Case Presentation 17- Eosinophilic Angiocentric Fibrosis co-existing with Granuloma Faciale: A rare form of Tumefactive Fibrosing Vasculitis presenting as an Orbital Pseudotumor

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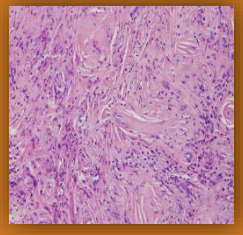
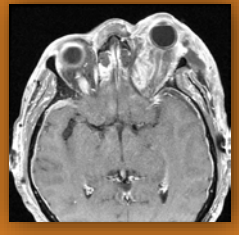
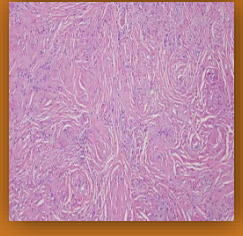
Weill Cornell Medicine Dermatopathology







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Clinical History

Our patient is a 67-year-old male with a history of unremitting chronic sinusitis. He was diagnosed with a pseudotumor of the orbit in 1996 after noticing blurry vision and a bulging left eye. He underwent radiation therapy, various medical treatments including corticosteroids, and chemotherapy, which were all ineffective in reducing the size of the tumor. Ultimately, the tumor was debulked. The diagnosis rendered at that time was fibrosis and chronic inflammation. The subsequent clinical course was one of recurrence and intractable progressive growth over a 1-2 year period. As the many pathology interpretations did not indicate a malignant process but rather one of scar-like fibroplasia, he was managed with intermittent debulking. He underwent five more rounds of debulking, with the second to last one being an osteoplastic frontal sinusotomy performed in 2015. The most recent radiographic images show a 4.2 x 2.9 x 4.1 cm retrobulbar mass causing left-sided proptosis which was inseparable from the optic nerve and ocular musculature (Figure 1). The most recent debulking specimen of presumed orbital pseudotumor was sent to our consultative dermatopathology practice for review. Of note, in 2015 prior to the most recent debulking, an asymptomatic cutaneous right cheek lesion was sampled, showing features consistent with granuloma faciale by the same consultant (CMM) .

Light Microscopy & Phenotypic Studies

The specimen showed an obliterative tumefactive fibrosing process that had a distinct whorled pattern storiform morphology. In particular, the collagen bundles were of wider caliber, exhibiting a hyalinized appearance showing a concentric onion skin pattern of fibroplasia around pre-existing blood vessels. While the dominant morphology was one of patterned angiocentric fibrosis, there were foci of nodular angiocentric inflammation comprising lymphocytes, plasma cells, and neutrophils with supervening leukocytoclasia and evidence of vascular compromise. The latter was characterized by focal hemorrhage along with mural and luminal fibrin deposition (Figure 2a-f). The material from the patient's prior debulking procedures was available and showed a similar pattern of angiocentric storiform fibrosis. The findings were held to be diagnostic of eosinophilic angiocentric fibrosis with co-existing granuloma faciale. Phenotypic studies conducted on the most recent debulking specimen revealed that the angiocentric infiltrate was predominated by a mixture of CD4+ T cells expressing GATA-3 and without staining for CXCR3 indicative of a Th2 T cell. In addition in certain high power fields there were over 100 IgG4 positive plasma cells per high power field.

Discussion

Eosinophilic angiocentric fibrosis (EAF) of the upper respiratory tract is a rare benign disorder of unknown etiology that is believed to represent a mucosal variant of granuloma faciale. Until 2003, only 14 cases of EAF had been described in the literature. The characteristic histological finding of a perivascular inflammatory infiltrate of neutrophils, lymphocytes and eosinophils with attendant mural and intraluminal fibrin deposition as well as onion skin whirling of stromal fibrotic tissue are useful for making the histologic diagnosis of EAF. Oftentimes and quite characteristically the dominant pattern is a pauci-inflammatory angiocentric fibrosing reaction without discernible vasculitic changes. Optimal treatment can be difficult as these cases respond poorly to oral medications. While the basis of the fibrosis is one that is undoubtedly cytokine driven with the initial lesion being a small vessel vasculitis the condition responds poorly to medical treatment and surgical excision of the fibrotic tissue of EAF remains s the most common modality used to treat anatomic obstruction (1). EAF represents a unique form of fibrosing small vessel vasculitis but is not associated with any systemic stigmata of vasculitis although co-existing cutaneous chronic small vessel vasculitis can occur in these patients falling under the designation of granuloma faciale. The first documented case is attributed to Homes and Panje who reported a case in 1983 of so called 'intranasal granuloma faciale,' recognizing its similarity to the cutaneous entity of granuloma faciale (2). The latter is a form of chronic cutaneous confined vasculitis with the majority of cases localized to the face and manifesting a peculiar predilection to involve middle aged men. Roberts and McCann subsequently introduced the term eosinophilic angiocentric fibrosis in 1985 (3, 4). In regards to the cutaneous equivalent namely granuloma faciale, this condition manifests as recurrent brown-red plaques on the forehead, cheeks, and ears with periods of relapses and partial remissions and in rare instances will co-exist with EAF (5).

Clinical demographics of EAF highlight several important patterns. There does not appear to be an obvious gender bias which of course is in contradistinction to the gender bias that one sees in granuloma faciale. Patients tend to be in overall good health, but there appears to be a higher incidence of allergic and atopic disorders in patients with EAF than in the general population. The reported age at diagnosis ranges from 25-79 years with a median of 49 years and a mean of 47 years. Patients often have a history of chronic symptoms; however, in some cases the symptoms may be significant including recurrent epistaxis and persistent nasal stuffiness. As with our patient the patients may be diagnosed as having chronic sinusitis. Given the supervening allergic history in a significant percent of patients, the diagnosis of chronic sinusitis is not unreasonable. Non-specific mucosal thickening and submucosal fullness may be seen on physical examination while a soft-tissue, polypoid mass may be detected on imaging (4, 6). In some instances however the vasculitis results in a saddle nose deformity reflective of insidious tissue ischemia. Conversely in cases where there is excessive fibroplasias, a convex hook nose deformity may eventuate.

There are two defining morphologic features of EAF: vasculitis and fibrosis. In this regard, there are two separate histologic phases reflecting the temporal evolution of these lesions. Early lesions show an active necrotizing vasculitis affecting capillaries and venules with a prominence of eosinophils in an angiocentric array. The more advanced lesions show a characteristic laminated scalloped pattern of fibrosis with accentuation around chronically injured vessels. The vessels typically show an onion bulb like pattern of laminated fibrosis, which can become very striking. Unlike classic cutaneous GF, in AEF the vasculitic changes may be very subtle while the fibrosis is extensive (4).

Other causes of extensive upper airway and orbital tumefactive fibrosis would encompass two principle entities, namely Erdheim Chester disease and idiopathic fibrosis. Erdheim-Chester disease is a rare non-Langerhans' cell histiocytosis. About half of those affected have extraskeletal manifestations, with extensive fibrosis involving the hypothalamus-pituitary axis, lung, heart, retroperitoneum, skin, liver kidneys, spleen, and orbit (7). Idiopathic fibrosis typically involves the retroperitoneum and mediastinum (8). However, involvement of the orbit has been described (8, 9). Cases showing dominant involvement of the nasopharynx have not been described. Furthermore, neither condition has inherent vasculitis.

Angiocentric eosinophilic fibrosis is not typically associated with lethal midline granuloma-like lesions although we have encountered cases showing extensive nasal fibrosis and obstruction as well as clinical features of lethal midline granuloma by virtue of the degree of destruction of the soft palate and uvula. The etiology of EAF remains elusive; however, there appears to be a higher incidence of allergic and atopic disorders consisting of asthma, drug allergy, environmental allergy, urticaria or allergic rhinitis in patients with EAF than in the general population(10,11,12). A potential trigger (viral or drug) may evoke a Type III hypersensitivity reaction; the tissue eosinophilia and extensive collagen synthesis suggests a Th2 dominant cytokine milieu (1). In addition, the patterned fibrosis is reminiscent of the laminated whorled fibroplasia seen in the setting of IgG4 positive sclerosing disease. This observation prompted the evaluation of these cases for the presence of IgG4 positive plasma cells in cases of EAF. Indeed there is at least a subset of cases of EAF which fulfill criteria to warrant categorization as a form of IgG4 related sclerosing disease,the latter encompassing a myriad of conditions characterized by the constellation of tumefactive fibroplasia with or without high serum IgG4 and increased numbers of IgG4 positive plasma cells on biopsy with an elevated IgG4 positive plasma cell to IgG positive plasma cell ratio in excess of 0.40. As with EAF, a significant percent of patients with IgG4 sclerosing disease have an allergic diathesis suggesting an interplay

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between what might be a Th2 dysregulatory state and a tendency for excessive production of polytypic IgG4 positive plasma cells. Recognizing the potential categorization of EAF as a form of IgG4 reactive sclerosing disease has critical therapeutic implications in regards to the administration of glucocorticoids and rituximab. One would expect a similar positive response as that noted in the setting of other forms of IgG4 reactive sclerosing disease(10). Mechanistically if one is to assume that EAF is part of the IgG4 reactive sclerosing diseases then a Th2 dominant immune dysregulatory state could define a critical impetus to the disease process. The Th2 cytokines interleukin 4 and interleukin 10 are able to class switch plasma cells into producing IgG4, normally the least common of all immunoglobulins. In addition other Th2 cytokines namely interleukin 13 and TGF beta are potent fibrogenic cytokines. Hence the actualy fibrosis per se may not be specifically induced by the IgG4 but rather may be the sequelae of a dysregulated Th2 dominant microenvironment. .If indeed an abnormal Th2 immune response is a driving force behind this disorder then interleukin-2-inducible kinase becomes an important therapeutic target since its ablation would subvert Th2 immunity. Ibrutinib is a potent ITK inhibitor that could prove to be useful in the treatment of this disorder.

Treatment of eosinophilic angiocentric fibrosis remains quite difficult. Oral corticosteroids, intralesional corticosteroids, as well as dapsone have been utilized for treatment with limited results. Local resection may result in progressive or persistent disease, as in our patient. There have been two reported cases where wide local excision in subglottic cases of EAF resulted in complete resolution of the disease (1, 6). However with the purported mechanisms involving T cells and IgG4 elaborating plasma cells immunomodulatory drug therapy suppressing the Th2 response such as ibrutinab and potentially depleting B cells (i.e. Rituximab and glucocorticoids) defines a logical approach based on proposed pathogenetic mechanisms that underlie this condition. In our patient the extent of Th2 T cell infiltration along with the degree of IgG4 plasma cell infiltration would certainly suggest a combined biologic approach to prevent recurrence of his disease.

Figure Legend

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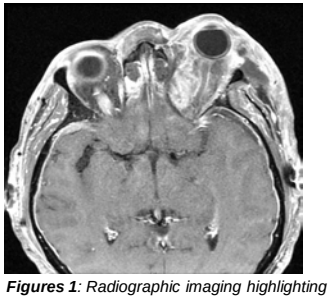

Figures 1*: Radiographic imaging highlighting an intraorbital soft tissue mass. This is from a sequence from the patient's MRI Brain with contrast study.*

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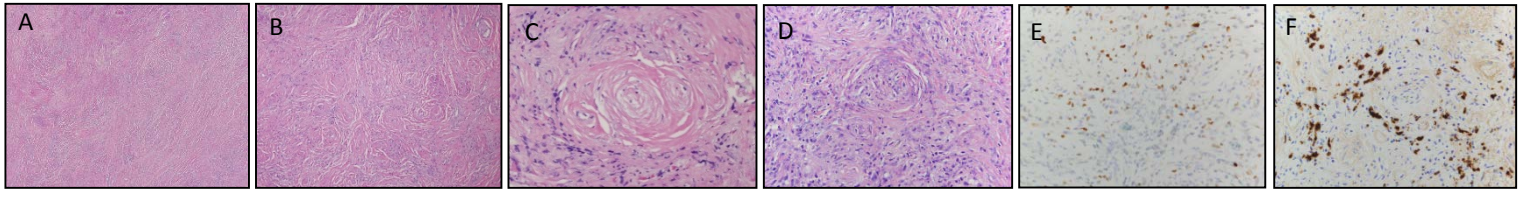

Figures 2A-F*: Light microscopy photomicrographs showing the salient features in EAF. (A-C; 4x, 10x, 20x respectively) The tumor has a distinct whorled pattern storiform morphology with a concentric onion skin pattern of fibroplasia around pre-existing blood vessels. There is a discernible inflammatory cell infiltrate. (D)There is a residual inflammatory vasculitic process within the vessels, defining the incipient prefibrotic lesion in EAF. (E) There is a Th2 dominant cytokine milieu as revealed by the extent of staining for GATA3. (F) Many IgG4 positive plasma cells are observed.*

Case References

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Under the direction of Dr. Cynthia M. Magro, the Weill Cornell Comprehensive Dermatopathology Service is a leading edge consultation service and CAP-accredited laboratory for dermatologists, plastic and general surgeons and other dermatopathologists. Dr. Magro is an internationally renowned dermatopathologist, educator and author. She is a Professor of Pathology and Laboratory Medicine at the Weill Cornell Medical College in Manhattan, and is board certified in anatomic pathology, dermatopathology and cytopathology. Dr. Magro is an expert in the diagnosis of complex inflammatory skin diseases. Her areas of expertise include cutaneous manifestations of auto-immune disease, systemic viral disease and vasculitis, atypical drug reactions, benign, atypical and overtly malignant lymphocytic infiltrates of the skin, and diagnostically difficult melanocytic proliferations.The award-winning author of *The Melanocytic Proliferation: A Comprehensive Textbook of Pigmented Lesions*, Dr. Magro has recently completed her second book, *The Cutaneous Lymphoid Proliferation, a comprehensive textbook on benign and malignant lymphocytic infiltrates*. She has co-authored over 300 peer reviewed papers and several textbook chapters. Dr. Magro frequently presents courses on inflammatory skin pathology and difficult melanocytic proliferations to the American Academy of Dermatology, the United States and Canadian Academy of Pathology, and the American Society of Clinical Pathology. Dr Magro has consistently been recognized in Who's Who in America®, Castle Connolly's renowned America's Top Doctors – New York Metro Area® edition and in the Super Doctors® list published in The New York Times Magazine.

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