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Multicentric Castleman disease with infiltration of eosinophils to the lung

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ABSTRACT

A 41-year-old man presented with multiple superficial lymph nodes (LNs) swollen with elevated levels of serum immunoglobulin (Ig)G4 and C-reactive protein. Histological findings of his left inguinal LN revealed lymphoplasmacytic infiltration with numerous IgG4-positive plasma cells; $IgG4^+/IgG^+$ plasma cell ratio >40%. Chest computed tomography (CT) showed poorly defined centrilobular nodules, interlobular septal thickening, consolidations, and mediastinal LNs swelling. Bronchoalveolar lavage fluid (BALF) showed elevated eosinophils. A surgical lung biopsy showed focal dense eosinophil infiltration, in addition to lymphoplasmacytic infiltration, but few $IgG4^+$ plasma cells. The diagnosis of multicentric Castleman disease (MCD) was made because of serum interleukin-6elevation. Treatment with prednisolone and tocilizumab improved his symptoms and lung lesions. This case shows that overlapping clinical and pathological features of MCD and IgG4-related disease may present in a single patient, showing the difficulty in distinguishing between these two diseases.

1. Introduction

Multicentric Castleman disease (MCD) is a rare lymphoproliferative disorder that involves multiple lymphoid regions. It frequently shows systemic manifestations and abnormal laboratory findings, due to interleukin (IL)-6 overproduction. Patients with MCD sometimes have elevated serum immunoglobulin (Ig)G4 and $IgG4^+$ plasma cell invasion with $IgG4^+/IgG^+$ plasma cell ratios of >40% in affected organs [1]. In these cases, differentiating MCD from IgG4-related disease (IgG4-RD) can be difficult. We herein describe a patient with MCD who showed numerous parenchymal eosinophil infiltration and abundant $IgG4^+$ plasma cells in lymph nodes (LNs) in addition to lymphoplasmacytic infiltrations. These pathological findings were similar to those of IgG4-RD [2,3]. Our patient demonstrated that MCD may show numerous parenchymal tissue eosinophilic infiltrations, and in these cases, it is difficult to distinguish between MCD and IgG4-RD.

2. Case report

A 41-year-old man developed swelling of the cervical, axillary and inguinal LNs up to 15 mm in diameter. Laboratory examinations were white blood cell (WBC): 11,800/μL (0.3% eosinophils); hemoglobin:12.6 g/dl; C-reactive protein (CRP): 1.1 mg/dl; total protein (TP): 9.3 g/dl; albumin: 2.8 g/dl. He had elevated levels of serum IgG (3945 mg/dl, normal range: 861–1747), IgG4 (1340 mg/dl, normal range: 11–121 mg/dl), and IL-6 (11.5 pg/ml, normal range: ≤4.0 pg/ml). Histological examination of his left inguinal LN revealed prominent lymphoplasmacytic infiltration in the inter-follicular area, but eosinophilic infiltrations were not apparent (Fig. 1a and b). Immunohistochemically, marked $IgG4^+$ plasma cell infiltration was observed and his $IgG4^+/IgG^+$ plasma cell ratio was over 40% (Fig. 1c and d). Chest computed tomography (CT) showed poorly defined centrilobular nodules, interlobular septal thickening, consolidations, thin-walled cysts, and mediastinal and bilateral axillary LNs enlargement. We presumptively diagnosed MCD and began treatment with oral prednisolone at 30 mg/day (0.5 mg/kg/day). This slightly improve his chest CT findings, but not other clinical and laboratory findings. He tapered off prednisolone over a 20-month period. Thereafter, he had no symptoms, but chest X-ray findings showed gradual progression.

Four years after tapered off prednisolone, he presented with a two-month history of gradually worsening dry cough. Chest CT findings showed progression of the previously observed findings. Laboratory findings were: WBC: 8400/μL (neutrophil: 73.2%, lymphocyte: 15.0%, eosinophil: 5.5%); hemoglobin:10.9 g/dl; CRP: 3.65 mg/dl; TP: 10.1 g/dl; and albumin: 2.5 g/dl. Bronchoalveolar lavage fluid (BALF) revealed 30.0% eosinophils, 4.3% lymphocytes, 4.0% neutrophils, 61.3%

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macrophages and a $CD4^+/CD8^+$ ratio of 0.42. Histological examination of his surgical lung biopsy at right S8 showed dense lymphoplasmacytic accumulations, mainly in the alveolar area adjacent to the peri-lymphatic stromal area (Fig. 2 a, b). Some focal dense eosinophilic infiltrations and collagenous fibrosis were also noted (Fig. 2 c, d), but few $IgG4^+$ plasma cells were observed. Serum level of IgG and IgG4 were increased (6858mg/dl and 3140 mg/dl, respectively). Rheumatoid factor was negative, but myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA) was positive at 117 U/ml (normal range: <3.5 U/ml) and total IgE level was elevated at 412 IU/ml (normal range: 10–340 IU/ml). The serum level of IL-6 and thymus and activation-regulated chemokine (TARC) was increased at 39.9 pg/ml (normal range < 4 pg/ml) and at 552 pg/ml (normal range < 450 pg/ml), respectively. Urinalysis showed no active sediment. He showed no cutaneous evidence of vasculitis or stigmata of collagen vascular disease.

Taken together, we concluded that these findings were consistent with MCD, and began treatment with oral prednisolone (30 mg/day: 0.5 mg/kg/day) combined with tocilizumab (8 mg/kg, every 2 weeks). Thereafter, his symptoms disappeared, and chest CT findings partially improved.

3. Discussion

For this patient, elevated serum IgG4 and histological findings for LN specimens fulfilled the comprehensive diagnostic criteria for IgG4-RD. However, his laboratory results showed inflammation and high IL-6 level, suggesting hyper-IL-6 syndrome. Reportedly, elevated serum IgG4 and marked tissue $IgG4^+$ plasma cell infiltration are occasionally observed in patients with MCD [1]. Although other organs are frequently affected in patients with IgG4-RD, only lungs were involved in this case. We therefore diagnosed our patient with MCD rather than IgG4-RD.

MCD occasionally exhibits diffuse parenchymal lung lesions; reported histological findings include marked lymphoplasmacytic infiltration with lymphoid follicles and focal dense collagenous fibrosis [2]; eosinophilic infiltrations and granulomas are rare [2]. However, lung lesions in IgG4-RD may show eosinophilic infiltrations and active fibrosis in addition to lymphoplasmacytic infiltrations [2,3]. Our case was unusual as tissue eosinophilic infiltrations were observed in the lung, as well as increased eosinophils in the BALF and peripheral blood eosinophilia. To our knowledge, only 2 patients with MCD have showed tissue eosinophilic infiltrations in the lung [4,5].

Increased eosinophils in the BALF and tissue eosinophilic infiltration in the lung may lead to the diagnosis of eosinophilic pneumonia (EP). EP encompasses a wide spectrum of lung diseases including eosinophilic granulomatosis with polyangiitis (EGPA). In our patient, serum level of MPO-ANCA was increased, which suggested the possibility of EGPA. However, we excluded EGPA based on the clinical findings that he showed no evidence suggestive of vasculitis or collagen vascular disease.

Some borderline cases, not clearly classified as either MCD or IgG4-RD, have been reported [1,4,5]. MCD is believed to be a hyper-IL-6 syndrome, with IL-6 inducing B cells to produce immunoglobulins [1], whereas IgG4-RD is characterized by a preferential T helper type-2 (Th2)-type response and increased expression of Th2 and regulatory T cell (Treg) cytokines [2]. Clinical findings for these borderline cases may rely on the balance between the two inflammatory processes. For example, a patient with both inflammatory processes who shows IL-6 dominant inflammation may have clinical findings more similar to MCD; whereas they might more resemble IgG4-RD if a Th2 or Treg response were dominant. Some patients may thus show overlapping clinical findings of these two diseases. Our patient showed elevation of

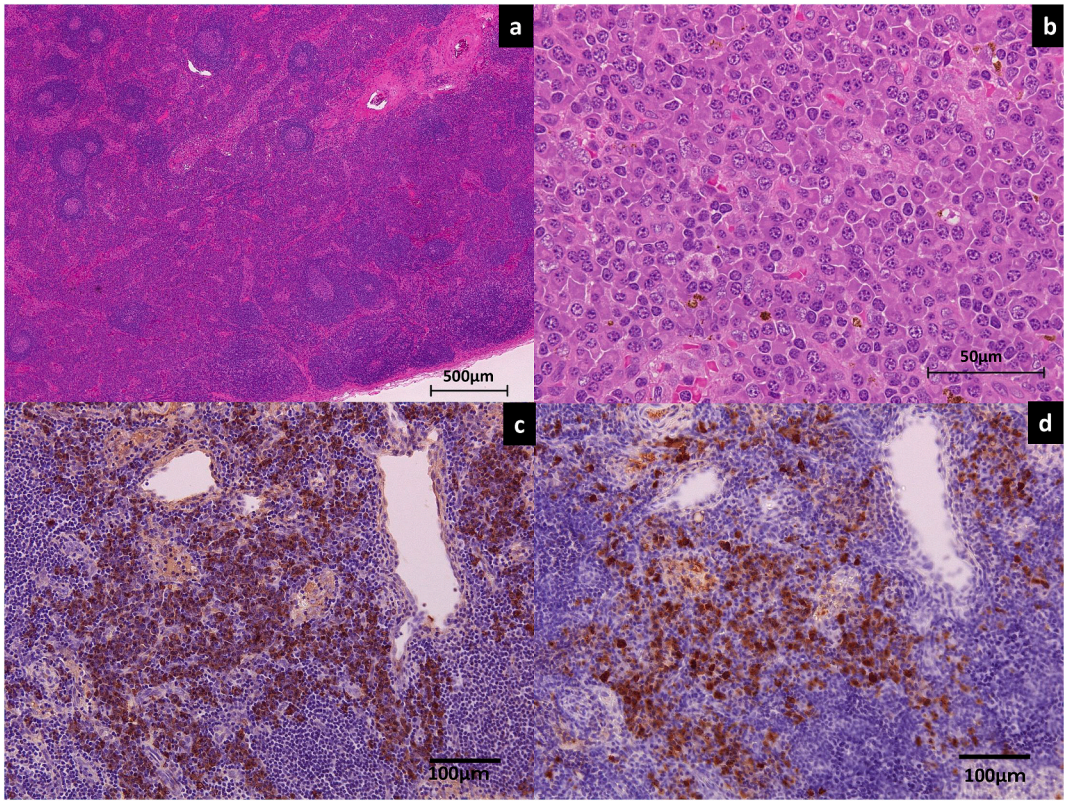

Fig. 1. (a)Histological examination of left inguinal lymph node revealed numerous lymphoid follicles with active germinal centers. (hematoxylin-eosin [HE] stain; low power view. Bar: 500μm). (b)High power view shows prominent lymphoplasmacytic infiltration in inter-follicular area, but obliterative phlebitis, dense fibrosis, or eosinophilic infiltrations were not apparent (HE stain; bar, 50μm).
Immunohistochemical stains show (c)IgG^+ and (d)$IgG4^+$ plasma cell infiltration; IgG4+/IgG + plasma cell ratio was over 40% (bar, 100μm).

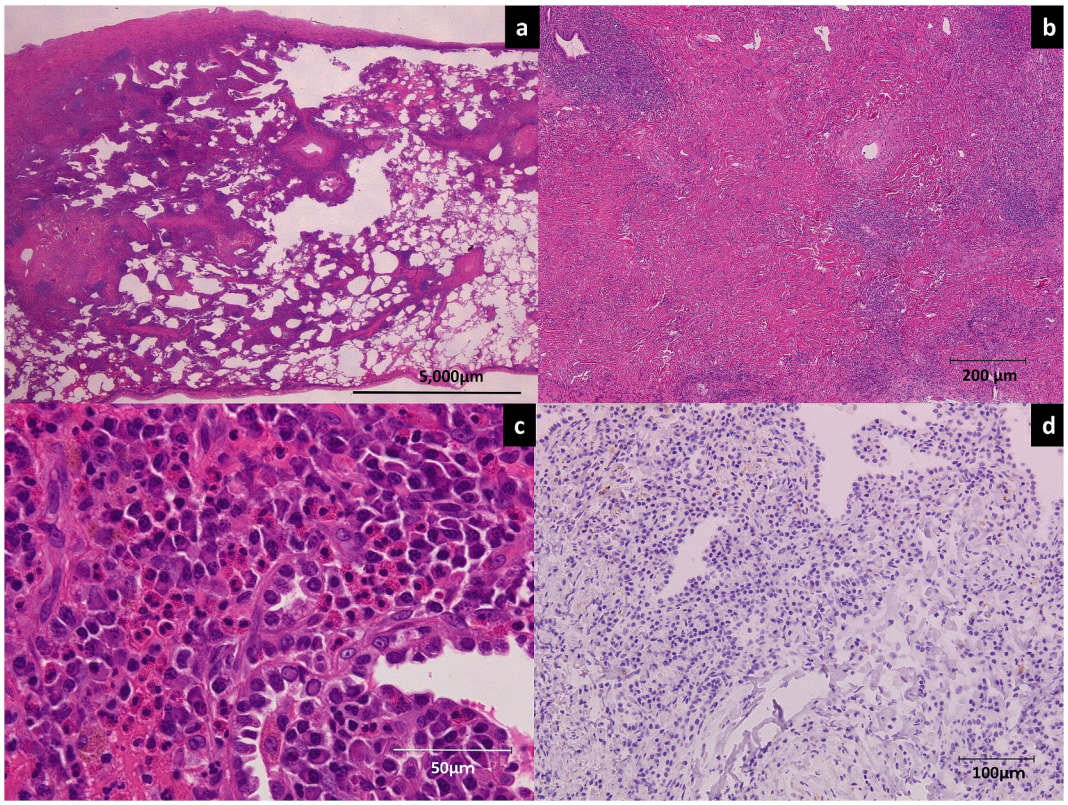

Fig. 2. (a) Histological examination of surgical lung biopsy at right S8 showed dense lymphoplasmacytic accumulations and collagenous fibrosis mainly in the alveolar area adjacent to the peri-lymphatic stromal area (hematoxylin-eosin [HE] stain; low power view; bar: 5000μm. (b)Some areas show dense collagenous fibrosis (HE stain;. bar; 200μm). (c)Focal dense eosinophilic infiltrations (HE stain: high power view; bar: 50μm). (d)Few $IgG4^{+}$ plasma cells were observed (bar: 100μm).

total IgE and TARC, which suggested the Th2-type response. But precise mechanisms were uncertain. Further investigations are needed to clarify this.

Authors' contributions

SN, TH, MM, SM, TU, JS, and SI contributed to decision of treatment, collecting clinical data, data analysis, and writing the manuscript. MM, TH, SM, TU, JS, and TS contributed to discussion about the patient. SN and SI were responsible for writing. All authors read and approved the final manuscript.

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Declaration of competing interest

I declare on behalf of my co-authors and myself that we do not have any conflict of interest to declare.

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