Sinonasal IgG4-related sclerosing disease: A rare entity and challenging diagnosis

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Abstract

Objectives: To describe the rare presentation, imaging and histological findings, and treatments in patients with IgG4-related disease (IgG4-RD) and diagnostic pitfalls and difficulties.

Methods: Cases of sinonasal IgG4-RD were retrieved, and clinicopathological features were reviewed.

Results: Seven cases of sinonasal IgG4-RD were identified over an 11-year period, including four males and three females, with an age range of 19–66 years (median 58 years). Patients presented with symptoms related to the mass effect of the lesions or the destructive nature of the disease including fullness, swelling, obstruction, and pain. Serum IgG and IgG4 levels, IgG/IgG4 ratios, storiform fibrosis, obliterative phlebitis, and plasma cell infiltration were seen in varying proportions. Bony erosion and tissue inflammation were present in some cases.

Conclusion: Sinonasal IgG4-RD is exceedingly rare among other IgG4-RD and varied in its clinical presentation thus posing as a clinically difficult disease to diagnosis. Proper clinical, pathological, and immunohistopathological analysis is required for accurate diagnosis. Such disease should be considered in all cases of similar presentation to those in this study.

Level of Evidence: 4.

KEYWORDS
IgG4, IgG4-related disease, paranasal sinus, sinonasal disease

1 | INTRODUCTION

Immunoglobulin G4-related disease (IgG4-RD), an autoimmune fibro-inflammatory disease characterized by tumefactive lesions, was first described by Hamano et al in 2001.1-3 These lesions have been known to involve single or multiple sites and span across virtually all organ systems including gastrointestinal, cardiovascular, endocrine, and renal.4-6 While head and neck involvement is the second most common location, localization to the nasal cavity and paranasal sinuses is exceedingly rare and difficult to diagnose.4,7,8

Multiple factors contribute to the overall difficulty in diagnosing IgG4-RD localized to the sinonasal cavity, notably the paucity of knowledge and poor understanding of pathogenesis.5 Additionally, IgG4-RD displays similar pathological features of malignant or
inflammatory processes. Diagnosis is also hindered by the inconsistency of laboratory and clinicopathological findings and lack of specific diagnostic criteria. Early diagnosis is paramount as early and aggressive treatment can prevent irreversible tissue damage. We present a series of seven cases to add to the literature and increase awareness of this disease for clinicians and pathologists alike.

2 | METHODS

After obtaining institutional review board approval, patients who had been diagnosed with IgG4-RD over a consecutive 11-year period were identified by searching the electronic medical records. Demographic data, presenting signs and symptoms, radiographic and laboratory studies, histopathological analysis, laboratory findings and treatments were recorded. No inclusion or exclusion criteria were used in analysis of patients.

3 | RESULTS

3.1 | Patient characteristics

All seven patients were cared for at the University of Florida from 2011 to 2022. The mean age was 49 years (range, 19–66 years). A complete description of patient characteristics is outlined in Table 1. Three of the seven patients were female. Seasonal allergies were part of the known history in two cases, and a third patient had a history of asthma and chronic rhinosinusitis with nasal polyps (CRSwNP). The most common presenting symptoms were in relation to the mass effect of the lesions or the destructive nature of the disease (Figure 1). These created symptoms of fullness, swelling, obstruction, and pain. Other reported symptoms were related to the location of disease such as vision loss and frontal headaches. The median duration of symptoms was 5 years (range, 2–50 years). Five of the seven patients had sinus involvement, with maxillary involvement being the most common sinus.

### TABLE 1 Patient demographics, disease location, and clinical presentation of cases

| Case no. | Age/sex | Side | Anatomic site | History of Allergies | Presenting symptoms |
|---------|---------|------|---------------|----------------------|---------------------|
| 1       | 59/F    | Bilateral | Entire sinonasal cavity and nasopharynx | Allergies to environmental factors (ragweed and cats) | Septal perforation x12 years |
| 2       | 19/M    | Left | Lateral orbital floor, erosion into maxillary sinus | No | Proptosis and vision loss x2 years |
| 3       | 66/F    | Right | Maxillary sinus, midline septum and palate | No | Hole in palate; mass in maxillary sinus; multiple oral and genital ulcers x5 years |
| 4       | 38/M    | Right | Nasal sill, right pyriform aperture | No | Swelling of right upper lip and right nasal vestibule; right nasolabial mass x6 years |
| 5       | 66/M    | Right | Nasal septum | No | Nasal obstruction x50 years |
| 6       | 58/M    | Right/Bilateral | R. facial soft tissue, B. sinonasal cavity | Asthma and history of CRSwNP | R facial swelling and nasal obstruction x3 years |
| 7       | 38/F    | Bilateral | Sphenoid sinus | Seasonal Allergies (Non specified) | Frontal headache x2 years |

*Allergies diagnosed by skin testing. CRSwNP chronic rhinosinusitis with nasal polyps.

![Figure 1](https://example.com/figure1.png)
The sinonasal cavity, Interestingly, up to 40% of patients with several cases have since been reported, but cases have been restricted to the head and neck. However, IgG4 appears to play a significant role in allergic reactions such as atopic eczema, bronchial asthma, and bullous skin lesions. Interestingly, up to 40% of patients with IgG4-RD have long standing histories of allergies and/or serum IgE elevation. In our patients, serum IgE elevation was seen in only 3 of the 7 cases (3, 4, 7). IgE levels were reported in three cases but were only elevated in case 6. Characteristic lymphoplasmacytic infiltration was described in all seven cases and storiform fibrosis was described in four cases (case 2, 3, 6, 7) (Figure 4AB). A complete outline of the pathological analysis can be found in Table 3.

### 3.4 Treatment and outcomes

After surgical biopsy to establish diagnosis, patients started immediate treatment with a corticosteroid (prednisone or a derivative) in all but one case (case 7). Rituximab was used as a second-line therapy in three patients as well (case 2, 3, 6). For the one patient who did not receive steroid treatment initially, she underwent surgical debridement with close follow-up. Two months after surgery disease recurrence was reported and the patient was started on corticosteroid treatment. Surgical management was not attempted in any of the other cases. Follow-up for patients ranges from 2 months to 4 years. Disease recurrence has been reported in one patient and is controlled with long-term steroids (case 6). Each patient's treatment and follow-up are shown in Table 4.

### 4 Discussion

IgG4-related disease is a systemic disease characterized by extensive IgG4-positive plasma cells and T-lymphocyte infiltration. The head and neck region is the second most common location of involvement for IgG4-RD as demonstrated by Mulholland. The sinonasal cavity, however, is rarely affected with the first sinonasal case not being described until 2009 by Ishida et al. Several cases have since been reported, but sinonasal involvement is still considered an extremely rare occurrence for this disease.

While autoimmune diseases tend to have a female sex predisposition, there is a stark contrast of male predominance seen in IgG4-RD, with male to female ratios ranging from 1.6 to 4.1. However, when the disease process is localized to the head and neck, the sex distribution is roughly equal. We saw a near equal male-to-female ratio in our cohort (4:3). The average age at diagnosis has been reported to be the 6th decade of life but cases have been reported for patients much younger including pediatric and adolescent ages. In this study, ages ranged from 19 to 66 years, with a mean of 49 years.

The exact pathogenesis of IgG4-RD is yet to be defined and could have genetic, infectious, atopic, or autoimmune contributions. Th2 polarization, a hallmark of allergic response, activates fibroblasts which drives the characteristic storiform fibrosis and induces IgG4 class switching in naïve B cells. IgG4 appears to play a significant role in allergic reactions such as atopic eczema, bronchial asthma, and bullous skin lesions. Interestingly, up to 40% of patients with IgG4-RD have long standing histories of allergies and/or serum IgE elevation. In our patients, serum IgE elevation was seen in only

### Table 2: Radiological features at diagnosis and full body follow-up scans

| Case no. | Radiology results                  | Full body workup          |
|----------|-----------------------------------|---------------------------|
| 1        | CT: End-stage erosive disease; total septal perforation, turbinates absent, lamina papyracea and cribiform absent | None                      |
| 2        | CT: Infiltrating process in L orbit with stretching of optic n and invasion into sup. L max sinus | None                      |
| 3        | CT: Destruction of palate and septum with right maxillary sinus mass MRI: erosion of hard palate | PET no evidence of active disease |
| 4        | CT: Right nasolabial pyriform aperture mass | None                      |
| 5        | CT: Bilateral swelling of nasal septal mucosa | PET no evidence of active disease |
| 6        | CT: Right sinonasal cavity; right nasal and facial soft tissue | CT chest, abdomen, pelvis (pending) |
| 7        | CT: bony destruction sphenoid sinus including anterior, posterior, and inferior walls, floor of sella turcica MRI: Mass lesion in sphenoid sinus, diffuse enhancement (T1) isointense to gray matter (T2) | PET/CT no evidence of active disease |

### 3.2 Radiologic findings

Radiologic images were reviewed for each patient and described (Table 2). Computerized tomography (CT) characteristics demonstrated bony erosion and destruction of soft tissue structures, with MRI imaging illustrating diffuse enhancement on T1-weighted image and isointensity to gray matter on T2-weighted image. Impressions for both CT and MRI were suggestive of malignant or infectious etiologies. Interestingly we found disease that had completely eradicated the nasal cavity (Figure 2A), that was isolated to the septum and nostril (Figure 2B,C) or had created a fistula (Figure 2D). Full body scans were obtained in three patients with an additional patient referred for imaging but not yet completed. For each patient who received full body imaging, a positron emission tomography (PET) scan was used. No active disease was detected on any of these scans outside of the previously recognized lesions.

### 3.3 Pathologic review

Histopathological and serological analysis was used to confirm diagnosis of IgG4-RD in each patient. Most common studies included IgG4 concentrations, IgG4/IgG ratios, and biopsy evaluation. An elevated IgG4 concentration (>135 mg/dl) was only found in one of our cases who had a concentration of 413 mg/dl. IgG4/IgG ratio >40% was found in all but one (case 2) of the patients for whom it was recorded with the greatest ratio being >70% (case 3 and 4). An example of this increased ratio can be seen in Figure 3. IgG4+ cells/HPF were found to be ≥150 in all three of the cases for which it was recorded (case 3,4,7).
one of the three patients whose serum IgE level was reported. The patient with an elevated IgE had a long-standing history of asthma and CRSwNP. Two other patients had been diagnosed with seasonal and environmental allergies. Because of this allergic link, it has been suggested that IgG4-RD is not autoimmune in nature but rather a hypersensitivity/allergic reaction.18

IgG4-RD presents insidiously as patients are not constitutionally ill, and diagnosis is made through a combination of imaging and histological studies.11 For our patients the duration of symptoms was quite extensive, up to 50 years in one patient, before a diagnosis was made. Although other IgG4-RD forms involve multiple organs, sinonasal involvement is typically isolated to sinonasal cavity as was the case in our cohort.17,16 Patients may have allergic features, however, presenting symptoms are often related to the destructive nature of the disease.11,17 In this study, the most common presenting symptoms were related to tissue erosion or disease expansion. This series demonstrates the broad manifestation of lesions. We found that lesions could be small and isolated to only the septum or quite extensive such as destruction of the entire nasal cavity or a nasal palatal fistula. In patients with a history of CRSwNP, symptoms of facial swelling and nasal obstruction may be mistaken for recalcitrant disease. Here, we demonstrate that these symptoms resulted from concurrent IgG4-RD and CRSwNP as was also the case in one other report.16

FIGURE 2  Total septal perforation, turbinates, lamina papyracea, and cribriform absent on coronal CT (A). Axial CT of bilateral anterior inferior nasal septal lesion (*) (B). Coronal CT showing right nasolabial pyriform aperture mass (*) (C). Destruction of hard palate and septum with right maxillary sinus mass and infiltration of lacrimal system on coronal CT (D)

FIGURE 3  Shows the same area of plasmacytic infiltrate stained with IgG (A) and IgG4 (B) at 20X. An increase in the number of IgG4 positive cells is evident when compared with the positive IgG plasma cells in the same area

FIGURE 4  Hematoxylin and eosin (H&E) stain at 10× (A) and 20× (B) show the characteristic storiform fibrosis commonly seen in IgG4-related disease in association with a lymphoplasmacytic infiltrate
| Case no. | Total IgG (norm 586–1602 mg/dl) | IgG1 (norm 248–810 mg/dl) | IgG2 (norm 130–555 mg/dl) | IgG3 (norm 15–102 mg/dl) | IgG4 (norm 2–96 mg/dl) | IgE (norm 6–495 IU/ml) | IgG4/IgG ratio | Biopsy site | Pathology Results |
|---------|---------------------------------|--------------------------|--------------------------|--------------------------|-----------------------|------------------------|----------------|-------------|------------------|
| 1       | 722 mg/dl                       | 278 mg/dl                | 309 mg/dl                | 16 mg/dl                 | 55 mg/dl              | NA                     | >40%            | Medial orbital walls and nasopharynx | Polytypic plasmacytosis with increased IgG4+ plasma cells |
| 2       | 1011 mg/dl                      | 521 mg/dl                | 361 mg/dl                | 33 mg/dl                 | 24 mg/dl              | NA                     | >30%            | Left maxillary sinus, left orbital floor | Storiform fibrotic tissue with increased IgG4(+) plasma cell infiltrate |
| 3       | 1021 mg/dl                      | 801 mg/dl                | 152 mg/dl                | 12 mg/dl                 | 56 mg/dl              | 198 IU/ml              | >70%            | Right maxillary sinus, septum, and palate | Storiform fibrosis and subepithelial infiltration of abundant lymphoplasmacytes; 150 IgG4+ cells/HPF |
| 4       | NA                              | NA                       | NA                       | NA                       | NA                    | NA                     | >70%            | Nasal sill, right pyriform aperture | Extensive plasma cell infiltrate; 200 IgG4+ cells/HPF |
| 5       | 1003 mg/dl                      | 557 mg/dl                | 372 mg/dl                | 46 mg/dl                 | 28 mg/dl              | 111 IU/ml              | >40%            | Anterior inferior nasal septum | Thickened basement membrane with fibrosis and lymphoplasmacytoid infiltrate |
| 6       | 1539 mg/dl                      | 609 mg/dl                | 320 mg/dl                | 37 mg/dl                 | 413 mg/dl             | 919 IU/ml              | >70%            | Right maxillary and ethmoid sinus; inferior turbinate | Storiform fibrosis, lymphoplasmacytic infiltrate with occasional eosinophils, obliterative phlebitis |
| 7       | NA                              | NA                       | NA                       | NA                       | NA                    | NA                     | NA              | Left sphenoid sinus | Storiform fibrosis, dense plasmacytic infiltrate; >150 IgG4+ cells/HPF |

Abbreviations: HPF, high powered field; NA, not available.
We had one patient.

It should be noted that storiform fibrosis and/or obliterative phlebitis generally exclude the diagnosis of IgG4-RD. A variety of cut-off points have been used to define the density of infiltrate ranging from >10 to >50 IgG4+ plasma cell per high powered field or immunohistochemical staining showing IgG4+/IgG+ plasma cell ratio >40–50%. In the present study, a plasma cell ratio >40% was used to define lymphoplasmacytic infiltration. Deshpande et al concluded that a confident diagnosis can be made if two of the three major histological features are found, with the first two features present in most cases. All of our cases showed the presence of at least one major histological feature with three cases demonstrating two features and one patient with all three. Therefore, given the most widely used diagnostic criteria, four patients would be categorized as “histologically highly suggestive of IgG4-related disease” with the remaining three categorized as “probable histological features of IgG4-related disease.”

Serological analysis has been controversial to the diagnostic approach because of the relative inconsistency of findings. Elevation of serum IgG4 is now thought to be a response and not an initiation of the disease process. This may explain why 20–40% of patients have normal serum IgG4 levels at diagnosis and 4–10% of both healthy and disease controls were found to have elevated IgG4 concentrations. Current guidelines suggest that a serum IgG4 concentration >135 mg/dl is indicative of disease, however, only one of our patients met this threshold. Moreover, elevated serum IgG4 is neither sensitive nor specific to IgG4-RD and can be seen in other disorders such as atopic dermatitis, pemphigus, Sjogren syndrome, asthma, hypereosinophilic syndrome, Behçet disease, and multicentric Castleman disease.

To date there are no organ specific diagnostic criteria for sinonasal or skull base IgG4-RD. It is thought that for previously unrecognized organ sites, such as the sinonasal cavity, diagnostic criteria should include characteristic histopathological findings, high serum IgG4 concentrations, effective response to glucocorticoid therapy, and reports of other organ involvement that is consistent with IgG4-related disease. While a variety of IgG4 analyses can be helpful in increasing a clinician’s suspicion of disease, IgG4-RD of the sinonasal cavity cannot be ruled out if these criteria are not met. Therefore, best practice for diagnosis should be based on a comprehensive assessment of clinical presentation, serological, histopathological, and immunohistochemical analyses to create the best diagnostic picture.

Beyond inconsistencies among diagnostic criteria, IgG4-RD is also difficult to diagnose due to several diagnostic pitfalls. Several diseases have similar histological features, such as GPA, Rosai-Dorfman disease (RDD), and fungal rhinosinusitis (FRS). High or low serum IgG4 concentrations and IgG4/IgG ratios can be red herrings for IgG4-RD as a potential diagnosis. Additionally, patients receiving immunosuppressants can alter their IgG levels thus leading to falsely elevated phlebitis without obliteration of the lumen and increased numbers of eosinophils.

The orbit is a commonly involved site in the head and neck region, and in cases with both maxillary sinus and orbital involvement it can be difficult to determine the primary lesion. We had one patient with both locations involved and destruction was described to start in the orbit and erode into the maxillary sinus. It is possible in this case that the sinonasal cavity was not the origin of disease and therefore would not meet the criteria of IgG4-RD of the sinonasal cavity.

IgG4-RD of the sinonasal cavity has non-specific imaging manifestations that vary considerably on both CT and MRI. Bony and tissue destruction on imaging raises concern for malignancy, which must be ruled out histologically. Our CT findings were non-descriptive of the etiology of disease. Impressions alluded to malignant or infectious processes, but no diagnosis could be confirmed. Other reports of radiologic imaging have included thickening of nasal septum, homogeneous and heterogenous enhancement.

Imaging alone is not enough to make an accurate diagnosis and should be included with histological and serological exams.

Histopathological analysis continues to be the cornerstone for diagnosing IgG4-RD in the sinonasal cavity. The three major histological features include dense lymphoplasmacytic infiltrate, storiform fibrosis, and obliterative phlebitis. Other associated features include

| Case no | Treatment | Follow-up |
|---------|-----------|-----------|
| 1       | Prednisone, MTX, and folic acid | Symptomatic improvement at 5 months. Nasal rinses |
| 2       | Prednisone, IV methylprednisolone and RTX added after disease progressed | Symptomatic improvement at 8 months. Nasal rinses |
| 3       | Prednisone, RTX added after disease progressed | Symptomatic improvement at 4 years. Nasal rinses |
| 4       | Prednisone | Symptomatic improvement at 4 years. Nasal rinses |
| 5       | Nasal steroids | Symptomatic improvement at 2 years. Nasal rinses |
| 6       | Prednisone, RTX added after disease progressed | Unable to wean steroids at 10 months. Continued with topical steroids and RTX indefinitely |
| 7       | Surgical debridement, fluticasone and nasal corticosteroids | Improved patency of sphenoid antrostomy at 2 months |

Abbreviations: MTX, methotrexate; RTX, rituximab.

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One pitfall we found in our patient cohort was the lack of consistent data between patients. Some IgG4 subclass concentrations and other lab values such as IgE concentrations were omitted or unable to be located in several patients. This variety in patient data is likely due to three factors: lack of guidelines for workup due to this being a newly recognized entity, possible lack of familiarity with the disease, and finally many of our patients lived several hours away and chose to follow with local specialists rather than come back to our tertiary center. Most lab values were obtained to rule out systemic diseases instead of looking to confirm IgG4-RD. We hope going forward a more standardized approach will be used as more otolaryngologists and rheumatologists alike become familiar with this entity.

The multitude of clinical manifestations of IgG4-RD of the sinonasal cavity makes developing a broad differential diagnosis uniquely challenging. Common categories for diseases to be considered are infectious, inflammatory, and malignant pathologies. Fungal, specifically invasive fungal sinusitis, and other infectious etiologies such as skull base osteomyelitis present with similar radiologic findings and can be excluded on tissue biopsy. CRS is often confused with sinonasal IgG4-RD as it can show elevated IgG4-positive cells in tissue and can also be complicated with IgG4-RD, but CRS alone would not show the same histological patterns. The differential for patients with malignant features such as bone and tissue destruction and intranasal necrosis should include ANCA-related vasculitis, malignant lymphoma, malignant tumor, natural killer/T-cell lymphoma, and inflammatory myofibroblast tumor. If a diagnosis cannot be confirmed through extensive evaluation, therapeutic response to treatment can act as a surrogate confirmation of an IgG4-RD diagnosis.

No randomized treatment trials or standardized therapies have been developed for IgG4-RD of the sinonasal cavity. Currently, first-line treatment is topical or systemic steroids for which up to 98% of patients have found effective. Less aggressive therapy may be used in mild cases or where surgery has previously removed diseased tissue. However, to decrease the possibility of disease recurrence, medication therapy should always follow surgical management. Monitoring serum IgG4 concentrations is useful for measuring treatment response as concentrations are known to decline considerably after steroid therapy has begun. Azathioprine, mycophenolate mofetil, and methotrexate have also been used as glucocorticoid-sparing agents. Fluticasone can be used to combine treatment for IgG4-RD and allergies. Rituximab (RTX) has also been used as a glucocorticoid alternative or in cases with recurrent or refractory disease. RTX depletes B-cells and therefore decrease IgG4 production, however, as understanding of the disease has increased, this treatment pathway may not be entirely effective, and the validity of this therapy is yet to be established. In the present series, a variety of treatment therapies were utilized with varying success. This further illustrates the need for a standard treatment protocol for sinonasal IgG4-RD. Regardless of therapy chosen, patients should expect to undergo long-term observation to detect recurrence of disease, or adverse effects from extended steroid use.

Prognosis for IgG4-RD is favorable provided treatment is started before the disease has severely progressed. Monitoring of recurrence should extend to other body regions as approximately 50% of relapses present with lesions in other organ systems. In the case of recurrence, corticosteroid doses should be increased, or immunosuppressants, such as RTX, should be added. Positive treatment outcomes were seen in all but one patient. In that patient, steroid weaning was found to not be possible without disease recurrence. All patients were advised to continue regular nasal rinses long term. Interestingly, although the association remains unclear, the incidence of cancer development within 3 years of IgG4-RD diagnosis is higher than that of the general population and should be monitored during follow-up.

5 | CONCLUSIONS

IgG4-RD of the sinonasal cavity is a rare disease requiring a high index of suspicion to diagnose. This disease should be considered as part of the differential diagnosis for all sinonasal inflammatory and mass-forming lesions. A combined clinical, radiological, and immunohistopathological analysis is required to confirm diagnosis and should be considered in all patients with similar presentations. Furthermore, surgeons should specifically request biopsies be evaluated for IgG4-RD to ensure accurate diagnosis. Early diagnosis and treatment will improve symptoms and prevent irreversible damage.

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CONFLICT OF INTEREST

Dr. Justice is a consultant for Medtronic. Dr. Lobo is a consultant for Medtronic and Acclarent.

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