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Case Report

Relapsing polychondritis or relapsing polychondritis-like symptoms associated with IgG4-RD. Case reports and review of the literature

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ABSTRACT

Relapsing polychondritis (RP) is a rare systemic disorder characterised by recurrent, widespread chondritis of the auricular, nasal, and tracheal cartilages. Immunoglobulin G4-related disease (IgG4-RD) is a systemic immune-mediated disease characterised by the infiltration of IgG4-bearing plasma cells into systemic organs. However, 25–35% of patients with RP have a concurrent autoimmune disease. The coexistence of RP and IgG4 is rare considering that, to the best of our knowledge, there are only four previous reports of RP or RP-like symptoms associated with IgG4-RD. We herein report two cases which could be RP or RP-like symptoms associated with IgG4-RD.

KEYWORDS: IgG4-RD; relapsing polychondritis (RP); RP-like symptoms

Introduction

There is great interest in the recently defined disease known as immunoglobulin G4-related disease (IgG4-RD); it is a newly recognised fibroinflammatory condition characterised by several features: a tendency to form tumefactive lesions at multiple sites; a dense lymphoplasmacytic infiltrate rich in IgG4 plasma cells; storiform fibrosis; and, often but not always, elevated serum IgG4 concentrations. The disease was initially recognised in the pancreas, disease now known as autoimmune pancreatitis.

Relapsing polychondritis (RP) is a rare disease characterised by recurrent systemic cartilage inflammation. Although the cause of RP is still unknown, an autoimmune aetiology is thought to be closely involved.

The coexistence of RP and IgG4 is rare considering that, to the best of our knowledge, there are only four previous reports of RP or RP-like symptoms associated with IgG4-RD [1–4].

We herein report two cases which could be RP or RP-like symptoms associated with IgG4-RD.

Case reports

Case 1

A 37-year-old woman, with a history of chronic rhinitis and early asthma in adulthood, having a swelling of bilateral auricular pavilions for a year, with periauricular erythematous cutaneous and painful nodules, which had been derived with a presumptive diagnosis of RP (Figure 1). The physical examination showed an increase in auricular cartilage and indurated erythematous and painful nodules, cervical and occipital adenopathies, bilateral tinnitus, and arthritis of small joints.

Examination of the skin and auricular cartilage specimens showed inflammatory lymphoplasmocytic infiltrate in skin and cartilage with storiform fibrosis, mild eosinophil infiltrate, and absence of obliterating phlebitis (Figure 2). There was no evidence of malignancy or granuloma or neutrophilic infiltrates. The immunohistochemistry in skin and cartilage presented >80 cells/high-power field (HPF) and IgG4/IgG ratio >85% (Figure 3). The audiometric studies showed bilateral and symmetric sensorineural hearing loss. A computed tomography (CT) scan with contrast revealed cervical, occipital, and retroaortic lymphadenopathy; a chest high-resolution CT scan detected ground-glass opacities.

Laboratory results showed that eosinophils (15%), erythrocyte sedimentation rate 34 mm/h [normal value (nv): 15 mm/h], and C-reactive protein 12 mg/l (nv: 5 mg/l) were elevated. Urinalysis, liver and kidney biochemistry, serum lipid profile, angiotensin-converting enzyme, and thyroid hormones were normal. Antithyroid autoantibodies were negative. Immunological tests showed elevated IgG and IgE levels. Serum protein electrophoresis showed diffuse hypergammaglobulinaemia without evidence of monoclonal protein. Serum complement levels (C3 and C4) were normal. Rheumatoid factor (RF), antineutrophil cytoplasmic antibody (ANCA), antinuclear antibody, and anti-double-stranded DNA antibodies were negative. Anti-SSA, anti-SSB, anti-SM,

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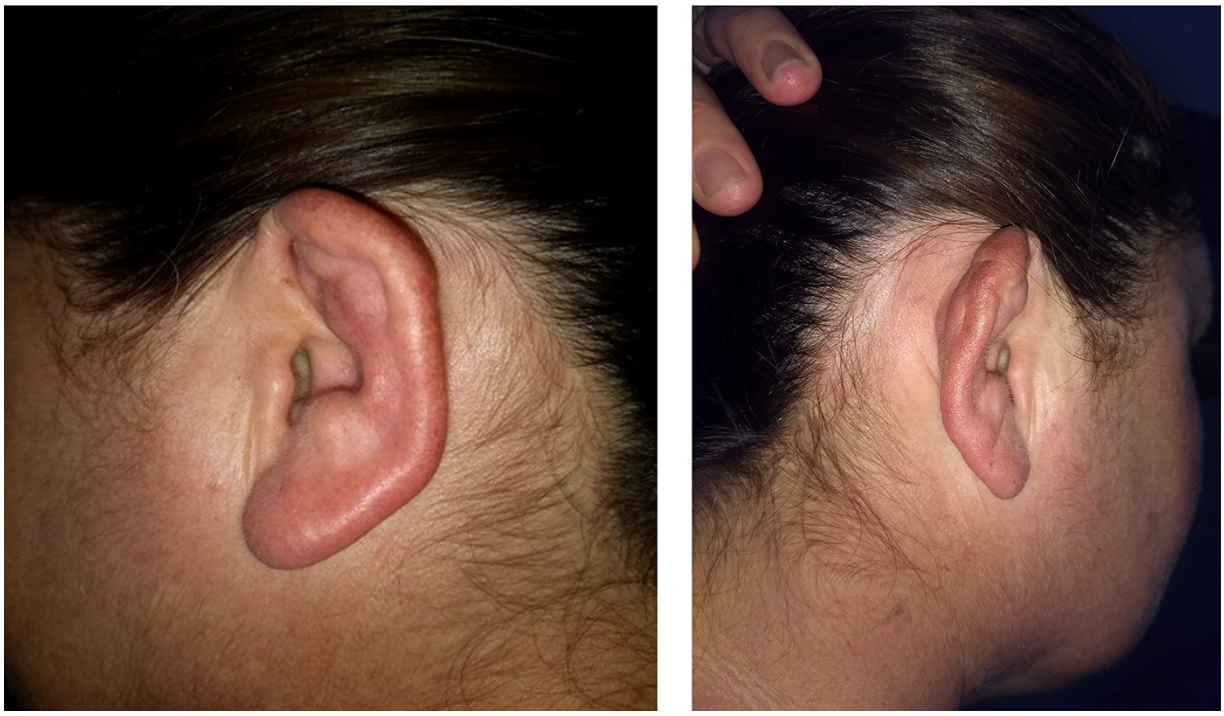

Figure 1. Physical examination on admission showed bilateral auricular deformity.

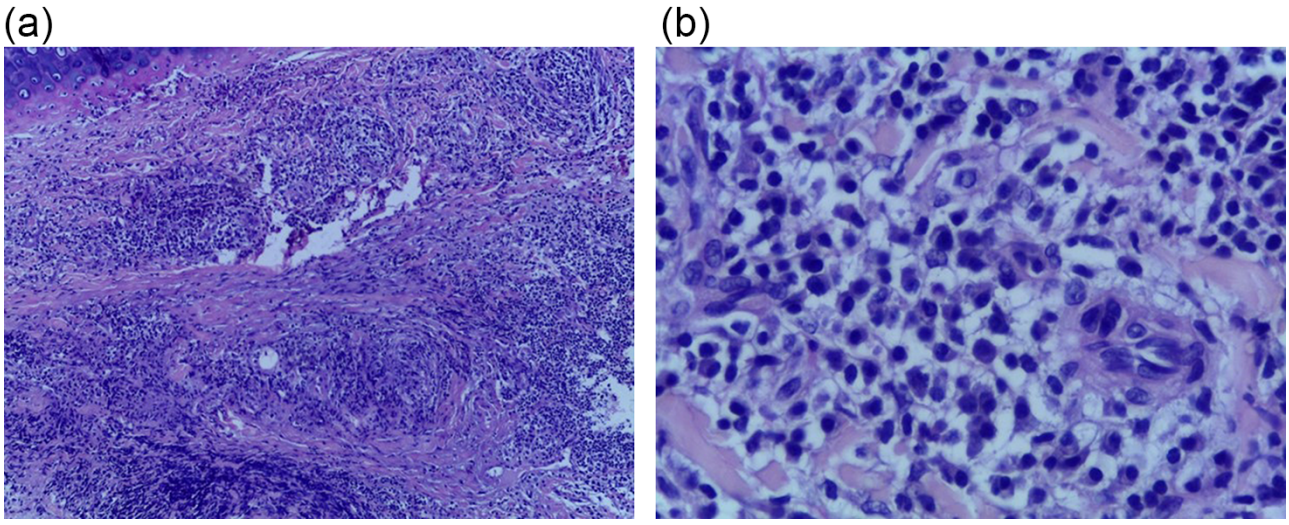

Figure 2. (a and b) Cartilage/skin biopsy: storiform fibrosis and inflammatory lymphoplasmocytic infiltrate (HE ×10).

and anti-ribonucleoprotein were all negative. The serum values were IgG4 2371 mg/dl (nv: 110–1570 mg/dl), IgG3 1760 mg/dl (nv: 230–1960 mg/dl), IgG2 nv: 6094.00 mg/dl (nv: 640–4950 mg/dl), and IgG1 15,150 mg/dl (nv: 3150–8550 mg/dl).

We prescribed pulse methylprednisolone therapy in doses from 1000 mg/day for 3 days and then prednisone 1 mg/kg/day and methotrexate 15 mg/week as steroid-sparing agent. This therapy improved the symptoms and CT scan findings.

Case 2

A 57-year-old man presented diplopia and proptosis that appeared 11 months earlier. His past medical history was unremarkable. He presented pain and swelling of the bilateral ears and was diagnosed with auricular chondritis and treated with short-term corticosteroid therapy. Magnetic resonance imaging (MRI) of orbits with contrast showed exophthalmos (infiltration of the retroorbital soft tissue), inferior and lateral rectus involvement, and lacrimal gland swelling (Figure 4(a,b)).

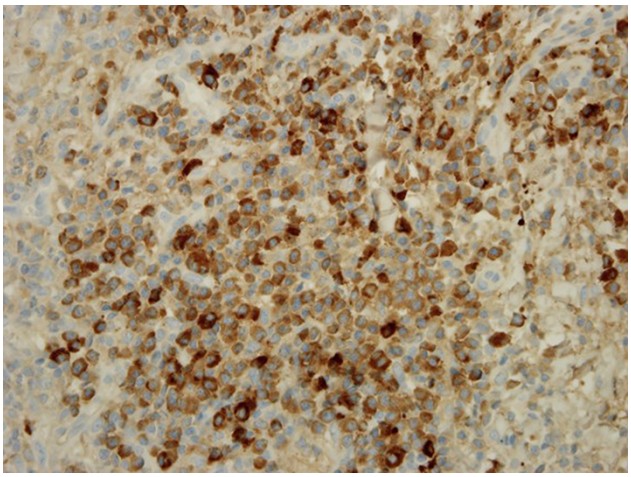

Figure 3. Immunohistochemistry of skin and cartilage presenting IgG4 cells.

He was advised to ask for a rheumatology consultation. Laboratory investigation showed RF, ANCAs, antinuclear antibody, and anti-double-stranded DNA antibodies were negative. Anti-SSA, anti-SSB, anti-SM, and anti-ribonucleoprotein were all negative. Serum level of IgG4 was 280 mg/dl (nv: 110–1570 mg/dl), IgG1 was 1296 mg/dl (nv: 3150–8550 mg/dl), IgG2 was 800 mg/dl (nv: 640–4950 mg/dl), and IgG3 2170 mg/dl (nv: 1230–1960 mg/dl).

The lacrimal gland histopathology showed fibrosis and lymphoplasmacytic infiltration with germinal centre and immunohistochemistry demonstrated abundant plasma cells with IgG and IgG4 staining, with elevated absolute numbers of IgG4 cells (over 100 cells/HPF and IgG4/IgG ratio >75%). There was no storiform fibrosis or obliterative phlebitis.

We prescribed prednisone 1 mg/kg/day and methotrexate 15 mg/week, as steroid-sparing agent. Our patient responded well to steroids.

The features of the immunohistopathological analysis, together with clinical and imaging finding, suggest that an IgG4-RD would explain the findings in the patient and his symptoms. In addition, the favourable response to glucocorticoids would support this diagnosis.

Discussion

Patient 1 fulfilled three McAdam's criteria for RP, but also for American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for IgG4-related disease [5, 6].

Patient 2 presented a swelling of bilateral auricular pavilions with ocular involvement. In the biopsy of this case, there was no obliterative phlebitis or storiform fibrosis, possibly because either the specimen was small and superficial or the biopsy was performed at an early stage of the process. It could also be possible that the patient had been treated previously with corticosteroid. Nonetheless, in the head and neck region, storiform fibrosis and obliterative phlebitis may always not be present [7].

In the RP auricle, neutrophil infiltration was observed in the early phase. Subsequently, plasma cell and lymphocyte infiltration and fibrosis were found in the mid to late phase. However, IgG4-RD pathology showed inflammatory lymphoplasmocytic infiltrate storiform fibrosis, obliterating phlebitis, and mild eosinophil infiltrate [2].

At present, the pancreas and salivary and lacrimal glands seem to be the most affected organs. Still, other forms of diffuse inflammation potentially leading to permanent tissue disruption in the head and the neck, such as recurrent mastoiditis, some forms of thyroiditis, and laryngeal and tracheal stenosis, among others, are being linked to IgG4-RD.

The key questions arising concerning the RP and IgG4-RD association are the following:

- First, is this association an incidental finding?

It could be. Yet, as far as we are concerned, no case of IgG4-RD presented with perichondritis of the ears has been described so far, except for the four cases mentioned here when this presentation was attributed to RP and not to IgG4-RD (Table 1).

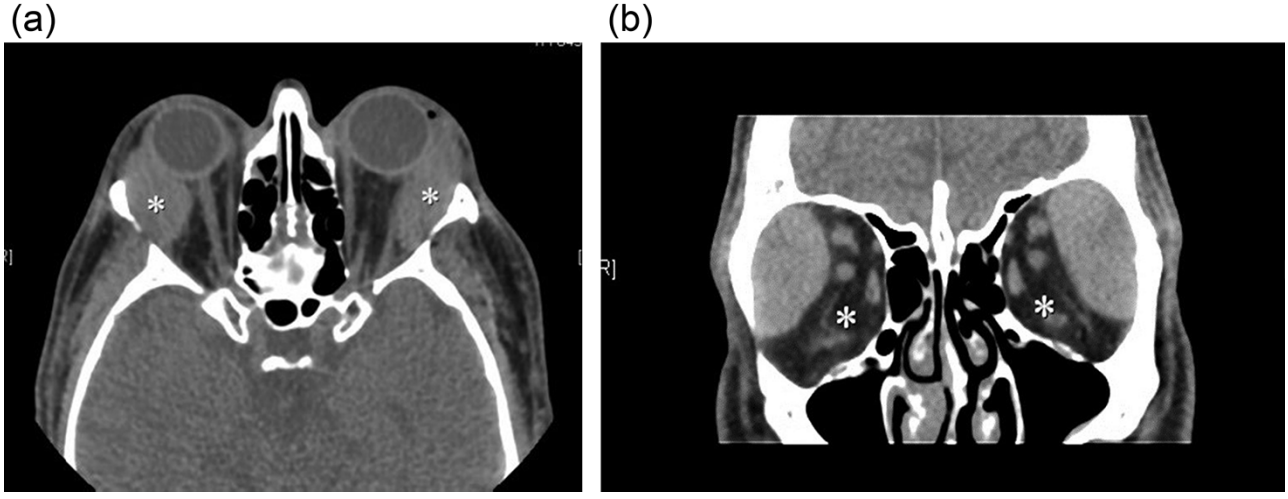

Figure 4. (a and b) MRI of orbits with contrast showed exophthalmos (infiltration of the retroorbital soft tissue), inferior and lateral rectus involvement, and lacrimal gland swelling.

Table 1. RP or RP-like symptoms associated with IgG4-RD.

Author	Gender	Age	Other organ involvement	Time IgG4-RD diagnosis	Serum levels of IgG4	Auricle cartilage biopsy	Immunohistochemistry	
							Ear cartilage	Other organs
Yamasue *et al.* [3]	M	63	Sensorineural hearing loss, submandibular glans, lymphadenopathy, kidneys, lungs	RP preceded 14 months	↑	Yes (inflammatory cells–fibrosis)	Not done	Yes
Horai *et al.* [2]	M	79	Audiovestibular damage, arthritis, ocular	Concomitant	Normal	Yes (Idem + infiltration of neutrophils)	Yes	Not done
Nagayama *et al.* [4]	M	45	Arthritis, ocular, pancreas, kidneys, wall abdominal aorta	RP preceded 20 years	↑	Yes (inflammatory cells)	Not done	Yes
Le Goueff *et al.* [1]	M	78	Lung, kidneys, sensorineural hearing loss, lymphadenopathy	Concomitant	↑	Not done	Not done	Yes
Case 1	F	37	Arthritis, lung, lymphadenopathy, sensorineural hearing loss	Concomitant	↑	Yes (inflammatory plasma cells–storiform fibrosis)	Yes	Not done
Case 2	M	57	Ocular	Concomitant	Normal	Not done	Not done	Yes

Idem: inflammatory cells–fibrosis.

However, to the best of our knowledge, these six patients presented perichondritis of the ears. Two of them had undergone an ear biopsy discarding IgG4 plasma cell infiltration; in three of them fibrosis was observed; only one patient presented storiform fibrosis (Patient 5). In two patients the ear cartilage biopsy was not done. Immunohistochemical staining of the auricle specimen for IgG4 revealed many IgG4-expressing plasmacytes. The amount of IgG4 as a percentage of the total IgG was 95% in two patients. The IgG4-positive cells were not observed in auricular cartilage in Yamasue's patient.

The serum IgG4 levels were elevated in four patients. In Horai's patients and in Case 2 the level was normal, although this may have been caused by the administration of prednisolone prior to the admission.

RP and IgG4-RD have common features, such as the participation of an autoimmune mechanism and steroid sensitivity in most cases. In RP patients, an acute respiratory distress caused by tracheobronchial chondritis is usually present; they can also present symptoms of pneumonia due to infections triggered by a secondary trachea–bronchomalacia and bronchiectasis. None of these patients had signs of chondritis in the CT scan. The IgG4-RD diagnosis was done in four out of six patients by biopsying other compromised organs.

- Second, or is this an association?

Indeed, the range of features and disease associations of IgG4-RD continues to expand while RP is associated with another autoimmune disease in 30% of the cases (rheumatic diseases, autoimmune diseases, malignancy, and miscellaneous). However, co-occurrence of RP and IgG4 has only been observed in the four cases mentioned in the table, where the RP diagnosis preceded the one of IgG4-RD by 20 years and 14 months (Patients 1 and 3) and the symptoms were resolved with steroid treatment. In the rest of the cases, there was a concomitant occurrence of RP and IgG4-RD.

Similar to Horai *et al.*, we think the reason why IgG4 has not been investigated in patients with RP is because RP is a rare disease and, on the contrary, IgG4-RD is a relatively new concept.

- Finally, are there some RP cases or similar RP symptoms part of the IgG4-RD spectrum?

At the International Symposium on IgG4-Related Diseases, where the consensus document on nomenclature was drafted, the attendees agreed on 'a minimum of 5 reports of involvement in any given organ should be published before such organ could be included as an individual manifestation of IgG4 related disease' [8].

To consider previously unrecognised organ or site as being involved in IgG4-RD, they recommend that the following criteria should be fulfilled: (1) characteristic histopathological finding with elevated IgG4 plasma cells and IgG4-to-IgG ratio; (2) high serum IgG4 concentrations; (3) effective response to glucocorticoid therapy; and (4) report of other organ involvement that is consistent with IgG4-related disease [9].

Herein, we report two new patients with RP or RP-like symptoms complicated by IgG4-RD. It is still unknown why both diseases coexist.

In this report, we have described two patients with perichondritis of the ears, which could be considered an

IgG4-RD. Although the association between RP and RP-like symptoms was not fully investigated, these cases suggest that RP or RP-like symptoms might be included in the concept of IgG4-related diseases.

Further studies should be performed to reveal the prevalence of IgG4 in patients with RP and its pathophysiological roles in the disease development.

Conflict of interest

None declared.

Funding

None declared.

Ethical approval

Not applicable.

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