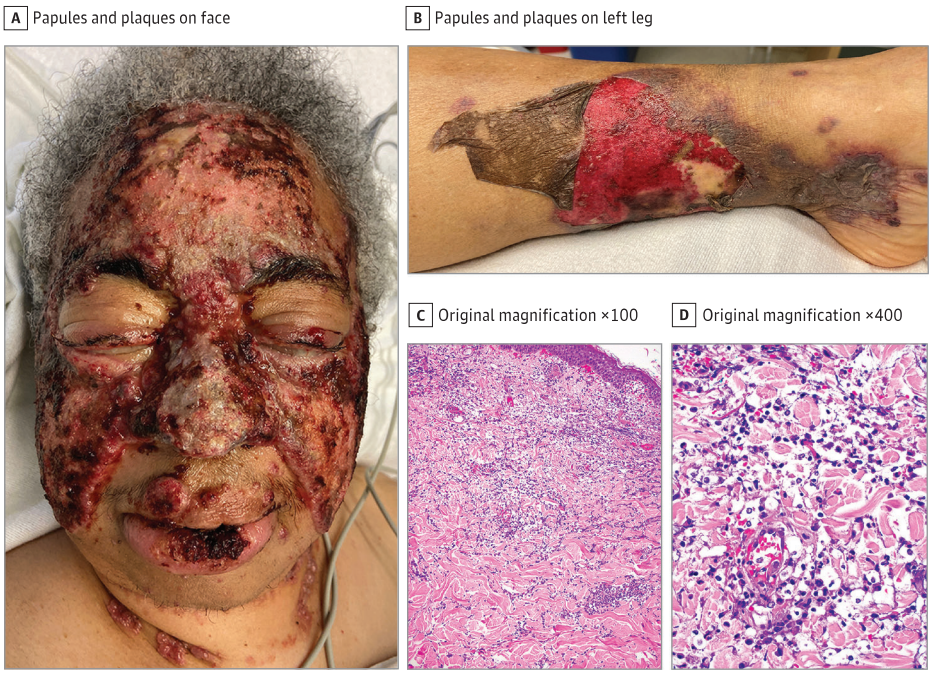


**Figure.** A, Edematous, ulcerated pink plaques confluent on forehead and cheeks with sharp demarcation at nasolabial fold are shown. B, Retiform purpuric plaque is shown on the left leg with overlying desquamation. C and D, Biopsy specimen findings (hematoxylin-eosin).

**A woman in her 70s** presented with a week of painless, rapidly progressive, edematous, necrotic papules and plaques on the extremities, buttocks, and face with sharp demarcation at the nasolabial folds and extension into the oral mucosa (**Figure**, A and B). Notable symptoms included 4 months of extreme fatigue, 20.4 kg weight loss, and a recent episode of hematochezia. Her medical history included diabetes, hyperlipidemia, and hypertension that were well controlled with simvastatin, chlorthalidone, hydralazine hydrochloride, lisinopril, and verapamil hydrochloride. She had been taking these medications for 5 years with no new exposures. Age-appropriate cancer screening was up to date. She was afebrile and hemodynamically stable, but laboratory evaluation revealed that she had leukocytosis, normocytic anemia, elevated erythrocyte sedimentation rate, hematuria, and proteinuria. On hospital day 2, she developed bright red blood per rectum, necessitating transfusion. A computed tomography of the chest, abdomen, and pelvis revealed parenchymal lung nodules. On admission, punch biopsies of the skin were performed for both histological examination and bacterial, fungal, and acid-fast bacterial cultures (Figure, C and D).

**WHAT IS YOUR DIAGNOSIS?**

- **A.** Granulomatosis with polyangiitis
- **B.** Cryptococcal infection
- **C.** Sweet syndrome
- **D.** Drug-induced vasculitis

## Diagnosis

**D.** Drug-induced vasculitis

## Microscopic Findings and Clinical Course

On presentation, the symptoms were suggestive of malignant neoplasm–induced or hydralazine-associated Sweet syndrome. In addition to cessation of hydralazine, high-dose corticosteroids were started, which were ineffective over several days but subsequently held after preliminary pathologic findings demonstrated possible fungal forms. Histological examination revealed a neutrophil-rich infiltrate in a predominately perivascular pattern with extravasated erythrocytes, leukocytoclasis with karyorrhectic debris, fibrinoid degeneration of vessels walls, and cryptococcoid forms. Subsequently, the results of microbial stains, including periodic

acid–Schiff, Grocott methenamine silver, Gram, and acid-fast bacillus, as well as tissue cultures were unremarkable. Rheumatological workup was notable for positive antinuclear antibody titer (1:160), antineutrophil cytoplasmic antibody (ANCA) with perinuclear staining (1:1280), myeloperoxidase (MPO) antibody level of 103 AU/mL (normal range, 0-19 AU/mL), serine proteinase 3 antibody level of 25 AU/mL (normal range, 0-19 AU/mL), and antihistone antibody level of 2.2 U (normal, <1.0 U). Negative levels of double-stranded DNA antibody and an antiphospholipid syndrome antibody panel were found. Results of a lung specimen biopsy showed reactive inflammation and were negative for malignant neoplasm.

## Patient Outcome

The patient did not meet the criteria for Sweet syndrome given the lack of the following: typical painful lesions, characteristic histological features, fever, or rapid response to corticosteroids. The clinical picture was not consistent with granulomatosis with polyangiitis, given the predominate ANCA with perinuclear staining in association with antihistone antibody, lack of granulomatous vasculitis, and improvement of all lesions rapidly over 2 weeks with supportive care and without high-dose immunosuppression. A diagnosis of drug-induced ANCA vasculitis secondary to hydralazine was rendered.

## Discussion

Hydralazine, an antihypertensive medication, has a well-established, dose-dependent association with drug-induced autoimmune disease and occurs on average 4.7 years after initiation. The aberrant immune system function is theorized to be the result of hydralazine accumulation within neutrophils, with subsequent binding to MPO antibody and production of cytotoxic products leading to apoptosis and exposure of self-antigens.[1-3]

The spectrum of autoimmunity varies, including drug-induced lupus erythematosus, drug-induced vasculitis, and antiphospholipid syndrome. Although Sweet syndrome is not an autoimmune disease, it is a condition of reactive immune dysfunction that may occur after hydralazine exposure.[4,5] Of these diseases, drug-induced lupus erythematosus is most common with a reported frequency of 5% to 10% and a clinical course featuring fever, arthralgia, myalgia, and serositis without renal involvement.[1] Cutaneous findings of acute systemic lupus erythematosus such as a malar rash are rarely reported in drug-induced lupus erythematosus. Drug-induced vasculitis is typically associated with ANCA, more severe, and characterized by multiorgan dysfunction, specifically a pauci-immune glomerulonephritis. In the largest review of 68 cases of hydralazine-associated drug-induced vasculitis, the most frequent organs involved were the kidney (81%), skin (25%), joints (24%), and lung (19%).[1] Antibodies present were MPO antibody (100%), antihistone antibody (100%), antinuclear antibody (96%), and double-stranded DNA antibody (26%).[1] Although uncommon, dual positivity of both MPO antibody and serine proteinase 3 antibody, such as that seen in this patient, has been reported previously, as has serine proteinase 3 antibody in isolation.[3,6] Aerodigestive vasculitis and hemorrhage, which the patient experienced, has also been reported.[7]

Hydralazine-induced autoimmunity has been associated with numerous combinations of autoantibodies that lead to 1 predominate syndrome but has overlapping clinical features of multiple autoimmune and autoinflammatory conditions, including drug-induced lupus erythematosus, drug-induced vasculitis, antiphospholipid syndrome, and Sweet syndrome.[1,4,5] The patient had ANCA-associated drug-induced vasculitis, but the malar distribution with sharp nasolabial sparing suggested an overlap with lupus and the edematous plaques suggested an overlap with Sweet syndrome. These overlap syndromes have been reported multiple times in the literature.[2,4-6,8] In addition, when a neutrophilic infiltrate is prominent on histological examination, cryptococcoid forms may be identified, presenting a diagnostic pitfall. Such forms that mimic *Cryptococcus* have been described in association with both Sweet syndrome and leukocytoclastic vasculitis. These cryptococcoid forms are thought to represent degenerating neutrophils because they are consistently negative for fungal stains but positive for MPO antibody stain.[9,10]

Clinicians should be wary of acute skin eruptions in the setting of hydralazine use. Skin eruptions should prompt skin biopsy, antibody profiling, cessation of the offending medication, and treatment with supportive care as well as consideration of immune suppression.


### ARTICLE INFORMATION

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