A case of proteinase 3 anti-neutrophil cytoplasmic antibody (PR3-ANCA) positive/IgG4-related lung disease

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1. Introduction

IgG4-related disease (IgG4-RD) has been of interest since 2001, when Hamano reported infiltration of IgG4-positive plasma cells in the pancreas [1]. IgG4-related lung disease (IgG4-RLD) has been described as interstitial pneumonia and inflammatory pseudo-tumor [2–7]. Proteinase 3 anti-neutrophil cytoplasmic antibody (PR3-ANCA) is well known as a disease marker in Wegener’s granulomatosis [8]. Here, we report a case of PR3-ANCA-positive IgG4-RLD with a 10-cm tumor lesion.

2. Case report

A 61-year-old man consulted a local general practitioner in August 2015 with a complaint of cough for a month. He was referred to our hospital because of a 10-cm diameter mass in the right lower lung field in chest X-ray. On admission, a physical examination revealed a temperature of 37.7 °C, and laboratory data showed a white blood cell count of 11,900/μL and serum C-reactive protein (CRP) of 12.3 mg/dL. Chest computed tomography (CT) showed right pleural effusion and a 10-cm diameter mass in the right lower lobe and swelling of mediastinal lymph nodes (Fig. 1A and B).

Flexible bronchial bronchoscopy and transbronchial lung biopsy were performed. The pathological findings from the biopsy showed inflammatory granuloma with infiltration of lymphocytes and plasma cells (Fig. 2A). Immunostaining showed >20 IgG4-positive plasma cells/high-power field (HPF) (Fig. 2B). Serum levels of IgG and IgG4 were elevated to 2,211 and 258 mg/dL, respectively. PR3-ANCA was 246 U/mL (normal range: <3.5 U/mL) with normal range of anti-nuclear antibodies.

Diagnosis of IgG4-RLD was made based on the high level of IgG4 and chest CT findings. The patient was started on 30 mg/day of prednisolone for two weeks, and then the dose was tapered to 20 mg/day. Over the following weeks, the patient began to report fewer symptoms. At one month after admission, there was marked reduction of pseudo-tumor and right pleural effusion (Fig. 1C and D) on chest CT, and the patient was discharged. After three months of treatment, IgG4 and PR3-ANCA decreased to 122 mg/dL and 61.6 U/mL, respectively.

3. Discussion

There are two unique aspects in the present case: infiltrated plasma cells in pseudo-tumor with high serum IgG4; and elevated PR3-ANCA at admission. IgG4-RLD occurs in 12–50% of patients...
with IgG4-RD [3–5]. Mediastinal adenopathy is most common and pulmonary involvement takes the form of pulmonary nodules or masses [3,6–8]. As shown in Fig. 1A and B, our case presented with mass formation in the right lower lung with mediastinal adenopathy. Pathologically, the lesion consisted of a diffuse lymphoplasmacytic infiltrate with pseudo-tumor (Fig. 2A). In histochemical staining, the case met diagnostic criteria for IgG4-RD published by Umehara et al. [9].

Histologically, granulomatosis with polyangiitis (GPA) can mimic IgG4-RD since the inflammatory background in GPA may be rich in plasma cells and accompanied by fibrosis or obliterated blood vessels, as in IgG4-RD [10]. Della-Torre et al. reported a case of PR3-ANCA-seropositive IgG4-RLD and GPA [11]. However, our case had no findings of GPA. PR3-ANCA is a disease marker autoantibody found in GPA [8] and the clinical manifestations of IgG4-RD and ANCA-associated vasculitis may overlap [12]. Previous case reports have described PR3-ANCA/IgG4-positive fibrotic diseases in the retroperitoneum [13], and cranium [14], without features of GPA. This is the reported case to present with PR3-ANCA/IgG4-positive fibrotic disease in the lung without any manifestation of GPA. Regarding the relationship between IgG4 and PR3-ANCA, several analyses have shown the importance of the IgG4 subclass of PR3-ANCA, which induces inflammation in patients with GPA [8,15,16]. IgG4 anti-proteinase 3 antibodies stimulate neutrophils to undergo a pro-inflammatory response and may play a role in the pathogenesis of small vessel vasculitis [8,17,18].

The predominance of IgG4 and IgG1 subclasses of ANCA was first reported in patients with GPA and other clinically related disorders by Brouwer et al., in 1991 [17]. Holland et al. later suggested a possible pathogenic role for the IgG4 subclass in GPA [8].

In vitro, ANCA activates neutrophils by co-ligating PR3 and FcγRIIa/IIIb receptors [8]. ANCA are predominantly of the IgG isotype, and the IgG1, IgG3, and IgG4 subclasses are particularly represented. The IgG4 subclass isolated from ANCA-positive sera has varying abilities to stimulate release of superoxide, unrelated to the PR3-ANCA titer, neutrophil donors in vitro, or neutrophil FcγRI expression [8]. Liu et al. suggested that the MPO-ANCA IgG4 subclass might play a role in development of GPA [18], based on titers of the anti-MPO IgG4 subclass in patients with GPA being significantly higher than those with microscopic polyangiitis (MPA). MPO-ANCA in GPA and MPA might recognize overlapping but different epitopes on native MPO molecules. The difference in immunological characteristics of MPO-ANCA might contribute to different disease entities, such as GPA and MPA, and spontaneous regression of both pulmonary and extrapulmonary lesions in IgG4-related lung diseases occurs in GPA, although most patients receive treatment [19–21].

In our case, the disease condition was improved following hormonal therapy. This is the rare reported case of IgG4-RLD with elevated PR3-ANCA. The mechanism of pseudo-tumor formation in this case may be associated with the IgG4 subclass of PR3-ANCA that induces inflammation in patients with Wegener’s granulomatosis. Further accumulation of similar cases is required to understand this mechanism.

4. Conclusion

This is the rare report of seropositive PR3-ANCA followed with IgG4- RLD. This case indicated that IgG4 subclass of PR3-ANCA might contribute to be different findings of MPA.
(A)

Fig. 2. (A) Pathological findings of inflammatory granuloma with infiltration of lymphocytes and plasma cells (red arrow) in trans-bronchial lung biopsy of the pseudo-tumor lesion. (B) Immunohistological images, the deep cells-lgG4-positive plasma cells and plasma cells (red arrow) in

Conclusions

Fig. 3. Immuno-reactivity of the expression of IgG4 and IgG1 in the gastrointestinal tract of patients with IgG4-related disease. The Staining of IgG4-positive plasma cells and plasma cells (red arrow) in

Conflict of interest

The authors have no conflict of interest.

References

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