

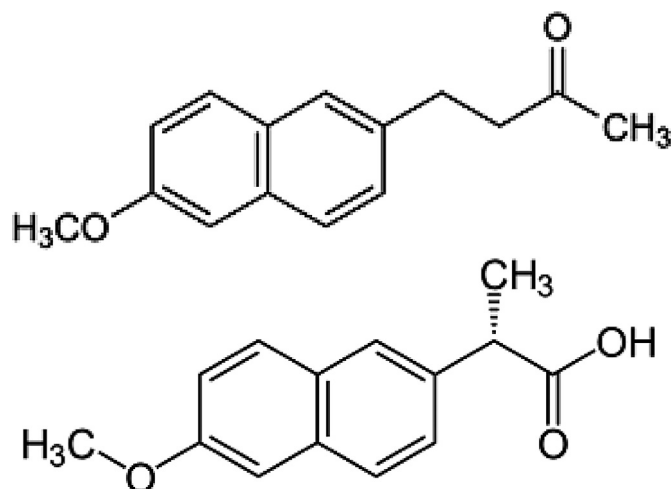


Figure 1. Top: Nabumetone: 4-(6-methoxy-2-naphthyl)-2-butanone. Bottom: Naproxen: (+)-(S)-2-(6-methoxynaphthalen-2-yl) propanoic acid.

Patient 1 presented angioedema of the lips 60 minutes after the last intake, although it resolved with intramuscular methylprednisolone (80 mg). Patients 2 and 3 tolerated naproxen.

The anti-inflammatory drug nabumetone is a preferential COX-2 inhibitor whose efficacy is similar to that of other NSAIDs. In addition, it has few gastrointestinal side effects.⁴ The drug is well tolerated, and only a few cases of systemic hypersensitivity reaction have been recorded.^{5–8}

Aspirin tolerance in the 3 patients suggests that COX-1 inhibition does not play any pathogenic role, as it could have a role in others.⁹ The reason 2 patients tolerated naproxen and 1 did not remains unclear. Therefore, a mechanism underlying the reactions has yet to be established. Nevertheless, various hypotheses have been put forward.

Gonzalo-Garijo et al⁶ reported a severe immediate reaction to nabumetone and an immunologic phenomenon type immunoglobulin E suspected. Symptoms developed rapidly after re-exposure, and no immunoglobulin E-related or other immune mechanism could be established. The 2 patients reported here tolerated other structurally different NSAIDs (indomethacin, diclofenac, piroxicam, and metamizole/ibuprofen) but were not challenged with naproxen and nabumetone because of the severity of the reactions.

Pérez-Calderón et al¹⁰ reported a nonimmediate hypersensitivity reaction: a fixed drug eruption caused by nabumetone in a patient with previous fixed drug eruption to naproxen. The authors believed that the reaction was a consequence of the similarity between the chemical structure of naproxen and that of the active metabolite of nabumetone.

We present 1 case of cross-reactive urticaria/angioedema between nabumetone and naproxen and 2 cases without cross-reactions. The mechanism of cross-reactivity escapes us, but our

primary hypothesis is that this is not cross-reactivity in the usual sense of the word. Our data indicate the reaction in these patients is not attributable to COX-1 inhibition but suggest a potential drug-specific reaction. Perhaps there are unique epitopes distinct from naproxen accounting for tolerance to naproxen in 2 of 3 cases. This cannot be a COX-1 cross-reaction because of the negative OCT to aspirin in all 3 patients and to naproxen in the other 2 patients. Further multicenter studies with large series of patients are needed to confirm diagnosis and management.

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Patricia Rojas Perez-Ezquerro, MD
Leticia Sanchez-Morillas, MD
Jose Julio Laguna Martinez, MD
Rosario Gonzalez Mendiola, MD
Carmen Gomez-Traseira, MD
Irene Carrasco Garcia, BSc
Mariana Herranz Mañas, BSc
Almudena Rubio Matos, BSc
Hospital Central de la Cruz Roja
Allergy Department
Madrid, Spain
patricia.rojas@salud.madrid.org

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Immunoglobulin G4-related disease presenting as an ethmoid and maxillary mass

Immunoglobulin (Ig) G4-related disease (IgG4-RD) is a fibroinflammatory condition characterized by tumefactive lesions and a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells. IgG4-RD typically presents as autoimmune pancreatitis,

sialadenitis, or orbital disease (typically affecting the lacrimal gland). However, the condition has been described in nearly every organ.^{1,2}

In 1999, a 50-year-old man developed a spontaneous cerebrospinal fluid leak in the area of his left ethmoid sinus. Ethmoid sinusitis was detected radiologically, but repair of the dura via craniotomy was performed without an ethmoid sinus biopsy at that time. Thirteen

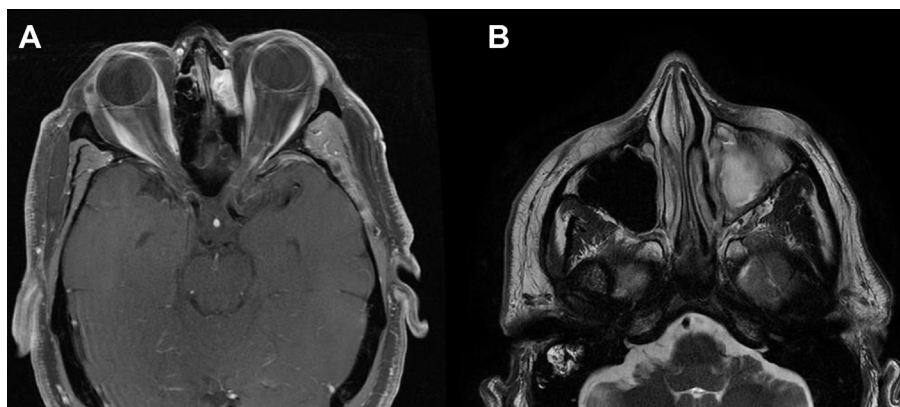


Figure 1. Magnetic resonance image before surgical procedure showing contrast enhancement in the left ethmoid (A) and maxillary sinuses (B).

years later, in 2012, the patient—now 63—presented with a 12-month history of sinus obstruction and recurrent sinus infections. His symptoms worsened despite nasal and systemic glucocorticoids and antibiotics. Computed tomography (CT) showed near complete opacification of all left sinuses. Magnetic resonance imaging demonstrated a contrast-enhancing mass, suspicious for malignancy (Fig 1).

The patient underwent endoscopic sinus surgery. Severe inflammatory changes were found in the mucosa of the left ethmoid sinus, with no obvious mass present. Generalized inflammatory changes were found in the mucosa of the left maxillary and frontal sinuses. Multiple frozen sections were consistent with chronic and acute inflammation. Closer pathologic evaluation on permanent sections showed an intense lymphoplasmacytic infiltrate with focal areas of fibrosis in a storiform pattern. Essentially all of the plasma cells within the lesion stained positively for IgG4. Kappa and lambda *in situ* hybridization showed mixed but predominantly kappa-positive plasma cells, with a 4:1 kappa to lambda ratio. IgG4-RD involving the ethmoid and maxillary sinuses was diagnosed. Despite the intense IgG4-positive plasma cell infiltrate within the affected sinuses, the serum IgG subclasses including IgG4 were normal (88 mg/dL; normal, <121 mg/dL). The serum levels of total IgG, IgM, IgA, and IgE were also within normal limits.

Immunoglobulin G4 is the least abundant IgG subclass and accounts for less than 5% of the total IgG in healthy individuals. Because of negligible binding of IgG4 to both C1q and Fcγ receptors, IgG4 is considered an ineffective activator of the classical complement pathway.³ Instability of the disulfide bonds between the heavy chains of the IgG4 molecule permits “Fab arm exchange,” a process whereby the heavy chains dissociate from each other, splitting the immunoglobulin molecule in half.⁴ This dissociation—unique among all IgG subclasses—is followed by the random recombination of half-molecules. Immunoglobulin G4 molecules re-formed in this manner possess 2 distinct Fab fragments, rendering them “asymmetric” or bispecific. This property interferes with the cross-linking of antigen and leads to the molecule’s weak binding properties.

Despite their allegedly weak antigen-binding capabilities, IgG4 autoantibodies are central to the pathogenesis of certain immune-mediated disorders. Examples include pemphigus vulgaris, an autoimmune blistering disease mediated by IgG4 autoantibodies against desmoglein; and idiopathic membranous glomerulonephritis, which is associated with an IgG4 autoantibody directed against the PLA-2 receptor. However, no definitive role for an antigen-specific autoantibody has been identified in IgG4-RD, and the contribution (if any) of autoantibodies to disease pathogenesis in this entity remain unclear.

Immunoglobulin G4-RD usually presents in middle-aged to elderly men.¹ An international, multidisciplinary symposium

recommended that the pathologic diagnosis of IgG4-RD be based primarily on histopathologic features of the tissue supplemented by immunostaining data (ie, the number of IgG4+ plasma cells/high-power field or the IgG4: total IgG ratio within tissue), rather than on the immunostaining characteristics alone.⁵ The 3 hallmark histopathologic features are a dense lymphoplasmacytic infiltrate, storiform fibrosis (characterized by a whorled appearance), and obliterative phlebitis.⁵ Phlebitis without obliteration of the lumen, mild to moderate eosinophilic infiltrates, germinal centers, lymphoid follicles, and obliterative arteritis (particularly in the lung) are also associated with IgG4-RD. The diagnosis generally requires 2 of the 3 hallmark histopathologic features supplemented by the minor features and immunostaining studies that demonstrate a high percentage of IgG4-positive plasma cells within the lesion. Thus, IgG4-RD is a multi-organ disease linked by distinctive histopathologic features that transcend patterns of organ involvement. The disease is similar to sarcoidosis in this regard.

The inflammatory infiltrate comprises both T and B lymphocytes, with T cells forming the largest cellular component. A diffuse plasma-cell infiltrate including more than 30 IgG4-positive cells per high-power field and an IgG4:total IgG ratio greater than 0.50 provides compelling evidence of IgG4-RD in most tissues. Many patients with IgG4-RD have elevations in their serum concentrations of IgG4, but the ranges vary widely. Approximately 30% have normal serum IgG4 concentrations.⁷

A modified Th2 response has been reported in this condition, but confirmation by more detailed studies is required.⁶ Immunoglobulin E and IgG4 synthesis are both driven by Th2 cytokines such as interleukin-4 and interleukin-13.¹⁰ Th2 cytokines are markedly elevated in IgG4-RD of the pancreas,¹¹ and IgG4-RD of the lacrimal glands.¹² These same studies also found an increase in regulatory cytokines transforming growth factor beta and interleukin-10 and CD4+CD25+FoxP3+ Tregulatory cells. It is not currently clear whether the Treg profile is part of the underlying pathologic condition, or whether it is secondarily induced in an attempt to inhibit the Th2-dominant response.

Many IgG4-RD patients have allergic features such as atopy, eczema, asthma, and a peripheral eosinophilia that is usually modest but sometimes exceeds 20%. In a series of 45 patients with type 1 (IgG4-related) autoimmune pancreatitis, 20 patients (44%) had a history of allergic rhinitis, atopic dermatitis, or asthma.⁸ Another review demonstrated that 10 of 23 patients (43%) had nasal symptoms such as obstruction and crusting.⁹ Immunoglobulin G4-RD involving the paranasal passages has been reported in the maxillary sinus,^{13,14} sphenoid sinus,¹³ and nasal septum.¹³ Bone destruction occurs in a minority of cases.¹⁴ Many patients undergo surgical resection before the diagnosis is made. First-line treatment

options are glucocorticoids, which appear to be effective at least initially in most cases, but disease recurrences over time are the rule. Few data exist concerning the efficacy of classic glucocorticoid-sparing agents such as azathioprine, mycophenolate mofetil, and methotrexate. B cell depletion with rituximab, a monoclonal antibody directed against CD20, appears to be effective in many patients. This approach may achieve its effects in part at least by preventing the repletion of short-lived plasma cells that generate IgG4 in this disease.¹⁵ Rituximab has been reported to provide clinical improvement in IgG4-RD of the paranasal sinuses.¹⁶ After a short, ineffective, and poorly tolerated course of glucocorticoids, our patient was enrolled in a clinical trial and treated with 2 doses of rituximab (1 g intravenously each dose, administered 2 weeks apart). He tolerated this treatment well and is symptom-free 8 months after treatment. A magnetic resonance scan 6 months after rituximab treatment demonstrated radiologic improvement in his maxillary sinus lesion.

Edward K. Hu, MD*
Christopher Parrish, MD*
Bozena Wrobel, MD*

Vikram Deshpande, MD†

John H. Stone, MD, MPH†

*University of Southern California
Los Angeles, California

†Massachusetts General Hospital
Boston, Massachusetts
edwardkh@usc.edu

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Multifunctional acrylates as possible sensitizers in electrocardiogram electrode allergy

A 64-year-old woman developed circular erythematous eczematous lesions at the sites where electrocardiogram (ECG) electrodes had been applied for several hours during shoulder surgery. Lesions lasted 7 days despite treatment with topical corticosteroids.

A patch test, with reading on day 2 (48 hours) and on day 4 (96 hours), was performed on the patient, with ECG electrodes used in the operation rooms at our hospital (Ambu White Sensor WS-00-S/00, Ambu Blue Sensor SP-00-S/50, Ambu White Sensor CFM-00-S/50 [all from Ambu, Ballerup, Denmark], and Unilect 0315M [Biotab, Madrid, Spain]) as they are, their individual parts and TrueTest 29 panel (Mekos Laboratories, Hillerød, Denmark). Results are shown in Table 1. The strongest reaction was obtained with Ambu White Sensor WS-00-S/00, particularly against its gel part, and so we looked into its composition compared with the Ambu Blue Sensor SP-00-S/50, which gave a weaker reaction. Both electrodes contained acrylates in the adhesive part, but only the first one contained acrylates in the gel part. Acrylates were also present in the adhesive part of Ambu White Sensor CFM-00-S/50-4; however, no positive result was found. No acrylates were described in the composition of the last electrode. All these data about composition of the electrodes were obtained from the manufacturers. No methylchloroisothiazolinone (kathon) was present in the electrodes. Patch tests were also performed with a battery of acrylates available at our allergy department and other allergens listed on Table 1, including monoacrylates (methyl methacrylate, MMA, 2%), and multifunctional acrylates (triethylen glycol dimethacrylate,

Table 1

Results for ECG electrodes and other allergens tested

Component	D2	D4
Ambu White Sensor WS-00-S/00	++	+++
Electrode WS-00-S/00—Adhesive part	+	+
Electrode WS-00-S/00—Gel part	++	+++
Electrode WS-00-S/00—Metal part	—	—
Ambu Blue Sensor SP-00-S/50	—	+
Electrode SP-00-S/50—Adhesive part	—	+
Electrode SP-00-S/50—Gel part	—	—
Electrode SP-00-S/50—Metal part	—	—
Unilect 0315M Biotab	—	—
Ambu White Sensor CFM-00-S/50	—	—
Electrode CFM-00-S/50—Adhesive part	—	—
Electrode CFM-00-S/50—Gel part	—	—
Methyl methacrylate 2% pet.	—	+
Triethylene glycol dimethacrylate 2% pet.	+	+++
Ethylene glycol dimethacrylate 2% pet.	+	+++
Colophony 20% pet.	—	—
Propylene glycol 4% aq.	—	—
Polyethylene glycol 4% pet.	—	—
Standard TRUE-test panel	—	++ Kathon

TREGDMA 2% and ethylene glycol dimethacrylate, EGDMA 2%), propylene glycol 4%, polyethylene glycol 4%, and Colophony 20% (Laboratory Bial, Aristegui, Spain), showing stronger reactions with multifunctional acrylates.

Several allergens, including acrylates, have been linked to electrode allergy.^{1–4} The intensity of the sensitization decreases