Angioimmunoblastic T-cell lymphoma with elevated serum IgA and infiltration of IgA-positive plasma cells into a skin lesion

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Abstract

Angioimmunoblastic T-cell lymphoma (AITL) is one of the most common types of peripheral T-cell lymphoma. Laboratory examination exhibits immunological abnormalities, such as polyclonal hypergammaglobulinemia and hemolytic anemia. Skin lesions are also observed in approximately half of AITL cases. However, the relationship of skin involvement with the clinical course and prognosis is unknown. Herein, we report the case of a patient with AITL with elevated serum immunoglobulin A (IgA) level, which was a predictive element of poor prognosis, and infiltration of IgA-positive plasma cells into the skin lesions. Based on this case, we believe that skin manifestations could be used to identify the characteristics of immune disorders and prognosis of AITL.

Keywords: angioimmunoblastic, IgA, plasma cell, T-cell lymphoma

Introduction

Angioimmunoblastic T-cell lymphoma (AITL) is classified as a subtype of mature T-cell lymphomas. Angioimmunoblastic T-cell lymphoma, follicular T-cell lymphoma, and nodal peripheral T-cell lymphoma not otherwise specified are grouped into nodal T-cell lymphoma with T follicular helper (TFH) cell phenotype based on TFH-related antigens [1]. Angioimmunoblastic T-cell lymphoma is clinically characterized by lymphadenopathy, hepatosplenomegaly, and immunological and/or hematological abnormalities, such as polyclonal hypergammaglobulinemia, hypereosinophilia, hemolytic anemia, lymphopenia, and thrombocytopenia [2]. Recent studies have found that elevated serum immunoglobulin A (IgA) in patients with AITL is a predictor of poor prognosis [3]. Herein, we report a patient with AITL with elevated serum IgA and extensive purpura. Although many cutaneous manifestations of AITL have been reported thus far, the clinical and histological patterns have not been established.

Case Synopsis

A 78-year-old man visited our hospital with a 3-month history of skin lesions. Two months before his visit, the patient had undergone a skin biopsy at another hospital for a purpuric lesion on his leg (**Figure 1A**). The results showed infiltration of various mononuclear lymphoid and polymorhonuclear cells, nuclear dust, and extravasation of blood cells (**Figure 1B**). During his visit to our hospital, the patient presented with numerous violaceous erythematous lesions on the trunk, irregular purpura on the lower and upper extremities, erosions on the labia and oral cavity, and lymph node swelling on the bilateral neck. Laboratory studies revealed thrombocytopenia and elevation of serum IgA and soluble IL2 receptor (sIL2R) levels. The serum levels of IgG and IgM were

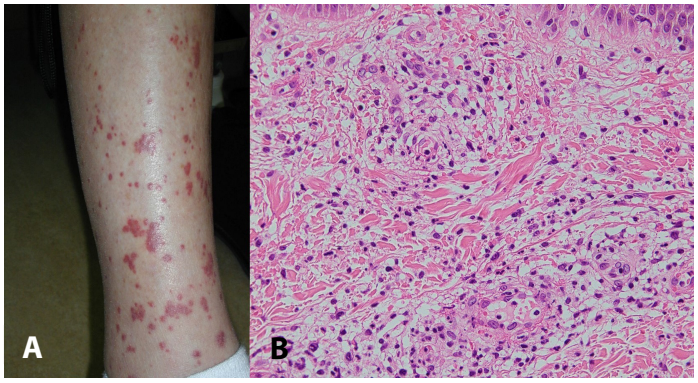

Figure 1. ***A)*** *The first biopsy was taken from a purpuric lesion on the left leg two months before the patient's first visit to this institution.* ***B)*** *Infiltration of mononuclear lymphoid and polymorphonuclear cells and nuclear dust, along with destruction*

within normal limits. Serum electrophoresis revealed no abnormalities. The abnormal results were as follows: white blood cell count, 8.87×10^3/μL (normal range, $3.3–8.6\times10^3$/μL); platelet count, 9.4×10^4/μL (normal range, $15.8–34.8\times10^4$/μL); lactate dehydrogenase, 265IU/L (normal range, 124–222 IU/L); C-reactive protein, 0.851 mg/μL (normal range, 0–0.14 mg/μL); IgA, 677mg/dL (normal range, 93–393mg/dL); and sIL2R, 14200U/mL (normal range, 145–519U/mL). Computed tomography revealed generalized lymphadenopathy (small to medium). A biopsy of a cervical lymph node revealed total effacement of the lymph node architecture

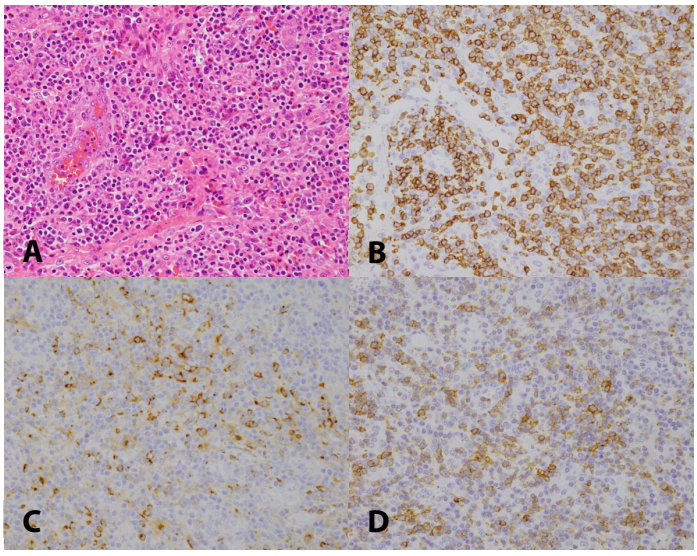

Figure 2. *Cervical lymph node biopsy.* ***A)*** *The aggregation of small-to-medium lymphoid cells with irregular nuclei and clear cytoplasm as well as proliferation of high endothelial venules are visible. H&E, 400×. Immunohistochemical examination showing positivity for* ***B)*** *CD3,* ***C)*** *CXCL 13, and* ***D)*** *PD1. 400×.*

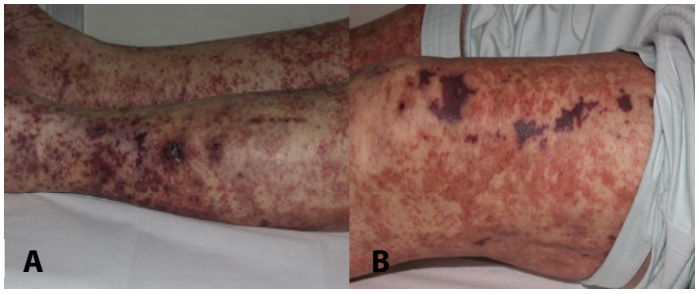

Figure 3. ***A), B)*** *Irregular purpuric lesions, crusts, and pigmentations were present on the lower legs and thighs 2.5 months after the first biopsy. The second skin biopsy was obtained from the left thigh,* ***B)***.

characterized by the infiltration of various inflammatory cells including eosinophils, polymorhonuclear cells, and a few plasma cells, marked vascular proliferation, and invasion of clear cells with mildly irregular nuclei (**Figure 2A**). Immunohistochemically, the neoplastic cells expressed CD3 (**Figure 2B**), CD5, CD7, CXCL13 (**Figure 2C**), and PD1 (**Figure 2D**). In situ hybridization revealed few scattered Epstein–Barr virus-encoded small RNA-positive cells (<1%). Molecular studies showed a monoclonal rearrangement of T-cell receptors and germ line configuration of immunoglobulin heavy chains. Based on these findings, a diagnosis of AITL was established. In two weeks, irregular purpuric lesions and ulcers with crusts had spread over the trunk and lower (**Figure 3A**, **B**) and upper extremities. Skin biopsy obtained from the left thigh (**Figure 3B**) showed the destruction of vessel walls by the infiltration of various cells similar to that on the first biopsy in the upper dermis (**Figure 4A**). In the subcutaneous tissue, dense infiltration into medium-sized vessel walls and obliteration of the vascular lumina were visible (**Figure 4B**). Immunohistochemical staining showed many IgA-positive (**Figure 4C**) and CD138-positive cells (**Figure 4D**) in the vessel walls. A few IgG-positive cells were observed among the perivascular infiltrating cells. Cyclophosphamide, doxorubicin, vincristine, and prednisolone therapy was started. After three cycles, purpura and ulcers had improved and pigmentation appeared. However, swelling in the cervical lymph nodes persisted.

Case Discussion

T follicular helper cells are a distinct subset of CD4+ T cells specialized in regulating of antibody responses. Through the initiation of class switch recombination, TFH cells functionally diversify the expressed B-cell receptor as each immunoglobulin class. They direct antigen-driven B cells to extrafollicular or follicular plasma cells under germinal center cycling [4]. Thus, the aberrations in TFH cell function are likely involved in the development of various pathologies related to the humoral immune response. The clinical effects of AITL were previously shown to be more seriously influenced by the dysregulation of the immune system rather than the direct complications of tumor growth [5]. Recent studies have found that elevated serum IgA in patients with AITL is a predictor of poor prognosis, along with leukocytosis, anemia, thrombocytopenia, extranodal involvement, and mediastinal lymphadenopathy [3]. The excessive production of IgA is considered attributable to excessive differentiation of IgA-plasmablasts, which is induced by TGFβ1 and IL21 released by neoplastic TFH cells [6].

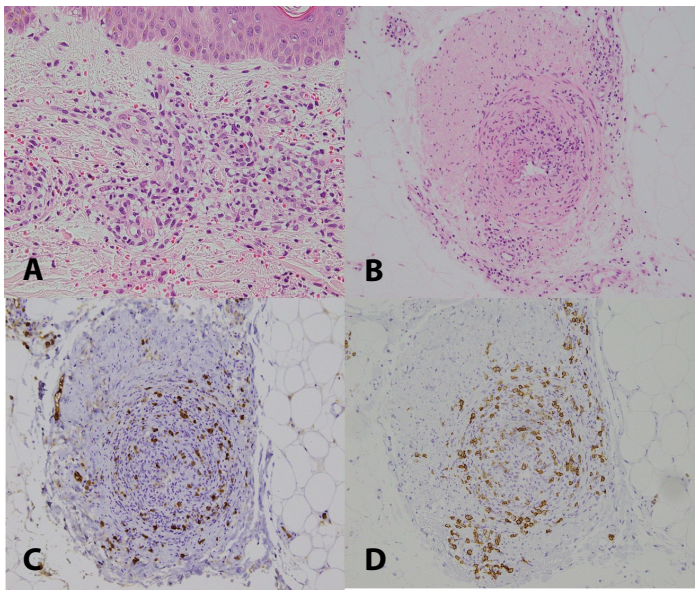

Figure 4. ***A)*** *Perivascular infiltration of atypical lymphoid cells, destruction of vessel walls, and extravasation of erythrocytes are observed in the dermis. H&E, 400×.* ***B)*** *Marked infiltration in medium vessel walls and obliteration of the vascular lumen in the subcutaneous tissue. H&E, 400×.* ***C)*** *Immunohistochemical staining for IgA and* ***D)*** *C138; the distribution of IgA-positive cells is very similar to that of CD138-positive cells, 400×.*

Cutaneous involvement occurs in approximately 50% of patients with AITL [2]. Nonspecific maculopapular morbilliform eruptions mimicking a viral exanthema and drug eruption are most commonly reported. Histological examination often shows a polymorphic infiltrate of nonneoplastic inflammatory cells. Thus far, the clinical and histopathological features have not been characterized. The rate of purpura and petechiae was 13.5% of cutaneous lesions in studies investigating cutaneous manifestations [2,7-12]. Histological findings included extravasation of erythrocytes, leukocytoclastic vasculitis, lymphohistiocytic vasculitis, and perivascular lymphoid infiltration with or without plasma cells, histiocytes, and eosinophils. It seems reasonable to think that the dysregulation of the immune system reduced by tumor cells can form skin lesions with AITL. However, the mechanism is unclear and making the diagnosis is often difficult based only on skin findings without a lymph node biopsy.

In our patient, skin biopsy performed during the early stage showed polymorphic infiltration localized to the upper dermis and did not reveal any specific histological findings. When the disease progressed, purpura expanded with a tendency to become confluent and epidermal necrosis and crusts formed. Histologically, the infiltration reached the subcutaneous layer, leading to the obstruction of blood vessels. A notable feature of this case is the infiltration of many IgA-positive cells. Because the distribution of these cells was very similar to that of CD138-positive cells, they were believed to be plasma cells. This finding may indicate an increased number or changes in the properties of IgA-positive plasma cells switched by tumor cells, and/or the presence of factors that attract plasma cells. Considering that elevated serum IgA is a predictor of poor prognosis, the infiltration of IgA-positive plasma cells might be an indication of a higher degree of malignancy.

Conclusion

Angioimmunoblastic T-cell lymphoma is characterized by marked dysregulation of the

immune system because TFH cells are the normal counterpart cell type of AITL. Immune disorders may affect the clinical course rather than development of tumor cells. Cutaneous involvement occurs in approximately half of the patients with AITL. However, the clinical and histopathological features have not been characterized and the reason why inflammatory cells are prone to homing into the skin remains unclear. Herein, we reported the case of a 78-year-old man with AITL with elevated serum IgA and infiltration of IgA-positive plasma cells into a skin lesion. Elevated serum IgA is a predictor of poor prognosis. This case demonstrated that skin manifestations may suggest the characteristics of immune disorders and prognosis of AITL.

Potential conflicts of interest

The authors declare no conflicts of interest.

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