Respiratory Medicine Case Reports 20 (2017) 92–94

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr

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

Hirokazu Touge [a, 1], Katsuyuki Tomita [a, *], Akira Yamasaki [b, 2], Eiji Shimizu [b, 2]

[a] Department of Respiratory Medicine, Yonago Medical Centre, Tottori, Japan
[b] Division of Medical Oncology and Molecular Respirology, Tottori University Faculty of Medicine, Tottori, Japan

ARTICLE INFO

Article history:
Received 16 December 2016
Received in revised form
4 January 2017
Accepted 5 January 2017

Keywords:
IgG4
Lung
PR3-ANCA

ABSTRACT

IgG4-related lung disease (IgG4-RLD) is a rare and chronic progressive autoimmune disease. We report a case of IgG4-related inflammatory pseudo-tumor of the lung that was seropositive for proteinase 3 anti-neutrophil cytoplasmic antibody (PR3-ANCA). A 61-year-old male had a mass lesion in the right lower lung field in chest X-ray. Transbronchial lung biopsy resulted in a pathological diagnosis of IgG4-RLD. The condition was improved by hormonal therapy.

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

* Corresponding author. Department of Respiratory Medicine, Yonago Medical Centre, 4-17-1 Kuzumo, Yonago, 683-8504, Japan. Tel.: +81 859 33 7111; fax: +81 859 34 1580.
E-mail address: tomita-katsuyuki@nho-yonago.jp (K. Tomita).
[1] Tel.: +81 859 33 7111; fax: +81 859 34 1580.
[2] Tel.: +81 859 38 6537; fax: +81 859 38 6539.

http://dx.doi.org/10.1016/j.rmcr.2017.01.001

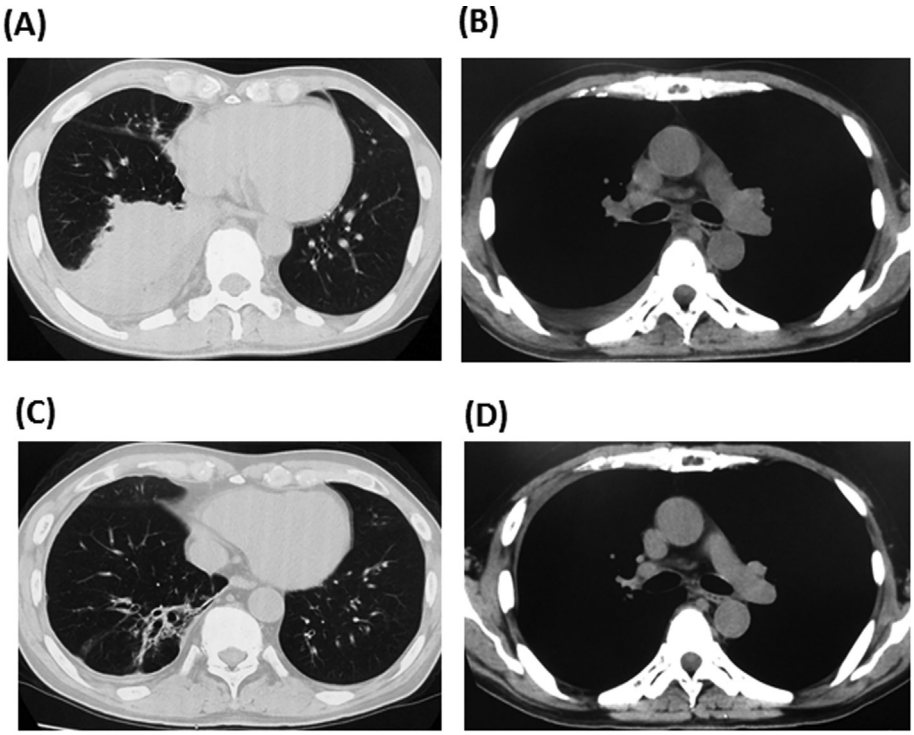

Fig. 1. (A, B) Plain chest CT on admission showed right pleural effusion and a 10-cm diameter mass in the right lower lobe. (C, D) Plain chest CT after hormonal treatment showed development of pleural effusion and pseudo-tumor.

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.

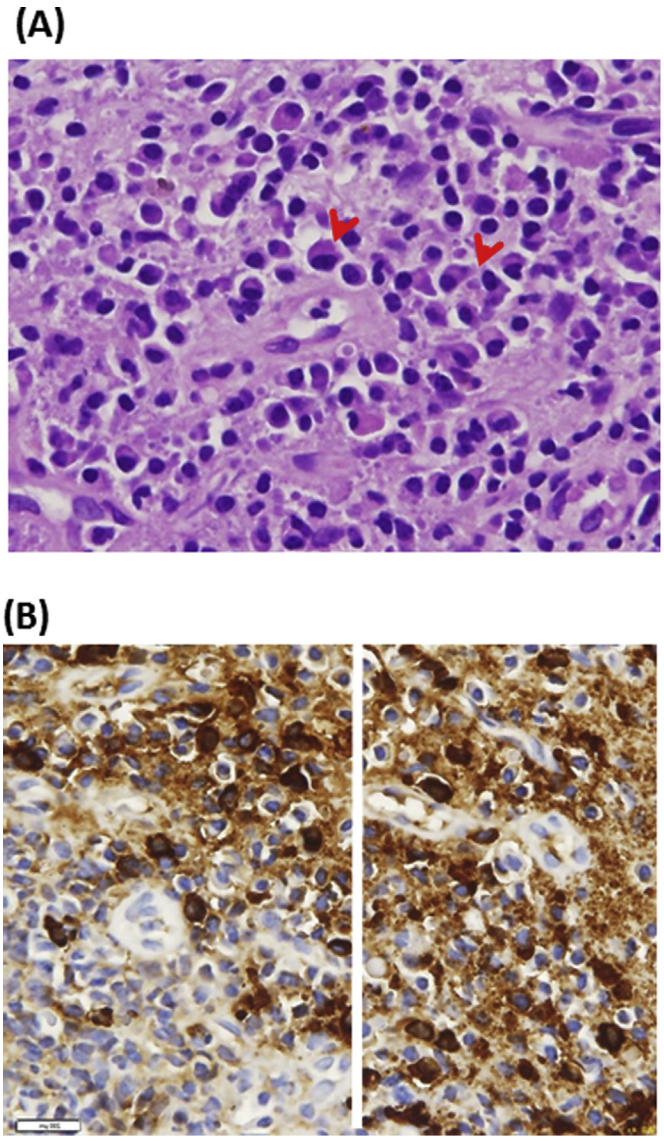

Fig. 2. (A) Pathological findings of inflammatory granuloma with infiltration of lymphocytes and plasma cells (red arrow) in *trans*-bronchial lung biopsy of the pseudotumor lesion. (B) Immunohistological images, the deep cells-IgG4-positive plasma cells (>20/HPF) (×400). HPF, high power field.

Conflict of interest

The authors have no conflict of interest.

References

[1] H. Hamano, N. Arakura, T. Muraki, Y. Ozaki, K. Kiyosawa, S. Kawa, Prevalence and distribution of extrapancreatic lesions complicating autoimmune pancreatitis, J. Gastroenterol. 41 (2006) 1197–1205.
[2] C. Duvic, J. Desrame, C. Lévêque, G. Nedelec, Retroperitoneal fibrosis, sclerosing pancreatitis and bronchiolitis obliterans with organizing pneumonia, Nephrol. Dial. Transpl. 19 (2004) 2397–2399.
[3] Y. Fujinaga, M. Kadoya, S. Kawa, H. Hamano, K. Ueda, M. Momose, S. Kawakami, S. Yamazaki, T. Hatta, Y. Sugiyama, Characteristic findings in images of extra-pancreatic lesions associated with autoimmune pancreatitis, Eur. J. Radiol. 76 (2010) 228–238, http://dx.doi.org/10.1016/j.ejrad.2009.06.010.
[4] H. Ohara, T. Nakazawa, H. Sano, T. Ando, T. Okamoto, H. Takada, K. Hayashi, Y. Kitajima, H. Nakao, T. Joh, Systemic extrapancreatic lesions associated with autoimmune pancreatitis, Pancreas 31 (2005) 232–237.
[5] Y. Zen, Y. Nakanuma, IgG4-related disease: a cross-sectional study of 114 cases, Am. J. Surg. Pathol. 34 (2010) 1812–1819, http://dx.doi.org/10.1097/PAS.0b013e3181f7266b.
[6] R. Raj, IgG4-related lung disease, Am. J. Respir. Crit. Care. Med. 188 (2013) 527–529, http://dx.doi.org/10.1164/rccm.201306-1121ED.
[7] R. Raj, V. Boddipalli, C. Brown, J. Dematte, K. Raparia, IgG4-related lung disease, Clin. Pulmon. Med. 21 (2014) 230–238, http://dx.doi.org/10.1097/CPM.0000000000000057.
[8] M. Holland, P. Hewins, M. Goodall, D. Adu, R. Jefferis, C.O. Savage, Anti-neutrophil cytoplasmic antibody IgG subclasses in Wegener's granulomatosis: a possible pathogenic role for the IgG4 subclass, Clin. Exp. Immunol. 138 (2004) 183–192.
[9] H. Umehara, K. Okazaki, Y. Masaki, M. Kawano, M. Yamamoto, T. Saeki, S. Matsui, T. Yoshino, S. Nakamura, S. Kawa, H. Hamano, T. Kamisawa, T. Shimosegawa, A. Shimatsu, S. Nakamura, T. Ito, K. Notohara, T. Sumida, Y. Tanaka, T. Mimori, T. Chiba, M. Mishima, T. Hibi, H. Tsubouchi, K. Inui, H. Ohara, Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011, Mod. Rheumatol. 22 (2012) 21–30, http://dx.doi.org/10.1007/s10165-011-0571-z.
[10] K.O. Leslie, M.R. Wick, Practical Pulmonary Pathology: a Diagnostic Approach, second ed., Elsevier Saunders, Philadelphia, PA, 2011.
[11] E. Della-Torre, M. Lanzillotta, C. Campochiaro, E. Bozzalla, E. Bozzolo, A. Bandiera, E. Bazzigaluppi, C. Canevari, G. Modorati, J.H. Stone, A. Manfredi, C. Doglioni, Antineutrophil cytoplasmic antibody positivity in IgG4-related disease: a case report and review of the literature, Med. (Baltimore) 95 (2016) e4633, http://dx.doi.org/10.1097/MD.0000000000004633.
[12] R. Perez Alamino, C. Martínez, L.R. Espinoza, IgG4-associated vasculitis, Curr. Rheumatol. Rep. 15 (2013) 348, http://dx.doi.org/10.1007/s11926-013-0348-9.
[13] S. Kotani, R. Wakamatsu, A. Itoh, K. Miyamoto, M. Yoshino, K. Takami, S. Ishihara, N. Miura, S. Banno, H. Imai, Proteinase 3 anti-neutrophil cytoplasmic antibody (PR3-ANCA) positive IgG4-related retroperitoneal fibrosis: utility of PET-CT with 18F-fluorodeoxy glucose (FDG), Intern. Med. 51 (2012) 755–758.
[14] A. Iguchi, Y. Wada, D. Kobayashi, H. Sato, T. Oyama, T. Nakatsue, S. Murakami, T. Kuroda, M. Nakano, I. Narita, A case of MPO- and PR3-ANCA-positive hypertrophic cranial pachymeningitis with elevated serum IgG4, Mod. Rheumatol. 23 (2013) 151–155, http://dx.doi.org/10.1007/s10165-012-0613-1.
[15] G. Almroth, G. Berlin, B. Andersson, M. Hahn-Zoric, Long-term treatment results and the immunoglobulin G subclass distribution patterns of proteinase-3-antineutrophil cytoplasm antibody (ANCA) and myeloperoxidase-ANCA in ANCA-associated vasculitis, Scand. J. Urol. Nephrol. 43 (2009) 160–170, http://dx.doi.org/10.1080/00365590802519354.
[16] A. Hussain, T. Pankhurst, M. Goodall, R. Colman, R. Jefferis, C.O. Savage, J.M. Williams, Chimeric IgG4 PR3-ANCA induces selective inflammatory responses from neutrophils through engagement of Fcγ receptors, Immunology 128 (2009) 236–244, http://dx.doi.org/10.1111/j.1365-2567.2009.03108.x.
[17] E. Brouwer, J.W. Tervaert, G. Horst, M.G. Huitema, M. van der Giesse, P.C. Limburg, C.G. Kallenberg, Predominance of IgG1 and IgG4 subclasses of anti-neutrophil cytoplasmic autoantibodies (ANCA) in patients with Wegener's granulomatosis and clinically related disorders, Clin. Exp. Immunol. 83 (1991) 379–386.
[18] L.J. Liu, M. Chen, F. Yu, M.H. Zhao, H.Y. Wang, IgG subclass distribution, affinity of anti-myeloperoxidase antibodies in sera from patients with Wegener's granulomatosis and microscopic polyangiitis, Nephrology 13 (2008) 629–635, http://dx.doi.org/10.1111/j.1440-1797.2008.00976.x.
[19] M. Gum, G.S. Firestein, IgG4-related diseases, Best. Pract. Res. Clin. Rheumatol. 26 (2012) 425–438, http://dx.doi.org/10.1016/j.berh.2012.07.001.
[20] A. Khosroshahi, M.N. Carruthers, V. Deshpande, S. Unizony, D.B. Bloch, J.H. Stone, Rituximab for the treatment of IgG4-related disease: lessons from 10 consecutive patients, Med. (Baltimore) 91 (2012) 57–66, http://dx.doi.org/10.1097/MD.0b013e3182431ef6.
[21] J. Murakami, S. Matsui, S. Ishizawa, K. Arita, A. Wada, T. Miyazono, H. Hounoki, K. Shinoda, H. Taki, T. Sugiyama, Recurrence of IgG4-related disease following treatment with rituximab, Mod. Rheumatol. 23 (2013) 1226–1230, http://dx.doi.org/10.1007/s10165-012-0738-2.