



Extra-pancreatic manifestations of IgG4-related systemic disease: a single-centre experience of treatment with combined immunosuppression

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Key words

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Abstract

Background/Aim: IgG4-related systemic disease (IgG4-RSD) is a systemic inflammatory disease distinguished by tissue infiltrates of IgG4⁺ plasma cells and elevated serum IgG4 levels. While IgG4-RSD often involves the pancreas, extra-pancreatic organs are also frequently affected. Here, we review the presentation and management of patients with extra-pancreatic IgG4-RSD.

Methods: A retrospective analysis was performed on patients diagnosed with extra-pancreatic IgG4-RSD identified from a single centre.

Results: Six patients with extra-pancreatic IgG4-RSD were identified. The median age of the patients was 64 years. The range of involved organs included lymph nodes (three patients), ocular adnexa, lung, kidneys, meninges and exocrine glands. The median delay in diagnosis was 13.5 months (4–60 months). Four patients had elevated serum IgG4 levels at diagnosis. Five symptomatic patients were commenced on combination immunosuppression, which included corticosteroids. Maintenance therapy with azathioprine was used in one patient, methotrexate and mycophenolate were each used in two patients, and cyclophosphamide in one patient. Four treated patients went into remission, while two patients had persistent radiological disease. One patient experienced two relapses.

Conclusion: IgG4-RSD can manifest in a variety of organs. Lack of awareness regarding this entity may delay diagnosis. Combination treatment of corticosteroids and conventional immunosuppression is effective.

Introduction

IgG4-related systemic disease (IgG4-RSD; also referred to as IgG4-multiorgan lymphoproliferative syndrome (IgG4-MOLPS))¹ is an inflammatory disease first recognised in the lesions of patients with type 1 autoimmune pancreatitis (AIP).^{2,3} The same pathological findings were subsequently identified in several extra-pancreatic organs, such as liver, lymph nodes and aorta, as well as being described in the lesions of previously unexplained chronic inflammatory diseases, such as retroperitoneal fibrosis, Riedel thyroiditis, Mikulicz chronic sclerosing dacryoadenitis of the lacrimal glands and Kuttner chronic sclerosing sialadenitis of the salivary glands.⁴ Regardless of location, IgG4-RSD is characterised by tissue infiltration with polyclonal IgG4⁺ plasma cells and lymphocytes with associated fibrosis.¹ Corticosteroids are the

established treatment for patients with pancreatic involvement.^{5,6} While there have been positive reports of corticosteroid treatment for extra-pancreatic IgG4-RSD, the optimal treatment regimen is less established.² We report on the treatment of six patients with extra-pancreatic IgG4-RSD with corticosteroid and conventional immunosuppressive drugs.

Methods

Cases and diagnosis of IgG4

Cases of confirmed extra-pancreatic IgG4-RSD seen in the clinical immunology department of Westmead Hospital between 2007 and 2010 were reviewed in association with the patients' medical histories, histopathology and imaging results. Cases of IgG4-RSD confined to the pancreas were excluded. The medical files were reviewed for data on clinical symptoms prior to a

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confirmed diagnosis of IgG4-RSD, duration of medical therapy, age, sex, volunteered ethnicity and comorbid medical conditions.

IgG4 quantitation

Serum IgG4 measurements at diagnosis were available for four of six patients. All measurements were performed on an IMMAGE nephelometer (Beckman Coulter Australia Pty Ltd, Gladesville, NSW, Australia), with a 3% coefficient of variation.

Immunohistochemistry

Immunohistochemistry was performed after heat-induced antigen retrieval with a mouse monoclonal antibody against human IgG4 (Zymed Laboratories, clone HP6025), followed by development with the automated Ventana Universal diaminobenzidine tetrahydrochloride (DAB) detection kit (Ventana Medical Systems, Tucson, AZ, USA). For each case, the number of IgG4⁺ plasma cells was manually counted in several non-overlapping high-power fields (HPF; $\times 40$ magnification). A diagnosis of IgG4-RSD was confirmed in the presence of (i) histopathological findings of a lymphoplasmacytic infiltrate, storiform fibrosis, sclerosis and obliterative phlebitis in affected organs; (ii) an absolute number of IgG4-positive plasma cells > 50 per HPF; and (iii) a percentage of IgG4⁺ to IgG⁺ cells $> 40\%$.

Results

Patient demographics

We identified six adult patients (four females) with extra-pancreatic IgG4-RSD disease between 2007 and 2010 (Table 1). Two patients had been previously reported – patient 1 after 8 weeks of treatment only,⁷ and patient 4 with AIP only.⁸ This report extends patient 1's observations to 72 months and extends patient 4's observations to include subsequent renal IgG4-RSD. The median age of the patients was 64.8 years (range from 51 to 72 years). In these six patients, the median time to diagnosis was 13.5 months from initial presentation (range 4–60 months). The median length of follow up after diagnosis was 15 months (range 10–72 months).

Extra-pancreatic IgG4-RSD can occur without pancreatic disease

Extra-pancreatic IgG4-RSD occurred in the exocrine glands (lacrimal, parotid and salivary), orbit, lymph nodes, lungs, kidneys and meninges (Fig. 1). Four patients had

no clinical, biochemical or computed tomography (CT) evidence of pancreatic involvement. In contrast, patient 1 developed a single episode of pancreatitis (abdominal pain and an elevated lipase of 1410 U/L ((normal range NR) < 110)) without CT evidence of AIP, and patient 4 had been diagnosed with AIP 2 years prior to renal involvement.⁸

Specific organ involvement

Our cohort mostly had symptomatic subacute involvement of a variety of organs (Table 1):

- Lymphadenopathy was the most common extra-pancreatic manifestation. Concurrent lymphadenopathy was present with IgG4-related lacrimal and pancreatic disease in patients 1 and 4 respectively. Patient 3 had asymptomatic multifocal lymphadenopathy (up to 1.6 cm) detected on CT (Fig. 1a). A biopsy of the internal mammary lymph node revealed a polyclonal infiltrate of IgG4⁺ plasma cells.
- IgG4-related pachymeningitis in patient 2 presented with progressive headaches, attributed to a meningioma, which was resected. Histology revealed chronic granulomatous inflammation. The diagnosis was only made on review of the biopsy after persistent symptoms from raised intracranial pressure and progressive dural thickening (Fig. 1b) despite empirical treatment for tuberculosis and then neurosarcoidosis (6 months of 25 mg prednisone).
- IgG4⁺ tubulointerstitial nephritis in patient 4 manifested with severe renal failure (eGFR 12 mL/min/1.73 m²) with bilateral renal infiltrates on CT (Fig. 1c). A kidney biopsy confirmed IgG4-RSD.
- IgG4⁺ pulmonary disease in patient 5 manifested with pleuritic chest pain, dyspnoea, fevers and weight loss (20 kg). Positron emission tomography (PET) revealed a 5.8-cm glucose avid lesion in the right upper lobe. Three separate biopsies were interpreted as an inflammatory pseudotumour. The patient subsequently developed bilateral cystoid macular oedema. Suspecting systemic illness, a review of the original lung biopsy revealed IgG4⁺ plasma cell infiltration and lymphoid aggregates in both subpleural lung and pleura.
- An orbital pseudotumour in patient 6 presented with proptosis, erythema, diplopia and radiological evidence of bone infiltration (Fig. 1d).
- Exocrine gland involvement in patient 1 manifested with progressive eyelid and facial swelling from lacrimal and submandibular gland enlargement. She did not have symptoms of glandular insufficiency or obstruction.
- IgG4-related involvement was suspected but not confirmed in two other sites – Patient 6 had multinodular thyroid enlargement on CT with normal thyroid biochemistry, while patient 3 had parotidomegaly.

Table 1 Clinical features and treatment outcomes for six patients with extra-pancreatic IgG4-related systemic disease

Patient	Sex, age, ethnicity	Comorbid disease	IgG4 organ involvement	Serum IgG4 at diagnosis (0.06–2.56 g/L)	Histopathology	Time from presentation to IgG4 diagnosis (months)	Treatment	Follow-up duration (months)	Outcome
1	F, 51, Vietnamese	—	Lacrimal, sublingual and submandibular gland LN – cervical Pancratis?	5.87	Lacrimal	12	PNL + AZA	72	Remission (two relapses on PNL monotherapy)
2	F, 72, Croatian	HT	Pachymeningitis	4.83†	Dura	60	PNL + MMF	24	Clinical improvement (stable radiology)
3	M, 68, Maltese	RA/SJS MGUS	Asymptomatic LN – mediastinal, thoracic, paraspinal Parotids?	13.9	Lymph node	36	PNL + MTX	18	Persistent LN
4	F, 68, Italian	T2DM	Bilateral diffuse tubulointerstitial nephritis 2 years before: Autoimmune pancreatitis and cholangiopathy LN – mediastinal	4.43	Renal Pancreas	5	MP/PNL + CYP	12	Remission (stable renal failure)
5	M, 58, white	—	Pulmonary pseudotumour Bilateral cystoid macular oedema	N/A	Lung	15	PNL + MTX	12	Remission
6	(F, 72, Italian	T2DM	Orbital pseudotumour Thyroid?	1.75	Orbital	4	PNL + MMF	10	Remission

†Serum IgG4 for patient 2 was measured on 10 mg prednisone. AZA, azathioprine; CRP, C-reactive protein; CYP, cyclophosphamide; HT, hypertension; ICP, raised intracranial pressure; LN, lymphadenopathy; MGUS, monoclonal gammopathy of uncertain significance; MMF, mycophenolate; MP, methylprednisolone; MTX, methotrexate; PNL, prednisone; RA, rheumatoid arthritis; SJS, Sjögrens; T2DM, type 2 diabetes.

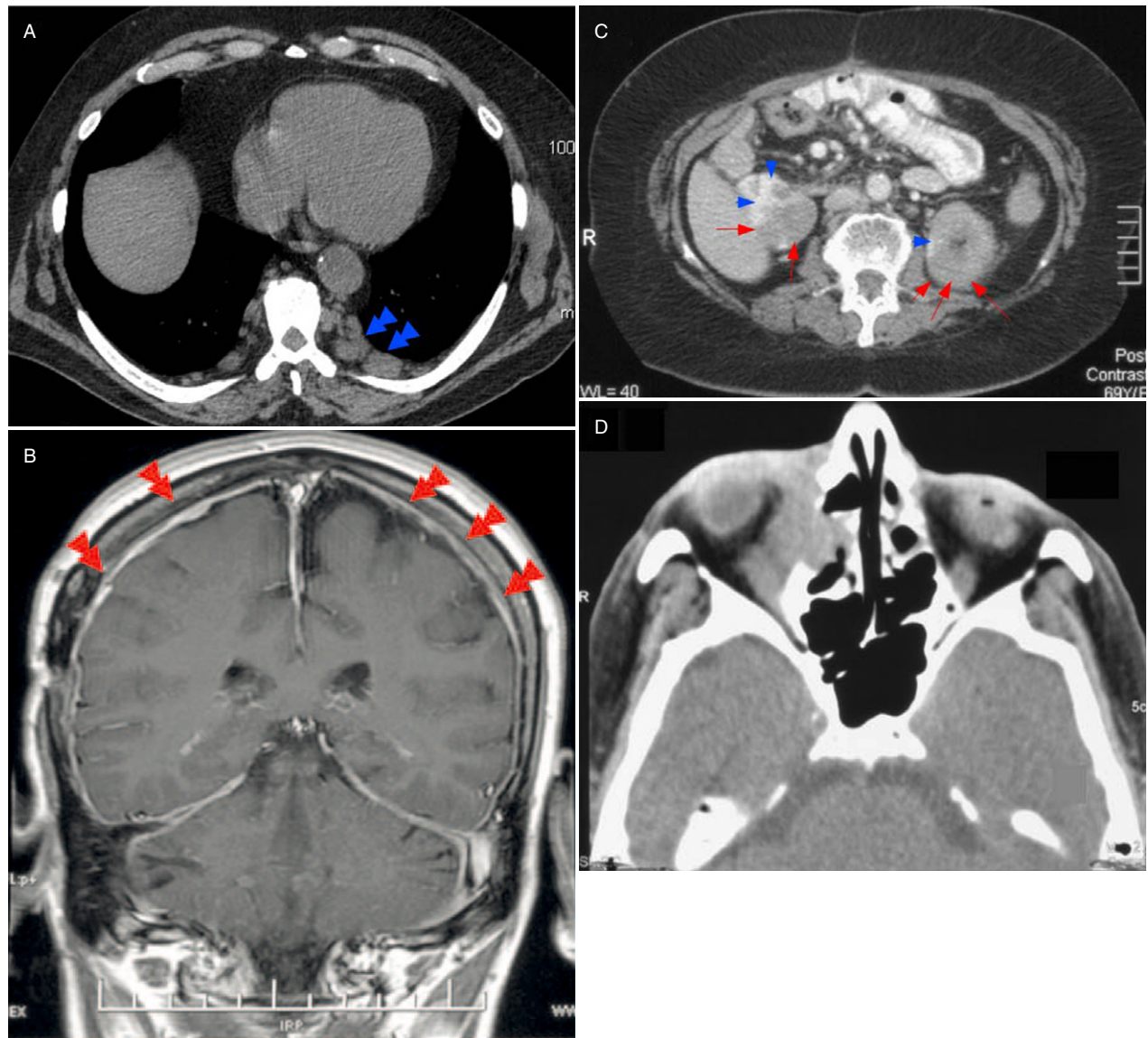


Figure 1 (A) Axial computed tomography (CT) demonstrating enlarged paraspinal lymph nodes (blue double arrowhead). (B) Coronal magnetic resonance imaging demonstrating thickened contrast-enhanced meninges over both cerebral hemispheres (red double arrowhead). (C) Axial CT demonstrating diffuse effacement of the kidneys by non-enhancing mass in the kidneys (red arrows) with displacement of normal contrast-enhanced renal parenchyma (blue arrowhead). (D) Axial CT through the orbits with medial soft tissue mass in the right orbital wall with infiltration into the adjacent sinus.

Laboratory features

Histological findings in all biopsies revealed polyclonal IgG4⁺ plasma cell consistent with IgG4-RSD by criteria (see Methods) (Fig. 2a). Mild eosinophilia was present in two biopsies, while non-caseating granulomas were only seen in the affected dura from patient 2 (Fig. 2b). In addition, scattered admixed mast cells were evident in the renal biopsies of patient 4 (Fig. 2c), while obliterative vascular thrombosis was seen in patient 6 with the orbital pseudotumour.

Serum IgG4 levels were elevated in four of the five patients, with results available prior to combination treatment (patient 4's level was measured while on 10 mg prednisone). C-reactive protein levels were elevated only in patient 5 (75 mg/L; NR < 10).

Treatment and outcomes

Five of the six patients had symptoms or organ-threatening manifestations sufficient to require treatment with prednisone (mean starting dose 40 mg/day,

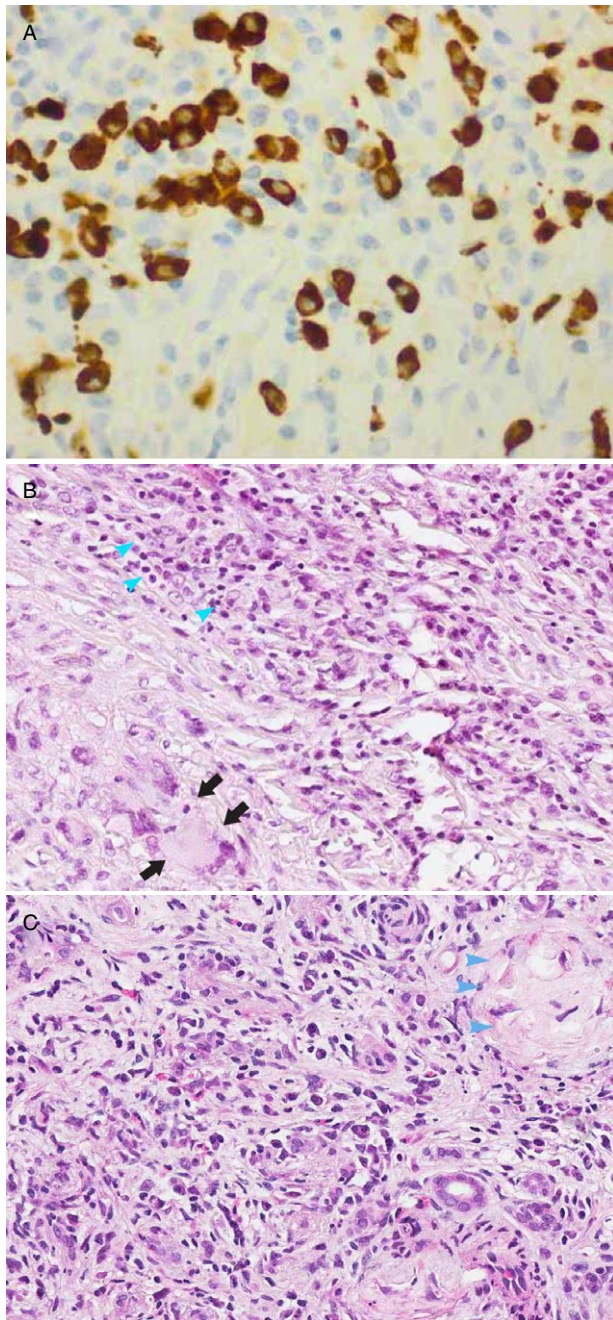


Figure 2 (A) IgG4⁺ plasma cells in dural biopsy (×40) magnification. (B) Dural inflammation characterised by plasma cells (arrowheads) and non-caseating granuloma (arrow) (×20; haematoxylin–eosin). (C) Tubulointerstitial infiltration by plasma cells and mast cells with sclerosed glomerulus (arrowhead) (×20; haematoxylin–eosin).

range 25–60 mg) in combination with an additional immunosuppressive drug (Table 1). Azathioprine (AZA; 2 mg/kg/day) was the most common agent chosen. Two patients with AZA-related gastrointestinal intolerance

were switched to mycophenolate (MMF; 2 g/day). Methotrexate (MTX; 20 mg/week) was initiated in patient 5 to treat the pulmonary lesion and concurrent cystoid macular oedema. Monthly intravenous cyclophosphamide (0.5 g/m²/month for six cycles) was used to stabilise the severe renal failure in patient 4.

As patient 3 had asymptomatic lymphadenopathy, he was continued on unaltered maintenance treatment for rheumatoid arthritis (prednisone 10 mg/day and MTX 20 mg/week).

In all treated patients, prednisone was gradually tapered by 5 mg/day every 2 weeks to a maintenance dose of 10 mg/day. Treatments with AZA, MMF and MTX were continued over the follow-up period.

Four patients (1, 4, 5, 6) had clinical and radiological remission on combination therapy. Patient 4's renal function stabilised but did not improve. Patient 2 had a partial response, with reported improvement in her headaches despite persistent radiological changes. Patient 3 remained asymptomatic, with stable lymphadenopathy on CT. Post-treatment serum IgG4 levels normalised in two of the three patients with available results.

Relapses only occurred in patient 1 (two separate episodes of salivary gland enlargement), which coincided with non-compliance with AZA.

Treatment was well tolerated. Apart from AZA-related gastrointestinal intolerance, the only other significant adverse effect was prednisone-related hyperglycaemia in the two diabetic patients.

Discussion

IgG4-RSD is a systemic multi-organ infiltrative disease.^{1,4} To date, much of the understanding of this entity is established from the pancreatic involvement of IgG4-RSD, or AIP. However, few reports focus on extra-pancreatic presentation and treatment. This retrospective analysis reviews six patients with histologically confirmed extra-pancreatic IgG4-RSD.

Our cohort's median age at diagnosis was 64 years, which is consistent with other published data.^{9,10} Lymphadenopathy was the most common organ involved in our cohort. Similarly, Hamano *et al.* reported that lymphadenopathy (80%; hilar region), and salivary and lacrimal gland (39%) involvement were the most common extra-pancreatic findings seen in 64 Japanese patients with established AIP.² One patient in our cohort had isolated dural involvement, a rarely reported manifestation of IgG4-RSD.^{11,12} Importantly, only two of the six patients in our cohort had multiple organ involvement with IgG4-RSD. In contrast, a recent report from a French survey of IgG4-RSD patients found that 88% of

25 patients had involvement of more than one organ.¹³ Apart from differences in data collection, these differences also reflect the varied nature of the disease which may remain isolated in a single organ or progress over time to multiple sites.¹⁴

Clinical manifestations of IgG4-RSD in four of six patients in our cohort occurred without any clinical or radiological pancreatic involvement, consistent with recent data published by Zen and Nakanuma.¹⁵ In this cohort of 114 Japanese patients, isolated extra-pancreatic disease occurred in the lung (14% of cases), salivary and lacrimal glands (20%), and lymph nodes (2%).¹⁵

The pathogenesis of IgG4-RSD is unknown. Differences in the IgG4 structure from other IgG subclasses render it susceptible to formation of 'half-antibodies'.¹⁶ Functionally, these half-antibodies may compete and block the inflammatory responses triggered by other antibody isotypes, thus serving a potential immunoregulatory role. It remains unclear, however, if the reason for preferential selection and proliferation of IgG4 plasma cells in IgG4-RSD is a by-product from a chronic immune response to an unidentified antigen, or if IgG4 has a key pathogenic role in the inflammatory reaction.^{3,17}

IgG4-RSD is rare and may mimic the presentation of other diseases. For example, presentations of IgG4-RSD lymphadenopathy may be wrongly considered secondary to tuberculosis, lymphoma or Castleman disease.¹⁸ This can delay diagnosis and result in unnecessary investigations, such as in patient 5, who had repeated lung biopsies for suspected malignancy. Physician awareness of the heterogeneous clinical presentations of IgG4-RSD is, therefore, important.

The diagnosis of IgG4-RSD also relies heavily on accurate and specific immunohistochemistry. While diagnostic criteria for IgG4-RSD are established for pancreatic disease,¹⁹ similar criteria for extra-pancreatic organ involvement, such as the lymph nodes, remain to be firmly established.²⁰ In addition, a recent study showed that IgG4⁺ plasma cells may be detected in non-specific chronic inflammatory lesions, such as rheumatoid synovium, localised oral inflammatory lesions or carcinomas.²¹ These findings emphasise that an IgG4-RSD diagnosis be made after careful histological interpretation by an experienced histopathologist, and correlation with the clinical manifestations and serum IgG4 levels.^{22–24}

Serum IgG4 is included in the current diagnostic criteria for IgG4-RSD pancreatic disease,^{25,26} with sensitivity approaching 70% and specificity of 90%–95%.²⁷ Furthermore, serum IgG4 levels may predict extra-pancreatic disease. Kamisawa *et al.* showed serum IgG4 levels greater than 2.2 g/L, measured by radial immunodiffusion, correlated with extra-pancreatic manifestations.²⁴

Four of the five patients in our cohort with extra-pancreatic disease had pretreatment levels higher than this level. In addition to diagnosis, serum IgG4 may be a useful marker of disease activity, response to immunosuppression²⁸ and risk of relapse.^{9,25,28}

Other investigations may include scintigraphic localisation studies with gallium-67 to identify and monitor sites of active disease.²⁰ More recently, PET scans have been used to monitor the treatment response in IgG4-RSD.²² Hence, serum IgG4 and scintigraphy may be useful adjuncts to detect subclinical disease, monitor treatment response and identify early relapse.

Treatment of IgG4-RSD is generally commenced for organ-threatening manifestations.

Corticosteroids are the mainstay of IgG4-RSD treatment, with remission rates approaching 100% in AIP-treated patients.^{9,25} However, relapses after corticosteroid therapy range from 23% to 60%,^{29,30} with reportedly higher rates in patients with extra-pancreatic manifestations.³⁰ In our cohort, combination treatment with either AZA, MMF or MTX resulted in clinical and radiological remission in four of six patients and stabilised disease in the remaining two patients, consistent with the reported success of these agents when used as second-line treatment.^{13,29–32} More recently, targeted treatments against antibody production in refractory disease have also been successful with rituximab³³ or bortezomib.³⁴ In addition to being effective, these immunosuppressants enabled us to minimise corticosteroid-induced hyperglycaemia in two diabetic patients without relapses over the course of follow up.

Conclusion

This analysis highlights the diverse nature of IgG4-RSD presentations in extra-pancreatic manifestations. While our analysis is subject to the inherent deficiencies of retrospective analysis, and possible referral bias to a single centre, we would argue that the spectrum of patients seen is representative of the diverse nature of IgG4-RSD presentations and is consistent with the reported literature. In conclusion, we provide short-term, follow-up data and demonstrate good outcomes with combined immunosuppression in IgG4-RSD. Larger multicentre collaborations are necessary to demonstrate long-term outcomes in this condition.

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