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Eosinophilic angiocentric fibrosis

Abtin Tabaee, M.D., Mani H. Zadeh, M.D., Maria Proytcheva, M.D.*, Anthony LaBruna, M.D.

Abstract
Eosinophilic angiocentric fibrosis of the upper respiratory tract is a rare disorder of unknown aetiology. Despite characteristic histological findings, the aetiology and management of this lesion remain unclear. We describe a case of nasal eosinophilic angiocentric fibrosis and discuss possible demographic and aetiological patterns.

Key words: Fibrosis, Eosinophilic Angiocentric; Nose

Introduction

Eosinophilic angiocentric fibrosis (EAF) of the upper respiratory tract is a rare disorder of unknown aetiology. To date, only 14 other cases have been described in the literature. The characteristic histological finding of a perivascular eosinophil-rich inflammatory infiltrate and onion-skin whorling of stromal fibrotic tissue[1] allows for an accurate and reproducible method of diagnosis. However, the idiopathic nature of the lesion in conjunction with the lack of effective therapy continues to pose a clinical challenge. We present an interesting case that highlights several important aspects of EAF.

Case report

A 79-year-old Caucasian male presented with a three-year history of progressive nasal congestion, nasal tip tenderness and nasal swelling. His history was notable for excision of a right nasal dorsum skin lesion two and a half years prior to evaluation. This lesion was diagnosed as granuloma faciale on pathology. He also underwent a Moh's excision of a left nasal squamous cell cancer 21 months prior to evaluation and two separate septoplasty procedures (childhood and 1996). His past medical history was significant for hypertension and benign prostatic hypertrophy. His past social history was significant for occasional alcohol consumption and cigar smoking as well as travel to a forest in Brazil prior to the onset of his nasal symptoms. He denied any drug or environmental allergies. Notable findings on physical examination included erythema, broadening and mild tenderness of the nasal tip, external fullness of the left lateral nasal wall and complete obstruction of the left nasal cavity by a submucosal fullness of the lateral nasal wall and septum (Figure 1). There was no mucosal irregularity, nasal polyposis, cervical lymphadenopathy nor cranial nerve weakness.

Computerized tomography (CT) and magnetic resonance imaging (MRI) revealed a large polypoid mass involving the cartilaginous portion of the nasal septum and lateral nasal wall (Figure 2). Pre-operative evaluation revealed a normal chest X-ray, normal serum chemistries, normal white blood cell count and normal haemoglobin level. However, the absolute eosinophil count was noted to be elevated at 0.6 K/μl (normal – 0.0–0.3 k/μl). Over a three-month period, two separate biopsies of the nasal mass were performed under anaesthesia. Pathologic examination of these specimens revealed both an acute

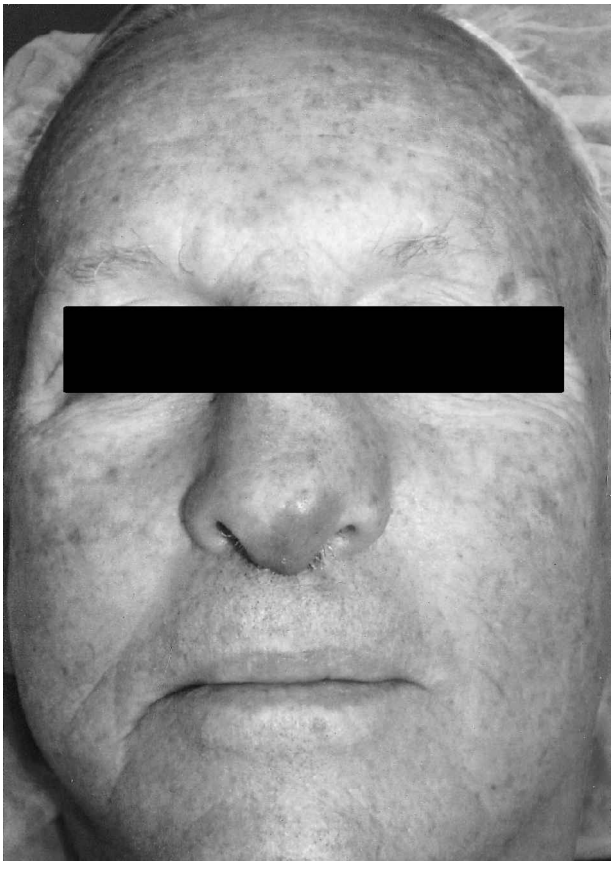

Fig. 1
Pre-operative photograph showing external fullness of the left lateral nasal wall and broadening of the nasal tip.

From the Departments of Otolaryngology–Head and Neck Surgery and Pathology*, New York Presbyterian Hospital and Weill Medical College at Cornell University, New York, NY, USA.
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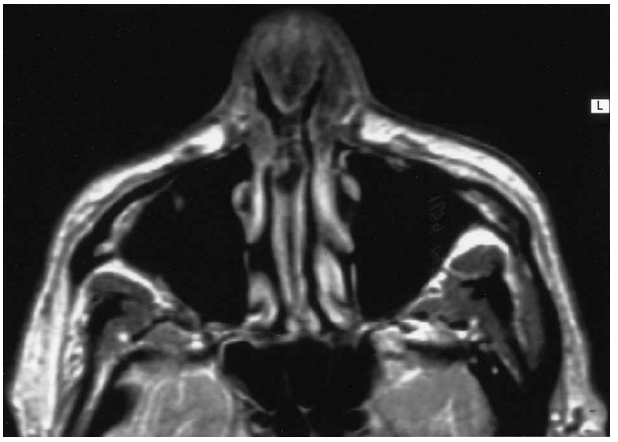


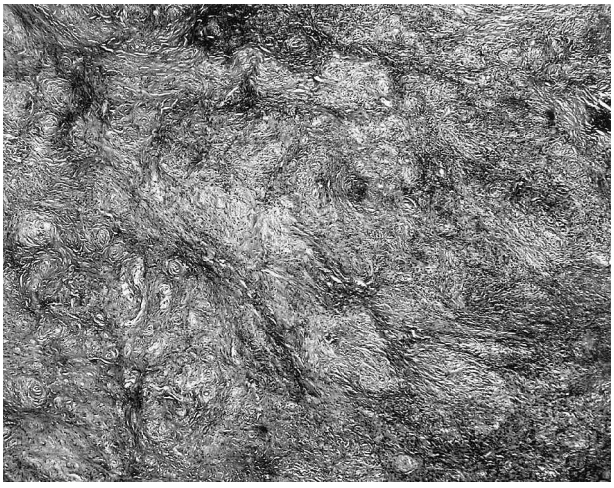
FIG. 2

T-2 weighted axial MRI demonstrates a large polypoid mass involving the septal cartilage and upper lateral cartilage.

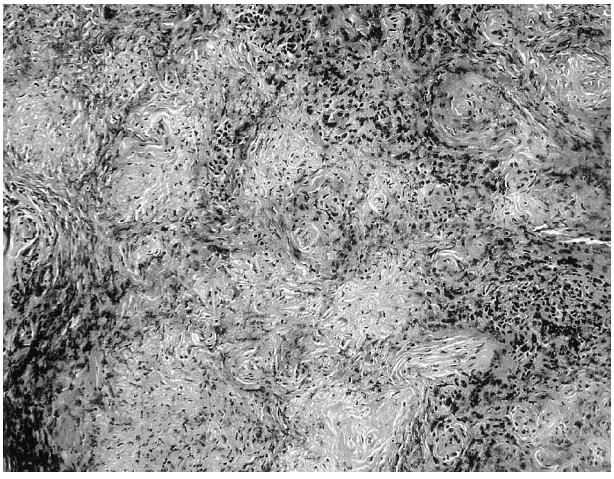
and chronic inflammatory reaction as well as degeneration of the cartilage. There was no evidence of granulomatous or malignant changes. Cultures for bacteria, acid fast bacilli and fungus were all negative. The patient was followed clinically for six more months and was noted to have local progression of his symptoms. The decision was made at this time to proceed with surgical extirpation for diagnosis. Of note, the patient was noted to have a positive cytoplasmic anti-neutrophil cytoplasmic antibody (c-ANCA) titre. However, he had no history of clinical, serological, radiographic or histological evidence of Wegener's granulomatosis.

An open rhinoplasty approach was performed for exposure. The tumour was a creamy-yellow fibrous material that had replaced the septal cartilage in the middle third of the nose in addition to overriding the left upper lateral cartilage and left side of the nasal region. The involved portions of the septum and left upper lateral cartilage were extracted. The resulting saddle nose deformity in the middle third of the nose was reconstructed using auricular cartilage. The patient had a marked improvement in nasal contour at the end of the reconstruction. In addition there was an increase in airflow secondary to debulking of the tumour. At one year follow-up, the patient's operative site was well healed. He was asymptomatic and without any clinical evidence of recurrence.

Microscopic examination of multiple haematoxylin and eosin (H and E) stained sections from the subcutaneous nasal mass showed a soft tissue infiltrate characterized by bands of alternating dense fibrosis and collections of small lymphocytes, plasma cells and eosinophils (Figure 3). Within the bands, the collagen fibres formed a characteristic perivascular onion-skin whorling. They were associated with occasional thin fibroblasts and abundant spindle cells with plump nuclei and clear cytoplasm. Immuno-histochemical stains were performed in order to demonstrate specific antigens expressed on the different cell types and aid in their characterization. These studies demonstrated that the spindle cells were a mixture of S-100 positive interdigitating cells and PGM-1/CD68 positive histiocytes. These cells did not express smooth muscle markers; i.e. they were not myofibroblasts. Many CD117 positive mast cells were also present. The small lymphocyte population was composed of both B-cells and T-cells and the plasma cell population was polyclonal. The residual cartilage was surrounded and eroded by this process. No necrotizing granulomatous vasculitis, similar to the one diagnostic for Wegener's granulomatosis, was present. Special stains for bacteria, fungi and acid fast microorganisms were negative.



(a)



(b)

FIG. 3

(a) Low magnification showing the alternating fibrous bands with whorled appearance and intervening inflammatory infiltrate. (b) Higher magnification demonstrates the onion-skin fibrosis and collections of small lymphocytes, plasma cells and eosinophils (H&E; ×40).

Discussion

Eosinophilic angiocentric fibrosis represents an exceedingly rare disorder of unclear aetiology. The first account of this disorder is attributed to Homes and Panje who reported a case in 1983 of what they termed 'intranasal granuloma faciale'.[2] The term eosinophilic angiocentric fibrosis was subsequently introduced by Roberts and McCann in 1985 in their description of three patients.[1] In total, 14 cases have been described in the literature to date. Although histological examination of these lesions has demonstrated consistent findings, a clear understanding of the pathophysiology of this disorder has been elusive.

A review of the clinical demographics of EAF highlights several important patterns (Table I). Despite the initial reports that indicated a female predominance, there does not appear to be an obvious gender bias with a cumulative male to female ratio of six to nine. The patients are overall in good health and the reported age at diagnosis ranges from 25 to 79 years with a median of 49 years and a mean

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of 47 years. Of the 15 cases described, 13 involved the nose and two involved the sub-glottis. No cases of multi-site involvement have been described. Patients with nasal disease typically presented with progressive nasal obstruction and swelling. Tenderness and bleeding, while not common, were occasionally present. The two patients with sub-glottic involvement experienced progressive respiratory complaints and were found to have a fixed obstruction on evaluation. It is important to note that the majority of patients experience a history of chronic (range – 11 months to 12 years) and progressive symptoms. Non-specific mucosal thickening and sub-mucosal fullness were seen on physical examination and a soft-tissue, polypoid mass was detected on imaging. However, the lack of specific signs or symptoms in conjunction with the rarity of this lesion mandate the need for histological evaluation and diagnosis.

The initial pathologic description of a unique inflammatory and fibrotic lesion by Roberts and McCann has been reproduced in subsequent reports.[1,3,4] Two separate histological phases, often within the same specimen, have been described. The early lesion is characterized by an eosinophilic predominant vasculitis of the capillaries and the venules. Eosinophils cluster and migrate through the vessel wall and are accompanied by a mixture of plasma cells, lymphocytes and fibroblasts. Although a pseudo-

TABLE I
REVIEW OF REPORTED CASES OF EAF

Reference	Case	Gender/ Age at diagnosis	Location	Symptoms/ Duration	Related findings	Treatment	Outcome at original publication
Holmes and Panje[2]	1	M/49	Nose (lateral wall)	Nasal obstruction /18 months	Granuloma faciale	Intra-lesional triamcinolone, single resection	Persistent disease
Roberts and McCann[1]	2	F/27	Nose (septum and lateral wall)	Nasal congestion /12 years	None	Antihistamine, nasal and systemic steroids, multiple resections	Persistent disease
Roberts and McCann[1]	3	F/33	Sub-glottis	Shortness of breath/4 years	Penicillin allergy	Tracheostomy, laryngo-tracheoplasty	Free of disease
Roberts and McCann[1]	4	F/59	Nose (septum and lateral wall)	Nasal congestion /8 years	Granuloma faciale, urticaria	Intra-lesional steroids, multiple resections	Persistent disease
Fageeh *et al.*[6]	5	F/25	Sub-glottis	Shortness of breath/many years	Environmental and antibiotic allergy	Tracheostomy, tamoxifen, laryngo-tracheoplasty	Free of disease
Altemani *et al.*[3]	6	F/54	Nose (septum and lateral wall)	Nasal obstruction /18 months	Allergic rhinitis	Multiple resections	Persistent disease
Roberts and McCann[7]	7	F/54	Nose (septum)	Nasal stuffiness /11 years	None	Multiple resections, radiotherapy	Not available
Roberts and McCann[7]	8	F/50	Nose (lateral wall)	Nasal stuffiness /3 years	None	Multiple resections	Persistent disease
Matai *et al.*[4]	9	M/51	Nose (septum)	Nasal obstruction/ few months	Hay fever, prior nasal trauma	Single resection	Improved symptoms
Thompson and Heffner[8]	10	M/28	Nose (septum and lateral wall)	Nasal obstruction, pain, epistaxis/11 months	None	Nasal and systemic steroids, single resection	Persistent disease
Thompson and Heffner[8]	11	F/49	Nose (septum)	Nasal obstruction /14 months	None	Nasal and systemic steroids, single resection	Persistent disease
Thompson and Heffner[8]	12	F/64	Nose (septum and lateral wall)	Nasal obstruction /8 years	None	Nasal and systemic steroids, multiple resections	Persistent disease
Burns *et al.*[9]	13	M/38	Nose (septum and lateral wall)	Nasal obstruction and swelling /2 years	Granuloma faciale	Intra-lesional and systemic steroids, multiple resections	Persistent disease
Loane *et al.*[5]	14	M/42	Nose (septum)	Nasal obstruction, post-nasal drip /5 years	Wegener's granulomatosis, asthma	Immuno-suppression, multiple resections	Not available
Present paper	15	M/79	Nose (septum and lateral wall)	Nasal congestion, swelling, tenderness /3 years	Granuloma faciale, c-ANCA, Squamous cell cancer, prior nasal surgery	Single resection	Not available

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granulomatous reaction is often seen, the multi-nucleated giant cells and epithelioid histiocytes that are seen in true granulomas are not present. Further, there is no necrosis or involvement of the arterioles or small arteries. The more advanced lesion is characterized by a dense, fibrous thickening of the stroma and a characteristic onion-skin whorling of collagen fibres and reticulin. Mild inflammatory reactions and lymphoid follicles often surround the periphery of these mature lesions. There is no cellular atypia and immunostaining confirms an inflammatory reaction.[1,3,4]

The differential diagnosis of EAF is extensive and includes infectious (granulomatous diseases), inflammatory (collagen vascular diseases, Churg-Strauss syndrome, Wegener's granulomatosis, sarcoidosis, Kimura's disease, angiolymphoid hyperplasia, inflammatory pseudo-tumour, sarcoidosis, Sjögren's syndrome) and neoplastic (neurogenic, vascular, mesenchymal tumours) conditions. An initial approach to a patient suspected of having EAF should include a complete head and neck examination, flexible endoscopy, complete blood count, erythrocyte sedimentation rate (ESR), anti-neutrophil cytoplasmic antibody, and chest X-ray. Laboratory evaluation, including the ESR and white blood cell count, is typically normal. Although our patient had a slight elevation in the peripheral absolute eosinophil count, this is uncommon. Radiographic imaging aids in defining the extent of local involvement and detecting other local lesions. However, pathologic examination is ultimately required for the diagnosis of EAF and for the exclusion of other conditions. Standard haematoxylin and eosin staining will reveal the typical features of EAF as outlined above and immunostaining may be used to delineate the inflammatory nature of the lesion. Cultures for bacteria, fungus and acid-fast bacilli should also be performed.

Despite the consistent pathologic findings outlined above, the aetiology of EAF remains unclear. There appears to be a higher incidence of allergic and atopic disorders in patients with EAF than in the general population. For example, six of the 15 reported patients were also diagnosed with asthma, drug allergy, environmental allergy, urticaria, or allergic rhinitis. This, in combination with the predominant eosinophilic infiltrate, suggests the possibility of an inappropriate inflammatory response to a local stimulus. Loane *et al.*[5] described a case of a 42-year-old male with a previous diagnosis of Wegener's granulomatosis and a nasal lesion that was found to be EAF. They suggest that EAF may represent an exaggerated fibrotic variant of Wegener's. Although our patient had a positive c-ANCA, he lacked any other clinical or objective evidence of Wegener's. In three of the patients with nasal EAF, a distant history of nasal trauma or surgery (septoplasty, antrostomy) was present. Further, multiple attempts at local resection of nasal EAF resulted in a more aggressive recurrence suggesting that local trauma, whether accidental or surgical, may act as a pro-inflammatory stimulus. These associations suggest that EAF may represent a non-specific fibrotic process of the upper airway in response to pro-inflammatory stimuli in a predisposed host. Contradictory to their theory is the lack of efficacy of nasal steroids, systemic steroids and other forms of immunosuppression as evidenced by previous reports.

Also unclear is the relation of granuloma faciale to EAF. Granuloma faciale is a benign disorder of the dermis characterized by a peri-vascular infiltrate of eosinophils and histiocytes. The onion skin whorling of collagen fibres characteristic of EAF is, however, absent in granuloma faciale. Four of the 15 reported patients with EAF were also diagnosed with granuloma faciale. In two of the patients, the skin lesion preceded the EAF, in the other two the EAF presented first. Three of the four patients were male. The clinical response of the skin lesions to therapy also seemed to be independent of the clinical course of the EAF.

The natural history of EAF seems to be that of a benign but potentially progressive disorder. Symptoms are usually present for years with minimal increase in aggressiveness over time. Although erosion of the cartilage is possible as evidenced by our report, malignant degeneration or invasion of adjacent structures has not been noted. Multiple different approaches to the treatment of EAF have all met with disappointing results. Attempts at decreasing the inflammatory response both locally (nasal and intra-lesional steroids) and systematically (steroids, immuno-suppressants) have been universally unsuccessful. Further, local resection often results in progressive or at least persistent disease. Interestingly, both cases of subglottic EAF were addressed with wide local excision of the lesion followed by a laryngo-tracheoplasty. Complete resolution of the disease was reported in both patients. This may imply that a wide excision of the lesion with replacement of the defect with non-involved tissue may be more efficacious. However, a larger case series is necessary before definitive surgical recommendations can be made. The long-term clinical outcomes of both past and future case series will hopefully identify the aetiology and the ideal management of this interesting disorder.

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Address for correspondence:
Dr Anthony LaBruna,
Weill Medical College,
520 East 70th Street – ST541,
New York, NY 10021,
USA.

Fax: 212-746-2253
E-mail: alabruna@aol.com

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