Angioimmunoblastic T-Cell Lymphoma With Cutaneous Involvement

A Case Report With Subtle Histologic Changes and Clonal T-Cell Proliferation

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• Angioimmunoblastic T-cell lymphoma is a nodal peripheral T-cell lymphoma that rarely involves the skin. We describe a 62-year-old Taiwanese man who developed a second relapse of angioimmunoblastic T-cell lymphoma with generalized erythroderma and numerous plaquelike and nodular lesions. Biopsy of the erythematous skin lesion demonstrated mild infiltrate of atypical small lymphocytes, some with clear cytoplasm. The lymphoid infiltrate was located mainly around skin appendages and in the upper dermis without epidermotropism. Immunohistochemically, these atypical lymphocytes expressed CD3. Polymerase chain reaction analysis for T-cell receptor γ-chain gene rearrangement using paraffin section showed the same-sized monoclonal bands in the skin and 2 previous nodal biopsies. We conclude that the histologic features of angioimmunoblastic T-cell lymphoma involving skin may be very subtle, showing only mild lymphoid infiltrate. Awareness of the history of angioimmunoblastic T-cell lymphoma with ancillary studies, including clonality testing for T-cell receptor gene rearrangement, is crucial for reaching an accurate diagnosis.

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Angioimmunoblastic T-cell lymphoma (AITL) is a peripheral T-cell lymphoma manifested by lymphadenopathy, hepatosplenomegaly, systemic symptoms, and laboratory abnormalities.[1] The involved lymph node is characterized by partial or complete effacement of nodal architecture due to proliferation of arborizing vessels and follicular dendritic cells, as well as polymorphous infiltration of lymphocytes, plasma cells, eosinophils, and occasional immunoblasts. The number of neoplastic T cells can be few, and they can be difficult to recognize; therefore, in the 1970s it was first regarded as an atypical reactive process, that is, angioimmunoblastic lymphadenopathy with dysproteinemia. Its neoplastic nature was not elucidated until cytogenetic and molecular studies consistently demonstrated clonal chromosomal abnormalities and monoclonal or oligoclonal T-cell populations.[2–4]

Angioimmunoblastic T-cell lymphoma is a primary nodal lymphoma with occasional cutaneous involvement. Patients with cutaneous involvement may present with transient morbilliform eruption of the trunk, generalized maculopapular eruptions, erythroderma, or petechiae, occurring prior to, concurrent with, or during disease progression.[5–7] The histologic changes of the cutaneous lesions may be subtle and nondiagnostic.[5,8] Definitive diagnosis may have to be based on finding the same clonal T-cell proliferation in both the nodal and cutaneous biopsies.[8,9] We report our experience with a case of AITL demonstrating histologically subtle lymphoid infiltrate, in which T-cell clonality was demonstrated by polymerase chain reaction (PCR) analysis for T-cell receptor γ (TCRγ)-chain gene rearrangement.

REPORT OF A CASE

A 62-year-old Taiwanese man presented with prolonged fever and inguinal lymphadenopathy in January 2000. His nodal biopsy was diagnosed as AITL. The staging result was IIIB. He achieved complete remission with 8 courses of cyclophosphamide, epirubicin, vincristine sulfate, and prednisolone (CEOP) chemotherapy. Two years later, he experienced a relapse in the same inguinal nodal region, and the second nodal biopsy was also diagnosed as AITL. He went into remission again after 4 courses of etoposide and mitoxantrone. Five months after his second remission, he developed a second relapse, with generalized erythroderma, numerous plaquelike and nodular lesions (Figure 1), and re-enlarged inguinal node. A skin biopsy was taken of the erythematous area instead of the nodular lesions. The patient died of leukopenia and septic shock 3 days after the first course of chemotherapy with methotrexate, ifosfamide, and etoposide, 3 years after initial presentation. No autopsy was performed.

PATHOLOGIC FINDINGS

Microscopic examination of the node at presentation and at first relapse revealed a similar picture of AITL with an anastomosing capillary network lined by high endothelial cells and polymorphous infiltrate, including small to medium-sized atypical lymphocytes with clear cytoplasm and occasional aggregates of large cells. Immunohistochemical study was performed using the labeled streptavidin-biotin peroxidase method (LSAB kit, Dako Corporation, Carpinteria, Calif), and an antigen-retrieval technique was applied as needed for each antibody. Florid

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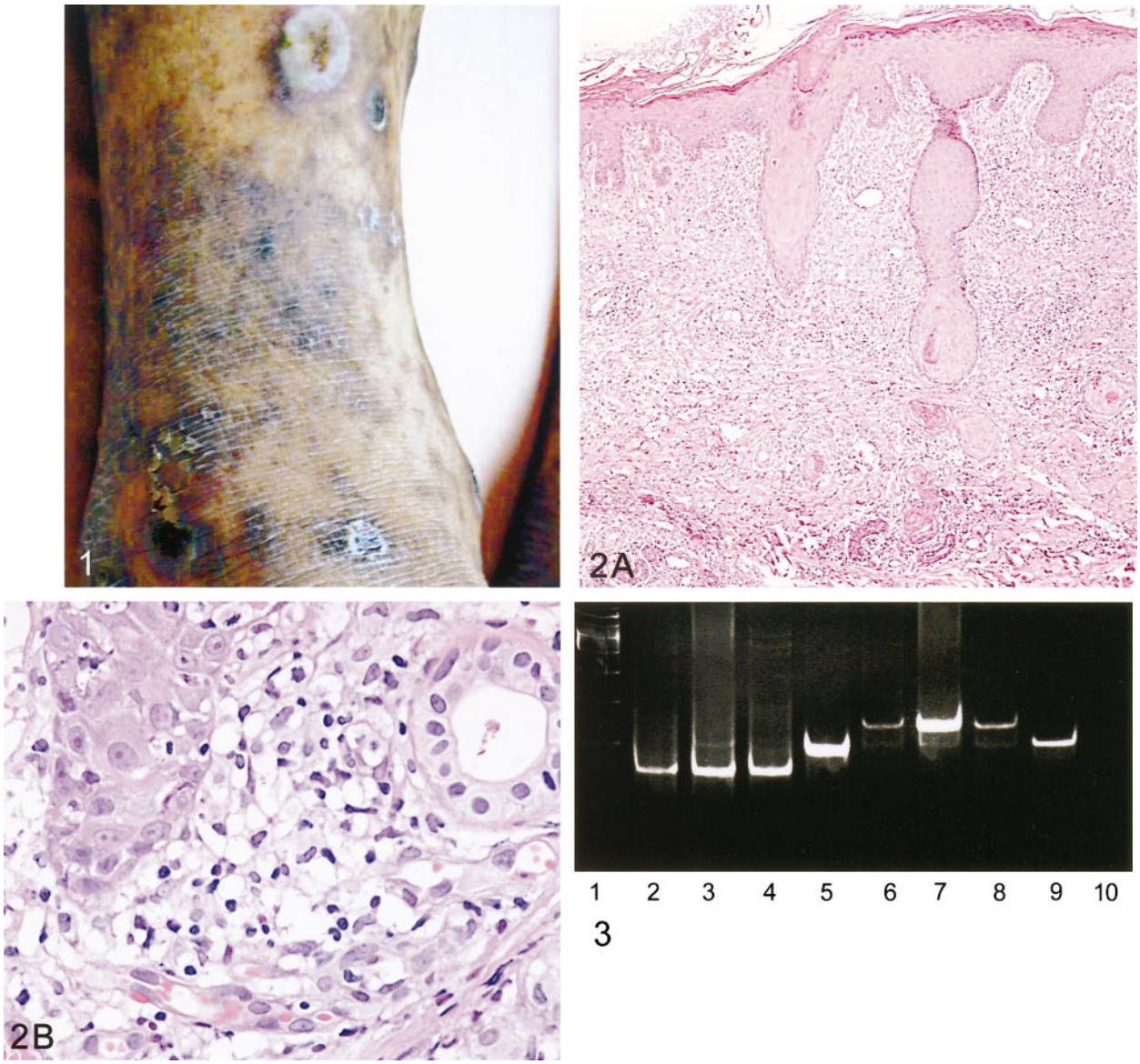

Figure 1. *Right lower leg with erythematous and scaling lesions and umbilicated nodules.*

Figure 2. *Skin biopsy. A, Parakeratotic epidermis and mild lymphoid infiltrate in the perivascular and periadnexal space and in the upper dermis (hematoxylin-eosin, original magnification ×40). B, Small atypical lymphocytes infiltrating around a sweat gland and hair follicle (hematoxylin-eosin, original magnification ×400).*

Figure 3. *Gel electrophoresis showing a single-sized monoclonal band in the 2 consecutive nodal biopsies and in the cutaneous biopsy using 2 primer sets for T-cell receptor γ-chain gene rearrangement. Lane 1, molecular size marker; lanes 2 through 5 (J-γ primers): lane 2, first lymph node; lane 3, second lymph node; lane 4, skin; lane 5, positive control; lanes 6–9 (JP-γ primers): lane 6, first lymph node; lane 7, second lymph node; lane 8, skin; lane 9, positive control; and lane 10, negative control.*

follicular dendritic cell proliferation wrapping around the arborizing vessels was highlighted by immunostains with anti-CD21 and anti-CD35. These atypical lymphocytes expressed T-cell markers (CD2, CD3, CD5, and CD7), with expression of CD10 in a small population of neoplastic T cells. Staining for CD4 was equivocal. Staining was negative for CD8 and CD20.

The skin biopsy at second relapse showed hyperkeratosis and parakeratosis with mild lymphoid infiltrate, mainly around skin appendages and in the upper dermis, accompanied by mild capillary hyperplasia (Figure 2, A). Under high-power examination, the infiltrate was composed of small lymphocytes with slightly irregular nuclear contours, some with clear cytoplasm (Figure 2, B). There was no epidermotropism or admixed eosinophils. Immunohistochemically, these atypical lymphocytes expressed CD3, but not CD4, CD8, or CD20. CD10 immunostaining was difficult to interpret because of high background staining caused by the stromal cells in the dermis. Polymerase chain reaction analysis for TCRγ-chain gene rearrangement using paraffin section, as described previously,[10] showed the same-sized monoclonal bands in the previous 2 nodal specimens and in this cutaneous specimen (Figure 3).

COMMENT

The cutaneous manifestations of AITL are variable and include maculopapular and papulonodular eruptions, generalized petechiae, erythroderma, and plaques.[5,6,8] The histologic features range from mild to dense infiltrate, with an occasional report of granulomatous inflammation mimicking sarcoidosis.[11] Martel et al[8] classified a series of 14 cutaneous biopsies from 10 AITL patients into 4 histologic groups as follows: (1) nonspecific pattern of mild perivascular infiltrates of eosinophils and lymphocytes with no atypia in the superficial dermis associated with capillary hyperplasia; (2) sparse superficial perivascular infiltrates by atypical lymphocytes with pleomorphic and kidney-shaped nuclei associated with vascular hyperplasia; (3) dense pleomorphic infiltrate composed of atypical lymphocytes in the superficial and deep dermis, suggestive of cutaneous lymphoma; and (4) vasculitis without cellular atypia. The biopsy of our case showed mild periadnexal and perivascular infiltrates by atypical small lymphocytes associated with capillary hyperplasia, similar to group 1 as described by Martel et al, except for the absence of eosinophils. These morphologic features are not diagnostic of lymphoma. The clonal nature of the infiltrate was confirmed by TCRγ-chain gene rearrangement analysis in our case and in 7 of 10 cases in the series reported by Martel et al.[8]

CD10 is a neural endopeptidase expressed on the surface of a wide variety of nonneoplastic human cells, including hematopoietic, epithelial, and stromal cells. In lymphoid neoplasms, CD10 expression is characteristic of follicular lymphomas, Burkitt lymphomas, and precursor B-cell acute lymphoblastic leukemia.[12] Recently, expression of CD10 was shown to be a good objective criterion for the diagnosis of AITL, especially for early lesions.[13] In our experience, CD10 expression is specific for AITL among various subtypes of peripheral T-cell lymphoma.[14] In the current case, CD10 expression was demonstrated by immunohistochemistry in the 2 nodal biopsies. However, application of this antibody in the skin biopsy is hampered by the fact that the abundant normal dermal stromal cells also express CD10. It is impossible to identify the CD10-expressing lymphoid cells in the dermal biopsy unless the lymphomatous infiltrate is so heavy that it has already replaced the normal stromal tissue.

In conclusion, the histologic changes of cutaneous involvement by AITL vary from subtle nonspecific changes to overt lymphomatous lesions. Immunohistochemistry and clonality studies might help in arriving at a correct diagnosis in those cases with minimal lymphoid infiltrate.

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