



Successful treatment with rituximab of IgG4-related disease coexisting with adult-onset asthma and periocular xanthogranuloma

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Abstract

Immunoglobulin G4-related disease (IgG4RD) is a systemic fibro-inflammatory disease of unknown aetiology, which is characterized by tumefactive lymphoplasmacytic infiltrative lesions, with a predominance of IgG4 positive plasma cells, fibrosis and obliterative phlebitis. Adult-onset asthma and periocular xanthogranuloma (AAPOX) is a rare disease of unknown aetiology characterized by violaceous or yellow cutaneous papules and nodules usually accompanied with adult-onset asthma. We report a case of IgG4RD associated with AAPOX. We also conducted a literature search with keywords including IgG4RD and AAPOX. A 36-year-old woman presented with bilateral exophthalmos and periorbital oedema. Keratoconjunctivitis sicca, painless left parotid gland and submandibular left lymph node enlargement were also noted. Two and half years ago biopsy of yellow plaques of her right lower eyelid confirmed periorbital xanthogranuloma. She underwent parotid gland biopsy which showed IgG4RD. She was treated with steroids and two cycles of rituximab with complete remission. The literature review revealed 8 articles describing 14 cases with IgG4RD and AAPOX, 9 men and 5 women (ratio M:F=1.8:1) were affected. The age at diagnosis was greater in men compared to women. In the majority of patients, ophthalmic presentation included bilateral upper and lower eyelid swelling while systemic features were asthma, lacrimal and parotid involvement, lymphadenopathy, sclerosing pancreatitis and sclerosing cholangitis. Prednisone and rituximab were effective treatments. It has to be clarified whether the association between IgG4RD and AAPOX represents shared pathophysiology, a common underlying cause or coincidence. Rituximab added to steroids resulted in complete remission of the two entities.

Keywords Asthma · Eye · Necrobiotic xanthogranuloma · Immunoglobulin G4-related disease · Rituximab

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Introduction

Immunoglobulin G4-related disease (IgG4RD) is a systemic fibro-inflammatory disease of unknown aetiology, which is characterized by tumefactive lymphoplasmacytic infiltrative lesions, with a predominance of IgG4-positive plasma cells and usually elevated serum IgG4 levels. It was first described in 2001 by Hamano et al. in a patient with sclerosing pancreatitis [1]. Multiple tissues and organs are affected, including lymph nodes, salivary glands, thyroid gland, pancreas, liver, biliary tree, retroperitoneum, kidneys, lungs, mediastinum, central nervous system, prostate and orbital adnexa. Different pathophysiological mechanisms, including genetic predisposition, bacterial infection and cross-reaction with human molecules and autoimmunity, have been proposed [2]. The disease occurs most commonly in middle-aged and older men. The mean age of presentation is 50 years, but it has also been reported in two paediatric patients [3] and no race correlation has been proven [4]. As this clinical entity is newly recognized, its prevalence has not yet been determined. Umehara et al. estimated its incidence in Japan at 0.28–1.08/100,000 [5]. Bilateral periorbital oedema and exophthalmos with no signs of ocular inflammation may occur. Elevated serum levels of the IgG4 and a compatible biopsy of the affected organ can help the clinician to establish the diagnosis.

On the other hand, adult-onset asthma and periocular xanthogranuloma (AAPOX) is a rare disease of unknown aetiology affecting adults aged between 29 and 74 years with a male to female ratio of 2:1 [6]. It is a form of non-Langerhans histiocytosis characterized by the development of red-brown violaceous or yellow cutaneous papules and nodules that evolve to form infiltrated plaques usually accompanied with adult-onset asthma. It was first described in 1993 by Jakobiec et al. as a specific granulomatous inflammation [7]. The periorbital skin is usually affected while extracutaneous involvement of ocular, respiratory, cardiac or other tissues may also occur. Characteristic histologic findings include foamy histiocytes and Touton giant cells. A strong relationship between IgG4RD and AAPOX has been described [8]. Steroids have been used to treat the two entities. Rituximab, a chimeric anti-CD20 monoclonal antibody, has shown efficacy in patients with IgG4RD [2]. This study aims to report a case of IgG4RD and AAPOX which was successfully treated with steroids and rituximab and to present the relevant literature about the coexistence of the two entities.

Search strategy

PubMed/MEDLINE, Scopus and OVID databases were screened according to the published guidance on narrative reviews [9] by entering the following keywords: IgG4RD,

AAPOX, coexistence, association with, from database inception to June 15, 2019. Case reports, case series, letters, original articles published in English that include IgG4RD and AAPOX were included. Duplicates and abstracts were removed. The following parameters were noted from included studies: age at diagnosis, gender, ophthalmic presentation, systemic presentation and treatment.

Case

A 36-year-old woman presented at the Ophthalmology outpatient department, with bilateral exophthalmos, periorbital oedema, foreign body sensation and intermittent retrobulbar discomfort (Fig. 1a). The patient experienced an episode of upper left eyelid yellow swelling 12 years ago, which subsided after a 6-month course of methylprednisolone, but recurred bilaterally when treatment was completed. She had a magnetic resonance imaging, which demonstrated expansion of the left lateral rectus and left lacrimal gland enlargement. At that time, the diagnosis of idiopathic orbital inflammation was made. Five years ago, she underwent surgical resection of enlarged cervical lymph nodes, which were pathologically diagnosed as lymphoid hyperplasia, with identification of plasmacytoid cells but no signs of malignancy. Two and a half years ago, she presented with bilateral periorbital oedema and exophthalmos and yellow plaques of her right lower eyelid. Histopathologic examination of the lid lesions displayed foamy histiocytes, Touton giant cells and lymphoid aggregates consistent with the diagnosis of periorbital xanthogranuloma. She received methylprednisolone orally as well as three courses of periorbital triamcinolone injections at her right orbit. Past medical history included arterial hypertension, hypothyroidism, asthma and allergic rhinitis. Clinical examination revealed that visual acuity was 20/20 in her both eyes. Ocular pressure was 20 mmHg in the right eye and 22 mmHg in the left eye with a slight increase in the upgaze position. Eye examination showed bilateral exophthalmos with soft, homogenous and painless yellow swelling of both the upper and lower eyelids. She also had ophthalmic findings of keratoconjunctivitis sicca and dilatation of episcleral vessels bilaterally. A painless left parotid gland enlargement and a submandibular left lymph node enlargement were also noted. The rest physical examination was unremarkable. Laboratory data including a complete blood count, biochemistry and thyroidal function tests as well as urine analysis were normal. Immunological examination was unremarkable and protein electrophoresis was normal. IgG4 serum levels were markedly elevated, reaching 900 mg/dl (normal values: < 135 mg/dl). Interferon-gamma release assay testing was negative. Plain and contrast-enhanced magnetic resonance imaging revealed orbital region involvement (Fig. 1b).

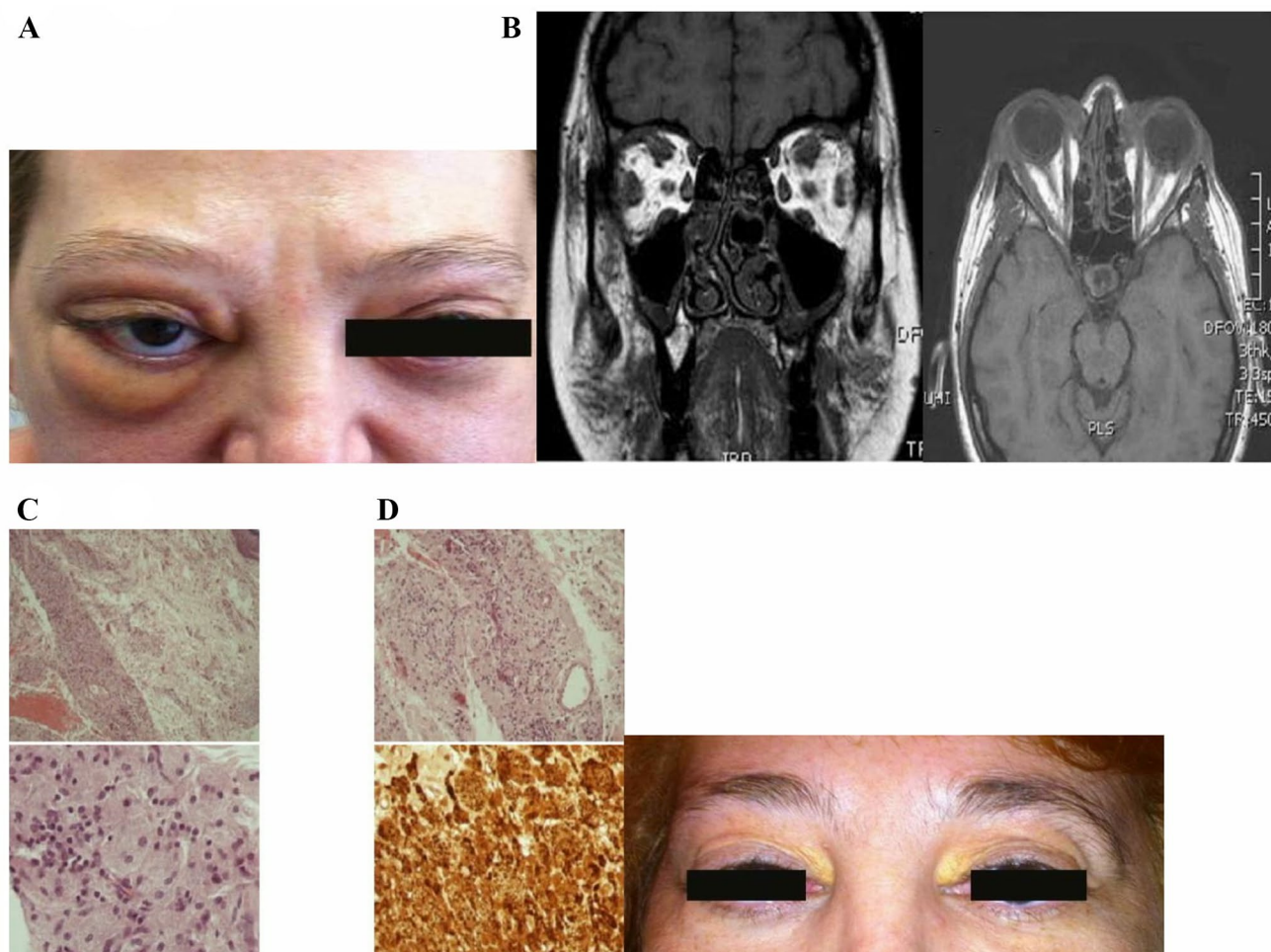


Fig. 1 **a** Periorbital oedema, bilateral exophthalmos and soft, homogeneous and painless yellow swelling of both the upper and lower eyelids. Before treatment. **b** Plain and contrast-enhanced magnetic resonance imaging of the orbital region which reveals enlargement and abnormal enhancement of all the extraocular muscles, abnormal enhancement of the retrobulbar orbital fat. **c** Biopsy of the left parotid

gland revealed the presence of moderate lymphoplasmacytic tissue infiltration bcl-2 negative. Immunohistochemical evaluation (CD23, CD20, Ki67, κ , λ , bcl2, IgD, IgA, IgG, IgM, cyclin D1) demonstrated the presence of mature IgG plasma cells, with a predominance (70%) of IgG4-positive plasma cells. Fibrosis was not demonstrated. **d** After 6 months of treatment

Biopsy of the left parotid gland and submandibular lymph node revealed lymphoplasmacytic tissue infiltration which was bcl-2 negative. Immunohistochemical evaluation (CD23, CD20, Ki67, κ , λ , bcl2, IgD, IgA, IgG, IgM, cyclin D1) demonstrated the presence of mature IgG plasma cells, with a predominance (70%) of IgG4-positive plasma cells. In fact, the number of IgG4-bearing plasma cells per high-power field (HPF) was greater than 100. In situ hybridization for kappa (κ) and lambda (λ) light chains showed a polyclonal plasma cell population without light chain restriction. Fibrosis was not demonstrated in the sample (Fig. 1c). The diagnosis of IgG4RD with orbital and parotid involvement was confirmed and she received prednisolone 40 mg per day with gradual tapering. She responded rapidly to steroid treatment: both clinical and imaging signs subsided significantly. Tapering of steroids resulted in symptom recurrence. The

patient was treated with rituximab 1 g (day 0 and day 15) followed by a second cycle after 6 months with excellent response (Fig. 1d). She discontinued steroids and she is free of symptoms for 12 months.

Patients with IgG4RD and AAPOX in the literature

The schematic overview of the studies included in this review is shown in Fig. 2. We identified 14 case reports in 8 studies [8, 10–16]. The characteristics of 14 patients from these articles along with the presented case are summarized in Table 1. Nine men and 5 women (ratio M:F 1.8:1) were affected with IgG4RD and AAPOX. The age at diagnosis was greater in men (mean 57.78 ± 12.6) compared to women (42.4 ± 8.2). In the majority of patients ophthalmic presentation included bilateral upper and lower eyelid swelling

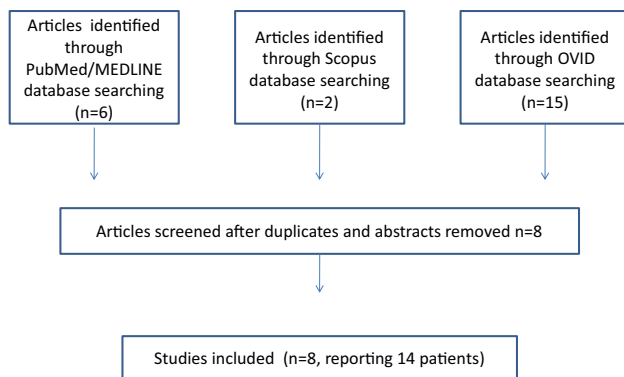


Fig. 2 Schematic overview of the studies of IgG4 related disease and adult-onset asthma and periocular xanthogranuloma included in the literature research

while systemic features were asthma, lacrimal and parotid involvement, lymphadenopathy—mainly cervical—sclerosing pancreatitis and sclerosing cholangitis. Steroids and rituximab were effective treatments. Azathioprine, methotrexate and cyclosporine were used without significant clinical improvement.

Discussion

IgG4RD patients share demographic, clinical, serological and some histological features with those diagnosed with AAPOX. The majority of patients with IgG4RD and AAPOX are diagnosed at fourth or fifth decade of life. Although both sexes are involved there is a higher frequency in men [16].

IgG4RD with orbital involvement has been described in several studies [4, 17, 18]. Bilateral involvement, common lacrimal gland involvement, lesions in other organs away from the orbit, greater disease duration and specific histopathologic findings support diagnosis [17]. A recent meta-analysis of 42 patients with periorbital oedema in Japan revealed that 60% of the IgG4RD group suffered from asthma, allergic rhinitis, chronic sinusitis and atopic dermatitis [4]. Our patient also had asthma which is also part of AAPOX. To date less than 30 cases of AAPOX have been published [19]. AAPOX may affect the orbit, lungs and lymph nodes. In a large cohort of patients with IgG4RD skin involvement, xanthogranuloma was found in 1.7% [20].

In IgG4RD, ocular adnexal tissue involvement is common, bilateral in almost half of the patients [17] and can be the first manifestation of the disease. The clinical hallmark of the disease is unilateral or bilateral painless chronic swelling of both the upper and lower eyelids and proptosis [17]. Visual acuity remains normal but a progressive visual deterioration due to compressive optic neuropathy

may occur. Intraocular pressure may be within normal limits or slightly elevated, probably due to increased episcleral pressure caused by the compression of the ophthalmic vein from the orbital infiltrative lesions. No signs of inflammation are noted in the majority of cases but mild signs of keratoconjunctivitis sicca are sometimes present as in our patient. Ocular motility is usually slightly or not at all restricted. During the late stage of the disease though, when fibrotic elements predominate, ocular motility can be significantly impaired. A case of posterior scleral involvement by IgG4RD that was confirmed pathologically following enucleation has been described [21]. Peripheral nerve enlargement is often asymptomatic—detected incidentally on imaging studies. Bone destruction is rarely noted. Almost all ocular adnexal tissues can be involved. Proptosis is noted in many cases and, if significant, can co-exist with optic nerve straightening.

AAPOX presents with bilateral yellow or orange indurated and nonulcerated xanthomatous periocular masses. In the literature, orbital involvement affects the anterior and preseptal compartments. Intraconal involvement has been reported [22]. Diplopia, a less common symptom, can be present when the disease affects the extraocular muscles [23]. In addition to eyelid swelling and plaques, physical examination can disclose proptosis and extraocular motility limitation [24]. All patients have late-onset asthma. Paraproteinemia and lymphadenopathy are not unusual while in some patients a subcutaneous mass of the mandibular area has been described [22].

Gallium citrate Ga 67 scintigraphy and fluorodeoxyglucose-positron emission tomography (FDG PET/CT) have been conducted and can depict accumulations of the agent in the adnexal lesions in IgG4RD which tend to decrease after steroid therapy. FDG PET/CT has been used in AAPOX patients showing FDG uptake of organs usually involved in IgG4RD, that is, lacrimal glands, lymph nodes and perirectal fat, the later two being asymptomatic [25].

In IgG4RD immunohistochemical analysis reveals a great number of plasma cells bearing IgG4 on their surface. The minimum number of these cells requested for establishing the diagnosis of the disease differs among various studies and ranges from 10 to above 50 cells per HPF [2, 17, 26]. Most importantly, the IgG4/IgG ratio should be greater than 40% [26], while fibrosis of varying degrees is observed. Although phlebitis or obliterative phlebitis is a common finding in other tissues' involvement, it is rarely demonstrated in orbital specimens [4, 17]. When the lacrimal gland is involved, inflammatory lesions are dominantly periductal and periacinar.

On the other hand AAPOX is characterized by fat necrosis and the presence of Touton giant cells. However, common histological features in IgG4RD and AAPOX include fibrosis, lymphoid follicles and increased IgG4 plasma

Table 1 Cases of IgG4-related disease with adult-onset asthma and periocular xanthogranuloma

First author of study	Age at diagnosis	Gender	Ophthalmic presentation	Systemic presentation	Treatment
Current case (2019)	36	F	Bilateral yellow upper and lower eyelid swelling	Adult-onset asthma left parotid gland and submandibular lymph node enlargement	MP, PS 40 mg, RTX (2 cycles, 1gx 2)
Leung (2018)	67	M	Bilateral swollen eyelids with yellowish lesions	Autoimmune pancreatitis	PD, AZA, RTX
Pomponio (2018)	50	F	Yellow eyelid plaque	Salivary and lacrimal gland enlargement, lymphadenopathy, pulmonary mass	Single-course RTX
Burris (2016)	57	M	Bilateral yellow upper and lower eyelid swelling	Adult-onset asthma, lymphoplasmacytic sclerosing pancreatitis	MP100 mg IV, RTX 1gx2
Honda (2016)	47	F	Bilateral upper and lower eyelid enlargement	Lacrimal gland enlargement, cervical lymphadenopathy	Steroids (topical and oral 0.5 mg/kg)
London (2015)	65	M	Bilateral yellow upper and lower eyelid swelling	Adult-onset asthma, allergic sinusitis, cervical lymphadenopathy, left cheek swelling	PD 1 mg/kg/day tapered to 5 mg/day
London (2015)	52	M	Bilateral orange upper and lower eyelid swelling	Adult-onset asthma, allergic sinusitis, right inguinal adenopathy	PD 1 mg/kg/day tapered to 5 mg/day and low-dose MTX
London (2015)	33	F	Yellow swelling of the left upper eyelid	Adult-onset asthma, allergic sinusitis, bilateral axillary adenopathy	PD 1 mg/kg/day tapered to 10 mg/day and transitioned to low-dose MTX
Kubota (2014)	38	M	Bilateral swollen eyelids	Autoimmune pancreatitis, asthma	PD tapered to 5 mg every other day
Kubota (2014)	41	M	Bilateral swollen eyelids	Asthma cervical lymphadenopathy	PD 7.5 mg/day
Kubota (2014)	48	F	Bilateral periocular mass	Asthma, ↑IgG4	PD 30 mg/day tapered to 2–7 mg/day
Kubota (2014)	34	F	Eyelid swelling	Asthma, ↑IgG4	PD 5 mg/day, CYS
Singh (2010)	67	M	Fullness of right periorbital region	Sclerosing cholangitis	NA
Singh (2010)	36	M	Orbital lesions	Adult-onset, upper respiratory and sinus problems	NA
Roggin (2007)	61	M	Bilateral yellow upper and lower eyelid swelling	Adult-onset asthma, nasal polyps, sclerosing pancreatitis, cervical lymphadenopathy	PD 5 mg/day

MP methylprednisolone, PS prednisolone, RTX rituximab, PD prednisone, AZA azathioprine, MTX methotrexate, CYS cyclosporine

cells and eosinophils [27]. Verdijk et al. reported that raised numbers of IgG4-positive plasma cells are a common histopathological finding in AAPOX [28]. However, the presence of IgG4 plasma cells has been reported in various diseases including lymphoma, Castleman disease, sarcoidosis, cancer and vasculitis [8]. Zen et al. showed that a large number of regulatory T cells (Tregs) infiltrated into the affected tissues in cases of IgG4RD [29] and Honda et al. described a case of AAPOX accompanied by IgG4RD with Treg infiltration [13].

The great majority (70%) of patients with IgG4RD show elevated IgG4 serum levels while the rest of them display normal (< 135 mg/dl) or slightly elevated values [2, 26]. Some studies suggest that levels are higher when multiple

organs are affected although IgG4 levels do not always correlate with disease activity. Carruthers et al. evaluated the test characteristics of the serum IgG4 and found a 90% sensitivity but both the specificity (60%) and positive predictive value (34%) were suboptimal using the standard laboratory cut-off for the upper limit of normal (135 mg/dl) [30]. However, increased IgG4 is noted in other inflammatory, neoplastic or infectious diseases as well as in 5% of normal population [5]. In addition elevated levels of IgG4 were described in one patient with IgG4RD and AAPOX [16]. Variable IgE levels are found in IgG4RD patients while elevated serum IgE levels are frequently measured in AAPOX patients [31].

The pathogenesis of IgG4RD and AAPOX is unclear. Upregulation of immune and inflammatory reactions may

be involved in both entities. Among patients with IgG4RD, plasmablasts were found to be expanded [30]. The plasmablast, CD19^{low} CD27⁺ CD20[–] CD38^{high}, represents a stage of B lymphocyte development between activated B cells and plasma cells and may be a biomarker of active IgG4RD. Recently, it was proposed that the pathogenesis of IgG4RD is associated with tissue infiltration by CD4⁺ cytotoxic T lymphocytes (granzyme A positive) that secrete interferon-gamma γ [32]. In AAPOX patients the accumulation of non-Langerhans histiocytes in the periorbital tissue implies an activation of the mononuclear phagocytic system and it is known that dendritic cells located in the airway epithelium and submucosa are important in producing immune responses to inhaled allergens [33]. In addition Tregs have been found in IgG4RD and granulomatous diseases. IgG4 production is controlled by interleukin-(IL)-4 and IL-10 which are produced by both Tregs and Th2 cells [29]. Although infiltration of Tregs in the xanthogranuloma tissue has been observed, it remains unknown if Tregs contribute in pathological mechanisms in AAPOX [13].

Corticosteroids are proposed as a first-line treatment for both IgG4RD and AAPOX. IgG4RD responds rapidly to systemic steroids (0.5–1 mg/kg/day) especially if commenced early in the disease process: the periocular oedema resolves, the lesions become smaller and IgG4 serum levels fall as a response to treatment, but usually remain above normal limits [2]. Patients with lower serum IgG4 and IgG4/IgG ratios at initial diagnosis were proved to have a poor response to treatment. Low dose of steroids may induce a durable response in patients with AAPOX while methotrexate could be used as an efficient corticosteroid sparing agent [25]. In recurrent IgG4RD, patients have to receive prolonged low-dose steroid or immunosuppressive treatment to control their symptoms [4]. Local radiotherapy and rituximab have also proved to be effective in controlling persistent inflammation. Rituximab has been used as first-line monotherapy, in a patient with IgG4RD and AAPOX, showing great and sustained efficacy and optimal tolerability [11].

AAPOX and IgG4RD have in common some clinical characteristics, pathological features and treatment outcomes. It has to be clarified whether the association between IgG4RD and AAPOX represents shared pathophysiology, a common underlying cause or coincidence. AAPOX syndrome could be considered an IgG4RD differential diagnosis or could be part of the spectrum of IgG4RD. Further studies are needed to answer if there is a link between AAPOX and IgG4RD.

In conclusion, we described a case of IgG4RD coexisting with AAPOX and we reviewed the literature. Steroids have been successfully used in the treatment of the two entities and rituximab may also be effective. Studies involving a greater number of patients will reveal the optimal treatment.

Author contributions IA diagnosed the patient, MK wrote the article, IN assisted in the literature review, AG and AB examined the histopathologic specimen and helped with figures, VR helped with figures and PVV contributed to diagnosis and treatment, assisted in the preparation of the manuscript and performed the literature review, drafted and critically revised the text, and approved the final version of the manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest

Informed consent Written informed consent was obtained from the presented patient.

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