Development of a reticular rash in a febrile woman: An unusual cutaneous presentation of angioimmunoblastic T-cell lymphoma

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Angioimmunoblastic T-cell lymphoma (AITL) is a peripheral T-cell lymphoma with a poor prognosis in which 50% of patients present with a rash.[1,2] Although AITL's cutaneous presentation is nonspecific, to our knowledge, a reticular rash is not described in published literature.[3] Herein, we report a patient who presented with a generalized, netlike rash, confirmed to be AITL upon histologic analysis of a skin biopsy specimen.

CASE REPORT

A 59-year-old woman presented with a week-long history of progressive, pruritic, pink, and lacy patches on her trunk and extremities. Upon closer inspection, physical examination revealed generalized erythematous papules, macules, and patches in a netlike, reticular pattern on her chest, abdomen, back, and bilateral upper and lower extremities (Fig 1). Lesions exhibited blanching with pressure but no scaling. Mucosal surfaces were spared. Other concerns for this patient included fever, abdominal pain, shortness of breath, and hypotension. Laboratory values were notable for elevated lactate dehydrogenase, elevated white blood cell count, anemia, hyperbilirubinemia, and hypofibrinogenemia. In addition, computed tomography imaging demonstrated worsening cervical, axillary, mediastinal, hilar, retroperitoneal, and inguinal lymphadenopathy. The patient had recently been admitted for recurrent pericardial effusions and pneumonia, but no antibiotics had been introduced within 2 weeks.

Biopsy specimen from the center of a lesion revealed dense, angulated, and small to medium lymphocytic infiltrates, showing a pronounced angiocentric pattern and syringocentricity (Fig 2, *A*). Small to medium vascular structures were involved and were effaced by the infiltrate (Fig 2, *B*). Atypical lymphocytes lined the dermoepidermal junction and exhibited epidermotropism in a mycosis fungoides-like pattern. With further immunohistology staining, the infiltrate was found to be overwhelmingly reactive for CD4, CD2, CD3, CD5, and CD7, focally reactive for CD8, and rarely positive for CD20. CD34 revealed effaced vessels within the dense lymphoid infiltrate. Ultimately, a diagnosis of AITL was confirmed on skin and node biopsy specimens.

The patient's course was complicated by recurrent pericardial effusions and multiple admissions for fever, attributed to both disease progress and pneumonia. The patient was treated with chemotherapy, including cyclophosphamide, doxorubicin, etoposide, vincristine, prednisone; ifosfamide, carboplatin, and etoposide; gemcitabine, dexamethasone, and cisplatin; brentuximab; and romidepsin. Weeks later, the patient developed sepsis secondary to *Clostridium difficile* infection. After worsening hypotension and subsequent cardiopulmonary arrest, she died.

DISCUSSION

AITL is an uncommon systemic lymphoproliferative disorder that comprises 18% of all peripheral T-cell lymphomas, with a mean onset age of 65 years.[1] Diagnosis is often preceded by allergic reaction, infection, or drug exposure with antibiotics being the most commonly associated drug. It is proposed that

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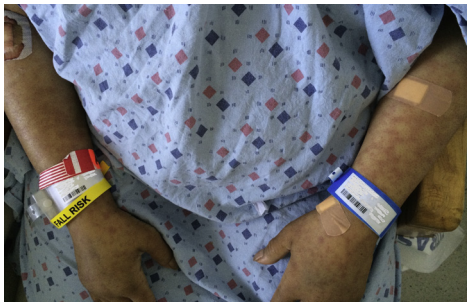

Fig 1. Angioimmunoblastic T-cell lymphoma: clinical image of generalized, pink, and lacy patches on bilateral upper extremities.

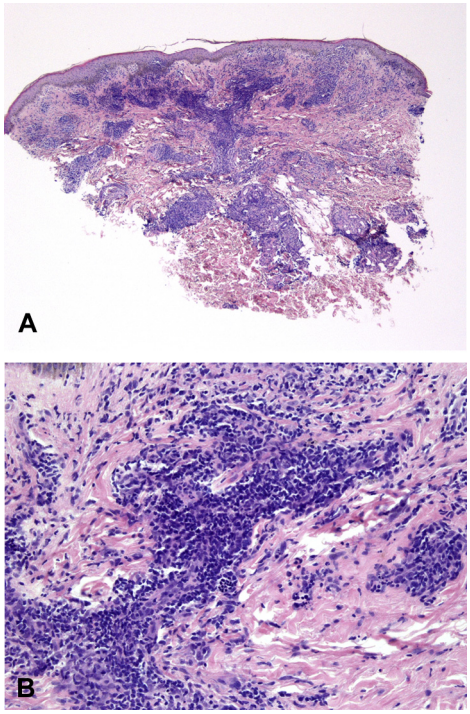

Fig 2. Angioimmunoblastic T-cell lymphoma. **A**, Skin biopsy specimen showed dense lymphoid infiltrates in the papillary and reticular dermis. **B**, Histology revealed dense, small to medium lymphocytes surrounding vessels, effacing vascular structures. (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**, ×40; **B**, ×200.)

immunity toward the offending agent results in immune dysregulation and therefore disease. However, the exact origin is unknown.[2]

In order of decreasing frequency, clinical features consist of generalized lymphadenopathy, constitutional symptoms (fever, weight loss, and night sweats), hepatosplenomegaly, cutaneous involvement, pleural effusion, edema, and ascites.[2] Cutaneous findings of AITL are nonspecific, although usually associated with pruritus, a symptom our patient endorsed. Most commonly, morbilliform eruptions are reported; however, purpura, urticaria, nodules, and petechiae have also been described.[3] Because of these nonspecific findings, AITL poses a diagnostic challenge when presenting as a rash but should be considered when systemic symptoms suggest AITL.[4]

Laboratory abnormalities associated with AITL include anemia, hypergammaglobulinemia, elevated serum lactate dehydrogenase, and elevated erythrocyte sedimentation rate.[3] Although features can be subtle or variable, histopathology is particularly essential for diagnosis. The most common finding is a superficial perivascular infiltrate with or without atypical lymphocytes. Specimens also usually demonstrate increased vascularity. Classically, perivascular infiltrates of neoplastic T cells express CD2, CD3, CD4, CD5, and occasionally CD8, as seen in our patient.[4] Although skin biopsy specimens of cutaneous T-cell lymphomas, such as mycosis fungoides, feature similar lymphoid infiltrates, systemic symptoms in cutaneous T-cell lymphoma typically manifest long after advanced skin involvement; in addition, cutaneous T-cell lymphoma can reliably be diagnosed by TCR gene arrangement studies via polymerase chain reaction.[5] If diagnosis is still unclear, stains for follicular T-helper cell markers (CD10, CXCL13, PD-1, BCL-6, and CD40-L) are more specific to AITL.[4,6] Node biopsy specimen further confirms the diagnosis.

The differential diagnosis for reticular eruptions includes livedo reticularis and drug hypersensitivity. Triggered by decreased vascular flow or vessel-wall pathology, causes of livedo reticularis include connective tissue diseases, hypercoagulable states (eg, antiphospholipid syndrome), and vasculitides (eg, polyarteritis nodosa, cryoglobulinemia). These diagnoses can be differentiated from AITL via clinical symptoms, skin biopsy specimen, and investigative laboratory tests (eg, coagulation studies, lupus anticoagulant, antiphospholipid antibodies, cryoglobulins, antinuclear antibodies).[7] Rarely, drugs can also cause a reticular eruption. Amantadine is a particular drug characterized in this context, but affected patients report recent introduction of amantadine and no other systemic side effects.[8] Our patient did not report a history or symptoms to suggest any of these other diagnoses.

Unfortunately, therapeutic options for AITL have been disappointing without improved survival rates during the last 20 years. In fact, survival probability is still less than 50% at 2 years after diagnosis.[9] Anthracycline-based therapy, including cyclophosphamide, doxorubicin, vincristine, and prednisone, is considered first-line, but early relapse and infectious complications are common.[10] Newer treatments have been implemented but with mixed success. These therapies include (1) rituximab, an

anti-CD20 therapy that targets B cells; (2) antiangiogenic agents, such as cyclosporine, interferon, bevacizumab, and thalidomide; (3) romidepsin, which leads to growth arrest and apoptosis; and (4) alemtuzumab, which targets CD52 on B and T cells.[2,10]

Rapid diagnosis and treatment of AITL is imperative. Because cutaneous presentations of AITL are variable, we suggest that clinicians consider AITL if a patient presents with a generalized, pruritic rash in the context of lymphadenopathy, fever, pleural effusions, and recent infections. Albeit rare, a reticular rash is a plausible cutaneous presentation of AITL. If concerned for AITL, clinicians should obtain a skin biopsy specimen and request immunohistological staining.

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