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## Angioimmunoblastic T-cell lymphoma accompanied by pure red cell aplasia: A case report

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### Abstract

#### BACKGROUND

Angioimmunoblastic T-cell lymphoma (AITL) is a peripheral T-cell lymphoma, which is a rare subtype of lymphoma. Patients with AITL often have skin lesions, which are observed in 50% of all cases; the chief complaint of this patient was palpable purpura. AITL often complicates autoimmune or hematological disorders; however, among these, pure red cell aplasia (PRCA) is a very rare complication of AITL. We herein report a case of AITL with PRCA.

#### CASE SUMMARY

A 77-year-old Japanese man presented to our hospital with complaints of loss of appetite for 2 mo and a 10-d history of palpable purpura. On physical examination, the patient was afebrile but had bilateral multiple palpable purpuric lesions over the lower extremities, lower abdomen, and part of the upper extremities. Moreover, lymphadenopathy of the bilateral inguinal, cervical, and supraclavicular nodes was noted. Laboratory and imaging studies and skin biopsy were conducted but were inconclusive. Based on inguinal lymph node excisional biopsy, we diagnosed the patient with AITL. Subsequently, the patient developed progressive normocytic normochromic anemia that necessitated almost daily blood transfusion. The clinical presentations and results of bone marrow assessment were consistent with those of PRCA, which is associated with AITL. Chemotherapy was initiated but was not effective. The patient refused further chemotherapy and opted to continue receiving best supportive care.

#### CONCLUSION

PRCA is an extremely rare complication of AITL. As the pathophysiology remains unclear, further research is warranted.

**Key words:** Palpable purpura; Lymphoma; Pure red cell aplasia; Case report

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**Core tip:** Angioimmunoblastic T-cell lymphoma (AITL) is an uncommon subtype of peripheral T-cell lymphoma. Moreover, the patient was diagnosed with pure red cell aplasia (PRCA) associated with AITL. Although AITL is often accompanied by various immunological and hematological diseases, PRCA with AITL is extremely rare.

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## INTRODUCTION

Angioimmunoblastic T-cell lymphoma (AITL) is an uncommon subtype of peripheral T-cell lymphoma, which comprises 1%-2% of all non-Hodgkin lymphomas<sup>[1]</sup>. Cutaneous involvement is one of the most important presentations of AITL and is seen in up to 50% of cases. Our case showed palpable purpura<sup>[2]</sup>. Our patient not only developed a rare subtype of lymphoma, AITL, but also its very rare complication, pure red cell aplasia (PRCA).

## CASE PRESENTATION

### Chief complaints

A 77-year-old Japanese man presented to our hospital with complaints of loss of appetite for 2 mo and a 10-d history of palpable purpura.

### History of present illness

The patient had developed progressive palpable purpura over his lower legs (Figure 1) without fever, chills, or other clinical signs.

### History of past illness

The medical history included hypertension, hyperlipidemia, old myocardial infarction, and appendicitis. The patient was on regular treatment with medications, including aspirin, lansoprazole, enalapril, valsartan, and carvedilol. He had no notable family or social history.

### Personal and family history

His family history was noncontributory.

### Physical examination upon admission

On physical examination, the patient's vital signs were normal: blood pressure, 102/58 mmHg; heart rate, 94 bpm; and percutaneous oxygen saturation, 99% in room air. However, multiple palpable purpuric lesions were noted on bilateral lower extremities, the lower abdomen, and part of the upper extremities (Figure 1). Lymphadenopathy was noted in bilateral inguinal, cervical, and supraclavicular nodes, measuring up to 1 cm in diameter. No clinically relevant abnormalities were observed on the electrocardiogram and chest radiograph.

### Laboratory examinations

Laboratory data on admission was shown in Table 1: White blood cells and platelet counts were normal but normocytic normochromic anemia was seen. An elevated level of serum lactate dehydrogenase has been found. Although several abnormalities were observed, none of them were specific to the diagnosis.

### Further diagnostic work-up

We performed skin biopsy, which demonstrated superficial perivascular dermatitis. However, this did not help in diagnosis. Subsequently, a right inguinal lymph node excisional biopsy was performed, which showed vascular proliferation with high endothelial cells, including small-to-medium-sized atypical lymphocytes and



**Figure 1** Palpable purpura on the lower extremities.

follicular dendritic cells. Immunohistochemical analysis revealed the expression of T-cell markers (CD2, CD3, CD4, and CD5) with CD10. These characteristics were consistent with those of AITL.

Subsequently, several days after hospitalization, the patient developed progressive normocytic normochromic anemia. His hemoglobin levels remained much lower than normal at 4.9-6.0 g/dL, with normal white blood cell and platelet counts, similar to those on admission. His absolute reticulocyte count also remained extremely low at less than 10000/ $\mu$ L, necessitating blood transfusion support almost every day. Peripheral blood smear examination revealed a normochromic normocytic picture and there was no evidence of hemolysis. We performed bone marrow aspiration and biopsy for evaluation, which showed characteristic findings of relative erythroid hypoplasia. The myeloid and lymphoid series were essentially unremarkable, whereas the megakaryocytes were slightly increased in number and had normal morphology. Based on these findings, the patient was diagnosed with PRCA.

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## FINAL DIAGNOSIS

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AITL and PRCA associated with AITL.

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## TREATMENT

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Chemotherapy every 3 wk was urgently initiated with intravenous cyclophosphamide at 750 mg/m<sup>2</sup>, doxorubicin at 50 mg/m<sup>2</sup>, and vincristine at 1.4 mg/m<sup>2</sup> on day 1 with oral prednisone at 60 mg/d from days 1 to 5 (cyclophosphamide, doxorubicin, vincristine, and prednisone). However, chemotherapy offered limited clinical benefit with partial regression of the lymphadenopathy; moreover, blood transfusions were required almost every day.

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## OUTCOME AND FOLLOW-UP

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The patient refused further chemotherapy in view of his age and disease status, and opted to continue with best supportive care, including a blood transfusion, at another local hospital.

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## DISCUSSION

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Skin lesions are one of the most important manifestations of AITL, affecting the skin in approximately 50% of cases. This poses a diagnostic challenge, particularly before obtaining lymph node biopsies<sup>[2]</sup>. In this case, although there was no evidence of tumor cell involvement and our institutional pathologist did not mention the possibility of lymphoma in the skin biopsy report, a negative skin biopsy is often observed in AITL patients with skin lesions. Previous reports showed the histological

**Table 1** Laboratory examinations

Complete blood count	Reference range		
White blood cells	3000-9700	4000	/ $\mu$ L
Neutrophils	36.6-79.9	72.8	%
Red blood cells	394-542	315	$\times 10^6$ / $\mu$ L
Hemoglobin	13.1-17.6	9.7	g/dL
Hematocrit	38.1-50.8	29.2	%
Mean corpuscular volume	84.6-100.6	92.7	fl
Mean corpuscular hemoglobin	28.0-34.6	30.8	pg
Mean corpuscular hemoglobin concentration	31.6-36.0	33.2	%
Platelets	12.4-30.5	14.9	$\times 10^4$ / $\mu$ L
Biochemical	Reference range		
AST	12-35	21	IU/L
ALT	6-40	9	IU/L
Total bilirubin	0.1-1.2	1.2	mg/dL
Lactate dehydrogenase	119-229	344	IU/L
Total protein	6.4-8.3	8.7	g/dL
Albumin	3.8-5.2	2.6	g/dL
Blood urea nitrogen	7.4-19.5	20	mg/dL
Creatine	0.5-1.2	0.67	mg/dL
Sodium	134-147	133	mEq/L
Potassium	3.4-4.8	4.1	mEq/L
Chloride	98-110	99	mEq/L
Calcium	8.3-10.4	7.4	mEq/L
Glucose	70-110	77	mg/L
C-reactive protein	0.0-0.3	2.217	mg/dL
Serum iron	50-170	144	$\mu$ g/mL
Ferritin	5-152	353	ng/mg
TIBC	270-460	199	$\mu$ g/mL
Haptoglobin	19-170	56	mg/dL
IgG	820-1740	3917	mg/dL
IgA	90-400	844	mg/dL
IgM	52-270	187	mg/dL
C3	65-135	20	mg/dL
C4	13-35	2	mg/dL
PR3-ANCA	0-3.5	1.2	U/mL
MPO-ANCA	0-3.5	0.1	U/mL
Folic Acid	3.89-26.8	3.7	ng/mg
sIL-2R	127-582	3412	U/mL
Direct coombs test		Positive	
Indirect coombs test		Negative	
Cryoglobulin		Negative	
Coagulation	Reference range		
PT-Sec	10.7-13.5	13.4	s
PT-%	77.8-130.0	71	%
PT-INR	0.89-1.12	1.17	
APTT	23.6-31.3	27.4	s
Infection			
CMV		IgG(+)/IgM(-)	
HSV		IgG(+)/IgM(-)	
HZV		IgG(+)/IgM(-)	
EBV		EBV-VCAIgG(+)/EBV-VCAIgM(-)/PCR(-)	
HIV 1+2 antibody		Negative	
Parvovirus B19		IgG(+)/IgM(-)	

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; TIBC: Total iron binding capacity; CMV: Cytomegalovirus; HSV: Herpes simplex virus; EBV: Epstein-Barr virus; HIV: Human immunodeficiency virus; APTT: Activated partial thromboplastin time; PT-INR: Prothrombin time-international standardized ratio.

findings of AITL cutaneous lesions can be quite variable<sup>[3]</sup>. Martel *et al*<sup>[3]</sup> described several histological findings of AITL, such as vasculitis without lymphocyte cytological atypia. Palpable purpura of our patient can also be one of the manifestations of lymphoma because there are no other special reasons for it.

If AITL was suspected, immunohistological studies might help; some immunological markers, such as CXCL13, PD-1, Bcl-6, and CD10, are known to be seen in AITL<sup>[1,2]</sup>. As a matter of course, lymph node biopsy is the most important tool for diagnosis. Although immunohistological studies of our case did not show any of these markers, except for CD10, we diagnosed AITL owing to its characteristic pathological findings, namely, high endothelial cell venules and follicular dendritic cells<sup>[1]</sup>. In addition, this patient was diagnosed with PRCA. The following criteria are used to diagnose PRCA: Normocytic normochromic anemia, absolute reticulocyte count < 10000/ $\mu$ L (or reticulocyte percentage < 0.5%), normal white blood cell and platelet counts, in the absence of concurrent disorder, normocellular bone, with erythroblasts total < 1%, no significant abnormalities in the myeloid, lymphocytic, or megakaryocyte lineages. Meeting all of these criteria results in a diagnosis of PRCA and our patient met all of them<sup>[4]</sup>.

Patients with lymphoma appear to have an increased risk of various autoimmune conditions, both hematological and non-hematological<sup>[5]</sup>. Among them, AITL is often accompanied by various immunological and hematological diseases, such as autoimmune hemolytic anemia (AIHA), vasculitis, and autoimmune thyroid disease<sup>[6]</sup>. This may be associated with the fact that AITL is thought to arise from CD4+ T-cells, which play an important role in the adaptive immune system, especially within the germinal centers<sup>[7]</sup>. Clonal rearrangements of T-cell receptor genes have already been demonstrated in most cases of AITL<sup>[7]</sup>. However, previous reports suggested that not only disturbance of the T cellular immunity but also proliferation of B cells contribute to the histologic and clinical picture in most cases<sup>[7]</sup>. One study showed that neoplastic T cells may promote antibody production by B-cells through excessive cytokine release. They demonstrated that the immune system in AITL is substantially activated, and an array of cytokines, such as interferon gamma, interleukin (IL)-6, IL-12, and tumor necrosis factor-alpha, are upregulated<sup>[8]</sup>. Because of this immune system dysregulation, we suppose that small amounts of antigens are sufficient to initiate an inflammatory reaction<sup>[8]</sup>. Multiple interactions among T-cell, B-cells, and multiple cytokines would contribute to the abnormal immune reaction in AITL.

PRCA, an autoimmune disorder resulting in isolated depletion of the erythroid series, has been reported in association with AITL, but it is extremely rare<sup>[6,9]</sup>. A PubMed search yielded just a few additional reported cases of PRCA associated with AITL and they are summarized in Table 2 (10 reports were found, but 3 were excluded due to lack of availability of the full-text article). Interestingly, previous reports have demonstrated that almost all patients showed a positive direct Coombs test<sup>[6]</sup>, which suggests an autoreactive antibody role<sup>[9]</sup>; this coincides with the positive test result found in our patient. In this case, a coexisting AIHA should be considered because of the severe anemia and positive direct Coombs test. However, we do not think that the patient has AIHA, based on the clinical findings: First, there was no evidence of hemolysis, such as jaundice, splenomegaly, elevated levels of indirect bilirubin, and decreased levels of haptoglobin. Second, the peripheral blood smear findings were not consistent with those of AIHA. There was no evidence of hemolysis or microspherocytosis. Third, the patient's other clinical findings were not consistent with those of AIHA. For example, he showed a very low absolute reticulocyte count and near-complete absence of erythroblasts from an otherwise normal marrow. Those findings were inconsistent with AIHA. In patients with PRCA, cyclosporine A should be routinely prescribe, although we did not do so. Previous reports have suggested that PRCA associated with AITL is improved only with the treatment of AITL, which is chemotherapy<sup>[5,6,9]</sup>. Therefore, we started treatment with chemotherapy for AITL, but no direct treatment of PRCA. However, the chemotherapy was not sufficiently effective for this patient, for both AITL and PRCA. Further research is needed to investigate optimal treatment strategies for the management of these patients.

The pathogenesis remains uncertain because of the limited number of reported cases of PRCA with AITL<sup>[6,9]</sup>, although it is reasonable to assume the possibility of multifactorial pathogenic involvement. Previous reports have suggested that AITL might trigger autoimmune alterations that lead to PRCA<sup>[5]</sup>. Another study demonstrated that malignant B-cell clones might produce autoreactive antibodies

**Table 2** Summaries of previous case reports of pure red cell aplasia associated with angioimmunoblastic T-cell lymphoma

No.	Ref.	Age (yr)	Sex	Hemoglobin on admission	Reticulocytes on admission	Direct coombs test	Indirect coombs test	Treatment	Outcome (AITL)	Outcome (PRCA)	Other complications
1	Vitorino <i>et al</i> <sup>[10]</sup> , 2020	72	Female	2.6 g/dL	0.70%	Positive	Positive	Chemotherapy	Remission	Remission	None
2	Tao <i>et al</i> <sup>[6]</sup> , 2013	71	Female	5.0 g/dL	0.10%	NA	NA	Sequential therapy	NA	NA	none
3	Choi <i>et al</i> <sup>[11]</sup> , 2010	43	Female	6.9 g/dL	0.20%	Positive	Positive	Chemotherapy	Remission	Remission	None
4	Wang <i>et al</i> <sup>[12]</sup> , 2007	37	Male	NA	NA	Positive	Positive	Chemotherapy	"Give some effect to cure"	NA	Warm-type autoimmune hemolytic anemia
5	Mizobe <i>et al</i> <sup>[13]</sup> , 2005	71	Female	5.5 g/dL	1%	Positive	Positive	Chemotherapy	Remission	Remission	None
6	Tsujimura <i>et al</i> <sup>[14]</sup> , 1999	46	Male	7.8 g/dL	0%	NA	NA	Chemotherapy	NA	NA	None
7	Al Hilali <i>et al</i> <sup>[15]</sup> , 1983	79	Female	6.5 g/dL	Less than 1%	NA	NA	NA	NA	NA	None

NA: Not available; AITL: Angioimmunoblastic T-cell lymphoma; PRCA: Pure red cell aplasia.

against erythroid progenitors, and neoplastic T-cells might directly or indirectly inhibit the erythroid differentiation of hematopoietic stem cells<sup>[9]</sup>.

## CONCLUSION

Owing to its rarity and nonspecific symptoms, the diagnosis of AITL is often challenging. It is sometimes misdiagnosed as an infection or another hematological disease. Detailed and specific diagnostic investigations, including excisional biopsies of lymph nodes, may be useful. Furthermore, the etiopathogenesis of PRCA is of interest, because the mechanisms underlying lymphoma-associated PRCA have not yet been elucidated. Therefore, further case studies and laboratory-based research is necessary to ascertain the pathogenesis of PRCA in AITL.

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