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Case Report

Nephrotic range of proteinuria in long standing rheumatoid arthritis: a diagnostic challenge

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ABSTRACT

A 54-year-old male, a sero positive rheumatoid arthritis on treatment for 5 years, switched over to native drugs for 6 months. He was admitted with features suggestive of nephrotic range of proteinuria (Urine PCR- 8.32). A differential diagnosis of drug induced rheumatoid arthritis-amyloidosis was entertained. He underwent renal biopsy showed Membranous nephropathy (MN) (anti-phospholipase A2 receptor antibody PLA2R-positive). He was treated with high dose steroids, angiotensin receptor blockers and leflunomide as DMARD for rheumatoid arthritis. Nephrologist did not want to start mycophenolate mofetil/ rituximab since it was 1° MN. The proteinuria even after 1 month of steroids did not show any reduction; though anti-phospholipase A2 receptor antibody positive is a negative predictor for other secondary causes, considering his age and being a chronic smoker, we did a PET scan to rule out an internal malignancy. It revealed a metabolically active lesion in right upper lobe of the lung; Bronchoalveolar lavage (BAL) was done in that CBNAAT showed *Mycobacterium tuberculosis* positive. ATT was started and steroids tapered; a month into ATT, then Urine PCR reduced to 2 and at 3rd month of ATT, PCR was <1 and disease is under remission.

Keywords: Tuberculosis, Rheumatoid Arthritis, Proteinuria

INTRODUCTION

Membranous nephropathy (MN) is a renal disorder that affects the glomeruli of the kidney and cause protein in urine with decreased kidney function. The Incidence of MN related with tuberculosis is rarely reported among rheumatoid arthritis patients whereas the incidence of tuberculosis in rheumatoid arthritis patients was four-fold than that of the general population.[1] Glomerulonephritis (GN) due to *Mycobacterium tuberculosis* is rare and MN associated with tuberculosis is seldom reported.[2] MN is a common cause for proteinuria and nephrotic syndrome.[3] The term "nephrotic syndrome" refers to a distinct constellation of clinical and laboratory features of kidney disease. It is specifically defined by the presence of heavy proteinuria (protein excretion greater than 3.5 gm/24 hours), hypoalbuminemia (less than 3.5 gm/dL), and peripheral edema. Several studies reported that rheumatoid arthritis has increased the risk of nephron damage and tuberculosis because of the side effects of its medications.[4] In contrast, tuberculosis has a gradual and cumulative effect on MN. To the best of our knowledge there was no previous studies reports of MN related with tuberculosis in male rheumatoid arthritis. Hence, we described a patient with tuberculosis related MN with high proteinuria in rheumatoid arthritis male patients.

CASE REPORT

A 54 years old male patient presented to the outpatient department with the complaint of loss of weight for one month. There is no history of fever, cough with expectoration, shortness of breath, chest pain and palpitations. He had a past history of rheumatoid arthritis

under medication for 5 years on regular rheumatology follow up, he was treated with high dose steroids, angiotensin receptor blockers and leflunomide. His urine analysis showed proteinuria (3+), Urine PCR-8.32, He underwent renal biopsy showed MN (anti-phospholipase A2 receptor antibody PLA2R-positive). Steroids was continued, but even after one month the proteinuria did not come down, so evaluation was done for any internal malignancy as patient was having significant weight loss. PET scan was done and it revealed a metabolically active lesion in right upper lobe of the lung. In view of radiological findings, the patient was taken up for BAL and biopsy. BAL CBNAAT showed MTB detected. First line LPA: INH and Rifampicin resistance not detected. The smear of the patient shows positive pulmonary tuberculosis. ATT (4 tabs) was started and steroids tapered; a month into ATT, then Urine PCR reduced to 2 and at 3rd month of ATT, PCR was <1 and disease is under remission.

PET CT scan

FDG PET-CT scan whole body (Figure 1) was done by using a radioisotope of ^{18}F-FDG that was injected intravenously with extend of study from head to toes.

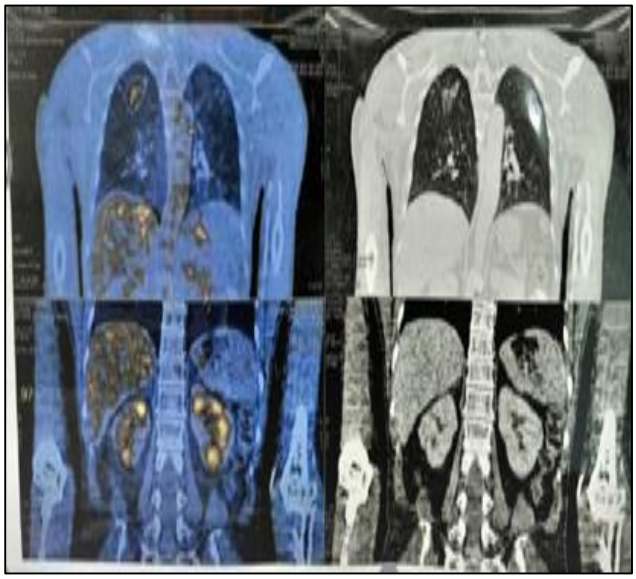

Figure 1: PET-CT scan whole body.

PETCT chest

Figure 2 showed confluent centrilobular nodules with patchy FDG uptake noted in apical segment of right upper lobe, apicoposterior segment of left upper lobe and superior segment of bilateral lower lobes. No evidence of metabolically active mediastinal lymphadenopathy. Rest of the study shows normal lung pattern with even distribution of pulmonary vascular branches and that of the bronchial tree. The anatomical configuration of the structures in the mediastinum and both hilar regions are within normal limits. No evidence of pleural effusion or pneumothorax. Lower trachea and main bronchi are unremarkable. Bony thorax shows no obvious abnormality.

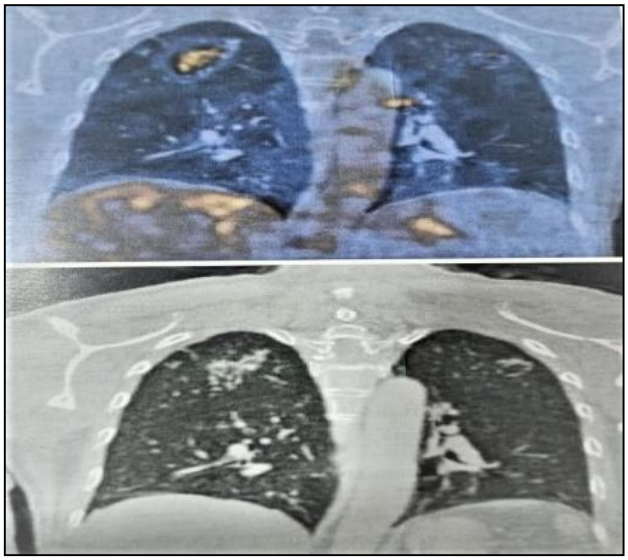

Figure 2: PETCT chest.

PETCT kidneys

Figure 3 showed that Right kidney is normal in size and shape, measures-73×44 mm. Patchy FDG uptake noted in the renal parenchyma (SUV max=3.4). The renal outlines are normal. No evidence of focal mass lesion/hydronephrosis. Parenchymal calcification / calculus (11 mm) is noted in the upper pole calyx. Left kidney is normal in size and shape-80×50 mm. Patchy FDG uptake noted in the renal parenchyma (SUV max=3.6). The renal outlines are normal. No evidence of focal mass lesion/hydronephrosis/calculi.

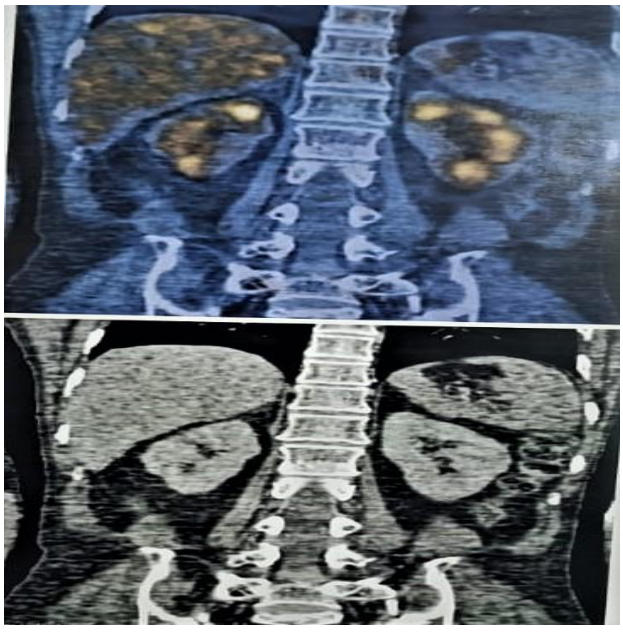

Figure 3: PETCT kidneys.

PETCT abdomen

Atherosclerotic wall calcification noted in the abdominal aorta. IVC appears normal. No significant retroperitoneal lymphadenopathy. The stomach is normal in site and size. The duodenum and proximal jejunal loops are normal in caliber. The ileum and ileo-cecal junction are normal. The colon and rectum are unremarkable.

The urinary bladder is moderately distended. Prostate appears normal in size. No evidence of 68Ga PSMA avid lytic/ sclerotic lesion noted in axial/visualized appendicular skeleton. There is no evidence of abnormal increased FDG accumulation in any visceral organs or elsewhere in the body.

PET CT brain

The cerebral hemispheres, brainstem and cerebellum appear normal. No evidence of midline shift or abnormal enhancement. The ventricles, sulci and basal cisterns are unremarkable. The calvarium is unremarkable.

DISCUSSION

In India, rheumatoid arthritis a systemic autoimmune disease affects about 0.92% of the adult population. Several studies reported that rheumatoid arthritis and its medication, mainly TNF α inhibitors may be associated with an increased risk of tuberculosis. The incidence of tuberculosis in rheumatoid arthritis patients was four-fold that of general population. We have reported a case of Rheumatoid arthritis with tuberculosis who had proteinuria and on evaluation found to have MN. Very few cases have reported the possibility of MN caused by RA itself, but its incidence and pathogenetic mechanisms are unknown. Regarding pathogenetic mechanisms, Honkanen et al found that 2 of 3 patients with MN directly induced by RA had positive finding for HLA DR4 antigen. They speculated that such specific HLA antigens might cause MN due to RA. Furthermore, they mentioned the possibility of involvement of RF like complexes in the development of this type of MN.[5] However, exact mechanisms for the development of MN in patients with rheumatoid arthritis were not clearly known. Generally, MN is induced by various clinical conditions including systemic lupus erythematosus, infections (hepatitis, syphilis), cancers, and drug exposure to agents such as disease-modifying antirheumatic drugs (DMARDs) including D-penicillamine, bucillamine, and gold salt. In the present case, there was no history of the use of the above-mentioned DMARDs.

MN also develop during the exposure to NSAIDs, MN was reported with all NSAIDs including selective cyclooxygenase 2 inhibitors, the mechanism of action on renal damage could be mediated through their common action cyclooxygenase inhibition.[6] The incidence of MN in patients with NSAIDs is not known. The lesions of RA related MN are similar those of primary MN on examination by light microscopy, electron microscopy and immunofluorescence.[7] The mechanism of RA related MN are unclear, the circulating autoantibodies in RA may target some podocyte proteins and eventually cause MN. Rituximab may probably represent the elective treatment of RA related MN, as it is helpful in both RA and MN.[8]

Shribman et al and Mercadal et al explained that the glomerulopathy associated tuberculosis have been due to immune complex deposition.[9,10] The patient in this case shows tuberculosis related MN in RA. Only there are few research evidence of tuberculous infection causing membranous glomerulopathy.[11,12] In the early stage of RA, drug induced proteinuria and renal dysfunction occurred in 1.7% and 1.5% of patients per year respectively.[13,14] Multiple chronic inflammatory conditions, among them rheumatologic, autoinflammatory, chronic infectious, and other disorders, have been associated with the development of AA amyloid. The most common organ system involved in this form of amyloidosis is the kidney, although other organ systems are often also affected.[15] In our case, the patient's laboratory investigation shows high proteinuria may results as MN. Therefore, with this report will help to enrich the experience of clinicians dealing with infectious diseases who may deals with numerous cases of tubercular infection presenting with various clinical manifestations.

CONCLUSION

Our case report highlights not all proteinuria in rheumatoid arthritis is due to amyloidosis. Tuberculosis as a secondary cause of MN in rheumatoid arthritis unless we look for it, very likely to miss it.

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