REVIEW ARTICLE

Granulomatosis with Polyangiitis

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Abstract: Wegner's Granulomatosis, now known as Granulomatosis with Polyangiitis, is a fairly uncommon vasculitis with varying presentations. Patients may present with ongoing sinusitis unresponsive to common treatments, or patients may present in respiratory distress and failure. The treatment of GPA has progressed so that now patients are able to survive this small and medium vessel vasculitis.

INTRODUCTION

Granulomatosis with polyangiitis (GPA), previously known as Wegner's granulomatosis, is a form of vasculitis affecting typically small to medium-sized blood vessels. Diagnosis of this form of vasculitis is difficult due to the nonspecific presentation of symptoms. The incidence of GPA is rare, occurring in 10-20 per million per year.[1] The patient described in this case of GPA is a 67 year-old Caucasian male who presented to the hospital after worsening upper respiratory symptoms and several episodes of hemoptysis. This case deteriorated quickly, showing the serious nature of Granulomatosis with polyangiitis and the need for a work-up in cases of prolonged and unimproved sinusitis.

BACKGROUND

GPA is a subset of vasculitis affecting several body systems. In GPA there is granulomatous inflammation involving the respiratory tract, as well as necrotizing vasculitis affecting capillaries, venules, arterioles, and arteries. As such, GPA is considered a vasculitis affecting primarily small and medium vessels. The renal system is commonly involved, leading to glomerulonephritis.

While GPA can occur in any age group, the peak-affected range is 40 to 60 years. It is rare to diagnose GPA in children. The incidence of GPA is 10-20 cases per million per year, and is less common in Japanese and African American individuals.[1] Both men and women are affected equally. Research is currently being performed regarding the genetic nature of the disease, yet there is no present evidence showing a hereditary link among GPA sufferers.

GPA has an autoimmune basis, though the genetic basis of the disease has not been fully explained. About 90 percent of people with GPA contain an abnormal immune protein named anti-neutrophil cytoplasmic antibody (ANCA) in their bloodstream. These abnormal proteins attach to normal human proteins, leading to an inflammatory reaction. In patients with GPA, the ANCA proteins typically attack human protein proteinase 3 (PR3).[2] Other individuals have expressed an ANCA that attacks the myeloperoxidase (MPO) protein. Currently research is being performed regarding the expression of these ANCA proteins in patients with GPA. The presence of a form of the HLA-DPB1 gene has been proven to be the greatest risk factor in developing GPA, but there are other genes involved that have not been described.[3,4] Theories exist that state a mixture of both genetic predisposal and environmental factors are related to the expression of GPA, complicating the ability to predict who will develop Granulomatosis with polyangiitis.

CLINICAL PRESENTATION

The onset of GPA can be slowly progressive or rapid and severe. When first presenting to their physician, patients with GPA will likely describe feelings of malaise, night sweats, weight loss, and fever. These initial symptoms are related to a general immune reaction. As the vasculitis becomes more severe, patient complaints will become more localized. The most common sites of inflammation are the upper respiratory tract and kidneys, presenting as nasal congestion, nosebleeds, cough, difficulty breathing, hematuria, and secondary hypertension.[6] In most cases of GPA, rhinitis is the first sign of GPA. In a prior case presentation by Shafiei et al, a 42-year-old male is described as having two years of chronic sinusitis.[7] In this particular case, a chest X-ray incidentally found a lung nodule. This patient was in the process of planning for biopsy when he became acutely ill with leukocytosis, arthralgias, and mouth ulcers. After a thorough work-up, the patient was found to have a positive c-ANCA and diagnosed with GPA. Another case presentation describes a 69-year-old female with chronic sinusitis who eventually developed a parotid abscess that was detected on a CT scan, and a thorough work-up was initiated due to the

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inability to explain the cause of the abscess.[8] Therefore, patients may present differently in varying stages of GPA.

The nose is a commonly involved area of inflammation in GPA. Approximately 90% of patients initially present with complaints of cold symptoms and sinusitis that fail to respond to the typical therapies.[9] General nasal congestion is a common and often overlooked sign of GPA. Patients with GPA may also develop a "saddle-nose deformity" due to collapse of the nasal septum. Severe inflammation of the vessels within the nasal tissue can lead to a perforation of the septum, causing a sunken in appearance. Nosebleeds occur after the vessels within the nasal mucosa have been irritated and inflamed. These nosebleeds may start intermittently as mild bleeding episodes, then become more serious as the vasculitis progresses.[6]

Another common area of ANCA attack in GPA is the kidney, causing elevated creatinine and decreased glomerular filtration rate (GFR). This form of kidney injury is classified as rapidly progressive glomerulonephritis (RPGN) type 3, occurring from the coalescence of ANCA proteins and a pauci-immune reaction.6 The presence of RPGN is characterized by hematuria, red blood cell casts seen on urinalysis, and proteinuria frequently exceeding 3g. Persons with this condition also commonly display secondary hypertension and edema due to failure of the kidneys to filter. Often, even after treatment, patients develop chronic kidney disease.

Other areas of the body that may be affected by GPA include the ears, oral cavity, eyes, pulmonary system, joints, skin, and nervous system. When involving the ears and oral cavity, patients often present with conductive hearing loss, gingivitis, and mouth ulcerations. Once ANCA proteins have infiltrated the lungs, the clinical signs and symptoms become more severe. Patients can have infiltrates, pulmonary nodules, cavitary lesions, and hemoptysis.10 In GPA the heart, gastrointestinal tract, and brain are rarely involved.[6]

DIAGNOSIS

The key to the diagnosis of GPA is early recognition. A thorough history and physical examination will alert the physician to initial suspicions of GPA. In a patient with prolonged symptoms of sinusitis not responding to traditional treatment, testing for anti-neutrophil cytoplasmic antibodies (c-ANCAs) will assist in diagnosis. This test, however, does not solidify a diagnosis and a negative test does not totally negate the possibility of GPA. A more specific c-ANCA in GPA is that which reacts with the enzyme proteinase-3.[2,11]

Since GPA can affect multiple organ systems, it is important to detect the extent of organ involvement. Routine laboratory testing, including a chemistry panel and CBC, will show possible renal damage or anemia related to hemoptysis. Urinalysis will show the presence of hematuria, proteinuria, or red cell casts. A chest X-ray must be done to evaluate the pulmonary system, and often CT scanning will be necessary to characterize nodules or infiltrates. The sinuses are also best evaluated with CT scanning if there is suspicion of nasal mucosa damage.

When a patient presents with kidney injury or cutaneous vasculitis, a tissue biopsy may be obtained. Histopathological investigation will show granulomatous inflammation as well as necrosis in a cresecentic pattern.[6,9] Specific staining will be performed to rule out the presence of anti-glomerular basement membrane antibodies, eliminating the diagnosis of Goodpasture's syndrome. Upper respiratory tract tissue biopsies are often non-diagnostic, therefore not recommended. Renal or pulmonary biopsy is the diagnostic test of choice for confirmation of GPA, however renal biopsy is typically more plausible with less risk for the patient.[10]

The American College of Rheumatology accepted classification criteria for GPA in 1990; such criteria is intended for inclusion in randomized trials, rather than diagnosis. A patient meets criteria for GPA when having two or more positive findings. These criteria include nasal/oral inflammation with ulcers/nasal discharge, abnormal chest x-ray with nodules/infiltrates/cavities, microhematuria or red cell casts on urinalysis, and biopsy showing granulomatous inflammation in the arterial wall or perivascular area. The Chapel Hill Consensus Conference in 1992 created another system for GPA diagnosis, stating that the diagnosis of GPA must include a granulomatous inflammation involving the respiratory tract and vasculitis of small to medium-sized vessels.[12]

CASE REPORT

PRESENTATION

A relatively healthy 66-year-old male presented to the emergency room in respiratory distress, complaining of upper respiratory symptoms with intermittent chills and subjective fever for approximately one week. The patient stated that his symptoms had been getting progressively worse, and he did not feel better after completing a course of amoxicillin prescribed by his primary care physician for acute sinusitis. He also reported recent shortness of breath worse with minimal exertion, which he had never experienced prior to the past few days. The patient denied chest pain, orthopnea, or dizziness. He also denied any nausea, vomiting, diarrhea, constipation, or urinary symptoms. The patient's wife stated that the recent episodes of thick, purulent sputum often tinged with blood as well as the onset of hemoptysis are what brought them into the emergency room. He had never had episodes of hemoptysis before, and denied frequent nosebleeds. She denied any recent travel and could not report any known sick contacts. Upon arrival to the ER, the patient had a respiratory rate of 40 and an oxygen saturation of 74% on room air.

HISTORY

The patient's medical history was only significant for lower extremity DVT, for which he was started on Xarelto approximately one month prior to his illness. He denied any other medical history and was taking no other medications or supplements. Many years ago the patient had hemorrhoid cauterization, but there was no other surgical history. The patient's wife reported no family history of cardiac or pulmonary disease. She stated that the patient was never a smoker or drug-user, and only occasionally drank alcohol at social events. At that time the patient was a school bus driver, and had worked in a shipyard as a welder many years ago.

LABORATORY/IMAGING

Laboratory studies revealed an elevated BUN (50) and creatinine (4.2), as well as a hemoglobin and hematocrit of 8.2 and 24.5, respectively. The patient's estimated GFR at that time was 15. Blood work done as an outpatient three months prior to this event was completely normal with a creatinine of 0.85 and hemoglobin of 13.2. Cardiac enzymes and flu testing were negative. Fecal occult blood was positive. EKG showed sinus tachycardia without other

FIGURE A:

Chest x-ray showing diffuse infiltrates bilaterally.

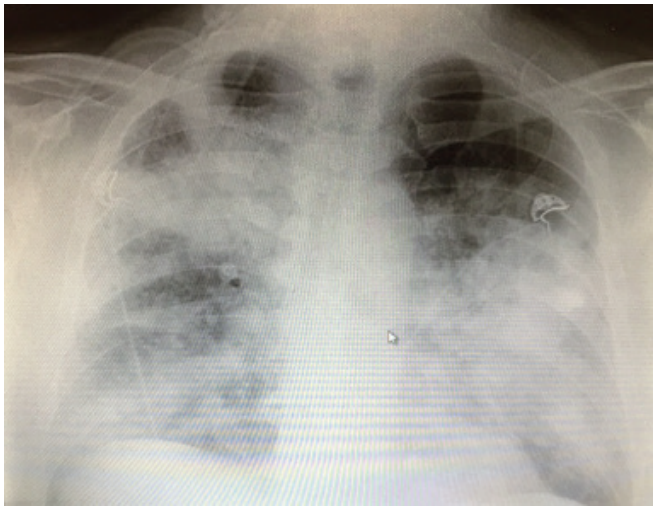


FIGURE B:

CTA of chest showing diffuse bilateral infiltrates and consolidation. No evidence of new pulmonary embolism.

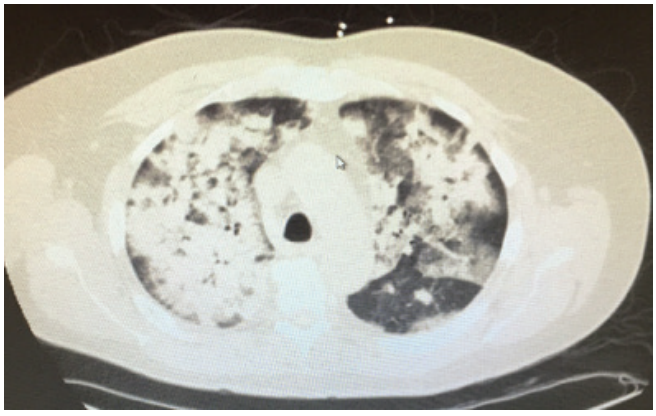
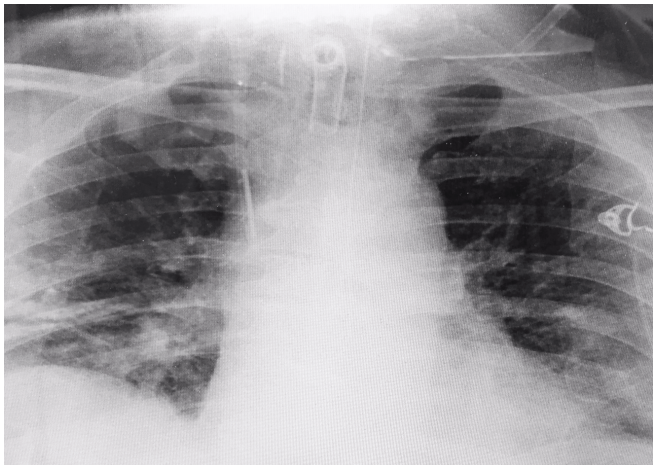


FIGURE C:

A temporary tracheostomy was placed



abnormalities, and chest x-ray showed diffuse infiltrates bilaterally (Figure A). At the time of admission, a CTA of the chest was pending. Shortly after admission, the patient received two units of packed red blood cells due to continued hemoptysis and rectal bleeding. A follow-up CBC performed two hours after transfusion showed that his hemoglobin had dropped to 6.7. The CTA of the chest showed diffuse bilateral infiltrates and consolidation, without evidence of new pulmonary embolism (Figure B). A more extensive work-up, including ANCA, myeloperoxidase, proteinase-3, legionella Ag, anti-GBM, and HIV testing, was pending at the time of transfer to a tertiary care center.

DIAGNOSIS

When initially evaluated, the patient was diagnosed with severe community acquired pneumonia, acute kidney injury, and anemia secondary to gastrointestinal bleed. After his symptoms and clinical picture worsened, he was diagnosed with Adult Respiratory Distress Disorder. The patient was intubated on the second day of hospitalization due to ARDS, then transferred to a tertiary care center. After his transfer, the work-up returned and showed a positive c-ANCA as well as severely elevated levels of proteinase-3. These test results combined with the patient's clinical case led to the diagnosis of GPA. While at the tertiary care center, the patient's BUN and Cr continued to rise, but his hemoglobin and hematocrit stabilized shortly after transfer.

TREATMENT

Initially the patient was placed on IV solumedrol as well as antibiotics to cover for community-acquired pneumonia. He was intubated on the second day of admission due to worsening respiratory status, and his PEEP was maximally titrated with a FiO2 of 100%. Blood transfusions were continued as needed to account for acute blood loss. Once the patient was transferred, he was placed on continuous dialysis. Plasmapharesis was performed, and the patient was started on a treatment regimen of Cytoxan and prednisone. The patient received the IV dosing of Cytoxan, performed at two-week increments. Plans were made for a long-term prednisone taper. A temporary tracheostomy was also placed due to the need for long-term mechanical ventilation (Figure C). The patient was placed on Atovaquone daily at bedtime for PCP (pneumocystis pneumonia) prophylaxis.

FOLLOW-UP

After presenting with his life-endangering symptoms, the patient received rapid treatment that was able to reverse many of the signs of GPA. Six months after initial presentation, the patient was off dialysis and on a prednisone taper. He had no further respiratory conditions requiring intubation, and his tracheostomy was removed. He will be followed closely, including checking routine chest X-rays and blood work.

TREATMENT

Goals in treating Granulomatosis with polyangiitis include treating the symptoms and manifestations of the condition, while also diminishing toxicities of treatment agents. The drug of choice in treating GPA is cyclophosphamide, and its efficacy is improved when combined with corticosteroids. Approximately 90% of those with GPA respond well to cyclophosphamide, and about 75% undergo complete remission.[13] The combination of

cyclophosphamide and prednisone dosed at 1 mg/kg/day is used to induce remission in GPA. Cyclophosphamide may be given orally at a daily dose of 2 mg/kg/day, or pulsed intravenously at a dose of 15 mg/kg every 2 weeks for the first 3 treatments, then every 3 weeks for a total of 6 pulsed doses.[14] While studies have shown that there are less adverse effects with the pulsed dosing, research is limited regarding which treatment option is most efficacious in inducing long-lasting remission.

Hemorrhagic cystitis is the most common toxic effect of cyclophosphamide, affecting 15-43% of patients using the oral regimen. The use of oral or intravenous Mesna with IV cyclophosphamide has been proven to limit the risk of hemorrhagic cystitis. Mesna is dosed at 20% of the IV cyclophosphamide dose divided over three equal doses, given 15-30 minutes prior to treatment and then at 4 and 8-hour intervals after treatment. When given orally, Mesna is given at 40% of the cyclophosphamide dose again in three equal doses. The oral dose of mesna is given two hours prior to treatment with cyclophosphamide, then again at 4 and 8 hours post-treatment.[15]

Other side effects of cyclophosphamide include bladder cancer, increased risk of malignancy, infertility, cytopenia, and infection due to cyclophosphamide-induced leukopenia. Due to all of the possible toxicities, frequent urinalyses should be performed while getting treatment and then throughout a patient's life as the risks of malignancy continue post-treatment. Complete blood counts should be monitored every 1-2 weeks during cyclophosphamide treatment, monitoring for leukopenia.[5,14]

An alternative treatment, rituximab with high-dose corticosteroids, was introduced and approved by the FDA in 2011. Infusions of rituximab lead to a 6-month depletion of circulating B cells, sparing plasma and pre-B cells. This process has been studied as a way to decrease the production of ANCA proteins.[16] Research exploring the use of rituximab for long-term maintenance therapy has shown positive outcomes, but trials are still ongoing. The adverse effects of rituximab include mucocutaneous reactions, cytopenia, malignancy, and increased opportunistic infections. One of the most serious reported opportunistic infections is progressive multifocal leukoencephalopathy (PML) caused by the JC virus. All of these risks must be taken into account when choosing a treatment regimen.

In cases of severe renal involvement with GPA, plasma exchange has been used to preserve renal function with the goal of avoiding dialysis.[5] Patients with a creatinine greater than 5.8 mg/dL benefited from plasma exchange in a multicenter European trial. Though there is evidence of improved renal function, studies have not shown overall improved survival or relapse rates with plasma exchange.

After the induction of remission, GPA requires at least 18 months of maintenance therapy. The agents used in maintenance therapy are azathioprine, methotrexate, and leflunomide.[5] Prior to the use of these agents, oral cyclophosphamide had been used with significant levels of toxicity. While being treated with these medications, patients should also receive a tapered dose of 10 mg/day of prednisone. Research is ongoing regarding the efficacy of Trimethoprim-Sulfamethoxazole when added to a maintenance therapy regimen.[16]

PROGNOSIS

In patients with GPA who have been treated with cyclophosphamide and corticosteroids, the 5-year survival rate is greater than 80%.8 While a large portion of patients with GPA who receive cyclophosphamide and corticosteroids experience remission, 30-50% of patients with an initial response to treatment will have at least one relapse of the condition. Factors that may predispose patients to relapse include advanced age, treatment with >10g of cyclophosphamide in the first 6 months, maintained high doses of prednisone, ANCA status, and organ involvement. Renal involvement at initial diagnosis leads to a higher likelihood of deterioration.[12] These relapses may present with symptoms similar to the initial manifestation of the condition, but they may also appear with new features. Therefore, it is important for patients with a known history of GPA to maintain their medical awareness and to report any new or unusual symptoms to their physician.

DISCUSSION

GPA can be a fatal disease if not recognized in time for appropriate management. The current incidence of GPA in the United States is three cases per 100,000.[1] It is estimated that the incidence of GPA may actually be higher than is currently reported due to the vague nature of the disease. Early symptoms of the condition vary among patients, making the diagnosis difficult. GPA may initially present with slowly progressive symptoms or severe and life-threatening organ failure, as shown in the presented clinical case. While this condition is rare, it must be considered in ongoing cases of sinusitis and other vague symptoms that do not respond to typical treatment.

Identification of cytoplasmic-ANCA proteins in patients with suspected cases of GPA is key in diagnosis. ANCA proteins that target human proteinase-3 are highly specific for diagnosis.[4] Research on the genetics behind GPA is ongoing, and in the future it may be more plausible to screen for conditions such as GPA. Though these blood tests are highly specific for detecting GPA, the physician has to first include GPA in the differential diagnosis and then include these tests in a work-up.

Once a work-up has been initiated, patients must be kept for close follow-up. Patients can develop symptoms slowly, or they can present with life-threatening conditions. The patient presented had initial complaints of sinus congestion with discharge and general fatigue that were not alarming symptoms when evaluated in an outpatient setting, and at that point did not ignite an elaborate work-up. This patient's case represents the dangers of GPA, exemplifying a seemingly insidious presentation of the condition. However, this case also shows the treatable nature of GPA. Whether diagnosed early or late in the course of the condition, treatment is generally successful in inducing remission of Granulomatosis with polyangiitis. The mainstay of treatment is cyclophosphamide and prednisone, but ongoing research is evaluating the other pharmacologic options that may be used to cure this condition.

Once treatment has been initiated in patients with GPA, patients and physicians must be vigilant for any medication toxicities. Patients need to be diligent in receiving treatment, and when remission is induced, they must be educated on the risk of relapse. Teaching a patient with GPA what to look for as far as signs of

relapse is difficult because GPA can present differently among patients and with each presentation. Therefore, patients and physicians should have open lines of communication and discuss any abnormalities. Blood counts and screenings for malignancy also have to be monitored thoroughly throughout a patient's life due to medication long-term complications.

CONCLUSION

Granulomatosis with polyangiitis is often difficult to recognize due to varying signs and symptoms. While the incidence is low, GPA must remain on the differential for patients with sinusitis and other medical complaints not responsive to classic treatment plans. There are proven treatment regimens developed for GPA with satisfactory rates of remission, though these patients must be followed throughout their lives due to the possibility of relapse and medication toxicity.

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