

Eosinophilic Angiocentric Fibrosis Is a Form of IgG4-related Systemic Disease

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Background: Eosinophilic angiocentric fibrosis (EAF) is an uncommon tumefactive lesion of the orbit and upper respiratory tract of unknown etiology. The condition is characterized histologically by concentric layers of fibrosis around small-caliber arteries and a mixed inflammatory infiltrate dominated by eosinophils. After the serendipitous observation of an elevated serum concentration of IgG4 in 1 patient with EAF, we investigated the hypothesis that EAF is an IgG4-related systemic disease.

Methods: We retrospectively identified 5 EAF cases from our files. Demographic, clinical, and serological data were reviewed, and the histologic features and tissue IgG4 staining patterns were examined on biopsies from each case.

Results: Patients (2 male, 3 female) ranged in age from 31 to 82 years (mean, 56 y). The extent of disease varied from isolated involvement of the nasal cavity or the lacrimal gland to multicentric disease affecting the sinuses, nasal tract, and lower respiratory tract. The duration of symptoms ranged from 6 months to >20 years. The demographic features of the patients and disease extent were consistent with previously published reports of EAF, except for involvement of the lower respiratory tract in 1 case. Four of the 5 cases showed concentric perivascular fibrosis surrounding small-caliber vascular channels, embedded in an inflammatory infiltrate composed of lymphocytes, plasma cells, and eosinophils. One lacrimal gland biopsy showed a periductal inflammatory infiltrate, and 2 cases showed a storiform pattern of fibrosis. The index case had a serum IgG4 concentration of 1490 mg/dL (normal, 8 to 140 mg/dL). IgG4-positive plasma cells were identified in biopsies from 4 of the 5 cases. The numbers of IgG4-positive plasma cells ranged from 43 to 118 per high-power field, and the IgG4:IgG ratios ranged from 0.68 to 0.97. Neither IgG4-bearing nor IgG-bearing plasma cells were identified in 1 patient, whose longstanding disease was characterized principally by concentric perivascular fibrosis.

Conclusion: Our data suggest that EAF is part of the spectrum of IgG4-related systemic disease.

Key Words: eosinophilic angiocentric fibrosis, IgG4, IgG4-related systemic disease

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Eosinophilic angiocentric fibrosis (EAF) is an uncommon tumefactive lesion of the orbit and upper respiratory tract. Although the inflammatory infiltrate within this lesion is an admixture of lymphocytes, plasma cells, and eosinophils, eosinophils are predominant. The characteristic histologic feature of EAF is the presence of small-caliber arterioles surrounded by concentric layers of fibrosis. Little has been discovered about the etiology of EAF since its first description in 1985.²⁵

We recently encountered a patient with EAF who had a dramatically elevated serum concentration of IgG4. This serendipitous discovery raised the possibility that EAF might be a form of IgG4-related systemic disease (IgG4-RSD).¹⁷ IgG4-RSD, similar to EAF, is also characterized by a tendency to form tumefactive lesions within the involved organs.³ Furthermore, eosinophils are invariably observed in IgG4-RSD, although they seldom dominate the histologic picture.^{2,7,8} In this study, we investigate the hypothesis that EAF is part of the spectrum of IgG4-RSD by analyzing the histologic and immunohistochemical features of our index case and also of 4 additional patients with EAF from our files.

MATERIALS AND METHODS

We identified 5 cases of EAF from the files of the Massachusetts General Hospital. The medical records of all 5 patients were reviewed to confirm the diagnosis of EAF and to identify organ involvement consistent with IgG4-RSD. The original hematoxylin and eosin-stained slides were reviewed, and these cases were stained immunohistochemically by using antibodies to IgG4 (Zymed; 1:200 dilution) and IgG (Dako; 1:3,000 dilution). The morphologic features were recorded, and IgG4 staining within biopsy samples was quantified. For each case, the number of plasma cells staining for IgG4 was assessed in 3 nonoverlapping high-power fields (HPF; magnification $\times 400$). The fields with the highest degree of IgG4 reactivity were selected for quantitation. The number of IgG4-positive plasma cells was then divided by the total number of IgG-bearing plasma cells in these fields.

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RESULTS

Case Reports

Case 1

The patient is a 63-year-old white man who was referred to a Rheumatology Clinic because of pulmonary infiltrates and an expanding mass in his sinus cavities. Seven years earlier, the patient had developed persistent ocular tearing, severe nasal congestion, and anosmia. On evaluation for bilateral tear duct obstruction, he was found to have an extensive mass involving the lacrimal glands (Fig. 1A). The mass extended into the nose, leading to expansion of the middle turbinates (Fig. 1B). A serum assay for antineutrophil cytoplasmic antibodies was negative. Biopsy of the right lacrimal gland showed features that were consistent with EAF. His symptoms and glandular swelling responded promptly to prednisone, but recurred on multiple occasions when his glucocorticoid doses were tapered.

Four years before his rheumatology evaluation, the patient had developed pneumonia with fever, cough, and sputum. A computed tomographic scan of the chest showed mediastinal, hilar, and axillary lymphadenopathies along with extensive bilateral ground-glass and nodular opacities in bronchovascular distributions (Fig. 2A). There was also a large prevertebral mass spanning multiple lower thoracic vertebral bodies. The patient had peripheral eosinophilia of 18% and a serum IgG concentration of 2450 mg/dL (normal, 614 to 1295 mg/dL). IgG subclass evaluations were not made at that time. The angiotensin-converting enzyme level was 28 U/L (normal, 7 to 46 U/L). The patient declined further diagnostic evaluations at that time. Follow-up imaging, performed on an annual basis, showed interval increases in his lymphadenopathy and pulmonary lesions. He was treated

intermittently with prednisone for episodes of worsening of proptosis, periorbital puffiness, and severe nasal congestion.

Seven years after his initial presentation, the patient was tested for IgG subclasses and was found to have a total serum IgG of 2450 mg/dL with a serum IgG4 concentration of 1490 mg/dL (normal, 8 to 140 mg/dL). Serum-free light chains were also elevated, but the $\kappa:\lambda$ ratio was normal. Repeat chest imaging showed worsening of his pulmonary lesions (Fig. 2B), an increase in the size of the lymph nodes and prevertebral mass, and a new mass lesion in the presplenic region. The patient underwent bronchoscopy, which showed a white polypoid lesion stemming from the medial bronchial wall and extending into the pulmonary lobe. Biopsies of the bronchial lesion and lymph nodes showed an admixture of lymphocytes, plasma cells, and eosinophils. An IgG4 stain of the bronchial biopsy showed significant background staining, obviating quantitative assessment. However, histologic review of his nasal biopsies showed typical features of EAF. Immunohistochemistry for IgG4 and IgG performed on nasal biopsy showed 118 IgG4-positive plasma cells/HPF and an IgG4:IgG ratio of 0.8.

Cases 2 to 5

The patients included 1 man and 3 women, ranging in age from 31 to 82 years (Table 1). The mean age of all 5 patients at presentation was 56 years. The disease extent varied from patient to patient, from the multicentric disease involving the sinuses, nasal tract, and lower respiratory tract to isolated involvement of the nasal cavity or the lacrimal gland. The duration of symptoms ranged from 6 months to >20 years. Only 1 patient reported a history of allergic rhinitis.

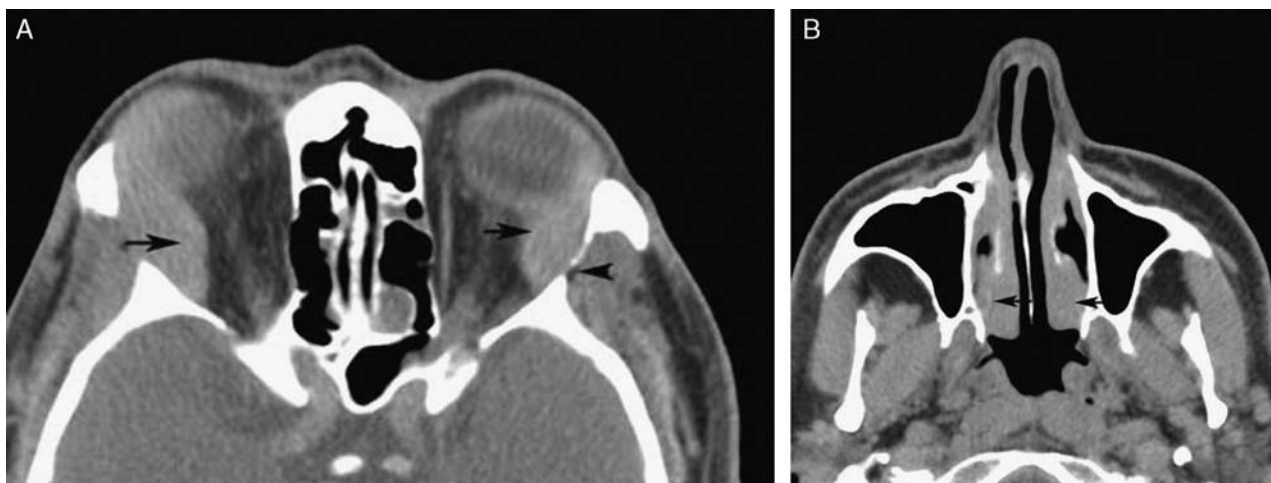


FIGURE 1. Computed tomographic study of the lacrimal glands and sinuses in case 1. A, There is marked enlargement of the lacrimal glands (arrows), right > left. There is expansion of bilateral nasolacrimal ducts, right > left. There is thinning or possible erosion of the lateral orbital walls (arrow head). B, The inferomedial orbital regions contain soft tissue of similar density to that of the enlarged lacrimal glands. This extends into the nasal cavity bilaterally with expansion of the soft tissue of the middle turbinates (arrows).

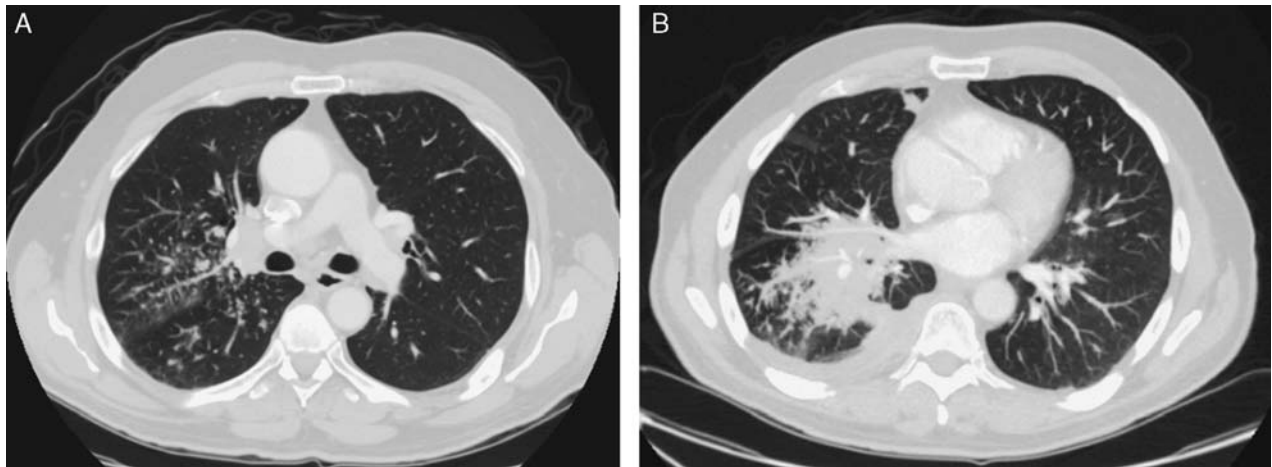


FIGURE 2. Computed tomographic images of the lungs, 4 years between studies, in case 1. A, There are extensive ground-glass and interstitial opacities in the bronchovascular distributions, with associated bronchial wall thickening, involving the posterior segment of the right upper lobe, the right lower lobe, and a portion of right middle lobe, to a lesser extent in the left upper lobe. B, Bilateral peribronchovascular nodular and reticular infiltrates that coalesce centrally and predominantly involve the right lung. These are increased in size and confluence since the study 4 years earlier (A). The opacities involve the superior segment of the right lower lobe and posterior segment of the right upper lobe.

Histology

The histologic appearance in 4 cases was virtually identical (cases 1, 2, 4, and 5). Eosinophils dominated the histologic picture, but a full complement of inflammatory cells, including lymphocytes, plasma cells, and neutrophils, was noted (Fig. 3). Evenly distributed small-caliber arterioles were noted in all biopsies, and the majority of these vessels were surrounded by a concentric, “onion-skin” fibrosis. Three cases (2, 4, and 5) showed neutrophils and eosinophils within the walls of these small-caliber vessels.

The lacrimal gland biopsy in case 4 showed a periductal inflammatory infiltrate consistent with the lesions observed in type 1 autoimmune pancreatitis, the pancreatic manifestation of IgG4-RSD (Fig. 3F). Cases 4 and 5 showed a storiform pattern of fibrosis. In cases in which multiple biopsies were performed over time, the inflammatory component tended to decrease with time. In contrast to the biopsies from other patients, 7 different biopsies from case 3 (Fig. 4) performed over multiple years showed only the perivascular concentric fibrosis typical of EAF and were devoid of an inflammatory component.

The bronchial biopsy from case 1 showed sub-epithelial lymphocytes, plasma cells, and eosinophils. An IgG4 stain showed 15 IgG4-positive plasma cells/HPF. However, periarterial concentric fibrosis was not seen in this biopsy. A transbronchial aspirate of a hilar lymph node showed features of reactive lymphadenitis. The intense background stain did not allow us to quantitate IgG4-bearing plasma cells in the lymph node biopsy.

Granulomas, foreign body-type giant cells, and geographic-type necrosis were not identified in any cases. Obliterative-type venulitis was not seen in any case.

Immunohistochemistry

IgG4-positive plasma cells were identified in cases 2, 4, and 5, and also in case 1. Neither IgG4-bearing nor IgG-bearing plasma cells were identified in case 3. The number of IgG4-positive cells/HPF among the patients who stained positively ranged from 43 to 118, with IgG4:IgG ratios that ranged from 0.68 to 0.97. The immunohistochemical staining features of the index case are shown in Figure 3B.

TABLE 1. Clinical and Immunohistochemical Data on 5 Cases of EAF

No.	Age/ Sex	Site(s)	Duration of Disease	Surgical Procedures	Allergy History	ANCA	Tissue IgG4/ HPF	Tissue IgG4/ IgG Ratio
1	63/M	Nasal and lacrimal glands, lung	6 y	2	None	Negative	118	0.8
2	81/F	Left nasal	3 y	2	Allergic rhinitis	NA	43	0.87
3	31/F	Orbit, maxillary sinus, ethmoid, nasal	20 y	7	None	NA	0	0
4	54/F	Right lacrimal gland	Unknown	1	None	NA	115	0.97
5	55/M	Orbit	6 mo	1	None	Negative	59	0.68

ANCA indicates antineutrophil cytoplasmic antibodies; F, female; M, male; NA, not applicable.

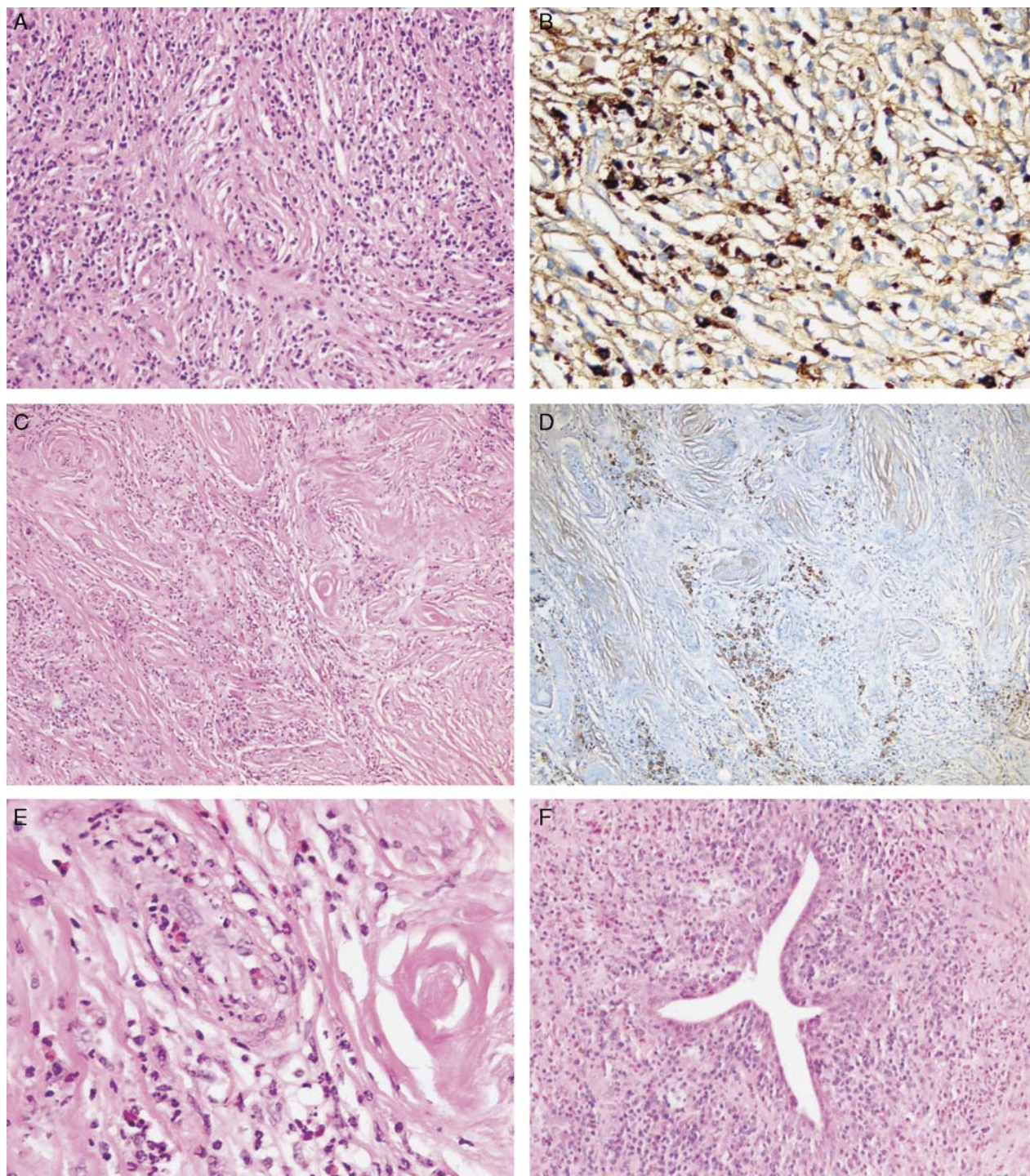


FIGURE 3. Histopathologic analysis of EAF. A, Nasal biopsy predominantly showing lymphoplasmacytic infiltrate with perivascular fibrosis in case 1. B, Immunohistochemical stain of (A) shows that the majority of the plasma cells are positive for IgG4. C, Nasal biopsy from case 2 showed marked prominent perivascular fibrosis. D, immunohistochemical stain of (C) shows large numbers of IgG4-positive cells. E, A high-power image from case 2 showing neutrophils and eosinophils infiltrating small-caliber vascular channels. The background infiltrate is composed of lymphocytes, plasma cells, eosinophils, and neutrophils. In addition, note the focus of concentric fibrosis. F, Biopsy of the lacrimal gland from case 4. The periductal inflammatory infiltrate closely resembles the infiltrates seen in autoimmune pancreatitis.

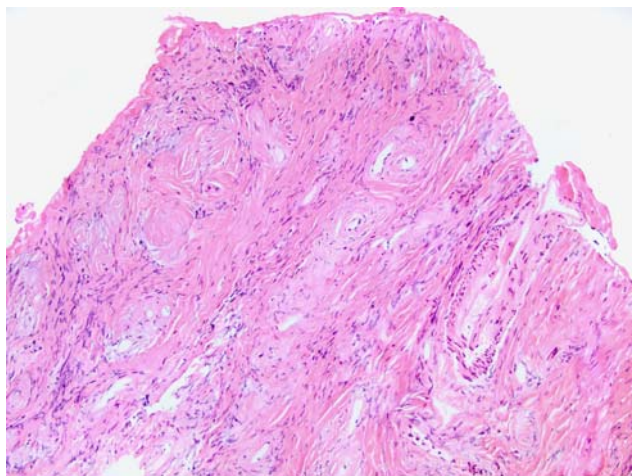


FIGURE 4. The orbital biopsy from case 3, while showing perivascular concentric fibrosis, lacked an inflammatory infiltrate. full color online

DISCUSSION

Since its description in the mid-1980s, there has been little progress in determining the etiology of EAF.²⁵ In this study, we describe the largest single institution series of EAF reported to date, and show that EAF lesions are associated with large numbers of IgG4-positive plasma cells. In addition, our index case, the only patient for whom serum was available, had a serum IgG4 concentration 10 times above the upper limit of the normal level. This case also showed evidence of involvement of the lower tracheobronchial tree. Although involvement of the larynx and trachea by EAF has been reported,¹¹ there are earlier descriptions of lower respiratory tract involvement.

The association of EAF with IgG4-RSD provides new potential insights into the etiology of this enigmatic disorder. In light of the large numbers of eosinophils, conventional wisdom would suggest that EAF is an allergic disease. However, among the 32 cases reported in the literature, only 3 cases were associated with allergic manifestations.^{1,14,24} IgG4-RSD is frequently associated with allergic manifestations. In a recent North American series, allergic manifestations were noted in 15% of patients with autoimmune pancreatitis,²⁷ and 44% of such patients from Japan had histories of allergic disease.¹⁶

Since the concept of IgG4-RSD was first introduced in 2003,¹⁵ there has been a dramatic increase in the number of entities linked with this disease.² The prototypical example of IgG4-RSD is the type-1 variant of autoimmune pancreatitis.^{10,26} IgG4-positive plasma cells and other characteristic histologic features have also been identified in inflammatory tumefactive lesions in the liver, lung, and kidney, thereby linking these diseases to IgG4-RSD.^{5,9,28} The IgG4-RSD spectrum is also known to include an array of other enigmatic entities such as Riedel thyroiditis,⁶ Mikulicz disease,¹² and pachymeningitis.²¹ We now propose that EAF is also a form of IgG4-

associated disease, part of the disease spectrum now termed as IgG4-RSD.

No consensus exists currently about criteria that need to be fulfilled before a disease condition can be classified as IgG4-RSD.² One key clinical feature of IgG4-RSD is the presence of a tumefactive lesion, which was present in all 5 of our cases. Virtually all disorders that comprise the condition now termed as IgG4-RSD share a common histologic appearance: a dense lymphoplasmacytic infiltrate, fibrosis, and obliterative phlebitis. The *sine qua non* of IgG4-RSD is the presence of elevated numbers of IgG4-positive plasma cells within lesions. However, there is no consensus regarding the minimal number of IgG4-positive cells required for a diagnosis. It is possible that the minimum number varies according to the specific organ involved. Four of our 5 cases clearly met the currently used standards for diagnosis in terms of the minimum number of IgG4-positive cells or the IgG4:IgG ratio.

The histology of EAF is distinctive: small-caliber arterioles surrounded by a concentric layers of fibrosis. This tumoral lesion is dominated by inflammatory cells, the vast majority of which are eosinophils. This histologic appearance differs from what is considered typical for IgG-RSD. Specifically, samples from patients with EAF lack obliterative phlebitis. However, virtually all entities now considered to be part of the IgG-RSD spectrum show substantial numbers of eosinophils, albeit in significantly lower numbers than those observed in EAF. Despite these pathologic differences, the striking elevation of IgG4-bearing plasma cells in 4 of our 5 cases and the elevated serum levels of IgG4 in our index patient support our hypothesis that EAF is a form of IgG4-RSD.

The early histopathologic features of EAF may differ from the later phases of this disease.²⁵ More precisely, inflammatory cells predominate in the early phase of EAF, whereas whorled fibrosis (onion skinning) is more prominent in the late stage, although some degree of eosinophilic infiltration generally persists.¹⁴ In this manner, EAF bears a striking resemblance to other components of the IgG4-RSD, such as Riedel thyroiditis.⁶ In Riedel thyroiditis, IgG4-bearing plasma cells are prominent in the early phases of the disease, but virtually absent in the late phase when overwhelming fibrosis supervenes and no plasma cells are found within the involved tissue.⁶ Case 3 fits this pattern in that the samples showed virtually no inflammatory cells; yet the periarteriolar fibrosis was remarkably similar to that found in the other 4 cases of EAF (Fig. 3F). One reasonable speculation is that case 3 represents a late phase of the disease, accounting for the lack of IgG4-positive plasma cells.

Necrosis, giant cells, and overt evidence of vasculitis are not observed in EAF, and help distinguish this disorder from some of its mimickers including Wegener granulomatosis and the Churg-Strauss syndrome. The differential diagnosis of sinonasal tract EAF also includes Kimura disease, angiolymphoid hyperplasia with eosinophilia, and parasitic infections. Granuloma faciale, an inflammatory cutaneous reaction, is considered by some to

represent the cutaneous manifestation of EAF. Granuloma faciale generally presents as papules localized to the face, typically in middle-aged individuals.²² There have been 5 earlier cases with concurrent EAF and granuloma faciale.¹³ Furthermore, some cases of granuloma faciale have a histologic appearance virtually identical to that of EAF.²² Thus, it is possible that granuloma faciale is also an IgG4-related systemic disease. In this regard, it is worth noting that cases of IgG4-RSD presenting with facial papules in the setting of other classic organ involvement have been reported recently.⁴

In general, the prognosis of sinonasal tract EAF seems to be indolent and progressive. When recurrences occur, they usually arise in the same anatomic site as the primary lesion and are therefore considered to represent progressive disease. Patients frequently undergo multiple surgeries for the alleviation of symptoms. A literature review suggests that immunosuppressive therapy is associated with only limited success in EAF. Paun et al²³ noted a response to immunosuppressive therapy—glucocorticoids in 1 case and the combination of glucocorticoids and azathioprine in the other—but these treatments had to be discontinued because of intolerable side effects. In other cases, glucocorticoids have been reported to effect little-to-no response.^{14,20,30} Dapsone has been used in granuloma faciale with variable success,²⁹ but we are not aware of any reports of its use in EAF.

In conclusion, we have shown that EAF lesions bear several hallmarks of IgG4-RSD, including the presence of a tumefactive lesion, elevated numbers of IgG4-bearing plasma cells, and an elevated lesional IgG4:IgG ratio. These observations may have important clinical implications. Recently, our group described 4 patients with IgG4-RSD who showed a swift response to rituximab, including a rapid decline in serum IgG4 levels, whereas serum levels of the other IgG subclasses remained stable, and there was swift improvement in tumefactive lesions and other disease manifestations.^{18,19} Rituximab may thus be a reasonable approach to therapy in patients with EAF whose disease features are refractory to glucocorticoids.

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