

A rare and emerging entity: Sinonasal IgG4-related sclerosing disease

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ABSTRACT

Background: Immunoglobulin G4 (IgG4) related sclerosing disease (rSD) is a new disease entity, first described in 2001, that involves autoimmune pancreatitis. Considered a systemic disease with lesions described in multiple organ systems, IgG4-rSD that affects the sinonasal region is rare. Our goal was to highlight the sinonasal presentation of this unique disease and to review previously reported adult cases from 2003 to 2014.

Methods: Case report (a 72-year-old man who presented with left exophthalmos, periorbital pain, and epiphora) and review of the literature.

Results: Radiographic workup with computed tomography and magnetic resonance imaging demonstrated a left sinonasal mass that involved the left maxillary and ethmoid sinuses, with surrounding bony destruction and orbital invasion. Nasal endoscopy demonstrated a fibrous lesion emanating in the middle meatus, with surrounding mucosal inflammation. The patient underwent an endoscopic biopsy, medial maxillectomy, and ethmoidectomy with tumor debulking. Pathology demonstrated inflamed respiratory mucosa with dense lymphoplasmacytic infiltrate and fibrosis; flow cytometry demonstrated no malignant cell populations; immunophenotyping demonstrated multiple foci of IgG4 cells. Plasma IgG4 was elevated in the setting of normal total IgG. The patient was treated with postoperative systemic and topical corticosteroids. Surveillance imaging studies and nasal endoscopy demonstrated disease resolution without recurrence.

Conclusions: Sinonasal IgG4-rSD is a rare disease that can present with bony and soft-tissue invasion. This was an exceptional case, with osseous involvement and orbital invasion. Immunohistologic workup is essential for diagnosis. It is important to differentiate this disease from sinonasal tumors. Treatment includes corticosteroids and surgical debulking. Sinonasal IgG4-rSD represents an emerging disease that may present challenges for future rhinologists.

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Immunoglobulin (IgG4) related sclerosing disease (rSD) is a new G4 disease entity first described in 2001¹ and is associated with autoimmune pancreatitis. It is considered a systemic disease with lesions described in multiple organ systems. IgG4-rSD that affects the nasal cavity and paranasal sinuses is an exceedingly rare benign entity, with the majority of cases demonstrating local bony destruction.^{2–8} We present a case of IgG4-rSD of the left maxillary and ethmoid sinuses with features that mimic a malignancy, including invasion into the orbit. Our goal was to highlight the sinonasal presentation of this unique disease and to review the literature.

METHODS

A case report of sinonasal IgG4-rSD with review of the literature.

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Literature Search

A literature search in PubMed (January 2001 to December 2014) for reported cases of sinonasal IgG4-rSD was performed. The key words used in search algorithms included “sinonasal IgG4,” “sinus IgG4,” “nasal IgG4,” and “paranasal IgG4.” Additional case reports were identified through review of the reference lists of all identified case reports. Included publications were case reports that describe IgG4-related disease or IgG4-rSD with associated lesions within the confines of the sinonasal region. Pediatric case reports (ages < 18 years) were excluded. Case reports were limited to human patients and English language publications.

CASE REPORT

A 72-year-old man presented with a 1-month history of left eye redness, periorbital pain, and tearing. He also reported left-sided postnasal drip and left-sided nasal fullness. The patient did not have any double vision or decreased visual acuity. His medical history included hypercholesterolemia, hypothyroidism, a pituitary macroadenoma, and a pterygium of the right eye. The patient was otherwise healthy and had no history of immune dysfunction or cancer. He initially presented to ophthalmology

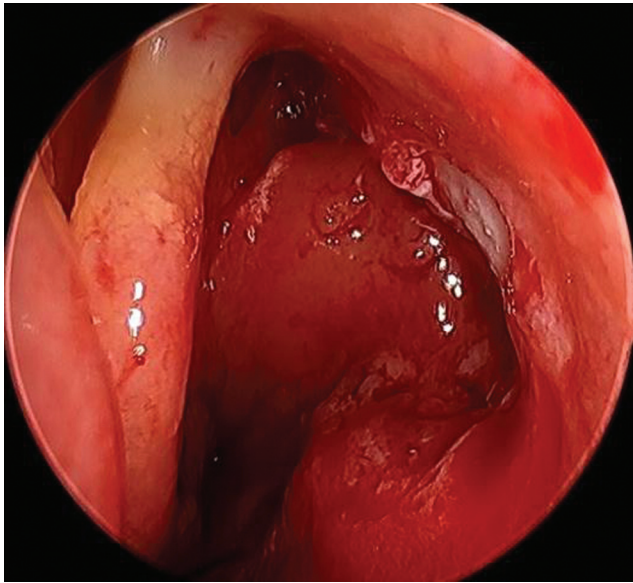


Figure 1. Endoscopic view of the fibrous sinonasal mass emerging from the left maxillary and ethmoid sinuses and filling a significant volume of the middle meatus and ethmoid cavity.

with left-sided exophthalmos, periorbital pain, and epiphora, and was found to have a sinonasal mass for which he was referred to otolaryngology.

On physical examination, the patient had left-sided epiphora, hyperglobus, and a 9-mm proptosis. Visual acuity testing demonstrated intact vision (20/20 oculus dexter, 20/25 oculus sinister). No periorbital or external nasal abnormalities were noted. Nasal endoscopy revealed a fleshy mass within the left middle meatus and bowing of the left lateral nasal wall of the inferior meatus (Fig. 1).

A diagnostic workup with computed tomography (CT) and magnetic resonance imaging (MRI) demonstrated a left sinonasal mass that involved the left maxillary and anterior ethmoid sinuses obstructing the middle meatus. CT highlighted erosion of the lamina papyracea and orbital floor, and MRI exhibited soft-tissue extension into the orbit without globe involvement (Fig. 2).

The patient underwent endoscopic biopsy for tissue diagnosis. Pathology demonstrated normal respiratory mucosa with a dense lymphoplasmacytic infiltrate in a background of fibrosis and an increased IgG4 plasma cell population (>50 /high power field [HPF]). The patient underwent endoscopic debulking of the mass, which included uncinectomy, medial maxillectomy, anterior ethmoidectomy, resection of the nasolacrimal duct, and partial inferior and middle turbinectomy. The sinonasal mass was excised in piecemeal fashion. Intraoperative cultures grew mixed skin flora and were negative for fungus and acid-fast bacilli. Flow cytometry was negative for malignant lymphocyte populations.

Final pathology demonstrated dense lymphoplasmacytic infiltrate and storiform fibrosis, highly suggestive of IgG4 disease (Fig. 3). Immunologic testing revealed elevated IgG4 of 94.5 mg/dL (reference range, 4–86 mg/dL) in the setting of normal total IgG levels of 1088 mg/dL (reference range, 694–1618 mg/dL). Results were negative for laboratory markers for other autoimmune processes.

Multidisciplinary management with rheumatology was initiated for the diagnosis of IgG4-rSD. The patient was treated with long-term oral corticosteroids after surgery. He started at 40 mg daily of prednisone and was tapered over a 3-month period. The patient demonstrated clinical improvement of his proptosis, epiphora, and periorbital pain 1 month after surgery. There also was radiographic resolution of disease (Fig. 4). Subsequent clinical evaluation at 6 months showed continued symptom resolution, with no evidence of disease recurrence (Fig. 5).

Review of the Literature

The literature search resulted in 989 publications, of which 7 met the inclusion criteria. Of these seven studies, six were case reports and one was a retrospective case series. These articles, published between 2009 and 2014, yielded a total of eight patients diagnosed with sinonasal IgG4-rSD (Table 1).

Patient Characteristics

Eight patients were identified with sinonasal IgG4-rSD (five men, three women) with a mean age of 64 years (range, 38–74 years). The most common presenting symptom was epistaxis (three of eight patients), but symptoms overall were nonspecific. The maxillary sinus was the most commonly affected sinonasal region, where five of eight patients had findings within this subsite. Upon radiographic imaging, six of eight patients demonstrated invasive features that consisted of local bone destruction. One patient with an absence of bony destruction on imaging, demonstrated other invasive features, including nerve and bone marrow invasion. Only one patient had limited soft-tissue disease devoid of invasive features.

Diagnostic Features

Based on the international consensus statement regarding the pathology of IgG4-rSD, a likely diagnosis can be made if two of the three major histopathologic features are present (Table 2).⁹ Two patients exhibited dense lymphoplasmacytic infiltration with IgG4 counts of >100 /HPF in addition to fibrosis, but these reports did not characterize the pattern of fibrosis. Four cases reported serum IgG4 levels in which only one patient exhibited abnormally high levels. In two cases, the

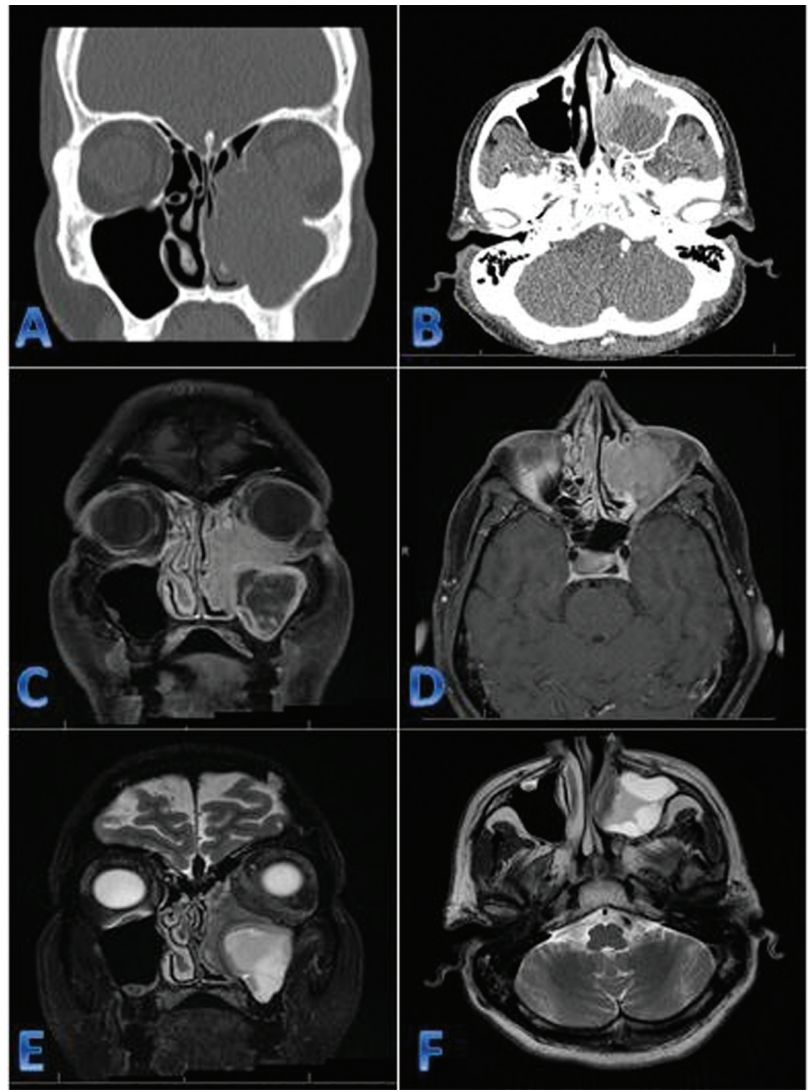


Figure 2. Radiographic images of left sinonasal mass. (A and B) CT without contrast, coronal and axial views demonstrating a mass filling the left maxillary and ethmoid sinuses with erosion of the left medial orbital floor and lamina papyracea. (C and D) MRI T1 with contrast, coronal and axial views demonstrating same lesion extending into the orbit with infiltration of the inferior and medial rectus muscles, but sparing the globe. Complete opacification of the left maxillary sinus also shown. (E and F) MRI T2, coronal and axial views further illustrating the aforementioned findings in panels C and D.

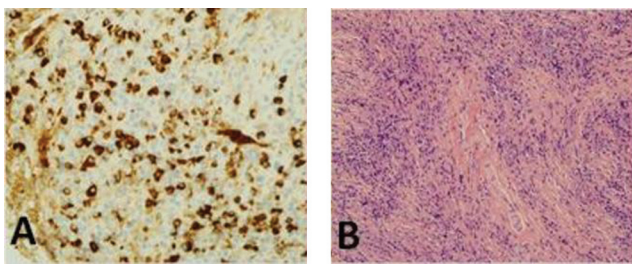


Figure 3. Histopathological specimens from surgical debulking of left nasal cavity pseudotumor. (A) IgG4 stain, $\times 400$ high power view. Diffuse infiltration of IgG4 plasma cells, >50 cells/HPF. (B) H&E stain, $\times 200$ medium power view. Respiratory mucosa demonstrating the characteristic irregular whorled pattern of fibrosis (storiform fibrosis) of IgG4-related disease.

patients did have multiorgan disease yet few cases were extensively examined in search of other affected subsites. Of the three cases that did report full-body imaging, none of the patients had multiorgan disease.

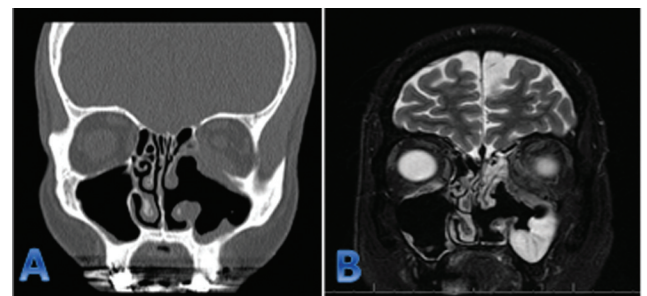


Figure 4. Post-surgical radiographic images of left sinonasal mass. (A) CT without contrast, 3 weeks after surgical debulking and initiation of high dose oral prednisone. (B) MRI T2, 6 weeks after surgical debulking.

Treatment and Outcomes

Four patients received systemic corticosteroids. Two patients received surgical debulking of the tumefactive lesion, with subsequent topical corticosteroids. One patient received an initial course of systemic steroids

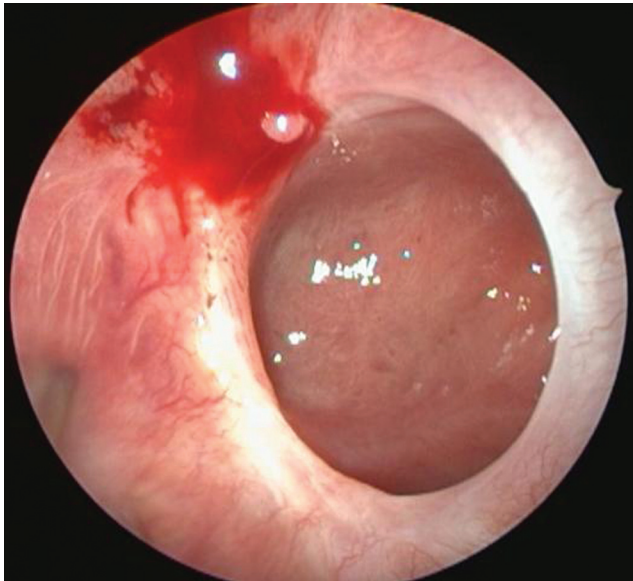


Figure 5. Endoscopic view of the left maxillary sinus status 6 months after surgical debulking and initiation of steroid therapy. There is a patent antrostomy, and the site of previous tumor shows no residual or recurrent disease.

but had persistence of disease. This patient then subsequently received surgical debulking, with adjuvant systemic corticosteroids and rituximab, and was able to achieve disease remission. One patient achieved remission of disease with serial surgical resections of the tumefactive lesion. All the patients were able to achieve remission of disease.

DISCUSSION

Sinonasal disease is a rare entity, with only eight reported adult cases in the literature, despite the head and neck region being the second most common site of disease.¹⁰ The majority of the cases (seven of eight) were reported from Japan and the United States, with only one reported case that originated from Europe. It remains unclear whether this represents a higher prevalence of disease in these populations or a higher awareness of disease in these countries.¹⁰

Due to the rarity of sinonasal IgG4-rSD, our review consisted of level-4 and level-5 data, and the total number of published cases was limited. The study was also limited by the variability in the criteria used to diagnose IgG4-rSD, and many of the reports did not detail key components of the histopathology that is now recommended to diagnose this condition. Being a new disease entity, diagnostic criteria were still an evolving process and only until recently was there a formally agreed upon diagnostic criteria, developed in 2011.

Sinonasal IgG4-rSD more commonly affected the older male population similar to other IgG4-rSD subsites. Yet, the data indicate that sinonasal disease may

more often be isolated to local disease in which only two of the eight patients had multiorgan disease, and just one of these two patients exhibited disease outside the head and neck region. This differs from other regions of the body where multiorgan disease is reported in 60% of cases.¹¹ However, only four cases reported imaging outside the head and neck region, and follow-up was limited to a mean of 8 months (two cases did not report a follow-up). Disease most commonly affected the maxillary sinus, yet the majority of cases (six of eight) exhibited local extension to multiple subsites in the sinonasal region.

The differential diagnosis of a unilateral sinonasal mass includes infection, malignancy, and other autoimmune processes. Although sinonasal IgG4-rSD is a benign process, it has exhibited a high propensity for invasive behavior, including bony destruction, perineural infiltration, and bone marrow infiltration,^{2,4-8} which often leads clinicians to suspect malignancy. It is extremely important to rule out more common malignant sinonasal neoplasms, including squamous cell carcinoma, lymphoma, undifferentiated carcinoma, and melanoma.

Common radiologic features consist of well-defined soft-tissue lesions that demonstrate homogenous attenuation and signal intensity on CT and MRI, respectively.¹² CT images without contrast enhancement demonstrated isoattenuation of the IgG4-rSD lesion. IgG4-rSD lesions of the head and neck are typically slow to expand and are often associated with bone remodeling, characterized by bony erosion or sclerosis. However, six of the eight cases, aside from the one presented, reported atypical expansile behavior that resulted in bony destruction of the sinus walls.^{2,4,5,7,8} T2-weighted MRIs exhibited iso- to hypointense signal attenuation compared with brain gray matter due to the combination of fibrosis and cellularity. After the administration of contrast, T1-weighted images demonstrated gradual homogenous enhancement.

Although radiographic imaging is helpful to determine the extent of disease, no radiographic features are highly sensitive or specific for IgG4-rSD. Oftentimes, these lesions are suspicious for malignancies. Therefore, biopsies are essential in differentiating IgG4-rSD from other disease processes. Based on the international consensus statement on the pathology of IgG4-related disease, a diagnosis of IgG-rSD requires the presence of two of the three major histologic features (Table 2).⁹

Dense lymphoplasmacytic infiltrate consists of diffuse infiltration of largely lymphocytes and a component of plasma cell infiltrate. IgG4 plasma cell numbers should be histopathologically elevated or have an elevated IgG4:IgG ratio of >40%. Other subsites in the head and neck have used >100/HPF as a diagnostic cutoff for the lacrimal and salivary gland disease.

Table 1 Review of the literature

Case Report	Age (y)/Sex	Presenting Symptoms	Affected Site	Invasive Feature	Treatment Course	Outcome
Ishida <i>et al.</i> , ² 2009	72/M	Nasal obstruction	Right maxillary sinus, septum, right parotid gland	Bone destruction	Serial surgical resections	Disease remission, follow-up 11 mo
Ikeda <i>et al.</i> , ³ 2010	50/F	Bloody rhinorrhea, postnasal drip	Left maxillary sinus, left ethmoid sinus	None	Prednisolone 30 mg/day, with slow taper over 6 mo	Disease remission, follow-up 6 mo
Pace and Ward, ⁴ 2010	73/M	Right facial swelling	Right maxillary sinus	Bone destruction	Prednisolone 20 mg/day for unknown duration	Disease remission, follow-up 5 mo
Alt <i>et al.</i> , ⁵ 2012	38/F	Headache	Bilateral sphenoid sinuses	Bone destruction	Surgical debridement, topical fluticasone for unknown duration	Initial recurrence of disease postsurgical debridement, disease remission after starting fluticasone 2 mo after surgery, follow-up 5 mo
Sasaki <i>et al.</i> , ⁶ 2012	71/M	Nasal obstruction, right facial swelling	Bilateral nasal cavities, bilateral maxillary sinuses, left pterygopalatine fossa	Perineural invasion, bone marrow invasion	Prednisolone 40 mg/day, with taper for duration of 18 mo	Disease remission, follow-up 18 mo
Lindau <i>et al.</i> , ⁷ 2013	69/M	Restricted right eye movement, diplopia	Right maxillary sinus, right ethmoid sinus, right sphenoid sinus	Bone destruction, orbital invasion	Prednisone burst, with taper >6 wk; surgical debridement; 2 cycles of rituximab and prednisone 4-wk course	Initial disease recurrence after primary steroids; disease remission with surgery, rituximab, and steroids; follow-up 5 mo
Cain <i>et al.</i> , ⁸ 2014	62/F	Epistaxis	Septum, bilateral ethmoid sinuses	Bone destruction	Prednisone 20 mg/day for unknown duration	Remission, follow-up duration not reported
Cain <i>et al.</i> , ⁸ 2014	79/M	Epistaxis	Septum	Bone destruction	Surgical resection, topical budesonide for unknown duration	Disease remission, follow-up duration not reported
Our case	72/M	Left eye proptosis, left eye epiphora, left periorbital pain, postnasal drip	Left maxillary sinus, left ethmoid sinus	Bone destruction, orbital invasion	Surgical debridement, prednisone 40 mg/day tapered over 3 mo	Disease remission, follow-up 6 mo

However, Deshpande *et al.*⁹ in the consensus statement assert that elevated levels of IgG4 plasma cells alone can be misleading because other inflammatory conditions can express elevated levels of all IgG plasma cell subtypes, but IgG4 plasma cells may only be a small component of the total IgG levels, therefore, making a diagnosis of IgG4-rSD less likely. An IgG4:IgG plasma cell ratio of >40% is a more sensitive histopathologic characteristic in diagnosing IgG4-rSD.

Although many patients may also express elevated serum IgG4, this has proven to be an insensitive assessment of disease in which serum levels are normal in 40% of patients with biopsy-proven disease.¹³ Serum IgG4 has also proven to be a poor predictor of disease in the sinonasal region; only one of the cases reviewed had elevated serum IgG4 levels. This further emphasizes the importance of obtaining a biopsy specimen to accurately make a diagnosis.

Table 2 Key histopathologic features of IgG4-rSD

Major Features#

Dense lymphoplasmacytic infiltrate defined as >50 IgG4 plasma cells/hpf or IgG4 to total IgG ratio of >40%
Fibrosis, arranged at least focally in a storiform pattern
Obliterative phlebitis

Minor features§

Phlebitis without obliteration of the lumen
Increased numbers of eosinophils

#A high confidence diagnosis can be made if two of the three major features are fulfilled.

§Minor features are associated with IgG4-rSD but are neither sensitive nor specific for the disease as isolated findings.

IgG4-rSD = Immunoglobulin G4-related sclerosing disease; IgG = immunoglobulin G.

Source: Ref. 9.

After diagnosis of IgG4-rSD, clinicians should consider imaging of other regions of the body because IgG4-rSD often affects multiple organs. Positron emission tomography-CT has shown promise in detecting multiorgan disease and for monitoring disease in which active disease expresses increased fluorodeoxyglucose uptake.¹⁴⁻¹⁶ However, lesions are difficult to differentiate from malignancy, and, therefore, detected lesions may require further evaluation by CT and MRI, and possible biopsy.

Treatment regimens have been extrapolated from the literature of IgG4-rSD of other organ systems and have largely been successful in attaining disease remission. Initial therapy consists of an oral corticosteroid, with an initial high-dose steroid burst (typically prednisone 40 mg/day) with a gradual taper (5 mg/wk) over a few months, with the ultimate goal of completely discontinuing steroids.¹⁷ If disease continues to proliferate or the patient is unable to control the disease with a steroid dose of <10 mg/day, the steroid sparing immunomodulating agents can be added (azathioprine 2 mg/kg/day, mycophenolic acid up to 2 g/day, or mercaptopurine 1 mg/kg/day). Although the literature has not shown improved control of disease with immunomodulators, most investigators would still consider these medications to either lower the maintenance steroid dose or wean the patient from steroids altogether.¹⁷ Furthermore, all previous case reports, except for Lindau *et al.*,⁷ demonstrated resolution of sinonasal disease with either complete surgical resection or with corticosteroid therapy. Overall, the literature supports a combination of medical therapy with corticosteroids and surgical therapy with debulking or resection for treatment of sinonasal IgG4-rSD.

Rituximab has shown promise as an effective agent and should be considered, especially with patients with immunomodulator or steroid intolerance.^{7,17,18} The treatment regimen has shown significant results in the treatment of other IgG4-rSD in other organ systems. Hart *et al.*¹⁷ reported a complete remission rate of

83% in those patients with autoimmune pancreatitis. Lindau *et al.*⁷ also had favorable results in the treatment of their patient with sinonasal IgG4-rSD in which disease persisted, despite an initial 6-week course of prednisone.⁷ The patient was then treated with two cycles of 375 mg/m² of rituximab weekly for 4 weeks with concurrent 40 mg/day of dexamethasone for 4 weeks; the patient, thereafter, demonstrated an appropriate clinical and biochemical response with stabilized but not completely resolved radiographic findings.

CONCLUSION

Sinonasal IgG4-rSD is a rare disease that can present with bony and soft-tissue invasion. Immunohistologic workup is essential for diagnosis to rule out other autoimmune processes. It is also important to differentiate this disease from sinonasal tumors and chronic rhinosinusitis. Initial therapy consists of corticosteroids. New immunomodulator therapy for treatment of nonsinonasal IgG4-rSD may broaden the armamentarium of medical therapy for the sinonasal entity. Surgical debulking is often a mainstay of therapy, especially for lesions that are larger or that have significant fibrosis. Sinonasal IgG4-rSD represents an emerging disease that may present both challenges and opportunities for future rhinologists.

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