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A case of immunoglobulin G4-related respiratory disease with multiple lung cysts: A case report

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ABSTRACT

A 48-year-old man was admitted for evaluation of abnormal shadows on chest radiograph. Chest computed tomography (CT) showed cysts, nodules, and cervical and axillary lymphadenopathies. Elevated serum levels of IgG4 and interleukin (IL)-6 suggested IgG4-related disease (IgG4-RD) or multicentric Castleman's disease (MCD). Histologic findings of the cervical lymph node and right lung S^6 biopsies revealed numerous IgG4-positive plasma cells. Although CT findings of the lungs were atypical for IgG4-RD, consistent histologic findings, clinical symptoms, and laboratory data made us conclude IgG4-RD. Because histologic findings of IgG4-RD and MCD have similarities, differentiating between the two diseases should consider the clinical presentation.

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1. Introduction

Immunoglobulin (Ig) G4-related disease (IgG4-RD) is a novel clinical entity characterized by elevated serum IgG4 concentration and tissue infiltration by IgG4+ plasma cells. Comprehensive diagnostic criteria for IgG4-RD had been established by Umehara et al. [1]. IgG4-RD, which is characterized by an association between elevated IgG4 levels and organ inflammation, was first reported in 2001 by Hamano et al. [2] in patients with autoimmune pancreatitis (AIP), and has been recognized as a systemic disease with various organs involvement. For IgG4-related respiratory disease (IgG4-RRD), the respiratory disease subcommittee for IgG4-RRD supported by the Health and Labor Sciences Research Grant for the Study of Intractable Diseases from the Ministry of Health, Labour and Welfare, Japan has proposed organ-specific diagnostic criteria [3]. IgG4-RRD is known to present with various abnormal radiographic patterns [4], but multiple cystic lesions are very rare [5]. Because this case also had cervical and axillary lymphadenopathy, it was necessary to discriminate between IgG4-RD and multicentric Castleman's disease (MCD). We report a rare case of IgG4-RRD that presented with multiple cysts on chest computed tomography (CT).

2. Case report

A 48-year-old man was admitted to our hospital because of abnormal shadows on chest radiograph and CT. Further diagnostic examinations, including bronchoscopy, failed to yield a definitive diagnosis. He was readmitted three years later because of new bilateral pulmonary cysts and nodules with cervical and axillary lymphadenopathies on chest radiograph and chest CT. He had no symptoms, such as fever, cough, sputum, and dyspnea, no particular personal and family medical history, and never smoked. On admission, physical examination showed no abnormal vital signs, but there were palpable cervical lymph nodes. There was no hepatosplenomegaly. Blood examination showed abnormally elevated

Abbreviations: CT, chest computed tomography; IL, interleukin; IgG4-RD, IgG4-related disease; AIP, autoimmune pancreatitis; IgG4-RRD, IgG4-related respiratory disease; MCD, multicentric Castleman's disease; CRP, C-reactive protein.

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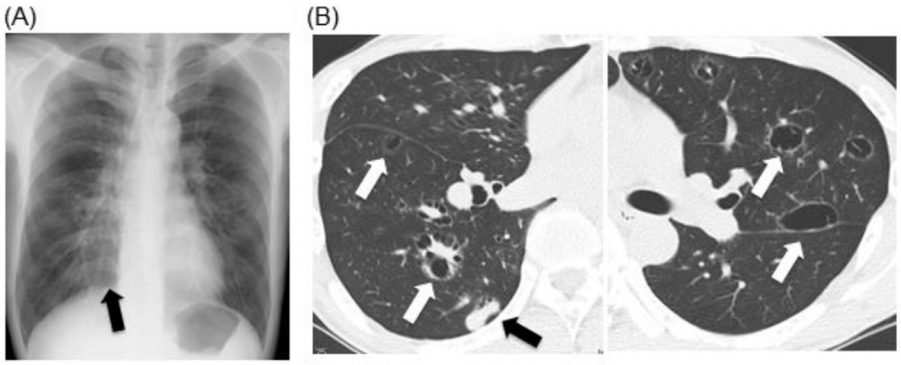

Fig. 1. Chest radiography and computed tomography obtained on admission. (A) Chest radiograph shows ground glass opacity in the right lower lung field (black arrow). (B) Chest computed tomography shows multiple cysts (white arrows) and nodules (black arrow) on both lungs.

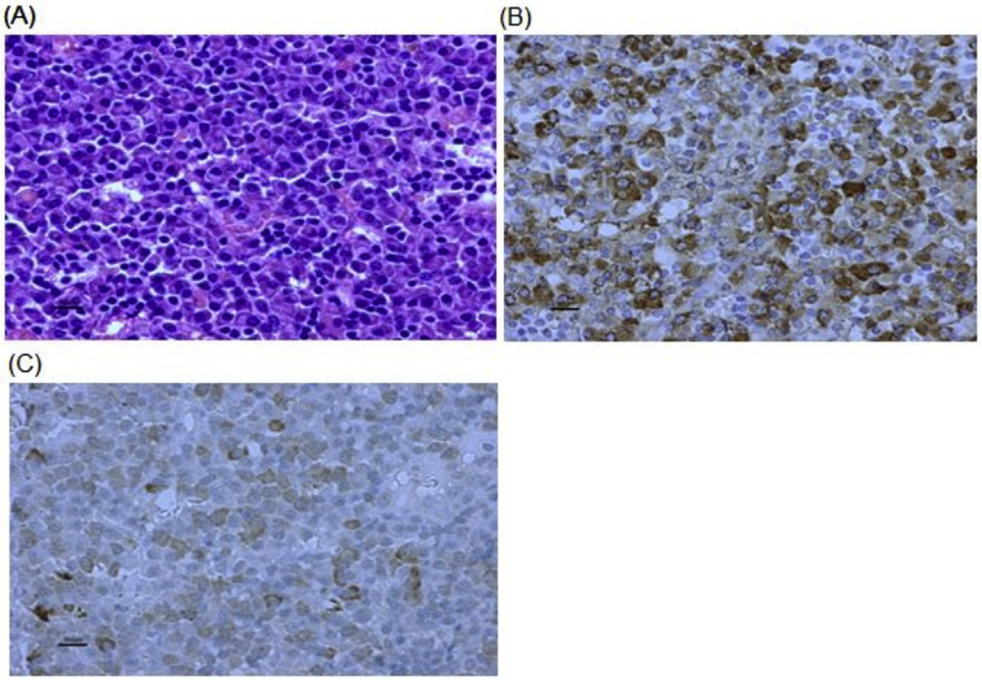

Fig. 2. Histopathological finding of the right cervical lymph node biopsied surgically (A) Cervical lymph node shows lymphocyte and plasma cell infiltration (Hematoxylin-eosin stain, ×400). Immunohistochemical staining with (B) IgG (×400) and (C) IgG4 (×400) shows an IgG4/IgG-positive cell ratio of about 40%.

values of C-reactive protein (CRP) at 2.72 mg/dl, IgG at 4309 mg/dl, IgG4 at 870 mg/dl, IgE at 5576 mg/dl, and interleukin (IL)-6 at 10.8 mg/dl. Other tests showed anemia, hypoalbuminemia, and normal levels of IgA, IgM, platelet, and cholesterol. Pulmonary function test was normal. Chest X-ray showed a ground glass opacity lesion in the right middle lung (Fig. 1A). Chest CT revealed multiple cysts and nodules on both lungs, with cervical and axillary lymph node swelling (Fig. 1B). Surgical biopsy from the right cervical lymph node showed lymphoplasmacytic infiltration (Fig. 2A). Immunohistochemicalstaining for biopsied lymph node indicated that more than 40% of the total plasma cells were IgG4-positive (Fig. 2B and 2C). Based on the elevated serum levels of IgG4 and IL-6, and histological findings, IgG4-RD or MCD were suspected, although the presence of cystic lesions in the lungs was atypical for IgG4-RRD. Therefore, we performed biopsy of the right S^6 nodule by video-assisted thoracic surgery to confirm the diagnosis. Histologic findings of the biopsied lung were similar with those of the lymph node, as well as the presence of some fibrotic areas on hematoxylin and eosin stain (Fig. 3), we diagnosed the case as IgG4-RD. The patient was started on oral prednisolone 30 mg/day for 28 days, then was gradually tapered. As of the time of writing, the patient has remained well without disease progression.

3. Discussion

Since the first description of IgG4-RD presenting as AIP in 2001 [2], IgG4-RRD has been reported only occasionally. Hirano et al. [6] reported that 13.3% of AIP patients showed pulmonary complications. Furthermore, Umeda et al. [4] reported the following 8 patterns of pulmonary findings in IgG4-RRD: 1) bronchial wall thickening, 2) consolidation, 3) nodule, 4) ground-glass opacity, 5) interlobular thickening, 6) honeycombing, 7) pleural thickening/effusion, and 8) mediastinal lymphadenopathy. This case was accompanied by multiple cysts and nodules. Elastica-Van-Gieson (EVG) staining demonstrated that alveolar wall fibroelastin had disappeared, suggesting alveolar wall destruction. It is presumed

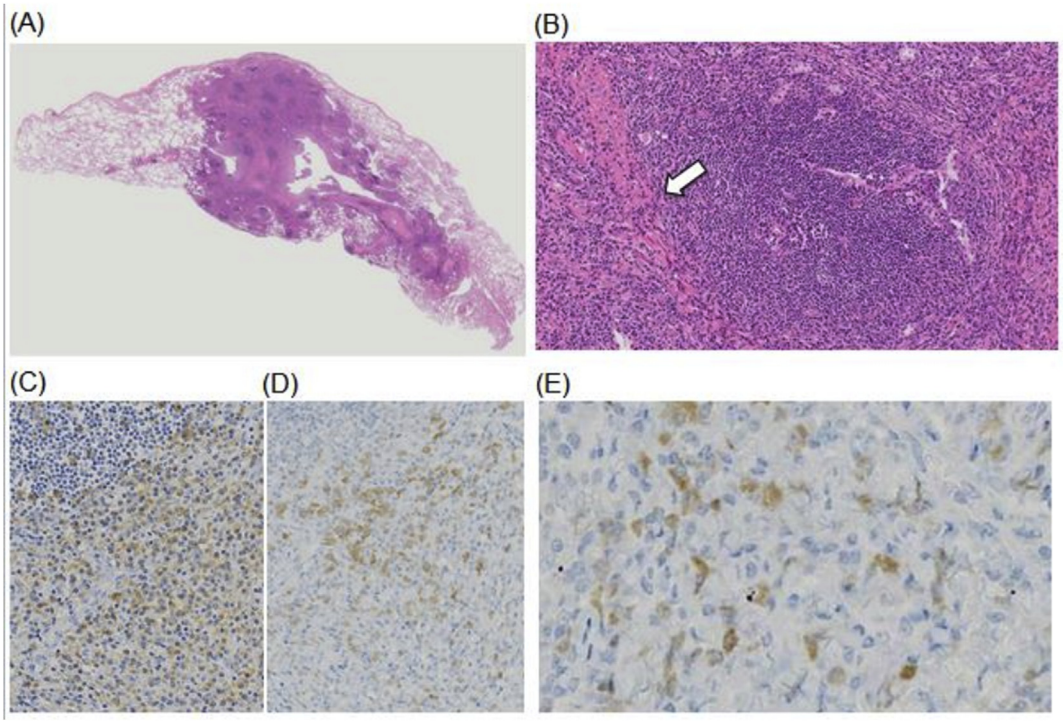

Fig. 3. Histopathological finding of video-assisted thoracic surgery specimen from the right S^6. (A) Video-assisted thoracic surgery specimen from the right S^6 shows lymphocyte and plasma cell infiltration and cysts (Hematoxylin-eosin, ×200), (B) as well as the presence of fibrosis (white arrow, Hematoxylin-eosin, ×400). (C) Immunohistochemical staining with IgG and (D) IgG4 (×400) shows an IgG4/IgG-positive cell ratio of about 40%. (E) Immunohistochemical staining with IgG4 (×800) shows 10 cells/hpf.

that the mechanism behind cyst formation is the destruction of the alveolar structure and fibrosis due to inflammatory cell infiltration. So far, only one case of IgG4-RRD with multiple cysts has been reported by Nakamoto et al. [5]. Apart from that, there has been only one case report of IgG4-RRD with cavitating lung disease by Jinnur PK et al. [7] that described somewhat similar finding, if not identical, to the present report. Generally, MCD needs to be ruled out if IgG4-RD is associated with lymphadenopathy [8] because MCD is characterized by excessive IL-6 production from enlarged lymph nodes. IL-6 causes B cells to differentiate into plasma cells, which produce polyclonal immunoglobulin [9]. Some MCD cases fulfill the diagnostic criteria for IgG4-RD and difficult to distinguish from IgG4-RD [10]. Some reports have stated that hemoglobin, serum albumin, and cholesterol were useful to differentiate between the two diseases [8]. IgG4-RD is often responsive to corticosteroid therapy, whereas MCD can be resistant to corticosteroid, and need immunosuppressive drugs such as methotrexate, azathioprine, mizoribine, cyclophosphamide + hydroxydaunorubicin + oncovine + prednisolone (CHOP), and rituximab or plasmapheresis [11]. Considering the excessive production of IL-6, tocilizumab is also a therapeutic option for MCD [11]. IgG4-RD is typically highly steroid-responsive and its prognosis is known to be relatively good [12]. On the other hand, the prognosis of MCD has not always been good and depends on the coexistence of pulmonary and renal diseases. Usually, causes of mortality of MCD include respiratory failure, renal failure, complication of infections, and progression to malignant lymphoma [11]. Previous reports have stated that IgG4-RD may develop as a complication of MCD in some cases, whereas both diseases may develop at the same time in some cases; therefore, discriminating one from the other has not been always easy [13–15]. The clinical picture of multicentric Castleman's disease (MCD) is characterized by various observations, such as fever due to excessive IL-6 production, high C-reactive protein (CRP) level, low albumin (Alb) level, and anemia; therefore, the effects of steroid monotherapy in patients with MCD are limited. These observations distinguish MCD from IgG4-related diseases, even though in many cases, IL-6 levels are mildly elevated in the latter. However, in comparison to MCD, in IG4-related diseases, the degree of IL-6 level increase is mild and anemia, CRP level, or platelet increase are minimal or absent; moreover, there is a positive response to moderate-dose steroid therapy. In the present case, we observed a mild elevation in IL-6 and CRP levels, a mild decrease in Alb level and anemia, and steroid therapy was effective. For this case, we concluded a diagnosis of IgG4-RD. Generally, the histologic findings of IgG4-RD and MCD are similar; therefore, clinical findings need to be taken into account. In the future, the possibility of MCD diagnosis in an out-patient clinic should be kept in mind because prognosis is very different between the two diseases and patients with MCD frequently require stronger therapy as well as corticosteroid therapy for longevity.

Conflict of interest

The authors have no conflicts of interest to declare.

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