CASE REPORT

Severe pulmonary arterial hypertension as a predominant manifestation of angioimmunoblastic T-cell lymphoma: a case report

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Abstract

Angioimmunoblastic T-cell lymphoma is a rare and unique disease with peculiar clinical features among malignant lymphomas. We report here a case of severe pulmonary arterial hypertension appearing as the main manifestation of angioimmunoblastic T-cell lymphoma in a 55-year-old woman. The patient was treated with the THP-COP regimen, consisting of pirarubicin, cyclophosphamide, vincristine, and prednisolone for 1 cycle, followed by the CHOP regimen, including doxorubicin instead of pirarubicin, for 5 cycles. Soon after the initiation of chemotherapy, all the patient's symptoms and abnormal findings, including an elevated pulmonary artery pressure, completely disappeared. As of 3 months after the end of therapy, the patient remains in complete remission. To our knowledge, this is the first report of pulmonary arterial hypertension secondary to angioimmunoblastic T-cell lymphoma.

Keywords

Pulmonary arterial hypertension, Angioimmunoblastic T-cell lymphoma, Peripheral T-cell lymphoma

1 Introduction

Angioimmunoblastic T-cell lymphoma (AITL) is a rare and aggressive neoplasm accounting for about 2% of all non-Hodgkin lymphoma but representing the most common subtype (15-20%) of peripheral T-cell lymphomas (PTCL) [1]. The clinical features are varied and include the sudden onset of constitutional symptoms, lymphadenopathy, hepatosplenomegaly, and various autoimmune phenomena, particularly hemolytic anemia and thrombocytopenia as well as polyclonal hypergammaglobulinemia [1]. Lung involvement can be observed on an X-ray image as diffuse patchy infiltrates or interstitial pneumonia in approximately 10% of cases [2]. This report describes the first case, to our knowledge, of AITL resulting in pulmonary hypertension.

2 Case report

A 55-year-old woman was admitted to the otorhinolaryngology department for tonsil swelling in March 2010. A tonsil biopsy showed no signs of malignancy; a careful follow-up was started at that time. In June, she complained of dyspnea, fatigue, and intermittent fever. One month later, a laboratory examination revealed slight anemia (hemoglobin, 11.7 g/dL)

and moderate thrombocytopenia (platelets, 70×10^9/L). In August, the patient visited our hospital complaining of a worsening of her symptoms of dyspnea and fatigue in addition to a low-grade fever. An initial physical examination demonstrated a body temperature of 37.6°C, a blood pressure of 115/61mmHg, a pulse of 107 regular beats per minute, and a respiratory rate of 32 breaths per minute. Moreover, the patient also had modest jugular turgescence, a loud pulmonary component of the second heart sound, moderate hepatosplenomegaly, and cervical lymph node swelling, but no pretibial edema.

Table 1. Laboratory findings

Hematology	Serum Chemistry		Coagulation		Others
	TP	7.7 g/dL			
	ALB	3.0 g/dL			
WBC 15,000 /μL	Glu	140 mg/dL			Ferritin1050 ng/mL
Band 16 %	BUN	17.7 mg/dL			Haptoglobin <10 mg/dL
Seg 56 %	Cre	0.60 mg/dL			sIL-2R 2270 U/mL
Mono 4 %	UA	8.4 mg/dL			IgG 2976 mg/dL
Lym 19 %	Na	137 mEq/L	PT	12.3 Sec	IgA 492 mg/dL
RBC 1.2×10^6/μL	K	4.0 mEq/L	APTT	27.8 Sec	IgM 64 mg/dL
Ery Blast 12 %	Cl	101 mEq/L	Fib	241 mg/dL	C3 64 mg/dL
Ret 9.2×10^4/μL	T-bil	1.7 mg/dL	D-dimer 2.6μg/mL		C4 9 mg/dL
Hb 3.8 g/dL	C-bil	0.4 mg/dL			D-Coombs （＋）
MCV 85.8 fL	AST	17 IU/L			I-Coombs （－）
MCH 31.4 pg	ALT	7 IU/L			ANA 40 times
MCHC 36.6 g/dL	LDH	704 IU/L			PAIgG 5880 ng/10^{7}cells
PLT 5.3×10^4/μL	ALP	248 IU/L			
	CK	34 IU/L			
	CRP	2.27 mg/dL			
	BNP	94.3 pg/mL			

As shown in Table 1, the laboratory data obtained upon admission revealed a severe decrease in the hemoglobin level and platelet count, together with a positive direct Coombs test result and an extremely elevated platelet-associated (PA) IgG level. These findings seemed to be compatible with the diagnostic criteria for immune-mediated hemolytic anemia and thrombocytopenia, or Evans syndrome. Moreover, markedly elevated levels of LDH and soluble interleukin-2 receptor suggested the existence of a malignant lymphoma. A chest radiography revealed cardiomegaly with moderate pulmonary congestion (Figure 1A), and whole-body computed tomography (CT) scans showed multiple lymph node swellings in the cervical, pulmonary hilar, bronchial, axillary and para-abdominal aorta regions, with prominent hepatosplenomegaly (Figure 1B). A scintigraphy examination demonstrated the accumulation of gallium, particularly in the cervical and mediastinal locations (Figure 1C). Pulmonary infiltrates and malignant lung lesions were not observed on chest radiographs and CT scans or a whole-body gallium scintigraphy scan. The examination of bone marrow aspirate and biopsy specimens did not reveal malignant involvement. On day 2, an excisional biopsy of a right cervical lymph node was performed.

On day 8, she exhibited a worsening of her breathlessness and general swelling, resulting in a rapid decrease in her performance status. An arterial blood gas test while the patient was breathing room air demonstrated hypoxemia with an oxygen tension of 63mmHg, a carbon dioxide tension of 34mmHg, and a pH of 7.419. A chest radiograph demonstrated further enlargement of the cardiac silhouette sign, compared with that observed upon admission, and an echocardiographic examination showed a severe increase in the right-side pressure, with a pulmonary arterial systolic pressure of approximately 107mmHg, although the atrial and ventricular cavities were normal in diameter. The patient was diagnosed as having pulmonary arterial hypertension (PAH). No proximal pulmonary embolism was found on thoracic CT scans and lung perfusion scintigraphy (data not shown). Symptomatic treatments using a calcium channel blocker (Nifedipine) and a phosphodiesterase type 5 inhibitor (Sildenafil) [3] were not effective.

Figure 1. Radiographic and scintigraphic images obtained upon admission. Chest radiography shows cardiomegaly with moderate pulmonary congestion (A). CT scans show swollen lymph nodes in the pulmonary hilar and bronchial aorta regions (arrows), with prominent hepatosplenomegaly (B). Scintigraphy shows the accumulation of gallium, especially at cervical and mediastinal locations (C).
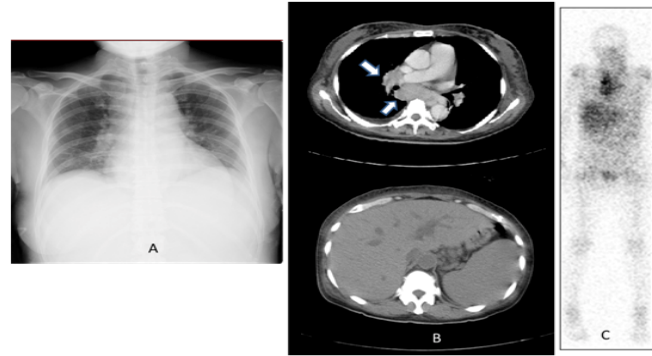
As shown in Figure 2A-E, a histopathological analysis of the cervical lymph node revealed AITL as evidenced by the presence of a diffuse proliferation pattern of atypical cells, in which neoplastic clear and follicular dendritic cells (FDCs) tended to be present around high endothelial venules and to express CD4 and CD10, and CD21, respectively. Furthermore, the atypical cells expressed VEGF (Figure 2F), and *In situ* hybridization for EBV EBER exhibited positive results in some large B-cells (Figure 2G). The karyotype was abnormal, with non-specific findings for AITL (data not shown).
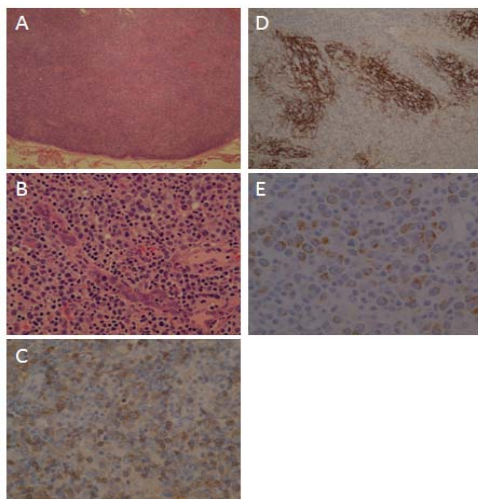

Figure 2. Histological staining of cervical lymph node. Lymph node involvement was characterized by the diffuse proliferation of atypical cells on hematoxylin-eosin sections (A; original magnification, ×100). Neoplastic clear cells and FDCs were present around high endothelial venules on hematoxylin-eosin sections (B; original magnification, ×200). The clear cells were positive for CD4 (C; original magnification, ×200), CD10 (D; original magnification, ×200) and VEGF (F; original magnification, ×200) immunostaining. FDCs were positive for CD21 (E; original magnification, ×100) immunostaining. In situ hybridization for EBV EBER exhibited positive results in some large B-cells (G; original magnification, ×200).

On day 14, oral prednisolone treatment (PSL; 30 mg/body) was started and was continued for 3 days; no significant improvement in the clinical findings was seen. The patient was next treated with the THP-COP regimen, consisting of pirarubicin (THP; 30 mg/m^2 [50 mg] for 1 day), cyclophosphamide (CTX; 500 mg/m^2 [800 mg] for 1 day), vincristine (VCR; 1 mg/m^2 [1.6 mg] for 1 day), and PSL (100 mg/body for 5 days) for 1 cycle, followed by the CHOP regimen (750 mg/m^2 [1100 mg] CTX and 1.4 mg/m^2 [2 mg] VCR for 1 day, and 100 mg/body PSL for 5 days) for 1 cycle including doxorubicin (50 mg/m^2 [74 mg] for 1 day) instead of THP for 2 cycles every 3 weeks (Figure 3). After these treatments, all the symptoms mentioned above improved rapidly, and the pulmonary artery pressure, platelet count, and LDH level normalized (Figure 3). Complete remission was achieved based on the disappearance of the swollen lymph nodes on CT scans and the normalization of the abnormal laboratory findings after 3 cycles of CHOP. As of 3 months after the completion of all 5 cycles of CHOP, the patient has remained in remission.
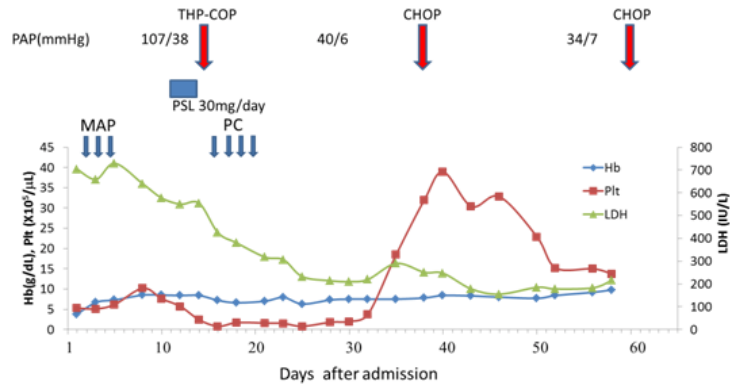
Figure 3. Clinical course of the patient. MAP: red blood infusion; PC: platelet infusion; Plt: platelet; Hb: hemoglobin; LDH: lactate dehydrogenase; PAP: pulmonary artery pressure; PSL: prednisolone; THP-COP: pirarubicin, cyclophosphamide, vincristine, and prednisolone; CHOP: CHOP regimen including doxorubicin instead of THP in THP-COP.

3 Discussion

Originally described in the 1970s as angioimmunoblastic lymphadenopathy with dysproteinemia [4], AITL was subsequently recognized as one of the most common forms of PTCL in the current World Health Organization classification of hematological malignancies based on the identification of clonal cytogenetic abnormalities and clonal T-cell receptor gene rearrangements. AITL is characterized by unique clinical and biological features. Many of the transient clinical features and laboratory abnormalities seen in the presently reported case, including fever, hepatosplenomegaly, Coombs-positive autoimmune hemolytic anemia, thrombocytopenia, and polyclonal hypergammaglobulinemia, were similar to those in previously reported cases [1, 2]. Lung involvement in AITL is less common, with a reported frequency of approximately 10% [2]. In the majority of cases, lung involvement presented as diffuse patchy infiltrates or interstitial lung disease, suggesting other pulmonary lymphoproliferations or malignancies [2]. However, no evidence of the involvement of PAH in an AITL case has been previously reported. PAH is a life-threatening disorder characterized by the progressive remodeling of the pulmonary vasculature, leading to an increase in pulmonary arterial pressure and pulmonary vascular resistance that often culminates in right ventricular failure [3]. The clinical characteristics of our patient, who exhibited hypoxemia, dyspnea, and an elevated pulmonary arterial pressure, were compatible with a diagnosis of PAH.

PAH has been reported in patients with several hematological diseases including myeloproliferative [5] and lymphoproliferative disorders [6] as well as intravascular lymphoma (IVL) [7, 8]. PAH is reportedly common among patients with myeloproliferative disorders or myelodysplastic syndromes, particularly among those with extremely elevated platelet counts. As a mechanism for the development of PAH in such patients, the stimulation of vascular endothelial cells by platelet-associated factors, such as platelet-derived serotonin, platelet-derived growth factor, or transforming growth factor β, has been suggested. Furthermore, tumor emboli in the pulmonary arterial vasculature in cases with IVL remain an underlying cause of PAH [7, 8]. In our case, no significant findings on imaging studies (CT and scintigraphy) were observed, excluding the presence of thromboemboli as a cause of the PAH.

Hyperviscosity syndrome, which is usually caused by immunoglobulin abnormalities, may also result in PAH [6]. Despite the presence of immunoglobulin abnormalities in this case, no clinical manifestations of hyperviscosity syndrome (including retinopathy or loss of vision, neurologic disorder, or rouleaux formation on peripheral smears) were observed, allowing hyperviscosity syndrome to be excluded as a possible cause of PAH in the present case.

PAH is also presumed to occur secondary to the extrinsic compression of the main pulmonary arteries by swollen mediastinal lymph nodes [9]. Although mediastinal lymph node swelling was observed in this case, no changes in the diameters of the pulmonary hilar arteries were observed on CT images after chemotherapy, compared with the initial state, enabling this possible cause to be ruled out.

Vasculitis can occur either as a primary condition or secondary to connective tissue diseases or malignancy [10]. Vasculitis occurring in association with systemic lupus erythematosus and Sjögren's syndrome, as well as primary necrotizing vasculitides, is known to lead to secondary PAH as a result of immunological abnormalities and to respond well to immunosuppressive agents, such as cyclophosphamide or corticosteroids [6, 10]. In this case, as immunological abnormalities including polyclonal hypergammaglobulinemia, Coombs-positive hemolytic anemia, and autoimmune thrombocytopenia were observed together with the occurrence of PAH and since all these problems were resolved after treatment with the CHOP regimen, which included cyclophosphamide and corticosteroids, the involvement of pulmonary vasculitis in the primary pathogenesis of AITL-associated PAH was suspected in the present case.

A recent investigation demonstrated that patients with PAH have an elevated serum VEGF level, which appears to stimulate endothelial cells and contributes to the pathogenesis of the disease [6]. Furthermore, in AITL, VEGF is also overexpressed by helper T-cells and FDCs and probably acts as an autocrine factor to promote vascular proliferation [2, 11]. In the present case, although the VEGF level in the patient's serum was not evaluated, VEGF expression in the tumor cells was revealed by a histopathological analysis (Figure 2F). Based on these observations, we hypothesized that an abnormal angiogenic response arising from an abnormal signaling pathway involving VEGF may have been associated with the primary pathogenesis of this disease.

In 50% of AITL cases, *in situ* hybridization for EBV EBER exhibited a positive pattern that was correlated with that of CD79a or CD20, consistent with EBV-associated B-cell proliferation [1]. Viral infection/reactivation is thought to occur probably as a consequence of the underlying immune dysfunction [12]. Therefore, in our case, the immune dysfunction symptoms, such as polyclonal hypergammaglobulinemia, Coombs-positive hemolytic anemia, and autoimmune thrombocytopenia, probably resulted from the EBV-related B-cell proliferation (Figure 2G).

This report describes the first case, to our knowledge, of PAH secondary to AITL. CHOP significantly alleviated the symptoms of AITL and PAH. Regardless of whether the symptoms of PAH resulted from pulmonary vasculitis or a high serum VEGF level, further studies are needed to elucidate the primary pathophysiological mechanisms of AITL-associated PAH.

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