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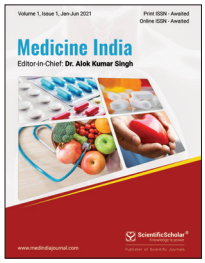

Case Report

Marked asymptomatic hyperuricemia; menace induced by antitubercular therapy – A case report

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ABSTRACT

Antitubercular therapy has revolutionized the treatment of all forms of tuberculosis however it is not devoid of adverse effects. Different drugs within the ATT have their specific as well as common side effects which may lead to non-adherence to the treatment as well as treatment failure. Hyperuricemia is one of the established adverse effects of pyrazinamide, with a little contribution from ethambutol. Pyrazinamide is known to have direct impact transport at the level of proximal convoluted tubule in kidney. In the case report that follows, we will be discussing an unusual case of asymptomatic ATT-induced hyperuricemia. A 28-year middle class female, without no known comorbidities who was started ATT empirically on clinical backgrounds develops profound hyperuricemia in the absence of any symptoms such as joint pain, swelling of joints, and flank pain.

Keywords: Antitubercular therapy, Pyrazinamide, Hyperuricemia, Asymptomatic, Case report

INTRODUCTION

ATT includes multiple drugs in different combinations each of which is associated with some specific as well as common adverseeffects. This may sometimes lead to treatment non adherence and treatment failure as well.[1,2]

Hyperuricemia is a common side effect of the antitubercular therapy. However, our case differs in terms of the level of uric acid level, asymptomaticity despite very high uric acid level and the period for rise in uric acid levels after the initiation of ATT. We want to emphasize on the deleterious effect of hyperuricemia in multisystem, though asymptomatic.

CASE REPORT

A 28-year female, resident of Bijnor, mother of two children, a homemaker, with no addictions and no previous comorbidities, presented with pain abdomen for 3 months that were insidious in onset, moderate to severe in intensity, localized to right upper quadrant and epigastric region, on and off in nature, without any typical exacerbating factor, non-radiating, no relation with meals. She developed shortness of breath for 2.5 months that was insidious in onset, Grade I MMRC at the onset that gradually progressed to Grade III in 1 week. It was associated with orthopnea and palpitation but no chest pain, syncopal attack. She was admitted in a local hospital for a few days and revisited primary health center in view of persistent fever. She received ATT on clinical backgrounds only. Initiation of ATT caused her multiple symptoms from the beginning. She developed vomiting multiple episodes, non-projectile, non-bilious, non-blood

stained, and containing food particles almost daily. It was associated increase in generalized weakness for 1 month. She noticed yellowish discoloration of the eyes and urine 4 days back, associated with dark yellowish stool not associated with itching. She developed altered mental sensorium manifested in the form of irrelevant talk, slurred speech, and disorientation for 4 days. There was no history of fever, neck stiffness, severe headache, trauma to head, abnormal body movements or bowel bladder disturbances.

She presented in the Emergency Department of AIIMS, Rishikesh, in the state of altered mental sensorium, with GCS of E4M4V4. She was grossly icteric, tachypneic, and tachycardic with RR of 24/min, pulse rate of 118 bpm, and oxygen saturation of 94% at room air and afebrile. Icterus and pallor were present. Positive systemic examination findings were raised JVP, lateral shifting of apical impulse, and shifting dullness in abdomen. Chest X-ray showed cardiomegaly with CT ratio of 0.6 [Figure 1]. ECG showed LBBB pattern without STE changes [Figure 2]. HRCT and CECT Chest showed necrotizing mediastinal lymphadenopathy likely tubercular etiology and confluent area of consolidation[Figure 3]. ABG was suggestive of mild respiratory alkalosis. Routine blood investigations showed normal CBC, slightly elevated urea and creatinine (68/1.03), elevated serum uric acid level (24.00), and phosphorus level of 7.03, with deranged LFT (total and direct bilirubin of 9.38/6.7, respectively, AST/ALT 464/281, ALP/GGT 281/195, and non-reactive viral markers). She was treated there in line of acute hepatic failure with inj. mannitol and N-acetyl cysteine and other supportive treatment.Ultrasonography abdomen and pelvis revealed mild bilateral pleural effusion with mild ascites. Pleural tap was transudative in nature. Her COVID RTPCR came negative and got shifted to general ward with GCS of 15/15 in hemodynamically stable condition. ATT was stopped and Tab. febuxostat started at a dose of 80 mg PO BID. 2D echo was done in the ward by the cardio team that revealed dilated four chambers of heart and global hypokinesia with left ventricular ejection fraction of 15%. Her cardiac biomarkers were within normal limits. During the stay in hospital, she was transferred to medicine ICU in view of cardiogenic shock, managed with inotropes noradrenaline and dobutamine. She is tapered off inotropic support, shifted back to general ward, and then discharged on patient's request [Table 1].

DISCUSSION

Pyrazinamide is one of the components of initiation phase of antitubercular therapy.[3] It is a well-known modulator of urate transport through the proximal tubules. Pyrazinamide undergoes metabolic conversion into its metabolite pyrazinoic acid which causes inhibition of renal tubular secretion of uric acid from the blood. Hyperuricemia is normally defined as serum uric acid level more than 7 mg/dl, the approximate level at which urate is supersaturated in plasma. As a result, when it exceeds the solubility threshold, it gets precipitated in the form of sodium urate crystals, which may be deposited in the joint space to cause gouty arthritis.

An article published in 2017 by Inayat *et al.* titled "Hyperuricemia and arthralgia during pyrazinamide therapy

Table 1: Investigations

Investigation	08 June, 2021	11 June, 2021	17 June, 2021	22 June, 2021	
HB	11.7	10.2			Ultrasound abdomen and pelvis: Mild ascites with mild bilateral pleural effusion HRCT and CECT chest Necrotizing mediastinal lymphadenopathy likely tubercular
TLC	9700	5.3			
DLC	67/23	53/31			
Platelet count	193	150			
Blood urea	68.2	17	35	22	
S. creatinine	1.03	0.45	0.72	0.67	
S. Na+	136	134	130	129	
S. K+	3.19	3.44	3.33	3.48	
S. calcium	8.7	8.1	8.4	8.6	
S. uric acid	24.88	16.99	12.0	8.1	
Phosphorus	7.03	2.0	3.5	2.5	
PT/INR	27.2/2.07				
T.BIL	9.38	4.94	2.11	2.71	
D.BIL	6.77	2.63	1.37	1.74	
SGPT	281	109	132	51	
SGOT	464	241	67	89	
ALP	195	90	74	80	
GGT	5.1	25	22	30	
T. protein	6.4	5.9	4.9	6.3	
S. albumin	3.64	2.4	2.2	2.7	

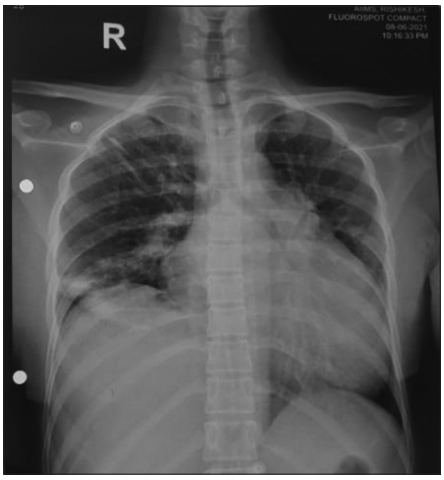

Figure 1: Chest X-ray PA view showing cardiomegaly (with cardiothoracic ratio of 0.6).

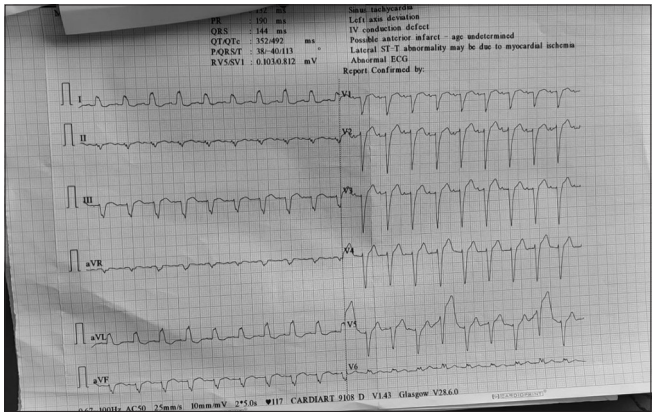

Figure 2: ECG showing left bundle branch block pattern.

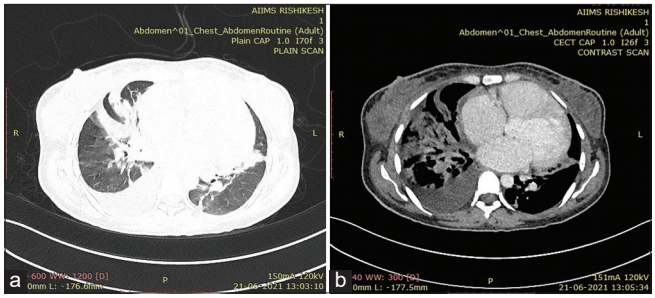

Figure 3: (a) HRCT chest image showing confluent areas of consolidation. (b) CECT chest image showing cardiomegaly with necrotic mediastinal lymphadenopathy and mild pleural effusion.

in patients with pulmonary tuberculosis" concluded that the mean uric acid level was significantly higher at 2 (6.8 mg/dl), 6 (7.2 mg/dl), and 7th (7.4 mg/dl) week compared to 0 week (5.1 mg/dl). In our case, the level of serum uric acid compared to the above article is very higher (24 mg/dl) after nearly 4 weeks of ATT. She is even not symptomatic despite this level of serum uric acid. About 21.7% of patients with ATT presented with hyperuricemic arthralgia.[4]

Pham *et al.* in an article entitled "Pyrazinamide-induced Hyperuricemia," emphasis is given to the risk of asymptomatic hyperuricemic effect on the genitourinary system. Although asymptomatic, hyperuricemia can potentially lead to three major disorders: Gout, urolithiasis, and urate nephropathy.[5] They presented a case report of suspected pyrazinamide-induced hyperuricemia in a kidney transplant patient resulting in acute renal injury.

Although major emphasis is given to pyrazinamide, ethambutol can also lead to hyperuricemia by impairing the uric acid excretion. Khanna *et al.* have published an article in 1984 regarding "Ethambutol-induced Hyperuricemia." In their study, the patient receiving SHE therapy showed significant hyperuricemia compared to the patient receiving SHT therapy. Only a few had arthralgia that resolved with withdrawal of ethambutol.[6]

Sasongko and Hasan performed a study to see the factors affecting the uric acid changes in tuberculosis patients who received oral antitubercular therapy with ethambutol and pyrazinamide. Study showed incidence of hyperuricemia to be 82.3% and symptomatic case were only 35.29%. No significant variability was noted in relation to sex, age, and BMI.[7]

It is a well-established fact that ATT, especially pyrazinamide, is responsible for causing hyperuricemia. The major difference that we saw in our case is the level of serum uric acid level being far more than the usually seen levels. The duration of treatment for which she took ATT was not the optimal time for maximum rise in serum uric acid level based on the previous studies. Moreover, no arthralgia was there despite this level of serum uric acid levels.

TREATMENT AND OUTCOME

She presented in emergency in the state of altered mental sensorium together with visible jaundice. She was initially stabilized in view of acute hepatic failure. Once the routine blood investigations were available, the uric acid level came to be 24.88 mg/dl. ATT was stopped and the serum uric acid levels decreased to 16.9 mg/dl 2 days and 8 mg/dl 10 days after starting Tab. febuxostat at a dose of 80 mg PO BID. She was given inotropic support in view of cardiogenic shock in ICU; ramipril, diuretics, and cardioselective beta-blocker in view of heart failure with reduced ejection fraction.

CONCLUSION

Hence, the issue of hyperuricemia in patients receiving ATT is a common one. We should not expect it to be symptomatically manifested always as arthralgia. Since hyperuricemia can potentially lead to gouty arthritis and urate nephropathy,

higher levels of the uric acid though asymptomatic should be taken care of. The choice of drugs for the reduction of uric acid levels depends on the clinicoinvestigative profile of the patient. In the presence of derangement of liver function, febuxostat, a xanthine oxidase inhibitor is preferred over the commonly used drug allopurinol. The ATT can be continued simply by managing the issue of hyperuricemia; there is no need to withhold ATT only for hyperuricemia.

TAKE HOME MESSAGE

Marked asymptomatic hyperuricemia can be seen with antitubercular therapy. Since hyperuricemia can affect the multiorgan system, it should be taken care of with the best pharmacotherapy even in the absence of symptoms of arthralgia.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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