Clinical Pathologic Conference Case 1: Wegener's Granulomatosis

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Received: 7 June 2011 / Accepted: 10 August 2011 / Published online: 23 August 2011
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History

A 75-year-old female with a 2-year history of Stage 3B infiltrating ductal carcinoma of the breast, status post mastectomy and chemotherapy, presents with complaints of recurrent sinus congestion with associated crusting. Over a 3-month period she developed a 2.5 cm defect of her forehead exposing her frontal sinus along with collapse of her nasal cartilage (Fig. 1). Otherwise, the patient had no complaints of headaches, visual changes, nor was there evidence of altered mental status. A sinus CT revealed evidence of “postsurgical changes from endoscopic sinus surgery” (Figs. 2, 3).

Differential Diagnosis

Several entities were considered for the differential diagnosis of bone loss and septal perforation. These were divided into neoplasms (benign, primary malignant or metastatic breast carcinoma), infections (fungal, bacterial or other), trauma, Wegener's granulomatosis, avascular necrosis as a complication of chemotherapy (Bisphosphonates or Avastin) and Cocaine abuse.

Primary neoplasms of the sinuses include Schneiderian papilloma, squamous cell carcinoma and variants, salivary gland neoplasms, and lymphoma [1]. Schneiderian papilloma is a benign neoplasm of respiratory mucosa that usually presents with nasal obstruction, stuffiness, or epistaxis and can cause bone erosion. Minor salivary gland tumors uncommonly arise in the nasal cavity and sinuses, usually in the nasal septum and the majority of these are usually malignant. Lymphomas may present as a sinonasal mass and are almost always non-Hodgkin's lymphoma. Metastatic breast carcinoma was also considered because of the patient's history. If a mass were present, then a biopsy would render a definitive diagnosis. However, these neoplastic processes were ruled out based on the fact that no evidence of a mass was seen on CT (Figs. 2, 3).

Also considered were infectious etiologies, including leprosy, congenital syphilis and fungal infections such as Aspergillosis and Mucormycosis, as well as chronic rhinosinusitis. Invasive Aspergillosis and Rhinocerebral mucormycosis are relatively common life-threatening fungal infections, associated with immunosuppression. Spread is rapid across nerves and tissue planes to blood vessels of the orbit and brain and causes thrombosis, hemorrhage and infarction [2]. Leprosy affects the nasal mucosa in 95% of patients and may be the initial manifestation of the disease. It usually affects the nasal septum and inferior turbinates [2]. Diagnosis is through a biopsy and identification of acid fast organisms. Late congenital syphilis can also present as a saddle nose deformity but is usually accompanied by other stigmata characteristic of the disease. Blood tests and identification of spirochetes in a biopsy would definitively rule out syphilis [2]. Chronic rhinosinusitis can show some of the CT findings present in the current case, including mucosal thickening and osteoneogenesis. However, no sinus opacification is present, air

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Fig. 1 75-year-old woman with a 2.5 cm defect of the forehead with direct communication with the frontal sinus. The nasal bridge is collapsed, resulting in a saddle nose deformity

Fig. 2 Coronal sinus CT showing extensive erosion of the septum and left turbinates and ethmoid sinus. Osteoneogenesis of the left frontal and maxillary sinus with mucosal thickening is present

fluid levels are not noted and the degree of bone erosion would be most unusual.

Wegener's granulomatosis is a rapidly progressing granulomatous condition involving nasal cavity, lungs and kidney. Blood tests for c-ANCA and PR-3 and histopathologic examination would be necessary for a diagnosis of Wegener's granulomatosis to be reached. Due to the atypical presentation (especially the defect of the forehead), Wegener's granulomatosis was also considered unlikely. Although rare, several reports in the literature are confirming the association of anti-vascular endothelial growth factor and chemotherapy as risk factors in nasal

Fig. 3 Axial sinus CT demonstrating the cutaneous defect of the forehead with bone erosion of the frontal sinus

septum perforation and avascular necrosis of bone [3–5]. Lastly, thorough investigation of the patient's social and medical history further ruled out the use of recreational drugs and possible trauma and/or sinus surgery, respectively.

Diagnosis and Discussion

The patient had complaints of sinus congestion for 1 year, with crusting of the nares. A 3 month history of collapsing nasal cartilage with development of a saddle nose deformity was noted by the referring physician. At the same time, a 2.5 cm defect of the forehead that exposed the frontal sinus developed (Fig. 1). Endoscopic examination revealed a large septal perforation but otherwise healthy sinus mucosa without ulceration or necrosis. A biopsy of the mucosa near the forehead defect was obtained and submitted for flow cytometry and fungal cultures. An additional biopsy of frontal sinus mucosa for routine pathology was collected. A sinus CT was ordered as were laboratory studies.

Radiographic findings included a large bony defect of the maxillary sinus with partial absence of the inferior turbinates (Fig. 2). The patient had no history of sinus surgery. Evidence of osteoneogenesis was present in the left maxillary sinus and ethmoid air cells. A destructive defect of the nasal septum was seen with flattening of the nasal bridge, more so on the left side. A large 3.6×2.4 cm osseous defect of the anterior wall of the frontal sinus that communicated with the overlying cutaneous tissue was seen (Fig. 3).

Laboratory studies were positive for c-ANCA (1:20) and negative for p-ANCA. Her PR-3 was significantly elevated at 70.2 EU/ml (normal < 5.0) and her anti-myeloperoxidase levels were normal. All other blood work was reported negative or in the normal range. Flow cytometry and fungal cultures were negative.

The biopsy of the skin demonstrated a mixed inflammatory cell infiltrate composed chiefly of lymphocytes and plasma cells, but also with histiocytes and granulocytes. Focal necrosis was seen and microabscesses were identified that were negative for organisms by GMS stain (Fig. 4). The biopsy from the frontal sinus showed scattered giant cells within a polymorphous inflammatory cell infiltrate adjacent to viable cortical bone exhibiting resorption (Fig. 5). Focal areas of tissue necrosis with a smudgy, basophilic appearance were noted (Fig. 6).

Further clinical workup included a chest CT which showed evidence of pulmonary nodules. The patient also had complaints of bilateral hearing loss and on examination chronic suppurative otitis media of the left ear was diagnosed. No renal involvement was present. Combining the results of the clinical, radiographic, and pathologic findings the patient was diagnosed with Wegener's granulomatosis, localized form. The patient was treated with Cyclophosphamide, trimethoprim-sulfamethoxazole and Prednisone with good results. The patient developed cytopenia after 1 year of treatment and discontinued the cyclophosphamide with no subsequent progression of her disease. The forehead defect was repaired and the patient had excellent

Fig. 4 A biopsy from the cutaneous forehead defect shows a polymorphous inflammatory cell infiltrate, which lacks atypia. A neutrophilic microabscess is present. There is no evidence of vasculitis in this biopsy

Fig. 5 A biopsy from the frontal sinus shows a mixed chronic inflammatory cell infiltrate with numerous scattered multinucleated giant cells, but well-formed granulomas are not present. The bone exhibits active resorption. No vasculitis was present on this biopsy

Fig. 6 High power photomicrograph illustrating areas of necrosis with a basophilic smudgy appearance (arrows)

healing of her surgical site (Fig. 7). The pulmonary nodules have remained stable on radiographic examination and it is uncertain as to whether they are related to the patient's diagnosis of WG since they have never been biopsied. Five years after her initial presentation, she has had no progression of her disease.

Fig. 7 The patient had her cutaneous defect repaired 1 year after her initial presentation

Wegener's Granulomatosis (WG) is an idiopathic, non-neoplastic systemic vasculitis originally described as affecting a triad of organ systems: lung, upper respiratory tract, and kidneys. WG is of unknown etiology but thought to be an autoimmune disorder. Elevated antineutrophil cytoplasmic antibody (ANCA) is a distinctive serologic finding in WG with a reported specificity of up to 98% of cases [5].

WG is characterized by aseptic necrotizing granulomata in combination with vasculitis of small and medium vessels and focal or proliferative glomerulonephritis [5]. Most patients do not present with this classic clinical triad at presentation and localized or limited forms of the disease involving a single organ system exist [6]. Localized upper aerodigestive tract WG affects men more than women with the exception of laryngeal WG. The sinonasal region is the most common site of head and neck WG, noted in up to 90% of cases [6]. The nasal cavity is the most frequent location followed by the maxillary, ethmoid, frontal, and sphenoid sinuses.

Clinical findings of sinonasal WG vary widely with mild changes such as nasal obstruction, rhinorrhea, and anosmia easily mistaken for nasal allergies or upper respiratory viral infection [7]. Advanced WG can present with septal perforation, epistaxis, pain, epiphora due to obstruction and/or blockage of the lacrimal duct, and a foul-smelling mucopurulent discharge. Nasal septal perforation is a common finding resulting from necrosis of the cartilage in the anterior nasal septum due to vasculitis in the area of the

vascular convergence known as Kiesselbach's plexus [5]. Septal perforation can progress to a saddle nose deformity in up to 25% of patients with nasal WG [6]. Nasal examination often reveals nasal crusting, edema, and mucosal cobblestoning. Superinfected stagnant mucous can coat the nasal cavity.

Radiographic findings of sinonasal WG on computed tomography (CT) scan vary with disease extent. Bony obliteration of the sinuses, septal and turbinate bone erosion, as well as sinus osteoneogenesis are some specific changes noted in sinus CT scans in WG patients [8]. It has been hypothesized that these bony changes are due to a chronic periostitis from the vasculitis and granulomatous inflammation. Other possibilities include periostitis due to bacterial infection common in WG patients [8].

Classically, a triad of microscopic findings of vasculitis, granulomatous inflammation and tissue necrosis are described. However, rarely will all three histologic features be present in sinonasal WG in a single or even multiple biopsies. One study reported that only 16% of biopsies in head and neck WG have all three defining criteria and in most cases (50–65%) only one criterion is found in the biopsy of the nose [5, 9]. Despite these drawbacks, biopsy remains an integral component of a diagnostic workup in patients suspected to have WG.

Vasculitis can be difficult to identify histologically and may be absent. The inflammatory cell infiltrate is polymorphous, composed of lymphocytes, histiocytes, and less often, eosinophils and neutrophils. Both angiocentric and angioinvasion of the inflammatory cells can be present and thrombosis can occur. Vasculitis is not limited to WG and can be seen in other disease processes. Infectious diseases including mucormycosis and aspergillus, as well as NK/T cell lymphoma can have angiocentric inflammatory cell infiltrates [1]. The granulomas in WG are not well-formed and contain multinucleated giant cells. The connective tissue stroma usually contains a polymorphous inflammatory infiltrate and micro-abscesses with or without granulomas may be identified. Necrosis within the connective tissue can be of an ischemic or geographic type (multifocal necrobiosis). The necrosis has a smudgy basophilic appearance. Histochemistry and immunohistochemistry are generally not useful in the diagnosis, but as WG is a diagnosis of exclusion, various stains can help in ruling out infection or lymphoma. Elastin stains may be helpful in highlighting the vasculitis.

Laboratory testing is critical for the diagnosis of WG. ANCA can be reported as cytoplasmic (c-ANCA) or perinuclear (p-ANCA) and WG is mostly associated with c-ANCA. A positive cANCA combined with positive anti-PR3 antibodies has a sensitivity and specificity of 90 and 98%, respectively, for WG [6]. c-ANCA and anti-PR3 antibody titers may reflect disease activity predicting a

disease flare or relapse. False positives can be seen however, including patients with midline destructive lesions due to cocaine inhalation abuse. In addition, about 10% of WG patient's have p-ANCA and some patients with WG have negative ANCA, but this is usually associated with the limited form of the disease [7].

Treatment of WG is dictated by disease extent but generally includes cyclophosphamide and prednisone along with trimethoprim-sulfamethoxazole, particularly for WG limited to the upper aerodigestive tract. Limited WG has a good prognosis and up to a 75% remission rate can be achieved, although relapses can occur. The goal of remission maintenance therapy is to limit morbidity associated with chronic immunosuppressive therapy while preventing disease relapse.

The sinonasal region is one of the most frequent sites for WG, particularly the limited forms of WG. A clinical suspicion for WG should be considered in patients with refractory sinus symptoms along with unusual radiographic findings. A single biopsy may not show all the microscopic features of WG. Multiple biopsies along with the appropriate laboratory studies accompanied by good communication between clinicians and pathologists will result in arriving at the diagnosis in a timely manner.

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