JAMA Oncology Clinical Challenge

Generalized Purpuric Papules and Nodules in a Man

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A Erythematous papules and purpuric lesions



B Purpura lesions on the feet



Figure. A, Clinical image of generalized erythematous papules and scattered palpable purpuric lesions on the trunk and upper extremities found on physical examination. The inset depicts a close-up view of the papules and purpuric lesions on the trunk. B, Clinical image of prominent palpable purpura lesions observed on the patient's feet.

A 56-year-old man presented with a 1-year history of recurrent, generalized violaceous papules and firm nodules. One year prior, he developed a sudden-onset painful and pruritic rash without obvious triggers, which largely resolved after oral methylprednisolone at 16 mg once daily. Methylprednisolone was gradually tapered after 3 months. Three months before presentation, similar but more extensive lesions recurred with a new-onset low-grade fever and showed little improvement despite ongoing methylprednisolone and intramuscular injection of compound betamethasone. His medical history was significant for angioimmunoblastic T-cell lymphoma (AITL), diagnosed 2 years earlier following a presentation of mediastinal lymphadenopathy. Complete remission had been achieved after 8 cycles of BV-CHP (brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone) chemotherapy. Physical examination revealed generalized erythematous papules on the trunk and extremities, with scattered firm nodules (**Figure**, A). Notably, multiple palpable, nonblanching purpuric lesions were prominent on his face, trunk, and limbs (Figure, B). Laboratory testing demonstrated an elevated erythrocyte sedimentation rate of 26 mm/h (reference range, 0-15 mm/h).

WHAT IS YOUR DIAGNOSIS?

- **A.** Antineutrophil cytoplasm antibody–associated vasculitis
- **B.** Angioimmunoblastic T-cell lymphoma with skin involvement
- **C.** IgA vasculitis
- **D.** Parvovirus B19-associated purpuric eruption

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Diagnosis

B. Angioimmunoblastic T-cell lymphoma with skin involvement

Discussion

Initial laboratory evaluation showed mild anemia (hemoglobin, 11.1 g/dL; to convert to g/L, multiply by 10), borderline thrombocytopenia (platelet count, 120 $\times 10^3$/μL; to convert to $\times 10^9$/L, multiply by 1), lymphopenia (absolute lymphocyte count, 530 /μL; to convert to $\times 10^9$/L, multiply by 0.001), a normal coagulation profile, and normal urinalysis findings without hematuria or proteinuria. Infectious screening was unrevealing, and procalcitonin level was low (0.08 ng/mL), while antineutrophil cytoplasm antibody (ANCA)–associated antibodies were negative and serum IgA was within the reference range (1.22 g/L). Skin biopsy of a purpuric lesion demonstrated leukocytoclastic vasculitis and fibrinoid degeneration of small dermal vessel walls, accompanied by atypical lymphocytic infiltration involving the epidermis and dermis. Immunohistochemically, these lymphocytes were positive for CD3, CD4, CD7, ICOS, programmed cell death 1 protein (PD-1), and CXCL13, with focal CD30 expression (5%), supporting a T-follicular helper (TFH) cell phenotype. Epstein-Barr virus–encoded RNA (EBER) in situ hybridization was negative. The Ki-67 proliferation index was ap-

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proximately 50%, and T-cell receptor (TCR) gene clonality assays demonstrated monoclonal *TCRD* gene rearrangement. Further evaluation disclosed generalized lymphadenopathy, and subsequent lymph node biopsy confirmed relapsed AITL with cutaneous involvement.

Given his prior severe hepatotoxicity during first-line BV-CHP therapy, we initiated chidamide monotherapy, an oral histone deacetylase inhibitor, at 30 mg twice weekly.[1] His skin lesions largely resolved after 1 month of treatment. At 6 months of follow-up, his cutaneous lesions had completely resolved, with complete relief of pain and pruritus, and the systemic lymphoma was assessed as having achieved a partial response.

AITL is an aggressive peripheral T-cell lymphoma derived from CD4+ TFH cells that predominantly affects older adults and usually presents in advanced stages with systemic symptoms and generalized lymphadenopathy. Its prominent immune dysregulation may produce inflammatory or autoimmune-like findings that obscure the diagnosis.[2]

Cutaneous involvement occurs in up to 50% of AITL cases and may precede, accompany, or signal relapse. In this patient, although the initial eruption was not biopsied, its similarity to the later biopsy-proven lesions and temporary improvement during prolonged corticosteroid therapy raise the possibility of an early, partially suppressed relapse. While maculopapules, plaques, and nodules are more common, rare forms like purpura and lichenoid changes pose a diagnostic challenge.[3] Histopathologic vasculitic change may further obscure the diagnosis if atypical lymphoid infiltrate is overlooked. In this setting, recognition of a TFH phenotype, supported by expression of 2 or more markers such as ICOS, PD-1, CD10, CXCL13, and BCL6, together with T-cell clonality analysis, is particularly helpful in distinguishing neoplastic from reactive infiltration.[4] Notably, EBER positivity appears to be less frequent in rare cutaneous variants, so a negative EBER result does not exclude the diagnosis.[5,6]

In this patient, the key diagnostic challenge was recognizing cutaneous relapse of AITL despite vasculitic clinical and histologic features. However, the purpuric morphology and leukocytoclastic vasculitis raised several non-neoplastic mimics. IgA vasculitis was unlikely because the purpura was generalized rather than lower-extremity predominant and was not accompanied by renal, gastrointestinal, or joint involvement.[7] ANCA-associated vasculitis was unsupported by negative ANCA serology and the absence of renal, pulmonary, or upper-airway disease.[8] Infectious purpura, including parvovirus B19-associated eruption, was less likely given the prolonged relapsing course and lack of evidence of active infection.[9] In this patient, the overall clinicopathologic features instead supported purpura secondary to malignant cutaneous infiltration, consistent with recurrent AITL involving the skin.

This case underscores that cutaneous findings may be inconspicuous at disease onset yet become the earliest visible clue to relapse.[10] In patients with a history of AITL, generalized, symptomatic, or steroid-refractory purpura, particularly when accompanied by other primary lesions, fever, or lymphadenopathy, clinicians should look beyond vasculitis alone and pursue early skin biopsy. Recognition of atypical lymphoid infiltration, followed by immunophenotyping and T-cell clonality testing, is critical for distinguishing malignant from non-neoplastic purpura and for identifying occult malignant recurrence.

ARTICLE INFORMATION

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Published Online: July 16, 2026. doi:10.1001/jamaoncol.2026.2379

Author Contributions: Drs Zhu and Sun contributed equally to this manuscript.

Conflict of Interest Disclosures: None reported.

Additional Contributions: We thank the patient for granting permission to publish this information.

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