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CASE REPORT

Nasal eosinophilic angiocentric fibrosis with IgG4-positive plasma cell infiltration

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Abstract

Introduction: Eosinophilic angiocentric fibrosis (EAF) is a rare lesion that predominantly affects the upper respiratory tract. Its etiology is unknown and it has been recently associated with the IgG4-related disease (IgG4-RD) spectrum. To the author's knowledge, this is the sixth case report of the relationship between EAF and IgG4-RD. *Case Report:* We report the case of a 37-year-old woman with nasal deformity and facial pain. The lesion was surgically excised. Histological examination revealed features of EAF with an IgG4/IgG plasma cell ratio >73% and 31 IgG4 stained cells per high power field. No clinical or radiological recurrence was detected during follow-up. Serum IgG4 quantification one year after surgery was within normal limits. *Discussion:* The relationship between both entities may have therapeutic impact because IgG4-RD of the head and neck has a high remission rate with corticosteroids and immunosuppressive therapy. Additional reports of this infrequent disease are necessary to elucidate appropriate treatment and prognosis.

Keywords: eosinophilic angiocentric fibrosis, IgG4-related disease, IgG4 immunoglobulin, nasal mass, rheumatic disease

CASE REPORT

A 37-year-old woman was referred to the otorhinolaryngology department because of a nasal deformity and facial pain. The patient had a 5-year history of chronic sinusitis and allergic rhinitis previously treated with immunotherapy with partial improvement and allergy to diclofenac. Twenty years ago, she had had a septoplasty with subsequent intermittent bleeding for 6 months. Her father had been diagnosed with an angioblastoma 4 years earlier.

She denied alcohol, tobacco, prescription medication or illegal drug use. The patient noticed a depression in the nasal region with widening of the nasal pyramid, bilateral nasal obstruction and facial pain one year before evaluation. The symptoms worsened during the following year. On examination, the patient had a depression of the cartilaginous nasal dorsum, absence of the distal nasal septum and nasal septum thickening particularly in the osteochondral junction, with widening of the nasal pyramid.

A CBC and chemical profile were within normal limits. Serological assays for autoimmune diseases were negative. A non-contrast-enhanced helical computed tomography (CT) of the nose and sinuses revealed bilateral nasal valve compromise, septum deviation to the right of the cartilaginous portion and deviation to the left of the bone portion, irregular thickening of the mucosa of the nasal septum and turbinates. Paranasal sinuses showed opacity due to increased mucosa volume and signs of polypoid degeneration. On MRI, a well-defined

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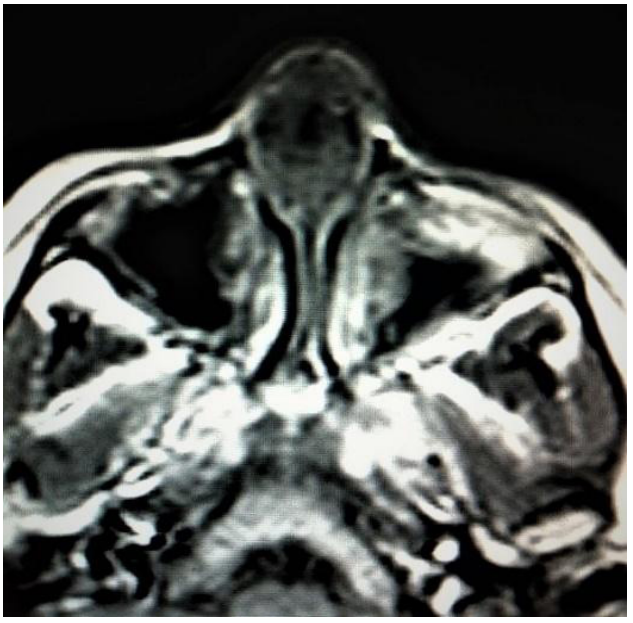

FIG. 1: Computerized tomography of the patient that highlights a central mass on the nasal region (white arrow), as well as, a deviation of the nasal septum away from the neoplasia, and irregular thickening of the mucosa of both paranasal sinuses and turbinates.

round mass 1.6 x 2.2 x 1.6 cm was identified on the septal nasal cartilage (Fig. 1). Surgical excision of the lesion was performed. An external approach exposed the external nasal valve complex, columella and nasal dorsum. A large mass-like thickening that involved the septum cartilage, lateral superior cartilage and the septal mucosa bilaterally and obstructed both sides of the dorsal septum region was noted. The mass was excised with scalpel and scissors. The intraoperative biopsy reported inflammatory tissue with abundant eosinophils. Plaster cast and intranasal splints were placed.

Histological examination of the resected tissue fragments revealed characteristic features of the fibrotic stage of eosinophilic angiocentric fibrosis (EAF) including the presence of small vessels in the center of concentric collagenous fibrosis (Figure 2). Collagen distribution exhibited an onion skin appearance with an inflammatory infiltrate with lymphocytes, plasma cells, and eosinophils. Masson's trichrome special stain highlighted the fibrosis. Additionally, some fragments showed granulation tissue with mixed inflammatory cell infiltrate dominated by plasma cells.

Immunohistochemical staining was performed with CD31 (Leica Biosystems Inc., Buffalo Grove, IL; dilution 1:50) and CD34 (Leica Biosystems Inc; dilution 1:100) to highlight the small vessels. Positive endothelial cells were detected within the sclerotic nodule. (Fig. 2) Perivascular, mixed T-cell and B-cell lymphocytic population was demonstrated with immunohistochemical stains CD3 (Dako North America, Inc. Carpinteria, CA; dilution 1:50) and CD20 (Dako North America, Inc.; dilution 1:100), respectively. Immunohistochemical IgG4 (Invitrogen, Carlsbad, CA, 1:100) and IgG (Dako North America, Inc.; dilution 1: 100) stains were performed highlighting the presence IgG4 and IgG plasma cells in the tumor (Fig. 3). The IgG4/IgG plasma cell ratio was > 73% and 31 IgG4 stained cells were found in a high-power field. The final diagnosis was eosinophilic angiocentric fibrosis with positive IgG4 stain (Figure 2). After surgery, immunoglobulin quantification by nephelometry revealed IgG of 1170 mg/dL (normal range 650-1600), IgA 200 mg/dL (normal range 40-350), and IgM 179 mg/dL (normal range: 50-300). IgE by chemiluminescence was 81.2IU/ml (normal range: 1.5-379). Six months after surgery, IgG4 was determined by nephelometry with a result of 53 mg/dL (normal range: 1-291). Control CT 1 and 6 months after surgery showed no sign of recurrence.

DISCUSSION

EAF is a rare benign lesion that predominantly affects the upper respiratory tract, specially

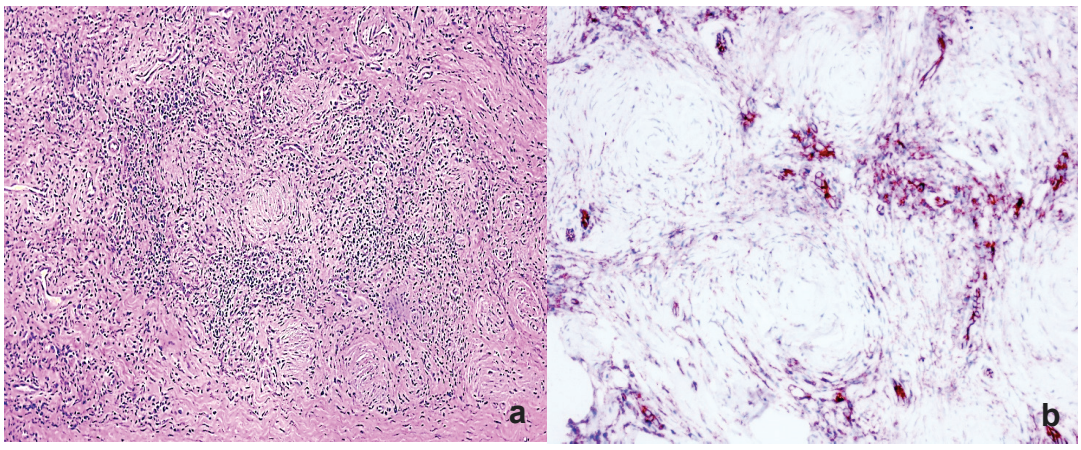

FIG. 2: (a) (H&E x 100) Lesion of eosinophilic angiocentric fibrosis: perivascular fibrosis with obliteration of vessel lumens. Note the amount of fibrosis that resembles whorls. (b) (x200) Immunohistochemistry stain with CD 34, highlighting the endothelial cells with color brown in the center of the fibrosis.

the nasal septum and paranasal sinuses.[1] Infrequently, it affects other areas including the orbit, larynx, and lung.[1] The first description was made by Holmes and Panje in 1983 coining the term intranasal granuloma faciale.[2] In 1985, Roberts and McCann renamed the entity as EAF owing to its histopathological characteristics.[3] A 2014 systematic review identified 34 articles and reported a total of 52 EAF cases.[1] Since then, two articles reporting six patients have been published.[4,5]

The age of presentation of sinonasal EAF is variable with a mean of 47 years (range 16 to 81) and no gender predilection.[1] The clinical picture

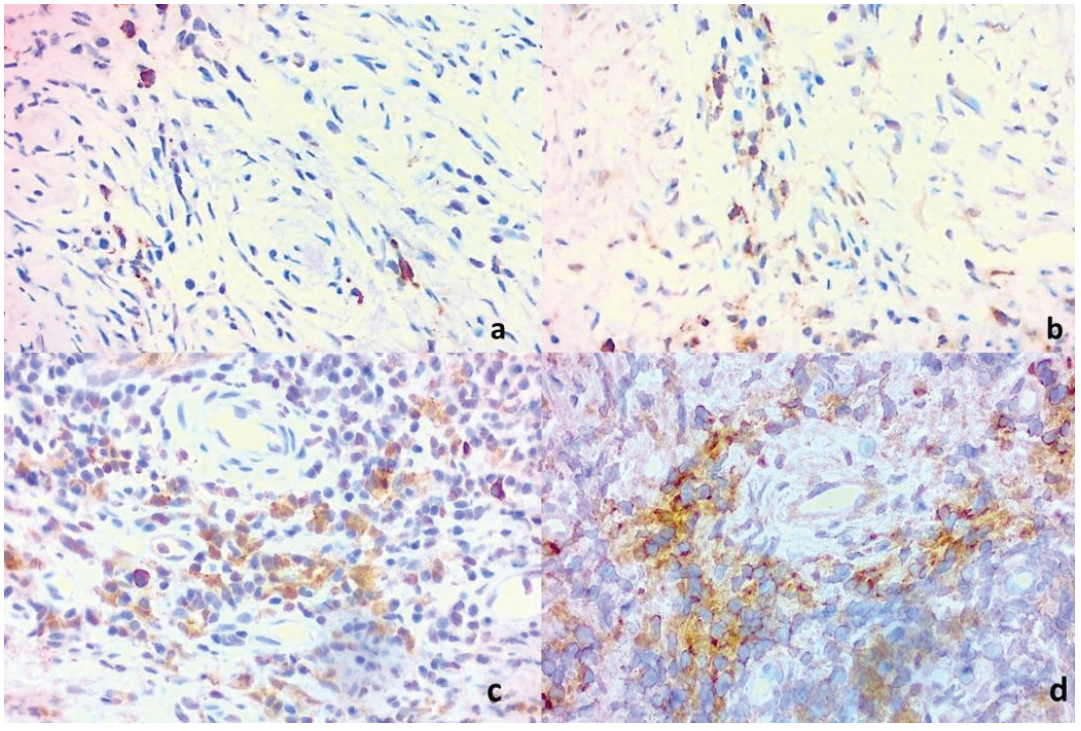

FIG. 3: (a) Immunohistochemistry stain for CD 3 (x200), where a few T cells can be identified within the fibrotic tissue. (b) CD 20 stain (x200), highlighting the B cells around the nasal neoplasm, within the angiocentric fibrosis. (c) IgG immunohistochemistry stain (x200), demonstrating the plasmacytic inflammatory cells around the vessels. d) IgG4 immunohistochemistry stain indicating the nature of the cells responsible for the inflammatory response.

is unspecific and include nasal obstruction, nasal swelling/deformity as well as epistaxis, nasal mass, epiphora, and facial/nasal pain.[1] Diagnosis is usually delayed several years due to its vague presentation and the rarity of the disease. The differential diagnosis of EAF includes neoplasias and non-infectious granulomatous diseases such as granulomatosis with polyangiitis (Wegener granulomatosis), eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome or allergic granulomatosis) and sarcoidosis.[4,5] A multidisciplinary evaluation is necessary to ensure a prompt diagnosis, adequate treatment, and best outcome.

The definitive diagnosis of EAF requires histopathological analysis[5]. The pathognomonic characteristics are a perivascular inflammatory infiltrate composed predominantly by eosinophils and fibrosis surrounding small blood vessels with an "onion skin" appearance.[6] EAF has been described as having two stages which often coexist in the same specimen. First, an early inflammatory polyclonal lesion is present which later progresses to dense fibrosis with an "onion skin" pattern.[6] The etiology of EAF is a matter of debate. Several factors have been associated, including granuloma faciale, previous surgery or trauma, allergy/atopy, and recently IgG4-related disease (IgG4-RD).[1,7] The patient in this report had previous surgery, nasal trauma, allergy/atopy, positive IgG4 staining, and a high IgG4/IgG ratio.

Granuloma faciale (GF) is a rare dermatologic entity that presents as single or multiple reddish to brownish plaques.[8] GF has been proposed to be the skin equivalent of EAF[8]. Furthermore, its histological appearance is similar to that of EAF.[8] Concurrent GF and EAF have been reported in 12 cases.[1,9] Just as in EAF, GF has been proposed as part of the IgG4-RD spectrum.[7,10] In a report of 31 GF cases, six fulfilled immunohistochemical criteria for IgG4-RD supporting the claim that it is a localized manifestation of IgG4-RD.[10]

Deshpande *et al*. reported for the first time the EAF relationship and IgG4-RD.[7] His series of 5 cases showed alterations in 4 with a number of IgG4-positive plasma cells with a range of 43-118 per high -power fields and a tissue IgG4/IgG ratio from 0.68 to 0.97. IgG4 in serum was quantified in one case with a result of more than 10 times the normal value. Two other reports have found similar histological characteristics although the IgG4 in serum was normal in both cases.[11,12]

Approximately 30% of patients with IgG4-RD have normal serum levels despite characteristic histological and immunohistological findings.[13] Our report fulfils the 2011 Comprehensive Diagnostic Criteria for IgG4-RD as probable IgG4-RD with positive clinical and histological criteria but negative serum concentration.[14] IgG4-RD of the head and neck treatment has been proven effective with medical treatment alone. Remission has been reported as high as 90% with corticosteroids and immunosuppressive therapy.[15] Corticosteroid therapy alone has been proven effective in 67% of cases.[15] Few reported EAF cases have utilised medical therapy alone and total resection is apparently the most effective approach.[1]

To our knowledge, this is the sixth case report of the relationship between EAF and the IgG4-RD spectrum. The relationship between both entities may have a therapeutic impact because IgG4-RD has a high remission rate with medical treatment alone. Additional reports of this infrequent disease are necessary to elucidate appropriate treatment strategies with or without surgery and long-term prognosis.

Disclosures:
Barbara, Saenz-Ibarra: none
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