Case report

Tin Lok Lai*, Cheuk Wan Yim

IgG4-related lung disease on the horizon

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Abstract: Immunoglobulin G4 (IgG4) related lung disease is an emerging entity. We report a case of a 42-year-old man presented with fever and cough with minimal sputum. Chest X-ray revealed diffuse reticulonodular shadows. Extensive investigations were performed, including video-assisted thoracoscopic lung biopsy, which confirmed the diagnosis of IgG4-related disease (IgG4-RD) with lung involvement. This case report aims to illustrate that IgG4-related lung involvement can present as diffuse lung nodules and can affect different pulmonary structures. IgG4-RD should always be considered when a similar scenario is encountered.

Keywords: IgG4-related disease, lung involvement, lung nodule

1 Introduction

Immunoglobulin G4-related disease (IgG4-RD) is an emerging autoimmune disorder entity, which was first proposed in 2011. Before that, various names were used to describe this syndrome. IgG4-RD can affect almost every organ including pancreas, lymph node, thyroid gland and so on. Pulmonary involvement is considered uncommon in this systemic illness, yet they have been increasingly reported over the past few years. In daily practice, it is common to encounter patients with fever, cough and radiological lung shadows. Differential diagnoses like pneumonia, pulmonary tuberculosis, malignancy or interstitial lung disease, are often considered.

Here we report a patient presented with this common scenario. Atypical pneumonia and hematological malignancy was suspected at the beginning, but the diagnosis turned out to be IgG4-related lung disease. In view of its increasing prevalence, rheumatologists should understand more and be alerted about its pulmonary manifestations.

2 Case report

A 42-year-old man was hospitalized because of on and off fever (38°C) for few days. He had a long history of smoking since the age of 18. He enjoyed good past health. Apart from fever, he noted dry cough for a few weeks. He did not complain of shortness of breath and did not have any weight loss. Physical examination was completely unremarkable, except for a palpable cervical lymph node (LN). It was firm in consistency and non-tender. It measured about 1.5 centimeters in diameter.

His chest X-ray (CXR) revealed diffuse reticulonodular shadows bilaterally (Fig. 1). Blood tests showed a normal white cell-count of 10.5 g/dL (3.7 – 9.3 x10^9/L), hemoglobin level of 10 g/dL (13.5 – 17.3 g/dL) and platelet of 605 x10^9/L (160 – 420 x10^9/L). Eosinophil count was elevated with 1.3 x10^9/L (< 0.6 x10^9/L). His renal and liver functions were grossly normal, except for a reversed albumin (23 g/L) to globulin (62 g/L) ratio. In addition, both erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were raised to 130 mm/hr and 140 mg/L (<= 8.2 mg/L) respectively. He was treated for pneumonia with intravenous antibiotics. However, his condition remained the same.

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Autoimmune markers including anti-nuclear antibody, anti-extractable nuclear antibody and anti-neutrophil cytoplasmic antibody were all negative. Fine needle aspiration (FNA) of the cervical LN revealed reactive changes with no evidence of metastasis. Sputum culture was unremarkable.

Urine for Bence-Jones protein was negative. Serum protein electrophoresis (SEP) detected monoclonal band in the gamma zone with a level of 8.1 g/L. Bone marrow aspiration was performed to exclude possible hematological malignancy. The result showed a
normocellular marrow with plasma cells at 16% without extensive infiltrates. The overall picture was suggestive of reactive changes.

In the thoracic computed tomography (CT), extensive centrilobular nodules and prominent mediastinal LNs were noted on both sides of the lung fields (Fig. 2). Fiberoptic Bronchoscopy (FOB) examination found no endobronchial lesion, and bronchoalveolar lavage for cytology and microbiological examinations including bacterial, fungal and acid-fast bacilli culture were all negative. Transbronchial lung biopsy of the right lower lobe was also unremarkable.

He complained of shortness of breath during the follow-up. His CXR findings remained similar. In view of the uncertain diagnosis, video-assisted thoracoscopic (VAT) lung biopsy was proceeded. Histological examination of the lung tissue revealed lymphoid infiltrates with reactive lymphoid follicles. There was some extension of infiltrates to the interstitium around the bronchioles. There was also an increased amount of plasma cells over the subpleural and peribronchiolar regions. Vasculitis, granuloma and malignancy were not seen. In view of the increased number of plasma cells, IgG4 related lung disease had to be considered. Nonetheless, immunostaining for IgG4/IgG ratio from this biopsy was not diagnostic of IgG4-RD.1,2 Since the diagnosis of IgG4 related lung disease had not been completely ruled out, the cervical LN specimen from the FNA was retrieved and IgG4 staining was performed. The result showed that the IgG4/IgG ratio was greater than 40%. His serum IgG4 level was 380 mg/dL (< 140 mg/dL). The final diagnosis of IgG4-related lung disease was made.

He was then started on prednisolone (0.6 mg/kg) therapy and was reviewed in our Rheumatology Clinic 4 weeks later. Although his follow-up chest X-ray was similar, his general condition remained stable without further worsening of shortness of breath.
Lung involvement in IgG4-RD is considered to be its uncommon association. However, IgG4-related lung disorders are increasingly reported over the past few years.\textsuperscript{1,2,3} The information of the incidence rate of IgG4-related lung disease is limited and confined to small case series.\textsuperscript{5} In the Italy cohorts, 2.4\% (1/41) of the IgG4-RD patients had lung involvement, while it was reported that up to 17.6\% (22/125) of the IgG4-RD patients in the United States.\textsuperscript{6,7} In the Hong Kong series, 12.7\% (7/55) of the patients was found to have this manifestation.\textsuperscript{8} Discrepancy between the results can be due to the different prevalence of IgG4-RD in various ethnicities, sample size and definition of IgG4-related lung disease.\textsuperscript{6,7,8} As the alertness and recognition of this disease increases, more lung cases in IgG4-RD are expected.

IgG4-RD can affect all the structures inside the thorax, including mediastinum, lung parenchyma, lung interstitium, airway and pleura.\textsuperscript{1,2,3} In this case report, we demonstrated a patient presented with extensive nodular lesions in the lung parenchyma. Duvic et al. in 2004 reported a 38-year-old man with retroperitoneal fibrosis, sclerosing pancreatitis and elevated IgG4 level of 346 mg/dL.\textsuperscript{9} Biopsy showed a lepidic pattern adenocarcinoma with infiltration of IgG4-positive plasma cells and obliterative phlebitis at the same time.\textsuperscript{10} A mass lesion can also occur in an extra-pulmonary site such as pleura. Zen et al. examined five specimens from pleural lesions in IgG4-RD patients.\textsuperscript{11} All these specimens showed diffuse lymphoplasmacytic infiltration with irregular fibrosis and obliterative vascular changes.\textsuperscript{11} Apart from presenting as a pulmonary or extra-pulmonary mass, ground-glass opacities with or without honeycombing had been well documented in multiple case series.\textsuperscript{12}

In our case, the patient had fever with cough, and was treated as pneumonia initially with antibiotic. A case of IgG4-RD presented as organizing pneumonia with right lung consolidation was reported by Taniguchi et al. and the lesion completely resolved after a two-week course of high dose prednisolone.\textsuperscript{13}

In the mediastinum, hilar lymph nodes enlargement is prevalent.\textsuperscript{2,3} Fujinga reviewed 90 patients with autoimmune pancreatitis and found 80\% of them had hilar adenopathy.\textsuperscript{14} Soft tissue surrounding the mediastinum can also be affected, with chronic inflammation and extensive fibrosis (sclerosing mediastinitis). Severe sclerosing mediastinitis can compress and occlude the anterior and even posterior mediastinal structures, and causing superior vena cava, central bronchial or esophageal obstruction.\textsuperscript{15,16} Inoue et al. in 2007 reported the first case of IgG4-related sclerosing mediastinitis with the main bronchus narrowing.\textsuperscript{14} Fortunately, the disease progression is usually slow and the relevant cases are still rare.\textsuperscript{15}

Within the airway, IgG4-RD can manifest as tracheobronchial stenosis or bronchial asthma.\textsuperscript{6,17,18} Ito et al. reported a case of a 63-year-old woman with autoimmune pancreatitis, who complained of dry cough. FOB revealed tracheobronchial stenosis.\textsuperscript{17} Transbronchial biopsy showed fibrosis with inflammatory infiltrates of plasma cells, lymphocytes and occasional eosinophil.\textsuperscript{17} IgG4-RD is closely related to asthma. In fact, some investigators suggested that IgG4-RD was driven by allergic mechanism.\textsuperscript{6,18} A history of atopy was noted in 31\% and 30\% of IgG4-RD patients by Della Torre et al. and Campochiaro et al., respectively.\textsuperscript{6,18} Della Torre et al. further described that many of them (25/70; 35\%) had abnormally high IgE level, and 27\% had eosinophilia.\textsuperscript{6} And a positive linear relationship between IgE and IgG4 level was found ($r = 0.07; p = 0.02$).\textsuperscript{18} Our patient did not have any atopy history, but the eosinophil count was elevated.

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<th>Table 1. Pulmonary manifestations in IgG4 related disease.</th>
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<td><strong>Structure</strong></td>
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| Lung parenchyma | Lung nodule or mass\textsuperscript{9}  
Ground glass opacity with or without honeycombing\textsuperscript{11}  
Interstitial lung disease\textsuperscript{8}  
Organizing pneumonia\textsuperscript{12} |
| Mediastinum | Hilar adenopathy\textsuperscript{11}  
Sclerosing mediastinitis\textsuperscript{14,15} |
| Airway | Tracheobronchial stenosis\textsuperscript{14}  
Asthma\textsuperscript{5,17} |
| Pleura | Pleural effusion\textsuperscript{18,19}  
Pleural nodule\textsuperscript{10} |
| Vasculture | Pulmonary hypertension\textsuperscript{11} |

Superscript refers to the reference article.
IgG4-RD can also affect pleura leading to significant effusion. Yamashita et al. reported three similar cases of massive pleural effusion in IgG4-RD patients.\(^9\) If no appropriate work-up and treatment is given for this IgG4-related effusion, the condition will recur soon after pleural drainage and can spread extensively to the pericardium, causing pericardial effusion and even cardiac tamponade.\(^2,20\) If the diagnosis of IgG4-RD can be made timely, the effusion will often respond rapidly to steroid therapy.\(^21\)

In addition to pulmonary tissues disease in IgG4-RD, pulmonary vasculature involvement had been noted by several clinicians.\(^22,23\) Ishida et al. reported the first case of pulmonary arterial hypertension in a 22-year-old woman with generalized lymphadenopathy, lacrimal and submandibular gland swellings. Echocardiography confirmed a high mean pulmonary arterial pressure, which rapidly improved with high dose prednisolone.\(^22\) Table 1 summaries all the possible IgG4-RD lung manifestations.

In histology, IgG4-related pulmonary specimens tend to have fewer plasma cells, less 'storiform' fibrosis, and have more arterial phlebitis, instead of venous phlebitis predominance.\(^23\) Some investigators proposed that the histological diagnostic criteria for IgG4-RD should be organ-specific, rather than general.\(^24,25\) That explains why the histological findings of the lung biopsy is different from that of LN biopsy in our patient. Although the IgG4 immunostaining density in his lung tissue did not fulfill the general criteria for IgG4-RD, his overall clinical picture was compatible with IgG4-related lung disease.

In conclusion, the recognition of IgG4-related lung disease is expanding. IgG4-RD can present with a wide variety of pulmonary manifestations. Rheumatologist should be more alert to this evolving autoimmune disease and its pulmonary involvement.

### References