CASE REPORT

Hypercalcaemia: atypical presentation of miliary tuberculosis

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SUMMARY

We report an unusual case of miliary tuberculosis in a 77-year-old Filipino man with hypertension, diabetes mellitus, nephrolithiasis status-post left nephrectomy, presenting with 1 month of fever, generalised weakness and weight loss. Laboratory data were significant for anaemia, hypercalcaemia and acute kidney injury. Chest radiograph showed ground glass opacities and interstitial infiltrates. Extensive workup was performed to evaluate fever and hypercalcaemia. Malignancy, hormonal and septic workup were all unremarkable. Tuberculin skin test was negative. Sputum, pleural fluid, bronchoalveolar lavage and cerebrospinal fluid were acid-fast bacilli (AFB) smear negative. Remarkably, urine AFB smear was positive. Caseating granulomas were seen on transbronchial biopsy. Antituberculosis therapy was initiated which led to defervescence and initial clinical improvement. However, hospital course became complicated by small bowel obstruction and respiratory failure. He subsequently developed pulseless electrical activity and expired. An autopsy confirmed the presence of tuberculosis in multiple organs including his remaining kidney.

BACKGROUND

Diagnosis of miliary tuberculosis (TB) can be very challenging as it may not present with typical chronic respiratory symptoms. Metabolic disturbances like hypercalcaemia may be an important clue to its diagnosis. As in our case, miliary TB should always be one of the differential diagnoses of fever of unknown origin and hypercalcaemia. Moreover, workup for renal TB with urine acid-fast bacilli (AFB) should be carried out in high-risk patients with a history of kidney stones.

CASE PRESENTATION

The patient was a 77-year-old Filipino man with type 2 diabetes mellitus, a remote history of left nephrectomy for possible nephrolithiasis, and a 40 pack-year smoking history who presented with 1 month of intermittent fever and generalised weakness. Accompanying symptoms included anorexia, episodic confusions, polyuria, low back pain and 10-pound weight loss. He denied recent sick contacts, travel, cough, haemoptysis or night sweats. He denied vitamin A, D or calcium supplements intake. He denied family history of malignancy. However, he was exposed to his brother, who had history of active TB, 25 years ago in the Philippines. He was uncertain whether he had a tuberculin skin test (TST) before but was never treated with anti-TB medication.

Initial vital signs were within normal limits except for a temperature of 39.3°C. Physical examination was remarkable for cachexia and bibasilar crackles but no lymphadenopathy, hepatosplenomegaly or bony tenderness.

INVESTIGATIONS

On admission, significant laboratory data were haemoglobin 10.6 g/dL, white cell count 7000/mm³, calcium 14.7 mg/dL, albumin 2.5 g/dL and creatinine 2.3 mg/dL (baseline: 1.8 mg/dL). Aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase were elevated at 42, 44 and 883 IU/L, respectively. Ultrasound of abdomen was remarkable for fatty liver and no bile duct dilation. Urinalysis showed trace proteinuria and mild haematuria. Blood and urine cultures were negative.

Serum protein electrophoresis and urine protein electrophoresis were within normal limits. Skeletal survey and bone scan did not show any osteolytic or osteoblastic lesions. Serum prostate-specific antigen was normal at 0.89 ng/mL. Serum intact parathyroid hormone level was 12 pg/mL, which is below normal. Serum parathyroid hormone-related peptide and calcitriol 1,25-dihydroxyvitamin D₃ (1,25-(OH)₂D₃) levels were normal at 16 and 55 pg/mL, respectively.

Chest radiograph showed ground glass opacities and interstitial infiltrates ([figure 1](#)), whereas CT scan of the chest revealed bibasilar consolidations, emphysematous changes, pleural effusions and a 4 mm right upper lobe (RUL) nodule which was unchanged from previous image 1 month ago ([figure 2](#)). Sputum Gram stain (G/S) and culture were negative. Bronchoscopy with bronchoalveolar lavage (BAL) was negative for G/S, culture, viruses, fungi and pneumocystis stains (silver and Diff-Quik stains). Pleural fluid was transudative and cytology was negative for malignancy.

HIV screening test and TST were negative. Blood, sputum, BAL and pleural fluid were negative for AFB smear and culture. Transbronchial biopsy of RUL nodule showed multiple caseating granulomas ([figure 3](#)) but negative for AFB smear and culture. Owing to episodic confusions, lumbar puncture was performed and cerebrospinal fluid was also negative for AFB smear and culture. Surprisingly, urine AFB smear was positive with the culture eventually growing *Mycobacterium tuberculosis*.

DIFFERENTIAL DIAGNOSIS

Malignancy and disseminated TB were the most highly considered diagnoses in this case. Multiple myeloma, lung cancer, renal cell carcinoma and

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Figure 1 Bilateral diffuse reticulonodular opacities.

lymphoma were suspected due to his age, smoking history, weight loss and degree of hypercalcaemia. On the other hand, TB was suspected based on his country of origin, remote TB exposure, fever and history of kidney stones which might suggest renal TB.

Community acquired pneumonia and/or pneumocystis jirovecii pneumonia were also considered as causes of fever of unknown origin, supported by diffuse bilateral infiltrates. Albeit, they would not explain the hypercalcaemia. However, sarcoidosis and other granulomatous diseases were entertained.

TREATMENT AND OUTCOME

Hypercalcaemia was treated with aggressive intravenous hydration, intravenous pamidronate and subcutaneous calcitonin. Serum calcium level normalised on hospital day 4. Antibiotics for community-acquired pneumonia were initiated empirically. Fever persisted for 9 days. After a week of diagnostic evaluation, urine was positive for AFB smear. As miliary TB was highly suspected, oral anti-TB therapy (isoniazid, rifampin, pyrazinamide, ethambutol) and intravenous corticosteroids were initiated. He defervesced 1 day after therapy, and improved clinically. However, after 1 week of anti-TB therapy, he developed small bowel obstruction of unclear aetiology. He was treated conservatively

Figure 2 Bibasilar consolidations, emphysematous changes, bilateral pleural effusions.

Figure 3 Lung, multiple caseating granulomas.

with intravenous hydration and bowel rest. Anti-TB medications were changed to an intravenous regimen (linezolid, moxifloxacin, rifampin). Colonoscopy was performed, however, the scope was unable to pass the splenic flexure due to a sharp angulation. No masses or structural lesions were noted. Two days later, he developed sudden dyspnoea leading to hypoxic respiratory failure and demise. He had requested Do-Not-Resuscitate status at admission. Postmortem examination confirmed the presence of TB in thyroid gland, lungs (figures 4 and 5), liver, right kidney, left peri-adrenal gland, colon and bone marrow. Also, ischaemia was noted in small bowel and colon.

DISCUSSION

Among all causes of hypercalcaemia, primary hyperparathyroidism and malignancy are the most common. Even though malignancy is a common cause of hypercalcaemia in hospitalised patients, granulomatous diseases should be part of the differential diagnosis. Among the granulomatous diseases, sarcoidosis and TB are probably most common. A clinical review finds that the mechanism of hypercalcaemia in these conditions is mainly due to dysregulated production of 1,25-(OH)₂D₃ (calcitriol) by activated macrophages trapped in pulmonary alveoli and granulomatous inflammation.¹ Interestingly, our patient had normal 1,25-(OH)₂D₃ levels which raises the question whether there is another mechanism of hypercalcaemia in patients with miliary TB.

Hypercalcaemia often manifests as polyuria, polydipsia, abdominal pain, vomiting, constipation and mental obtundation. If hypercalcaemia is long-standing, one may develop chronic hypercalciuria which in turn causes nephrolithiasis.

Figure 4 Lung, caseating granuloma with multinucleated giant cell.

Figure 5 Lung, acid-fast bacilli stain highlighting multiple tuberculosis organisms as red rods.

Genitourinary TB occurs by haematological dissemination of pulmonary TB in almost all cases. From a review of 102 cases of genitourinary TB, 16% showed renal calcification.² Our patient presented with classic symptoms of hypercalcaemia and had a history of nephrectomy due to possible nephrolithiasis. At autopsy, he was confirmed to have TB in his remaining kidney. Therefore, in a patient with history of kidney stones, fever and hypercalcaemia, a urine AFB should be checked to rule out genitourinary or miliary TB.

Establishing a diagnosis of miliary TB requires sufficient clinical suspicion; the diagnosis can be challenging due to non-specific clinical symptoms and signs. The TST can be a supportive diagnostic tool if positive, but a negative skin test does not exclude the diagnosis. Just like our patient, anergy was observed more frequently among patients with miliary TB than those with pulmonary or isolated extrapulmonary involvement. Mycobacterial culture of tissue, fluid or drainage from an infected locus is the standard tool for establishing the diagnosis of TB. Acid-fast microscopy may support a diagnosis of TB, especially if organisms or caseating granulomas are seen. Based from two retrospective studies, the frequency of positive smears or cultures from different sources is summarised in table 1.^{3 4} These two studies also found that only 7–14% of patients with miliary TB will give a positive urine AFB smear whereas 33–36% will give a positive sputum AFB smear.^{3 4}

Table 1 Frequency of positive smear or culture in patients with miliary tuberculosis

Site	Maartens <i>et al</i> ³	Kim <i>et al</i> ⁴
Sputum smear	33*	36
Sputum culture	62	76
BAL smear	27	9
BAL culture	55	54
Gastric aspirate smear	43	0
Gastric aspirate culture	100	75
Urine smear	14	7
Urine culture	33	59
CSF smear	8	0
CSF culture	60	0
Serosal smear	6	0
Serosal culture	44†	14‡

*All numbers are percentages.

†9 Ascites, 7 pleural and 2 pericardial.

‡All pleural.

BAL, bronchoalveolar lavage; CSF, cerebrospinal fluid.

There was a reported case of miliary TB in a 3-month-old boy who had a positive urine culture for *M tuberculosis* but negative for urine AFB smear.⁵ Interestingly, our case had a positive urine AFB smear but negative sputum and BAL AFB smear, which makes it unique. Smears for AFB were positive in a minority of patients when only a single site was sampled; the probability of a positive smear increased with the number of sites sampled. Thus when possible, samples of multiple sites (sputum, gastric aspirate, pleural fluid, ascites, urine) should be examined for the presence of AFB.^{3 4}

CONCLUSION

Diagnosis of miliary TB can be very challenging especially in patients with an unusual presentation. It is essential to recognise the clinical manifestations of hypercalcaemia as it is an atypical presentation of miliary TB. A high index of suspicion is warranted. As in our case, miliary TB should always be one of the differential diagnoses of fever of unknown origin and hypercalcaemia. Moreover, workup for renal TB with urine AFB smear should be carried out in high-risk patients with history of kidney stones. Checking a 1,25-(OH)2VD3 level might also aid in the diagnosis of granulomatous disease-induced hypercalcaemia.¹ On the other hand, a normal 1,25-(OH)2VD3 level does not rule out a granulomatous disease-related hypercalcaemia, as exemplified in this case. It is also of utmost importance to empirically treat miliary TB early in its course even without culture results, especially with a positive urine AFB and a high clinical suspicion. Finally, a future study to further understand the mechanism(s) of hypercalcaemia in miliary TB might contribute to a better understanding of our case.

Learning points

- ▶ Granulomatous diseases, such as miliary tuberculosis, should always be part of differential diagnoses in patients with hypercalcaemia.
- ▶ Urine acid-fast bacilli smear should be included as part of the work up if miliary tuberculosis is suspected, especially in patients with history of kidney stones.
- ▶ A negative tuberculin skin test or purified protein derivative test is frequently observed in patients with miliary tuberculosis.
- ▶ A normal 1,25-dihydroxyvitamin D₃ level does not rule out miliary tuberculosis as a cause of hypercalcaemia.

Competing interests None.

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