

Multiple Erythematous Plaques with Palpable Purpura in a Febrile Patient

A 71-year-old Malay man was admitted to the Medicine department with complaints of swelling of the left submandibular area with sore throat and rashes for 1 month. His past medical history included hypertension, hyperlipidaemia, bilateral cataracts and haemorrhoids. The rash started on his arms and rapidly progressed to involve the trunk and lower limbs. He denied taking any new medications and was well prior to these symptoms. On examination, he was persistently febrile and had an enlarged 6 cm x 6 cm left submandibular lymph node. He also had multiple erythematous and dusky plaques over his trunk and limbs (Fig. 1). Computed tomography (CT) scan of the neck, thorax, abdomen and pelvis revealed enlarged bilateral cervical, right intraparotid, axillary, obturator, iliac, aortocaval and para-aortic lymph



Fig. 1. Erythematous plaques over the patient's upper limbs.

nodes. Further investigations revealed a normocytic and normochromic anaemia, an elevated leukocyte count of $13.9 \times 10^9/L$ with lymphocytosis and raised serum levels of immunoglobulin (Ig)A, IgG and IgM. A detailed infection screen including multiple blood cultures was negative. Skin biopsy demonstrated superficial and deep, perivascular and periadnexal infiltration by atypical, medium-sized lymphoid cells which stained positive for CD3, CD4 and CD10 (Fig. 2). Cervical lymph node core biopsy showed diffuse effacement of nodal architecture with atypical lymphocytes showing CD2, CD3 and CD4 positive cells with scattered CD10 positivity (Fig. 3). There was also reduced CD7 and CD5 staining which is consistent with neoplastic aberrancy, and the proliferation index was raised. CD23 staining showed some follicular dendritic cells juxtaposed against high endothelial venules. Epstein-Barr virus-encoded small ribonucleic acid (EBER) was not detected in both biopsies. Bone marrow trephine biopsy showed hypercellular trilineage haematopoiesis without any immunohistochemical evidence of lymphomatous involvement. During his hospitalisation,

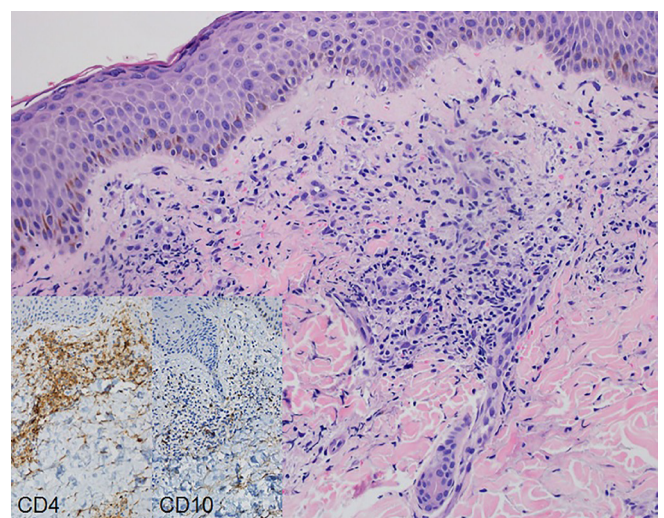


Fig. 2. Superficial dermal perivascular polymorphous lymphoid infiltrate with atypical lymphoid cells (haematoxylin and eosin, 40x) which are immunoreactive to CD4 and CD10.

the patient developed new onset rapidly progressive palpable purpura over his lower legs (Fig. 4). Biopsy of these lesions for histology and direct immunofluorescence revealed leukocytoclastic vasculitis with IgA and C3 deposits within the blood vessels, without any atypical lymphocytes. The patient was started on chemotherapy with the cyclophosphamide, doxorubicin, etoposide, vincristine

and prednisolone (CHEOP) regime, which led to complete and rapid resolution of his skin lesions.

What is your diagnosis?

- A. Lupus erythematosus
- B. Sarcoidosis
- C. Angioimmunoblastic T-cell lymphoma (AITL) with vasculitis
- D. Adverse drug reaction
- E. Septic vasculitis

Discussion

AITL is a distinct subtype of peripheral T-cell lymphoma affecting older patients and has an aggressive clinical course.¹ It arises from the malignant transformation of follicular T helper cells. Epstein-Barr virus (EBV) has been implicated in the pathogenesis, although this was not found in our patient. Other factors recently described to be important in the pathogenesis include vascular endothelial growth factor (VEGF) and over production of the CXCL13 cytokine.² The latter is responsible for B-cell activation and causes the polyclonal hypergammaglobulinaemia (as seen in our patient) frequently found in AITL. This also causes other manifestations of immune dysregulation including haemolytic anaemia, cold agglutins and autoantibodies.¹ Recently, novel mutations in *RHOA* genes as well as in epigenetic factors like *TET2*, *IDH2* and *DNMT3A* have been identified in AITL subsets.³ On histology, it is noted to cause effacement of lymph node architecture and formation of high endothelial venules. Immunohistochemistry reveals the expression of CD4 and CD10 on the neoplastic T-cells.² The absence of granulomas, interface changes and any bacteria rule out the other diagnoses.

AITL frequently presents with fever, weight loss, generalised lymphadenopathy and hepatosplenomegaly. Skin manifestations have been reported in 21% to 49% cases of AITL and include maculopapular eruptions, erythroderma and nodules, as well as urticarial and vasculitic lesions. IgA-related paraneoplastic manifestations including vasculitis have been described in relation to haematologic and solid tumour malignancies.⁴ However, IgA vasculitis in association with AITL is very rare with only 1 published case report so far.⁵ It is not clear why this association exists, but immunological defects have been postulated, especially since immunoregulatory dysfunction is commonly found in AITL. The fact that our patient's purpuric lesions developed shortly after his initial presentation and resolved promptly with chemotherapy suggests that the vasculitis may have been causally linked to his AITL.

The presence of IgA-related autoimmune manifestations in adulthood warrants a workup for underlying malignancy. In our patient, the vasculitis developed after the onset of his

Answer: C

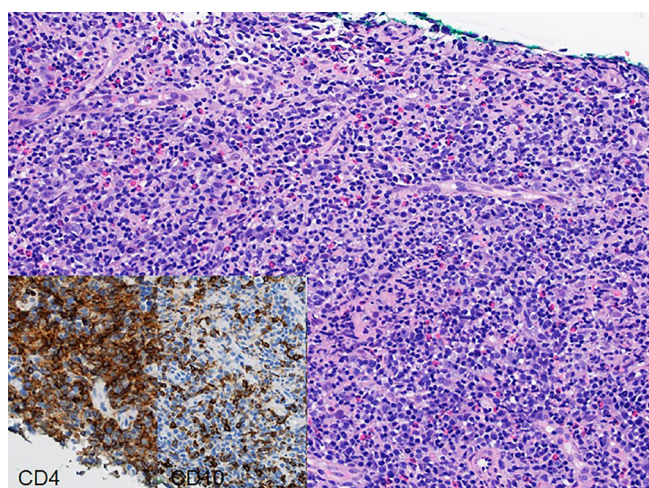


Fig. 3. Polymorphous lymphoid infiltrate with some eosinophils and larger lymphoid cells (haematoxylin and eosin, 40x) which are immunoreactive to CD4 and CD10 (400x).



Fig. 4. Purpuric lesions over the patient's legs.

skin and systemic manifestations. However, it is possible for vasculitis to occur before or even concomitantly with the primary malignancy.

To our knowledge, this is the second case report of AITL with associated IgA vasculitis. We would also like to highlight the significance of IgA vasculitis in an adult when it can be a harbinger of an underlying malignancy.

REFERENCES

1. Federico M, Rudiger T, Bellei M, Nathwani BN, Luminari S, Coiffier B, et al. Clinicopathologic characteristics of angioimmunoblastic T-cell lymphoma: analysis of the International Peripheral T-Cell Lymphoma Project. *J Clin Oncol* 2013;31:240-6.
2. Dunleavy K, Wilson WH, Jaffe ES. Angioimmunoblastic T cell lymphoma: pathobiological insights and clinical implications. *Curr Opin Hematol* 2007;14:348-53.
3. Rodríguez-Cortés J, Palomero T. The curious origins of angioimmunoblastic T-cell lymphoma. *Curr Opin Hematol* 2016;23:434-43.
4. Taintor AR, Leiferman KM, Hashimoto T, Ishii N, Zone JJ, Hull CM. A novel case of IgA paraneoplastic pemphigus associated with chronic lymphocytic leukemia. *J Am Acad Dermatol* 2007;56:S73-6.
5. Sugaya M, Nakamura K, Asahina A, Tamaki K. Leukocytoclastic vasculitis with IgA deposits in angioimmunoblastic T cell lymphoma. *J Dermatol* 2001;28:32-7.

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