IgG4-Related Lung Disease Exhibiting the Invasion into the Diaphragm: A Case Report

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Immunoglobulin G4-related disease (IgG4-RD) is a fibroinflammatory condition which involves various organs. This is a very rare case of IgG4-related lung disease (IgG4-RLD) with the invasion into diaphragm. The patient was a 71-year-old man with a long-term exposure to asbestos who had a mass shadow in the left lower lung lobe, which was suspected to invade the left diaphragm on computed tomography (CT). Positron emission tomography (PET)/CT also presented an avid intake of fluorodeoxyglucose in the mass, which suspected lung cancer. Although bronchoscopic biopsy could not lead to the definite diagnosis, we performed left lower lobectomy combined with the resection of left diaphragm. The specimen showed the features of IgG4-RLD on pathology: the vein stenosis and fibrosis around the vein, the infiltration of IgG4-positive cells, and IgG cells to IgG4 cells ratio of 40%. Furthermore, there were inflammatory cells infiltrating to the diaphragm.

Keywords: IgG4-related lung disease, diaphragm, lung cancer

Introduction

Immunoglobulin G4-related disease (IgG4-RD) was first introduced by Kamisawa et al. in 2003.1 They reported that IgG4-RD was an inflammatory disease characterized by the invasion of IgG4-positive cells into various organs, such as pancreas, thyroid, retroperitoneal, and lung. IgG4-related lung disease (IgG4-RLD) occupies 14% of all IgG4-RD,2 and the pattern of lung involvement of IgG4-RD mainly shows lung hilar lymphadenopathy, thickness of bronchovascular bundles, round-shaped ground glass opacities, and consolidation.2 Thus, since IgG4-RLD presents various patterns of respiratory lesion, it is sometimes difficult to differentiate IgG4-RLD from lung cancer.3,4 Because treatment strategy differs between IgG4-RLD and malignancy,2 it is important to differentiate them correctly. In addition, very few reports showed the invasion of IgG4-RLD into adjacent organs. Herein, we report an extremely rare case of IgG4-RLD with the invasion into left diaphragm and review the previous literature.

Case Report

A 71-year-old man, who had been engaged in cement work with a smoking history of 20 packs per a year, regularly saw a doctor because of asbestos lung. Although physical examination did not detect any findings, X-ray presented a mass shadow in left lower lung field (Fig. 1A). Computed tomography (CT) image showed a 63 mm mass in left lower lung lobe, which possibly invaded the...
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adjacent diaphragm (Fig. 1B and 1C). Lymphadenopathy on lung hilum and a lot of nodules on both pleura were also observed (Fig. 1D). An abdominal CT scan showed no remarkable findings in pancreas and all the other organs. 18F-fluorodeoxyglucose-positron emission tomography (18F-FDG-PET) scan revealed high accumulation of FDG in the mass and the bilateral lung hilar lymphnodes, with the maximum standardized uptake value of 25.6 and 4.83, respectively (Fig. 2A and 2B). No abnormal accumulation of FDG in other organs was observed.

Tumor markers, such as carcinoembryonic antigen, were within normal limit. A transbronchial biopsy with bronchoscopy was performed, which revealed no malignant tissue. Based on these findings, he was preoperatively diagnosed with lung cancer, suspected (T3N1M0, Stage IIIIB). In the operation, since intraoperative aspiration cytology revealed the tumor as class V, adenocarcinoma, because of the nuclear swelling and remarkable nucleolus (Fig. 3A), left lower lobectomy was performed. Resection and reconstruction of left diaphragm was also performed because of the definite invasion of the tumor into the diaphragm. On postoperative day 5, the chest drain was removed and he was discharged on day 11 after surgery without any complications.

Pathological findings revealed no malignancy and vein stenosis, fibrosis around the vein, the infiltrating of plasma cells, and the high ratio of IgG4/IgG were observed (Fig. 3B–3D). Furthermore, inflammatory cells invaded the diaphragm (Fig. 3E). Immunohistochemical analysis showed that CD138-positive plasma cells were infiltrating (Fig. 3C). Based on these findings and a higher level of serum IgG4 even after surgery, the patient was finally diagnosed with IgG4-RLD.

**Fig. 1** The findings of a chest radiograph and CT. Chest radiograph shows mass shadow in the left lower lung field (A). Chest CT shows 63 mm mass shadows in the left lower lung lobe (B). CT in sagittal plane indicates invasion of the mass into the left diaphragm (C). Chest CT shows a lymphadenopathy in the left hilum (D). CT: computed tomography

**Fig. 2** PET-CT examination of a 71-year old with immunoglobulin G4-related disease. There is high accumulation of 18F-fluorodeoxyglucose in the mass (A) and hilar lymph node (B). CT: computed tomography; PECT: positron emission tomography
Discussion

Diagnosis of IgG4-RD requires high concentrations of serum IgG4 and pathologic findings, such as diffuse lymphoplasmacytic infiltration, irregular fibrosis, occasional eosinophilic infiltration, and obliterative vasculitis. IgG4-RD arises from multiple organs such as salivary/lacrimal gland, lung, retroperitoneum, pancreas, and sometimes present clinical features as autoimmune disease. In most cases (75%), it presents as an asymptomatic lesion which is found incidentally by imaging modalities. Most of the patients with IgG4-RLD often exhibit non-specific symptoms like cough, dyspnea, fever, chest pain, and hemoptysis.

Biological role of IgG4, a type of IgG, is not fully understood. Although it is known that the elevation of serum IgG4 level may be seen in allergy and autoimmune diseases, its mechanism has yet to be elucidated. With regard to the association between asbestos exposure and IgG4-RD, Onishi et al. speculated that asbestos induced immunological disorder, which might result in the IgG4-RD. According to the report by Miura et al., asbestos upregulate functions of regulatory T lymphocytes. Given the finding that regulatory T lymphocyte is upregulated in IgG4-related pancreatitis and cholangitis, asbestos may play a role in the pathogenesis of IgG4-RD. On the other hand, Zen et al. proposed a possible relationship between IgG4-RLD and atopic conditions.
Since this case did not have atopic disease, asbestos exposure may be the trigger of IgG4-RLD. It is reported that some cases with IgG4-RLD are mistakenly diagnosed as lung cancer because IgG4-RLD often exhibit similar findings as lung cancer on CT. Generally, the respiratory lesions of IgG4-RLD can be divided into four groups on CT images: solid nodular, round-shaped ground glass opacity, alveolar interstitial, and bronchovascular bundles. Inoue et al. reported the solid nodular type was characterized by the presence of a solitary solid lesion larger than 1.0 cm and a mass shadow observed in this case can be categorized into the solid nodular type. Thus, preoperative CT findings do not suffice for the differentiation of IgG4-RLD from lung cancer.

Regarding the therapeutic options for IgG4-RLD, glucocorticoid is mainly used and immunosuppressants, such as tacrolimus, are sometimes added. Significance of surgical resection remains to be unclear; however, the resection may possibly be considered to be one of the treatment options when drug therapy is not effective. If he was preoperatively diagnosed as IgG4-RLD, we would first choose the steroid therapy. However, when he had not responded to steroid well, we might have chosen surgical resection because of the possibility of the coexistence of lung cancer. With the invasion into the adjacent structures, very few reports exist regarding the invasion of IgG4-RLD. Alexandros et al. reported a case of IgG4-RLD extending to the thoracic vertebra and Fei et al. also reported a case of IgG4-RLD which invaded the adjacent pleura. Thus, IgG4-RLD sometimes exhibits features like malignancy, such as the invasion, although IgG4-RLD is not regarded as a malignant disease.

Conclusion

We experienced an extremely rare case of IgG4-RLD which invaded the adjacent diaphragm. Because it is sometimes difficult to differentiate IgG4-RLD and lung cancer, it possibly mislead us. There are many unclear features including pathology, so we expect a further research to the disease and the accumulation of cases.

Acknowledgments

We thank Brian Quinn for his critical comments on the manuscript.

Disclosure Statement

The authors declare no conflicts of interest in relation to this article.

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