An Unusual Case of Multicentric Castleman's Disease, Complicated by Pleural Effusion

Shuhei NOZAWA, Masanori YASUO*, Hiroshi YAMAMOTO, Mineyuki HAMA
Kazunari TATEISHI, Atsuhito USHIKI and Masayuki HANAOKA
First Department of Internal Medicine, Shinshu University School of Medicine

A 72-year-old female with systemic lymphadenopathy was diagnosed with multicentric Castleman's disease (MCD), following a needle biopsy of her axillary lymph node. She experienced recurrent fever and a rash, and was then transferred to our respiratory department. She had fever and dyspnea with consolidation and pleural effusion on computed tomography (CT). Lung lesions are common but pleural effusion is an unusual symptom in Castleman's disease. We administered antibacterial agents but her condition worsened. Symptoms rapidly improved following administration of systemic corticosteroid, and the consolidation and pleural effusion also disappeared. We suggest that pleural effusion in Castleman's disease should be considered as a differential diagnosis for pleural effusion that is unresponsive to antibacterial treatment. *Shinshu Med J 65 : 51—56, 2017*

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I Introduction

Castleman's disease was first described by B. Castleman in 1956[1]. This disease is a polyclonal lymphoproliferative disorder, characterized by a tumor-forming lymphadenopathy. The cause of the disease is unknown, but an infectious etiology, including infections by hepatitis B virus (HBV), Epstein-Barr virus (EBV), human herpesvirus 8 (HHV8), or human immunodeficiency virus (HIV)[2], have all been suggested. Causal roles for abnormal immune responses, including immunopathy, and aberrant cytokine production, have also been proposed. Clinically, cases involving a single lymphadenopathy are defined as unicentric Castleman's disease (UCD), while those with multiple lymphadenopathy are defined as multicentric Castleman's disease (MCD)[3]. Patients with MCD generally present with fever and multiorgan disease. Pathologically, MCD is classified as either a hyaline vascular type (HV type), which comprises 90 % of cases, or as the plasma cell type (PC type), or a third variant, which is a mix of HV and PC. The HV pathologic variant is characterized by the growth of vascular endothelial cells and angioneogenesis ; the PC variant is typified by infiltration of plasma cells between lymphatic follicles[4]. The PC type is generally associated with multiple lymphadenopathy and generalized symptoms. Many MCD cases with pulmonary lesions were reported. In general the clinical features of MCD are mediastinal lymphadenopathy, hyperplasia of bronchovascular and interlobular septa, and cyst[5] ; however, pleural effusion is unusual.

Here we describe a case of a 72-year-old female diagnosed with MCD with pleural effusion that was difficult to distinguish from effusion associated with pneumonia who was successfully treated with corticosteroids.

II Case Report

A 72-year-old Japanese woman with multiple lymphadenopathy had been diagnosed with the PC variant of MCD following biopsy of her axillary lymph

* Corresponding author : Masanori Yasuo
First Department of Internal Medicine, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto, Nagano 390-8621, Japan
E-mail : yasumasa@shinshu-u.ac.jp

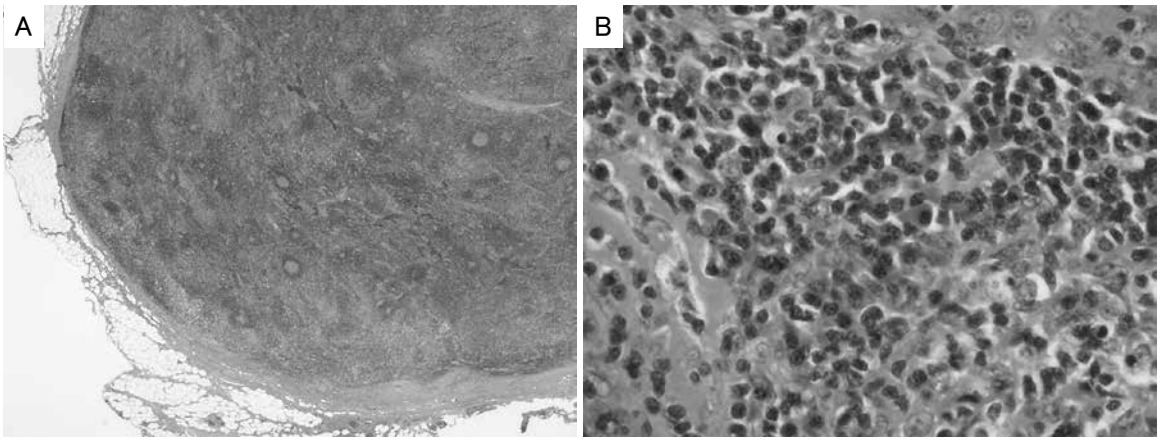

Fig. 1　Photomicrograph of a biopsy specimen obtained from an axillary lymph node
Scattered, variously sized, lymph node follicles (A), with plasma cell (PC) infiltration (B).
This phenotype denotes the PC variant. Hematoxylin & Eosin staining,
(A) original magnification × 40 ; (B) original magnification × 100.

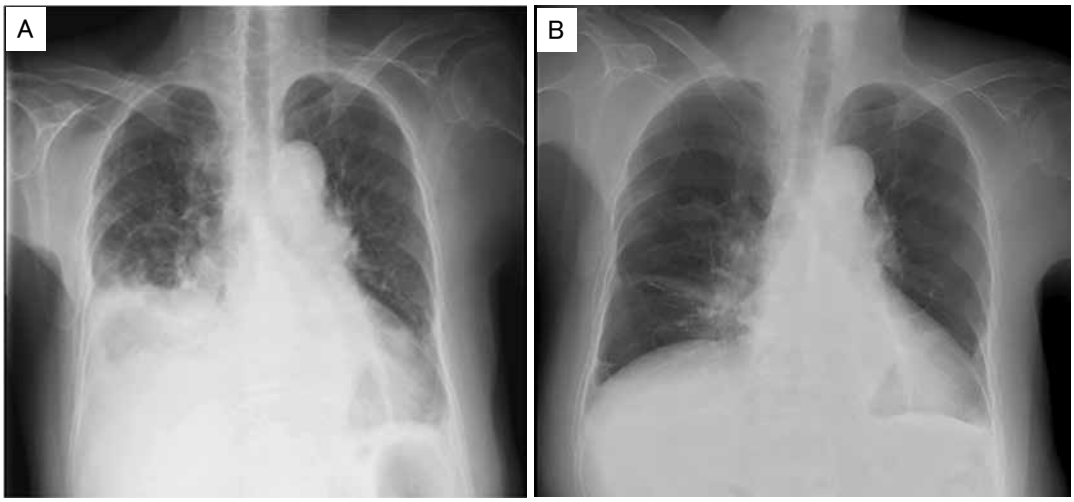

Fig. 2　Chest radiography on admission, and after corticosteroid administration
A right pleural effusion was observed (A), which was barely evident after 14 days (B).

node one year earlier at her local hospital (**Fig. 1**). Six months after the diagnosis, she developed recurrent fever, and a rash but received conservative treatment (antipyretic analgesic) at that time.

She visited the hematology department in our hospital, and continued the conservative treatment and follow-up of laboratory examinations. After a five-month follow-up in the hematology department, she was transferred to our respiratory department due to fever and dyspnea with radiographic abnormalities. The pleural effusion was observed by chest X-ray (**Fig. 2A**), and CT scan also revealed right-sided dominant pleural effusion with consolidation (**Fig. 3A,B**). Laboratory examinations (**Table. 1**) revealed neutrophilia, and elevated serum IgG and IL-6 levels. A chest drainage tube was inserted into her right thoracic cavity to drain the effusion and ameliorate dyspnea. Yellow turbid fluid was drained. Bacterial culture of the pleural effusion was negative and the feature was exudative with neutrophils predominating (the neutrophil rate was 96% and lymphocyte was 3 % : **Table 2**). Pneumonia with pleurisy was therefore suspected and meropenem 1.5 g/day was administered as treatment.

On day 5 of the antibacterial therapy, her dyspnea worsened and wheezing developed. Levels of C-reactive protein and white blood cells were elevated with no eosinophilia. Re-examination of her pleural

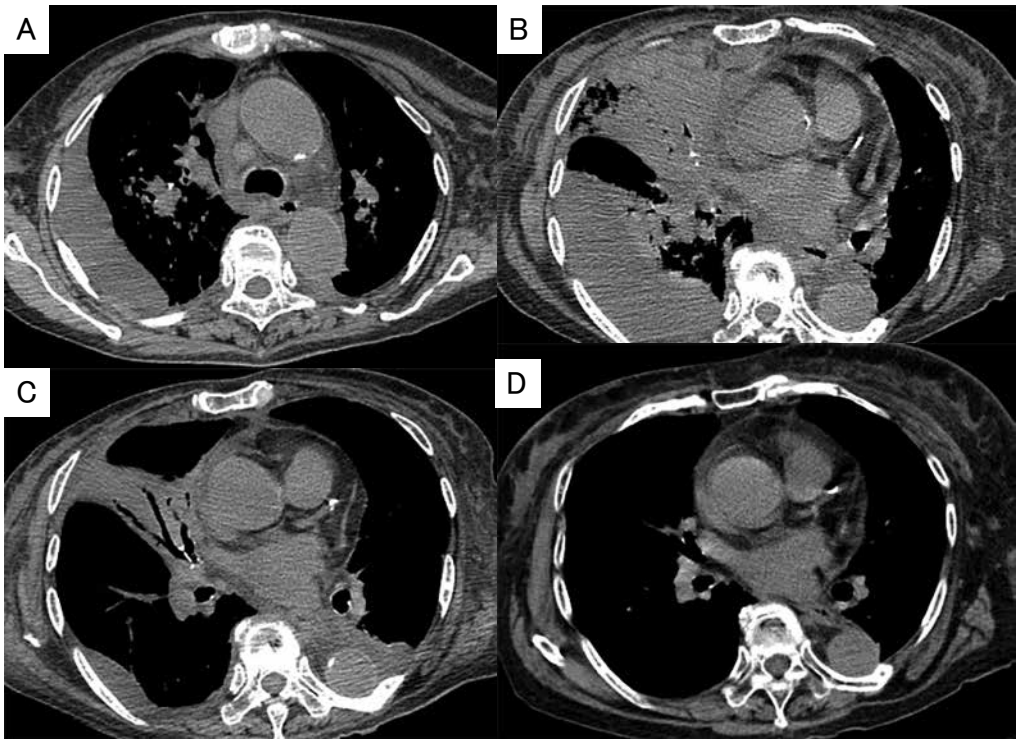

Fig. 3 Chest CT scan on admission and after corticosteroid administration
Mediastinal lymphadenopathies (A), and a right predomint pleural effusion (B), were apparent on admission. After 10 days the pleural effusion had diminished (C), and after 5 months the effusion was almost gone (D).

Table 1 Laboratory data on admission

Peripheral blood						
WBC	24.1[3]	$10^3/\mu$	Na	137	mEq/l	
Neu	94.0	%	K	4.3	mEq/l	
Lym	4.1	%	Cl	96	mEq/l	
Mo	1.3	%	Ca	7.2	mg/dl	
Eo	0	%	CRP	29.4	mg/dl	
Ba	0	%	IL-6	321	pg/ml	(≦4)
RBC	385	$10^4/\mu$	HIV	0.2	C.O.I	(≦0.9)
Hb	10.3	g/dl	HBsAg	0.2	C.O.I	(≦0.6)
Ht	33.8	%	HCV	0.5	ng/ml	(≦0.9)
MCV	90.1	fl	PCT	0.70	ng/ml	(0.00-0.5)
Plt	37.8	$10^4/\mu$	BNP	24.7	pg/ml	(0.1-20.0)
Biochemistry			IgA	488	mg/ml	(110-410)
TP	8.1	mg/dl	IgM	88	mg/ml	(35-220)
Alb	2.2	mg/dl	IgG	3021	mg/ml	(870-1700)
AST	48	IU/l	IgE	234	IU/ml	(≦173)
ALT	39	IU/l	Arterial blood gas (O_2 2 l/min)			
LDH	154	IU/l				
ALP	422	IU/l	pH	7.451		
γ GTP	62	IU/l	PaO_2	61.8	torr	
T-Bil	0.57	IU/l	$PaCO_2$	38.2	torr	
BUN	28	IU/l	HCO^3	26.2	torr	
CRE	0.97	mg/dl				

WBC, white blood cells ; Neu, neutrophils ; Lym, lymphocytes ; Mo, mononucleosis ; Eo, eosinophils ; Ba, basophils ; RBC, red blood cells ; Hb, hemoglobin ; Ht, hematocrit ; MCV, mean cell volume ; Plt, platelets ; TP, total protein ; Alb, albumin ; AST, aspartate aminotransferase ; ALT, alanine aminotransferase ; LDH, lactate dehydrogenase ; ALP, alkaline phosphatase ; γGTP, γ-glutamyl transpeptidase ; T-Bil, total bilirubin ; BUN, blood urea nitrogen ; CRE, creatinine ; Na, sodium ; K, potassium ; Cl, chlorine ; Ca, calcium ; CRP, C-reactive protein ; IL-6, interleukin-6 ; HIV, human immunodeficiency virus ; HBsAg, hepatitis B virus surface antigen ; HCV, hepatitis C virus ; PCT, procalcitonin ; BNP, brain natriuretic peptide ; Ig, Immunoglobulin ;
PaO_2, arterial oxygen pressure ; $PaCO_2$, arterial carbon dioxide pressure ; HCO^3, bicarbonate ion.

Table 2 Data of pleural effusion

On admission			Day 5 after admission		
TP	6.3	g/dl	TP	4.4	g/dl
Alb	2.0	g/dl	Alb	1.3	g/dl
LDH	467	IU/l	LDH	121	IU/l
GLU	119	mg/dl	GLU	125	mg/dl
pH	8.0		pH	8.5	
Total cell count	13333	/μl	Total cell count	1128	/μl
MONO	533	/μl	MONO	677	/μl
SEG	12800	/μl	SEG	451	/μl
Bacterial culture : negative			Bacterial culture : negative		

TP, total protein ; Alb, albumin ; LDH, lactate dehydrogenase ; Glu, glucose ; MONO mononucleosis ; SEG, segmented neutrophils.

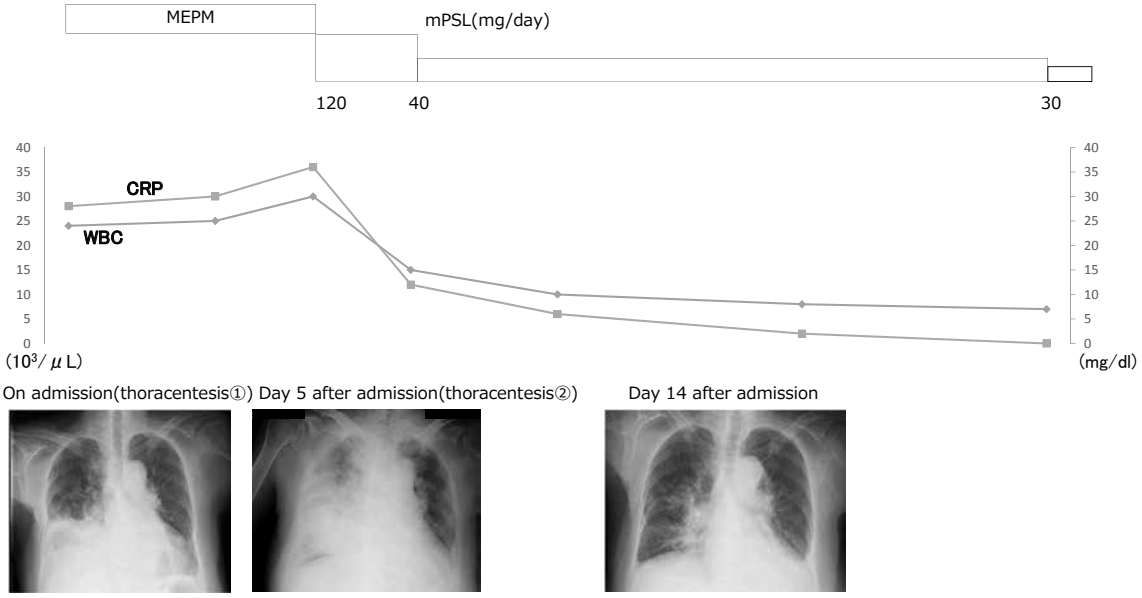

Fig. 4 Treatment progress in this patient
Antibiotics were not effective. In contrast, corticosteroid therapy was effective for the patient's disease.

effusion revealed predominant lymphocytes (the neutrophil rate was 39 % and lymphocyte was 60 %) and bacterial culture was negative (**Table 2**). Non-bacterial pleural effusion was confirmed twice in bacterial culture, therefore, corticosteroid therapy was administrated with methylprednisolone 120 mg/day on the assumption that the effusion was associated with MCD. A few days after corticosteroid administration, her dyspnea, wheezing, and inflammatory blood markers were dramatically improved and the pleural effusion was diminished.

Thereafter, the corticosteroid treatment was tapered to a dose of 30 mg/day prednisolone. The clinical course is illustrated in **Fig. 4**. The patient was subsequently discharged from hospital with no symptoms after a total of 29 days of corticosteroid treatment. The serum IL-6 levels subsequently fell to 2.10 pg/ml, after another six months of corticosteroid treatment.

Ⅲ Discussion

We here report a case of MCD with pleural effusion and its successful treatment using corticosteroid. Generally, the clinical manifestations of MCD are fever, multiple lymphadenopathy, anemia, hepatosplenomegaly, polyclonal hypergammaglobulinaemia, and other organ pathology, but pleural effusion is unusual. Polyneuropathy, organomegaly, endocr-

inopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome, similar to MCD, usually cause pleural effusion[6], but this case failed to meet the criteria of a diagnosis of POEMS. To our knowledge, there were two case reports that described MCD with pleural effusion. The differential cell counts in these pleural effusions showed predominant lymphocytes (the lymphocyte rate was 96 %[7] and 70 %[8] respectively). In our patient, the pleural effusion was bilateral with predominance on the right side of the chest (**Fig. 3A–C**), with the characteristic of neutrophils being predominant. No previous case reports describing MCD with pleural effusion having consolidation are available. The improvement of consolidation was not as marked as that of pleural effusion. From these facts, we suggest that the first neutrophil-dominant pleural effusion was influenced by bacterial pneumonia and the second, lymphocyte-dominant effusion after antibacterial therapy was influenced by MCD. Although we did not detect bacteria in the first pleural effusion, it might be the reason for the cell fraction change in the effusion before and after the antibacterial agent (the neutrophil and lymphocyte rates were 96 % and 3 %, to 39 % and 60 %, respectively). The IL-6 levels in the pleural effusion of an MCD patient are markedly higher than serum levels[9][10] although, unfortunately in this case, we did not measure the IL-6 in the effusion.

The standard therapy for MCD has not yet been established, but several successfully treated cases have been reported in which corticosteroids, immunosuppressive therapy, rituximab, and chemotherapy were administered[11]-[13]. However, most of these cases will ultimately relapse as the disease progresses[14]. In the current case, corticosteroid therapy has, thus far, proven to be effective. However, the advanced age and frailty of our patient requires us to provide a strict follow-up schedule as intervention will have to be tolerable if required.

It is thought that the symptoms of MCD are caused by excessive IL-6 production[15]-[17], which provokes multiple physiologic effects. This hypothesis agrees with data showing that patients with MCD frequently demonstrate increased serum IL-6 levels. Kawabata et al.[18] reported that serum IL-6 was elevated, on average, to 21.9 pg/ml (normal value≦4.0 pg/ml), which correlated significantly with CRP levels in 21 cases of MCD. Similarly, the serum IL-6 level in the current case rose to 321 pg/ml, then declined to 2.10 pg/ml after corticosteroid treatment. Tocilizumab (approved in April 2005 in Japan) is an antibody directed against the IL-6 receptor ; its blockade of that receptor has proven to be an effective therapeutic strategy for MCD patients. Nishimoto et al.[19] reported that 28 cases of MCD improved rapidly with the administration of tocilizumab, which was well tolerated. We would suggest that tocilizumab might be considered as a second-line therapy for the recurrence of MCD for the present case.

Ⅳ Conclusion

Castleman's disease with pleural effusion is unusual but it should be considered. It is important to distinguish it from other diseases and select the appropriate therapy.

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