Case Report

A 76 year old Japanese man was admitted to the hospital because of acute renal failure and hematuria. During a routine physical exam 6 months prior to admission, the patient was found to have microscopic hematuria. He was treated for presumed urinary tract infection, but his urine analysis continued to show proteinuria (100 mg/dl), 50-100 red blood cells/HPF, 4-10 hyaline casts per low power field (LPF) and 5-20 white blood cell/ high power field (HPF).

One month prior to admission, the patient was referred to his primary care physician with a history of seven kilogram unintentional weight loss over two months as well as bilateral leg swelling, increased fatigue and decrease in exercise tolerance. Laboratory abnormalities included an elevated BUN and Creatinine of 23 mg/dl and 1.9 mg/dl respectively, a hemoglobin of 11.7 g/dl, a hematocrit of 35.6% with normal indices, a white count of 18.8 x 10^3/mm^3 without a left shift and a thrombocytosis of 737 x 10^3/mm^3. An urinalysis revealed proteinuria (100 mg/dl), significant blood with > 100 RBC/HPF, 4-10 hyaline casts/LPF, 5-20 WBC/HPF and many bacteria.

One week prior to admission, the patient was referred to a nephrologist due to hematuria and progressive renal failure with a BUN of 32 mg/dl and a creatinine of 2.3 mg/dl. His anemia had worsened (Hb 9.6 g/dl, hematocrit 28.7%) and his white count continued to rise (23.2 x 10^3/mm^3). His serum iron level and total iron binding capacity were both low (15 mcg/dl, 164 mcg/dl respectively) while the serum ferritin level was elevated (1050 ng/ml). Reticulocyte count was normal and an elevated Haptoglobin was elevated. PSA was 0.3 ng/ml.

Further evaluation showed a 24 hour creatinine clearance of 25 ml/min and a protein excretion of 2.088 mg/24 hours. Tests for hepatitis A, B, C, anti-glomerular basement membrane antibodies, ANA, C3, C4 levels and a c-ANCA (Anti-Proteinase-3) of 1.2 Units/ml were normal. His p-ANCA was strongly positive with > 100 Units/ml (normal <9 U/ml). ESR was elevated with 59 mm/hr. Serum electrophoresis showed hypoalbuminemia and a high alpha-1, gamma fraction with a normal beta fraction and no monoclonal bands. The urine electrophoresis showed proteinuria with predominance of the albumin fraction. Because of rapidly progressive glomerulonephritis he was admitted to the hospital.

Further review of systems revealed a chronic non-productive cough. He denied any fever, chills, night sweats, sinus or hearing problems, hemoptysis, nose bleeding, chest pain, palpitations, nausea, vomiting, constipation, diarrhea, musculoskeletal pain, arthritis, dysuria, rash or pruritus.

Past medical history included hypertension, COPD, hypercholesteremia and hyperuricemia. The patient had surgery for a spontaneous pneumothorax 2 years ago. His medications included Allopurinol and Atorvastatin.

Physical exam on admission showed an alert older gentleman in mild respiratory distress. His blood pressure was 140/70mmHg with a heart rate of 68/min. Temperature was 39.3°C and his oxygen saturation was 93% on room air. Several scars were noted on the right chest from his prior surgery. There were no petechiae, purpura or other rashes. Head, ear, nose and throat exam was normal. Auscultation of the chest revealed a mild expiratory wheeze with a prolonged expiratory phase. Abdominal including a guaiac stool, cardiac and neurologic exam were normal. There was moderate bilateral pitting edema up to both knees present.

Chest X-Ray on admission showed a mild congestive pattern with cardiomegaly and small right pleural effusion.

The patient was admitted to the hospital and started on ceftriaxone. Tuberculosis was considered and the patient was placed on into respiratory isolation. Subsequently his PPD, blood- and sputum cultures were all negative including AFB. The patient continued to have persistent fever up to 39.4 °C.

Due to his acute renal failure and positive p-ANCA he underwent a left kidney biopsy on hospital day 2.

The kidneys appeared normal during the kidney biopsy.

The patient was treated with Methylprednisolone 750 mg IV daily for 3 doses followed by Prednisone 80 mg per day that was initiated because of the high suspicion for rapid progressive glomerulonephritis (RPGN).
The biopsy subsequently showed segmental necrotizing glomerulonephritis (GN) with focal necrotizing arteritis most consistent with pauci-immune glomerulonephritis. Immunofluorescence did not show significant immune complex deposits. 5-6 out of 18 glomeruli had global cellular crescent formation and moderate tubulointerstitial necrosis with mononuclear infiltrate on light microscopy. The findings on electron microscopy confirmed the ones from light microscopy. Overall these findings are compatible with the diagnosis of small vessel vasculitis. There was no report of necrotizing granulomas.

Because of the biopsy results and his positive p-ANCA the diagnosis of microscopic polyarteritis nodosa (PAN) was most likely. The patient was also started on 100 mg Cyclophosphamide orally. The patient became afebrile after the first dose of steroids. He was started on Vitamin D and Calcium supplements to prevent steroid induced osteoporosis. Trimethoprim-Sulfamethoxazole was initiated for PCP prophylaxis as well as a small additional treatment benefit. His creatinine peaked at 3.5 mg/dl before returning to his preadmission level. His WBC count also improved. His anemia remained stable and the patient was discharged on Cyclophosphamide and Prednisone. The patient expired one year later with a normal creatinine due to unrelated respiratory failure.

**Discussion**

Asymptomatic microscopic hematuria has a broad differential diagnosis ranging from benign conditions such as vigorous exercise, sexual activity, menstruation over urinary tract infections and nephrolithiasis to serious conditions such as glomerulonephritis or cancer. A repeat urinanalysis is recommended to see if the hematuria is persistent and to guide further evaluation. A follow up in 6 months in case of isolated glomerular hematuria is reasonable to check for the development of proteinuria or renal insufficiency.

The combination of hematuria and proteinuria suggested a glomerular site of the bleeding and nonglomerular causes like neoplasm, nephrolithiasis, cystic disease, papillary necrosis or metabolic reasons were unlikely. The urinanalysis suggested a nephritic syndrom. The rapid progression of symptoms and accompanying renal failure represented a rapid progressive glomerulonephritis (RPGN) which is a clinical presentation of many different glomerulonephritis.

There are three broad categories of nephritic syndrome. The first is grouped together as immune-complex glomerulonephropathies and includes immune mediated Ig-A nephritis, membrano-proliferative GN and postinfectious GN. The history did not reveal a prior acute respiratory or abdominal infection which may suggest Ig-A nephropathy the most common form of glomerular hematuria. Although he presented with symptoms of pneumonia the time course does not suggest postinfectious glomerulonephritis. On physical exam and history there were also no signs suggesting secondary causes such as systemic lupus erythematosus (SLE) or other rheumatological diseases. Diagnostic workup for postinfectious GN with Antistreptolysin O +/- anti-deoxyribonuclease B and C3 was negative. SLE was unlikely with normal levels of C4, ANA and C3 which in contrast to postinfectious GN remains low after 2-3 months.

Membranoproliferative GN associated with HCV and cryoglobulins were ruled out. The second category of nephritic syndrome are the anti-basement glomerulonephropathies including Goodpasture’s
syndrome and localized anti-GBM disease which should be suspected in patients with concomitant lung involvement as in this case. Anti-glomerular basement antibodies were negative.

The third category is grouped under small vessel vasculitis or pauci-immune disease (due to virtually no antibody deposition in the nephron) and consists of three major entities with Wegener granulomatosis, Churg-Strauss syndrome and microscopic polyangiitis. They are all closely related and distinct from polyarteritis nodosa. The triad of symptoms include systemic necrotizing angiitis, necrotizing inflammation of the respiratory tract and necrotizing glomerulonephritis. The original description of the Churg-Strauss syndrome included asthma, eosinophilia, granulomatous inflammation, necrotizing systemic vasculitis and necrotizing glomerulonephritis. To distinguish between the other two entities p-ANCA for microscopic polyangiitis and c-ANCA for Wegener granulomatosis should be ordered. Our patient had positive p-ANCA suggestive of microscopic PAN (m-PAN). Even with this positive ANCA constellation the diagnosis of m-PAN is not definite. Nonetheless, the treatment of WG and m-PAN is the same. In m-PAN approximately 70% have ANCA. It is useful in supporting the diagnosis when the clinical setting is suggestive of m-PAN. Histopathology remains the gold standard for diagnosis. A negative ANCA assay does not exclude ANCA-associated vasculitis (10-50% may be negative). ANCA may also be used to monitor disease activity.

In most cases, definite diagnosis is made by kidney biopsy. A kidney biopsy is evaluated in three different modalities: light microscopy, immunofluorescence and electron microscopy. Antibody deposits can be found either subepithelial (membranous and postinfectious GN), subendothelial (SLE) or in the mesangium (Ig-A nephropathy). A report of necrotizing granulomas would be more suggestive of granulomatosis.

Since the patient had pulmonary infiltrates on his initial presentation in the hospital the question arises if he had systemic involvement of the lung. Microscopic polyangiitis is the most common cause of the pulmonary-renal syndrome. Sometimes a lung biopsy is performed to confirm this suspicion, but was not done in our case. The patient improved with treatment although it was unclear whether this was related to treatment of his COPD or his underlying vasculitis.

Epidemiology

There is little epidemiologic data for small vessel vasculitis because of the rarity as well as the different classifications of the disease. In a French study the estimated prevalence per 1,000,000 adults was 90.3 for all 4 vasculitides, 30.7 for PAN, 25.1 for microscopic PAN, 23.7 for Wegener and 10.7 for Churg-Strauss. The overall prevalence was 2.0 times higher for Europeans compared with non-Europeans. Results of previous studies suggested latitudinal differences, with Wegener being more frequent in northern countries and microscopic-PAN prevailing in the south. Ethnic variations and differences between rural and urban areas might also play a role. The estimated prevalence rate per 1,000,000 for microscopic PAN was 9.0 in a northern area of Germany, whereas no cases were found in the southern part. Conversely, Watts et al reported an annual incidence of 8/1,000,000. The significantly higher prevalence observed for Europeans may infer a genetic susceptibility of Caucasians.

Pathophysiology

The ANCA associated vasculitides are an immune disorder with inflammatory and specific immune responses against neutrophile granule proteins. ANCA's are directly involved in the pathologic process by interaction with neutrophil and endothelial cells. The theory is that ANCA induce a release of cytokines from leukocytes and thereby start an inflammatory response which leads to a necrotizing vasculitis. Other cellular responses involving T and B-cells are not as well understood, but certainly take part in the pathogenetic process.

Treatment

Treatment of ANCA associated small-vessel vasculitis is divided into acute, maintenance and relapse phase. Current induction therapy of more severe cases as in our case starts often with IV pulse steroids (Methylprednisolone 7 mg/kg) to ameliorate symptoms, addition of Cyclophosphamide (2mg/kg PO daily or 0.5 g/m2 IV per month) therapy with a subsequent switch to oral steroids follows. This therapy leads to improvement of 80 percent of patients. Oral Cyclophosphamide is more toxic due to accumulative effects, but the advantage is less relapses during the treatment course.

This patient had already a prognostic factor for poor renal outcome because he had renal failure on presentation. The associated glomerulonephritis is progressive if not treated promptly. For severe life-threatening disease, plasmapheresis is another option. Untreated small vessel vasculitis has a poor prognosis with 90% of the patients dying within two years. One third of the patients develop relapse, but two thirds of these patients respond to the same initial treatment. Another therapy option in less severe disease consists of Methotrexate. Patients should also be started on Trimethoprim- Sulfamethoxazole for PCP prophylaxis since it has been shown that six percent of Patients develop this disease during the immunosuppressive treatment with steroids and that preventing it is cost-effective.

Maintenance treatment should involve a quicker taper of steroids than in the past which was about one year. Once complete remission is achieved, cyclophosphamide is discontinued and either methotrexate (which is an option only among those with a serum creatinine concentration ≤2.0 mg/dL [177 μmol/L]) or azathioprine is initiated. If there is a minor relapse during maintenance therapy, a trial of increasing dose of corticosteroids and immunosuppressive agents can be considered. Another option is treating the disease with the initial induction regimen in patients with more severe disease and in those who are no longer on immunosuppressive therapy. Other options which have to be considered with further progressive disease include maintenance dialysis and renal transplantation. Future medical options might include IVIG, leflunomide, mycophenolate mofetil and TNF-alpha.

Conclusion

The differential diagnosis of hematuria can include benign disease to life-threatening diseases such as microscopic PAN; therefore a systematic approach to the evaluation of hematuria needs to be taken.

If the patient has clinical features suggesting glomerulonephritis, a nephrologist should be involved early in the course. Treatment of microscopic PAN with cytotoxic therapy has improved the outcome.

See "Hematuria with...", p. 197
There are still questions which remain unsolved including the role of renal transplant in patients with severe small vessel vasculitis or new therapeutic drug regimens which might be less toxic.

References