CLINICAL REPORT

Granulomatosis with Polyangiitis (Wegener's) and Review of Latest Updates on Pathogenesis and Treatment

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Introduction

Case

A 24-year-old man without significant past medical history presented to a local emergency room with a 2-week history of fevers up to 39.4°C, night sweats, malaise, and sinus congestion. He was in his usual state of health up until 5 weeks ago when he developed a runny nose that subsequently progressed to nasal congestion, sinus pressure, and headaches. He was seen by multiple physicians and given several courses of antibiotics, nasal decongestants, and antihistamines without relief.

He was also prescribed prednisone 20 mg daily, which he took for 2 weeks before he discontinued due to undesirable side effects that included insomnia, increased appetite, and bloating.

Review of systems was notable for joint pains, left ear hearing loss, redness of the eyes with decreased visual acuity, epistaxis, chest pain with deep inspiration, palpitations, cough productive of blood-tinged yellow mucus, numbness and tingling in both feet, and generalized weakness.

His family history is relevant for a grandmother with systemic lupus erythematosus (SLE). There is no history of tobacco, alcohol, or illicit drug use.

His only medication was acetaminophen as needed for fevers and aches.

Vital signs on presentation were temperature 37.2°C, blood pressure 108/70, and heart rate 107 with oxygen saturation of 99% on ambient air.

Clinical exam revealed a tired appearing young man who was in no acute distress. He had bilateral conjunctival injection and friable nasal mucosa. His lungs were clear and heart exam was notable for tachycardia with normal S1 and S2 and no evidence of murmurs, rubs, or gallops. His abdomen was soft and non-tender. Joint exam revealed no evidence of tenosynovitis. The rest of his exam was unremarkable.

Laboratory investigations by the emergency room revealed the following abnormalities:

- WBC 23 x 10E3/uL (Neutrophil 88.5%, Eosinophil 3.2%)
- Creatinine 1.55 mg/dL
- ESR 95 mm/hr
- C-reactive protein 286 mg/dL
- UA: 100 protein 21-40 WBC, 60+ RBC's, 4-5 granular casts
- Urine protein-creatinine ratio 0.77 mg/mg (<0.2mg/mg)

Radiologic studies showed (Figure 1):

- A normal chest radiograph
- CT sinuses

Given the clinical presentation and abnormal studies concerning for vasculitis, the patient was admitted to the hospital.

Rheumatologic labs included elevated c-ANCA and Proteinase 3 Antibody with titers of 1:80 and 56.9, respectively. ANA, Anti-double-stranded DNA, C3 and C4 complements, p-ANCA, and Myeloperoxidase Antibody (MPO) titers were all within normal limits.

Infectious testing included unremarkable HIV, HSV ½, and syphilis serologies. His Mycobacterium tuberculosis QuantiFERON test was indeterminate, but sputum AFBs and TB antigen were negative.

The patient's rising creatinine, abnormal proteinuria, and declining urine output prompted a kidney biopsy.

The final surgical pathology report of the kidney biopsy showed diffuse segmental necrotizing and extracapillary proliferative glomerulonephritis with cellular crescents in 5 of 16 glomeruli, consistent with ANCA-associated glomerulonephritis.

A diagnosis of Granulomatosis with polyangiitis was established given the clinical presentations, laboratory abnormalities of elevated c-ANCA and Proteinase 3 antibody

titers, and biopsy results. The patient was started on a combination of glucocorticoids and rituximab.

Discussion

Presentations and diagnosis

Granulomatosis polyangiitis (GPA) is an immune-mediated disease caused by a combination of non-specific inflammation and specific immune-mediated damages, leading to small and medium-vessel granulomatous inflammation. GPA most commonly affects ear, nose, and throat (ENT), upper and lower respiratory systems, and kidneys; however, skin and joints can be frequently involved, while peripheral nervous system and gastrointestinal tracts are less commonly affected (Table 1).

Table 1. Symptoms and Signs of GPA.

Organ System Involved	Symptoms and Signs	Frequency
Constitutional Features	Fatigue, malaise, fever, night sweats, anorexia, weight loss	Very common
Ears and Eyes	Otorrhea, eye redness, pain, and blurry vision	Common
Upper Respiratory System	Rhinorrhea, nasal congestion, sinus pain, epistaxis, hoarseness, oral/nasal ulcers	Very common, often the initial presenting symptoms
Lower Respiratory System	Cough, dyspnea, hemoptysis, crackles, rhonchi, and focal dullness to percussion	Common
Renal System	Microscopic hematuria and RBC casts; late manifestations include lower extremity edema and hypertension	Common
GI System	Nausea, vomiting, diarrhea, abdominal pain, blood or mucous in stool	Uncommon
Nervous System	Peripheral neuropathy including numbness and tingling with preservation of sensorimotor function in general	Uncommon
Skin and Musculoskeletal System	Rash, petechial and purpura, myalgia, arthralgia, joint swelling	Common

Commonly, chronic sinusitis unresponsive to antibiotic treatment is an initial presentation. GPA should be suspected in patients with multi-system inflammation based on history and physical exam. Diagnosis of GPA is aided by laboratory and radiographic findings suggestive of pulmonary and renal involvement and positive ANCA serology.

Confirmation is obtained through tissue biopsy of the involved organs, most often kidney or lung, demonstrating necrotizing vasculitis, granuloma formation, and minimal/absent immune complex deposits on immunofluorescence staining or electron microscopy (Table 2).

Table 2. Diagnostic tests and their utilities in GPA.

Tests	Findings	Utilities
CBC	Anemia	Required; abnormalities in WBCs and platelets may suggest alternative diagnosis
BMP	Elevated Cr	Required to assess renal function and other electrolyte abnormalities
ESR and CRP	Elevated	Required; indicative of inflammatory states, elevated in vasculitides and other autoimmune diseases
Urinalysis	Hematuria, proteinuria, RBC casts	Required to assess renal pathology; often first abnormal findings, prior to Cr elevation
CXR/CT Chest	Pulmonary nodules (may show cavitation), diffuse ground glass infiltrates	Required to assess pulmonary involvement; CT chest is preferred over CXR
ANCA Serology	Positive in 85% of the cases (75% c-ANCA (PR3) and 10% p-ANCA (MPO))	Required, although 15% of GPA may be ANCA negative
Other Autoantibody Tests	Negative ANA, anti-GBM	Useful to rule out SLE and Goodpasture's disease
Tissue Biopsy	Necrotizing vasculitis, granuloma formation, minimal to absence immune complex deposits	Sometimes not required, but should be obtained whenever possible to confirm diagnosis and rule out other etiologies; radiographic abnormal lung tissue or renal tissue are preferred; ENT biopsy has a low yield (~20%) while skin biopsy is often nonspecific.
EMG/Nerve Conduction Study	Peripheral sensorimotor polyneuropathy; mononeuritis multiplex	Only indicated in patients with neurologic symptoms not seen in GPA
CT Sinuses	Sinus mucosal thickening	May consider to rule out abscess or malignancy

A combination of a classical clinical presentation involving ENT, lung and kidney, and a positive ANCA serology is generally sufficient to make the diagnosis. However, whenever possible, tissue biopsy should be obtained to confirm diagnosis. In addition, negative ANCA serology does not exclude the diagnosis of GPA in the correct clinical context as up to 15% of GPA has negative ANCA serology.

Together with microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (eGPA) (formerly known as Churg-Strauss syndrome), GPA is part of a group of small and medium vessel vasculitides characterized by presence of circulating ANCA autoantibodies and absence of immune complex deposition of the affected organs on histopathology.

There is considerable overlap in the clinical presentations, serology, and histopathology among the subtypes of ANCA-associated vasculitides. However, there are key distinguishing features as their names suggest.

Granulomatous inflammation is a key feature in both GPA and eGPA but is absent in MPA; in addition, granuloma in eGPA often contains eosinophils. Upper respiratory involvement is necrotizing, ulcerating, and destructive in GPA, allergic and asthmatic in eGPA, and absent in MPA.

ANCA serology also differs as GPA is predominantly PR3-ANCA positive, and MPA is more commonly MPO-ANCA positive, while eGPA has a much higher frequency of being ANCA negative (Table 3). Distinguishing the subtypes of ANCA-associated vasculitides is important, especially for eGPA, as they have different prognosis and treatment implications.

Table 3. Distinguishing features between GPA, MPA and eGPA. Adapted from Langford 2012.[1]

	GPA	MPA	Eosinophilic GPA
ENT	Necrotizing, destructive	Absent	Allergy, asthma
Lung	Cavitary nodules, diffuse infiltrates	Infiltrates	Nodules, infiltrates
Kidney	Frequently involved	Frequently involved	Less frequently involved
Granuloma	Characteristic lesion on biopsy	Absent	Characteristic lesion on biopsy
Eosinophilia	Rare	Rare	Characteristic feature
ANCA	70-80% PR3 10% MPO Up to 15% ANCA negative	40-80% MPO 35% PR3 Up to 20% ANCA negative	40% MPO 35% PR3 Up to 60% ANCA negative

Pathogenesis

The precise pathogenesis of GPA and the other ANCA-associated vasculitides remains unclear. It is currently thought that multiple factors contribute to the development of GPA, including genetic factors, infections, and exposure to drugs and environmental toxins.

A combination of these inciting factors leads to abnormal activation of the immune cells and the breakdown of immune tolerance. The production of autoantibodies against neutrophil granule proteins, as known as ANCA antibodies, is at least in part directly contributing to the systemic inflammation and vascular injuries in the affected organs.

Genetic variations in the HLA-DPB1 allele, part of the major histocompatibility complex (MHC) class II molecule responsible for antigen presentation, are consistently associated with the risk of developing GPA, supporting the notion that the inherited differences in our immune system play a role in the pathogenesis.

Outside MHC locus, other single nucleotide polymorphisms (SNPs) have also been found to be associated with the risk of developing GPA. One most notable example is an SNP in the SERPINA1 gene, commonly known as alpha-1-antitripsin. Alpha-1-antitripsin is a major inhibitor of proteinase 3, limiting the proteinase 3 damage to local endothelial tissue. Although it remains to be proven, it makes intuitive sense that an SNP associated with a reduced activity or expression of alpha-1-antitripsin can potentiate inflammatory injuries to endothelial tissues when neutrophils release proteinase 3.[1]

The discovery of the autoantibodies against neutrophils has led to the longstanding speculation that these autoantibodies may be directly pathologic. ANCA are autoantibodies produced by a patient's immune system that recognizes neutrophil granule proteins.

Two general patterns of neutrophil staining are seen: a cytoplasmic pattern (c-ANCA pattern) and a perinuclear pattern (p-ANCA pattern). PR3-ANCA autoantibody produces a c-ANCA pattern, and MPO-ANCA autoantibody produces a p-ANCA pattern.

ANCA is positive in about 85% of patients with GPA with 75% of ANCA directed against proteinase 3 (PR3-ANCA) and 10% directed against myeloperoxidase (MPO-ANCA). ANCAs that recognize other antigens have also been described. In particular, a type of ANCAs against lysosome-associated membrane protein-2 (LAMP-2) is common in pauci-immune rapidly progressing glomerulonephritis (RPGN). A large percentage of pauci-immune RPGN is also MPO-ANCA positive and will go on to develop the systemic symptoms of GPA.

LAMP-2-ANCA may be particularly interesting and pathologically important because LAMP-2-ANCA cross-reacts with FimH, a bacterial adhesion molecule commonly present on the surface of E. coli and Salmonella species. Furthermore, anti-LAMP-2 ANCA antibodies can activate neutrophils, resulting in endothelial vascular injuries, supporting a direct pathogenetic role of ANCA antibodies.

Bacterial FimH and human LAMP2 share a stretch of common epitope, and many patients appear to have antecedent infections with fimbriated bacteria prior the development of pauci-immune RPGN. This strongly suggests that molecular mimicry (an infection triggers an antibody production that also cross-reacts with a self-antigen, resulting in autoimmunity) may be at heart of the pathogenesis of many ANCA-associated vasculitides.[2]

Other experimental and clinical evidence support a role of ANCA antibodies in the disease pathogenesis. There are two case reports of newborns who developed glomerulonephritis and lung hemorrhage after delivery from mothers with circulating MPO-ANCA antibodies and active vasculitis. These newborns responded rapidly to plasmapheresis treatment, providing the direct evidence in humans that ANCA antibodies are causally related.[3]

It is generally accepted that the abnormal immune activation and loss of immune tolerance to self-antigen, including the development of ANCA autoantibodies, is the underlying cause of GPA and other ANCA-related vasculitides. However, it remains widely debatable as what is the initial trigger.

There is limited evidence that some common infections, such as S. aureus or E. coli, in susceptible hosts can trigger an immune response through molecular mimicry, production of autoantibodies to complementary proteins, and induction of excessive neutrophil extracellular traps.[1,4] The initial inciting factors remain to be uncovered and may have significant impact on the prevention and treatment of ANCA-related vasculitides.

Treatment

The mainstay treatment of GPA is aimed at suppressing the immune system and removing the pathologic antibodies. There are generally two phases of the treatment.

The goal of the initial phase is to induce remission with potent immunosuppressive medications for rapid control of the disease, followed by the maintenance phase to prevent disease relapse with medications that have less long-term toxicities.

In general, the therapy is tailored to the disease severity and stages. For localized disease with only upper or lower respiratory tract symptoms without other organ involvement or constitutional symptoms, sulfamethoxazole and trimethoprim with or without glucocorticoids is a reasonable initial option.

However whenever there is systemic involvement outside of the respiratory tract, stronger immunosuppressive regimens are recommended. Currently, there are several acceptable first-line combination regimens for remission induction of systemic GPA, including oral or intravenous pulse cyclophosphamide with glucocorticoids, rituximab with glucocorticoids, or methotrexate with glucocorticoids.

In severe cases, plasma exchange can be added as an adjuvant therapy.[5,6] For diseases that are refractory to the initial first-line treatment, other first-line treatments can be tried. Patients unresponsive to cyclophosphamide may be tried on rituximab. Despite the lack of randomized controlled trials, a variety of other treatments, including infliximab, antithymocyte globulin, alemtuzumab, high-dose azathioprine, mycophenolate mofetil, IVIG and autologous stem cell transplant have all been used in refractory or relapsing patients with variable success.[7]

For maintenance therapy, single agent oral azathioprine is the standard of care. Methotrexate can also be used in the first-line setting with similar efficacy for patients who cannot tolerate azathioprine. Leflunomide or rituximab may also be used as maintenance therapy.

Conclusions

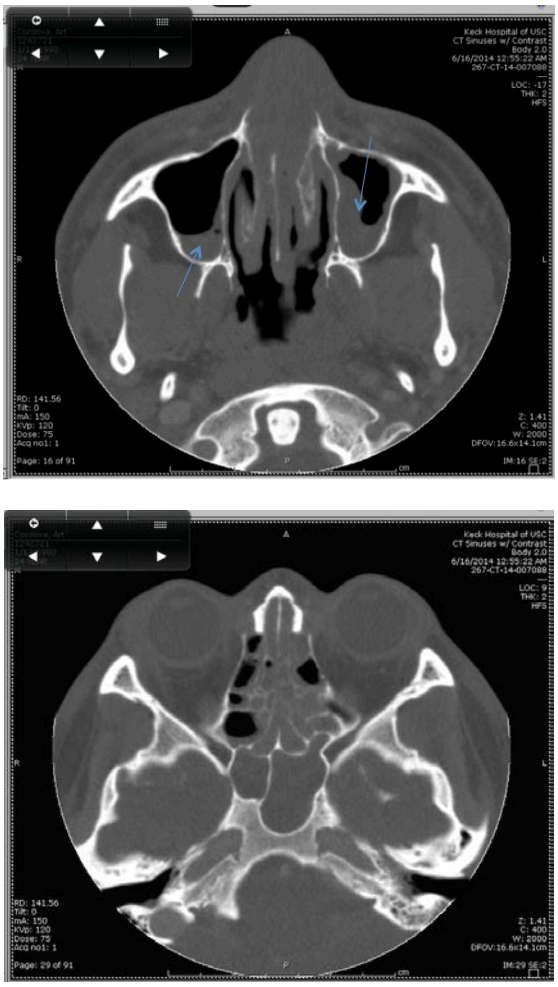
Increased recognition and prompt diagnosis of GPA, in conjunction with modern immunosuppressive therapy, have significantly improved the survival of GPA patients. However, GPA remains a chronic incurable condition with significant morbidity associated with recurrent relapses and long-term, treatment-related toxicities.

Future research is directed at further understanding of the pathogenesis of GPA and the long-term, treatment-related adverse effects of newer immunosuppressive medications, such as rituximab.

Clinical trials examining optimal treatment regimens (single vs. a combination of agents) and length of treatment to minimize the risk of relapse will be enormously valuable in the long-term management of GPA patients.

Figures

Figure 1: CT imaging of the sinuses. Prominent mucosal thickening within ethmoid air cells, sphenoid sinuses, and left maxillary sinuses.



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