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Case report

Tocilizumab-effective multicentric Castleman's disease with infiltration of eosinophil and IgG_4-positive plasma cells: A case report

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ABSTRACT

A 67-year-old woman with fever and cough was diagnosed with eosinophilic pneumonia because of eosinophilia and increased eosinophil levels in the bronchoalveolar lavage fluid and transbronchial biopsy lung specimens. However, prednisolone therapy at a previous hospital was ineffective. Histological findings from thoracoscopic lung and lymph node biopsies were consistent with multicentric Castleman's disease (MCD). Since specimens also showed prominent eosinophil and IgG_4-positive plasma cell infiltration, it was difficult to distinguish IgG_4-related disease (IgG_4-RD) from MCD. Administration of prednisolone plus tocilizumab improved the symptoms and lung lesions, and prednisolone administration was successfully reduced and then terminated. The present case highlights the difficulty in diagnosing MCD and IgG_4-RD, and suggests that combined administration of tocilizumab and prednisolone might be effective in such a case.

1. Introduction

Multicentric Castleman's disease (MCD) is a benign lymphoproliferative disorder presenting with multiple enlarged lymph nodes associated with plasma cell invasion, and is characterized by polyclonal hypergammaglobulinemia due to IL-6 overproduction [1,2]. IgG_4-related disease (IgG_4-RD) is a novel disease entity characterized by high serum IgG_4 levels and tissue infiltration of IgG_4-producing plasma cells, and occasionally by eosinophilia and tissue eosinophil infiltration [3]. Since these diseases exhibit similar pathological findings, it can be difficult to differentiate MCD from IgG_4-RD [4–6]. Here, we report a tocilizumab-effective case that was initially diagnosed with eosinophilic pneumonia (EP), but was later diagnosed with MCD, with difficulty in excluding IgG_4-RD.

2. Case report

A 67-year-old woman with fever and cough was referred to a general hospital. A chest computed tomography (CT) scan revealed mediastinal lymphadenopathy and ground glass opacities in both lung fields. Initial blood examinations revealed a white blood cell (WBC) count of 11700/μL and an eosinophil count of 2925/μL. Cellular analysis of the bronchoalveolar lavage fluid (BALF) revealed 12.5% eosinophils. Histological findings from transbronchial lung biopsy (TBLB) specimens showed eosinophilic infiltration (5 cells/high-powered field [HPF]) (Fig. 1a). The patient was initially diagnosed with eosinophilic pneumonia, and oral prednisolone (PSL) was started at 30 mg/day. Thereafter, the ground glass opacities partially disappeared, and PSL was reduced to 10 mg/day. However, infiltrative opacities started appearing in the right middle lobe and the left lingula segment in chest CT. The patient was referred to our department for further examination.

Her medical history included steroid diabetes mellitus, surgery for extra-uterine pregnancy at the age of 30 years, and retinal detachment surgery at the age of 53. She had smoked four cigarettes a day for 20 years. She was receiving PSL 10 mg/day (prescribed for EP by the previous doctor), famotidine 20 mg/day, carbocysteine 1500 mg/day, and insulin lispro (8 U/day) for steroid diabetes mellitus. Her body temperature was 35.9 °C and her oxygen saturation was 98% on room air. Fine crackles were heard in the bilateral lower lungs, without wheezing. Superficial lymph nodes and submandibular glands were not palpable. She had no obvious symptoms of dry eyes, dry mouth, eruption, or numbness in the extremities.

Abbreviations: BALF, bronchoalveolar lavage fluid; CRP, C-reactive protein; CT, computed tomography; EGPA, eosinophilic granulomatosis with polyangiitis; EP, eosinophilic pneumonia; HPF, high-powered field; IgG_4-RD, IgG_4-related disease; MCD, multicentric Castleman's disease; PSL, prednisolone; TBLB, transbronchial lung biopsy; UCD, unicentric Castleman's disease; WBC, white blood cell

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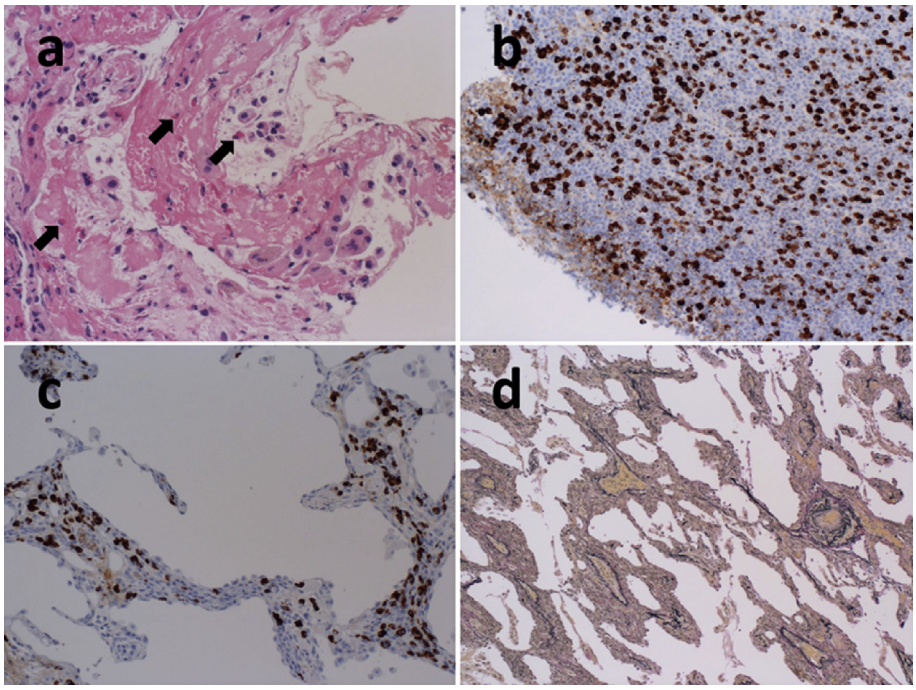

Fig. 1. a (400×): Histological findings of the transbronchial lung biopsy sample showed eosinophilic infiltration (arrows) (hematoxylin and eosin staining). b, c (200×): Immunohistochemically dense infiltration of IgG_4^+ plasma cells was evident in the #4R LN (b) and right S10 (c) sample. d (100×): Fibrosis of interstitium was not observed in the right S10 sample (Elastica van Gieson staining).

Laboratory data on admission were as follows: C-reactive protein (CRP), 17.8 mg/dL (normal range, < 0.30 mg/dL); WBC count of 10100/μL (eosinophil count of 0/μL); IL-6, 35.9 pg/mL (normal range, < 4.0); IgE, 237 IU/mL (normal range, < 170); IgG, 3916 mg/dL (normal range, 870–1700); IgG_4, 435 mg/dL (normal range, 4.5–117); KL-6, 573 U/mL (normal range, < 500); RF, 110 IU/mL (normal range, < 15); ANA, titer 1/80; MPO-ANCA < 1.0 IU/mL; ACE 7.1 IU/L (normal range, 8.3–21.4). She had negative findings for human immunodeficiency virus antibodies and human herpesvirus 8 on polymerase chain reaction tests. Arterial blood gas analysis on room air yielded the following findings: partial pressure of oxygen, 79 mmHg; partial pressure of carbon dioxide, 36 mmHg; pH 7.47.

A chest CT scan showed swelling of the mediastinal lymph nodes, centrilobular granular nodules, ground glass opacity, thickening of the interlobular septa predominantly in the lower lung, and invasive opacity in the right middle lobe and the left lingula segment (Fig. 2). Gallium scintigraphy showed accumulation in the lower lungs, but not in the submandibular or lacrimal glands (Fig. 3). An abdominal CT scan did not show any abnormal findings in the structure of the pancreas or other abdominal organs.

MCD was suspected on the basis of clinical features such as the steroid-refractory nature of the condition, chest CT findings, polyclonal hypergammaglobulinemia, thrombocytosis (platelet count of 61.9×10^4/μL), anemia (hemoglobin, 9.1 g/dL), high IL-6 and CRP levels, and normal ANA, ACE, and MPO-ANCA levels. Bronchoscopy was therefore performed again and cellular analysis of BALF from the right B3 yielded the following findings: neutrophils, 2.0%; lymphocytes, 7.1%; eosinophils, 0.4%; macrophages, 90.6%; and $CD4^+/CD8^+$

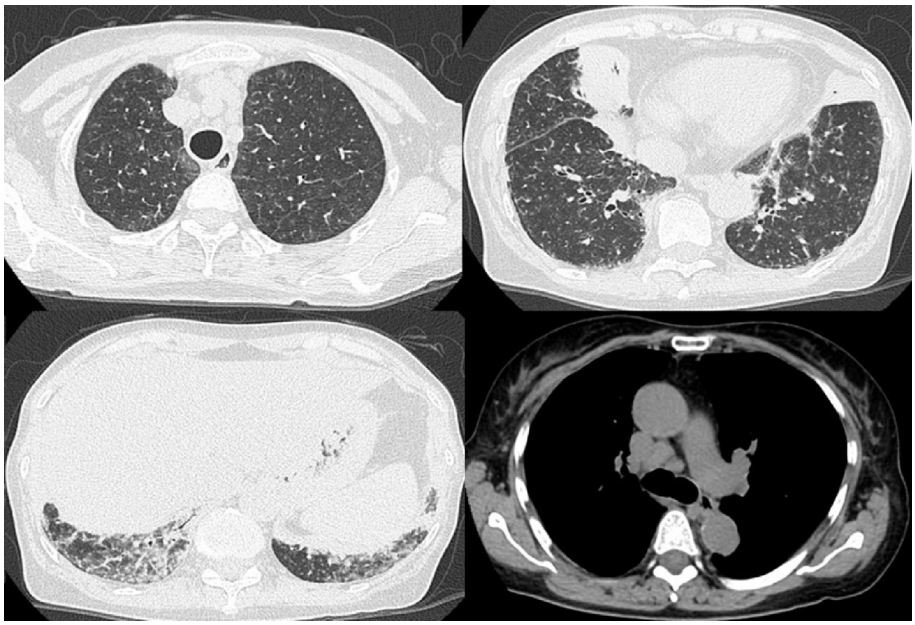

Fig. 2. Chest computed tomography scan obtained at the first admission showed centrilobular granular nodules, ground glass opacity, thickening of the interlobular septa predominantly in the lower lung, consolidation in the right middle lobe and left lingula segment and swelling of the #4R lymph node.

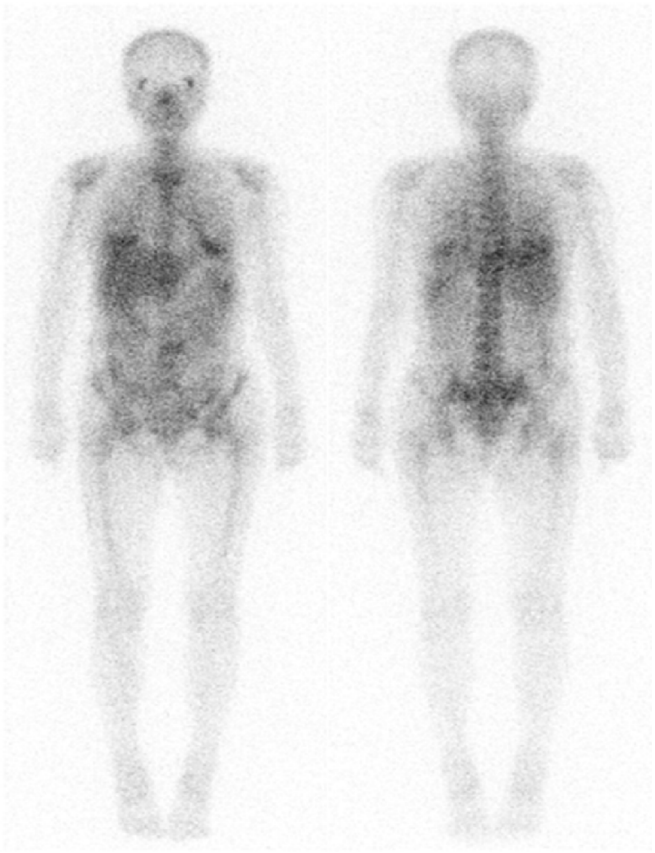

Fig. 3. Gallium scintigraphy obtained at the first admission showed accumulation in the lower lungs.

ratio, 0.51. No pathogen was cultured and TBLB specimens showed mild alveolitis with fibrosis, and alveolar macrophage proliferation. A lower paratracheal right lymph node (#4R LN) specimen obtained by endobronchial ultrasound-guided transbronchial needle aspirate showed IgG_4-positive plasma cell infiltration, with an IgG_4^+ to IgG^+ plasma cell ratio of 12.9% (17/132 cells).

Since histological diagnosis could not be confirmed by lung and lymph node specimens, thoracoscopic surgical biopsy samples were obtained from the right S10 lung and #4R LN. In the right S10 specimen, patchy plasma cell-dominant inflammatory cell infiltration was apparent, but interstitial fibrosis or eosinophilic infiltration was not observed (Fig. 1d). In the #4R LN specimen, an atrophic germinal center and plasma cell proliferation in the follicle center were observed, but obliterative phlebitis, dense fibrosis, or eosinophilic infiltration were not apparent. IgG_4^+ plasma cells were observed in both the #4R LN and right S10 specimens (Fig. 1b and c), and the IgG_4^+/IgG^+ plasma cell ratio was 36.4% (242/665 cells) in the #4R LN and 24.1% (123/510 cells) in the right S10, neither of which met the Comprehensive Diagnostic Criteria for IgG_4-RD (IgG_4^+/IgG^+ plasma cell ratio > 40%).

Taken together, we concluded that the clinical and histological findings of the patient were consistent with those of MCD. Since PSL monotherapy (at 10 mg/day) was not effective, we implemented administration of tocilizumab (8 mg/kg q2w) in addition to PSL, and the fever and cough disappeared. In the chest CT scan, the ground glass opacities in the left lower lobe and the consolidation in the left lingula segment and the right middle lobe improved partially (Fig. 4). Thereafter, tocilizumab administration was continued and the dose of PSL was successfully reduced until no further administration was required.

3. Discussion

This is a rare case of MCD with pulmonary eosinophil infiltration. Since eosinophilia and pulmonary eosinophil infiltration are rare manifestations in MCD, it was necessary to consider the possibility of IgG_4-RD.

Castleman's disease (CD) is a benign lymphoproliferative disease characterized by lymph node enlargement and polyclonal hypergammaglobulinemia [2]. CD is clinically classified into unicentric CD (UCD) and MCD, and histologically classified into the hyaline vascular-type and plasma cell-type. The hyaline vascular-type accounts for the majority of UCD cases, and large percentages of MCD cases are of the plasma cell-type.

In MCD, differentiation of B cells into plasma cells is promoted by IL-6 overproduction from the enlarged lymph node [1]. IL-6 promotes plasma cell proliferation, hypergammaglobulinemia and production of CRP, serum amyloid A, and fibrinogen. MCD is characterized by various manifestations, such as fever, respiratory failure, secondary infection, secondary amyloidosis, and various other symptoms. Johkoh et al. examined chest CT findings of 12 MCD patients with pulmonary lesions [7]. In all 12 cases, hilar/mediastinal lymph node enlargement and pale centrilobular nodules were observed, and in 10 cases, thickening of the bronchial vascular bundle, interlobular septal thickening, thin-walled cysts, and less frequently, ground-glass opacity, invasive shadows, and subpleural nodules were found. The chest CT findings in the current case, such as swollen mediastinal lymph nodes, ground glass opacity, and thickening of the interlobular septa, were consistent with those of MCD. We concluded that the clinical findings in this patient were consistent with those of plasma cell-type MCD.

IgG_4-RD is an immune-mediated condition characterized by an elevated serum IgG_4 concentration and tissue infiltration by IgG_4-positive plasma cells [8]. IgG_4-related lung disease, in which IgG_4^+ cells infiltrate into the lung, have recently been recognized [9]. Common chest CT findings of IgG_4-RD are solid nodules, ground-glass opacity, alveolar interstitial opacity, bronchovascular thickening, and hilar mediastinal lymph node swelling [12]. Chest CT findings in the current case, such as swelling of the mediastinal lymph nodes, ground glass opacity, thickening of the interlobular septa, were consistent with these features. On the basis of histological characteristics, IgG_4-related lymphadenopathies are classified into five patterns: MCD-like patterns,

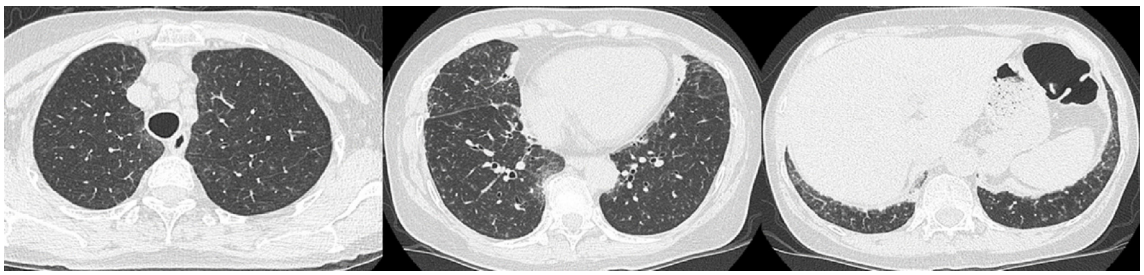

Fig. 4. In chest computed tomography scans performed after 3 months of tocilizumab and prednisolone therapy, ground glass opacities in the lower lobe, on both sides, and consolidation in the left lingula segment and the right middle lobe were improved.

Table 1
Summary of case reports in which it was difficult to distinguish MCD from IgG_4-RD.

Author	Sex	Age	Diagnosis	Organ	Pathological findings	IgG_4/IgG (%)	Organ eosinophilic infiltration	IL-6 level (pg/mL)	Blood eosinophil (/μL)	Therapy	Outcome
Ogoshi et al.	female	42	MCD > IgG_4-RD	lung, mediastinal lymph node, hilar lymph node	PC type, obliterating phlebitis	> 50	–	19.9	120	PSL 0.6 mg/kg/day	response
Miwa et al.	male	48	Castleman's disease	cervical lymph node, axillary lymph node, kidney	PC type	unknown	–	38.2	unknown	PSL 55 mg/day	response
Izumi et al.	female	50	MCD	axillary lymph node, hilar lymph node, sabdominal paraaortic lymph node, inguinal lymph node	PC type	37.3	–	9.3	155	PSL 50 mg/day	response
Mochizuki et al.	male	59	MCD, IgG_4-RD	lacrimal gland, skin	PC type	70	–	19.5	unknown	rituximab + PSL 0.2 mg/kg	no change
Ikeura et al.	female	63	IgG_4-RD	liver, gallbladder, pancreas, abdominal paraaortic lymph node, splenic hilum lymph node	eosinophil and IgG_4 positive cell invasion	> 40	+	34	3850	methylPSL 500 mg/day	response
Ikari et al.	male	67	MCD, IgG_4-RD	lung, submandibular gland	HV and PC type, eosinophil and IgG_4 positive cell invasion	unknown	+	8.5	930	PSL	no change
Hara et al.	male	69	IgG_4-RD > MCD	pleura, mediastinal lymph node, hilar lymph node	lymphocyte, plasma cell and IgG_4 positive cell invasion, fibrosis, obliterating phlebitis	50	–	6.7	441	PSL 0.5 mg/kg/day	response
Miwa et al.	male	74	Castleman's disease, AIP	right subclavian lymph node, abdominal paraaortic lymph node, mediastinal lymph node, hilar lymph node, pancreas	PC type	unknown	–	4.38	unknown	PSL 40 mg/day	response

follicular hyperplasia, interfollicular expansion, progressive transformation of germinal centers, and nodal inflammatory pseudotumor-like patterns [3,13]. Zen et al. indicated the following specific histological findings in IgG_4-RD: dense fibrosis in dacryoadenitis, numerous lymph follicles in sialadenitis and dacryoadenitis, and obliterative arteritis in lung lesions [10].

The histological findings in the present case were consistent with an MCD-like pattern. On the other hand, IgG_4-related lymphadenopathy generally needs to be distinguished from MCD, and it is suggested that cases with high serum levels of IL-6 should not be diagnosed as IgG4-RD [14]. Cheuk et al. proposed that the IgG_4^+/IgG^+ plasma cell ratio should be over 40% in IgG_4-related lymphadenopathy. Although the IgG_4^+ plasma cell ratios were quite high in the current case, they did not meet the IgG_4-RD criteria [15]. However, a possible reduction in IgG_4^+ cells in the surgical specimens due to PSL administration could not be excluded.

In the current case, eosinophilia and increased eosinophils in the BALF, as well as pulmonary eosinophil infiltration, led to the initial diagnosis of EP. EP encompasses a wide spectrum of lung diseases, such as eosinophilic granulomatosis with polyangiitis (EGPA) and idiopathic acute/chronic EP characterized by peripheral blood eosinophilia (> 1000 eosinophils/μL) and/or a high ratio of eosinophils in BALF (> 25%) [16]. However, EGPA was not suspected given the physical findings and low MPO-ANCA levels. Furthermore, no case of idiopathic acute or chronic EP with IgG_4 invasion has been reported. Thus, the presence of 12.5% eosinophils in BALF and the IgG_4^+ plasma cell infiltration were suggestive of IgG_4-RD. The possibility of IgG_4-RD is greater than that of MCD when eosinophil infiltration is detected in lymph node lesions [3,17]. Zen et al. reported that eosinophilic infiltration in the lung specimens was over 5 cells/HPF in 9 of 21 cases of IgG_4-RD with lung lesions [18]. Moreover, cases of IgG_4-RD with eosinophilia [19], and increased eosinophils in BALF have been reported [19,20]. On the other hand, the number of eosinophils in lung lesions with MCD was reported to be very low (1.47 cells/HPF) [21]. Thus, the eosinophil infiltration into the lung and lymph nodes supported the possibility of IgG_4-RD.

In MCD patients, the efficacy of PSL monotherapy is generally limited, but the efficacy of anti-IL-6 receptor antibody (tocilizumab) has been established [24]. On the other hand, IgG_4-RD, unaccompanied by fibrosis, is responsive to steroid treatment [18,26,27]. In the current case, it was difficult to distinguish MCD from IgG_4-RD [4,6,28]. Since this case was diagnosed as MCD and was steroid-refractory, tocilizumab was added to the therapeutic regimen. The combination therapy safely improved the symptoms and chest CT findings (Fig. 4).

We searched for other case reports in which it was difficult to distinguish MCD from IgG_4-RD using PubMed, and found 8 case reports. Steroid monotherapy was effective in 6 of 7 cases, combination therapy of rituximab and prednisolone showed no obvious improvement in the remaining 1 case (Table 1). Furthermore, the efficacy of tocilizumab in such a case has not been reported.

Combined administration of tocilizumab and PSL improved lung lesions and general symptoms in our case, suggesting that combination therapy of tocilizumab and PSL may be effective, and that tocilizumab administration may contribute to the successful reduction of PSL treatment in such a case.

Conflict of interest

None to declare.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmcr.2018.06.001.

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