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Thrombophlebitis Migrans As the Prodrome of Adult T-Cell Leukemia-Lymphoma

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Dear Editor:

A 70s male smoker (20 cigarettes/day for 23 years) and human T-lymphotropic virus type 1 (HTLV-1) carrier, developed painful nodular erythema in both wrist joints, the lower extremities and in the testes, each of which underwent 1-month cycles of repeating spontaneous regression and recurrence without any medications. He presented to our hospital 4 months after the initial symptom appeared (data not shown).

A biopsy of a representative lesion revealed thrombosis in the deep dermis without leukocytoclastic vasculitis (Fig. 1A). There was neither fibrinoid necrosis nor a granulomatous lesion. A diagnosis of thrombophlebitis migrans was made. The white blood cell count (9,580/μl; normal range 2,950~8,970/μl) was increased, with 3% abnormal lymphocytes. Southern blot analysis of peripheral blood revealed an HTLV-1 provirus DNA monoclonal band. Serum levels of C-reactive protein (3.57 mg/dl; normal range <0.21 mg/dl), soluble interleukin-2 receptor (2,498 U/ml; normal range 145~519 U/ml) and immunoglobulin A (459 mg/dl; normal range 110~410 mg/dl) also were increased. Because of a history of atrial fibrillation he was taking warfarin, therefore, prothrombin time international-normalized ratio was moderately prolonged (2.13; normal range 0.9~1.1). Protein C, protein S, antithrombin III, and fibrin/fibrinogen degradation products were within normal limits under transient heparinization after interruption of warfarin. Lupus anticoagulant, anticardiolipin antibodies, rapid plasma reagin test, treponema pallidum hemagglutination test and several tumor markers (i.e., squamous cell carcinoma antigen, α-fetoprotein, carcinoembryonic antigen, prostate specific antigen, carbohydrate antigen 19-9) were all negative or within the normal range. Computed tomography (CT) of the total body except for extremities and CT angiography revealed neither a solid mass nor vessel stenosis. His human leukocyte antigen (HLA) alleles were HLA-A*24, A*31, B*07, B*35, which are not associated with Behçet disease. He was diagnosed as smoldering adult T-cell leukemia-lymphoma (ATL) according to the Shimoyama criteria at the initial diagnosis.

The clinical course of the present case is described in Fig. 2. Oral administration of rivaroxaban was started instead of warfarin and, thereafter, thrombophlebitis resolved with no further recurrence. Around the disappearance of thrombophlebitis, erythematous maculopapular eruptions were noted to be scattered over the entire body (data not shown); this was followed by HTLV-1-associated arthropathy, and lung disease. Findings of histological findings including immunohistochemical analysis of erythematous areas were consistent with those of ATL (Fig. 1B). His disease status changed to intermediate types between

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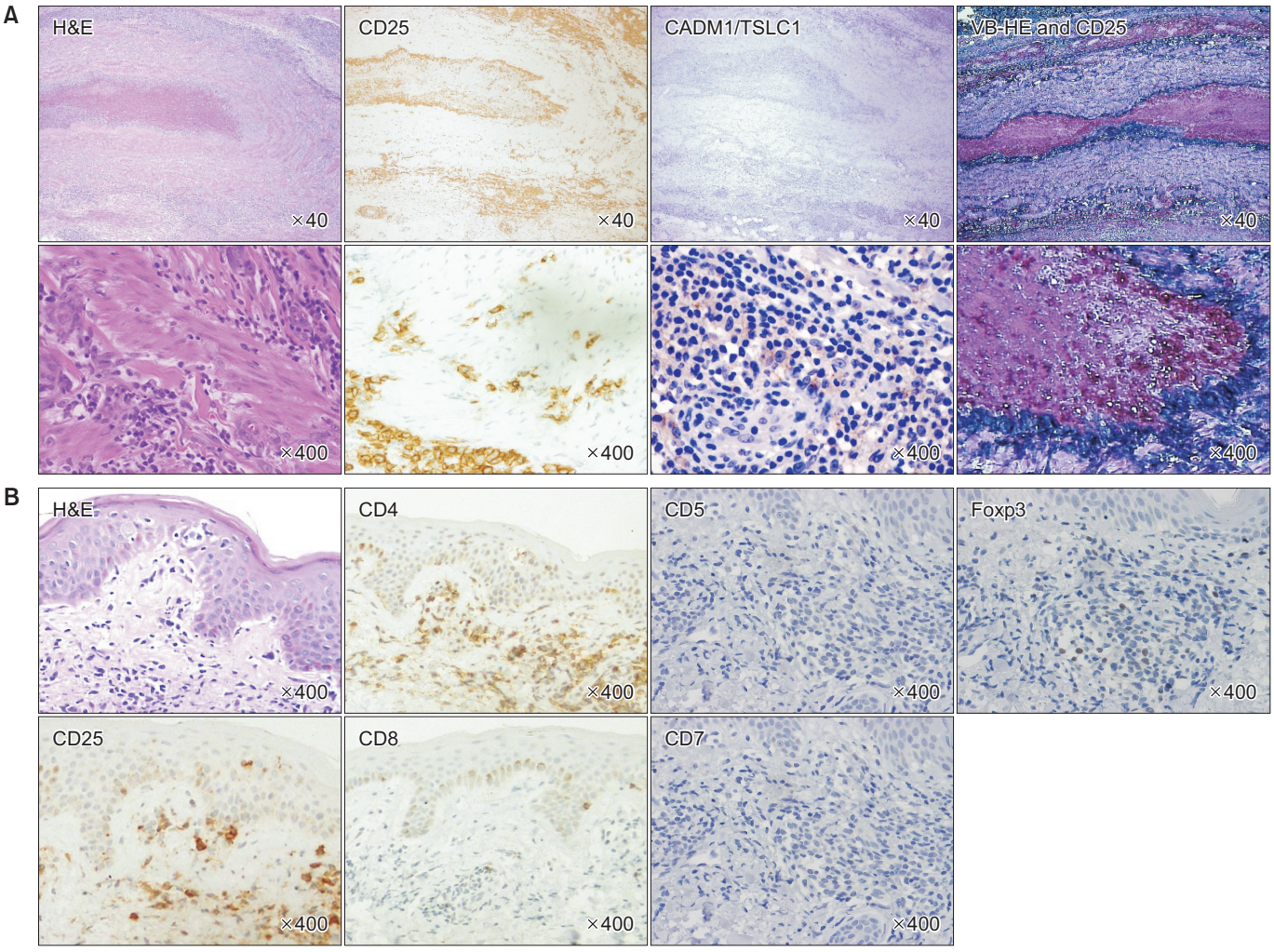

Fig. 1. (A) Skin biopsy specimen from the right lower leg showed thrombosis of a hypodermal vein (H&E, ×40). There were no changes in the epidermis such as epidermotropism of atypical lymphocytes. Immunohistochemistry revealed CD25-positive lymphocyte and CADM1/TSLC1-positive lymphocytes infiltration around the vein and thrombosis in the right lower leg (×40 and ×400). The presence of venous invasion was diagnosed based on Victoria blue-H&E staining (VB-HE) and CD25 antibody staining. Clinical pictures are not available due to lack of the signed consent because the patient is deceased and his next of kin are impossible to trace. (B) Skin biopsy from erythematous eruption revealed Pautrier's microabscess, disproportionate epidermotropism and a dense mononuclear cell infiltration with atypical convoluted nuclei in the dermis. The cells were positive for CD4, CD25, but negative for CD5, CD7, CD8, and Foxp3. Clinical pictures are not available due to lack of the signed consent because the patient is deceased and his next of kin are impossible to trace.

the chronic and acute ones. His symptoms improved after oral sobuzoxane and etoposide therapy, however the disease became refractory, he died 39 months after his first visit.

Although an association between malignancy and thrombophlebitis migrans is known as Trousseau's syndrome[1], it has rarely been reported for hematological malignancies, especially ATL. In this case, clinical findings, the clinical course and other the pertinent examinations excluded the other diseases, including Buerger's disease[2].

Although the pathological association between thrombophlebitis migrans and ATL remains obscure, HTLV-1 infection might be associated with endothelial damage, leading to hypercoagulable states[3]. In the current case, there was infiltration by CD25-positive cells and CADM1/TSLC1-positive ones around the thrombosis areas (Fig. 1A). These findings might suggest the direct involvement of ATL in thrombophlebitis migrans occurrence[4,5], although clear atypia was not found in the cells.

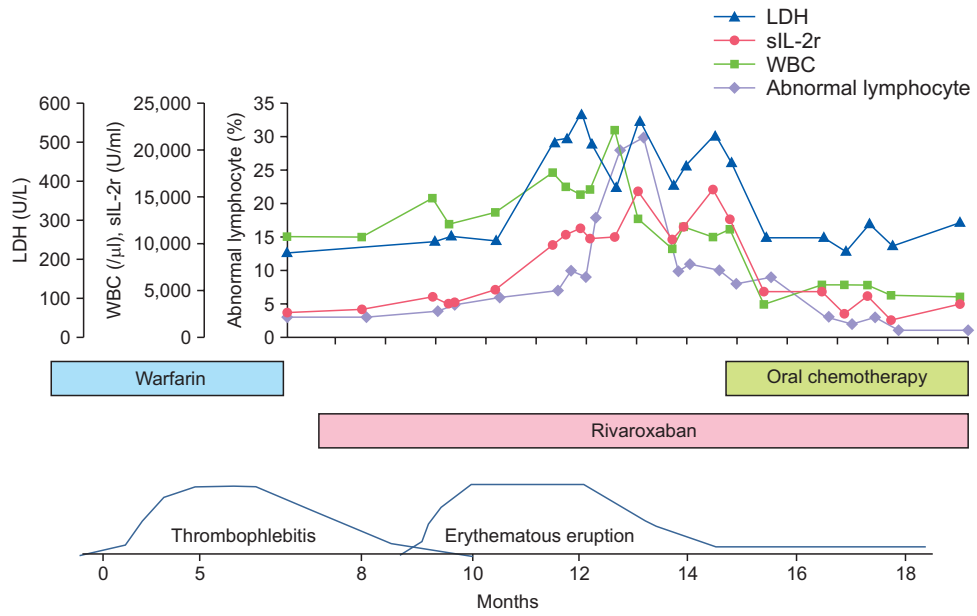

Fig. 2. Clinical course of the present case. He was diagnosed as smoldering adult T-cell leukemia-lymphoma (ATL) according to the Shimoyama criteria at the initial diagnosis. About half a year later, he complained of joint swelling, and positron emission tomography-computed tomography scans indicated fluorodeoxyglucose uptake in joints. Arthrocentesis was performed and demonstrated the presence of $CD4^+$ $CD25^+$ $CD8^-$ lymphocytes in the swelling joint. After a few more months, progression of fever, cough, breathlessness, and skin eruption were observed, and lung biopsy by bronchoscopy revealed invasion by abnormal lymphocytes. Therefore, these lung and joint findings were considered extranodal involvement of ATL. WBC count (20,000/μl; normal range 2,950~8,970/μl) was increased, with 30% abnormal lymphocytes. sIL-2r (15,000 U/ml; normal range 145~519 U/ml) was further increased. He progressed to intermediate between the chronic and acute types. LDH: lactate dehydrogenase, sIL-2r: soluble interleukin-2 receptor, WBC: white blood cell.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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