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【 CASE REPORT 】

Pure Red Cell Aplasia in a Patient with Thymic Hyperplasia, Hypogammaglobulinemia and Adult T-cell Leukemia/Lymphoma

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Abstract:
Acquired pure red cell aplasia (PRCA), caused by thymic hyperplasia, is extremely rare. We herein report a previously healthy 41-year-old man who presented with severe anemia, lymphadenopathy, an upper mediastinal mass, and hypogammaglobulinemia. The patient was eventually diagnosed with PRCA and adult T-cell leukemia/lymphoma (ATLL). The mediastinal mass was pathologically diagnosed as thymic hyperplasia without clear ATLL invasion. Although his anemia improved rapidly after thymectomy, PRCA recurred approximately 500 days later and was accompanied by ATLL exacerbation. The findings in this patient suggest that the Good's syndrome-like symptoms (thymic hyperplasia and hypogammaglobulinemia) in this patient and PRCA may have been paraneoplastic syndromes caused by ATLL.

Key words: pure red cell aplasia, lymphoma, thymectomy, Good's syndrome, *STAT3*, paraneoplastic syndrome

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Introduction

Acquired pure red cell aplasia (PRCA) is a type of anemia caused by a selective defect in the proliferation and differentiation of erythroid progenitor cells and is characterized by a marked decrease in bone marrow erythroblasts. In addition, thymomas have been detected in 7-10% of patients with acquired PRCA (1). Secondary PRCA is frequently caused by thymomas and large granular lymphocytic leukemia (LGLL) but rarely by thymic hyperplasia.

T-LGLL and adult T-cell leukemia/lymphoma (ATLL) are both T-cell malignancies, although the majority of T-LGLLs arise from CD8 cells, and ATL is a CD4-positive malignancy. To date, there have been few reports of PRCA complications in patients with ATLL.

To our knowledge, only five patients with concurrent PRCA and thymic hyperplasia have been reported in the English literature (2-6). The present report describes a patient with ATLL and concurrent PRCA accompanied by Good's syndrome (GS) (7)-like symptoms, including thymic hyperplasia and hypogammaglobulinemia. Interestingly, the findings in this patient suggested two distinct PRCA onset patterns: thymic hyperplasia at the time of the PRCA diagnosis and ATLL exacerbation at the time of recurrence.

Case Report

A 41-year-old man was referred to our hospital with a 2-month history of a fever, night sweats, and swelling of the

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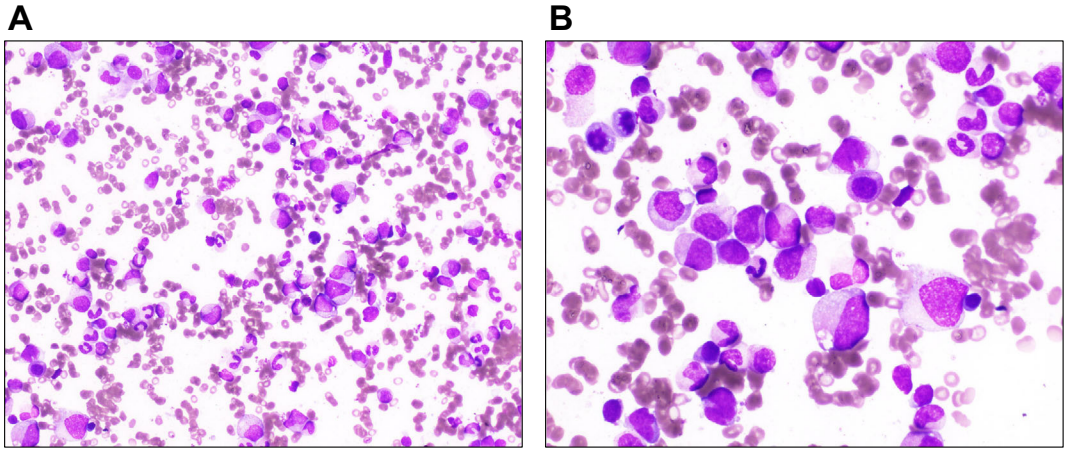

Figure 1. **Bone marrow morphology at the time of the PRCA diagnosis. (A and B) May-Grunwald Giemsa staining of the bone marrow aspirate (A: original magnification ×200, B: original magnification ×400).**

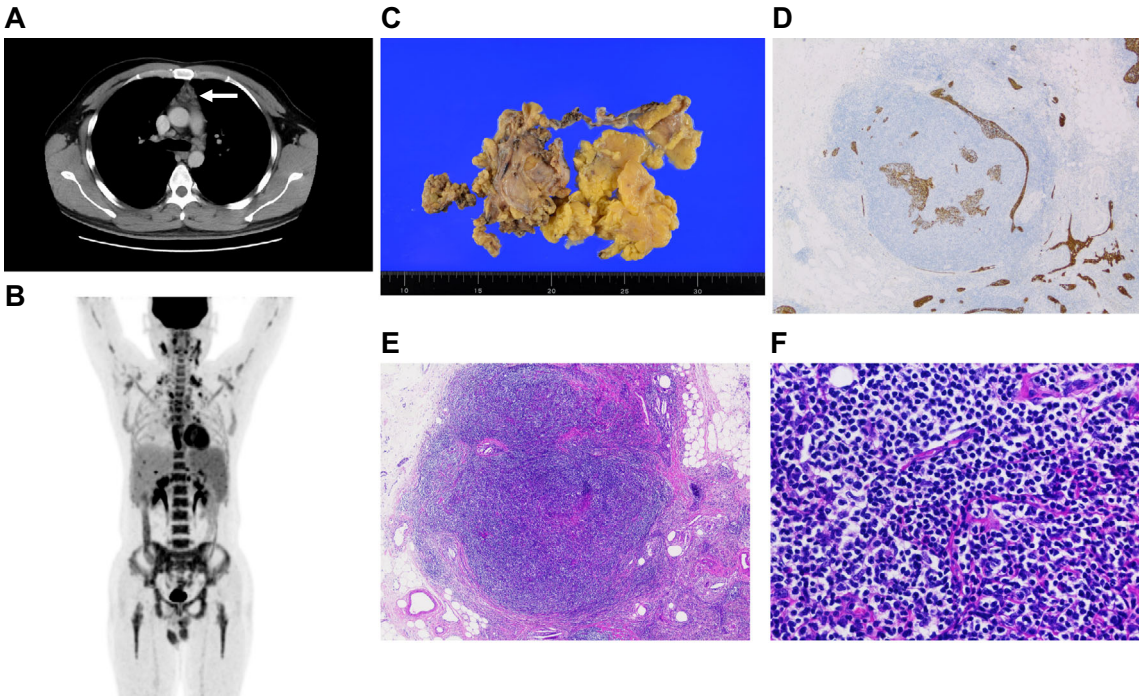

Figure 2. **The findings of thymic hyperplasia at the initial presentation. (A) CT scan showing anterior mediastinal soft tissue (arrow). (B) PET-CT scan showing the increased accumulation of ^{18}F-FDG in the bilateral cervical, supraclavicular fossa, mediastinal and paraaortic lymph nodes. A diffuse ^{18}F-FDG uptake in the bone marrow was also seen, but hyperaccumulation of FDG in the thymus was not observed. (C-F) Thymic gland showing reactive lymphoid follicles. (C) Macroscopic appearance of the resected thymus tissue. (D) Cytokeratin AE1/AE3 staining showing that the thymic epithelium was hyperplastic. (E, F) Hematoxylin and Eosin staining showing the diffuse infiltration of lymphocytes. The infiltrating lymphocytes were not noticeably atypical.**

left submandibular lymph node (LN). ATLL was suspected because he was seropositive for human T-cell leukemia virus type-1 (HTLV-1) and had elevated soluble interleukin-2 receptor levels. The patient's medical history was unremarkable. Laboratory tests showed severe normocytic anemia with a red blood cell (RBC) count of 2.27×10^9/L (reference $4.10\text{-}5.30\times10^9$/L), hemoglobin concentration of 63 g/L (reference 135-176 g/L), and reticulocyte count of 0.2% (reference 1.1-6.1%). His leukocyte count was 4.2×10^9/L (reference $3.9\text{-}9.8\times10^9$/L), including 84.5% neutrophils, 9% lymphocytes, 4.5% monocytes, and 1% abnormal lymphocytes. Serum vitamin B_{12} and folic acid concentrations were normal. Bone marrow (BM) aspiration showed severe erythroid hypoplasia with normal cells of myeloid and megakaryocytic lineages, consistent with PRCA (Fig. 1).

The patient tested negative for parvovirus IgM antibody,

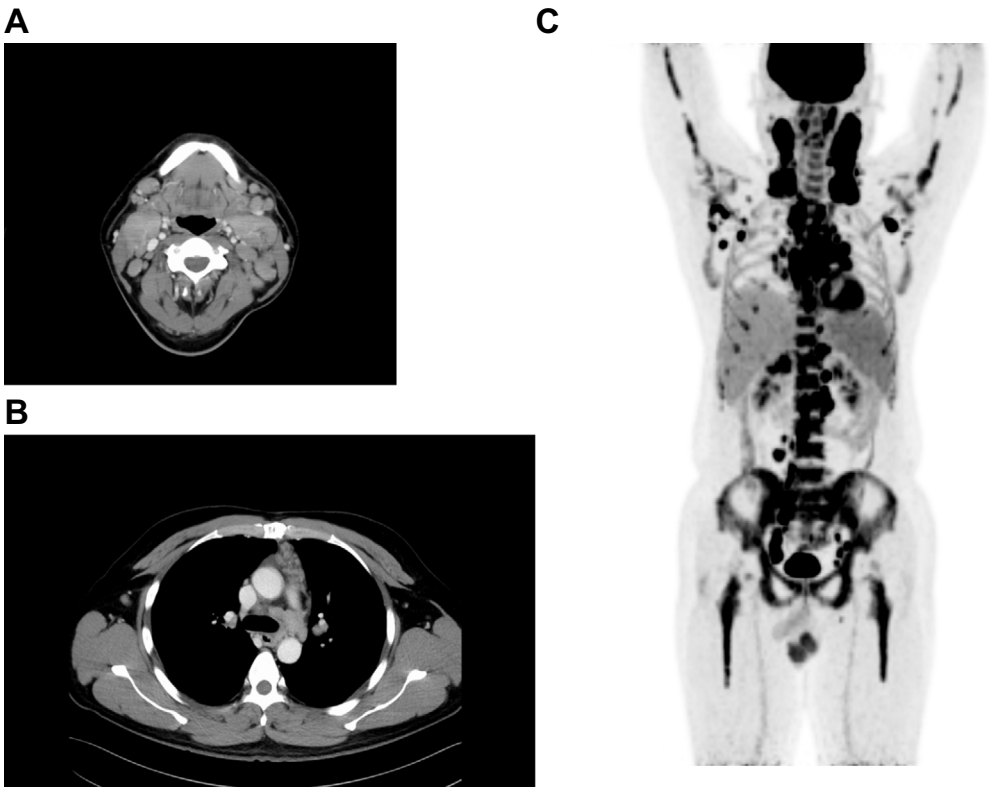

Figure 3. Imaging findings at ATLL relapse. (A, B) CT scan showing (A) multiple enlarged lymph nodes in the bilateral cervical region and (B) anterior mediastinal masses. (C) PET-CT scan showing an increased accumulation of ^{18}F-FDG in the bilateral cervical, supraclavicular fossa, mediastinal, paraaortic, and bilateral common iliac artery lymph nodes.

parvovirus B19 DNA, Epstein-Barr virus viral capsid antigen, anti-cytomegalovirus IgM antibody, anti-HIV antibody, anti-hepatitis C virus antibody, hepatitis B surface antigen, anti-nuclear antibodies, and anti-double-stranded DNA-IgG. The patient was also hypogammaglobulinemic, with IgG, IgA, and IgM concentrations of 7.32 g/L (reference, 8.60-16.40 g/L), 0.53 g/L (reference, 1.0-4.3 g/L), and 0.05 g/L (reference, 0.35-2.20 g/L), respectively. A flow cytometric analysis of the peripheral blood showed a small number of $CD3^{dim}CADM1^{+}CD7^{-}CD4^{+}$ cells, consistent with ATLL and 0.1% $CD19^{+}$ B cells. Chest radiography was normal, whereas computed tomography (CT) revealed an upper mediastinal mass corresponding to the thymus gland (Fig. 2A). ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET)/CT showed an increased ^{18}F-FDG accumulation in enlarged LNs in the bilateral cervical to supraclavicular fossa, mediastinum, and abdominal para-aortic regions but no FDG uptake by the thymus (Fig. 2B). Partial thymectomy showed hyperplastic thymic tissue with lymphoid follicles in adipose tissue. None of the serial sections examined showed indications of thymoma (Fig. 2C-F). An analysis of the resected thymus revealed no evidence of T-cell receptor rearrangement or monoclonal integration of HTLV-1 proviral DNA.

Immediately following thymectomy, the patient showed dramatic improvement in erythropoiesis. His Hb level increased from 66 g/L at the time of thymectomy to 118 g/L 17 days later with no RBC transfusion. A Southern blot analysis of an enlarged mediastinal LN biopsied at the time of thymectomy revealed monoclonal integration of HTLV-1 proviral DNA, resulting in a diagnosis of lymphoma-type ATLL. As multiple superficial lymphadenopathies disappeared spontaneously, and ATLL did not progress further, the patient was monitored without further treatment.

However, normocytic anemia reappeared 16 months later. BM aspiration showed severe erythroid lineage hypoplasia and proliferation of abnormal lymphocytes (40%), resulting in a diagnosis of recurrent PRCA and ATLL invasion. Multiple lymphadenopathies simultaneously emerged. CT showed enlarged cervical, axillary, mediastinal, and paraaortic LNs, and anterior mediastinal structures (Fig. 3A, B). PET-CT showed increased ^{18}F-FDG accumulation in enlarged LNs around the neck, supraclavicular fossa, mediastinum, abdominal aorta, common iliac arteries, and external iliac arteries. The lesion size and degree of ^{18}F-FDG accumulation were greater than those observed prior to thymectomy (Fig. 3C). Because PRCA recurrence due to thymic hyperplasia and acute exacerbation of ATLL were suspected, a second thymectomy procedure and mediastinal LN biopsy were performed to reexamine the anterior mediastinal structures and LN swelling. In contrast to the results after the initial thymectomy procedure, anemia did not improve after the second procedure. The resected tumor and mediastinal LN were histopathologically diagnosed as ATLL (Fig. 4).

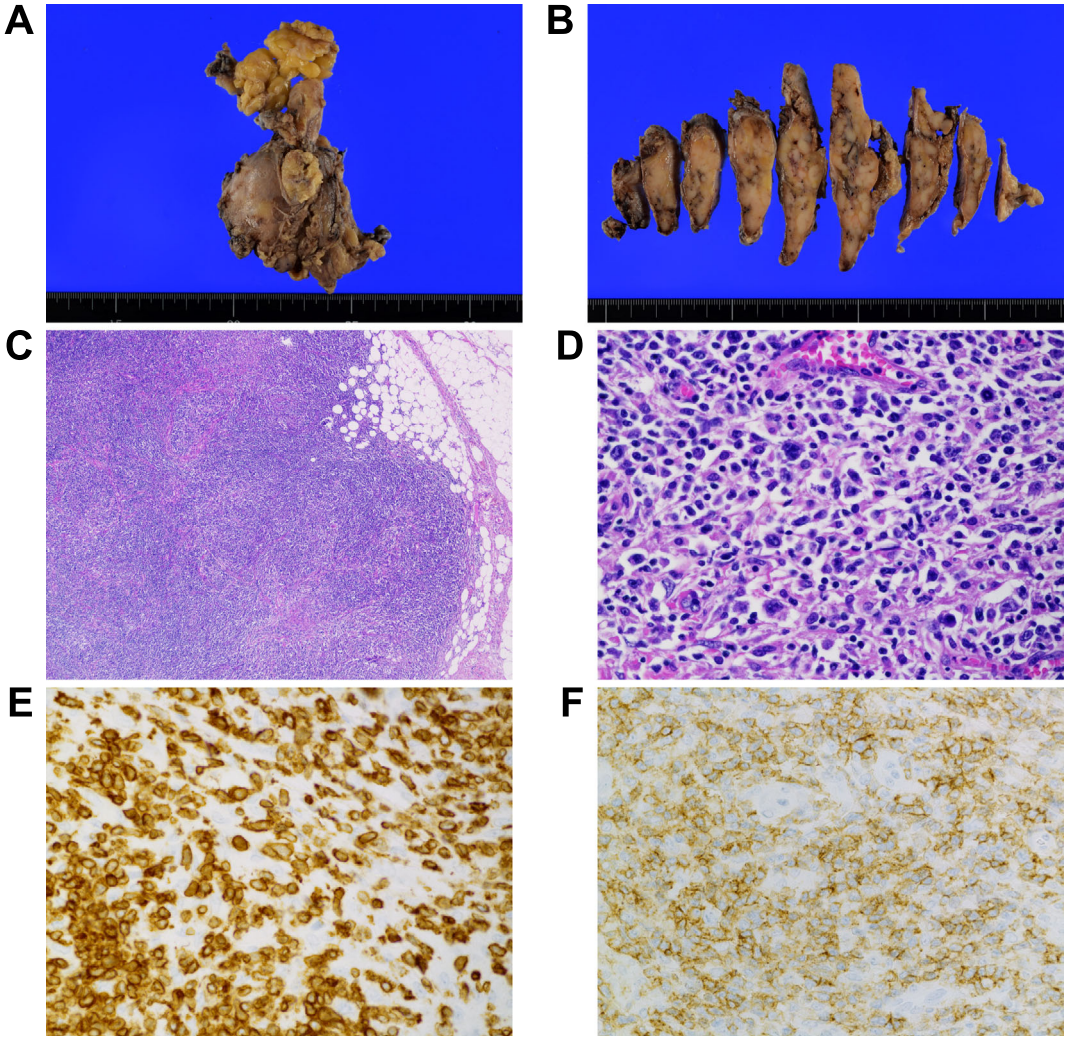

Figure 4. **The mediastinal mass at the time ATLL relapse. (A, B) Macroscopic appearance of the thymic mass. (C-F) Histopathological and immunohistochemical analyses of the thymic mass. (C and D) Hematoxylin and Eosin staining showing clusters of large, atypical lymphocytes. (E and F) Immunohistochemical analyses showing that the atypical lymphocytes were positive for (E) CD3 and (F) CD4.**

The patient was started on a modified LSG15 regimen consisting of vincristine, cyclophosphamide, doxorubicin, and prednisolone; doxorubicin, ranimustine, and prednisolone; and vindesine, etoposide, carboplatin, and prednisolone (8), with a complete response achieved after three courses of treatment.

Allogeneic peripheral blood stem cell transplantation was planned from a human leukocyte antigen-haploidentical younger sister, who was positive for anti-HTLV-1 antibodies but negative for proviral DNA monoclonal integration. The patient received a myeloablative conditioning regimen consisting of fludarabine (90 mg/m^2) plus total body irradiation (12 Gy), followed by transplantation with a G-CSF-mobilized, unmanipulated graft containing 3.23×10^6/kg CD34$^+$ cells. Prophylaxis for graft-versus-host disease (GVHD) consisted of tacrolimus, mycophenolate mofetil, and post-transplant cyclophosphamide. Neutrophil and platelet engraftment were prompt. The patient's course was complicated by cytomegalovirus antigenemia on day 19, stage 3 acute skin GVHD on day 21, and human herpes virus 6 encephalitis on day 30. He achieved complete chimerism and remission. The PRCA also improved gradually. Subsequently, ATLL relapsed with subcutaneous nodular lesions, but the patient was in remission with low-dose lenalidomide therapy (Fig. 5).

Discussion

The present report describes a patient with PRCA associated with thymic hyperplasia and hypogammaglobulinemia as well as concurrent ATLL following a mediastinal LN biopsy. The rapid improvement in anemia after thymectomy suggests that thymic hyperplasia may have played a significant role in PRCA at the time of the initial diagnosis. However, PRCA recurred with exacerbation of ATLL. A second operation showed a thymic mass invaded by ATLL cells, with PRCA not resolved until the engraftment of donor blood cells following allogeneic hematopoietic stem cell

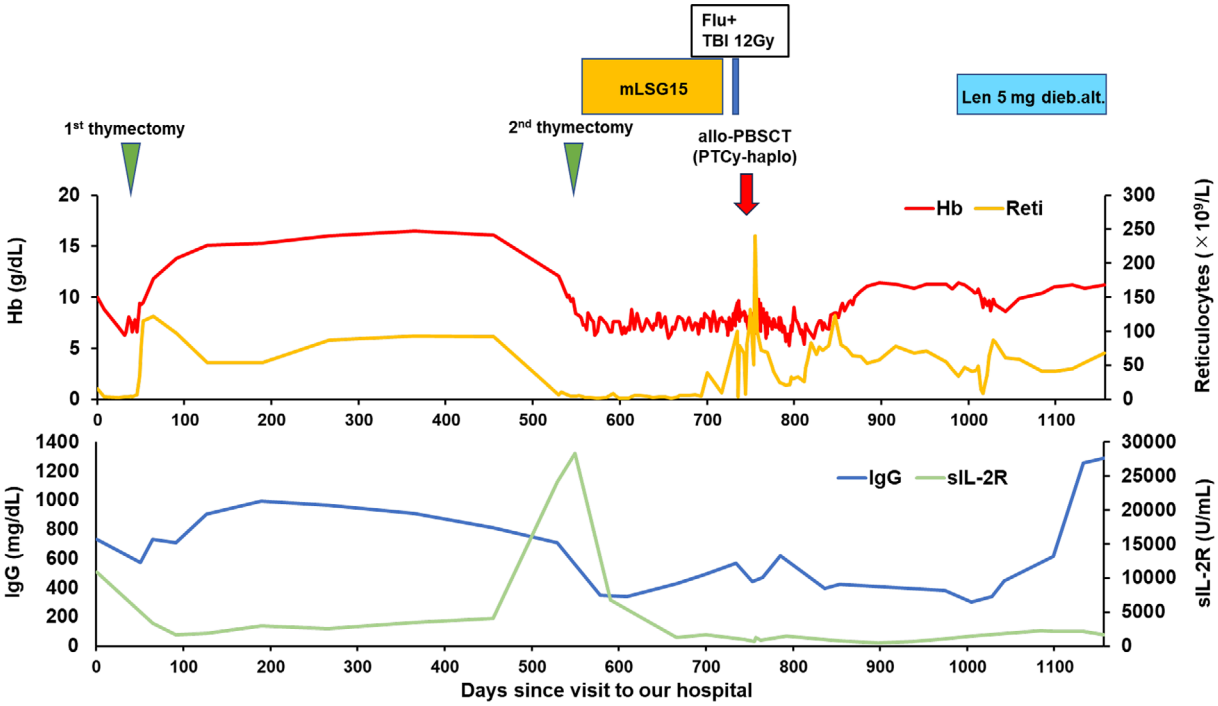

Figure 5. **Clinical course of the patient after the first visit to our hospital. Reticulocyte counts (Reti) and hemoglobin (Hb), immunoglobulin (IgG), and soluble interleukin-2 receptor (sIL-2R) concentrations throughout the clinical course are shown. mLSG: modified LSG15 regimen, consisting of vincristine, cyclophosphamide, doxorubicin, and prednisolone (VCAP); doxorubicin, ranimustine, and prednisolone (AMP); and vindesine, etoposide, carboplatin, and prednisolone (VECP). Flu: fludarabine, TBI: total body irradiation, allo-PBSCT: allogeneic peripheral blood stem cell transplantation, PTCy-haplo: HLA-haploidentical transplantation with high-dose cyclophosphamide, Len: lenalidomide, dieb.alt.: every other day**

Table. **Previous Studies Describing Patients with Pure Red Cell Aplasia Complicated by Thymic Hyperplasia.**

Case	Age	Sex	Comorbidity	Hypogamma globulinemia	Thymectomy	Immuno-suppressant	Other therapy	Outcome	Reference
1	28	F	End-stage renal failure	ND	(+)	-	Erythropoietin	Improved	2
2	35	F	(-)	ND	(+)	-	(-)	Improved	3
3	31	F	Myasthenia gravis	ND	(+)	Cyclosporine	(-)	Improved	4
4	27	F	(-)	ND	(+)	-	(-)	Improved	5
5	25	F	(-)	ND	(+)	Corticosteroid	(-)	Improved	6
6	41	M	ATLL	(+)	(+)	-	(-)	Improved	Present case

transplantation. Apparent BM invasion by ATLL cells may also influence PRCA relapse. At the same time, hypogammablobulinemia flared up, suggesting that GS like symptoms (thymic hyperplasia and hypogammaglobulinemia) and PRCA may have been paraneoplastic syndromes caused by ATLL.

The co-occurrence of PRCA with thymic hyperplasia is very rare, with only five case reports identified in PubMed (Table) (2-6). Interestingly, all previous patients were women. All patients underwent thymectomy, with anemia improving after thymectomy alone, except for one who had myasthenia gravis and was treated with cyclosporine (4). These previous case studies did not report whether hypogammaglobulinemia occurred. Although publication bias may favor reports of patients treated successfully, thymectomy was effective in patients with PRCA and concomitant thymic hyperplasia.

The patient was diagnosed with thymic hyperplasia and hypogammaglobulinemia. The co-occurrence of thymoma with hypogammaglobulinemia is known as GS (7), a condition rarely associated with PRCA (9). Although thymectomy does not improve hypogammaglobulinemia in patients with GS (10), the present patient showed increases in peripheral blood B cells and gammaglobulin levels after thymus removal.

Patients with lymphoma appear to be at an increased risk of autoimmune conditions, both hematological and non-hematological. Although several case series have described

patients with lymphoma-related PRCA, only one patient was reported to have PRCA with underlying ATLL (11-14). The patient was treated with cyclosporine for PRCA and achieved complete remission but died from ATLL progression (14). T-cell abnormalities are closely related to three types of PRCA: idiopathic, LGLL-associated, and thymoma-associated PRCA; however, many aspects of these conditions remain unknown (15). Recurrent somatic variants of the *signal transducer and activator of transcription 3* (*STAT 3*) gene have been frequently detected in patients with T-LGLL (16-19). Subsequent analyses have shown that *STAT3* variants are also found in patients with idiopathic or thymoma-associated PRCA that is not associated with LGLL (15, 17, 20). A comprehensive analysis of genomic abnormalities in a large cohort of patients with ATLL showed that *STAT3* variants are present in 21% of these patients (21). Furthermore, an analysis of the association between genetic alterations and disease phenotypes showed that *STAT3* variants are significantly more common in patients with indolent ATLL (22). Although a mutational analysis of the present patient was not performed, it would be interesting to determine whether *STAT3* variants were present in similar patients. Fujishima et al. analyzed myeloid neoplasm-associated genes in 38 PRCA cases and identified gene mutations such as *TET2* and *DNMT3A* in 29% of cases (23). These findings are suggestive of clonal hematopoiesis, and further investigation is required to determine if there is an association between these mutations and the clinical presentation of PRCA.

This report describes the clinical course of a patient diagnosed with ATLL, PRCA, thymic hyperplasia, and hypogammaglobulinemia. Effective chemotherapy against underlying lymphoma has been reported to improve anemia in patients with malignant lymphomas and concurrent PRCA (13). Anemia in the present patient improved promptly following thymectomy alone, and chemotherapy was not necessary. Spontaneous remission of ATLL after the first thymectomy procedure may also have resulted in improvement of anemia. Detailed pathological analyses, including genetic analyses, of additional patients are required.

Informed consent was obtained from the patient for publication of this case report.

The authors state that they have no Conflict of Interest (COI).

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