Immunoglobulin G4–related sclerosing disease of the paranasal sinuses: A case report and literature review

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ABSTRACT

Objective: *Immunoglobulin G4 (IgG4) related sclerosing disease (RSD) of the paranasal sinuses is a rare lesion of dense lymphoplasmacytic tissue, with a high proportion of IgG4+ plasma cells. We presented a rare case of IgG4-RSD with isolated involvement of the paranasal sinuses in the absence of multiorgan involvement.*

Methods: *A case report and comprehensive literature review.*

Results: *To our knowledge, only 11 cases of IgG4-RSD with paranasal sinus involvement have been reported. Patients with IgG4-RSD commonly present with epistaxis and symptoms that mimic chronic rhinosinusitis, e.g., rhinorrhea, nasal obstruction, and facial pressure. On imaging, an expansive and erosive process is described. Surgery provides tissue for immunohistologic evaluation; however, there is a paucity of evidence about the direct extent of surgical resection or medical therapies. Postoperative steroids were typically started, although the regimen was not standardized.*

Conclusion: *Few cases of paranasal sinus IgG4-RSD have been reported in the literature. Evidence-based recommendations regarding treatment and surveillance of paranasal sinus IgG4-RSD are lacking; however, most reports describe systemic steroids as the mainstay of treatment. This single subject analysis, with a review of previously reported cases adds to the expanding body of data related to this rare disorder.*

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Humoral immunity is mediated by immunoglobulins secreted by plasma cells. There are four immunoglobulin G (IgG) isozymes, labeled 1 to 4; IgG4 accounts for <6% of the total IgG fraction in healthy subjects.[1] The pathogenesis of IgG4–related sclerosing disease (RSD) has not been fully elucidated; however, an immune reaction, predominately mediated by T-helper type 2 and regulatory T cells, has been proposed.[2] T-helper type 2 lymphocytes produce various interleukins, cytokines, and growth factors, which may result in chronic lymphoplasmacytic infiltration and fibrosis when produced in disproportionate amounts. Previously, Masaki *et al.*[3] performed a retrospective review of 132 patients with systemic IgG4-RSD and described quantitative serologic criteria (Table 1). However, in a 2012 consensus statement, a diagnostic algorithm of IgG4-RSD was developed based primarily on the histologic characteristics of involved tissue, whereas serum IgG4 measurements were considered of secondary importance.[4] Imaging, although not pathognomonic, is helpful in the workup of this lesion. IgG4-RSD that involves the sinonasal cavities is uncommon, with only a few cases previously described. We present a rare case of a patient with IgG4-RSD with isolated involvement of the paranasal sinuses in the absence of systemic disease.

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CASE STUDY

A 46-year-old man presented to the otolaryngology clinic with recurrent right-sided epistaxis, facial pain, nasal congestion, rhinorrhea, and nasal crusting for 1 year. Review of systems and results of basic laboratory investigations (*i.e.*, complete blood count and comprehensive metabolic panel) were unremarkable, and, therefore, there was low suspicion for systemic disease. No serum IgG4 measurements were collected. High-resolution computerized tomography (CT) of the sinuses revealed a well demarcated but expansive mass of the right ethmoid sinus with erosion of the lamina papyracea (Figs. 1 and 2). There was no evidence of infiltration within the surrounding structures (*i.e.*, periorbita or skull base). Intraoperative endoscopic visualization confirmed the presence of a polypoid mass that primarily involved the right ethmoid sinus with extension into the frontal recess and erosion of the lamina papyracea. The periorbita and skull base were uninvolved. The patient underwent endoscopic sinus surgery with excisional biopsy of the lesion.

Results of a histologic analysis of the sinus lesion demonstrated dense infiltrates of plasma cells and fibrosis deep within the tissue. Immunostain for CD138,

Table 1 **Quantitative cutoff values for the diagnosis of systemic IgG4-RSD***

	Sensitivity, %	Specificity, %
Serum IgG4 level, >135 mg/dL	97.0	79.6
Serum IgG4:IgG ratio, >8%	95.5	87.5
>10 IgG4+ cells per high-powered field	100	38.1
IgG4+ cell to IgG+ cell ratio, >40%	94.4	85.7

IgG4 = immunoglobulin G4; RSD = related sclerosing disease.
From Ref. 3.

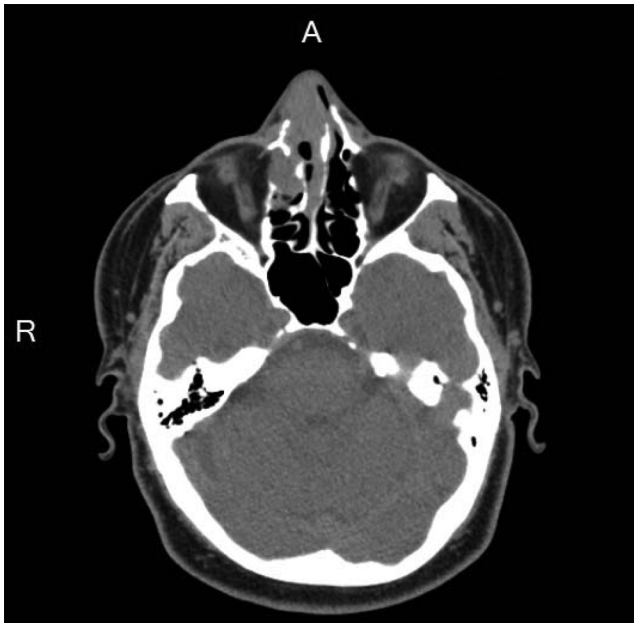

Figure 1. *Axial view of the soft-tissue lesion with osseous destruction at the anteroinferior right-sided lamina papyracea.*

a generic plasma cell marker, labeled >50% of the visible cells (Fig. 3) and anti-IgG4 stains of the sinus lesion demonstrated >50% of the IgG4 subclass (Fig. 4). Postoperative management included oral antibiotics for 7 days, saline solution irrigations, and prednisone 30 mg per day for 4 weeks tapered by 5 mg per week until completed. Routine postoperative debridement in the office was performed. At 1-year of follow-up, there had been no endoscopic evidence of persistent or recurrent disease. All of the patient's symptoms had resolved, without the need for continued therapy.

LITERATURE REVIEW

A search of the literature located only 11 cases of IgG4-RSD with sinonasal involvement (Table 2). In

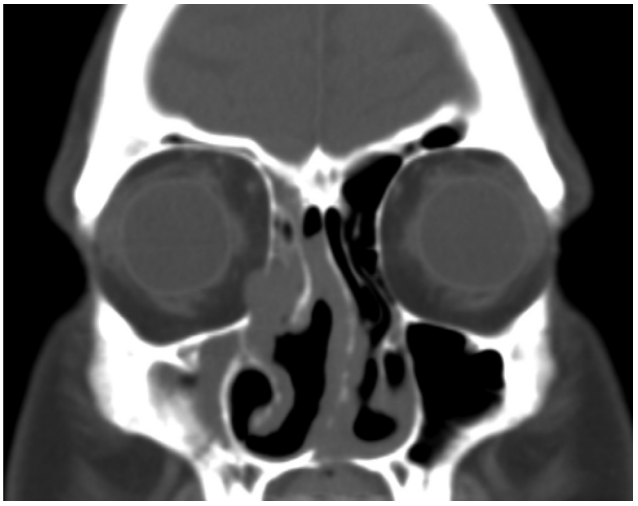

Figure 2. *Coronal view, demonstrating erosion of the right lamina papyracea with maxillary outflow obstruction.*

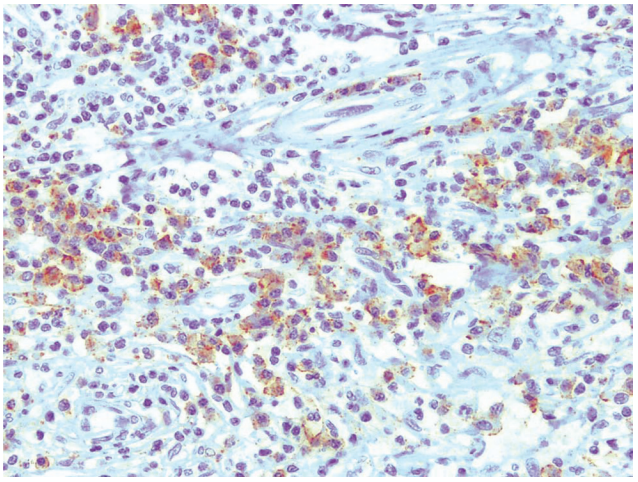

Figure 3. *CD138 immunostain, demonstrating plasma cell population within inflammatory infiltrate (anti-CD138 immunostain, original magnification ×200).*

2009, Ishida *et al.*[5] described the first case of sinonasal IgG4-RSD. Including our case, IgG4-RSD of the paranasal sinuses affects men somewhat more often than women (7:5) and afflicts all age groups, with a mean presentation at 55.3 years (standard deviation, 21.6 years; range, 15–79 years). All reported cases describe patients with locally destructive disease, with the most common symptoms being nasal obstruction, epistaxis, and facial pain. The maxillary sinus was involved most commonly, followed by the ethmoid sinus and nasal septum. Alt *et al.*[6] reported isolated sphenoid sinus involvement with symptoms of constant frontal headaches. Ishida *et al.*[5] found concomitant parotid gland IgG4-RSD in addition to disease of the right maxillary sinus and nasal septum; however, isolated sinonasal disease was found in the remainder of patients.

To establish the diagnosis, a tissue biopsy rather than primary resection was performed in the majority of

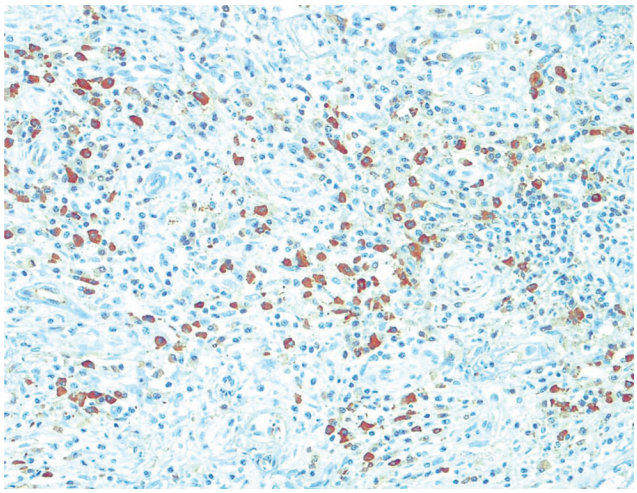

Figure 4. *Immunostain for immunoglobulin G4 (IgG4) shows many plasma cells that contain the IgG4 subclass (anti-IgG4 immunostain, original magnification ×150).*

patients. After surgery, a systemic steroid was immediately started in several patients; although the dosage and duration was not consistent. Alt *et al.*[6] noted recurrent and/or recidivistic disease 2 months after surgery of primary debulking; thus, fluticasone was initiated with no reported progression. Lindau *et al.*[7] and Prabhu *et al.*[8] described the use of rituximab in patients with poor response to oral steroids after biopsy.

DISCUSSION

The prototype of IgG4-RSD has become IgG4–related sclerosing pancreatitis, also known as autoimmune pancreatitis.[9] Extrapancreatic pathology has been reported in many organ systems, including regions within the head and neck.[10,11] Although most cases of IgG4-RSD are systemic, clinicians should be aware of possible isolated sinonasal disease. As in our case, most cases of paranasal IgG4-RSD report locally destructive disease. Many of the presenting symptoms mimic other forms of rhinitis or rhinosinusitis with rhinorrhea, nasal obstruction, facial pressure, and epistaxis being the most common. Based on symptomatology, this could prompt the clinician to initiate intranasal steroid sprays that possibly aid in the treatment of both rhinosinusitis and paranasal IgG4-RSD, thus potentially delaying the diagnosis.

Endoscopic biopsy for immunohistochemistry may be the primary role of surgery. A characteristic histologic appearance with marked plasma cell IgG4 expression supports a diagnosis of IgG4-RSD. Serum IgG4 levels are potentially misleading because IgG subtypes can be elevated in other inflammatory conditions.[4,12] In the cases reviewed, most surgeons performed a tissue biopsy rather than complete excision of the lesion. In our case, a complete excision was performed. There does not seem to be a correlation between the extent of biopsy and disease recurrence (*i.e.*, biopsy versus excisional biopsy). Therefore, it is unclear whether an attempt at surgical excision needs to be or should be performed.

Due to limited evidence, the management of sclerosing diseases that affect the sinuses is largely based on extrapolations from other organ systems. Currently, the suggested treatment for systemic IgG4-RSD is an oral corticosteroid taper over several weeks, the dose and duration of which is poorly defined. Except for two patients, in the cases reviewed, there were no recurrences or progression of disease reported in patients started on oral prednisolone soon after a tissue diagnosis. However, the follow-up time documented was not consistent or standardized, the sample size was small, and, therefore, an evidence-base recommendation was lacking. One case noted recidivistic disease 2 months after surgery, and fluticasone intranasal spray was started with no progression reported.[6] In cases isolated to the paranasal sinuses, a nasal steroid irrigation, *e.g.*, budesonide 0.5 mg in 240 mL normal saline solution, could target nasal symptoms; although, this has never been studied or reported.

Disease surveillance should be directed by clinical examination and symptomatology, including endoscopic examination and, possibly, imaging. Periodic serology studies (*i.e.*, IgG4 levels) may be indicated with suspicion of systemic involvement.[13] Further, there is no standard for treating recurrence; re-treatment with high-dose corticosteroid is an option, alternatively, immunomodulating medications (*i.e.*, rituximab) may be beneficial in refractory cases.[13–15] In our case, there had been no recurrence of disease after 12 months of observation.

CONCLUSION

Only several cases of IgG4-RSD isolated to the paranasal sinuses have been described in the literature. The disease typically presents as a nasal lesion with obstructive symptoms. Imaging is nonspecific and demonstrates an expansive and erosive process, usually without infiltrative characteristics. Surgery at minimum provides tissue for histologic analysis but may provide relief of symptomatic nasal obstruction or may alleviate mucociliary obstruction and restore effective paranasal sinus ventilation when more extensive excisional procedures are performed. There is a paucity of evidence to guide management strategies. Local and systemic medical therapies are unproven and poorly studied; however, most reports describe symptom control and improved endoscopic appearance, with systemic steroid use. It is unclear whether IgG4-RSD lesions of the sinuses recur and, if so, when. Therefore, evidence-based recommendations for follow-up are lacking. It seems prudent that endoscopic surveillance

Table 2 **Review of sinonasal IgG4-RSD**

Study, y	Country	Age, y/Sex	Location	Chief Concern	Serum IgG4 level, mg/dL	Immunohistochemistry	Treatment	Recurrence
Ishida *et al.*,[5] 2009	Japan	73/M	Right maxillary sinus, nasal septum, and parotid gland	Nasal obstruction	63.4	IgG4 expression in >70% of plasma cells	Resection of the maxillary sinus tumor and resection of the parotid tumor 6 wk later	No recurrence in the maxillary sinus or parotid; however, nasal septal mass was found 1 year later
Pace and Ward,[16] 2010	United Kingdom	73/M	Right maxillary sinus	Facial swelling	Not reported	IgG4 expression in >20% of plasma cells	Biopsy and 20 mg/day prednisolone	No recurrence at 5 mo
Ikeda *et al.*,[17] 2010	Japan	50/F	Left maxillary and ethmoid sinuses	Bloody rhinorrhea and postnasal drip	258	Numerous IgG4+ plasma cells	Biopsy and 30 mg/day of prednisolone	No recurrence at 6 mo
Sasaki *et al.*,[18] 2012	Japan	71/M	Bilateral maxillary sinuses and nasal cavity	Nasal occlusion and facial swelling	114	Plasma cells expressing IgG4	Biopsy and oral prednisolone for 18 mo (tapered to 10 mg/day from an initial dose of 40 mg/day)	Tumor remained stable
Alt *et al.*,[6]2012	USA	38/F	Sphenoid sinus	Frontal headaches	20	>150 IgG4+ plasma cells/hpf	Debulking primarily and fluticasone was initiated when recurrence was noted	Recurrence noted at 2 mo
Lindau *et al.*,[7] 2013	USA	69/M	Maxillary sinus	Chronic sinusitis and diplopia	74	>30 IgG4+ plasma cells/hpf	Debulking and prednisone, then dexamethasone pulse therapy and rituximab	Progression on dexamethasone alone; improvement when on dexamethasone with rituximab
Prabhu *et al.*,[8] 2014	India	15/F	Nasal septum, right lateral nasal wall, extension into the right maxillary sinus	Nasal obstruction and epistaxis	206	IgG4 expression in 50% of plasma cells	Biopsy and prednisolone	No recurrence noted
Prabhu *et al.*,[8] 2014	India	15/F	Right lateral nasal wall, nasal roof, nasal septum, right maxillary, ethmoid and sphenoid sinus	Bloody rhinorrhea, facial swelling, and trismus	579	IgG4 expression in 50% of plasma cells and >30 IgG4+ plasma cells/hpf	Biopsy and prednisolone (1 mg/kg/day) and rituximab (two intravenous infusions of 600 mg, 15 days apart)	Progression of disease, rituximab started
Cain *et al.*,[15] 2014	USA	62/F	Nasal septum and ethmoid sinuses	Epistaxis	Not reported	Approaching 50 IgG4+ plasma cells/hpf	Biopsy and prednisone 20 mg/day	No progression
Cain *et al.*,[15] 2014	USA	79/M	Anterior inferior nasal septum with erosion of premaxilla	Epistaxis	Not reported	30–50 IgG4+ plasma cells/hpf	Biopsy and nasal budesonide (0.5 μg in 240 mL of normal saline solution) because the patient declined systemic steroids	Without progression
Song *et al.*,[19]2015	USA	72/M	Maxillary and anterior ethmoid sinuses	Exophthalmos, periorbital pain, and epiphora	94.5	>50 IgG4+ plasma cells/hpf	Biopsy and prednisone 40 mg/day tapered over 3 mo	Resolution at 6 mo
Vandjelovic and Humphreys, 2015	USA	46/M	Ethmoid sinus with extension into the frontal recess	Epistaxis, facial pain, nasal congestion, rhinorrhea, and nasal crusting	Did not obtain	IgG4 expression in >50% of plasma cells	Excisional biopsy and prednisone 30 mg/day for 1 mo, with gradual taper; nasal saline solution rinses	No recurrence at 12 mo

IgG4 = immunoglobulin G4; RSD = related sclerosing disease; hpf = high-powered field.

continues yearly or as directed by symptomatology. Imaging may be best reserved for those with clinical evidence of recurrence.

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