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A Human T Lymphotropic Virus Type 1 Carrier Coinfected with *Mycobacterium intracellulare* and *Pneumocystis jirovecii* with a Characteristic Compositional Change of Bone Marrow Cells

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Abstract

Human T lymphotropic virus type 1 (HTLV-1) is endemic in the southern part of Japan. Infection of the virus can cause adult T cell leukemia/lymphoma (ATL), while most infected individuals remain in a carrier state for a long period of time. Although rare cases of carriers, like ATL patients, who developed opportunistic infections, have been reported, hematological changes of carriers who are prone to opportunistic infections have not been well defined. Here, we present a case of an HTLV-1 carrier who developed *Mycobacterium intracellulare* infection and *Pneumocystis jirovecii* pneumonia (PcP) simultaneously. Flow cytometric analysis of bone marrow cells revealed an aberrant compositional change similar to that in ATL patients. This suggests the presence of a pre-ATL state prior to the development of ATL, which is notable in terms of underlying cellular immunodeficiency.

Keywords

Human T Lymphotropic Virus Type 1, Carrier, Immunodeficiency, *Pneumocystis jirovecii*

1. Introduction

HITV-1 is an endemic retrovirus and infects $CD4^+$ T cells. A part of HTLV-1-infected patients develop ATL, who often suffer from opportunistic infections due to cellular immunodeficiency. Most infected patients remain asymptomatic

defined as a carrier state [1]. Although rare, carriers have been also reported to develop opportunistic infections. Immune state of carriers, however, has not been clarified compared with that of ATL patients. Here, we present a case of an HTLV-1 carrier who developed *Mycobacterium intracellulare* infection and *Pneumocystis jirovecii* pneumonia simultaneously. Additionally, the proportion of $CD4^+CD25^+$ T cells was aberrantly increased in her bone marrow samples, which is characteristically seen in ATL patients. This implies the presence of a pre-ATL state in carriers based on their immunological changes, which is clinically relevant because of their immunodeficiency.

2. Case Report

A 68-year-old woman, who had previously been in a healthy state, developed a productive cough that lasted for approximately 2 months and was referred to our hospital for further examinations (Day 1). The patient exhibited a blood pressure of 115/79 mmHg, SpO_2 of 96% (room air), pulse rate of 104 beats/min (regular), and body temperature of 36.8˚C. Chest computed tomography (CT) findings obtained at the referring clinic revealed areas of patchy consolidation and ground-glass nodules (**Figure 1(a)**). Serum KL-6 (reference range: <500 IU/mL) was elevated to 710 IU/mL and soluble interleukin-2 receptor level (reference range: 145 - 519 U/mL) to 4080 U/mL (**Table 1**). Findings of cultures of sputum and bronchial washing fluid yielded *Mycobacterium intracellulare*. She was diagnosed with a non-tuberculous mycobacterium (NTM) infection and treated with clarithromycin (800 mg), rifampicin (450 mg), and ethambutol (750 mg). Nevertheless, respiratory failure rapidly progressed in a week and the patient was admitted for further examinations. Upon admission (Day 10), the patient exhibited SpO_2 of 88% (room air) and body temperature of 37˚C to 38˚C. Another chest CT examination demonstrated diffuse consolidation, ground-glass nodules, and thickening of bronchovascular bundles with no lymphadenopathy (**Figure 1(b)**). Another medical interview revealed that she was born in Kagoshima Prefecture, southern part of Japan, and additional laboratory examinations showed seropositivity for HTLV-1. She was diagnosed with an HTLV-1 carrier based on no abnormal lymphocytes noted in peripheral blood and bone

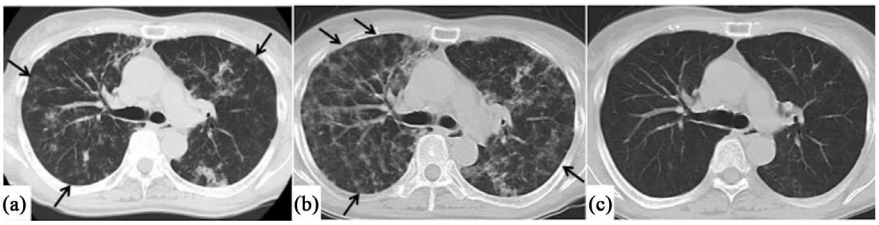

Figure 1. CT images. (a) A computed tomography (CT) scan taken at the referring clinic on Day -10, showing patchy consolidation and ground-glass nodules (arrows); (b) A CT scan taken upon admission due to respiratory failure on Day 6, showing diffuse consolidation, ground-glass nodules (arrows) and thickening of bronchovascular bundles; (c) A CT scan taken at 2 months after treatment, revealing disappearance of consolidation and ground-glass nodules.

Table 1. Laboratory data (Day 1).

Peripheral blood counts			Serology		
WBC	14,190/μL	4000 - 8000	CRP	2.03 mg/dL	<0.30
Neu.	52%	40 - 72	KL-6	710 IU/mL	<500
Eos.	0.4%	0.2 - 7.0	ANA	<40	<40
Baso.	0.6%	0.0 - 1.0	PR3-ANCA	<1.0 EU	<3.5
Lym.	42%	26 - 47	MPO-ANCA	<1.0 EU	<3.5
Mon.	5.0%	2.0 - 8.0	sIL-2 receptor	4080 U/mL	145 - 519
RBC	443 × 10^4/μL	336 - 500 × 10^4	ACE	10.2 IU/L	8.3 - 21.4
Hb	13.4 g/dL	11.3 - 15.2	IgG	704 mg/dL	870 - 1700
Ht	41.2%	33.4 - 44.9	IgA	188 mg/dL	110 - 410
Plt	39.8 × 10^4/μL	15 - 35 × 10^4	IgM	97 mg/dL	35 - 220
			Anti-MAC antibody	(−)	
Biochemistry			**Sputum**		
TP	6.2 g/dL	6.7 - 8.3	Smear	Acid-fast bacilli (±)	
Alb	3.1 g/dL	4.0 - 5.0	MAC-PCR	M. intracellulare (+)	
T-bil	0.5 mg/dL	0.3 - 1.2	Culture	M. intracellulare (+)	
AST	31 IU/L	13 - 33			
ALT	12 IU/L	6 - 27	**Bronchial washing fluid (Day 3)**		
LDH	350 IU/L	119 - 229	Smear	Acid-fast bacilli (±)	
BUN	16 mg/dL	8 - 22	MAC-PCR	M. intracellulare (+)	
Cre	0.81 mg/dL	0.46 - 0.79	Culture	M. intracellulare (+)	
Na	138 mEq/L	138 - 146			
K	4.5 mEq/L	3.6 - 4.9			
Cl	99 mEq/L	99 - 109			
Glu	100 mg/dL	70 - 109			
Ca	9.1 mg/dL	8.7 - 10.3			

CRP: C-reactive protein, KL-6: Krebs von den Lungen-6, ANA: antinuclear antigen, PR3-ANCA: proteinase-3-antinuclear cytoplasmic antibody, MPO-ANCA: myeloperoxidase-antinuclear cytoplasmic antibody, sIL2-R: solubue interleukin-2 receptor, ACE: angiotensin converting enzyme, MAC: Mycobacterium avium complex, PCR: polymerase chain reaction.

marrow specimens. Flow cytometric analyses of her bone marrow samples demonstrated that the proportion of $CD4^+CD25^+$ T cells was abnormally increased (Figure 2).

We performed another bronchoscopy to further examine her lung disease (Day 7). Grocott staining of bronchoalveolar lavage fluid (BALF) and transbronchial lung biopsy specimens revealed *Pneumocystis jirovecii* cysts (Figure 3(a) and Figure 3(b)), with no evidence of ATL cell infiltration. Another laboratory finding revealed elevated β-D glucan, while HIV-antibody was negative and $CD4^+$ T cell count was 5464/μL (Table 2). We administered trimethoprim-

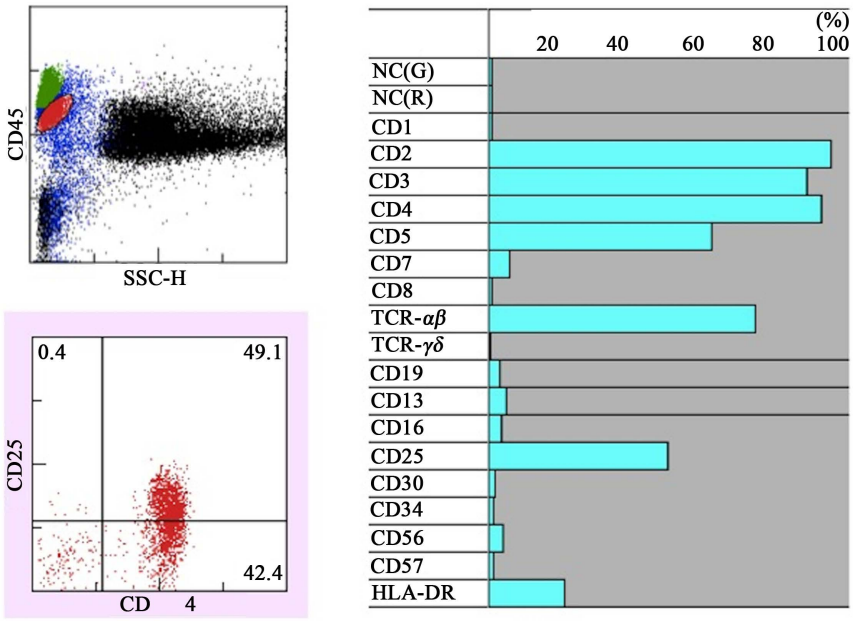

Figure 2. Flow cytometric analysis of the bone marrow aspirate. Flow cytometric analysis of the bone marrow aspirate, performed on Day 13, revealed the proliferation of $CD4^+CD25^+$ T cell subset. SSC: Side scatter.

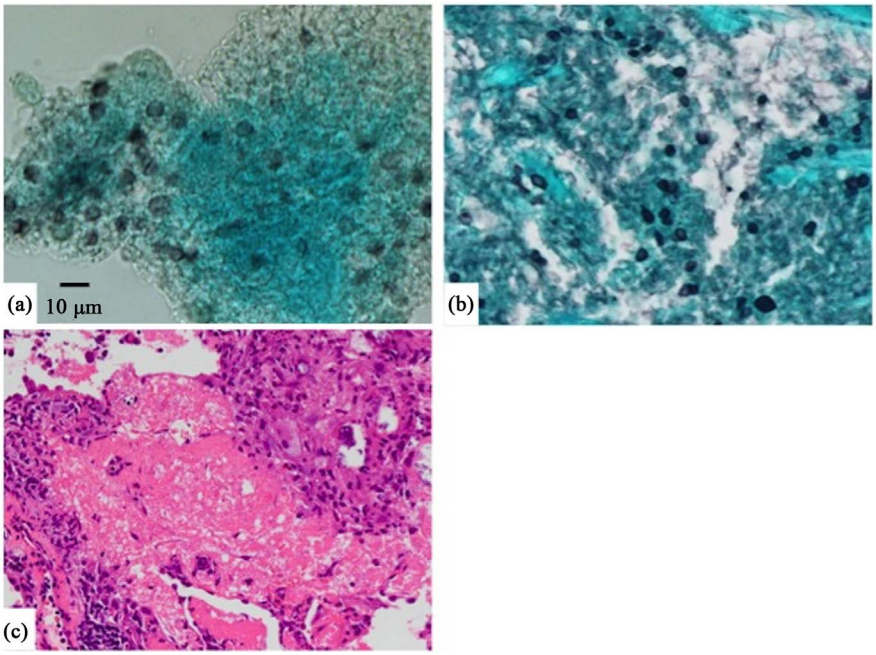

Figure 3. Grocott staining of (a) bronchoalveolar lavage fluid smear and (b) transbronchial lung biopsy specimens. *Pneumocystis jirovecii* cysts were seen in both; (c) Hematoxylin-eosin staining of a transbronchial lung biopsy specimen showing foamy exudate within alveolar space.

sulfamethoxazole (720 mg trimethoprim and 3600 mg sulfamethoxazole) and the patient recovered from respiratory failure in 5 days. One-week after diagnosis of carrier state, abnormal lymphocytes appeared in peripheral blood (Day 21), suggesting progression of the disease to smoldering ATL. Two months later,

Table 2. Additional examinations.

Bronchoalveolar lavage fluid (Day 14)		
Recovery rate	60/150 ml (40%)	
Total cell count	1.0×10^5/mL	
AM	58%	
Lym.	24%	
Eos.	6.0%	
Neu.	12%	
CD4/8 ratio	1.57	
Smear	Acid-fast bacilli (+)	
Culture	*M. intracellulare* (+)	
Pneumocystis jiroveci PCR	(+)	
Another laboratory data (Day 19)		
HIV-Ab	(−)	
$CD4^+$ T cell count	5464/μL	
133pg/mL	133 pg/mL	<20

AM = alveolar macrophage, HIV = human immunodeficiency virus.

follow-up chest CT findings showed no consolidation or ground-glass nodules (**Figure 1(c)**). At the time of writing, the patient is receiving medication for NTM infection as well as trimethoprim-sulfamethoxazole as a prophylactic.

3. Discussion

HTLV-1 is a retrovirus and endemic in southern part of Japan. While most infected patients remain asymptomatic carriers, approximately 5% of infected patients develop ATL and suffer from opportunistic infections because of cellular immunodeficiency [1]. Although there are some reports suggesting that HTLV-1 carriers are also prone to bacterial or fungal infections [2] [3] [4] [5], their immunological states have not been elucidated compared with that of ATL patients. In this report, we presented an HTLV-1 carrier who developed NTM infection and PcP simultaneously, and showed cellular compositional changes similar to ATL patients in her bone marrow.

Diagnosis of HTLV-1 carrier state and ATL are based on Shimoyama criteria [6]. This defines that the detection of abnormal lymphocytes in peripheral blood or organs such as lymph nodes is required for the diagnosis of ATL. Based on this, the patient was diagnosed with a carrier state when she developed PcP because of no apparent abnormal lymphocytes in her blood and bone marrow samples. On the other hand, flow cytometric analyses of bone marrow cells revealed aberrantly increased $CD4^+CD25^+$ T cells, indicating abnormal clonality of $CD4^+$ T cells.

$CD4^+CD25^+$ T cells represent regulatory T cells (Tregs) in healthy subjects. In ATL patients, ATL cells also express CD4 and CD25, and reportedly function like Tregs to suppress immunoreaction [7]. How compositional changes of bone marrow cells occurred in the progression from carrier state to ATL remains to be unknown. From findings of this patient, it is possible that there is a pre-ATL state, where subclinical immunological changes and immunodeficiency equivalent to ATL patients exist in the absence of abnormal lymphocytes noted in clinical samples. As in the present case, the fact that HTLV-1 carriers complicated with opportunistic infections are likely to develop ATL thereafter [8] supports this hypothesis. Whether increased $CD4^+CD25^+$ cells are Tregs or ATL cells needs to be defined to characterize this immunological abnormality in carrier patients.

The previous study reported that HTLV-1 carriers suffered from various kinds of opportunistic infections including PcP, cryptococcal meningitis and strongyloidiasis and, moreover, many of them progressed ATL in a few years following those infectious diseases [9]. In patients with opportunistic infections of unknown origin, an HTLV-1 infection should be considered as a cause of immunodeficiency in HTLV-1 endemic areas.

In the present case, acute respiratory failure progressed during treatment of an NTM infection. Another medical interview and bronchoscopy helped us diagnose HTLV-1 infection and PcP. Because HTLV-1-infected patients exhibit various types of abnormalities in chest CT [10], bronchoscopy is of importance to differentiate pulmonary infections from HTLV-1-derived lung disease. In addition, the possibilities of multiple pathogen infections, like the present case, should be always kept in mind. The present patient is now treated with watchful waiting as smoldering ATL, however the long-term prognosis of smoldering ATL was reported to be poor [11]. She may progress acute ATL and opportunistic infections in the future and therefore should be carefully observed in clinical practice.

4. Conclusion

In conclusion, we reported an HTLV carrier who developed NTM infection and PcP simultaneously. We also indicated the possibilities of cellular compositional changes in her bone marrow in the basis of the development of this opportunistic infection. Further evaluation is warranted to assess clinical implications of this immunological abnormality in HTLV-1 carriers.

Consent

Informed consent was obtained from the patient to report this case.

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