J Clin Exp Hematopathol
Vol. 52, No. 3, Dec 2012

Case Study

CD5-Positive Diffuse Large B Cell Lymphoma Infiltrating the Central Nervous System Presenting Guillain-Barré-Like Syndrome after Chemotherapy

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An 83-year-old woman was admitted to our hospital with abdominal pain. Examination revealed mediastinal lymphoadenopathy, hepatosplenomegaly, and infiltration of abnormal cells into the bone marrow with hemophagocytosis, and CD5-positive diffuse large B cell lymphoma was diagnosed. Chemotherapy was administered and progressive weakness of the limbs, resembling a Guillain-Barré-like syndrome, subsequently appeared. Cerebrospinal fluid examination indicated lymphoma cell infiltration. Although immune globulin and steroid therapies were not effective, intrathecal injection of methotrexate, predonisolone, and cytarabine improved these symptoms. Subsequent to chemotherapy, cell surface antigen changes were observed in the cerebrospinal fluid relative to those in bone marrow. 〔*J Clin Exp Hematopathol 52(3) : 199-204, 2012*〕

Keywords: CD5-positive lymphoma, Guillain-Barré syndrome, diffuse large B cell lymphoma, Asian variant of IVL, cell surface marker

INTRODUCTION

Diffuse large B cell lymphoma (DLBCL) is the most common subtype of malignant lymphoma. Approximately 10% of DLBCL is $CD5^+$ DLBCL (*de novo* CD5-positive DLBCL), which has very poor prognosis. The CD5 molecule is a glycoprotein that is commonly expressed by T cells, sometimes expressed in B cell lymphomas, mantle cell lymphoma, and chronic lymphoid leukemia, including patients with Richter's transformation, and is rarely expressed in DLBCL.[1,2] Intravascular lymphomatosis (IVL) is also a rare form of DLBCL, and is characterized by predominant proliferation of neoplastic cells within vascular lumina, particularly capillaries.[2,3] The Asian variant of IVL (AIVL), in particular, is characterized by the development of hemophagocytic syndrome and disseminated intravascular coagulopathy.[4] *De novo* CD5-positive DLBCL and AIVL are thought to be different disease entities, where AIVL lymphoma cells are not restricted by immune surface markers but by B cell type, according to disease criteria ; the two have many common signs and symptoms and overlapping clinical characteristics.[1,3,4] For example, lymphadenopathy is seldom seen and each disease can result in disseminated intravascular coagulopathy, with both having very poor prognoses and occurring more frequently in the elderly.

Guillain-Barré syndrome (GBS) is an acute inflammatory polyneuropathy characterized by rapidly progressive, predominantly motor, impairments. Most cases are caused by an immune response after antecedent infection, such as with *Campylobacter jejuni*, *Cytomegalovirus*, or *Haemophilus influenza*.[5] However, a few cases associated with lymphoma, especially Hodgkin's disease,[6] have been reported. To the best of our knowledge, this case was the first report of *de novo* CD5-positive DLBCL where lymphoma cell invasion to the central nervous system was seen and presented with GBS-like symptoms.

Received: August 14, 2012
Revised : October 22, 2012
Accepted: November 3, 2012
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CASE REPORT

An 83-year-old woman was admitted to our hospital with complaints of dyspnea on exertion, abdominal pain, and facial edema. Past medical history included renal lithiasis at the age of 79. Physical examination at admission revealed a petite, elderly woman 145 cm in height and 33 kg in weight with a body temperature of 36.6℃ and blood pressure of 126/78

mmHg. Her performance status score was 3 by the Eastern Co-operative Oncology Group.[7] Conjunctivae were anemic but not icteric. Chest auscultation revealed normal respiratory sounds and a slightly rapid heart rate with no murmur. The liver was palpable approximately 5 cm below the right costal margin ; the spleen was not palpable. Superficial lymphadenopathy was not found. Neurological examination was unremarkable. Laboratory findings at admission were listed in Table 1. Bone marrow (BM) aspirate examination revealed infiltration by abnormal cells with vacuoles and histopathological findings indicating B cell lymphoma with hemophagocytosis (Table 2 and Figs. 1&2). Flow cytometric analysis of abnormal BM cells revealed $CD5^+$, $CD19^+$, $CD20^+$, $CD23^-$, and surface membrane immunoglobulin-κ chain (SmIg-κ)$^+$ cells (Table 2). An abdominal computed tomography scan disclosed a few enlarged mediastinal lymph nodes, hepatomegaly, and mild splenomegaly.

A diagnosis of DLBCL was given, and treatment with age-appropriate, reduced-dose CHOP (**c**yclophosphamide, hydroxydaunorubicin, vincristine and predonisolone) was initiated ; chemotherapy dosage considerations also included the patient's performance status and concern about the precipitation of tumor lysis syndrome. Subsequently, the platelet count and general condition improved and rituximab (R-CHOP) was administered.

After these treatments, symmetrical paralysis of the lower limbs with paresthesia ensued with subsequent progression to the upper body ; bilateral arm weakness and facial nerve

Table 1. Laboratory data and spinal fluid analysis at admission

RBC	$507 \times 10^4/\mu L$	AST	167 IU/L	PT	13.8 s			
Hematocrit	46.6%	ALT	117 IU/L	PT activity	79%			
Hemoglobin	15.0 g/dL	ALP	622 IU/L	PT-INR	1.15			
Platelet	$15.1 \times 10^4/\mu L$	γGTP	76 IU/L	APTT	32.1 sec			
WBC	26,300/μL	LDH	2,228 IU/L	Fibrinogen	114 mg/dL			
Neutrophil	71.0%	T-Bil	0.85 mg/dL					
Lymphocyte	17.0%	BUN	56.1 mg/dL	**Spinal fluid**				
Monocyte	3.0%	Cre	1.08 mg/dL	Date	5/18	5/25	5/31	6/18
Eosinophil	0%	CRP	14.65 mg/dL	Cells (cells/3 HPF)	85/3	65/3	28/3	4/3
Basophil	0%	Na	139 mEq/L	Neutrophil	6/3	1/3	0/3	0/3
Metamyelocyte	1.0%	K	5.4 mEq/L	Monocyte	79/3	64/3	28/3	4/3
Promyelocyte	1.0%	Cl	95 mEq/L	Protein (mg/dL)	177.2	270.4	45.7	51.4
Abnormal cell	7.0%			Glucose (mg/dL)	31	11	59	62
Anti-ganglioside antibody (−)		Anti-acetylcholine receptor antibody (−)						

RBC, red blood cell count ; WBC, white blood cell count ; PT, prothrombin time ; PT-INR, prothrombin time-international normalized ratio ; APTT, activated partial thromboplastin time ; HPF, high power field

Table 2. Myelogram and chromosomal analysis before chemotherapy, and lymphoma cell surface markers before and after chemotherapy

Myelogram		**Cell surface marker (Bone marrow)**		**Cell surface marker (Spinal fluid)**	
Blast	1.0%	CD2	0%	CD2	7%
Promyelocyte	3.2%	CD3	0%	CD3	10%
Myel.ocyte	11.4%	CD4	0%	CD4	8%
Metamyelocyte	3.0%	CD5	87.0%	CD5	87.0%
Stab-cell	5.8%	CD7	1.0%	CD7	12.0%
Segmented cell	4.8%	CD8	0%	CD8	7.0%
Eosinophil	2.4%	CD10	30.0%	CD10	55.0%
Basophil	0.0%	CD19	86.0%	CD19	91.0%
Monocyte	0.4%	CD20	87.0%	CD20	88.0%
Lymphocyte	8.2%	CD23	0%	CD23	0%
Plasmacyte	0.6%	SmIg-K	9.0%	SmIg-K	0%
Erythrocyte	30.4%	SmIg-L	96.0%	SmIg-L	0%
Reticulumocyte	0.0%	CD11c	9.0%	CD11c	10.0%
Abnormal cell	28.6%	CD25	0%	CD25	59.0%
Megakaryocyte	62.0/μL	CD34	0%	CD34	0%
		CD56	0%	CD56	0%
Chromosomal abnormality : 46, X, del (X) (q24)[6]/46, XX[14]					

SmIg-K, surface membrane immunoglobulin-κ light chain ; SmIg-L, surface membrane immunoglobulin-λ light chain

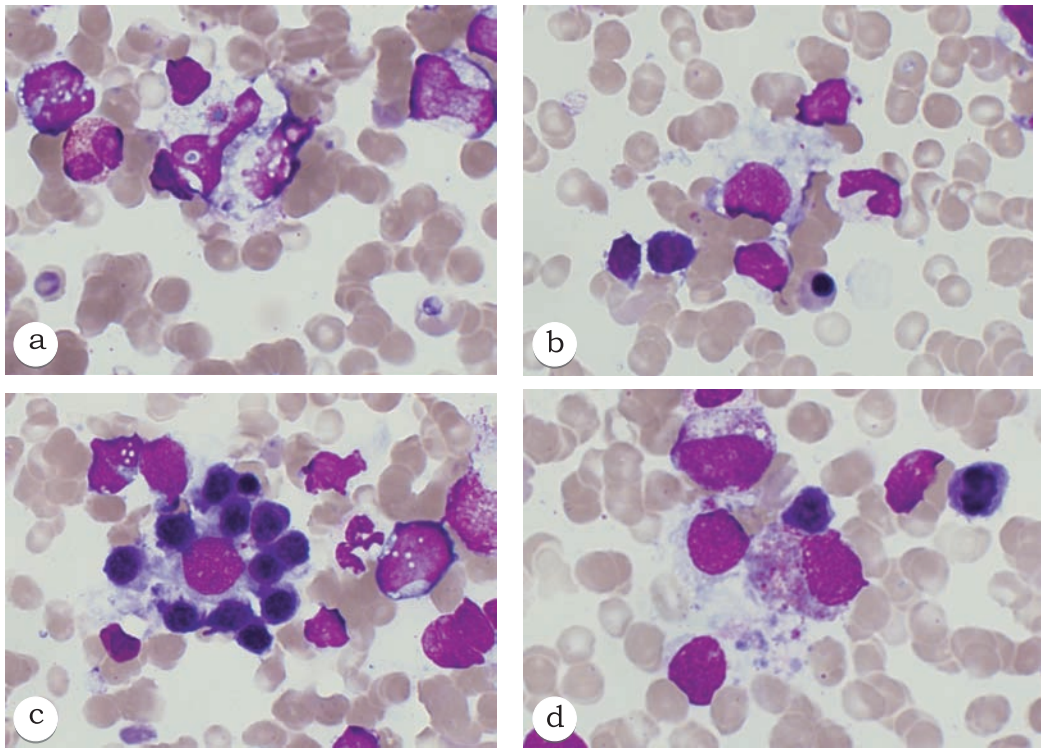

Fig. 1. May-Grünwald Giemsa staining of bone marrow aspirate. Hemophagocytosis by reticulum cells of neutrophils and platelets (*1a*), red blood cells (*1b*), erythroblasts (*1c*), and platelets (*1d*).

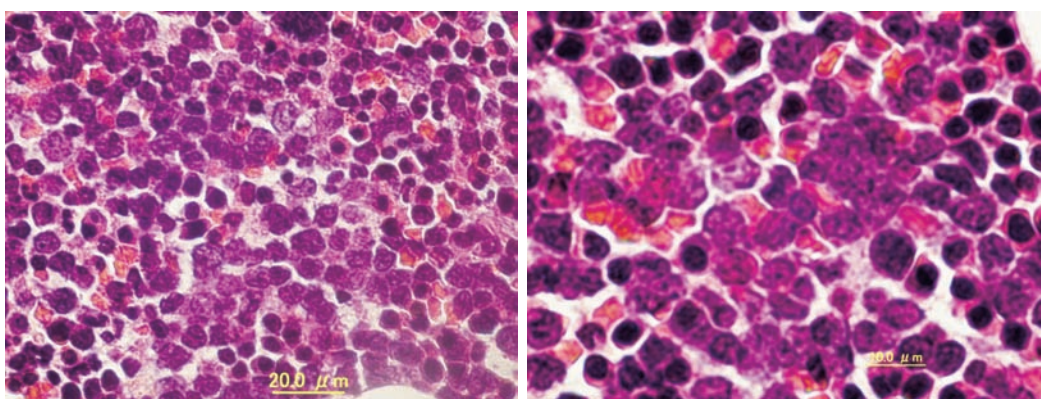

Fig. 2. Hematoxylin & eosin staining of bone marrow aspirate. Abnormal cells with large and irregular shaped nuclei and scanty cytoplasm occupied about 30% of nucleated blood cells. These cells were mostly $CD20^{+}$ and naphthol AS-D chloroacetate esterase stain $(nASD)^{-}$ by immunostaining (data not shown).

palsy were observed a few days later. This acute progression was reminiscent of GBS, so the cerebrospinal fluid (CSF) was examined ; increased protein and a small increase in mononuclear cells were found. Since this result could not rule out GBS, immune globulin and steroid pulse therapies were administrated. However, cytological examination of the CSF revealed lymphoma cells resembling the abnormal cells in the BM ; flow cytometric analysis revealed that cells floating in the CSF were similar to cells in the BM, except they were SmIg-λ^{-}. Cytarabine, predonisolone, and methotrexate were administered 3 times by intrathecal injection. Subsequently, facial paralysis improved and counts of cells infiltrating the CSF decreased. However, in an immune compromised state, infection with cytomegalovirus (diagnosed by cytomegalovi-

rus antigenemia) ensued, melena and respiratory failure developed, and death occurred on day 104 of hospitalization (Fig. 3).

DISCUSSION

Examination of aspirated BM led to the diagnosis of DLBCL, and flow cytometry indicated that tumor cells were $CD5^+$. Although immunohistochemistry of the BM clot section revealed quite a few cyclin $D1^+$ lymphoma cells, most cells were negative (data not shown), and since the chromosomal abnormality was 46, X, del (X) (q24) rather than t(11;14), a diagnosis of mantle cell lymphoma[2] was excluded. These results, along with CD23 negativity and the absence of a history of lymphocytosis excluded a chronic lymphoid leukemia diagnosis.[7,8] Considered together, these findings indicated that this case was *de novo* $CD5^+$ DLBCL. Although hemophagocytosis was seen on the BM smear and laboratory findings indicated the progression of thrombocytopenia with coagulopathy, the two disease entities could not be definitely distinguished.

Neurological findings (development of rapid progressions in limb weakness) favored a diagnosis of GBS. When encountering GBS-like symptoms during chemotherapy for lymphoma, certain causes are usually considered, such as drug administration, especially vincristine[9,10] and methotrexate,[11] immune responses,[12-14] and paraneoplastic syndrome-like mechanisms without central nervous system invasion.[15-17] We reviewed non-Hodgkin's lymphomas coexisting with Guillain-Barré (-like) syndrome in the past 10 years (Table 3). Most cases developed GBS after chemotherapy and the administration of rituximab, and were responsive to treatment with intravenous immunoglobulin. It cannot be denied that these therapies influenced the immune system. However, in another two IVL cases, neurological findings occurred at the onset of lymphoma and these cases did not respond to immunoglobulin. This may indicate the direct infiltration of IVL cells to peripheral nerves or feeding vessels. In any case, GBS due to the infiltration of lymphoma cells in the CSF was not seen.[9,14-16,18-22] In our DLBCL case, which was difficult to distinguish from IVL, GBS-like symptoms were also seen after chemotherapy. However, the accumulated dosage of vincristine was not more than 4 mg,[23] antecedent symptoms, such as diarrhea due to *Campylobacter jejuni*, were not seen, and CSF examination indicated lymphoma cell invasion. These may have infiltrated the central nerve, but not peripheral nerves because symptoms improved with intrathecal (into the central nerve) injection of anti-tumor drugs. Interestingly, flow cytometric analysis of invading CSF lymphoma cells revealed a loss in SmIg-λ after chemotherapy ; the cause of

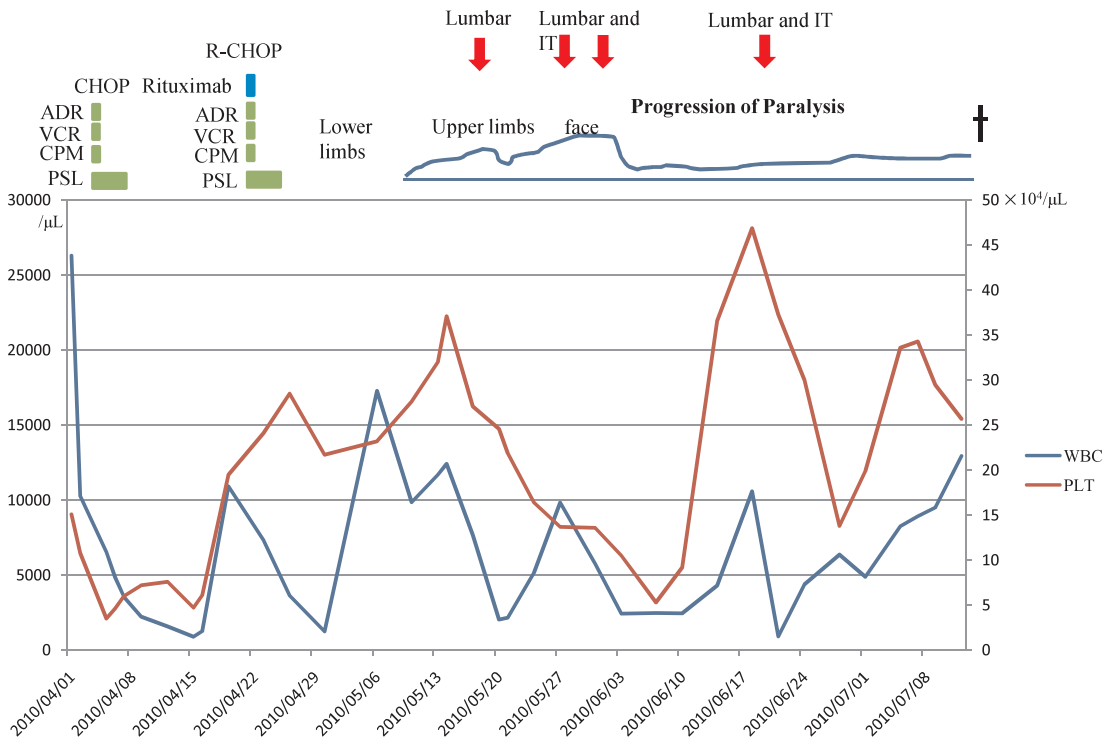

Fig. 3. Clinical course during hospitalization. ADR, Adriamycin ; VCR, Vincristine ; CPM, Cyclophosphamide ; PSL, Predonisolone ; Lumbar, Lumbar puncture ; IT, Intrathecal injection ; Lumbar, Lumbar puncture

Table 3. Non-Hodgkin's lymphoma cases coexisting with Guillain-Barré syndrome in recent years

Case[ref]	Type of lymphoma	Age	Sex	Onset	CSF invasion	Treatment	Effect
1[18]	B-NHL	8	M	After chemotherapy (vincristine, dexamethasone, ifosphamide, cytosine arabinoside, etoposide)	negative	Intravenous immunoglobulin	Effective
2[14]	T/NK-cell NHL	70	F	After chemotherapy (CHOP : cyclophosphamide, doxorubicin, vincristine, prednisolone)	negative	No treatment and hospice	
3[19]	B-NHL	51	M	After chemotherapy (CHOP and R-CHOP : rituximab)	negative	Intravenous immunoglobulin, plasmapheresis, & methylpredonisolone	Effective
4[20]	B-NHL	57	M	After chemotherapy (CHOP, Promace-Cytabon, rituximab)	negative	Intravenous immunoglobulin	Effective
5[9]	Burkitt's lymphoma	36	F	After chemotherapy (CHOP)	negative	Intravenous immunoglobulin & plasmapheresis	Effective
6[15]	IVL	78	F	Symptoms at diagnosis	negative	Intravenous immunoglobulin	Ineffective
7[21]	T-NHL	21	F	After chemotherapy (vincristine, dexamethasone, daunorubicin, l-asparaginase, prednisolone)	negative	Intravenous immunoglobulin & plasmapheresis	Effective
8[16]	IVL	55	M	Symptoms at diagnosis	not examined	Intravenous immunoglobulin & steroids	Ineffective
9[22]	Burkitt's lymphoma	59	F	After chemotherapy (cyclophosphamide, epirubicin, vinblastine, etoposide, prednisone, methotrexate)	negative but positive at autopsy	No treatment	

CSF, Central nervous system ; B-NHL, B-cell non-Hodgkin's lymphoma ; T/NK-cell NHL, T-cell/natural killer cell non-Hodgkin's lymphoma ; IVL, Intravascular lymphomatosis ; T-NHL, T-cell Non-Hodgkin's lymphoma

this is not known. However, previous case reports detail $SmIg^+$ lymphoma cell invasion of the cerebrospinal space;[24,25] therefore, the lack of this marker may not be essential for infiltration. $SmIg^+$ cells may be changed in the CSF environment to $SmIg^-$ cells after invasion to the CSF. Further studies are required to examine this situation.

In summary, this is a case of *de novo* $CD5^+$ DLBCL in which GBS-like symptoms with meningeal involvement developed after 2 courses of lymphoma chemotherapy. When progressive limb paralysis occurs during the course of aggressive lymphoma, the possibility of lymphoma cell infiltration to the central nervous system should be considered, even if symptoms begin after chemotherapy is administered.

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