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Case report

Hodgkin-like adult T-cell leukemia/lymphoma that developed during the follow-up of HTLV-1 associated myelopathy/tropical spastic paraparesis

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Hodgkin-like adult T-cell leukemia/lymphoma (ATLL) is a rare variant of ATLL, which represents the early neoplastic phase of ATLL that follows an indolent clinical course compared with typical ATLL. Human T-lymphotropic virus type 1 (HTLV-1)-associated myelopathy/tropical spastic paraparesis (HAM/TSP) is a neurological disorder characterized by the paralysis of lower limbs and urinary disturbance. Although these diseases are caused by HTLV-1 infection, there are no reports describing the coexistence of Hodgkin-like ATLL and HAM/TSP. Here, we report the first case of Hodgkin-like ATLL complicated by HAM/TSP. The patient was a 56-year-old man with right inguinal lymphadenopathy who had been using the neurology outpatient service for 13 years after being diagnosed with HAM/TSP. He was unable to receive intensive chemotherapy or allogeneic stem cell transplantation due to a poor performance status, but his condition was stable for approximately two years.

Keywords: Hodgkin-like ATLL, HAM/TSP, Reed-Sternberg cells

INTRODUCTION

Adult T-cell leukemia/lymphoma (ATLL) is a peripheral T-cell neoplasm associated with human T-lymphotropic virus type 1 (HTLV-1) infection and a poor prognosis. In the incipient neoplastic phase of ATLL, Hodgkin-like morphology, the rare variation of which is called Hodgkin-like ATLL, may be observed on histology.[1] HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) is a chronic progressive disease induced by HTLV-1 infection characterized by bilateral spastic paralysis of the lower extremities, and bladder and bowel dysfunction. There are several reports describing the concomitant occurrence of ATLL and HAM/TSP, but there is no report of Hodgkin-like ATLL complicated by HAM/TSP.

We report the first case of Hodgkin-like ATLL with HAM/TSP, which exhibited an indolent clinical course, and discuss the association between these diseases.

CASE REPORT

A 56-year-old man was referred to our department due to right inguinal lymphadenopathy. He developed weakness in the lower extremities at the age of 32, and the condition gradually worsened. At the age of 42, he was unable to walk and had dysuria. He was then diagnosed with HAM/TSP by the detection of anti-HTLV-1 antibody in the blood and cerebrospinal fluid examination. He regularly visited the neurology department of our hospital thereafter. At his initial visit to our department, he had no B symptoms. The swelling of the right inguinal lymph node was elastic to hard with no tenderness and poor mobility, and with a major axis of 3.0 cm. Both lower limbs were slightly atrophied and presented spastic paralysis, including muscle weakness (manual muscle testing: 0/5), Achilles and patellar hyperreflexia, and a positive Babinski sign. Blood examination revealed a high soluble interleukin (IL)-2 receptor level of 1000 U/L and positivity of anti-HTLV-1 antibody (ELISA and western blotting assay). The serum lactate dehydrogenase (LDH) level was

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within the normal range. There were no atypical lymphoid cells in the peripheral blood film, but the cells were noted later. Lymph node biopsy revealed diffuse infiltration of small to medium-sized lymphocytes with rare nuclear irregularities, which distorted the nodal architecture. Giant cells with irregularly lobulated nuclei, like Reed-Sternberg cells, were scattered among the background lymphocytes (Fig. 1). Some macrophages and angiogenesis were also observed. On immunohistochemical analysis, the giant cells were positive for CD30 and CD15, and negative for CD3, CD20, PAX5, and Epstein-Barr virus-encoded RNA1 in situ hybridization (EBER-ISH). The background lymphocytes were positive for CD3, CD4, CD5, and CD25 (partially). These findings were consistent with lymphocyte-rich classic Hodgkin lymphoma (cHL). Based on fluorodeoxyglucose-positron emission tomography and bone marrow core biopsy, the clinical stage was IIA according to the Ann Arbor staging system. However, di-clonal proviral HTLV-1 DNA bands were detected in the lymph node and peripheral blood samples on Southern blot analysis (Fig. 2); therefore, we confirmed the diagnosis of Hodgkin-like ATLL (lymphoma type). C-C chemokine receptor 4 (CCR4) expression was detected in tumor cells, as confirmed by immunohistochemical staining. Doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) were first administered because the diagnosis was cHL. However, after one cycle of ABVD, the treatment regimen was changed to pirarubicin, cyclophosphamide, vincristine, and prednisolone (THP-COP) due to the diagnosis

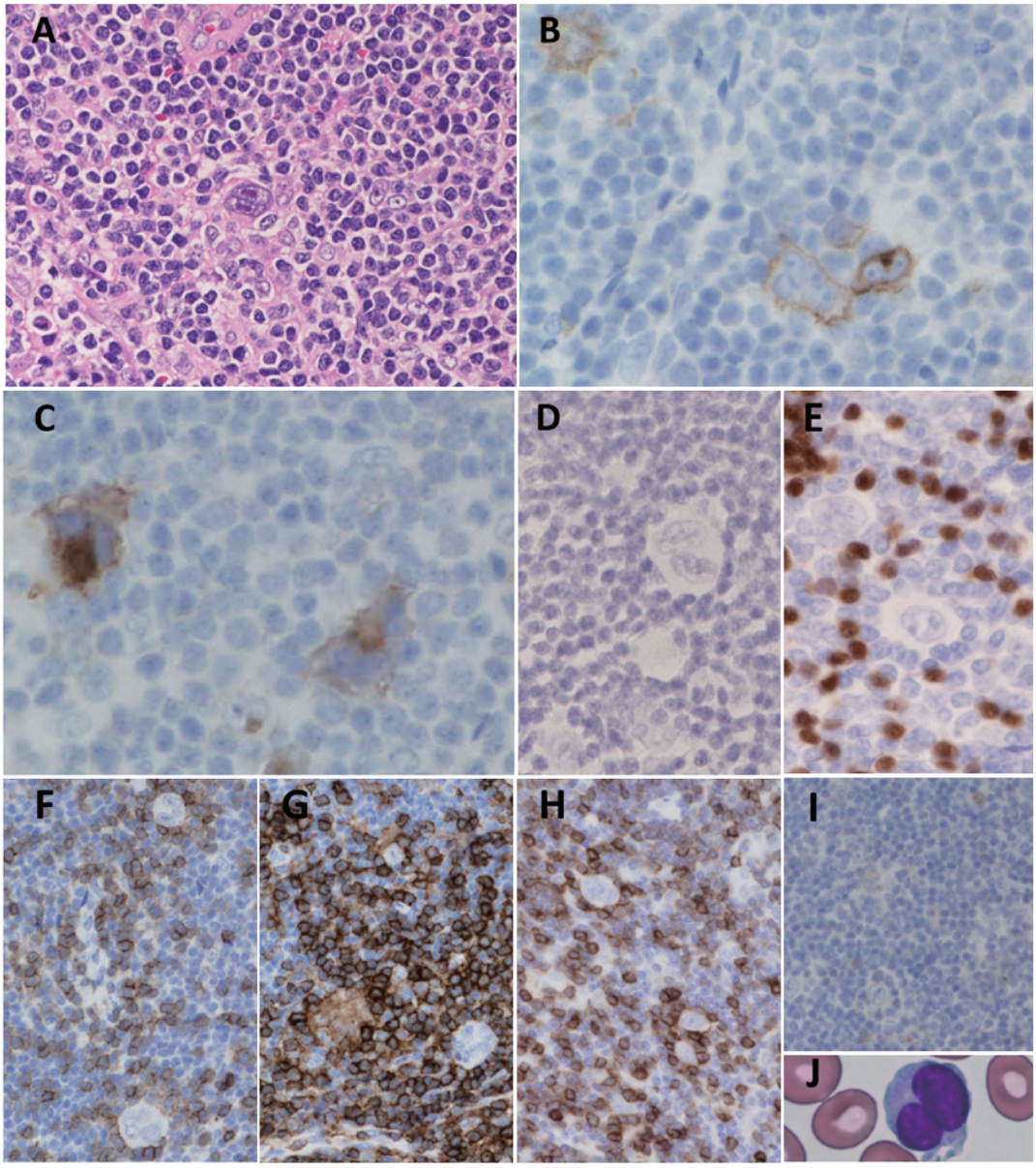

Fig. 1. Right inguinal lymph node biopsy. Hematoxylin-eosin staining showed diffuse infiltration of small to medium-sized lymphocytes with rare nuclear irregularity (***A***). Reed-Sternberg-like giant cells were scattered among the lymphocytes. The giant cells were positive for CD30 (***B***) and CD15 (***C***), but negative for EBER-ISH (***D***) and PAX5 (***E***). Background cells were positive for CD3 (***F***), CD4 (***G***), CD5 (***H***), and CD25 (partially) (***I***). Atypical lymphoid cell in a peripheral blood film (***J***).

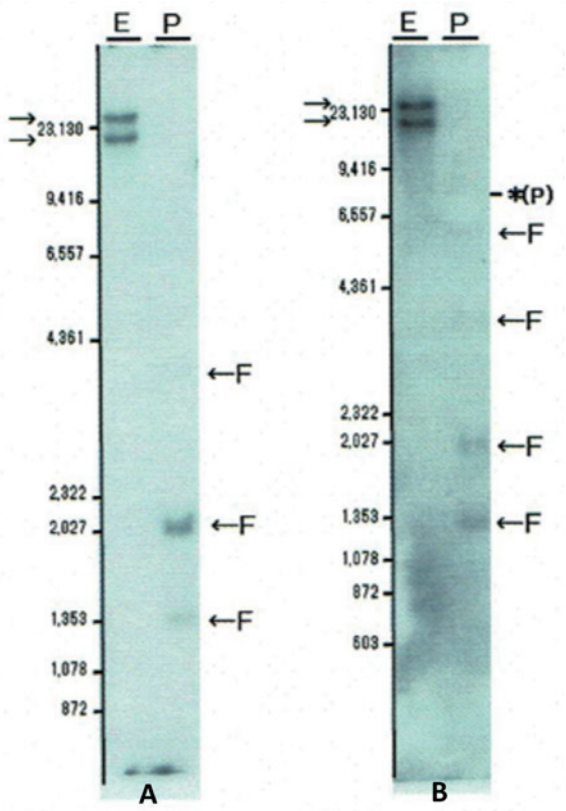

Fig. 2. Southern blot hybridization analysis of peripheral blood (***A***) and right inguinal lymph node (***B***) after digestion with *Eco RI* (***E***) or *Pst I* (***P***) restriction enzyme. Di-clonal proviral HTLV-1 DNA bands (arrow) were detected in both samples.
F: Franking band, *: nonspecific band

changing to Hodgkin-like ATLL. During the first cycle of THP-COP, the patient developed drug induced eruptions and grade 3 febrile neutropenia. Considering these side effects, he refused a second cycle of THP-COP and decided to receive low-dose oral chemotherapy (400 mg of sobuzoxane, 25 mg of etoposide, and 10 mg of prednisolone for 3 days every 2-3 weeks) in an outpatient setting. We observed a temporary increase in the soluble IL-2 receptor level (maximum: 2018 U/L) and the appearance of atypical lymphoid cells (maximum: 160/μl) in the peripheral blood; however, computed tomography suggested stable disease for approximately 2 years.

DISCUSSION

Hodgkin-like ATLL is a rare morphological variant of ATLL, which is observed in the incipient or early neoplastic phase. Ohshima *et al*. examined 18 patients with Hodgkin-like ATLL and reported that in most patients, the disease followed an indolent clinical course, but approximately half of the patients developed typical ATLL within 2 or 3 years.[1] Differential diagnosis between Hodgkin-like ATLL and cHL is difficult without a molecular HTLV-1 analysis such as Southern blotting or inverse polymerase chain reaction. In Hodgkin-like ATLL, Reed-Sternberg-like giant cells express CD30 and/or CD15 antigen, similar to cells in cHL; however, the background infiltrating lymphocytes with slight nuclear abnormalities exhibit a CD4-positive T-cell phenotype.[1,2] The giant cells of Hodgkin-like ATLL were reported to exhibit several products of IgH by single-cell PCR, which confirmed them to be reactive cells of B-cell origin. In contrast, HTLV-1-infected CD4-positive T-cells in the background demonstrated clonality on molecular analysis.[1] Our patient exhibited stable disease without progression to typical ATLL, and the pathological findings were similar to those previously reported, but the origin of the giant cells was unknown because they were negative for lymphoid markers. In most cHL cases, the giant cells are B-cell neoplasms, and nearly all patients are positive for the B-cell specific marker PAX5, whereas there are few reports describing PAX5-negative cHL.[3] PAX5-negative cHL may be caused by the reduction of B-cell specific transcription and suppression of immunoglobulin production.[4] In our patient, the giant cells were negative for PAX5, which may be due to the above reasons.

HAM/TSP is a slowly progressive immune-mediated spinal disorder caused by HTLV-I infection. The disease is characterized by the weakness or paralysis of bilateral lower extremities, lumbar pain, and urinary disturbance. The cumulative incidence of HAM/TSP is 0.3% to 2%,[5] whereas that of ATLL is 2.5% to 5%[6] among HTLV-1 carriers. Although we found 13 cases of ATLL with HAM/TSP by PubMed search[7-17] (Table 1), there was no report describing Hodgkin-like type ATLL complicated by HAM/TSP. Most cases of ATLL with HAM/TSP were reported from Japan. The median age of the patients was 53 years old (range: 35-63), there were 7 males and 6 females, and the clinical subtypes were as follows: 4 acute, 3 lymphoma, 2 chronic, and 4 smoldering. Nine patients developed ATLL during the follow-up of HAM, similar to our patient, whereas the others developed the diseases in the reverse order or at the same time. Recently, HTLV-1 proviral load levels have been reported to be a significant predictor of the onset of HAM/TSP and ATLL. Iwanaga *et al*. prospectively assessed 1218 asymptomatic HTLV-1 carriers for a median follow-up period of 1.0 year (range, 0-6.6 years), and reported that 14 patients developed ATLL (2 acute, 2 lymphoma, and 10 smoldering). The median duration from enrollment to diagnosis of ATLL was of 13.8 months (range, 2.8-64.4 months). The proviral loads in these patients were significantly higher than those in patients who did not progress to ATLL.[18] Martins *et al*. prospectively analyzed 82 asymptomatic HTLV-1 carriers and 18 HAM/TSP patients, including 6 asymptomatic carriers who developed HAM/TSP during follow-up, and found that the proviral loads in HAM/TSP patients were significantly higher than those in asymptomatic carriers.[19] Considering these studies, patients with HAM/TSP have a greater risk of developing ATLL than asymptomatic HTLV-1 carriers.

Mogamulizumab is a humanized afucosylated monoclonal antibody targeting CCR4, which demonstrates significant efficacy against ATLL.[20,21] Sato *et al*. evaluated 21

Table 1. Previous reports of ATLL with HAM/TSP

No	Age	Sex	Clinical course	Type of ATLL	Reference
1	49	M	HAM→ATLL	acute	7
2	42	F	HAM→ATLL	chronic	8
3	57	F	HAM+ATLL	smoldering	9
4	60	F	HAM→ATLL	chronic	9
5	46	F	HAM→ATLL	lymphoma	10
6	63	M	HAM→ATLL	smoldering	11
7	60	M	ATLL→HAM	smoldering	12
8	59	M	ATLL→HAM	smoldering	13
9	47	F	HAM→ATLL	acute	14
10	53	F	HAM→ATLL	lymphoma	15
11	56	M	HAM→ATLL	lymphoma	15
12	35	M	HAM→ATLL	acute	16
13	35	M	ATLL→HAM	acute	17

glucocorticoid-refractory HAM/TSP patients who received mogamulizumab in a phase 1-2a study. They reported that the Modified Ashworth Scale score (assessment of spasticity) and Osame Motor Disability score (assessment of motor dysfunction) improved in 79% and 32% of HAM/TSP patients, respectively,[22] which suggests that mogamulizumab improves the neurological dysfunction in HAM/TSP. We considered administering mogamulizumab because of CCR4 positivity, but the patient refused treatment because he was concerned that his skin condition would become exacerbated.

Clinicians and pathologists should be aware of the entity of Hodgkin-like ATLL, and understand the potential association between HAM/TSP and ATLL for a correct diagnosis and prompt intervention.

In conclusion, we report the first case of Hodgkin-like ATLL in a HAM/TSP patient. The histopathological features and indolent clinical course are consistent with the cases previously reported. Thus, ATLL, including a Hodgkin-like variant, may develop in HAM/TSP patients.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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