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Case Report

An unusual case of anti-neutrophilic cytoplasmic autoantibodies associated vasculitis with pauci-immune crescentic glomerulonephritis in young? Wegener's? Churg Strauss

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ABSTRACT

Anti-neutrophilic cytoplasmic autoantibodies-associated vasculitis (AAV) is very rare in India. It normally affects older population around 6th and 7th decade of life. The management of cases is also complicated. We present a case of 18 year old male patient who came with complaints of epistaxis and had hematuria and pain in the joints. He had sub conjunctival haemorrhage on presentation. On and off he had respiratory symptoms and epistaxis in the past for which he was treated as allergy and bronchial asthma. At admission he had high absolute eosinophil count and had blood 3+ positive in urine. Initially he was treated as post viral vasculitis. But patient had involvement of kidney, lung, skin, joints, eyes and on further evaluation he was found to have AAV. The case was unique due to the age of presentation and patient also had overlapping symptoms of both Wegner's granulomatosis and Churg-Strauss syndrome.

Keywords: ANCA-associated vasculitis, Pauci-immune crescentic glomerulonephritis, Corticosteroids, Cyclophosphamide, Rituximab

INTRODUCTION

Vasculitis is defined as pathological process which causes inflammation and necrosis of blood vessel walls. It can affect vessels of any type, size and location and can cause damage and dysfunction of any organ system.[1,2]

ANCA-associated vasculitides consists of 4 syndromes: granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA, formerly known as Churg-Strauss syndrome) and renal limited vasculitis (RLV).[1] These are generally accompanied by pauci-immune crescentic glomerulonephritis (PICG).[3] It is most commonly is seen in older people with equal gender distribution. 85-90% of active untreated cases of PICG are ANCA positive.[3]

ANCA vasculitis have an annual incidence of 10-20 per million.[4]

The presence of ANCA-associated vasculitis is very rare in children and young adults. In younger age group females are more prominently affected. The mean age of presentation of EGPA is 3rd and 5th decade of life, it's presentation is very rare in children.[5]

The involvement of kidney in systemic vasculitis patients are usually diagnosed relatively later in the course of disease and has impact on prognosis and choice of therapy. Microscopic hematuria with or without proteinuria is found in renal vasculitis patients. Renal functions are relatively well preserved in the early phase of the disease, whereas, a rapid deterioration is an ominous sign.[1]

Pauci-immune pattern in kidney biopsy indicates the lack of immunoglobulin and complement deposition with in the kidney when demonstrated by indirect immunofluorescence techniques.[1]

In PICG without treatment, 80% 1 year mortality rate is present. Up to 75% for 5 years was seen in cases with aggressive immunosuppression. Older age, dialysis dependency and pulmonary haemorrhage worsen the chance of survival. 25% of patients progress to ESRD.[5]

The major elements in the management of ANCA associated glomerulonephritis and/or vasculitis are early diagnosis and the initiation of immunosuppressive therapy to avoid irreversible kidney damage or death.[3]

Serum creatinine, extent of renal injury and fibrosis on biopsy are the best predictors of renal outcome. Even though remission is induced in most patients, about 40% of patients end up with relapse. Hence, it requires close monitoring.[5]

Below, we present a case of young male patient who was treated for recurrent respiratory infection, but on further evaluation it turned out to be AAV. He had multi system involvement involving kidneys, lungs, eyes, joints and dermatological manifestations. Hence, it was a very unique and challenging case to diagnose and to treat due to his age of presentation and varied symptoms.

CASE REPORT

A 18 year old male presented with history of fever, cough and sore throat on and off since 3 weeks, the symptoms did not subside with medications. He also had epistaxis and pain in the right hand and smaller joints at presentation. Right wrist showed synovitis with tenderness. On taking a detailed history, he had on and off episodes of epistaxis since 2-3 months. Quite frequently he had cold, sneezing for past 2 months. He had history of allergy and wheezing for 8-9 years for which he was being treated with inhalers. 2 months prior to admission parents gave history of rash on the back and hands for which dermatologist was consulted. His initial chest X-ray done was normal (Figure 1).

ENT opinion was taken for epistaxis and was treated. His initial investigations showed total leucocyte count of 12.6 and haemoglobin 14.4 gm/dl, platelets 530×103 /cmm, absolute eosinophil counts were 2.6 cells/cu.mm, urine routine done showed blood 3+, pus cells 2 /hpf, RBC 30 /hpf. Ferritin levels was 396 ng/ml, CRP was 138 mg/dl, RBS 127 mg/dl, HBA1C was 6.3% with ESR-2 mm/hr. Liver function tests done showed total protein of 7.4 g/dl, with albumin 3.4 g/dl, globulin of 4.1 g/dl, ALP 134 U/l, A/G ratio of 0.83. COVID RT-PCR was negative.

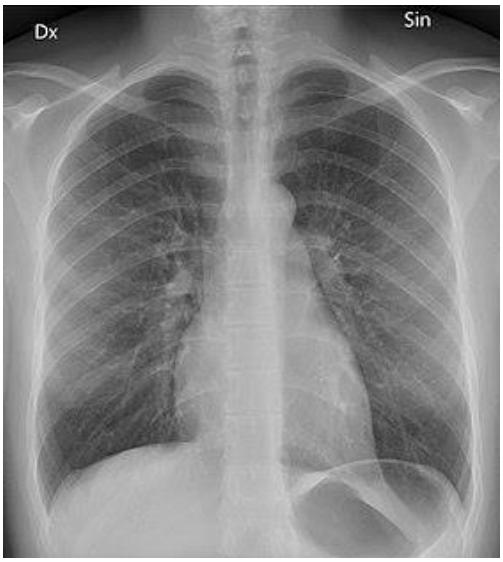

Figure 1: Normal chest X-ray of the patient.

Ophthalmology opinion was taken for sub conjunctival haemorrhage and was started on medications. His serum calcium level was 8.9 mg/dl, phosphorous 4.2 mg/dl, uric acid 3.2 mg/dl. Renal function tests done showed creatinine of 1.13 mg/dl, sodium was 140 mmol/l, potassium was 5.13 mmol/l Right upper limb Doppler done was normal, it was done in view of pain in the limb. Dengue, Weil Felix and leptospira serology done were negative. ASLO titers were 35.7 IU/ml with procalcitonin levels 0.25 ng/ml. Urine PCR was 0.95 mg/dl. Blood culture and urine culture showed no growth. Repeat urine routine done showed blood 3+, with RBC of 63 /hpf. His serum creatinine level got gradually elevated to 1.31 mg/dl. eGFR was 23 ml/min/1.73 sq.m. USG abdomen and pelvis done showed both kidneys parenchymal heterogeneity with accentuated corticomedullary differentiation suggestive of glomerulonephritis. The case was discussed in detail with nephrologist and rheumatologist. He was further investigated for autoimmune diseases.

In view of persistent hematuria and fever he underwent USG guided renal biopsy. He tolerated the procedure well and had no complications. ANA was negative but ANA profile showed neucleosome borderline positive. Complement C3 was 185 mg/dl, complement C4 levels were 30.90 mg/dl and PR3-ANCA levels were 200 RU/ml. Anti GBM antibody was negative. After evaluating the reports he was diagnosed to have ANCA vasculitis with glomerulonephritis and was given pulse therapy with 2.5 grams of IV solumedrol infusion over 1 hour in 3 divided doses.

His renal biopsy done showed crescentic glomerulonephritis with cellular crescents in 10/13 glomeruli, fibrinoid necrosis in 3/13 glomeruli. Acute tubular injury and mild interstitial inflammation suggestive of PICG (Figure 2). He was diagnosed as ANCA vasculitis with crescentic glomerulonephritis involving kidneys, lungs, eyes, joints, skin and upper respiratory tract. His PR3 ANCA was strongly positive.

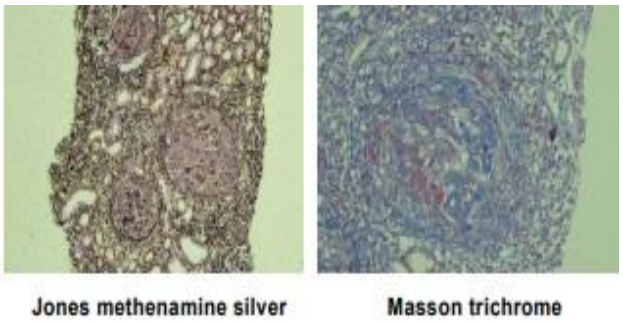

Figure 2: Renal biopsy showing pauci-immune crescentic glomerulonephritis.

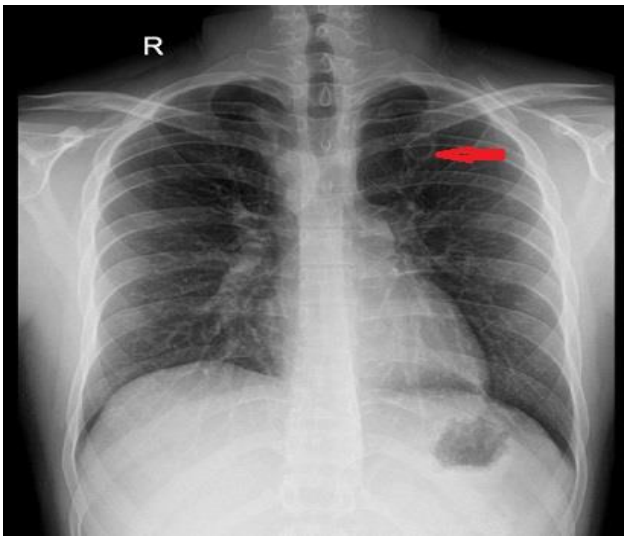

Figure 3: Chest X-ray showing left upper lobe cavity.

Post biopsy, the diagnosis of the patient along with the prognosis and management with steroids and long term immunosuppressive therapy was discussed in detail with parents. Rituximab 1 gram infusion was given over 6 hours. Following day solumedrol 500 mg injection was given. He was later started on oral prednisolone tablets 1 mg/kg for 2 weeks.

Patient developed low grade fever and his repeat counts were 19.1×103 /cmm and creatinine values were 2.35 mg/dl. Repeat blood and urine culture done were negative. Film array done was also negative. Infectious disease opinion was taken and was advised to continue same antibiotics along with steroids. Other probable causes for fever were evaluated. CMV IgM and IgG done were negative. He continued to have fever spikes with chest discomfort. Repeat chest X-ray was done showed cavitatory lesion in the left upper lobe, in view of which HRCT thorax was done which showed thick walled cavities in the left upper lobe suggestive of infective etiology? Koch's (Figure 3,4). His repeat ESR was 11 mm/hr. TB quantiferon gold test done was indeterminate.

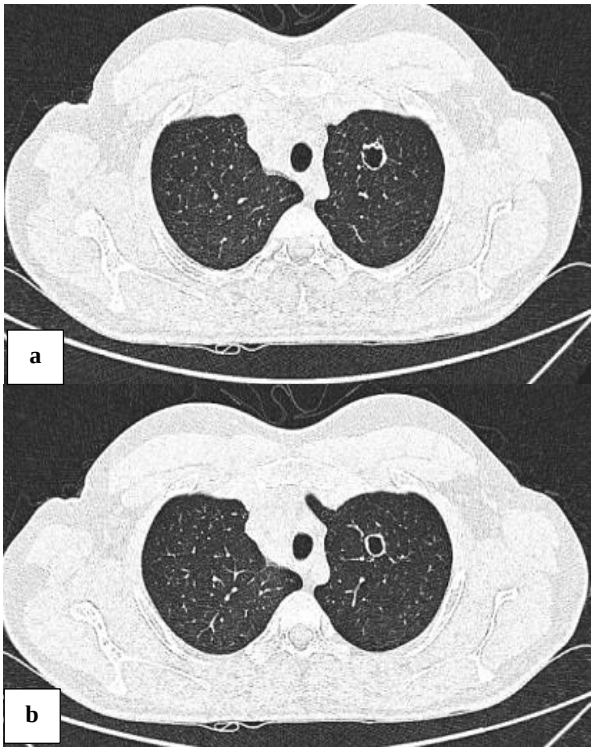

Figure 4 (a, b): HRCT thorax showing left upper lobe cavitatory lesion.

Pulmonology opinion was taken and he underwent bronchoscopy with BAL. BAL fluid analysis was within normal limits and AFB was negative on culture and gene x-pert.

Despite of being on injection meropenem he developed on and off fever in view of which he was started on broad spectrum antibiotics, antivirals and anti fungals. His fever gradually came under control.

In view of raising creatinine values repeat dose of 500 mg of injection solumedrol infusion was given. A dose of 500mg cyclophosphamide infusion over 2 hours along with injection Mesna 400 mg was also given. 2nd dose of rituximab infusion was given 2 weeks after the first dose. His creatinine was 3.71 mg/dl at discharge.

The patient was on regular follow up and he is symptomatically doing well. At follow up he was on azathioprine and rituximab treatment. Steroid therapy with injection solumedrol was given depending on rheumatologist assessment and orders. In his current reports the creatinine levels reduced to 1.26 mg/dl. IgG-773 mg/dl, IgM-27 mg/dl, IgA-123 mg/dl, ESR-7 mm/hr, urine PCR-1.26 mg/dl, his eGFR improved to 85

ml/min/1.73 sq.m. His repeat PR3 done in month of March was negative. Repeat kidney biopsy done on follow up after 6 months of treatment showed global glomerular sclerosis: 7/11, focal segmental glomerulosclerosis: 2/11 with features suggestive of inactive disease with >50% glomerulosclerosis.

It was quite challenging rare case for diagnosis and management. It could have been easily overlooked and misdiagnosed as simple URTI with LRTI. It is vital to keep in mind the systemic manifestations of autoimmune disease if symptoms are not subsiding with treatment. Hence, a thorough investigation along with multidisciplinary involvement is necessary for management of such difficult cases.

DISCUSSION

ANCA are specific for proteins in the cytoplasm of neutrophils and monocytes. The major target antigens are myeloperoxidase (MPO) and proteinase 3 (PR3). PR3-ANCA is associated with more extensive extrarenal involvement and higher relapse rate. MPO-ANCA is more frequently seen in renal-limited disease. It causes more kidney scarring and carries worse renal prognosis.[5]

Genetic susceptibility and environment triggers like silica, drug exposure and infections are associated with development of AAV. Drug induced vasculitis is seen with use of minocycline, allopurinol, propylthiouracil, hydralazine, cefotaxime, phenytoin, D-penicillamine, sulfasalazine and levimasole-adulterated cocaine.[6]

Some patients with PICG were found to be ANCA negative. On further investigation, they were found to have higher levels of proteinuria, poorer renal outcomes. The pathogenesis of the disease is not known, but neutrophils and complement activation were found to play a major role.[8]

Clinical symptoms

The patients with AAV can present with varied symptoms like low-grade fever, fatigue, weight loss, myalgias, arthralgias. These precede before actual symptoms of the disease start. Most patients present with flu like symptoms before presenting with overt vasculitic syndrome. 90% of patients with MPA present with clinical or pathological evidence of renal disease, whereas, 80% of GPA and 45% of EGPA present with renal symptoms. The common symptoms with which the patients of glomerulonephritis present are asymptomatic hematuria and they have active urine sediments, elevated serum creatinine levels, dysmorphic erythrocyturia, with or without red cells cast and proteinuria.[3] Our patient presented with similar flu like symptoms and had joint pains and hematuria which led to initial suspicion of post viral vasculitis. Similarly, he had hematuria.

People having EGPA most commonly presented with asthma, eosinophilia and granulomatous inflammation in the lungs. Renal disease is very less frequent in these cases. 50% of deaths occurred due to coronary arteritis and myocarditis.[3] In our case, patient had overlapping of symptoms of EGPA and GPA, as he had allergies and asthma, eosinophilia and along with hematuria and renal involvement. Hence, it made the management of case very difficult.

Treatment

Induction therapy

The gold standard of treatment for cases of AAV is combination of corticosteroids and cytotoxic agent cyclophosphamide.[2]

Cyclophosphamide is an alkylating agent which inhibits DNA replication and in turn affecting rapidly dividing cell population. It has been used in induction therapy in GPA since 1971.[4]

Methyprednisolone is initially given as pulse therapy 7 mg/kg body weight for 3 consecutive days. Later, it is changed to oral prednisone 1 mg/kg for 4 weeks and is gradually tapered over 3-5 months period. Cyclophosphamide is started intravenously as monthly dose. The initial starting dose being 0.5 g/m^2 of body surface area and it is later increased to 1 g/m^2, or an oral dose of 2 mg/kg body weight per day is started. The dosage is adjusted depending on the leukocyte count and current glomerular filtration rate. The duration of therapy is around 6-12 months depending upon patient's response.[3]

Rituximab is a chimeric monoclonal antibody directed against the CD20 antigen of B lymphocyte. It is used in inductive therapy either in combination with steroids or steroids and cyclophosphamide.[2] Rituximab treatment over cyclophosphamide was recommended in patients in >65 years who had high hemotological toxicity and in younger patients in whom fertility had to be preserved.[4]

In our case, intravenous rituximab was given along with steroids and 2 doses of intravenous cyclophosphamide. His creatinine, complete blood count, input and output were regularly monitored. There was improvement in patient's symptoms after starting the treatment.

The main indication for adding plasma exchange in inductive phase was presence of pulmonary haemorrhage and severe renal dysfunction. Both are critical condition leading to death in the patients.[3]

Although mycophenolate mofetil (MMF) was non-inferior to cyclophosphamide in inducing remission, high relapses were seen in MMF group. Hence, MMF may have a role in nonlife threatening vasculitis.[4]

Maintenance therapy

The decision regarding maintenance therapy is made on individual basis. It is general given in patients who have risk of high rate relapse or who have high risk of developing relapse.[3]

Over the past two decades, drugs like rituximab, azathioprine, mycophenolate, methotrexate and glucocorticoids have been used for maintenance therapy.[4]

Usually low dose glucocorticoids plus an immunomodulatory therapy such as azathioprine, rituximab or MMF are given for 12-18 months. MMF can be given in condition where patient has allergy to azathioprine. Rituximab is better than azathioprine for preventing relapse.[7] Our patient was started on azathioprine and was later switched to rituximab monthly injection for maintenance therapy.

Renal transplant

The timing for kidney transplants in patients with ANCA vasculitis is not clear. United States renal data system showed 70% reduction in all cause mortality if renal transplant was done in patients with ESRD from GPA. However, kidney disease improving global outcomes recommends waiting at least for 1 year after clinical remission before transplant.[4]

CONCLUSION

The treatment of AAV is complicated. It can affect all age groups. Patient presents with varied symptoms involving multiple organs. A case presenting with recurrent URTI and LRTI with epistaxis and eosinophilia can be missed as simple respiratory bronchitis as with our case. Even if the patient symptoms are not improving with treatment, patient history and routine investigations should be re-evaluated. Like in our case urine routine, elevated ferritin and CRP were helpful for clinching the diagnosis. A suspicion and look out for AAV makes the cases easy to diagnose.

Several advances have been made in treatment of ANCA vasculitis. Now a days, the patient prognosis with earlier remissions and lower relapse rates have been seen. However, further targeted therapies to tailor the treatment on the basis of ANCA type, comorbidities, relapse rate and patient preference is required for management of AAV.

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