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CASE REPORT

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A case of idiopathic multicentric Castleman's disease with secondary autoimmune neutropenia

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Abstract

A 73-year-old Japanese woman with productive cough and dyspnoea on exertion was admitted, and she showed neutropenia and pulmonary reticular opacities and axial and mediastinal lymphadenopathies on chest computed tomography. The clinical findings and surgical lung and lymph node biopsies were diagnostic for idiopathic multicentric Castleman's disease (iMCD) complicated by secondary autoimmune neutropenia (AIN). iMCD is often complicated with hematologic disorders, however, iMCD complicated with AIN has not been reported; therefore, if iMCD is accompanied by neutropenia, the anti-neutrophil antibodies should be measured.

KEYWORDS

anti-neutrophil antibody, autoimmune neutropenia, hematologic disorders, idiopathic multicentric Castleman's disease

INTRODUCTION

Idiopathic multicentric Castleman's disease (iMCD) is a rare lymphoproliferative disease.[1] iMCD is believed to be due to the overproduction of cytokines, such as interleukin-6 (IL-6)[1] which often leads to hematologic disorders,[1–3] although the comprehensive mechanisms of iMCD remain unclear.

Thrombocytopenia and anaemia are common complications of iMCD-induced hematologic disorders,[2,3] however, neutropenia associated with iMCD is rare. The association between iMCD and autoimmune neutropenia (AIN) involving anti-neutrophil antibodies has not yet been elucidated.[4]

Here, we present the first case report of iMCD complicated by secondary AIN with positive anti-neutrophil antibodies.

CASE REPORT

A 73-year-old Japanese woman visited a local clinic in 2015 with productive cough. She had no history of smoking or dust exposure and no relevant family history. She had no notable physical findings suspicious of TAFRO syndrome, including anasarca. High-resolution computed tomography (HRCT) of the chest revealed reticular opacities in the right middle lobe and right axillary and mediastinal lymphadenopathies (Figure 1A) and no hepatosplenomegaly. The patient underwent right axillary lymph node biopsy and bronchoscopic lung biopsies of right S^5, though no specific pathological findings were reported. She subsequently had dyspnoea on exertion and presented to our hospital in 2021. Her HRCT of the chest revealed worsening of the reticular opacities and new consolidations in the right middle lobe (Figure 1B). Blood tests revealed elevated C-reactive protein (1.78 mg/dL) and IL-6 (22.2 pg/mL) (Table 1). The patient tested negative for autoimmune antibodies, and her serum IgG4 level was low (134 mg/dL) (Table 1). The bronchoalveolar lavage fluid obtained from right S^4 showed lymphoid (not atypical lymphocyte)-dominant (Table 1), and however, lung biopsy specimens were pathologically nonspecific. She underwent in July 2021 pathological examination of surgical lung biopsy (partial excision of the right middle lobe and mediastinal hilar lymph node via video-assisted thoracic

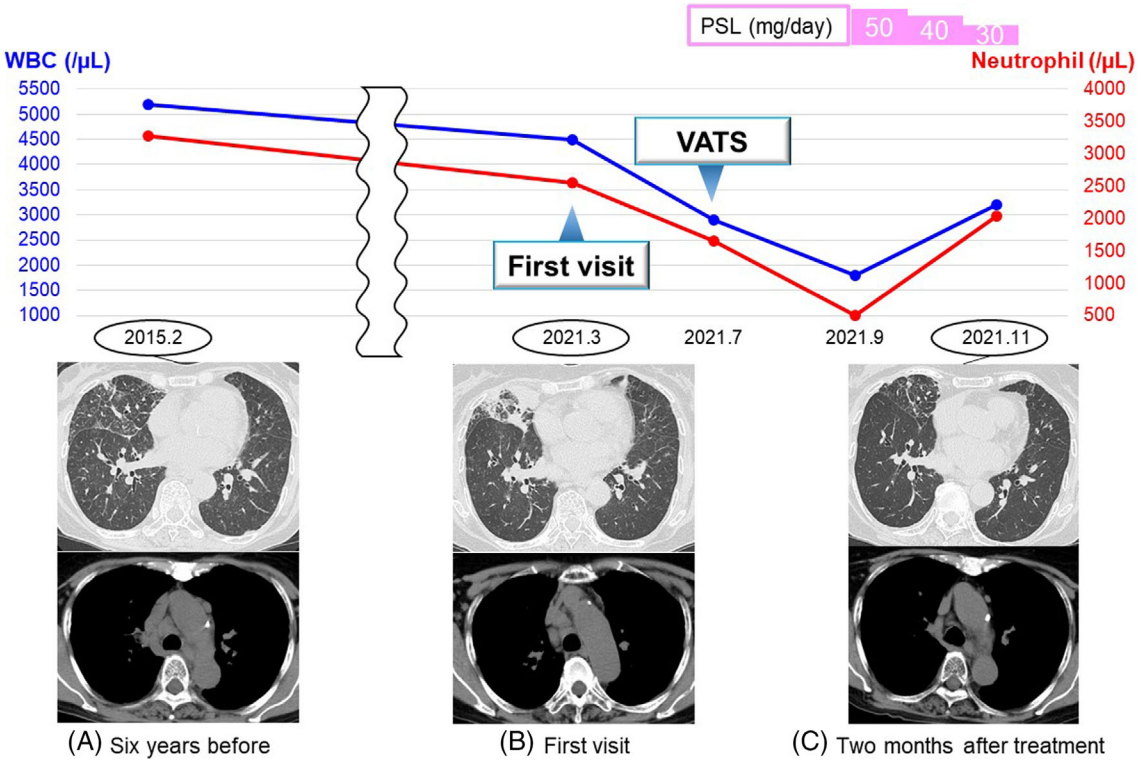

FIGURE 1 Clinical course and chest computed tomography images. (A) High-resolution computed tomography of the chest reveals a reticular shadow in the middle lobe of the right lung and axillary and mediastinal lymphadenopathy in 2015. (B) In 2021, worsened reticular opacity and consolidation are revealed in the middle lobe of the right lung. (C) After 2 months of treatment with prednisolone, the patient's symptoms and imagining findings improved. PSL, prednisolone; VATS, video-assisted thoracic surgery; WBC, white blood cell.

TABLE 1 Laboratory findings on admission.

Blood cell counts			Blood chemistry			Serology			BALF findings (rt.B^{4b})		
WBC	2600	/μL	TP	9.5	g/dL	IL-6	22.2	Pg/mL	Recovery	64/150	mL
Neutrophils	46.3	%	Alb	3.7	g/dL	KL-6	489	U/mL	Total cell count	0.8×10^5	/mL
Lymphocytes	42.5	%	AST	22	IU/L	SP-D	232	ng/mL	Macrophages	30.5	%
Eosinophils	0.4	%	ALT	12	IU/L	CEA	1.4	ng/mL	Neutrophils	8.5	%
Monocytes	10.0	%	LDH	163	IU/L	ACE	9.2	U/mL	Lymphocytes	59.0	%
Basophils	0.0	%	BUN	14.0	mg/dL	Anti-neutrophil antibody	>1.7	titres	Eosinophils	2.0	%
RBC	383×10^4	/μL	Cre	0.71	mg/dL	Rheumatoid factor	8.7	U/mL	CD4/8	2.4	
Hb	10.7	g/dL	Na	138	mmol/L	Anti SS-A antibody	1.5	U/mL			
Ht	32.8	%	K	4.2	mmol/L	Anti SS-B antibody	1.9	U/mL			
Platelets	19.6×10^4	/μL	Cl	103	mmol/L	Anti ds-DNA antibody	6.4	U/mL			
			CRP	1.78	mg/dL	Anti SM antibody	2.8				
			IgG	3884	mg/dL	Anti ARS antibody	(−)	pg/mL			
			IgG4	134	mg/dL	β-D glucan	7.1				
						QFT-gold	(−)				

Abbreviations: ACE, angiotensin converting enzyme; Alb, albumin; ALT, alanine aminotransferase; ARS, aminoacyl tRNA synthetase; AST, aspartate aminotransferase; BALF, bronchoalveolar lavage fluid; BUN, blood urea nitrogen; CEA, carcinoembryonic antigen; Cre, creatinine; CRP, C-reactive protein; Hb, haemoglobin; Ht, haematocrit; IgG, immunoglobulin G; IL-6, interleukin-6; KL-6, sialylated carbohydrate antigen Krebs von den Lungen-6; LDH, lactate dehydrogenase; RBC, red blood cell; SP-D, pulmonary surfactant protein-D; TP, total protein; WBC, white blood cell.

surgery) revealed plasma cells with multiple lymphoid follicles, with prominent germinal centres in the lymph node (Figure 2). The lung tissue showed diffuse infiltration of lymphocytes or plasma cells and lymphoid follicles with germinal centres located around lymphatic routes, which were consistent with chest HRCT findings, diagnostic for

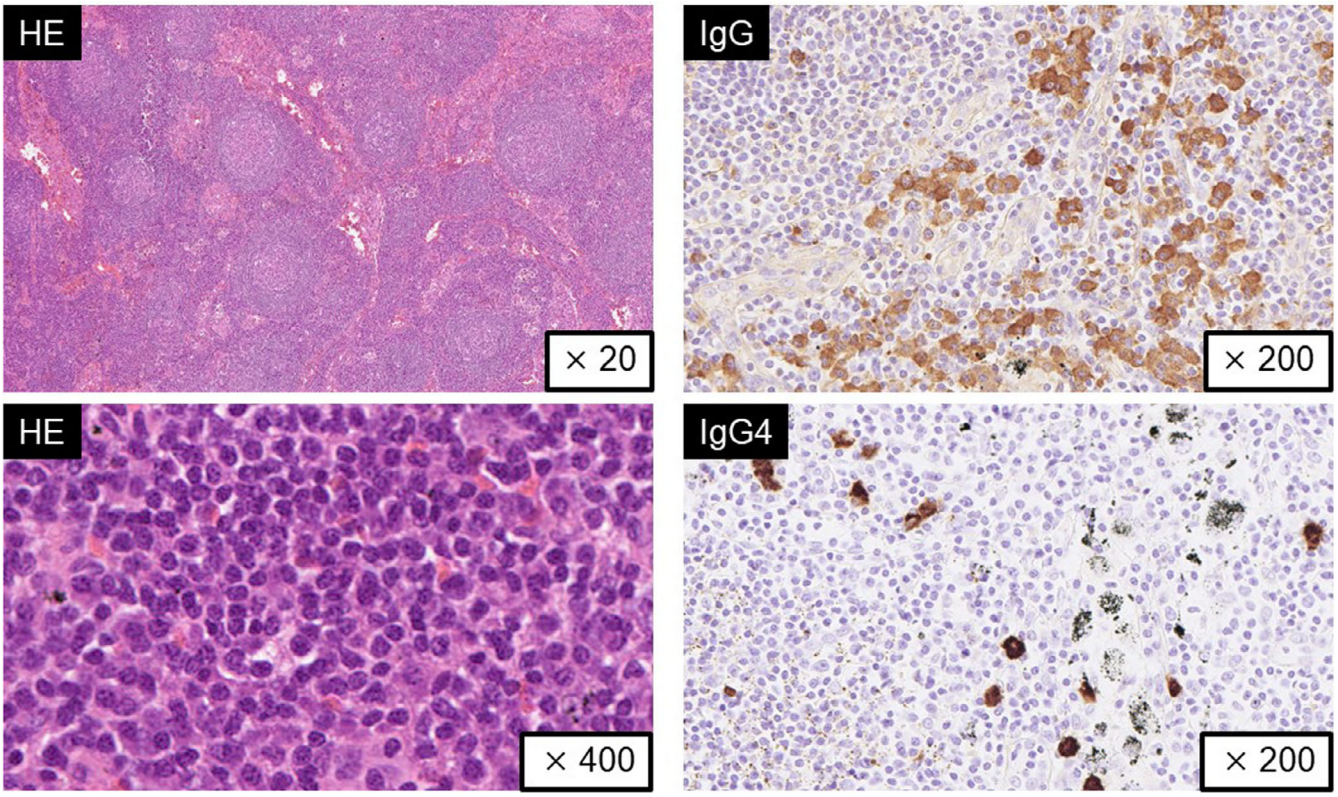

FIGURE 2 Histopathological findings of the mediastinal lymph node. Haematoxylin-eosin stain reveals multiple lymphoid follicles with prominent germinal centres and a dense infiltrate of plasma cells in the interfollicular areas of the mediastinal lymph node. Immunoglobulin G4/G staining shows <10% staining.

Castleman's disease, then she was diagnosed with iMCD. She was also diagnosed with AIN associated with iMCD, because of neutropenia (1203/μL; Table 1) with no specific findings in her bone marrow biopsy specimen and positive for serum anti-neutrophil antibodies. Prednisolone treatment was effective for her respiratory symptoms, chest image findings (Figure 1C), and peripheral blood neutrophil count (Figure 1).

DISCUSSION

We herein first present a patient with serologically-proven secondary AIN due to iMCD successfully treated with prednisolone.

iMCD is a lymphoproliferative disease characterized by systemic inflammatory symptoms, lymphadenopathy, pancytopenia, and multiorgan failure.[1] The diagnostic criteria for iMCD include multicentric lymphadenopathy and characteristic lymph node histopathology with the exclusion of infections, malignancies, and autoimmune diseases.[1] The aetiology of human herpes virus-8 (HHV-8)-induced MCD is primarily hypercytokinaemia, including IL-6 due to uncontrolled HHV-8 infection, whereas the aetiology of iMCD remains unknown.[1] Our patient was diagnosed with iMCD based on the characteristic lymph node histopathology and high serum IL-6 without HHV-8 infection, malignancy, or autoimmune diseases.

Neutropenia secondary to iMCD was complicated in our patient. iMCD is often complicated by hematologic disorders such as thrombocytopenia and anaemia,[2,3] though iMCD-associated neutropenia is rare. Neutropenia (a neutrophil count <1500/μL) may be due to AIN caused by the production of autoantibodies against neutrophil antigens that promote peripheral neutrophil destruction in patients with iMCD.[4] AIN is often associated with autoimmune diseases, such as systemic lupus erythematosus (SLE), drug-induced diseases, and lymphoproliferative diseases in adults,[4] and AIN associated with SLE involves an activation of antibody-producing cells, such as B cells, that are responsible for antibody production enhanced by cytokines, including IL-6.[5] In our patient, iMCD resulted in IL-6 overproduction and B cell activation that enhanced antibody production such as anti-neutrophil antibodies, which might led to secondary AIN.

The treatment for iMCD is dependent on the patient's performance status and organ failure.[3] Siltuximab or tocilizumab are often used in combination with corticosteroids. The treatment of secondary AIN is prioritized over that of the primary disease.[4] Our patient had dyspnoea on exertion with pulmonary impairment, but her performance status was maintained without other organ failure. She was successfully treated with oral corticosteroids,

siltuximab or tocilizumab were avoided due to the diagnosis of secondary AIN.

This is the first case report of the patient successfully treated of secondary AIN due to iMCD using oral corticosteroids. When neutropenia is observed in patients with iMCD, the serum anti-neutrophil antibody level should be measured and the presence of other autoimmune diseases, including secondary AIN, should be actively investigated.

AUTHOR CONTRIBUTIONS

Toshiki Morimoto and Takako Kawaguchi drafted the manuscript. Kei Yamasaki and Kazuhiro Yatera revised the manuscript critically. All authors have read and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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