Immunoglobulin G4-related disease: a rare steroid-responsive disease

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Keywords
IgG4-related disease, inflammation, rare disease.

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Respirology Case Reports, 5 (3), 2017, e00231
doi: 10.1002/rcr2.231

Abstract
A 70-year-old man presented with progressive dyspnoea and weight loss. Physical examination revealed only mild pale conjunctiva. The workup showed mild anaemia, mild impaired renal function, and high globulin level. Multiple myeloma was excluded by normal serum protein electrophoresis. The chest radiography and computed tomography (CT) revealed bilateral multifocal patchy infiltration with mediastinal adenopathy. Bronchoscopy was performed. Bronchoalveolar lavage (BAL) fluid examination was negative for infection and malignancy. Tissue pathology revealed diffuse lymphoplasmacytic cell infiltration. Immunohistochemistry revealed positive highlight for CD38, immunoglobulin G (IgG), and IgG4. Serum IgG subclass was requested and showed an IgG4 level of 7230 mg/dL. Examination of bone marrow and submental lymph node pathology were also positive for IgG4. IgG4-related disease with pulmonary involvement was diagnosed. Treatment with prednisolone (30 mg/day) resulted in improvement in his dyspnoea and almost complete resolution of the pulmonary infiltration on repeated CT at 6 month. This case highlighted a rare occurrence of IgG4-related disease which was successfully treated with steroid.

Introduction
Immunoglobulin G4 (IgG4)-related disease was first reported in 2003 [1]. This disease may be considered difficult to diagnose because it is known to have different types of presentations. It can mimic other diseases including malignancy, infection, and inflammatory disorders. Physicians have to be concerned if patients’ clinical presentations are not typical for the disease that they are mostly familiar with. Generally, pulmonary manifestation of IgG4-related disease is rare, and it can involve any structures of the respiratory system including airway, parenchyma, mediastinal lymph node, and pleura.

Case Report
A 70-year-old Thai man, ex-smoker with underlying hypertension and dyslipidaemia, presented with progressive dyspnoea on exertion for 3 months. He denied any history of fever, coughing, chest tightness, orthopnoea, or nocturnal dyspnoea. He had lost his appetite, resulting in 7-kg weight loss. Physical examination was unremarkable, except for mild pale conjunctiva.

A complete blood count revealed haemoglobin of 10.7 g/dL, white blood cell count of 4600 cell/mm3, and platelet count of 450,000/mm3. He also had mild renal impairment with creatinine of 2.01 mg/dL. Globulin level was 9.0 g/dL and serum protein electrophoresis showed polyclonal gammopathy with negative immunofixation. He underwent bone marrow study to exclude multiple myeloma, and the result showed hypercellular trilineage with no malignancy.

Chest radiography and computed tomography (CT) of the chest revealed bilateral multifocal patchy opacities with thickening of the interlobular septa and multiple mediastinal lymphadenopathies.
Bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsy were performed. BAL fluid examination was negative for bacteria, mycobacterium, and fungus. The BAL cytology was also negative for malignancy. Pathology revealed multiple area of lymphoplasmacytic infiltration. Immunohistochemistry was positive for CD38, and plasma cells with IgG expression were highlighted (Fig. 1). Many of these plasma cells were also positive for IgG4, with an IgG4 to IgG ratio greater than 20%. Serum IgG subclass also showed IgG4 level above 7230 mg/dL. Pathology from bone marrow and submental lymph node revealed positive result for CD38, IgG, and IgG4.

Prednisolone at 30 mg per day was started. After 1 month of treatment, he responded well clinically with

Figure 1. (A) Interstitial infiltration is composed of many plasma cells mixed with lymphocytes and few eosinophils (original magnification 200×, high power in the inset showing plasma cells). A fine fibrocollagenous background is present. The infiltration is focally noted within and around the blood vessels (arrow). (B) Immunohistochemical study revealed large amount of plasma cells as highlighted by CD38. IgG4+/IgG+ plasma cell ratio of greater than 20% is noted (immunoperoxidase, original magnification 400×).

Figure 2. Computed tomography of chest revealed multifocal patchy infiltration and thickening of interstitium with multiple mediastinal adenopathy before treatment (A, B) and complete resolution after 6 months of treatment with prednisolone (C, D).
resolution of the dyspnoea. Chest radiography and CT of the chest were followed up at 6 months and revealed significantly decreased pulmonary infiltration and mediastinal lymphadenopathy when comparison was made with previous imaging studies (Fig. 2).

Discussion

IgG4-related disease is a rare immune-mediated disorder that shares particular pathological, serological, and clinical features with other diseases. Common characteristics include tumour-like swelling, lymphoplasmacytic infiltration with IgG4-positive plasma cells, and variable degree of fibrosis [2]. Its presentation can mimic many conditions including infection, malignancy, and inflammatory diseases. Pathology is a key diagnostic tool for IgG4-related disease. Typical pathological features are dense lymphoplasmacytic infiltration organized in storiform pattern, obliterative phlebitis, and eosinophil infiltration [2]. Although tissue pathology is the gold standard for diagnosis, clinicopathological correlation is also required to confirm the diagnosis in this disease.

Pulmonary manifestations in IgG4-related disease is rare, and may involve the airway (stenosis of tracheobronchial lumen), parenchyma (pulmonary nodules, alveolar infiltration, and interstitial infiltration), pleura (pleural nodules or pleural effusion), and mediastinum (lymphadenopathy or fibrosing mediastinitis) [3]. Our patient was found to have both parenchymal and mediastinal lymph node involvement.

Radiological findings in IgG4-related disease with pulmonary involvement include solid nodules or mass, diffuse round-shaped ground-glass opacity, alveolar-interstitial infiltration, and peribronchovascular infiltration/thickening [3,4].

The goal for the treatment of IgG4-related disease is the prevention of organ dysfunction/failure. Degree of fibrosis in the organ is one of the determinant markers for treatment response. There is currently no randomized controlled trial or clinical practice guideline on IgG4-related disease treatment. The usual recommended treatment involves systemic corticosteroid (prednisolone 0.6 mg/kg/day) for 2–4 weeks with gradual tapering to 5 mg/day in 3–6 months, then maintenance with prednisolone 2.5–5 mg/day for about 3 years to prevent disease recurrence [5].

In summary, IgG4-related disease is a rare immune-mediated disorder with various clinical presentations. This case study illustrates an excellent response of both pulmonary and nodal disease after treatment with oral corticosteroids.

Disclosure Statements

No conflict of interest declared.
Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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