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Case Report

Internal Medicine Section

Hyperuricaemia, Hypoparathyroidism and Acute Hypercalcaemia: Unusual Complications in Extrapulmonary Tuberculosis

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ABSTRACT

Hypercalcaemia may occur in patients with pulmonary tuberculosis because of abnormal extrarenal production of 1,25-dihydroxy Vitamin D3 by activated macrophages in granulomatous tissues. In Extrapulmonary Tuberculosis, derangements of calcium, Parathyroid levels are usually not seen. Rarely, serum calcium levels are raised with a normal vitamin D levels in background of an adequate sunlight exposure. Here, authors report a case of a patient with tubercular meningitis who presented with hypercalcaemia, hyperuricaemia, and hypoparathyroidism.

Keywords: Granulomatous, Parathyroid, Serum calcium

CASE REPORT

A 74-year-old male patient presented with altered behaviour characterised by use of abusive language without any provocation since last four months and from last 10 days he developed moderate grade fever, alteration in sensorium, decreased appetite and lethargy with occasional urinary and faecal incontinence. The patient was a known case of diabetes mellitus since last 20 years and has maintained blood glucose levels within normal range on Tab. Metformin 500 mg once daily and was also receiving Tab. Risperidone for the last four months for his abnormal behaviour. There was no history of pulmonary tuberculosis in past.

On general physical examination, he was emaciated, dehydrated and confused. His vitals were normal with BP-154/90 and pulse rate 84 beats/minute. On Neurological examination, Glasgow Coma Scale (GCS) was 12/15(E3V4M5), detailed higher mental functions could not be assessed because of irritability and confused sensorium. On cranial nerve examination, his pupils were mid-dilated, reactive to light with a normal fundoscopic examination. All Deep tendon reflexes were exaggerated; power could not be assessed but he was moving all four limbs. Planters were bilateral extensor, Kernig's and Brudzinski's signs were positive. Rest of his systemic examination was unremarkable.

On admission, his blood investigations revealed haemoglobin of 10.5 g/dL, total white cell count of 5900/cubic mm with 83% neutrophils, 9% lymphocytes, 8% monocytes and normal platelets counts. His baseline biochemical parameters were within normal range except serum calcium level 12.1 mg/dL (normal range = 8.5-10.50). His serum phosphate level was 3.5 mg/dL (normal range = 2.5-4.5) and serum uric acid 6.2 mg/dL (normal range = 3-7) that is, both were within normal range, Erythrocyte sedimentations rate 33 mm/hour, lipid profile normal, Viral markers HIV, HBsAg, and HCV were non-reactive. Thyroid profile- T3-112 ng/dL (normal range = 70-200), T4-6.8 ug/dL (normal range = 5.5-13.5). TSH 0.8 ulU/mL (normal range = 0.3-5.0) were also normal.

Chest X-ray, ultrasound of abdomen and MRI Brain and CECT chest and abdomen were done, no additional finding was found. CSF analysis was done showed total leucocytes count 15/cumm with 100% lymphocytes, proteins 210 mg/dL, sugar 79 mg/dL, ADA 11 U/L, India ink-negative, HSV-negative, ZN staining-negative, no malignant cells were seen.

In view of old age, long-standing behavioural changes, hypercalcaemia and hyperuricaemia, patient was evaluated further, his Ionised calcium was 1.41 mmol/L, serum 25(OH) Vitamin D -64.16 nmol/L (normal range = 75.00-250.00), parathyroid hormone level 5.20 pg/mL (normal range = 18.50-88.00), 24-hour urine creatinine 13.29 mg/kg/day (normal range = 14.00-26.00), 24-hour urine calcium -546 mg/dL (normal range = 100.00-300.00). The urine 24 hour measured 4980 mL with a 24 hour urinary calcium of 408 mg/24 hour (<240 mg/24 hour).

Serum electrophoresis, urine Bence Jones protein, skeletal survey did not show any evidence to suggest paraproteinemias and malignancy. His serum ACE level was 10 microlitres (8-53 µL).

So, on the basis of clinical features, examination and cerebrospinal fluid analysis findings, a diagnosis of tubercular meningitis was made; final diagnosis being Type 2 Diabetes Mellitus (T2DM) with TBM with parathyroid independent hypercalcaemia.

He was initiated on weight-based antitubercular therapy for TBM along with steroids and hypercalcaemia was managed with low calcium diet and tab hydrochlorothiazide 12.5 mg once a day with Saline diuresis. The patient started showing improvement in sensorium within a week. His sensorium was improved and was discharged in stable condition with GCS 15/15 after a hospital stay of 15 days. Prior to discharge, his biochemical profile showed raised serum uric acid levels (11.0 mg/dL) with the rest of the parameters within normal range. Hence, the patient was advised low uric acid diet and was prescribed tab febuxostat 1 BD because of hyperuricaemia, Tab. Pyrazinamide was withdrawn. On follow-up, the patient remained asymptomatic. S. calcium was 9.0 mg/dL, serum 25(OH) vitamin D was 84.0 ng/mL (normal range = 30-100) and serum uric acid was 5.9 mg/dL. He was advised to continue the same treatment.

DISCUSSION

Hypercalcaemia may occur before or after initiation of therapy in patients with active TB and other granulomatous diseases and is due to dysregulated extrarenal production of $1,25(OH)_2D_3$ from activated macrophages [1]. Hypercalcaemia is much more common in pulmonary TB and is seen rarely in extrapulmonary TB. Payne HA et al., reviewed all previously reported 12 paediatric patients and found that only two had extrapulmonary TB [2]. None, however, had Tubercular Meningitis (TBM) as seen in the present case. The diagnosis of TBM in the present patient was based on the sub-acute presentation, CSF findings with high ADA levels which have a sensitivity of 94.7%, specificity 90.4%, positive

predictive value 90.0% and a negative predictive value of 95.0% for the diagnosis of TBM [3].

In TB, hypercalcaemia can occur possibly due to increased production of $1,25(OH)_2D_3$ by alveolar immune cells, which is not under feedback control by parathyroid hormone. This $1,25(OH)_2D_3$ overproduction is a protective mechanism against oxidative injuries due to the nitric oxide burst from granulomatous macrophages [4]. However, not every patient with TB develops hypercalcaemia due to the reason that $1,25(OH)_2D_3$ is produced in small quantities locally and is not carried to target sites for the regulation of calcium homeostasis. This mechanism of hypercalcaemia has been stipulated in patients with pulmonary TB. However, the underlying mechanism in extrapulmonary TB, as seen in the present patient, remains uncertain. A study indicates that circulating monocytes may be an alternative source of 1-α hydroxylase that could convert 25(OH)D3 to $1,25(OH)_2D_3$. This $1,25(OH)_2D_3$ produced by monocytes act locally, and when these cells are carried by blood to target tissues, it may play a role in calcium homeostasis, unlike alveolar immune cells. Although, the relative contribution of monocyte source of $1,25(OH)_2D_3$ to the total $1,25(OH)_2D_3$ level is small in most cases of TB [5]. Elevated circulating $1,25(OH)_2D_3$ concentrations may lead to enhanced absorption of calcium from the gastrointestinal tract resulting in hypercalcaemia.

Hypercalcaemia in patients with tuberculosis was generally due to Hypervitaminosis D but some studies have also shown that it was independent of calcitriol levels [6]. A calciotropic hormone study conducted in untreated active Pulmonary Tuberculosis (PTB) patients among Hong Kong Chinese, demonstrated higher albumin-adjusted serum calcium despite a lower calcium intake. There was no significant change in serum 25(OH)D or $1,25(OH)_2D_3$ concentrations and serum Parathyroid hormone level was significantly lower in these patients. In the present study also patient with tubercular meningitis with near normal $1,25(OH)_2D_3$ levels developed hypercalcaemia with low parathyroid levels.

In a study, it was found that subjects with PTB had low $1,25(OH)_2D_3$ and low Parathormone (PTH) along with hypercalcaemia which subsided spontaneously. One possible explanation can be that hypercalcaemia unrelated to vitamin D would be expected to decrease parathyroid gland activity and cause a secondary lowering of serum level of 1,25-dihydroxy vitamin D since 1-hydroxylation of 25-hydroxyvitamin D in kidneys is regulated by parathyroid hormone. Hence, there are studies describing parathyroid independent hypercalcaemia in tuberculosis patients [7].

In the present case, the patient developed hyperuricaemia after two weeks of starting Antitubercular treatment. Among various antitubercular drugs, Pyrazinamide and ethambutol are notorious for causing hyperuricaemia. Pyrazinamide is a strong urate retention agent, causing a decrease in renal clearance of uric acid by more than 80% at a therapeutic dose of 300 mg/day. Pyrazinecarboxylic acid or Pyrazinoate (PZA), an active metabolite of pyrazinamide, increases serum uric acid based on its trans-stimulatory effect on Uric Acid Transporter 1(URAT1), which is a member of the Organic Anion Transporter (OAT) family. This results in increased re-absorption of urate from the luminal side into tubular cells, and is likely responsible for the hyperuricaemic effect. Hyperuricaemia has been reported in 43 to 80 percent of patients treated with pyrazinamide (alone or in combination) [8]. Furthermore, gouty attacks have been associated with patients taking pyrazinamide. Hyperuricaemia can also occur with ethambutol by decreasing renal uric acid clearance, but it occurs less frequently and to a lesser degree than pyrazinamide [9]. Hence, in the present scenario, hyperuricaemia is most likely drug-induced which reverted back to pre-treatment levels after dietary and anti-tubercular treatment modification.

CONCLUSION

We present a rare occurrence of hypercalcaemia in a 70-year-old male with extra-pulmonary tuberculosis. In the context of current recommendations on vitamin D supplementation, it is important to observe caution while initiating vitamin D and calcium supplements before anti-tubercular therapy. Close clinical and laboratory monitoring for hypercalcaemia is essential in these cases.

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