

Immunoglobulin G4 sinusitis in association with aspirin-exacerbated respiratory disease

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ABSTRACT

Background: Immunoglobulin G4 (IgG4) related disease is a systemic inflammatory disease characterized by tumor-like tissue infiltration with IgG4 positive (IgG4+) plasma cells. Aspirin-exacerbated respiratory disease (AERD) is defined as asthma, chronic rhinosinusitis with nasal polyposis, and hypersensitivity to cyclooxygenase-1 inhibitors.

Objective: We described a case of a non-smoking 61-year-old male with prior NSAID sensitivity who presented with a 1-year history of left eye proptosis associated with chronic nasal symptoms, ultimately identified as concurrent AERD and IgG4 sinusitis.

Methods: The patient was evaluated in the clinic and diagnosed by using clinical, radiographic, and surgical biopsy findings.

Results: Although initial concern was greatest for malignancy, a biopsy specimen confirmed the presence of a dense lymphoplasmacytic infiltrate and storiform fibrosis, associated with increased IgG4+ plasma cells. Therefore, IgG4-related disease (RD) was identified in this patient with AERD.

Conclusion: Shared type II inflammation may be responsible for the coexistence of IgG4-RD and AERD as observed in our patient. Health care workers must be cognizant of the simultaneous presentation of both IgG4-RD and AERD.

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Immunoglobulin G4 (IgG4) related disease (RD) is an emerging systemic inflammatory disease. First identified in 2001 in the form of sclerosing pancreatitis, tissue infiltration with IgG4 positive (IgG4+) plasma cells has now been recognized in numerous organs.¹ Commonly affected are the salivary glands, bile ducts, liver, and pancreas.² More recently, IgG4-RD has been recognized in the sinuses, associated with a possible atopic phenotype.^{3–5} A definitive diagnosis may be made if characteristic clinical manifestations are present, in addition to an elevated IgG4 serum concentration and histopathology demonstrating lymphoplasmacytosis with fibrosis (often in a storiform pattern) as well as an infiltration of IgG4+ plasma cells.⁶

Aspirin-exacerbated respiratory disease (AERD) is defined as asthma, chronic rhinosinusitis with nasal polyposis, and hypersensitivity to cyclooxygenase 1 inhibitors. On histologic examination, AERD is characterized by significant upper and lower airway eosinophilic inflammation.⁷ Given the presence of significant eosinophilia and elevated interleukin (IL) 4 levels, a type II inflammatory mechanism has been suggested.^{7,8} We introduce, to our knowledge, the first reported case of IgG4 sinusitis in an individual with coexisting AERD.

CASE PRESENTATION

A non-smoking 61 year old male with history of AERD presented with left eye proptosis and epiphora, which worsened over 1 year. He stated that he did not have changes in visual acuity, diplopia, or facial numbness but reported chronic anosmia associated with bilateral nasal congestion (left greater than right) and discolored mucoid drainage of 8 years.

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The patient had sinonasal symptoms for >35 years. Allergy testing as a young adult revealed sensitivity to mold, dust mites, and ragweed. Over the course of his adulthood, he required a total of eight sinus surgeries, the first occurred in the 1980s when he was diagnosed with nasal polyps. He demonstrated an allergy to aspirin ~25 years age when he developed chest tightness and dyspnea with exposure. He similarly demonstrated nonsteroidal anti-inflammatory drug (NSAID) sensitivity with dyspnea after ingestion of ibuprofen. His history was significant for chest tightness with wheezing two to three times a year, when he would be treated with inhaled steroids. Spirometry in the office demonstrated mild airway obstruction. One of our limitations is that the patient did not have a formal aspirin challenge, however, his history was convincing for AERD given prior symptoms with NSAIDs.

Left eye proptosis and infraorbital edema was appreciated on examination. Initial endoscopy demonstrated bilateral nasal polyps, with extensive involvement of the ethmoid roof and frontal recess, as well as significant mucoid drainage and mucosal edema. A CT scan (Fig. 1) of the paranasal sinuses identified widespread mucosal thickening that involved all the sinuses, evidence of osteitis, and soft-tissue densities that represented polyps. In addition, the CT scan demonstrated asymmetric enlargement of the left orbit extraocular muscles as well as asymmetric bony expansion of the pterygopalatine fossa, sphenopalatine foramen, and retroantral fat. Erosion along the anterior margin of the pterygoid process of the left sphenoid bone was also noted, with possible involvement of the left infraorbital nerve. Magnetic resonance imaging (MRI) confirmed evidence of myositis of the left extraocular rectus muscles and identified enhancing soft tissue infiltrating the pterygopalatine fossa, inferior orbital fissure, infraorbital canal, and foramen rotundum.

Endoscopic sinus surgery was performed with bilateral medial maxillectomies, in combination with an endoscopic modified Lothrop procedure. A biopsy specimen of the left pterygopalatine mass demonstrated sinonasal mucosa with dense lymphoplasmacytic infiltrate, increased IgG4+ plasma cells (>80% per hpf, with an IgG4:IgG ratio of >40%), and associated focally increased fibrosis (Fig. 2, Fig. 3). Similar histopathology findings were also observed of sinonasal tissue obtained from the right sinuses as well as in the inferior turbinate. Laboratory findings included a mild leukocytosis (14.1 K/UL), with 4% eosinophils, as well as an elevated sedimentation rate of 47 mm/hr. The IgG level was 1180 mg/dL (reference range, 700–1600 mg/dL). The IgG1, IgG2, and IgG3 subclasses were all within normal limits; however, the IgG4



Figure 1. Computed tomography (CT) without contrast of the sinuses. CT sinuses demonstrate left-sided proptosis, with enlargement of the left medial rectus, inferior rectus, and lateral rectus muscles; pansinusitis is observed, with bilateral opacification of the frontoethmoidal sinuses.

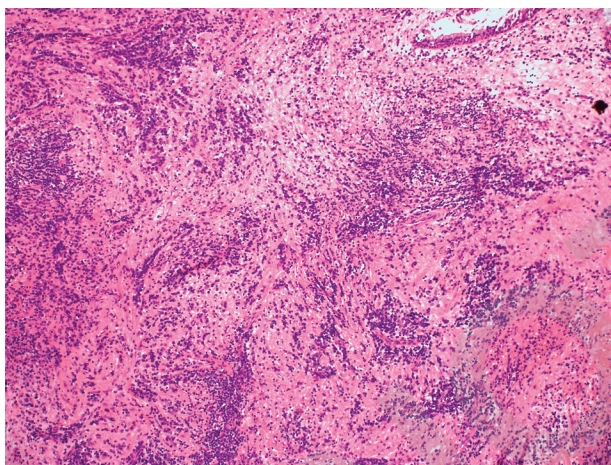


Figure 2. Left sinus. Left sinus contents after endoscopic sinus surgery demonstrate sinonasal mucosa with dense lymphoplasmacytic infiltrate with focally increased storiform fibrosis (H&E stain, 100× magnification).

subclass was elevated to 256 mg/dL (reference range, 4–86 mg/dL). The IgA level was elevated to 471 mg/dL (reference range, 70–400 mg/dL); the IgE level was within normal limits, at 25.5 mg/dL (reference value, <114 mg/dL). The patient was continued on prednisone. He had no ocular or sinus symptoms after surgical intervention.

DISCUSSION

We describe a case of IgG4-RD of the sinuses in the setting of concurrent AERD. IgG4-RD has previously been identified in the sinuses as sclerosing disease, associated with bone destruction as well as nasal septal injury; however, to the best of our knowledge, there have been no previous reports of an association with AERD.^{2–4}

Our patient presented with proptosis, erosion of the anterior pterygoid process, and pansinusitis secondary to a large mass. Concern was initially greatest for lymphoma; however, the results of the flow cytometry were negative. On further review of his history with the presumed presence of AERD, as well as the characteristically elevated IgG4:IgG ratio and lymphoplasmacytic infiltrate with storiform fibrosis, the diagnosis of IgG4-RD was made.⁹ He was started on prednisone 20 mg daily, without disease recurrence.

Until recently, guidelines and supporting data for the medical management of IgG4-RD had been limited. Published in 2015, the

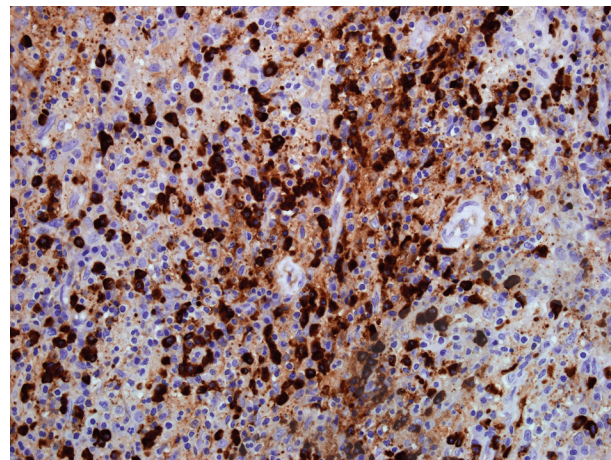


Figure 3. Sinus biopsy specimen. Immunoglobulin G4 (IgG4) immunohistochemical stains demonstrate an increased prevalence of IgG4 positive (IgG4+) plasma cells, representing >80 per hpf and >40% of the IgG positive (IgG+) plasma cells, in association with fibrosis 400× magnification.

International Consensus Statement,¹⁰ created by numerous subspecialists from >18 nations, now provides initial recommendations. Before the initiation of treatment, diagnostic tissue confirmation by biopsy should be obtained to exclude malignancy and other processes that may mimic IgG4-RD.¹⁰ The mainstay of treatment involves the use of systemic glucocorticoids; significant improvement with administration of steroids is characteristic of the disease. For those who develop flares with glucocorticoid tapers but are unable to continue therapy due to the long-term steroid adverse effects, steroid-sparing agents such as azathioprine, mycophenolate, and rituximab are available.⁶ Rituximab, an anti-CD20 monoclonal antibody, depletes plasma cells and can decrease IgG4 levels without impairing the levels of other immunoglobulins.^{6,11} Maintenance therapy with either low-dose glucocorticoids or a steroid-sparing agent is recommended after successful induction therapy. For those patients who relapse when treatment is discontinued after successful induction therapy, re-treatment with glucocorticoids is indicated. Some cases may require a steroid-sparing agent at this time.¹⁰

Although the precise mechanism of IgG4-RD is still being elucidated and IgG4-RD is a systemic disease that affects multiple organs, there is evidence that both IgG4-RD and AERD share some similar features. Type II eosinophilic inflammation is characteristic of AERD, often with systemic or local IgE production. In addition, elevated serum IgG4 levels are not specific (or pathognomonic) for IgG4-RD, but rather the entire series of clinical criteria including clinical symptoms, biopsy confirmation with lymphoplasmacytic infiltration and fibrosis, and an elevated serum IgG4 level should be observed for diagnosis of IgG4-RD. Of note, an elevated IgG4 level may be found in other inflammatory diseases including eosinophilic granulomatosis with polyangiitis, therefore it is important to review both laboratory and clinical findings.¹² Shared type II inflammation may be responsible for the coexistence of IgG4-RD and AERD, as observed in our patient.

CONCLUSION

We report a case of IgG4-RD that occurred concurrently with AERD. Although thought to be rare, IgG4-RD is increasingly being recognized as affecting many organ systems. Health care workers who treat patients with AERD should be aware that IgG4-RD and AERD can occur together in the sinonasal cavity. Early recognition

and treatment of IgG4-RD is important to prevent the potentially destructive process that is typical of IgG4-RD.

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REFERENCES

1. Hamano H, Kawa S, Horiuchi A, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med* 344:732–738, 2001.
2. Ishida M, Hotta M, Kushima R, et al. Multiple IgG4-related sclerosing lesions in the maxillary sinus, parotid gland and nasal septum. *Pathol Int* 59:670–675, 2009.
3. Pace C, and Ward S. A rare case of IgG4-related sclerosing disease of the maxillary sinus associated with bone destruction. *J Oral Maxillofac Surg* 68:2591–2593, 2010.
4. Ikeda R, Awataguchi T, Shoji F, and Oshima T. A case of paranasal sinus lesions in IgG4-related sclerosing disease. *Otolaryngol Head Neck Surg* 142:458–459, 2010.
5. Inoue A, Wada K, Matsuura K, et al. IgG4-related disease in the sinonasal cavity accompanied by intranasal structure loss. *Auris Nasus Larynx* 43:100–104, 2016.
6. Ghably JG, Borthwick T, O’Neil TJ, et al. IgG4-related disease: A primer on diagnosis and management. *Ann Allergy Asthma Immunol* 114:447–454, 2015.
7. Laidlaw TM, and Boyce JA. Pathogenesis of aspirin-exacerbated respiratory disease and reactions. *Immunol Allergy Clin North Am* 33:195–210, 2013.
8. Narayanankutty A, Resendiz-Hernandez JM, Falfan-Valencia R, and Teran LM. Biochemical pathogenesis of aspirin exacerbated respiratory disease (AERD). *Clin Biochem* 46:566–578, 2013.
9. Deshpande V, Zen, Y, Chan J, et al. Consensus statement on the pathology of IgG4-related disease. *Mod Pathol* 25(9):1181–1192, 2012.
10. Khosroshahi A, Wallace Z, Crowe J, et al. International consensus guidance statement on the management and treatment of IgG4-related disease. *Arthritis and Rheumatology* 67(1):1688–1699, 2015.
11. Carruthers M, Topazian M, Khosroshahi A, et al. Rituximab for IgG4-related disease: a prospective open-label trial. *Ann Rheum Dis* 74:1171–1177, 2015.
12. Giofreddi A, Maritati F, Oliva E, et al. Eosinophilic granulomatosis with polyangiitis: an overview. *Frontiers in Immunology* 5:549, 2014. □

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