*The Journal of Laryngology & Otology (2015)*, ***129*** (Suppl. S1), *S57–S59*.

doi:10.1017/S0022215114001911

**CLINICAL RECORD**

# Immunoglobulin G4 related disease isolated to the nasal cavity: a rare cause of nasal obstruction

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## Abstract

*Background*: Immunoglobulin G4 related disease is a rare condition. Cases involving the sinonasal region are exceptionally uncommon. This paper describes a case of immunoglobulin G4 related disease isolated solely to the nasal cavity.

*Methods*: Case report and literature review.

*Results*: A 34-year-old man presented with painless, progressive bilateral nasal obstruction. Clinical examination and imaging findings demonstrated bilateral submucosal swelling of the anterior septum and right external nasal wall. Biopsy revealed immunoglobulin G4 related disease. The patient responded to oral corticosteroids initially, followed by long-term methotrexate.

*Conclusion*: To the best of our knowledge, this case represents the first report in the literature of immunoglobulin G4 related disease isolated solely to the nasal cavity.

**Key words:** IgG4; IgG4-Related Sclerosing Disease; IgG4-Related Disease; Nasal Cavity; Nasal Obstruction; Immunoglobulin G; Methotrexate; Autoimmune Disease; Eosinophils

## Introduction

Immunoglobulin G4 related disease is a recently described clinicopathological entity characterised by extensive tissue infiltration by immunoglobulin G4 (IgG4) positive plasma cells and T lymphocytes.[1] It is known to affect various organs including the pancreas, liver and lungs, as well as the salivary and lacrimal glands and pituitary gland in the head and neck region.[1,2] The sinonasal cavity is an extremely rare site for this disease and has previously only been reported to be involved in association with other sites.[2]

## Case report

This report was approved by the institutional review boards of the Western Sydney Local Health District Human Research Ethics Committee and the Westmead Scientific Advisory Committee. Informed consent was obtained from the patient, prior to chart review.

A 34-year-old man presented with a 2-year history of progressively increasing, painless, bilateral nasal obstruction and right external nasal swelling, with no other sinonasal symptoms. Clinical examination, computed tomography and magnetic resonance imaging findings (Figure 1) demonstrated a firm submucosal mass, present bilaterally over the anterior septum, with intact underlying cartilage. A synchronous, firm, subcutaneous mass was identified over the right lateral nasal wall. Initial conservative biopsy results were inconclusive. Extensive submucosal and mucosal tissue, and septal cartilage, were dissected under general anaesthesia and sent for histology.

### *Histopathology*

Microscopic examination revealed fibrosclerosing tissue containing dense aggregates of mixed inflammatory cells, particularly lymphocytes and plasma cells, along with histiocytes and scattered eosinophils, often centred around prominent endothelial cells. These findings indicated obliterative phlebitis (Figure 2). Based on these characteristic histological findings, immunostaining for IgG4 and immunoglobulin G (IgG) was undertaken. Results revealed numerous plasma cells positive for IgG4 (more than 50 cells per high power field) (Figure 3). The ratio of IgG4-positive to IgG-positive cells was over 40 per cent, confirming the diagnosis of IgG4-related disease.[2,3]

### *Management*

Clinical examination and imaging did not reveal any further lesions within the abdominal cavity or elsewhere. Serum IgG4 was within the normal range at 2.30 g/l (normal range, 0.06–2.56 g/l). The patient was referred for immunology review. The patient initially responded to high-dose oral steroids (40 mg prednisone daily), but relapsed when the dose was weaned. Long-term treatment with methotrexate (10 mg per week increasing to 20 mg per week), with folic acid (0.5 mg twice daily), resulted in good symptomatic

Presented as a poster at the Australian Society of Otolaryngology Head and Neck Surgery annual scientific meeting, 3–7 April 2011, Melbourne, Australia.
Accepted for publication 10 January 2014 First published online 27 August 2014

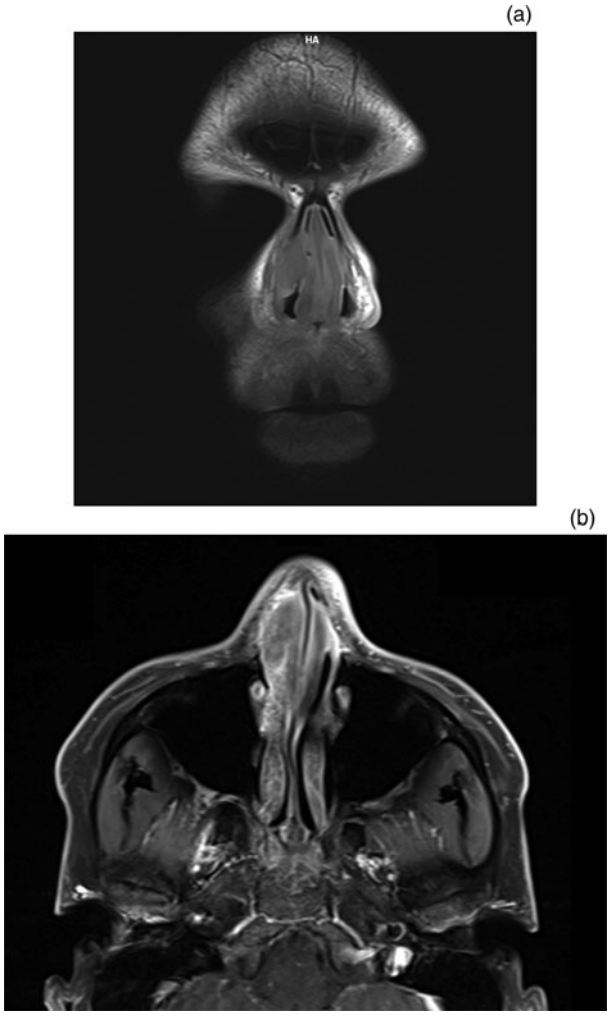


FIG. 1

Coronal, T1-weighted (a) and axial, T1-weighted, fluid-attenuated inversion recovery (b) magnetic resonance imaging scans, demonstrating a contrast-enhanced submucosal mass over the anterior septum bilaterally. H = head; A = anterior

relief. Repeat imaging at 18 months demonstrated a reduction in the volume of the involved tissue.

- **Immunoglobulin G4 (IgG4) related disease is characterised by extensive tissue infiltration by IgG4-positive plasma cells and T lymphocytes**
- **Presenting signs and symptoms vary according to the infiltration site**
- **In the sinonasal region, isolated deposits may result in nasal obstruction, whereas generalised infiltration may result in chronic rhinosinusitis symptoms**
- **Diagnosis is based on strict histological criteria and IgG4 immunostaining findings**
- **Immunosuppressive treatments, including oral steroids (short-term) and anti-metabolites (long-term, steroid-sparing), are effective in controlling this condition**

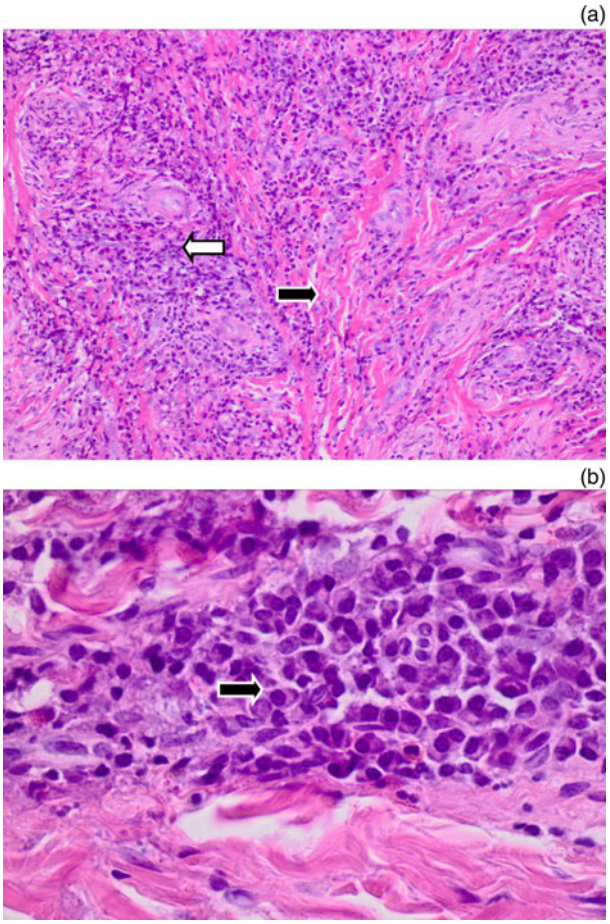


FIG. 2

(a) Low power photomicrograph demonstrating fibrosclerosis (black arrow) with mixed inflammatory cells (white arrow) (H&E; ×100), and (b) high power photomicrograph demonstrating inflammatory cells (black arrow indicates a typical plasma cell within a cluster of plasma cells) (H&E; ×400).

## Discussion

This report demonstrates a case of IgG4-related disease isolated solely to the nasal cavity. Immunoglobulin G4 is the least common of the four subclasses of IgG, typically representing 3–6 per cent of the entire IgG fraction.[4] It is thought to play a significant role in allergic reactions and parasitic infestations.[2] Immunoglobulin G4 related disease was first proposed as a new clinicopathological entity in 2001, following the identification of high serum IgG4 concentrations in patients with autoimmune pancreatitis.[1] This led to the identification of pancreatic and extrapancreatic fibro-inflammatory lesions rich in IgG4-bearing cells. This rare condition has since been characterised by extensive tissue infiltration of various organs by IgG4-positive plasma cells and T lymphocytes. The aetiology remains unknown.[2]

The main pathological findings in IgG4-related disease include a dense lymphoplasmacytic infiltrate, a storiform pattern of fibrosis and obliterative phlebitis.[2,3] Diagnosis relies on identification of these characteristic changes, along with high tissue IgG4 levels and/or an elevated IgG4 to total IgG ratio. Immunostaining for IgG4 is essential for diagnosis; however, the cut-off for the required number of IgG4 cells per high power field varies from 10 to 200, according to the site of the lesion and the degree of fibrosis.[3] The IgG4-positive to IgG-positive ratio is a more specific

https://doi.org/10.1017/S0022215114001911 Published online by Cambridge University Press

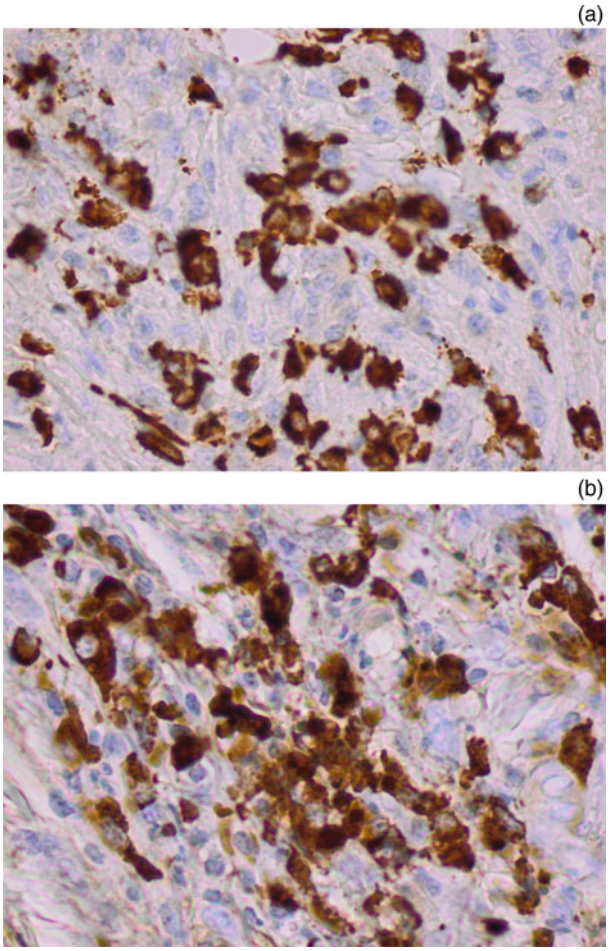


FIG. 3
Immunostaining of plasma cells for immunoglobulin G4 (IgG4) (a) was compared with immunostaining for total immunoglobulin G (IgG) (b); the ratio of IgG4-positive to IgG-positive cells was over 40 per cent. (×400)

measure, with a consensus figure of more than 40 per cent considered diagnostic.[3] However, a raised IgG4-positive to IgG-positive ratio alone, without the associated characteristic histological findings, is insufficient for diagnosis. Our case meets all the established criteria for diagnosis.

Whilst it has been noted that increased serum IgG4 may assist in identification of the disease, it is not essential for or specific to this condition, with up to 40 per cent of patients demonstrating normal serum IgG4 levels.[2,3,5] Serum IgG4 has been correlated with disease activity and the number of involved organs.[2] It is therefore unsurprising that our case, with disease isolated to the nasal cavity, did not demonstrate raised serum IgG4.

Immunoglobulin G4 related disease is most commonly found to affect the pancreas, gallbladder and bile duct. As regards the head and neck region, IgG4-related disease has been described in the submandibular gland (Kuttner's tumour), lacrimal and parotid glands (Mikulicz's disease), and pituitary gland (IgG4-related infundibulo-hypophysitis).[2] With regard to the sinonasal region, two recent papers have reported cases of IgG4-related rhinosinusitis.[5,6] To date, these cases of sinonasal involvement have been described in association with disease in other sites and all with raised serum IgG4 levels.[5,6] The predominant symptoms were those of chronic rhinosinusitis, including rhinorrhoea (70 per cent) and postnasal drip (80 per cent), with only 30 per cent complaining of nasal obstruction. To our knowledge, there have been no previous reports of IgG4-related disease isolated solely to the nasal cavity.

The natural history of the condition typically, but not exclusively, results in multiple sites of involvement over time.[2] The function of the involved tissues may be affected as a result of the inflammatory and infiltrative components of the condition. Immunoglobulin G4 related disease has been found to respond well to immunosuppressive medical management, namely steroid therapy.[1,2] Surgical intervention is thus largely limited to diagnostic evaluation via tissue biopsy.[1] Loss of function has been reported to have a component of reversibility with therapy; however, relapse is typical with steroid weaning or cessation.[2] Accordingly, long-term therapy with steroid-sparing anti-metabolites, such as methotrexate, is often required.

## Conclusion

To the best of our knowledge, this case represents the first report in the literature of IgG4-related disease isolated to the nasal cavity.

## Acknowledgements

The authors would like to thank Professor Nicholas Manolios, from the Department of Rheumatology, Westmead Hospital, for his assistance and continued care of this patient.

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Dr N Singh takes responsibility for the integrity of the content of the paper
Competing interests: None declared