CASE REPORT

Hypercalcaemia caused by active pulmonary tuberculosis in an elderly person without fever or pulmonary symptoms

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SUMMARY

Many diseases can cause hypercalcaemia, including primary hyperparathyroidism, cancer, drugs and granulomatous diseases. A nursing home resident aged 81 years was admitted because of altered mental status. The patient did not have fever, cough, sputum or night sweat. Hypercalcaemia was identified as a cause of the consciousness disturbance. Chest radiograph showed no acute process. Laboratory workups revealed elevated serum levels of 1,25-(OH)₂ vitamin D₃ and positive T-spot test. Microscopic examination of the suctioned sputum identified acid-fast bacilli, which was confirmed as *Mycobacterium tuberculosis*. Tuberculosis should be considered as the important cause of hypercalcaemia since early diagnosis and treatment is recommended for preventing its outbreak among people with close contacts with patients.

BACKGROUND

Tuberculosis remains important infectious disease worldwide as well as in Japan with recent annual incidence of about 19 000 cases for new diseases overall and about 76 000 for smear-positive pulmonary diseases in the country.¹ Most tuberculosis in elderly Japanese is a reactivation disease, but it may lead to secondary contagion to other nearby people through air-borne infection. Patients with active pulmonary tuberculosis in a nursing home may result in new infection of tuberculosis among care providers.

Thus, timely diagnosis of tuberculosis is important, but active pulmonary tuberculosis in elderly patients may lack typical symptoms such as fever or pulmonary symptoms including cough or sputum. Hypercalcaemia can be a sign of tuberculosis, although it is rare. Only a few per cent of hypercalcaemic patients admitted to hospitals were identified as caused by tuberculosis.²⁻³ We herein report a case of an elderly person with active pulmonary tuberculosis who developed hypercalcaemia but did not have fever or respiratory symptoms.

CASE PRESENTATION

A Japanese man aged 81 years, who had lived in a nursing home, was brought to our hospital because of altered mental status noted by a home staff in the morning of the admission day. The patient had right cerebral haemorrhage and dementia and thus required nursing home care for several years. He was admitted for respiratory infection 5 months ago, which was treated by ceftriaxone and azithromycin and gastrostomy tube had been placed 2 months

earlier. There were no documentations of fever, chills, recent weight loss, cough, sputum, headache, abdominal pain, arthralgia, seizure or involuntary movement. He did not have history of allergy, sick contacts, recent travels or exposure to animals. His regular medications included famotidine and magnesium oxide laxative and he did not use any supplements including vitamins or calcium. The family history was not contributory.

The patient appeared ill. The temperature was 36.8°, the heart rate of 87 bpm, the blood pressure 128/60 mm Hg, the respiration rate of 20/min. The body mass index was 22. The Glasgow Coma Scale was E4V3M6 (total score of 13). The pulse oximetry oxygen saturation was 97%, while he was breathing ambient air. There was no neck stiffness. The cardiovascular examination was normal and lungs were clear to auscultation. The abdominal examination was unremarkable with no hepatosplenomegaly. There was new-onset weakness of right upper and lower extremities in addition to the residual weakness of left upper and lower extremities. The remainder of the physical examination was normal.

INVESTIGATIONS

Blood tests showed glucose 145 mg/dL, urea nitrogen 58 mg/dL, creatinine 2.6 mg/dL, sodium 136 mEq/L, chloride 92 mEq/L, potassium 3.3 mEq/L, calcium 11.9 mg/dL, phosphate 4.4 mg/dL, magnesium 3.2 mg/dL, total protein 8.2 g/dL and albumin 2.6 g/dL. At the time of the gastrostomy placement 2 months ago, serum creatinine level of the patient was 1.08 mg/dL. The remainder of laboratory test results is shown in box 1.

Chest radiograph (figure 1) showed bilateral hazy ground glass opacities, which was considered as unchanged in comparison to the previous film obtained 2 months earlier. CT scan of the head showed no haemorrhagic lesion and MRI did not show infarction of new onset. Abdominal ultrasonography showed no hydronephrosis, intra-abdominal mass or hepatosplenomegaly.

DIFFERENTIAL DIAGNOSIS

Altered mental status and acute kidney injury due to hypercalcaemia was considered. Although the patient developed right hemiparesis, we considered that this finding might have reflected possible generalised weakness caused by hypercalcaemia since he had had residual left hemiparesis from a prior ischaemic stroke. By hospital day 4, his serum calcium level decreased gradually by careful hydration. The

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Box 1 The remainder of laboratory test results of the patient

1. Complete blood count
 Haemoglobin 10.2 g/dL (13.6–18.3)
 Mean cell volume 81 fL (83–101)
 White cell count 6500/ μ L (3500–9700)
 Neutrophils 70% (42–74)
 Lymphocytes 21% (18–50)
 Monocytes 7.2% (1–8)
 Eosinophils 0.5% (0–7)
 Basophils 1.4% (0–2)
 Platelet 334 000/ μ L (140 000–379 000)
 2. Serum chemistry test
 Total bilirubin 0.2 mg/dL (0.3–1.2)
 Aspartate aminotransferase 52 U/L (10–40)
 Alanine aminotransferase 42 U/L (5–45)
 Alkaline phosphatase 230 U/L (104–338)
 Lactate dehydrogenase 169 IU/L (120–245)
 Gamma glutamyl transferase 11 U/L (0–79)
 3. Coagulation test
 International normalised ratio of prothrombin time 0.84 (0.91–1.08)
 Activated partial thromboplastin time 26 s (26–38)
 4. Urinalysis
 Protein 2+
 Occult blood 1+
 No pyuria
 5. Urine chemistry test
 Urine sodium 55 mEq/L (40–90)
 Urine potassium 26 mEq/L (20–60)
 Osmolality 319 mosm/L (50–1300)
 Urine urea nitrogen 435 mg/dL (100–500)
 Urine creatinine 38 mg/dL (5–40)
- *Data inside all parentheses in this box indicate reference values.

Figure 1 Chest radiograph of the patient.

hydration was carefully performed from 2 L on day 1 followed by gradual tapering of hydration in the several days. We did not use bisphosphonate, calcitonin or steroids.

The cause of hypercalcaemia was investigated. Blood and urine immunoelectrophoresis showed there was no plasma monoclonal protein or urine Bence-Jones protein. There were no punched-out lesions in the skull X-ray image. Serum levels of PTH-related protein, intact PTH and thyrotropin were normal.

However, serum level of 1,25-(OH)₂ vitamin D₃ was elevated at 95 pg/mL. Although serum level of ACE inhibitor was normal, T-spot test was positive. On hospital day 10, sputum collection by suctioning was performed and microscopic examination for acid-fast bacilli staining of the sputum revealed positive result for Gaffky grade-3. This was confirmed by a PCR test as *Mycobacterium tuberculosis*.

TREATMENT

The patient received medications for treatment of pulmonary tuberculosis, including isoniazid 200 mg, rifampin 450 mg, pyrazinamide 500 mg and ethambutol 500 mg each day for 3 months. After we obtained drug sensitivity test showing the drug-sensitive strain, we used isoniazid 200 mg, rifampin 450 mg and ethambutol 500 mg each day for 2 months. He was then administered isoniazid 200 mg and rifampin 450 mg for 2 months.

OUTCOME AND FOLLOW-UP

The patient was transferred to another hospital for continuing treatment. He was stable and there had been no recurrence of hypercalcaemia at the previous contact 9 months after the transfer.

DISCUSSION

The current case reminds us of the importance of tuberculosis as a cause of hypercalcaemia and an infectious disease without fever and respiratory symptoms in elderly patients. Tuberculosis should be considered in patients with hypercalcaemia and elevated serum level of 1,25-(OH)₂ vitamin D. Patients with active pulmonary tuberculosis may not have fever or respiratory symptoms. Whenever tuberculosis is suspected, swift diagnostic test is mandatory.

Main causes of hypercalcaemia include primary hyperparathyroidism, cancers, drugs and granulomatous diseases, although relative frequency is different between various regions.⁴ Primary hyperparathyroidism is the most frequent cause, but cancer and drugs have been recently identified as the causes with increased frequency, especially in elderly patients because of the greater risk for cancer and increased use of vitamin D supplements. However, following these three major causes of hypercalcaemia, granulomatous diseases remain important causes for hypercalcaemia and these include sarcoidosis, histoplasmosis, coccidioidomycosis and candidiasis in addition to tuberculosis. Finally, other rare causes include hyperthyroidism.

Investigations for causes of hypercalcaemia include detailed history-taking, physical examination and logical use of laboratory tests. The use of vitamin D or calcium should be sought and physical examination should be performed for looking for a clue suggestive of possible malignancy or granulomatous diseases.

The logical use of laboratory tests that should be conducted after ruling out drug-induced hypercalcaemia usually includes the determination of serum levels of PTH and PTH-related protein and the identification of plasma or urine monoclonal protein when appropriate. If granulomatous diseases are considered as causes of hypercalcaemia, serum level of 1,25-(OH)₂ vitamin D₃ should be checked.

Activated macrophages within granulomatous lesions are considered to increasingly produce this vitamin.⁵ There is variation

of proportions for developing hypercalcaemia in tuberculosis between international regions.⁶ This regional variation in the prevalence of hypercalcaemia in tuberculosis may be due to differences in the baseline calcium intakes between populations.⁶

Timely diagnosis and treatment of active pulmonary tuberculosis is important since it can cause secondary infection to others if not identified and treated. Elderly patients with active pulmonary tuberculosis may not have fever or respiratory symptoms as in the current case. The abnormality of chest radiograph may be non-specific and may appear unchanged over several months, which was also true in the current case. Thus, high index of suspicion and swift microbiological examination is recommended when tuberculosis is considered. T-spot test may be helpful as the adjunct test for increasing probability of tuberculosis as used in the current case. Sputum was obtained in the current case for microbiological examination as the first-line test. If it might not be available, collection of gastric juice might be considered.

In conclusion, authors recently experienced a case of hypercalcaemia caused by active pulmonary tuberculosis, which did not accompany fever or pulmonary symptoms. Active pulmonary tuberculosis should be considered in patients with hypercalcaemia and elevated serum level of 1,25-(OH)₂ vitamin D even in cases of no fever or pulmonary symptoms.

Patient's perspective

We, as the family of the patient, know that prognosis of the patient is not good. But it was very important that his illness was correctly diagnosed as tuberculosis and treated accordingly since it could cause outbreak among other residents and caregivers in the nursing home. We appreciate it if the case report of the patient could contribute to the improvement of quality of diagnosis of tuberculosis in elderly patients.

Learning points

- ▶ Hypercalcaemia can be caused by primary hyperparathyroidism, cancer, and drugs, as well as granulomatous diseases.
- ▶ Pulmonary tuberculosis is a rare but important cause of hypercalcaemia because of its possibility of the transmission to other people and the treatability.
- ▶ Patients with active pulmonary tuberculosis may not present with cough, sputum or fever.

Contributors SH, TS and DI cared the patient. SH and YT wrote the manuscript. All authors reviewed and approved the final version of the manuscript.

Competing interests None declared.

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