Treatment-resistant granulomatosis with polyangiitis: An unusual presentation

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Abstract

Granulomatosis with polyangiitis (GPA) is a rare systemic small-vessel vasculitis. This inflammatory reaction can affect the upper and lower respiratory tract, as well as the kidneys. The expected age of presentation is in the sixth and seventh decades of life, and Caucasians are mostly affected. The cornerstone of treatment is high-dose glucocorticoids in combination with immunosuppressant, steroid-sparing drugs, which leads to remission in almost 80% of patients. We present an unusual case of a 55-year-old Hispanic woman presenting with acute kidney injury secondary to treatment-resistant GPA. The failure of standard treatment is extremely rare. In addition, this patient presented with primarily renal symptoms, even though head and neck and airway symptoms are expected in almost all cases initially.

Keywords: Granulomatosis with polyangiitis, renal failure, treatment failure

Introduction

Granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis, is a rare immune mediated systemic small-vessel vasculitis. This inflammatory reaction can involve the upper and lower respiratory tract and the kidneys. This pathology can occur at any age, but typically occurs between 65–75 years of age. The etiology is still unclear. Treatment involves high dose-glucocorticoids with methotrexate, cyclophosphamide, or rituximab. Glucocorticoids and immunosuppressant drugs can lead to remission in about 80% of patients.[1]

Case

A 55-year-old Hispanic woman with a 22-year past medical history of hypertension controlled with metoprolol and losartan presented to the emergency room with lower extremity edema, right-sided low back pain, and abnormal laboratory tests based on her nephrologist's clinic notes. She denied chest pain, shortness of breath, abdominal pain, nausea, vomiting, and diarrhea. She denied headaches, vision changes, falls, and syncopal episodes. The patient was referred to nephrology by her primary care physician due to abnormal kidney function during the prior three months. At this appointment, the patient had abnormal kidney function, an abnormal urinalysis, bilateral calf pain, and hyperkalemia and was advised to go to the emergency room by her nephrologist. Her creatinine was 5.2 mg/dL during her office visit, and her urinalysis showed 3+ protein and 3+ blood. The patient was admitted to the hospital the same day.

The patient stated that she usually has swelling in her hands and legs when she drives for long periods of time as part of her job. She also reported some numbness and tingling in the toes of her right foot, but denied any weakness or cramps. Furthermore, she stated she sometimes has a mild throbbing right flank pain that does not radiate. The pain is not associated with nausea, vomiting, or fever. The patient stated that she has noticed pink urine during her first void

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DOI: 10.12746/swrccc.v11i47.1115

in the morning for the past three months. She denied dysuria, frequency, or urgency. She denied having any abdominal pain or change in her bowel habits.

At the time of admission, her potassium level was 6 mEq/L and her creatinine level was 5.2 mg/dL. She also presented with bilateral leg swelling on physical examination. Due to her hyperkalemia, her losartan was held, but metoprolol was continued. Sodium polystyrene sulfonate, furosemide, albuterol, insulin, and dextrose were ordered for the hyperkalemia. Her nephrologist recommended a kidney biopsy, autoimmune panel, and hepatitis panel. A bilateral lower extremity venous Doppler ultrasound, coagulation studies, and an autoimmune panel were ordered due to her history of bilateral lower extremity edema. The ultrasound was negative for deep venous thrombosis. Computed topography (CT) of the abdomen and pelvis without contrast did not reveal any abnormalities in her urinary tract. At this time, the hepatitis panel was negative. The autoimmune panel was negative except for a positive rheumatoid factor. A cyclic citrullinated peptide antibody test was ordered due to a positive rheumatoid factor. A Quinton catheter was placed for hemodialysis scheduled on Monday, Wednesday, and Friday.

On hospital day four, a dose of epoetin alfa was given due to a hemoglobin of 7.1 g/dl secondary to anemia of chronic disease. Her iron level was within normal limits, but her TIBC was low. At this time, she only had 1+ pitting edema on her lower extremities. Her potassium level continued to improve to 3.6 mEq/L. The next day, the patient's hemoglobin dropped to 6.5 g/dl, and she received one unit of packed red blood cells. A CT of the abdomen without contrast was done due to her reduced hematocrit and did not reveal any important abnormalities. The nephrologist ordered 40,000 units of epoetin alfa and scheduled weekly doses. The patient was informed at this time of the presence of sickle cell trait disease.

On hospital day seven, the renal biopsy reported showed anti-neutrophil cytoplasmic antibodies (ANCA)-induced pauci-immune glomerulonephritis. The patient was started on a high dose methylprednisone for three days. This inpatient steroid treatment caused emotional lability. The patient was observed to be crying or laughing abnormally after administration began. At this time, her ANCA profile and cryoglobulins were still pending. The patient was started on amlodipine for increased blood pressure secondary to the administration of steroids. Her laboratory test showed a positive anti-proteinase 3 leading to a high suspicion of GPA. A rheumatology consultant was asked to manage rituximab initiation and related management. The dose of IV corticosteroids was decreased to 60 mg daily for a few days and with plans to decrease it to 40 mg daily.

On hospital day 12, the rheumatologist saw the patient, and she was given her first dose of rituximab. A one-time dose of 80 mg furosemide was given to treat her edema. On hospital day 13, her corticosteroids were decreased to 40 mg daily. The plan was to complete her rituximab and corticosteroids and transfer her to a dialysis center for outpatient management. On hospital day 19, after her completion of rituximab and corticosteroids and placement at an outpatient dialysis center, the patient was discharged.

A month later the patient was once again admitted from the nephrology clinic due to a one-week history of gradual swelling, as well as waxing and waning pain in her abdomen. She rated this pain as a three to four on a scale of one to ten. The patient denied any radiation of stomach pain accompanied by passage of semisolid stool 5 times/day for the same duration. Since her previous discharge from the hospital 2 weeks ago, she has been checking her blood pressure, sugars, and weight. This resulted in the patient realizing that she was rapidly gaining weight with significant swelling around her eyes and lower extremity edema. She denied any fever, chest pain, palpitations, dysuria, highly colored urine, and increased bleeding tendency. At this time, a Quinton catheter was placed, and a chest x-ray was done, which was normal.

The patient went through hemodialysis as well as plasmapheresis. Her swelling started to decrease. An 80 mg dose of furosemide was given at this time. Thrombocytopenia was noted on her laboratory tests with a platelet count of 57 k/mcL, possibly secondary to rituximab. Heparin was held on this day. On hospital day 2, an ultrasound showed an occlusive deep venous thrombosis in the right internal jugular vein. Heparin 5000 IU q 8 hrs was ordered. The patient had an episode of anaphylaxis following an infusion

of fresh frozen plasma. On hospital day three, a non-formulary request for approval of avacopan capsules was submitted. Methylprednisolone sodium succinate was administered before each episode of plasmapheresis due to previous anaphylaxis. A CT of the head and brain without contrast was ordered due to concerns of an orbital contusion or fracture and was negative. The patient continued to receive hemodialysis.

On hospital day five, bleeding was noted from the left Quinton catheter and the pillows were soaked with blood. The heparin drip was stopped. There was an increase in facial and leg swelling. With dialysis, the patient was improving with less swelling in her face and eyes. Then a platelet transfusion was started. After two thirds of the infusion, the patient developed hypertension with a blood pressure of 190/110 mmHg. She became tachycardic and then unresponsive for about 15 seconds, according to her nurse monitoring her in real-time. After this, the patient became awake and alert. There were no jerking motions described. There was no hypotension or wheezing. The patient reported that prior to this episode she was feeling stuffy nose and unusual sensation in her abdomen. The patient's platelet count fell to 39 k/mcL. A chest x-ray was done, which was clear. She then received protamine sulfate as well as IV methylprednisolone.

On hospital day six, the patient reported blood accumulating underneath the skin of her left arm. Her platelets continued to decrease, and HIT was excluded at this time. Her left arm had mild swelling. There was bruising in the arms at sites of blood draws. She also reported to have had some oozing from the left IJ catheter site last night. An ultrasound was ordered, which found no venous thrombus in the left upper extremity. The patient underwent hemodialysis with 2 L of ultrafiltrate removed.

Hematology was consulted due to a platelet count of 30 k/mcL with significant bruising. The hematologist noted that heparin-induced thrombocytopenia (HIT) could not be excluded as a diagnosis due to previous heparin exposure and a corresponding platelet count. A HIT panel and serotonin release assay were ordered. The hematologist recommended 7.5 mg of fondaparinux anticoagulation since the possible diagnosis of HIT put her at high risk for further blood clotting. A DIC panel was ordered to exclude this possibility. The hematologist suggested supportive care including cryoprecipitate to keep the fibrinogen greater than 150 mg/dL in case of DIC. Immune thrombocytopenia purpura was also a part of his differential, but this was expected to improve with the corticosteroids from treatment of GPA. Since the patient's fibrinogen was 144 mg/dL, a cryoprecipitate infusion was ordered based on the hematologist's recommendations. The platelet count continued to drop. Cryoprecipitate transfusion was ordered again due to a low fibrinogen. Fondaparinux 7.5 mg daily was started.

On hospital day nine, plasmapheresis was stopped because of her anaphylactic reactions. Her platelet count improved from 25 k/mcL to 32 k/mcL and the team planned for a tunnel catheter when this platelet counts stabilized. Corticosteroids were continued, and the patient continued on 2.5 mg of fondaparinux daily. Avacopan approval was still pending at this time.

Discussion

Granulomatosis with polyangiitis is a rare autoimmune disorder characterized by damage to the small and medium cell blood vessels in the body. This results in damage to the lungs and kidneys. This disease is a part of a spectrum of disorders known as anti-neutrophil-cytoplasmic-antibody (ANCA) associated vasculitis (AAVs). The etiology of this autoimmune disease is still not known and is the subject of current research.[2] This case demonstrates the potential complexity in diagnosis and management of these patients which may require prolonged hospital courses.

The traditional presentation of this disease involves the upper and lower respiratory systems, the renal system, and symptoms involving the ear, nose and throat. This is described as the typical triad of involvement: upper airway, lungs, and kidney. The upper and lower airway involvement is often the initial presentation of GPA. Involvement of the ear, nose, and throat is very common and seen in approximately 90% of patients. In contrast, our patient presented with only renal symptoms, which is unusual. Renal symptoms on initial presentation are present only in 10–20% of patients, although most patients will develop renal symptoms

within the first two years of onset. Our patient was unusual as she was diagnosed with active glomerulonephritis on initial admission, proven by biopsy.[3]

The early identification and treatment of GPA is an important factor in reducing the mortality of this disease. New treatment strategies within recent years have also improved mortality.[4] Initial treatment of GPA presenting with organ damage involves a regimen of corticosteroids in conjunction with rituximab or cyclophosphamide.[5] This patient received glucocorticoid monotherapy initially, then combined glucocorticoid and rituximab treatment. The patient failed rituximab maintenance, and her kidney function continued to worsen, resulting in a case of treatment-resistant GPA. Since rituximab and cyclophosphamide have been shown to be equivalent in trials, the team did not switch to this regimen after failure of rituxamab.[6] Also, there is little evidence to support cyclophosphamide efficacy after rituximab therapy. Mycophenolate is another alternative therapy but was not started as there are no studies suggesting the success of mycophenolate therapy after failure of rituximab.

Treatment-resistant GPA numbers rates vary, with some studies reporting anywhere from 10 to 40% resistance. Risk factors possibly associated with treatment-resistant GPA include older age, severe kidney disease at presentation, female sex, African American race, and the presence of myeloperoxidase (MPO)-ANCA.[7] There is also a possibility that cases may be mislabeled as resistant disease due to unclear symptoms. Since our diagnosis was confirmed with a kidney biopsy, this possibility seems unlikely.

Avacopan was ordered as an alternative therapy. This medication is a complement C5a receptor inhibitor used in conjunction with glucocorticoids.[8] Current trials involve patients who had successful remission with the use of traditional therapies. This patient did not fall into this category. However, studies have shown that remission at 52 weeks was greater in avacopan in comparison to traditional therapy. This cohort included 80% of participants having renal involvement, which was the primary involvement in our patient.[8–10] The patient felt better and her urine output improved significantly, but she was discharged on hemodialysis for further outpatient care.

Conclusion

Clinicians need to be aware of different presentations of GPA, as expected symptoms might be absent. Early diagnosis and treatment of GPA are important for improved mortality. Our case involves a patient with an unusual age, ethnicity, and initial presentation, which involved primarily renal symptoms. Due to failure of standard therapies, treatment-resistant GPA was diagnosed. As our patient had initial corticosteroid treatment and returned in a month off corticosteroids, early discontinuation of steroids during rituximab therapy may precipitate reoccurrence. Treatment resistant GPA is difficult, but remission might be possible with newer therapies, such as avacopan.

Article citation: Rahesh J, Mapp T, Gonugunta A, Kazi I, Day S, Diab M, Ratheesh R, Naguib T. Treatment-resistant granulomatosis with polyangiitis: An unusual presentation. The Southwest Respiratory and Critical Care Chronicles 2023;11(47):47–51
From: Department of Internal Medicine, Texas Tech University Health Sciences Center, Amarillo, Texas
Submitted: 11/26/2022
Accepted: 3/29/2023
Conflicts of interest: none

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