

Case Study

Intravascular Large B-Cell Lymphoma Complicated by Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis that was Successfully Treated with Rituximab-Containing Chemotherapy

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A 64-year-old woman had suffered from painful livedo reticularis for 2 years and was referred to us due to fever, anasarca and paresthesia of the lower limbs. Serum proteinase-3-anti-neutrophil cytoplasmic antibody (ANCA) was positive. Abnormal lymphocytes were found in the cerebrospinal fluid and bone marrow. Skin biopsy revealed large atypical lymphoid cells with CD20 positivity lodged in the small vessels and neutrophilic infiltration into the arterial vascular wall with fibrinoid degeneration. A diagnosis of intravascular large B-cell lymphoma complicated by ANCA-associated vasculitis was made, and rituximab-containing chemotherapy followed by prednisolone was quite effective for both lymphoma and ANCA-associated vasculitis. [*J Clin Exp Hematop* 55(1) : 39-43, 2015]

Keywords: intravascular large B-cell lymphoma, anti-neutrophil cytoplasmic antibody-associated vasculitis, rituximab

INTRODUCTION

Intravascular large B-cell lymphoma (IVLBCL) is a rare entity of diffuse large B-cell lymphoma. IVLBCL cells proliferate within the microvasculature and infiltrate into the skin, liver, spleen, bone marrow, lungs and central nervous system.¹ Since lymphadenopathy is uncommon, establishing a diagnosis of IVLBCL can be difficult. Skin biopsy from affected or even normal skin often reveals clusters of large lymphoma cells in small to medium-sized vessels.²

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a systemic autoimmune small vessel vasculitis comprised of several different disorders, including granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with pol-

yangiitis (EGPA).³ Two types of ANCA are differentially detected in these syndromes. ANCA directed against proteinase 3 (PR3) is predominantly seen in GPA and less common in MPA. On the other hand, ANCA directed against myeloperoxidase (MPO) is seen in the majority of cases of MPA and in about 5-10% of cases of GPA. In EGPA, ANCA is usually the MPO type and is detected in 30-70% of cases.³

Hematological malignancies, including malignant lymphomas, are sometimes complicated by autoimmune disorders.⁴ Malignant lymphomas with ANCA positivity have been described, but only a small number are associated with vasculitis confirmed histologically.⁵

The present report describes a rare case of IVLBCL complicated by AAV that was successfully treated with rituximab-containing chemotherapy.

CASE REPORT

A 64-year-old woman had suffered from painful livedo reticularis for 2 years and was referred to our hospital due to general fatigue, fever and anasarca. She had gained 10 kg over the past six months and had painful livedo reticularis on her shoulders, abdomen, buttock and thighs. In terms of her consciousness, she was alert. She had paraplegia and paresthesia affecting her lower limbs.

Received: February 10, 2015

Revised : February 24, 2015

Accepted: March 19, 2015

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Laboratory data on admission demonstrated pancytopenia; hemoglobin level was 8.1 g/dL, white blood cell count was $3.06 \times 10^9/L$ and platelet count was $80 \times 10^9/L$. Serum levels of creatinine, lactate dehydrogenase, C-reactive protein, soluble interleukin-2 receptor and PR3-ANCA were 0.54 mg/dL (reference range, < 0.79 mg/dL), 624 U/L (reference range, 119-229 U/L), 7.33 mg/dL (reference range, < 0.10 mg/dL), 820.4 U/mL (reference range, 206-713 U/mL) and > 350 U/mL (reference range, < 3.5 U/mL), respectively. No hematuria or proteinuria was evident by urinalysis.

^{18}F -fluorodeoxy glucose-positron emission tomography/computed tomography revealed hotspots in the nasal mucosa, systemic bones and spleen. No lymphadenopathy was detected. Skin biopsy from livedo reticularis showed two different histological findings (Fig. 1A). The section in the derma showed neutrophilic infiltration into the arterial vaso-

lar wall and fibrinoid degeneration in small vessels (Fig. 1B), and the section in the subcutaneous fatty tissue showed large atypical lymphoid cells lodged in the lumina of small vessels (Fig. 1C). Those atypical cells were positive for CD20 (Fig. 1D) and negative for CD3, CD4, CD8 and CD56. Bone marrow biopsy demonstrated infiltration with atypical large lymphoid cells with CD20 positivity. These findings confirmed a diagnosis of IVLBCL complicated by AAV. The specimen from nasal mucosa showed chronic active inflammation with fibrous stroma without findings of malignancy or vasculitis.

The symptoms of weakness and paresthesia on her lower limbs gradually worsened, and she developed urinary retention on the 17th day of her hospitalization. Head and spinal magnetic resonance imaging revealed enhancement of the cauda equina, and cerebrospinal fluid examination showed

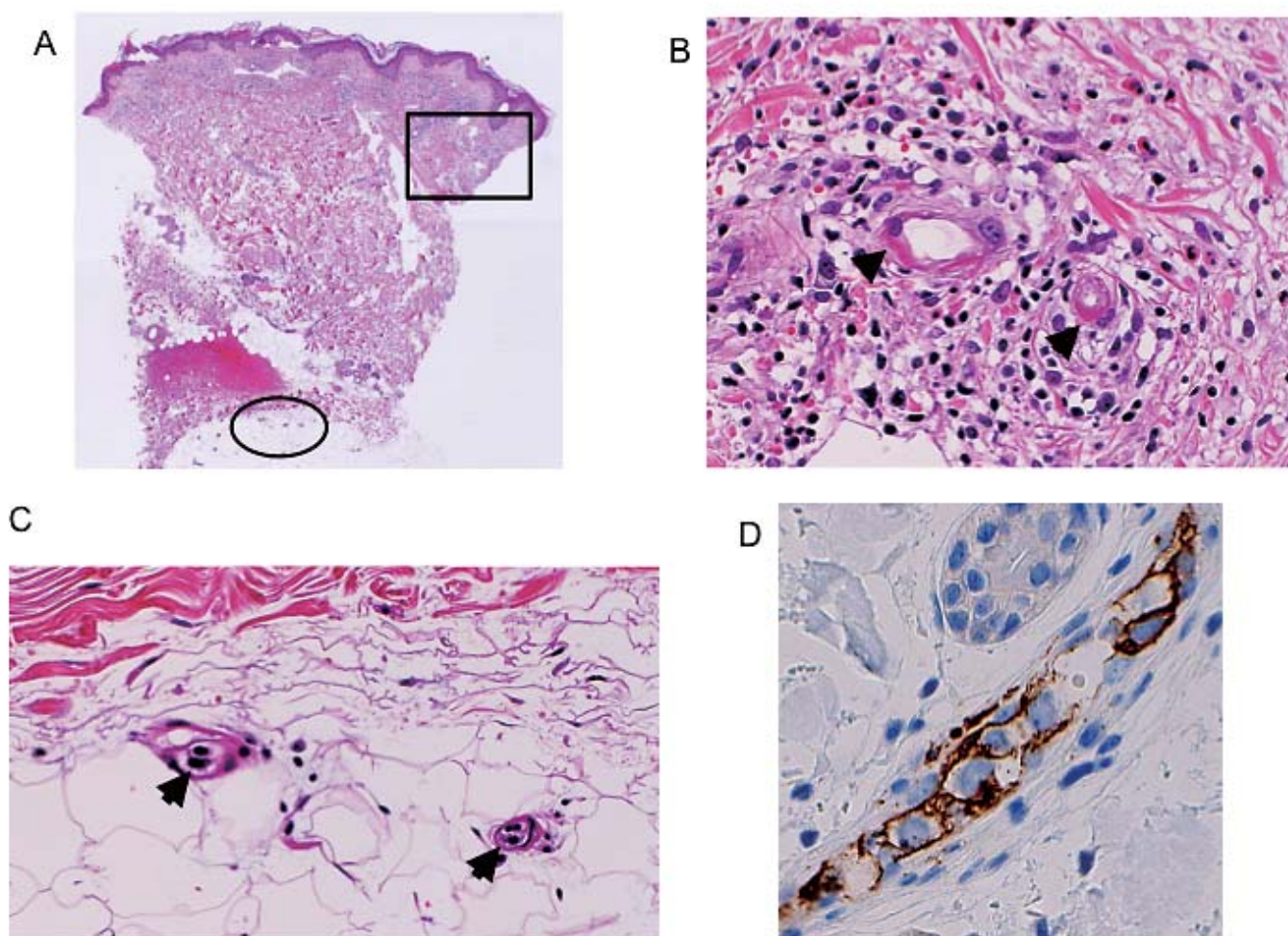


Fig. 1. Histology of the skin. (**1A**) The section shows vasculitis in the derma (*rectangle*) and intravascular large B-cell lymphoma in the subcutaneous fat tissue (*circle*). H&E stain, $\times 40$. (**1B**) The area in the rectangle. This section shows vasculitis with fibrinoid degeneration (*arrowheads*) in small vessels of the derma. H&E stain, $\times 200$. (**1C**) The area in the circle. This section shows large atypical lymphoid cells lodged in the lumina of small vessels in the subcutaneous fatty tissue (*arrowheads*). H&E stain, $\times 200$. (**1D**) CD20 immunostaining. These atypical cells are positive for CD20. $\times 400$.

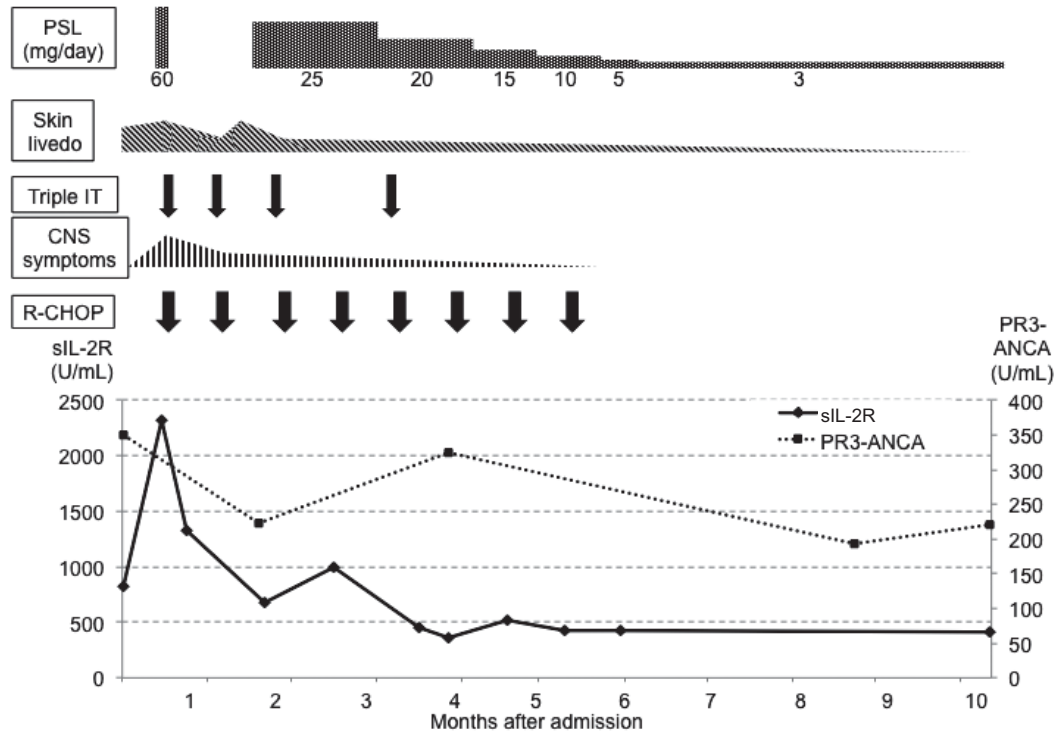


Fig. 2. Clinical course. PSL, prednisolone; triple IT, intrathecal injection of methotrexate, cytarabine and PSL; CNS, central nervous system; R-CHOP, rituximab, cyclophosphamide, vincristine, doxorubicin and PSL; sIL-2R, soluble interleukin-2 receptor; PR3-ANCA, proteinase 3-anti-neutrophil cytoplasmic antibody

infiltration with abnormal lymphocytes. Those findings suggested the involvement of the central nervous system with the lymphoma rather than AAV-associated symptoms.

The patient was immediately started on R-CHOP [rituximab, cyclophosphamide, vincristine, doxorubicin and prednisolone (PSL)] chemotherapy combined with intrathecal injection of methotrexate, cytarabine and PSL. The clinical course is shown in Fig. 2. Urinary retention gradually improved during the course of chemotherapy. Painful livedo reticularis improved soon after the first course of R-CHOP, but worsened after the second course. Therefore, we started oral PSL (0.5 mg/kg/day) to treat the vasculitis and subsequently gradually tapered this medication.

After the patient received eight courses of the R-CHOP chemotherapy and four courses of intrathecal therapy, she achieved complete remission of IVLBCL, as confirmed by the histology of bone marrow and cytology of spinal fluid. The symptoms of vasculitis were markedly improved. Her Birmingham vasculitis activity score improved from 9 points to 1 point. Serum level of sIL-2R was further elevated at 2,300 U/L just before the first R-CHOP course and gradually decreased to the reference range along with improvement in the lymphoma. Although the paraplegia remained, she has been able to walk with a cane. Her overall survival time is 28

months from the diagnosis of IVLBCL to the last follow-up.

DISCUSSION

The present report describes an extremely rare case of IVLBCL complicated by PR3-ANCA-positive AAV. Positivities of PR3-ANCA or MPO-ANCA have been reported in the context of hematological malignancies.⁵ However, only a small proportion of those ANCA-positive patients had symptoms of vasculitides.⁶⁻⁸ In a prospective study, 140 patients with lymphoid malignancy, including lymphoma, Waldenström macroglobulinemia, multiple myeloma, chronic lymphoid leukemia and hairy cell leukemia, were tested for ANCA.⁵ Three patients were positive for ANCA (two p-ANCA and one atypical ANCA), but no patients had AAV. One report described false positivity for PR3-ANCA and MPO-ANCA in a patient with a lymphoma with plasmacytoid differentiation.⁹ Increased serum immunoglobulin might cause false positive test results.

Malignant lymphomas are sometimes complicated by autoimmune diseases, but complication with ANCA-positive vasculitis is rarely seen.¹⁰⁻¹⁴ In the present case, the patient had sinusitis and the titer of PR3-ANCA was high, but the histology demonstrated small vessel vasculitis without granu-

Table 1. Summary of case reports of lymphoma complicated with ANCA-associated vasculitis

Age/Gender	Symptoms	Type of ANCA	Diagnosis of vasculitis	Type of lymphoma	Time between diagnosis	Treatment	Results (Cause of death)	Reference
56/M	Fever, Weight loss, Lymphadenopathy, Nevritis, Purpura	c-ANCA	c-ANCA positive vasculitis	Angioimmunoblastic T-cell lymphoma	Concurrent	CHOP, mPSL	Dead (Vasculitis)	6
65/M	Fever, Dyspnea, Purpura, Sinusitis	c-ANCA	c-ANCA positive vasculitis	Chronic lymphocytic leukemia	8 years	CHOP	Dead (Vasculitis)	6
43/M	Renal failure	PR3-ANCA	Wegener's granulomatosis	Hodgkin lymphoma	16 months	CPA, mPSL	Alive	15
nd	nd	p-ANCA	p-ANCA positive vasculitis	Chronic lymphocytic leukemia	Concurrent	CPA, PSL	nd	16
73/F	Myalgia, Weight loss, Skin rash	MPO-ANCA	MPA	B-cell lymphoma	2 months	CHOP, CPA, steroids	Dead (nd)	17
64/F	Livedo reticularis, Fever, Paraplegia	PR3-ANCA	Probable GPA	IVLBCL	Concurrent	R-CHOP, PSL	Alive	Our case

ANCA: anti-neutrophil antibody, M: male, F: female, MPO: myeloperoxidase, CPA: cyclophosphamide, mPSL: methyl prednisolone, IVLBCL: intravascular large B-cell lymphoma, PR3: proteinase 3, R-CHOP: rituximab, CPA, doxorubicin, vincristine, prednisolone, nd: not described MPO, myeloperoxidase: MPA, microscopic polyangiitis: GPA, granulomatosis with polyangiitis

lomatous lesion. We diagnosed PR3-ANCA-positive AAV according to the International Chapel Hill Consensus Conference (CHCC2012) nomenclature.¹⁵

There are only five such cases with a definitive diagnosis of vasculitis confirmed by biopsy reported in the literature (Table 1).^{6,16-18} Two cases were positive for MPO-ANCA or p-ANCA, and three cases were positive for PR3-ANCA or c-ANCA. Four cases were B-cell malignancies and one case was a T-cell malignancy. Two cases were diagnosed with concurrent lymphoma and AAV. In two cases, chronic lymphocytic leukemia and Hodgkin lymphoma were followed by AAV, suggesting that immune abnormality due to lymphoma might cause an autoimmune disorder.⁶ In the remaining case, AAV was followed by lymphoma, suggesting that an immunosuppressive state or the use of cytotoxic drugs, such as cyclophosphamide, might cause lymphoproliferative disorders.^{16,18} In the pathogenesis of AAV, ANCA activates neutrophils and vascular endothelial cells.¹⁹ Activated endothelial cells up-regulate adhesion molecules and we could speculate that lymphoma cells can easily aggregate in the microvasculature.

All five lymphoma cases complicated by AAV received steroids and chemotherapy, including cyclophosphamide. Three of four cases died of AAV-associated complications. Our patient is the only case that was treated with a rituximab-containing chemotherapy. Recent reports demonstrated that rituximab might be effective for the treatment of AAV.^{20,21} A randomized clinical trial suggested that rituximab therapy was not inferior to daily cyclophosphamide treatment for the induction of remission in severe AAV.²¹ In the present case, we treated IVLBCL with R-CHOP therapy, expecting that a rituximab- and cyclophosphamide-containing regimen would be effective for the management of AAV. Although we applied this treatment together with oral PSL for the vasculitis and the severity of AAV was mild, there might have been a synergistic effect between PSL and rituximab on the vasculitis.

In conclusion, this report describes an extremely rare case of IVLBCL complicated by PR3-ANCA-positive AAV. Skin biopsy including the subcutaneous lesion was useful to diagnose both AAV and IVLBCL. Although previous cases of

lymphoma complicated by AAV had poor outcomes, rituximab-containing chemotherapy was effective for the treatment of both IVLBCL and AAV.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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