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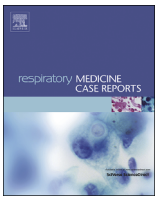

Case Report

Adult T-cell leukemia/lymphoma complicated by *Pneumocystis* pneumonia in a non-endemic area

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ABSTRACT

Adult T-cell leukemia/lymphoma (ATLL) is a human T-cell leukemia virus type 1-inducing unevenly-distributed T-cell malignancy, which is often complicated by opportunistic infections. Here, we discuss the case of a 75-year-old woman presenting with *Pneumocystis* pneumonia (PCP) who was subsequently diagnosed with ATLL in Tokyo, a non-endemic area of ATLL. In addition to the elevated soluble interleukin-2 receptor and the detection of flower cells in the screening blood test, the high-resolution computed tomography findings, atypical of PCP, were clues to the diagnosis of ATLL. ATLL should be considered as an underlying disease when patients present with PCP, even in non-endemic areas.

1. Introduction

Adult T-cell leukemia/lymphoma (ATLL) is a peripheral T-cell neoplasia that is caused by an extended period of human T-cell leukemia virus type 1 (HTLV-1) infection [1,2]. It is prevalent in Southwestern Japan, the Caribbean Basin, sub-Saharan Africa, and South America [3]. Opportunistic infections, including *Pneumocystis* pneumonia (PCP), are common in ATLL patients [4–6]; however, only a few reports of PCP in ATLL patients in non-endemic areas have been noted.

Here, we report the case of a patient who was diagnosed with ATLL with characteristic computed tomography (CT) findings in the process of examinations for PCP at a hospital in Tokyo, which is a non-endemic area for ATLL.

2. Case presentation

A 75-year-old woman was referred to our hospital after a 1-month period of exertional dyspnea and general malaise. She was originally diagnosed with pneumonia and treated with clarithromycin for 2 days at the referring clinic, with no change in symptoms.

The patient had no significant medical history, no known food or drug allergies, and was not taking any prescribed or over-the-counter medication. Between the ages of 25–32 years, the patient had a daily habit of smoking 10–15 cigarettes, but she did not regu-

Abbreviations: ATLL, adult T-cell leukemia/lymphoma; HTLV-1, human T-cell leukemia virus type 1; PCP, *Pneumocystis* pneumonia; CT, computed tomography; LD, lactate dehydrogenase; sIL-2R, soluble interleukin-2 receptor; HRCT, high-resolution CT; GGO, ground glass opacity.

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larly consume alcohol. The patient's family history included a deceased aunt who was previously diagnosed with ATLL. The patient was originally from Okinawa in southwest Japan, and her relatives and immediate family were also of Okinawan descent.

On the day of admission, the patient's body temperature was 36.7 °C, respiratory rate was 24/min, and saturation of percutaneous oxygen was 96% under 3L/min of oxygen provided by nasal cannula. Difficulty in breathing and tachypnea were notable, especially while speaking, and physical examination revealed bibasilar fine crackles. Cervical lymph nodes were not detected, and no skin abnormalities were found.

The laboratory findings are shown in Table 1. White blood cells were elevated to 18980/μL (Seg 82.5%), and flower cells were detected under a microscope. High levels of lactate dehydrogenase (LD) (489 U/L), serum soluble interleukin-2 receptor (sIL-2R) (59995 U/mL), and β-D glucan (84.9 pg/mL) were also found. The result of a passive particle agglutination test for the detection of HTLV-1 antibodies was high (8192 times), and the monoclonal proliferation of HTLV-1 proviral DNA was confirmed 15 days later. Other markers of infectious and auto-immune diseases were negative except for cytomegalovirus IgG, which was positive.

A chest radiograph showed diffuse consolidation in both lower lobes (Fig. 1). High-resolution CT (HRCT) revealed bilateral craniocaudally and horizontally diffuse ground glass opacity (GGO) accompanied by a mosaic pattern. Thickened interlobular septa and bronchial walls were noted (Fig. 2A and B). Air trapping in expiratory CT (Fig. 2C) and enlarged hilar and mediastinal lymph nodes in the mediastinal window setting CT (Fig. 2D) were also observed. A respiratory function test showed preserved vital capacity (1.77 L, 80.7%) and forced expiratory volume in 1 second (81.3%) but also increased V50/V25 (3.98) and decreased % diffusing capacity for carbon monoxide (26.4%).

The patient underwent a bronchoscopy on the day after hospitalization. A cryobiopsy sample of the right B^8b indicated severe infiltration in the bronchiole walls by atypical lymphocytes with irregularly shaped and chromatin-dyed nuclei, and the bronchial lumen was narrowed (Fig. 3A and B). Immunostaining of lymphocytes was positive for CD3 (Fig. 3D), CD4 (Fig. 3E), and CD5 (Fig. 3F) but negative for CD7, CD8, and CD20. Furthermore, the cryobiopsy sample indicated Grocott-stained boat-shaped cyst forms of *Pneumocystis* (Fig. 3C). *Pneumocystis jirovecci* polymerase chain reaction was 1×10^6 copies/mL ($>4 \times 10$) in bronchoalveolar lavage fluid from the right B^5.

A conlusive diagnosis of acute-type ATLL and PCP was made in light of the aforementioned results. The clinical course of the patient is shown in Fig. 4. The patient was first treated with sulfamethoxazole-trimethoprim (9 g/day as sulfamethoxazole) and 3 days of methylprednisolone (1 g/day), followed by 2, 1, 0.5, 0.25 mg/kg/day of prednisolone for 5 days each, for PCP. Subsequent chest radiographs showed a slight improvement in consolidation. However, the patient remained reliant on supplemental oxygen, and the number of white blood cells kept increasing, which was suspected to be due to ATLL. The patient was transferred to the hematology department on day 8 and began chemotherapy (pirarubicin, cyclophosphamide, vincristine, and prednisolone; first-course) immediately. From day 12 onwards, the patient stopped requiring supplemental oxygen, and her blood tests began to indicate improvement. CT scans on day 15 revealed that GGO had become pale, and the size of the lymph nodes had reduced (Fig. 5A and B). Because the patient preferred to receive treatment in her hometown, she was discharged on day 23 and referred to a hospital in Okinawa.

Table 1
Laboratory test results.

Complete blood count			Infectious disease		
WBC	18980	/μL	HTLV-1 antibody	8192	times
St	3	%	β-D glucan	84.9	pg/mL
Seg	82.5	%	CMV IgG	>250	AU/mL
Ly	4.5	%	CMV IgM	negative	
Mono	4	%	CMV pp65 antigenemia C10/C11	9/5	
flower cells	6	%	EBV VCA-IgG	160	times
HGB	11.9	g/dL	EBV VCA-IgM	<10	times
PLT	65.2	x10^4/μL	Cryptococcus antibody	negative	
			Aspergillus antibody	negative	
Blood chemistry			HIV-AgAb	negative	
AST	22	U/L	IGRA(T-SPOT®)	negative	
ALT	13	U/L			
LD	489	U/L	Immunology		
ALP	140	U/L	IgG	861	mg/dL
γ-GT	49	U/L	IgA	165	mg/dL
TP	6.6	g/dL	IgM	75	mg/dL
ALB	2.7	g/dL	IgE	<1	IU/mL
BUN	18	mg/dL			
Cre	0.66	mg/dL	Arterial blood gas analysis (5L/min by nasal cannula) (day3)		
Ca	9.2	mg/dL	PH	7.391	
Na	138	mmol/L	$PaCO_2$	36	mmHg
K	4.2	mmol/L	PaO_2	64	mmHg
Cl	100	mmol/L	HCO_3	21.3	mmol/dL
CRP	24.19	mg/dL			
KL-6	571	U/mL	Coagulation fibrinolysis		
SP-D	169	ng/mL	PT-INR	1.08	
sIL-2R	59995	U/mL	APTT-Pt.	28	sec.
			D-dimer	0.6	μg/mL

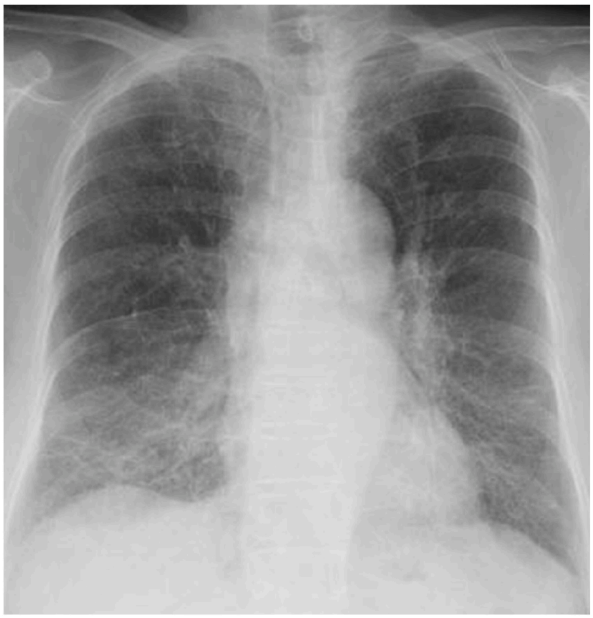

Fig. 1. Chest radiograph on admission
Chest radiograph shows diffuse consolidation in both lower lobes.

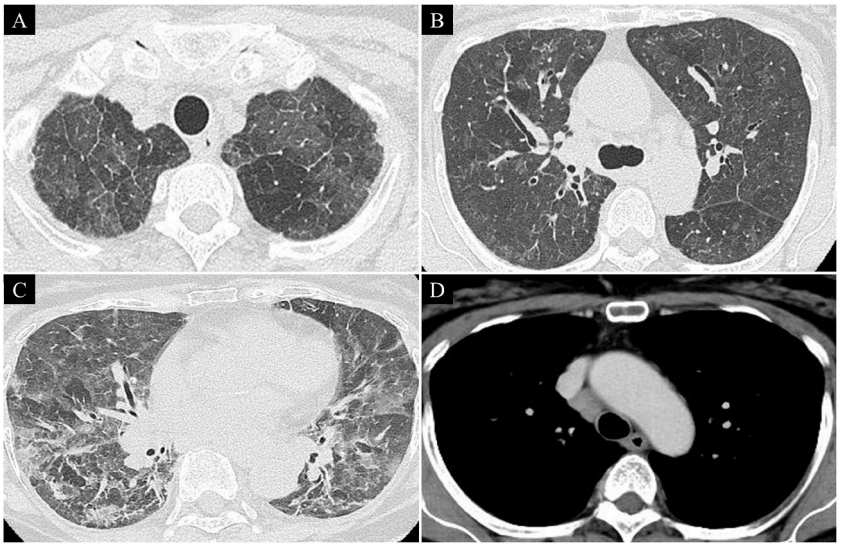

Fig. 2. HRCT on admission
HRCT reveals bilateral craniocaudally and horizontally diffuse ground glass opacity accompanied by a mosaic pattern, and thickening of interlobular septa and bronchial walls (A, B). Air trapping in expiratory CT (C) and enlarged hilar and mediastinal lymph nodes in the mediastinal window setting CT (D) are also observed. HRCT: high-resolution computed tomography.

3. Discussion

We reported a case of a patient, who was initially thought to have contracted PCP due to her respiratory symptoms, high levels of inflammatory markers and β-D glucan in blood, and the presence of diffuse GGO in CT scans, but was later diagnosed with ATLL too at a hospital in Tokyo, a non-endemic area of ATLL. CT findings, atypical of PCP, in addition to elevated sIL-2R and the presence of flower cells in blood, brought about the possibility of the presence of ATLL.

ATLL is an HTLV-1 infection-inducing mature T-cell malignancy featuring lymphoma and/or leukemia [1,2], with a poor prognosis of less than a year in acute types [7,8]. Opportunistic infections are common due to immunodeficiency, even without immune-depressive treatments [9,10], and PCP is one of the most common ones. A study showed that approximately 31.1% of all ATLL patients had at least one opportunistic infection, with PCP being the most prevalent (13.7%) [11].

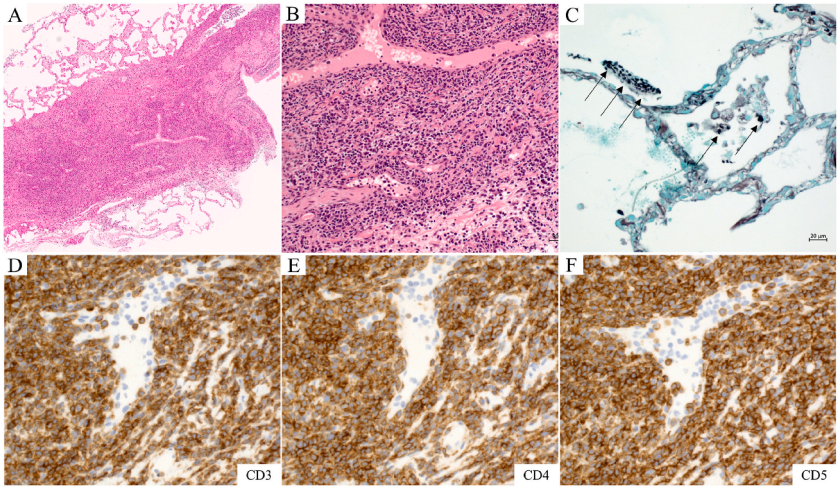

Fig. 3. Pathological findings of the cryobiopsy sample from the right B^8b
A sample of bronchioles and surrounding alveoli was obtained from the right B^8b. The hematoxylin and eosin-stained section reveals severe infiltration of atypical lymphocytes with irregularly shaped and chromatin-dyed nuclei in the bronchiole walls, and the narrowed bronchial lumen (A, B). Immunostaining is positive for CD3 (D), CD4 (E), and CD5 (F), but negative for CD7, CD8, and CD20. Boat-shaped cyst forms of *Pneumocystis* in the Grocott-stained slice are also observed (C).

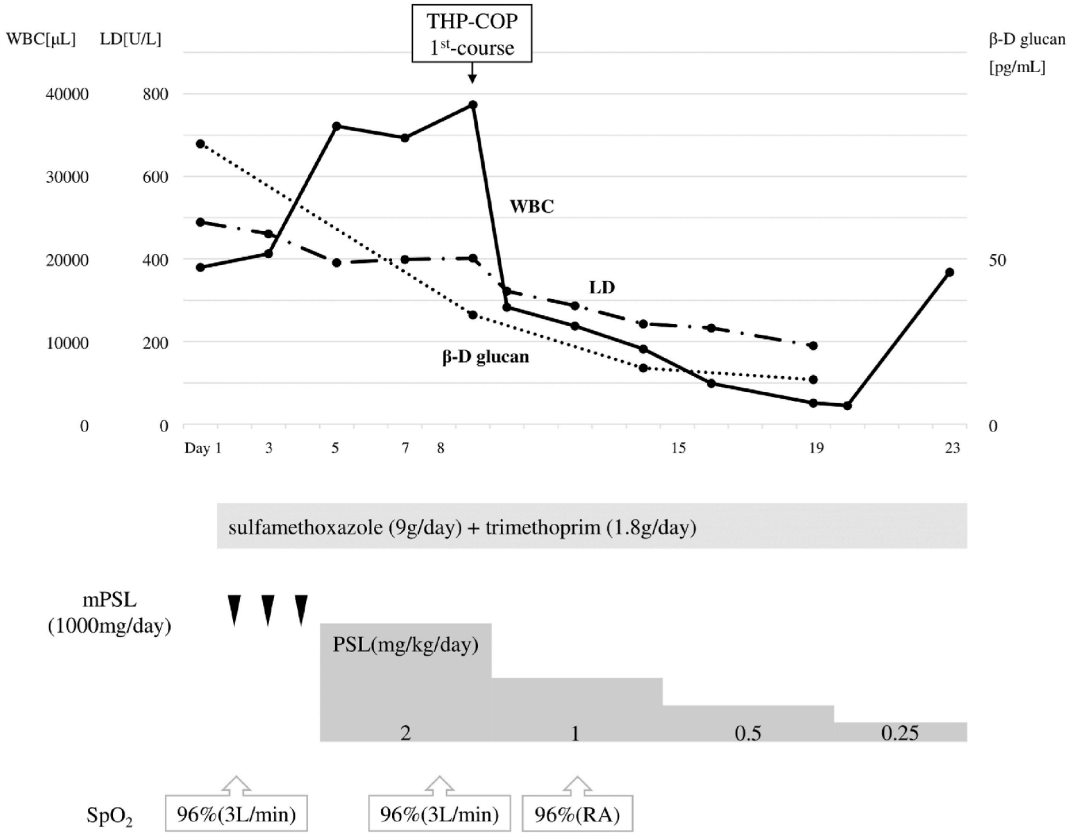

Fig. 4. Clinical course of the patient
The patient was transferred from the respiratory medicine department to the hematology department on day 8, and the first course of THP-COP was started on the next day. The patient no longer required supplemental oxygen after day 12. THP-COP: pirarubicin, cyclophosphamide, vincristine, and prednisolone, WBC: white blood cell, LD: lactate dehydrogenase, mPSL: methylprednisolone, PSL: prednisolone, SpO_2: saturation of percutaneous oxygen, RA: room air.

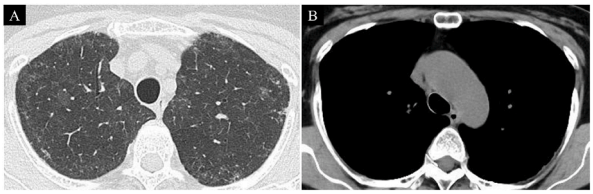

Fig. 5. HRCT after initiation of treatment
HRCT on day 15 reveals improvement of the diffuse ground glass opacity (A) and reduced size of the enlarged lymph nodes (B). HRCT: high-resolution computed tomography.

Being vigilant for ATLL when patients present with PCP has become more important in areas where ATLL is not endemic. HTLV-1 infection and subsequent ATLL onset is clustered in some limted areas, mainly because the most common route of transmission is from mother to child through breast-feeding, and occasionally through blood transfusion or sexual intercourse (usually from men to women) [12–14]. Southwestern Japan is one of the endemic areas along with the Caribbean Basin, sub-Saharan Africa, and South America [3]. There are in fact dozens of case reports of PCP in non-treated ATLL patients, but only three of them are from non-endemic areas [15–17] and the rest are from Southwestern Japan. However, the number of ATLL cases has been increasing recently in non-endemic areas such as Tokyo, due to growing numbers of HTLV-1 carriers migrating from endemic areas to non-endemic areas [18]. Therefore, even in non-endemic areas, a greater number of PCP patients with underlying ATLL are expected to require timely and correct treatments for both PCP and ATLL.

Imaging, especially HRCT, can help doctors to identify ATLL. Our patient's CT scans on admission showed diffuse GGO, which is a common CT characteristic of PCP, in addition to reticulations, consolidation, and crazy-paving pattern [4,19]. This led us to consider PCP as the first differential diagnosis based on her symptoms. However, it also showed thickening of interlobular septa and bronchial walls, and enlarged hilar and mediastinal lymph nodes, which are not typical of PCP and would thus imply other conditions.

In acute and lymphoma-type ATLL, CT findings of ATLL lung lesions include enlarged lymph nodes, ground-glass attenuation, bronchial wall thickening, nodules, which are not characteristic of PCP, and centrilobular opacities [20]. In our patient, the main pathological findings of the cryobiopsy sample were CD3, 4, and 5 positive atypical lymphocytes infiltrating into the bronchiole walls, corresponding to bronchial wall thickening on CT. Thickened interlobular septa and enlarged hilar and mediastinal lymph nodes were consistent with lung lesions of ATLL as written above. The mosaic pattern of the lung field was considered to be caused by PCP, but the mosaic pattern and air-trapping may also have been caused by the infiltration of atypical lymphocytes into bronchioles. Therefore, the patient's CT was retrospectively assessed to have aspects of both PCP and lung lesions due to ATLL, and the CT findings were useful in suspecting the presence of ATLL.

4. Conclusion

It is critical for medical practitioners to remain vigilant of ATLL, even in non-endemic areas, when PCP is present. Imaging can be helpful in detecting the presence of ATLL.

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Declaration of competing interest

None.

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