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Case Report

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Hydralazine Associated Antineutrophil Cytoplasmic Antibody-Associated Vasculitis with Glomerulonephritis and Dsdna Antibody

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ABSTRACT

Hydralazine is a very commonly used blood pressure medication. Though safe it can be associated with a lupus-like syndrome and antineutrophil cytoplasmic antibody-associated vasculitis due to its immunogenic nature, and rarely pulmonary-renal syndrome which can be fatal if not recognized promptly. Here we describe a case of hydralazine induced vasculitis with glomerulonephritis with positive dsDNA antibody, but the biopsy showed tubular injury with RBC casts and glomerulonephritis. We use this case to review the current literature and discuss the importance of early diagnosis, treatment options, and clinical outcomes of this rare complication from hydralazine use.

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Background

Hydralazine was approved for hypertension by FDA in 1953 and it is one of the first antihypertensive medications that could be taken by mouth. In 2017 it is on the WHO's list of essential medications, and 105th most prescribed medication in the United States. It is relatively very safe, common side effects include headache and increased heart rate. Prolonged use may cause a syndrome like lupus first reported in 1953 and occurs in 5 to 10% of patients taking hydralazine, presents with arthralgia, myalgia, fever, and serositis. Kidney, lung, central nervous system, visceral organs are usually spared. Hydralazine associated ANCA vasculitis (HAAV) is a rare phenomenon and the pulmonary-renal syndrome is a most severe form and can be fatal. The cause of HAAV is unknown. There are three hypotheses. 1. binding of hydralazine to myeloperoxidase leading to neutrophil apoptosis resulting in the production of multiple at autoantibodies. 2. Hydralazine decreases DNA methyltransferase expression and induces autoimmunity by inhibiting extracellular signal-regulated kinase (ERK) pathway signaling and that may be responsible for disrupting the suppression of proteinase 3 (PR3) and MPO. 3. slow acetylators versus fast acetylators of hydralazine. Here we will be presenting a case of severe rapidly progressive glomerulonephritis is a complication of prolonged hydralazine use.

Case presentation

A58-year-old Caucasian male with a history of hypertension, antiphospholipid antibody, CKD stage III, coronary artery disease, hyperlipidemia, atrial fibrillation, sleep apnea was sent from the PCP office for abnormal kidney function on routine yearly checkup. On presentation to our Emergency room, he was afebrile with a blood pressure of 86/58 mmHg, heart rate of 74 bpm, pulse oxygenation of 95% on room air. The physical examination was notable for an obese man with a normal cardiovascular examination with 1+ pitting edema. Initial laboratory workup showed serum creatinine of 5.9 mg/dl, baseline creatinine was 1.7 mg/dl with an estimated GFR of 12 mL/min per 1.73 m², blood urea nitrogen of 74 mg/dL, potassium of 4 mmol/L, hemoglobin of 7 g/dL, white blood cell count of 2.2 x 10^9/L and platelets of 84,000. Urinalysis, negative glucose, large blood, negative WBC, RBC more than 100 per high-power field, RBC casts present, specific gravity 1.013, pH 5, Protein dipstick 30, protein random urine 17.2, urine creatinine, 72.1. The chest x-ray was clear. A renal sonogram showed normal size kidneys with no hydronephrosis or calculi. His home medications are aspirin, atorvastatin, hydralazine, insulin glargine, apixaban, metoprolol, and amlodipine. He was admitted for management of pancytopenia and acute renal failure. He received IV hydration, nephrology, and hematology was consulted. He underwent Bone marrow biopsy with normocellular marrow, 40% cellularity with an active trilineage present. No evidence of carcinoma, lymphoma, granuloma. There was suspicion that he could have vasculitis given renal failure and anemia. His serology work-up is shown in table 1. Serum protein electrophoresis, total protein 5.5, albumin 2.7, alpha-1 globulin 0.4, alpha-2 globulin 0.8, beta globulin 0.6, gamma globulin 1, suggestive of decreased albumin and elevated acute phase reactant suggestive of acute inflammation. Upon suspicion for possible lupus vasculitis based on dsDNA antibodies, he was started on IV Solu-Medrol on day 3 of admission and renal biopsy was done to confirm the same. To our surprise, Renal biopsy showed severe acute tubular

injury with extensive RBC casts, very positive ANCA status, pauci immune focal necrotizing crescentic glomerulonephritis. Figures 1,2 and 3. The patient has been on hydralazine for over 3 years and was taking 100 mg 3 times a day. His hydralazine was stopped and was started on isosorbide mononitrate and methyldopa for better blood pressure management. On day 6 he received rituximab weekly for 4 weeks, he was leukopenic but tolerated it well. He received Bactrim 3 times a week for prophylaxis while on rituximab, he was discharged to home 10 days after admission and required hemodialysis as he remained oliguric. He was transitioned to oral prednisone 40 mg daily. The patient was followed up for a period of 6 months, unfortunately, he remained on scheduled Hemodialysis.

Table 1

Double-stranded DNA antibodies, IgG	Positive,15 International Units (IU)
ASO titers	Negative, 28 IU/ml
C3 complement levels	69 mg/dL, normal range 82 to 182 mg/dL
C4 complement levels	13.5 mg/dL, normal range 15 to 53 mg/dL
ANA screen	positive, homogeneous pattern, more than 1 is to 640
Anti-Smith antibody, anti-SSA antibody, anti-SSB antibody, scleroderma antibody, Smith/ RNP antibody	Negative
anti-histone antibody	2.8 units, more than 2.5 strong positive
ANCA screen	Positive
Myeloperoxidase antibody (PR3)	>800, normal < 1.
Glomerular basement antibody	< 1.2, normal < 2.
HIV antibodies, Hepatitis B surface Ag	negative

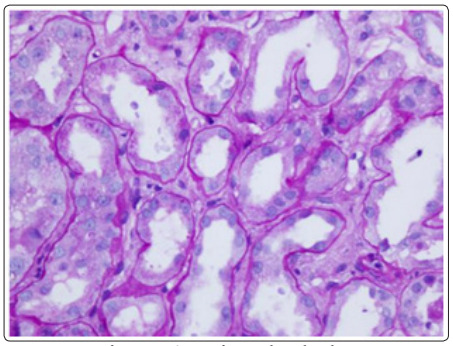

Figure 1: Injured tubules

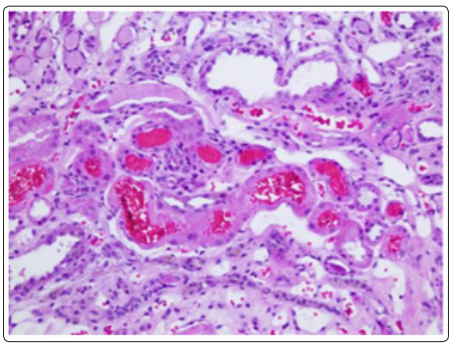

Figure 2: RBC casts

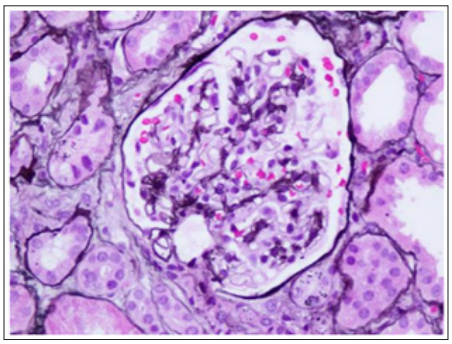

Figure 3: crescent in the glomerulus

Differential diagnosis

- Hydralazine associated vasculitis with glomerulonephritis.
- Plasma cell dyscrasia.
- Systemic Lupus Erythematosus (SLE) with nephritis
- Acute renal failure and Gastrointestinal bleed.

Discussion

Hydralazine is associated with two clinical autoimmune syndromes, Hydralazine-induced lupus (HIL) and hydralazine-associated ANCA vasculitis (HAAV). Risk factors include dose more than 200 mg/day, duration of treatment at least more than 3 years, female sex, slow hepatic escalation, HLA-DR4 genotype, and then Null gene for the fourth component of complement C4. Unlike classic SLE, diagnostic criteria do not exist for Hydralazine-induced lupus (HIL). Hence diagnosis is mainly clinical. The temporal association between drug use and symptom onset is important in establishing the diagnosis. Symptom disappearance with the discontinuation of hydralazine can be considered highly suggestive of hydralazine induced lupus. The majority of hydralazine induced lupus syndrome presents with positive ANA, positive anti histone antibody, negative double-stranded DNA antibody, but few case reports exist where ANA was negative. Discontinuation of hydralazine is the mainstay for the treatment of HIL. A short course of steroids, NSAIDs can be used if joint pain, serosal involvement symptoms persist [1].

Drug-induced lupus and ANCA associated vasculitis are considered as a large spectrum of a single disease, however, it's very rare to have both at the same time. Drug-induced lupus is manifested by positive ANA and anti-histone antibody, thrombocytopenia, and hypocomplementemia. ANCA associated vasculitis was evidenced by positive ANCA, anti-proteinase 3 antibodies, and the presence of multiple antibodies indicating a drug-induced autoimmune process. The involvement of small-vessel vasculitis of the skin, kidney disease, and lung disease is classic for any vasculitis [2].

The clinical presentation of hydralazine induced vasculitis is more severe than hydralazine induced lupus, it generally involves skin, kidneys, and lungs. It can manifest as rapidly progressive glomerulonephritis, upper and lower airway disease, cutaneous vasculitis. Clinically this disease resembles the idiopathic ANCA associated vasculitis, like pauci immune glomerulonephritis. Generally, the serologies reveal a high ANCA titer to MPO with p-ANCA pattern and sometimes c-ANCA with PR-3 titer. C-ANCA with PR-3 titer is more common with P-ANCA. The prognosis of this case may be a complete resolution of symptoms, developing chronic kidney disease, or ending on hemodialysis. Pulmonary involvement can be severe, they may develop acute respiratory distress syndrome from hemorrhage and can be fatal. In the absence of skin and lung involvement diagnosis-related on positive serologies and renal histopathology. Discontinuation

of the drug followed with IV steroids, oral steroids, rituximab, cyclophosphamide, plasmapheresis are helpful in management. The therapeutic approach is based on the patient's comorbidities, renal involvement, age, and organ involvement [3].

To our knowledge, this is the first case where the patient has positive ANCA, anti-proteinase 3 antibodies, positive ANA, positive anti-histone antibody, thrombocytopenia, and hypocomplementemia along with dsDNA antibody. Presence of multiple antibodies with the use of hydralazine, kidney biopsy showing glomerulonephritis with RBC casts we confirmed that this is a drug-induced phenomenon with a combination of lupus and vasculitis like symptoms.

Conclusion

Despite the poor understanding of pathogenesis and variable clinical presentations of hydralazine-induced lupus and vasculitis, discontinuation of hydralazine remains the mainstay of therapy. Lupus symptoms should resolve with discontinuation of hydralazine. In suspected cases with vasculitis patients will benefit from a course of steroid and immunosuppressive therapy depending on the disease severity. The involvement of lung disease might also require plasma exchange and ventilatory support. Hemodialysis should be given to support renal function. Long-term use of hydralazine in the elderly population and African American race is discouraged, a suitable alternative antihypertensive regimen should be used instead of hydralazine to prevent this complex and challenging complication of hydralazine.

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