Sinonasal Eosinophilic Angiocentric Fibrosis: A Report of Four Cases and Review of Literature

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Abstract Eosinophilic angiocentric fibrosis (EAF) is a rare, benign condition of unknown etiology involving the sinonasal tract and the upper respiratory airways, and rarely, larynx, and orbit. We report four cases of EAF identified, in three women and one man, aged 31, 57, 27, and 51 years, respectively. The patients complained of sinonasal obstructive symptoms of long duration, nasal masses, epiphora, and/or proptosis. Histologically, all cases demonstrated a dense fibrotic stroma with a perivascular “onion-skin” whorling pattern, and a dense inflammatory infiltrate consisting of lymphocytes, plasma cells, eosinophils, and some neutrophils. In addition, one patient demonstrated modest acute neutrophilic inflammation with

focal endothelial proliferation. No patient exhibited clinical or histological evidence of Wegener’s granulomatosis, granuloma faciale, Kimura’s disease, and malignant lymphomas. Surgical excision was performed in all cases, and to date, medical therapy has been of limited help. The clinical and histopathological features and differential diagnoses of this underreported EAF condition are discussed.

Keywords Eosinophilic angiocentric fibrosis · Sinonasal tract · Fibrosis · Eosinophils

Introduction

Eosinophilic angiocentric fibrosis (EAF) is a rare condition of unknown etiology. It was first described by Holmes and Panje in 1983 [1]. Two years later, Roberts and McCann reported two cases of female patients with an unusual stenosing lesion involving the upper respiratory tract and gave a descriptive diagnosis: *eosinophilic angiocentric fibrosis* (EAF) [2]. A review of the English literature reveals 28 additional cases of EAF involving the sinonasal tract have been reported [3–22]. EAF typically presents in young to middle-aged females as a slowly progressive upper airway obstruction in association with a submucosal inflammatory, fibrosing tumor-like lesion. Histologically, the lesion is characterized by a perivascular, eosinophil-rich inflammatory infiltrate and progressive fibrosis leading to a characteristic whorling, ‘onion-skin’-type pattern [1]. The unresolving fibrosis and consequent stenosis requires surgical intervention. We report an additional four cases of EAF centered around the nasal cavity and review of pertinent literature available on the previously reported cases.

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Materials and Methods

Four patients diagnosed with eosinophilic angiocentric fibrosis from 1998 to 2008 and originating in the head and neck region were identified from a review of the files of the Department of Pathology at Massachusetts General Hospital, Virginia Commonwealth University Health System and University Health Network of University of Toronto. Clinical records and surgical pathology reports together with follow-up information was reviewed.

Results

Patient Information

The patients included three females and one male who ranged in age from 27 to 57 years (Table 1). The most common presentation was a submucosal or soft tissue mass in the upper respiratory tract (sinonasal cavity) and orbit, progressive nasal obstruction, and epiphora. One patient (case #2) had a history of allergy to mold, dust and ragweed, decreased sense of smell and proptosis. The other patient (case#3) had a history of cocaine abuse and nasal septal perforation (Fig. 1).

Pathologic Findings

The masses ranged from 2.3 to 5.0 cm in size. Histologically, all cases demonstrated a dense fibrotic stroma with a perivascular 'onion-skin'-type whorling pattern and an inflammatory infiltrate rich in eosinophils, lymphocytes, and plasma cells (Fig. 2). In addition, case #3 demonstrated modest acute inflammation and focal endothelial proliferation. No vasculitis, granuloma formation, giant-cell histiocytic reaction, or necrosis was identified in any of these cases.

Immunohistochemical Studies

Immunohistochemical studies were performed on only case #4. CD31 and CD34 positive endothelial cells were seen within the sclerotic nodule. Perivascular, mixed T-cell and B-cell lymphocytic population was demonstrated by CD5 and CD20 immunohistochemical stains, respectively.

Flow Cytometric Studies

Lymphoma work-up by flow cytometry was performed on two cases (#1&2) and revealed polyclonal kappa and lambda positive, CD19 positive B cells, as well as CD4 and CD8 positive T-cells. No evidence of monoclonal B- or unusual T-cell population was identified.

Table 1 Summary of clinical features of our four cases of sinonasal eosinophilic angiocentric fibrosis

Case #	Age/sex	Clinical symptoms	Site	Laboratory tests	Radiological findings	Treatment	Follow-up
1	31/F	Right epiphora, left orbital mass	Sinuses (left maxillary & ethmoid), orbit	ANCA, p29, MPO	Not done	Multiple biopsies, steroids, single resection	Rec. × 3,4 years; SOB
2	57/M	Nasal congestion, epiphora, proptosis, decreased sense of smell	Nose (bilateral lateral wall), multiple sinuses, lacrimal gland	ANCA, p29, MPO, ANA, anti-DNA, peripheral eosinophilia	Mass involving lacrimal gland and multiple sinus cavities	Steroids, single resection	Rec. × 2 years; SOB
3	27/F	Nasal obstruction	Nose (bilateral lateral wall)	ANA, ANCA	Not done	Biopsy	Lost to follow-up
4	51/F	Nasal mass, obstruction & epiphora	Nose (right lateral wall)	Not done	Mass involving right nasal cavity, medial canthus and nasolacrimal duct	Single resection (debulking)	Persistent mass; small increase in size

Rec., recurrence; SOB, shortness of breath

Fig. 1 A 27-years-old woman affected with bilateral nasal obstructing lesion

Fig. 2 Nasal mass biopsy. (a) Inflammatory infiltrate consisting of lymphocytes, plasma cells, and eosinophils. (b) Perivascular fibrosis and eosinophil-rich inflammatory infiltrate (hematoxylin and eosin; $\times 400$). (c) Thick collagen bundle with perivascular fibrosis ('onion-skin'-type whorling pattern)

Fig. 3 A 51-year-old woman with contrast head CT-images. (a) With bone window showing no bone erosion. (b) Soft tissue mass along the right nasal bone extending medially into the nasal cavity

Immunological Studies

Indirect immunofluorescence testing for anti-neutrophil cytoplasmic antibodies (ANCA) performed in three patients (cases #1–3) was negative. In addition, ELISA for antibodies to p29 (proteinase 3) and myeloperoxidase (MPO) performed in two patients (cases #1&2) was also negative. In case #2, cryoglobulin, ANA, and anti-DNA were also negative.

Radiologic Findings

Radiographic evaluation by computed tomography (CT) was available in all the cases and showed expanding soft tissue masses in the nasal turbinate extending into the sinuses (Fig. 3). All lesions, except the case #4, extended into the orbital soft tissue.

Table 2 Literature review of reported cases of sinonasal eosinophilic angiocentric fibrosis

Report	Age/sex	Clinical symptoms	Site	Related findings	Treatment	EV	OS	Follow-up
Holmes and Panje [1]	49/M	Nasal obstruction	Nose (lateral wall)	Granuloma faciale	Intra-lesional triamcinolone, single resection			PD
Roberts and McCann [2]	27/F	Nasal congestion	Nose (septum & lateral wall)	None	Antihistamine, nasal & systemic steroids, multiple resection	+	+	PD
Roberts and McCann [3]	59/F	Nasal congestion	Nose (septum & lateral wall)	Granuloma faciale, urticaria	Intra-lesional steroids, multiple resection	+	+	PD
	54/F	Nasal stuffiness	Nose (septum)	None	Multiple resections, radiotherapy			N/A
Altamiani et al. [4]	50/F	Nasal stuffiness	Nose (lateral wall)	None	Multiple resections			PD
	54/F	Nasal obstruction	Nose (septum & lateral wall)	Allergic rhinitis	Multiple resections	+	+	PD
Matai et al. [5]	51/M	Nasal obstruction	Nose (septum)	Hay fever, prior nasal trauma	Single resection	+	+	FD
Thompson and Hefner [6]	28/M	Nasal obstruction, epistaxis, pain	Nose (septum & lateral wall), maxillary sinus	None	Nasal & systemic steroids, single resection	+	+	PD
49/F		Nasal obstruction	Nose (septum)	None	Nasal & systemic steroids, single resection	+	+	PD
64/F		Nasal obstruction	Nose (septum & lateral wall), maxillary sinus	None	Nasal & systemic steroids, multiple resection	+	+	PD
Burns et al. [7]	38/M	Nasal obstruction & swelling	Nose (septum & lateral wall)	Granuloma faciale	Intra-lesional & systemic steroids, multiple resection, YAG laser	+	+	PD
Loane et al. [8]	42/M	Nasal obstruction, post-nasal drip	Nose (septum)	Wegener's granulomatosis, asthma	Immunosuppression, multiple resections		+	N/A
Pereira et al. [9]	52/M	Nasal obstruction	Nose (septum)	Allergic rhinitis	Partial resection	+	+	PD
Owa et al. [10]	41/M	Nasal obstruction	Nose (septum)	None	Single resection	+		FD
Goldman [11]	50/F	Nasal obstruction	Nose (septum & lateral wall)	None	Intra-lesional steroids, multiple resection			PD
Tabaee et al. [12]	79/M	Nasal congestion, swelling, tenderness	Nose (septum & lateral wall)	Granuloma faciale, c-ANCA, Squamous cell cancer, prior nasal surgery	Single resection		+	Resolution at 1 year follow-up
Onder and Sungur [13]	45/M	Nasal obstruction	Nose (septum)	None	Single resection		+	N/A
Chinell et al. [14]	31/F	Nasal obstruction	Nose (septum)	Granuloma faciale	Biopsy and dapsone	+	+	PD

Table 2 Literature review of reported cases of sinonasal eosinophilic angiocentric fibrosis

Report	Age/sex	Clinical symptoms	Site	Related findings	Treatment	EV	OS	Follow-up
Nguyen et al. [15] Narayan and Douglas-Jones [16]	31/F	Nasal obstruction	Nose (septum)	None	Single resection		+	N/A
	72/F	Nasal obstruction & swelling	Nose (septum & lateral wall)	Granuloma faciale	Biopsy		+	PD
Paun et al. [17]	37/F	Epistaxis, epiphora	Nose (lateral wall)	Granuloma faciale, penicillin-sensitive	Multiple resections, oral steroids and azathioprine			PD
	68/M	Nasal obstruction	Nose (septum)	None	Single resection	+	+	FD
Yung et al. [18]	57/F	Nasal obstruction	Nose (septum), orbit	None	Single resection, dapson, hydroxychloroquine, azathioprine, systemic steroids	+	+	PD
	58/F	Nasal obstruction	Nose (lateral wall)	None	Single resection		+	FD
	66/F	Recurrent epistaxis	Nose (septum)	Granuloma faciale	Biopsy	+	+	PD
	45/F	Recurrent epistaxis, nasal obstruction	Nose (septum & lateral wall), maxillary sinus	Granuloma faciale	Biopsy, oral prednisolone, azathioprine	+	+	PD
Holme et al. [19]	72/F	Nasal obstruction	Nose (septum & lateral wall)	Granuloma faciale	Biopsy, pulsed dye laser, dapsone and clofazimine		+	PD
	45/M	Nasal obstruction	Nose	Rheumatoid arthritis, chronic inflammatory bowel disease	Biopsy			PD
Clauser et al. [21] Watanabe and Moriaki [22] Nigar et al. [23]	31/M	Nasal obstruction	Nose (septum)	None	Single resection	+	+	PD
	51/M	Nasal obstruction	Nose (septum)	None	Single resection	–	–	FD
	67/F	Nasal obstruction & swelling	Nose (lateral wall), gingiva	Granuloma faciale	Single resection		+	PD
Present paper	31/F	Epiphora, orbital mass	Sinuses (maxillary, ethmoid), orbit	None	Multiple biopsies, steroids, single resection	–	+	PD
	57/M	Nasal congestion, epiphora, proptosis	Nose (lateral wall), multiple sinuses, lacrimal gland	Allergic rhinitis, peripheral eosinophilia	Steroids, single resection	–	+	PD
	27/F	Nasal obstruction	Nose (lateral wall)	Cocaine abuse	Biopsy	+	+	Lost to follow-up
	51/F	Nasal mass, obstruction & epiphora	Nose (lateral wall)	None	Single resection	–	+	PD

EV, eosinophilic vasculitis; OS, onion skinning; Blank, pathology not reported; PD, persistent disease; FD, free of disease; N/A, not available

Table 3 Differential diagnosis of eosinophilic angiocentric fibrosis in sinonasal and upper respiratory tract

Disease	Sites	Clinical presentation	Laboratory tests	Histopathological features
Eosinophilic angiocentric fibrosis	Upper respiratory tract, lacrimal sac, orbit	Nasal obstruction, epiphora, proptosis	None	Dense fibrosis with perivascular 'onion-skin' whorling pattern, eosinophil-rich inflammatory infiltrate
Wegener's granulomatosis	Upper respiratory tract, lungs, kidneys	Nasal pain, stuffiness, rhinitis, hearing loss, saddle-nose deformity (later stage)	Cytoplasmic (antiproteinase 3) c-ANCA positive (85%)	Geographic zones of bionecrosis, foreign-body giant cells, granuloma (rare)
Churg-Strauss syndrome	Upper and lower respiratory tract, skin, kidney, gastrointestinal tract, heart, nerve	Asthma, sinusitis	Blood eosinophilia, perinuclear (anti-myeloperoxidase) p-ANCA positive	Fibrinoid necrosis, extravascular granulomas with eosinophilia
Kimura's disease	Skin (head and neck)	Subcutaneous nodules, lymphadenopathy, salivary gland enlargement	Blood eosinophilia, raised ESR and serum IgE levels	Dense lymphoid aggregates with prominent germinal centers, fibrous tissue
Granuloma faciale	Skin (face)	Plaques and nodules	None	Polymorphous infiltrate (N, E) in the dermis, fibrosis, Grenz zone

ANCA, antineutrophil cytoplasmic antibodies; ESR, erythrocyte sedimentation rate; N, neutrophils; E, eosinophils

Follow-up and Treatment

In case #1, the patient was on steroid therapy and underwent surgical excision of the lesion. The lesion recurred after 4 years, and recently, the patient has developed shortness of breath and pulmonary nodularity. In case #2, the lesion was excised and the patient has been on Prednisone to relieve nasal congestion. He, too, has developed pulmonary symptoms.

Discussion

EAF is a rare benign lesion of the sinonasal and the upper respiratory tract, and rarely, subglottis and orbit [2, 24–27]. Since 1983, when it was first described by Holmes and Panje [1], there have been only 31 cases of EAF involving the sinonasal tract reported within the English literature to date (Table 2). Its etiology is unknown, although trauma and allergy have been implicated [2, 9]. Women are more commonly affected than men, but the reason is unknown. The symptoms are non-specific in all cases, and includes nasal obstruction, epistaxis, breathing difficulties, epiphora and less likely, proptosis; however, they tend to be chronic and progressive [1–23]. Radiographic evaluations are also usually non-specific and shows clouding and opacification of the nasal cavity and sinuses with or without bony erosion.

The histology of EAF is pathognomonic and is characterized by perivascular inflammatory cell infiltration with progressive fibrosis around small vessels, leading to a

characteristic 'onion-skin'-type pattern [2]. Eosinophils are the predominant inflammatory cells. The main histologic differential diagnosis includes lesions with prominent eosinophilic infiltrates (Table 3). Absence of geographic necrosis, necrotizing vasculitis, and granulomatous inflammation excludes Wegener's granulomatosis (WG) and Churg-Strauss syndrome (CS). Blood test positive for c-ANCA and p-ANCA supports the diagnosis of WG and CS, respectively. Absence of dense lymphoid aggregates with prominent germinal centers excludes Kimura's disease. Some authors have suggested an association between EAF and granuloma faciale, a benign cutaneous disease of unknown etiology characterized by sharply circumscribed plaques and skin nodules, with a predilection for the facial region [28]. While there are some histopathologic features in common among these diseases, granuloma faciale lacks the 'onion-skin' pattern of collagen whorling around a central vessel that is characteristic of EAF. The debate, therefore, continues as to whether EAF is a mucosal variant of granuloma faciale, or whether they are distinct entities [9, 12, 18]. Nasal polyps and chronic sinusitis are also included in the differential diagnosis, however, the presence of progressive inflammatory process should warrant further clinical, radiological and histologic evaluation.

Based on the literature to date, the most common treatment modality of EAF is surgical resection. The recurrence rate is extremely high, with persistence of disease seen following most nasal resections [2–4, 6, 7, 9, 11]. Other treatment modalities, including local and systemic corticosteroid therapy have been tried with minimal

clinical resolution of disease [2, 6, 7, 17, 18, 25]. No definitive treatment of choice has been recognized, and the etiology of EAF remains elusive despite the consistency of pathological findings in the described EAF cases.

In conclusion, EAF is a rare, benign, progressive fibro-inflammatory lesion of unknown etiology with predilection for the upper respiratory tract, especially the sinonasal tract. It is a diagnosis of exclusion. Surgical resection is the treatment of choice, though multiple procedures are often required. Though a possible association between GF and EAF, and WG and EAF have been reported, further case reports of this rare lesion are necessary before the etiology, pathogenesis and management can be clearly defined [1, 2, 7, 8, 12, 14–18, 23].

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