



## CLINICAL LETTER

# Vision loss caused by immunoglobulin G4-related disease of the skull base complicated by a mucocele of the sphenoid sinus

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## Abstract

**Background:** Immunoglobulin G4-related disease (IgG4-RD) is a fibro-inflammatory disorder and manifestation in the paranasal and sphenoid sinus is well recognized. In this patient, IgG4-RD presented in an unusual manner with vision loss due to mucocele formation in the sphenoid sinus.

**Case Description:** A 19-year-old man, with an unremarkable medical history, was referred with decreased vision in the left eye, headaches, and a sharp pain in the left orbit and ear. Compression of the left optic nerve due to a large mucocele caused papillary edema and emergency endoscopic marsupialization of the mucocele was performed. When the vision decreased again, a more extensive decompressing sphenoidotomy was performed. Histopathology showed IgG4-RD. Despite dexamethasone, the lesion expanded to the anterior skull base and the patient required repeat endoscopic surgery. After 3 months, a decrease in smell and vision warranted for a fourth extensive decompressing surgery, complicated by a cerebrospinal fluid leak. Prednisone and later rituximab were commenced. Unfortunately, the patient reported a complete loss of vision after 4 months of rituximab due to increased mass effect on the optic nerve. An extensive combined craniofacial-endoscopic surgery was performed to remove the entire mucocele and to prevent further contralateral and intracranial progression. Methylprednisolone monthly was commenced to prevent further complications.

**Discussion:** This case illustrates that in therapy-resistant sino-orbital IgG4-RD, extensive surgery might be necessary at an earlier stage. It may even be the only option to prevent irreversible damage to the surrounding tissues. A

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multidisciplinary approach in the management of sino-orbital IgG4-RD is therefore warranted.

#### KEYWORDS

IgG4-related disease, IgG4, mucocele, sphenoid sinus

## 1 | INTRODUCTION

Immunoglobulin G4-related disease (IgG4-RD) is a fibroinflammatory disorder that can involve many different sites in the body.<sup>1</sup> Manifestation in the paranasal sinus is relatively common and involvement of the sphenoid sinus is well recognized.<sup>2</sup> We describe an unusual presentation of IgG4-RD in a patient with vision loss of the left eye caused by mucocele formation in the sphenoid sinus as a result of IgG4-RD. The study was approved by the medical ethics committee of the Erasmus University Medical Center Rotterdam (MEC-2021-0811) and conducted according to the criteria set by the Declaration of Helsinki. Informed consent was obtained.

## 2 | CASE REPORT

A 19-year-old man with an unremarkable medical history was referred to the ophthalmologist for decreased vision in the left eye to counting fingers, headaches, and a sharp pain in the left orbit and ear. At funduscopy we found papillary edema, which was found to be caused by compression of the left optic nerve attributed to a large mucocele originating from the sphenoid sinus (Figure 1A). Emergency marsupialization of the mucocele was achieved through endoscopic sphenoidotomy and restored the vision to 20/25 (Table 1, supplementary Video S1). However, 2 weeks later, his vision decreased to 20/50. A more extensive, bilateral decompressing sphenoidotomy with biopsies was performed. The histopathology showed a fibrosing lymphoplasmacellular infiltration with an IgG4/IgG ratio of 0.33 and was therefore suggestive of IgG4-RD, but the criteria for a definitive diagnosis were not met (Table 2). Dexamethasone 0.5 mg 3 times a day was commenced and vision improved to 20/32. Follow-up magnetic resonance imaging (MRI) after 2 months demonstrated new multicystic lesions, this time expanding to the complete anterior skull base. Additional endoscopic decompressing surgery was performed, complicated by a small cerebrospinal fluid leak that was sealed using absorbable hemostat and fibrin sealant. The postoperative MRI still showed mass effect on the orbit, including the optic nerve (Figure 1B). After 3 months, the patient reported a decrease in smell and loss

of vision to counting fingers, and findings on MRI showed a mass effect on the frontal lobes. Additional extensive endoscopic decompressing surgery with new biopsies was performed, again complicated by a cerebrospinal fluid leak sealed by allogeneic fascia lata, absorbable hemostat, and fibrin sealant (Supplementary Video S2). Histopathology now confirmed the diagnosis of IgG4-RD with extravasated mucus and extensive chronic inflammation. Results from 18F-fluorodeoxyglucose positron emission tomography/computed tomography did not show localizations in other parts of the body. After 3 months, the patient was started on prednisone 65 mg/d because of an increase of the lesion on MRI and vision reduced to only light perception. Rituximab was commenced after tapering of prednisone when the exophthalmos increased. After 4 months of rituximab treatment the patient reported a complete loss of vision in the left eye, likely caused by an increased mass effect on the optic nerve. An extensive combined craniofacial-endoscopic surgery was planned, which included a bifrontal and left pretemporal trepanation made to remove the cysts while preserving most of the dura (Supplementary Video S3). After the cranial resection, an endoscopic dissection toward the caudal part of the left orbital apex was performed and multiple cystic lesions with yellow-brownish fluid were opened. A defect of the anterior skull base was reconstructed with allogeneic fascia lata, a galea flap, free abdominal fat, and fibrin sealant. Last, the bone flap was fixated. Histopathology showed only features of a mucocele. No residual multicystic mass was identified on follow-up MRI (Figure 1C). The patient will receive intravenous methylprednisolone monthly for the next 6 months to prevent further complications, such as compression of the contralateral optic nerve.

## 3 | DISCUSSION

Involvement of the sphenoid sinus is a recognized manifestation of IgG4-RD. However, in our patient, it distinctly presented as a mucocele that evolved into a progressive multicystic mucocele covering the entire anterior skull base. To the best of our knowledge, this specific presentation has not been previously described. Mucocele formation secondary to trauma or surgery is common, but it is

TABLE 1 Histopathology and treatment

Presentation	Findings	Therapeutic intervention
Serum IgG4 <sup>a</sup> presystemic treatment	281 mg/dL	Endoscopic marsupialization
Serum IgG4 after initiating prednisone	181 mg/dL after 6 wk 178 mg/dL 2 mo after cessation	Bilateral sphenoidotomy with small biopsies Dexamethasone 0.5 mg 3 times a day and tapered over a course of 15 days Additional endoscopic debulking
Histopathology small biopsies	Fibrosing lymphoplasmacellular inflammation No evidence of an inclusion mucocele or malignancy was found Immunohistochemical analysis: 190 IgG-positive plasma cells/HPF, 48 IgG2 positive plasma cells/HPF, and 51 IgG4-positive plasma cells/HPF (mean of 3 HPF) IgG4/IgG ratio 0.33 and IgG2/IgG4 ratio 0.75 Histologically suggestive of IgG4-RD	Extensive endoscopic debulking with larger biopsies
Histopathology larger biopsies	Chronic nongranulomatous lymphoplasmacytic inflammation Fibrosis was found, but no storiform pattern or obliterative phlebitis Immunohistochemical analysis: 300 IgG-positive plasma cells/HPF, 8 IgG2-positive plasma cells/HPF, and 274 IgG4-positive plasma cells/HPF (mean of 3 HPF) IgG4/IgG ratio 0.91 and IgG2/IgG4 ratio 0.03 Histologically highly suggestive of IgG4-RD	Prednisone 65 mg/d and tapered within 3 mo Rituximab 1000 mg for 4 mo Extensive combined cranoendoscopic surgery
Histopathology extensive combined cranoendoscopic surgery	Fibrous shards of epithelium with mucus, fibrosis and hemosiderin pigment. Histologically consistent with a mucocele	Intravenous methylprednisolone monthly for the next 6 months

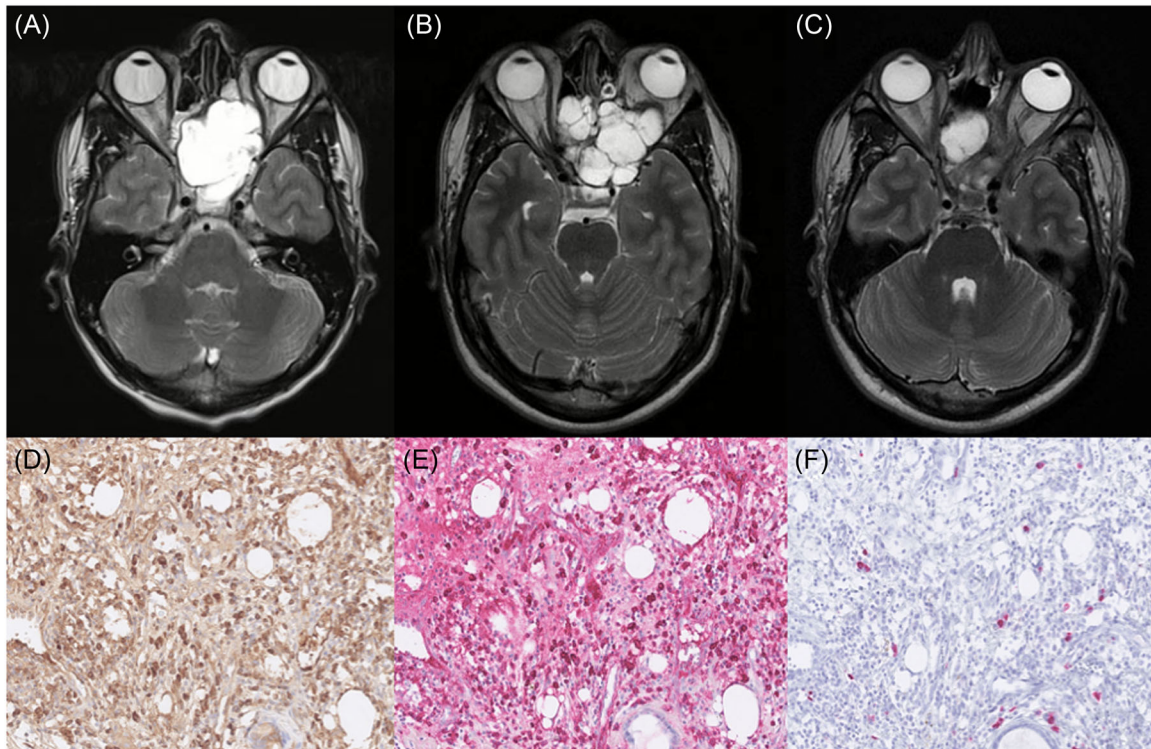
Abbreviations: HPF, high-power field (400× magnification); Ig, immunoglobulin; IgG4-RD, immunoglobulin G4-related disease.

<sup>a</sup>Serum IgG4 (normal values 80–140 mg/dL).

TABLE 2 Summary of the Boston consensus statement on the criteria for IgG4-RD according to Deshpande et al<sup>4</sup>

Characteristic histological features	Histologically highly suggestive of IgG4-RD	Probable histological features of IgG4-RD	Insufficient histological evidence of IgG4-RD
1: A total number >100 IgG4-positive plasma cells per HPF and IgG4/IgG ratio >0.40	Feature 1 with at least 2 other characteristic histological features	One histological feature Additional clinical evidence might be needed Including but not limited to elevated serum IgG4 or other organ involvement	No characteristic histological features This does not exclude IgG4-RD This might be attributable to sampling error, effects of therapy or too much fibrotic change
2: Dense lymphoplasmacytic infiltrate			
3: Fibrosis, usually storiform in character			
4: Obliterative phlebitis			

Abbreviations: HPF, high-power field (400× magnification); Ig, immunoglobulin; IgG4-RD, immunoglobulin G4-related disease.



**FIGURE 1** (A) Axial turbo spin echo T2-weighted magnetic resonance imaging before treatment shows a single large mucocele of the sphenoid sinus with mass effect, particularly of the left orbit. (B) After 3 rounds of endoscopic debulking surgery and prednisone, mass effect on the orbit was still present. (C) Complete resolution after extensive combined cranoendoscopic surgery. The hyperintense paraorbital signal is caused by cerebral spinal fluid. (D) Immunohistochemical staining showing immunoglobulin G (IgG)-positive plasma cells with an average of 300/high-power field (HPF). (E) Immunohistochemical staining showing IgG4-positive plasma cells with an average of 274/HPF. (F) Immunohistochemical staining showing IgG2-positive plasma cells with an average of 8/HPF. Panels D–F are all at an original magnification of 200 $\times$

seldom associated with IgG4-RD.<sup>3</sup> We hypothesize that the inflammation of the IgG4-RD has caused the formation of the primary mucocele and complicated healing resulted in the multicystic process.

Histopathology of the first biopsy showed features suggestive of IgG4-RD, but did not meet the criteria in accordance with the Boston consensus statement.<sup>4</sup> Larger biopsies were necessary to confirm the diagnosis of IgG4-RD. Especially in smaller biopsies, sampling error may lead to relatively low IgG4-positive plasma cell counts or insufficiently elevated IgG4/IgG ratio.<sup>4</sup> In cases with typical histopathological features of a tumorous lesion with a lymphoplasmacellular infiltration and storiform fibrosis, a suggestion to test for serum IgG4 may be made in the pathology report and repeat biopsies should be considered for confirmation of the diagnosis.

In most IgG4-RD cases, steroids or rituximab result in disease remission.<sup>5</sup> However, standard therapy failed in our patient, presumably because of the continued mucocele formation. Despite multiple endoscopic decompressions, the vision of the left eye could not be restored. Ultimately, an extensive combined craniofacial and endo-

scopic surgical procedure was necessary to remove the entire lesion to prevent further contralateral and intracranial progression.

This case illustrates that in therapy-resistant sino-orbital IgG4-RD, extensive surgery might be necessary at an earlier stage. It may even be the only option to prevent irreversible damage to the optic nerve. A multidisciplinary approach in the management of sino-orbital IgG4-RD is therefore warranted.

#### 4 | CONCLUSION

IgG4-RD of the paranasal sinuses can present as a multicystic mucocele. While early treatment is necessary to relieve symptoms and prevent further damage such as vision loss, some cases may prove therapy resistant and might require extensive surgery.

#### CONFLICT OF INTEREST

All authors give consent for publication and have no conflict of interest.

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**SUPPORTING INFORMATION**

Additional supporting information may be found in the online version of the article at the publisher's website.

**How to cite this article:** Detiger SE, Paridaens D, Verdijk RM, et al. Vision loss caused by immunoglobulin G4-related disease of the skull base complicated by a mucocele of the sphenoid sinus. *Int Forum Allergy Rhinol.* 2022;12:1216–1220. <https://doi.org/10.1002/alr.22993>