Corticosteroid Therapy for a Patient with Relapsing Polychondritis Complicated by IgG4-Related Disease

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Relapsing polychondritis (RP) is a rare systemic disorder characterized by recurrent, widespread chondritis of the auricular, nasal, and tracheal cartilages. IgG4-related disease (IgG4-RD) is a systemic immune-mediated disease characterized by the infiltration of IgG4-bearing plasma cells into systemic organs. Although 25% to 35% of patients with RP have a concurrent autoimmune disease, coexistence of RP and IgG4-RD is rare. We herein report a case of RP complicated by IgG4-RD. A 63-year-old man developed recurrent bilateral ear pain and swelling, recurrent blurred and decreased vision, and migratory multiple joint pain, sequentially within one year. Fourteen months after the first symptom, he experienced dry cough and dyspnea with exertion. A computed tomography (CT) scan detected interstitial pneumonia, swelling of bilateral submandibular glands, bilateral hilar and mediastinal lymphadenopathy, and several nodules in bilateral kidneys. His serum levels of IgG and IgG4 were elevated. The biopsy specimen of auricular cartilage showed infiltrations of inflammatory cells and fibrosis consistent with RP. The IgG4-positive cells were not observed in auricular cartilage. The patient met the diagnostic criteria of RP, including bilateral auricular chondritis, conjunctivitis, iritis and polyarthritis. The biopsy specimens of lung and kidney revealed the significant infiltrations of IgG4-positive plasma cells and fibrosis. We also diagnosed him as having IgG4-RD, affecting bilateral submandibular glands, hilar and mediastinal lymph nodes, lungs, and kidneys. Thus, RP preceded the onset of IgG4-RD. Corticosteroid therapy improved the symptoms and CT scan findings. In conclusion, RP and IgG4-RD do coexist; however, the pathogenesis of their coexistence is unknown.

Keywords: coexistence; corticosteroid therapy; fibrosis; IgG4-related disease; relapsing polycondritis

Introduction

The disorder referred to as IgG4-related disease (IgG4-RD) is characterized by diffuse infiltration of IgG4-positive plasma cells into multiple organs with fibrosis and elevation of serum IgG4 level (Umehara et al. 2012). Its target organs are lacrimal and salivary glands, thyroid, lymph nodes, lungs, pancreas, biliary duct, liver, kidneys, retroperitoneum, aorta, and prostate gland. The potential initiating mechanisms of IgG4-RD are thought to be genetic risk factors (Kawa et al. 2002), bacterial infection and molecular mimicry (Guarneri et al. 2005; Frulloni et al. 2009; Kawano et al. 2009; Siddiquee et al. 2012), and autoimmunity (Aparisi et al. 2005; Asada et al. 2006; Lohr et al. 2010). Th2-biased inflammation is observed in affected tissue (Zen et al. 2007) and tissue inflammation could cause organ dysfunction and epithelial cell damage (Stone et al. 2012).
al. 1976). The case report of RP associated with IgG4-RD is rare (Nagayama et al. 2015). Herein we present a rare case of RP complicated by IgG4-RD.

Case Presentation

In February 2015, a 63-year-old man was admitted to our hospital for the close examination of recurrent bilateral auricular chondritis and iritis, and abnormal chest shadow. He had a past medical history of benign prostatic hyperplasia and hyperuricemia. He was not suffering from gout. He was an ex-smoker of one pack × 40 years. He developed pain and swelling of the bilateral ears in August 2013. The ear symptoms remitted after two weeks, and then worsened with an interval of one week. He was diagnosed with auricular chondritis and was treated with short-term corticosteroid therapy (maximum dose was prednisolone 20 mg·day⁻¹, for two weeks). Thereafter, his ear symptoms remitted. He had complained of recurrent bilateral blurred and decreased vision in October 2013. He was also diagnosed with iritis and treated with corticosteroid eye-drop therapy. The eye symptoms recurred four times before admission to our hospital for the close examination of recurrent bilateral auricular chondritis and iritis, and abnormal chest shadow.

A physical examination on admission detected bilateral auricular deformity and pigmentation (Fig. 1). A hearing test showed mild sensorineural hearing loss in both ears. Saddle nose was not observed. Bilateral bulbar conjunctival hyperemia was observed. Tenderness and swelling were observed in bilateral wrist joints, elbow joints, II-IV metacarpophalangeal joints, and ankle joints. Fine crackles were heard in the bilateral lower lung fields. His body temperature was 36.5°C; pulse rate 60 beats·min⁻¹; respiratory rate 18 breaths·min⁻¹; and SpO₂ 97% at room air. Laboratory data on admission included a white blood cell count of 4,900 cells·mm⁻³ with 56.5% neutrophils, 32.2% lymphocytes, 3.1% eosinophils and C-reactive protein of 0.55 mg·dL⁻¹. Serum levels of IgG and IgG4 were elevated to 2,965 mg·dL⁻¹ and 688 mg·dL⁻¹, respectively. Serum levels of C3, C4, and CH50 decreased to 46.6 mg·dL⁻¹, less than 2.0 mg·dL⁻¹, and less than 10.0 U·mL⁻¹, respectively. Serum titer of an antinuclear antibody was elevated to ×640. Serum titers of autoantibodies, including anti-cyclic-citrullinated protein antibodies, anti-SS-A and B antibodies, myeloperoxidase-anti-neutrophil cytoplasmic autoantibody (ANCA), and proteinase 3-ANCA, were within normal range. Tumor markers, interleukin (IL)-6, and angiotensin converting enzyme in serum were not elevated. Serum levels of KL-6 and surfactant protein-D were within normal range. Serum levels of uric acid, creatinine, and blood urea nitrogen were not elevated. Urinalysis did not show protein and occult blood. Microscopic examination of the urine sediment did not reveal any red blood cells, white blood cells, or cellular casts. Urinary β₂-microglobulin and N-acetyl-β-D-glucosaminidase levels were 1,272 µg·mL⁻¹ (normal range; < 200 µg·mL⁻¹) and 8.3 U·L⁻¹ (normal range; < 11.5 U·L⁻¹), respectively. Pulmonary function tests showed normal percentages of vital capacity (96.2%) and forced expiratory volume 1 second (83.3%); however, % diffusing capacity for carbon monoxide (DLco) was decreased to 67.6%. A chest high-resolution CT scan detected ground-glass opacity with interlobular septal thickening in the bilateral lower lobes (Fig. 2a) and contrast-enhanced CT revealed, bilateral submandibular glands swelling (Fig. 2c), bilateral hilar and mediastinal lymphadenopathy (Fig. 2e), and several low-attenuation lesions in the bilateral kidneys (Fig. 2g). Gallium-67 (⁶⁷Ga) scintigraphy detected abnormal accumulations in bilateral submandibular glands, hilar and mediastinal lymph nodes, lower lobes of lungs, kidneys, and bilateral wrist and elbow joints (Fig. 3a, b). The hands X-rays did not reveal bone erosions. A bronchofiberscopy also did not detect the stenosis nor the abnormal mucous membrane of the trachea nor bronchi. Bronchoalveolar lavage showed elevated ratios of lymphocytes and eosinophils to 18.6% and 5.5%, respectively.

A biopsy specimen of the right auricle revealed infiltrations of lymphocytes including plasma cells and fibrosis in the auricular cartilage that were consistent with RP (Fig. 4a-c). Immunohistochemistry against the auricle biopsy specimen did not reveal any infiltrations of IgG4-positive plasma cells into the auricular cartilage (Fig. 4d). We diagnosed him as having RP according to the diagnostic criteria proposed by McAdam, et al. with the positive findings of bilateral auricular chondritis, ocular inflammation (scleritis and uveitis), audiovestibular damage (sensorineural hearing disorder), and nonerosive seronegative inflammatory polyarthritis (McAdam et al. 1976). A biopsy of the right kidney revealed moderate and patchy infiltrations of lymphocytes, including plasma cells, and focally surrounding sclerofibrosis in the interstitium (Fig. 5a-c). The ratio of IgG4-positive/IgG-positive plasma cell in the kidney speci-
men was elevated to 41.1% (Fig. 5d). A transbronchial lung biopsy showed alveolar interstitium thickening with plasma cells infiltration and fibrosis (Fig. 6a, b), and IgG4-positive plasma cells were observed over ten cells in a high power field of the lung specimen (Fig. 6c). We, therefore, diagnosed him as having the following: definite IgG4-related kidney disease (IgG4-RKD), according to the diagnostic criteria of IgG4-RKD proposed by Kawano et al. (2011), probable lung complication of IgG4-RD, and possible submandibular glands and hilar and mediastinal lymph node involvements of IgG4-RD, according to the Japanese comprehensive diagnostic criteria for IgG4-RD (Umehara et al. 2012).

We started 50 mg·day−1 of oral prednisolone therapy and all of his symptoms gradually improved. One month later, CT scan showed the improvement of interstitial shadows in the bilateral lower lobes (Fig. 2b); shrinkage of the submandibular glands (Fig. 2d) and bilateral hilar and
Fig. 3. Gallium-67 scintigraphy.
Gallium-67 scintigraphy detected abnormal accumulation in bilateral submandibular glands, bilateral hilar and mediastinal lymph nodes, bilateral lower lobes of lungs, both kidneys, and bilateral wrist and elbow joints on admission (a: anterior, b: posterior). Gallium-67 scintigraphy revealed the improvement of abnormal accumulation one month after corticosteroid therapy (c: anterior, d: posterior).

Fig. 4. Biopsy specimens of the right auricle.
(a)-(c) A biopsy specimen of the right auricle showed infiltration of lymphocytes, including plasma cells (a, Haematoxylin and eosin stain, ×200, arrow), with fibrosis (b, Azan stain, ×200, dark blue; c, Elastica van Gieson stain, ×200, red) into the auricular cartilage. (d) Immunohistochemistry against the auricular cartilage specimen detected no IgG4-positive plasma cells (×200).
mediastinal lymph nodes (Fig. 2f); decreased sizes of the low-attenuation lesions in bilateral kidneys (Fig. 2h).  \(^{67}\)Ga scintigraphy revealed the improvement of abnormal accumulation in bilateral submandibular glands, hilar and mediastinal lymph nodes, lower lobes of lungs, kidneys, and bilateral wrist and elbow joints (Fig. 3c, d). The serum levels of IgG and IgG4 were decreased to 1,306 mg·dL\(^{-1}\) and 306 mg·dL\(^{-1}\), respectively. Hypocomplementemia was normalized. Urinary \(\beta\)2-microglobulin was decreased to 128 \(\mu\)g·mL\(^{-1}\). \%DLco was normalized to 82.3%. We have tapered the oral dose of prednisolone by five mg·day\(^{-1}\) every two weeks. He is now treated with 20 mg·day\(^{-1}\) of oral prednisolone therapy and his symptoms are stable.

**Discussion**

The etiologies of RP and IgG4-RD are not fully understood. In both RP and IgG4-RD, the pathogenesis might be the autoimmune response to bacterial antigen and genetic susceptibility. An antibody, derived from the B cells of a RP patient, bound to both the cartilage and heat shock protein 60 derived from *Mycobacterium tuberculosis* (Menge et al. 2002). *Borrelia garinii* caused ear perichondritis, mimicking RP (Belot et al. 2013). A significant increase in DR4 antigen frequency was found in the RP patients as compared with that in healthy controls (Lang et al. 1993). Infections with various species of bacteria, such as *Helicobacter pylori* (Guarneri et al. 2005; Frulloni et al. 2009), gram-positive bacteria (Siddiquee et al. 2012), and *Mycobacterium tuberculosis* (Kawano et al. 2009), could be the pathogenesis of IgG4-RD. Autoimmune pancreatitis (AIP) is the major retroperitoneal manifestations of IgG4-RD. DRB1*0405-DQB1*0401 haplotype is associated with AIP in the Japanese population (Kawa et al. 2002).

Approximately 30% of patients with RP have a coexistence of rheumatic or autoimmune disease (McAdam et al. 1976). The coexistence of RP and IgG4-RD is very rare (Nagayama et al. 2015). The associated autoimmune disease usually preceded the development of RP, sometimes by many years. RP preceded the development of IgG4-RD both in the previous case and in our case. Nagayama et al. (2015) reported the case of a 45-year-old man who exhibited bilateral auricular chondritis, polyarthritis, and ocular inflammation. The patient was diagnosed as having RP. He was successfully treated with corticosteroid therapy and his symptoms of RP had remitted. Twenty years after the diag-

![Fig. 5. Biopsy specimens of the right kidney.](image-url)

(a)-(c) A biopsy specimen of the right kidney showed moderate infiltration of lymphocytes, including plasma cells (a, Haematoxylin and eosin stain, \(\times200\)), and focally surrounding sclerofibrosis in interstitium (b, Masson’s Trichrome stain, \(\times200\), blue; c, Periodic acid-methenamine-silver stain, \(\times200\), dark brown). (d) Immunohistochemistry against the kidney specimen showed IgG4-positive plasma cells (brown, arrow) in the kidney specimen (\(\times200\)).
nosis of RP, he developed IgG4-RD of the pancreas and bilateral kidneys. The authors suggest that RP might have been incidentally complicated by IgG4-RD, because IgG4-RD occurred approximately 20 years after the diagnosis of RP and RP has been in a state of reduced activity at the development of IgG4-RD (Nagayama et al. 2015). In our case, the development of IgG4-RD would be related to the underlying RP, because our patient developed IgG4-RD 14 months after the onset of RP and during the active state of RP. After the remission of auricular chondritis, the patient developed symptoms of scleritis, uveitis, and arthritis probably due to RP. Ga-scintigraphy did not show abnormal accumulations in the auricle; however, it could detect abnormal accumulations in bilateral wrist and elbow joints at the time of admission to our hospital. RP would be also active at the development of IgG4-RD.

In the aspect of Th1 and Th2 paradigms, it has been reported that RP would be the Th1-biased autoimmune disease (Kraus et al. 2003; Takagi et al. 2004; Arnaud et al. 2014). Serum levels of interferon-γ, IL-12, and IL-2 paralleled changes in disease activity in a patient with RP, while the levels of Th2 cytokines (IL-4, IL-5, IL-6, and IL-10) did not (Kraus et al. 2003). The CD4-positive T cells from patients with RP exhibited a Th1-bias and NKT cells played a regulatory role in Th1 autoimmunity in patients with RP (Takagi et al. 2004). In contrast, Okazaki et al. (2011) suggest a biphasic pathogenic mechanism in IgG4-RD. During the initial “induction phase”, the decreased levels of naive regulatory T cells (T-regs) cause Th1-biased immune response and release of proinflammatory cytokines. The persistent presence of triggering pathogens maintains activation of the immune system, which eventually induces a Th2 and peripheral T-regs response in the “progression phase”. In our case, up-regulation of Th1-biased state in RP might set off the “induction phase” of IgG4-RD; and then the up-regulation of Th2 cytokines and T-reg cytokines might occur in the “progression phase” of IgG4-RD.

The patients with RP were usually treated with a non-steroidal anti-inflammatory drug, dapsone, or colchicine (Gergely and Poor 2004). Systemic corticosteroid therapy is introduced for acute exacerbation of RP. Systemic corticosteroid with immunosuppressive therapy has been recommended for recurrent cases of RP. Clinicians have the choice of watchful waiting for IgG4-RD patients without organ dysfunction (Stone et al. 2012). Corticosteroid is a first-line therapy for patients with IgG4-RD with organ dys-
function. Immunosuppressants could be used as steroid-sparing agents. For recurrent or refractory cases of IgG4-RD, B cell depletion by rituximab therapy could be effective. Therapeutic strategy for coexisted cases of RP and IgG4-RD is not established because of its paucity. A previous coexisted case of RP and IgG4-RD was observed without therapy because the patient did not have organ dysfunction (Nagayama et al. 2015). We treated our patient with corticosteroid therapy because he had the symptoms of RP and IgG4-RD. Although good clinical response has been obtained so far in our case, we would need the observation for the long term prognosis.

Herein, we report a patient with RP complicated by IgG4-RD. It is still unknown why both diseases coexist. Corticosteroid therapy was effective for our patient. Further accumulation of case experiences is needed to clarify the pathophysiology of RP complicated by IgG4-RD.

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Conflict of Interest
The authors declare no conflict of interest.

References


