INTRODUCTION

Angioimmunoblastic T-cell lymphoma (AITL) is a rare but aggressive lymphoma that commonly presents with skin involvement, often morphologically similar to viral or drug-induced morbilliform eruptions. Morbilliform rashes with systemic symptoms of unclear etiology mandate a thorough workup; empiric corticosteroid therapy is best avoided and may delay diagnosis of underlying malignancy such as AITL.

CASE REPORT

A 52-year-old man presented to dermatology clinic with a pruritic rash that he thought was hives. The rash was accompanied by intermittent fevers, chills, and a dry cough. Over the previous 4 months, he had experienced 3-4 similar episodes with symptoms lasting a few weeks each time. With each episode, a prednisone taper provided some relief, though the rash never completely resolved. He reported that his current rash was somewhat different and more extensive than his prior rashes; he wondered whether it was related to a viral illness his family members had recently experienced. The patient reported taking no new or chronic medications and was up to date on immunizations. He denied recent travel, environmental exposures, or personal or family history of autoimmune disorders.

On examination, erythematous coalescing macules and papules covered his upper body, and a palpable anterior cervical lymph node was noted. The morphology of the rash and recent family history suggested a viral exanthem, although the history of previous episodes of rash was confounding. His most recent complete blood count was normal. It was
recommended that he see his primary care provider (PCP) for workup of the lymph node and return to the dermatology clinic if the rash persisted.

One month later, the patient returned with worsening symptoms, including daily fevers to 40°C, rigors, night sweats, myalgias, and arthralgias. The rash was now more confluent and flaring several times per week despite additional prednisone tapers (Figure 1). Workup performed by his PCP, including HIV panel, rapid plasma reagin, hepatitis panel, and QuantiFERON-TB Gold, was negative. Other significant laboratory results included normocytic anemia with a hemoglobin level of 11.8 g/dL, elevated eosinophil count of 1100/μL, elevated ferritin of 577 ng/mL, elevated C-reactive protein of 4.8 mg/L, positive antinuclear antibody (ANA) at 1:640 titer, and positive anti-double-stranded-DNA antibody. A skin punch biopsy was performed at this time due to concern for an ongoing systemic process. He was admitted to the hospital for systemic inflammatory response syndrome and started on empiric antibiotic therapy.

On admission, white blood cell count was elevated at 19,100/μL with 20% bands and 10% eosinophils. Lactic acid was elevated at 5.2 mmol/L. Blood and urine cultures were negative. Epstein-Barr virus (EBV), cytomegalovirus (CMV), and Lyme serologies were negative for active infection. CT of the chest and abdomen showed bilateral axillary lymphadenopathy and hepatosplenomegaly with enlarged inguinal and iliac nodes (Figure 2A,B). Subsequent PET scan showed metabolically active areas in bilateral cervical, axillary, mediastinal, inguinal, internal, and external iliac nodes (Figure 2C). The patient’s clinical deterioration in the context of diffuse lymphadenopathy prompted a cervical lymph node biopsy.

Histopathology of the cervical lymph node showed diffuse effacement of normal nodal architecture with extension of lymphoid tissue into adjacent fat (Figure 3A). A heterogeneous infiltrate of histiocytes, eosinophils, plasma cells, small lymphoid cells, and large pleomorphic lymphoid cells surrounded prominent hyalinized blood vessels (Figure 3B).

Immunohistochemical staining of the lymph node revealed infiltrative CD3+ T cells with cuffing and concentration around vessels (Figure 3C). Immunohistochemistry also showed that the malignant T cells had aberrantly gained BCL6 (a germinal center marker; Figure 3D) and CD10. Subsets of lymphoid cells stained positive for CD4, CD5, and CD7. EBV was also detected.

Bone marrow biopsy showed prominent vessels, eosinophils, and atypical lymphocytes (Figure 3E). T-cell gene rearrangement studies were negative.

Skin biopsy of the abdomen (Figure 4) showed nonspecific superficial and deep perivascular infiltrate consisting of many histiocytes, plasma cells, eosinophils, and pleomorphic lymphoid cells. The pleomorphic lymphoid cells were CD3+, and a subset also expressed CD10 and BCL6. CMV and EBV were not detected.

Given these pathology results in a patient with a 4-month history of morbilliform rash, worsening B symptoms, diffuse lymphadenopathy, and hepatosplenomegaly, a diagnosis of angioimmunoblastic T-cell lymphoma (AITL) was made.

3 | DISCUSSION

Angioimmunoblastic T-cell lymphoma, a subset of T-cell lymphoma, is thought to be derived from mature centrofollicular T helper cells. The pathogenesis of AITL is unclear, but drugs (eg, penicillin and other antibiotics, allopurinol, NSAIDs) or latent viral infections (eg, EBV and CMV) are thought to cause immune cell dysregulation, resulting in cytokine cascade and aberrant gene expression. These abnormalities of immune and inflammatory regulation may explain the elevations in acute phase reactants and production of autoantibodies seen in AITL. AITL is characterized by high fever, B symptoms, generalized lymphadenopathy, cutaneous involvement, and autoimmune features such as production of autoantibodies. At presentation, 60%-70% of patients have bone marrow involvement. Cutaneous features are found in up to 50% of patients, and a morbilliform rash involving the trunk is the most common skin manifestation; others include prurigo-like lesions, purpura, urticarial eruptions, erythroderma, and necrotizing granulomas.
Histopathology typically shows effacement of lymph node architecture (often with extranodal extension), prominent hyalinized arborizing high endothelial venules (HEVs), and clusters of neoplastic cells around follicles and HEVs with a background of small reactive lymphocytes, eosinophils, plasma cells, and histiocytes. As in
our patient, neoplastic cells are positive for CD3 and CD4 and are often also positive for CD10, BCL6, CXCL13, and/or PD-1. Clonal rearrangement of T-cell receptor genes is common, as are EBV + B cells. Skin biopsy is often nonspecific but may show angiocentric atypical lymphoid infiltrates; EBV is infrequently detected. Our patient was diagnosed with stage IVb AITL with bone marrow involvement. Management of AITL consists of chemotherapy with CHOP-based regimens (cyclophosphamide, doxorubicin, vincristine, and prednisone) and stem cell transplant. Skin involvement is associated with worse prognosis, as are thrombocytopenia, anemia, leukocytosis, hypoalbuminemia, renal failure, and circulating atypical cells. The leading cause of death is infection. Younger patients typically have better survival, but prognosis is poor with a 5-year overall survival rate of 26%-36% and a median survival of less than 3 years.

In the case of AITL presenting with cutaneous manifestations, empiric treatment with systemic corticosteroids or other immunosuppressive agents in order to reduce symptoms can lead to a delay in workup and diagnosis, which likely occurred in this case. Of note, uncomplicated morbilliform rashes due to medications and viral triggers do not typically warrant treatment with systemic corticosteroids. Importantly, morbilliform rashes with systemic symptoms of unclear etiology mandate a thorough work-up during which time empiric corticosteroid therapy might be best avoided.

In summary, morbilliform rash is an uncommon presentation of underlying malignancy, but the most common cutaneous manifestation of AITL. Nondrug-triggered morbilliform rash in an adult presents a diagnostic challenge. This case underscores the importance of a thorough history with review of systems, physical examination with palpation of lymph node basins, liver, and spleen, and subsequent low threshold for tissue biopsy and appropriate imaging studies.

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CONFLICT OF INTEREST
None declared.
AUTHOR CONTRIBUTIONS
All authors had access to the data and a role in writing the manuscript. WB: wrote the first draft of the article. KLB and LSD: critically reviewed and edited drafts and approved the final version for submission.

ETHICAL APPROVAL
Patient consent was unable to be obtained due to the patient’s death prior to the time of publication; however, this case report has been anonymized to preserve patient privacy.

DATA AVAILABILITY STATEMENT
Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID
Wendi Bao https://orcid.org/0000-0001-7557-9887

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