Background

Granulomatosis with Polyangitis (GPA) is a systemic disease characterized by necrotizing granulomatous vasculitis that involves a classic triad including the upper respiratory tract, lower respiratory tract, and kidneys. In 1897, Peter McBride, a Scottish physician, became the first physician to recognize and describe aspects of the disease. In 1931, Heinz Klinger added new pathological findings to McBride’s description. Friedrich Wegener, a German pathologist, further added to previous descriptions, bringing all of the aspects together, and clearly defined the disease in two different articles published in 1936 and 1939. In 1985, the discovery of c-ANCA (cytoplasmic antineutrophil cytoplasmic antibody) autoantibodies significantly enhanced understanding of the disease’s pathophysiology and opened the door for advancements in disease detection. After Wegener’s association with the Nazi party became widely publicized in 2011, several medical societies decided to rename the disease to Granulomatosis with Polyangitis (GPA).

Epidemiology

The incidence of GPA varies in the literature, but the disease has an average reported incidence of 1-2 cases per 100,000 in the U.S. The most common age range for presentation is between 30-50 years old, but this is variable as well. Males and females are equally affected by the disease, and unlike most autoimmune disorders, caucasians represent the majority (about 90%) of patients affected.

Etiology

The exact etiology of GPA has yet to be scientifically proven. Many believe that the cause is autoimmune in the form of c-ANCA autoantibodies. Cytoplasmic antineutrophil cytoplasmic antibodies target proteinase-3, a serine protease enzyme present in neutrophils. It is believed that through their interaction with proteinase-3, c-ANCA autoantibodies cause activation of neutrophils that results in increased
adherence to blood vessel endothelium and degranulation of neutrophil granules. However, a complex of c-ANCA autoantibodies bound to circulating neutrophils has yet to be isolated, and thus, this theory remains scientifically unproven. Other theories include molecular mimicry secondary to exposure to drugs, bacteria, viruses, or environmental toxins and genetic factors that predispose to developing the disease.

**Prognosis (Systemic GPA)**

The prognosis for systemic GPA has improved significantly in recent decades. However, if left untreated, GPA is a fatal disease. Left untreated, systemic GPA has a mortality rate of about 80% at 1 year and 90% at 2 years after disease onset. With appropriate treatment, the 5-year survival rate has risen to around 90%. Disease remission with treatment is possible, and there are reports of patients being in remission for over 20 years after receiving treatment. However, 50% of patients experience flare-ups or relapse within 2 years of achieving disease remission.

**Pathology**

Proteinase-3 is a serine protease enzyme that is associated with the primary (azurophilic) granules located in the cytoplasm of neutrophils. c-ANCA autoantibodies target proteinase-3, and this interaction is believed to cause neutrophil activation (e.g. endothelial adhesion) and degranulation. With increased neutrophil adhesion to endothelium, degranulation of the primary granules releases several enzymes (i.e. Myeloperoxidase, Bactericidal/Permeability-Increasing protein [BPI], Defensins, Neutrophil Elastase, and Cathepsin-G) that directly damage the endothelial cells. In addition, neutrophils may also release cytokines and chemokines that can exacerbate the process through increased expression of endothelial adhesion molecules and recruitment of additional neutrophils and other immune cells. This process ultimately results in a localized or systemic small vessel necrotizing vasculitis with granulomatous inflammation that primarily involves small-to-medium sized blood vessels.

**Presentation**

Head and neck manifestations represent the first symptom(s) experienced in approximately 70% of patients presenting with Granulomatosis with Polyangitis, and of these manifestations, sinonasal symptoms are the most common. More specifically, recurrent or chronic rhinosinusitis that is unresponsive to traditional treatment is the most common initial presentation of the disease. Other symptoms such as nasal obstruction, septal perforation, and recurrent epistaxis are also common sinonasal symptoms. Saddle-nose deformity may occur secondary to a perforated nasal septum, and it does not usually appear until later in the disease process. The saddle-nose deformity may also occur in other conditions, such as congenital syphilis, cocaine abuse, and relapsing polychondritis.
Otologic manifestations in GPA are relatively rare, and their incidence reported in the literature varies from 5% to 50%. The most common otologic manifestation is serous otitis media with or without CHL (conductive hearing loss), and it is usually due to the presence of granulation tissue in the middle ear or nasopharynx resulting in eustachian tube dysfunction. Acute and chronic otitis media occur less frequently and can result in mastoiditis if left untreated. Furthermore, patients may also develop SNHL (sensorineural hearing loss). The leading theories for the cause of the SNHL associated with Wegener’s includes compression of CN VIII by granulomatous tissue, vasculitis of the cochlear vasa vasorum or the vasa nervosum of CN VIII, and immune complex deposition in the cochlea (presumably damaging the cochlea’s hair cells).

Involvement of the larynx and trachea is not uncommon, and subglottic ulcerations or stenosis is the most common manifestation reported. Although variable in the literature, subglottic involvement is present in 5-20% of presenting patients, and subglottic stenosis (SGS) develops in approximately 20% of cases. Patients typically present with varying degrees of biphasic stridor, dyspnea, or hoarseness, and if these symptoms are not put into context, patients are in danger of having their time-to-diagnosis prolonged. Unlike other etiologies of subglottic stenosis, the subglottic involvement seen in Wegener’s Granulomatosis is usually localized to approximately 1.5-2 cm below the true vocal cords and above the trachea. The theory for this localization is that subglottic vessels are inherently predisposed to being affected by disease (i.e. vasculitides) because they are located at a junction of two embryological growth centers.

Pulmonary disease develops in approximately 80% of cases (present in 40% of patients at initial presentation). Symptoms of pulmonary involvement include cough, stridor, hemoptysis, and dyspnea. Patients suspected of having pulmonary involvement should undergo radiological imaging for confirmation. Imaging tends to show multiple bilateral, cavitating infiltrates or nodules that tend to wax and wane in appearance. The nodules may be as large as 10 cm, and 25% of nodules larger than >2 cm will have cavitations, which can be foci for concomitant infections. Ground glass opacities or the “Halo sign” (pulmonary hemorrhaging) around the nodules and consolidation are common as well.

Renal disease develops in about 75% of patients with systemic disease. Renal involvement is usually subclinical until the patient develops renal failure, and patients may experience malaise, fever, and weight loss. The most common form of renal disease seen in GPA is Crescentic or Rapidly Progressive Glomerulonephritis.

**Differential Diagnosis**

The differential for Granulomatosis with Polyangitis is broad and includes Churg-Strauss Syndrome (p-ANCA), Microscopic Polyangitis (p-ANCA), Sarcoidosis, Rheumatoid Arthritis, and infection (especially fungal and mycobacterial). The presenting symptoms and extent of disease involvement at the time of presentation
will affect each patient’s differential. Of the three small-vessel vasculitides, GPA is more commonly associated with c-ANCA autoantibodies, whereas Churg-Strauss Syndrome and Microscopic Polyangitis are more commonly associated with p-ANCA autoantibodies; however, these associations are not absolute, and by itself, the presence of either of the ANCA antibodies is not sufficient to completely rule out the other small-vessel vasculitides.

Workup and Diagnosis

The clinical presentation and exam findings are an essential piece of the puzzle in the diagnosis of Granulomatosis with Polyangitis (GPA). Because of the wide ranges in both disease severity and involvement (i.e. systemic or localized), it is not uncommon for these patients to go undiagnosed or be misdiagnosed at the time of their initial presentation. It is important that the patients’ presentation, history, and physical exam findings are recognized and correctly correlated in order for the treatment team to proceed with a workup that will yield the correct diagnosis.

The gold standard for the diagnosis of GPA remains a tissue biopsy of diseased tissue showing a triad of vasculitis, necrosis, and granulomatous inflammation. Histologically, the classic description is that of a necrotizing vasculitis with granulomatous inflammation consisting of multinucleated giant cells and palisading histiocytes. If the pulmonary system is involved, lung biopsies are the most reliable for histological diagnosis, and nasal biopsies are associated with more false-negative results than either lung or renal biopsy.

In regard to using c-ANCA autoantibodies as a tool for diagnosing GPA, the specificity of c-ANCA has been reported to be as high as 98%, and the sensitivity of c-ANCA varies with disease activity: 90% (active systemic), 60% (localized), and 30% (remission). Although c-ANCA antibodies are highly suggestive of GPA, their presence is not sufficient for definitive diagnosis. It has been reported that p-ANCA is the primary antibody present in approximately 10-25% of patients with GPA, and there are some cases of GPA in which no ANCA antibodies are present. In cases of GPA with a positive ANCA test result, it has been shown that the ANCA titer may be used as a marker to follow disease activity (e.g. in a patient whose disease is in remission, increasing titers may herald an impending relapse).

Since there is not always a “surefire” test that diagnoses each case, the most reliable path to arriving at a diagnosis of GPA is for the treatment team to recognize GPA as a possible diagnosis, proceed with the appropriate workup, analyze the various test results, and then correlate all of the results with the clinical picture on an individual basis.

All specimens or biopsies taken should also be cultured to rule out infectious causes of granulomatous inflammation (e.g. Fungal, TB). CXR or CT may also be performed if there is suspicion of pulmonary involvement. Imaging usually shows
consolidation or multiple bilateral opacities (nodules) with or without cavitations. A urinalysis should be obtained to assess for renal involvement as well. Other tests that may be appropriate in the workup for GPA include: sinus films, Basic Metabolic Panel, ESR, CRP, autoimmune panel, and a VDRL or RPR to screen for syphilis.

Treatment

After diagnosis, the treatment for GPA is aimed at inducing remission of the disease using a combination of cyclophosphamide and a corticosteroid. Cyclophosphamide is continued for a period of 6-12 months, but treatment is sometimes switched to Methotrexate or Azathioprine during this time because of their less toxic side effects. Corticosteroid treatment is gradually tapered and is normally continued for at least 1 year. After disease remission is achieved, Bactrim is commonly used for disease prophylaxis, but its mechanism of action for preventing relapse is currently unknown. Bactrim also provides bacterial prophylaxis in these patients, as most of them receive immunosuppressant therapy. In cases of severe or resistant disease, Rituximab, Infliximab, Etanercept, or Lefunomide may be used concurrently with corticosteroids. In cases with sinonasal involvement, saline irrigations (with or without antibiotics) are essential to prevent scabbing and scar formation.

The treatment of subglottic stenosis (SGS) associated with GPA is unique when compared to the treatment of SGS associated with other etiologies (e.g. trauma). Because the stenosis results from vasculitis secondary to a systemic autoimmune disorder (GPA), in addition to relieving the local stenosis, the treatment must focus on controlling or reversing the systemic process that underlies the condition. In some cases, stenosis may resolve with systemic corticosteroids and immunosuppressant therapy as outlined earlier. For patients that don’t respond to medical treatment alone, dilation of the stenotic ring is indicated. In this procedure, methylprednisolone acetate is normally injected into the stenotic segment, then endoscopic lysis of the stenotic ring with microlaryngeal blades is performed, and lastly, serial dilatation is performed with Maloney dilators or a Fogarty catheter balloon. Topical Mitomycin-C may be used at the end of the procedure to inhibit fibrosis and scarring, but its efficacy in is controversial in this case since most GPA patients with SGS display old, advanced scarring. For patients with severe acute or chronic airway compromise, a temporary or permanent tracheotomy may be indicated, respectively. Other therapies (i.e. laser therapy, local resection, laryngotraheal reconstruction) that may be used to treat SGS associated with other etiologies (e.g. trauma) are less efficacious in treating SGS associated with GPA because these treatments do not treat the underlying systemic cause, and for this reason, these treatments are generally not advised in GPA patients with SGS.
References


