CASE REPORT

Sarcoidosis as a cause of unappreciated hypercalcaemia in a patient with end-stage renal disease on peritoneal dialysis

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SUMMARY

The differential diagnosis of hypercalcaemia in patients with end-stage renal disease undergoing dialysis should be considered for causes related or unrelated to renal failure itself or therapies for renal failure. In particular, peritoneal dialysis may hinder awareness of a clinical problem due to its own peculiarities and effects on homeostasis of the body, thus creating misconceptions in interpreting laboratory data and diagnosing a disease. We describe here a case of systemic sarcoidosis which was delayed due to failure to recognise underestimated hypercalcaemia in a patient undergoing peritoneal dialysis. Clinicians need to remain aware of the change of minerals that may arise from peritoneal dialysis and should perform an extensive investigation for the cause of hypercalcaemia.

supraclavicular area and splenomegaly. No specific skin lesions were observed.

INVESTIGATIONS

Simple chest X-rays revealed pneumonic infiltration in the right lower lobe. CT scan of the chest showed a patchy consolidation in the right lower lobe with a small amount of right pleural effusion and multifocal lymphadenopathy. A subsequent positron emission tomography (PET) scan study demonstrated nodular fluorodeoxyglucose (FDG) uptake in the left posterior cervical space, right internal mammary region and anterior pericardial regions as well as in the lower internal jugular, supraclavicular and axillary areas (figure 1). It also showed multifocal FDG uptake in the retroperitoneal region and nodular FDG uptake in the common iliac, obturator

BACKGROUND

Sarcoidosis is a multisystem inflammatory disorder of undetermined aetiology that may cause significant morbidity. Although the diagnosis of sarcoidosis is usually made by clinical, radiological and histological evidence, there are often delays in the diagnosis and management due to the lack of the criterion diagnostic test.¹ In the field of clinical nephrology, renal involvement of systemic sarcoidosis or renal-limited sarcoidosis remains a major focus for nephrologists.^{1 2} Although rare, sarcoidosis has also been reported as a cause of elevated serum calcium levels in patients with end-stage renal disease (ESRD) treated with long-term haemodialysis.^{3 4} Herein we describe a case of systemic sarcoidosis as a cause of hypercalcaemia, which was overlooked due to the low plasma albumin level, in a patient with ESRD undergoing peritoneal dialysis (PD).

CASE PRESENTATION

A 52-year-old female patient was admitted to our hospital with progressive general weakness and loss of appetite for the past 1 month. She had been on PD for 5 years due to ESRD secondary to hypertension. During the first 4 years of PD, her clinical course was uneventful. One year prior to this presentation, recurrent episodes of pneumonia in the right lower lobe caused by an unknown pathogen had required the patient to make frequent admissions to the hospital. On admission, physical examination revealed no remarkable findings except for the presence of a palpable mass in her left

Figure 1 Position emission tomography (PET) finding shows multinodular fluorodeoxyglucose (FDG) uptake in the thoracic and abdominal regions.

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and inguinal regions with localised FDG uptake of the spleen. Bronchoscopic findings revealed airway narrowing, blunted carina and impacted mucus in the right lower lobe. An analysis of bronchial washing fluid disclosed some neutrophils, macrophages and reactive bronchial epithelial cells with negative results for PCR and hybridisation for *Mycobacterium tuberculosis*. The laboratory data were as follows: white blood cell (WBC) count 2600/mm³ (range, 5000–10 000), haemoglobin 6.6 g/dL (12.0–16.0), haematocrit 22.0% (37.0–47.0), platelet count 156 000/mm³ (150 000–450 000), blood urea nitrogen (BUN) 46.5 mg/dL (8.0–23.0), serum creatine 9.20 mg/dL (0.5–1.2), total protein 7.0 g/dL (6.5–8.3), albumin 2.59 g/dL (3.5–5.3), uric acid 9.1 mg/dL (2.5–8.3; 541 µmol/L), calcium 10.1 mg/dL (8.2–10.2; 2.52 mmol/L), phosphorus 7.7 mg/dL (2.5–4.5; 2.49 mmol/L), alkaline phosphatase 307 IU/L, IgG 2472 mg/dL (700–1600), IgA 928 mg/dL (70–400) and IgM 85 mg/dL (40–230). Serum protein electrophoresis showed polyclonal gammopathy.

DIFFERENTIAL DIAGNOSIS

Initially, multiple lymphadenopathy was considered because of systemic involvement of haematologic malignancies such as lymphoma or chronic infectious diseases such as tuberculosis. Serum cytomegalovirus (CMV), Epstein–Barr virus (EBV), hepatitis B Virus, hepatitis C virus and HIV antibodies were all negative. CMV-DNA and EBV-DNA were undetectable. Both tuberculin skin test and interferon γ release assay (TB-spot) were negative. A biopsy of the left enlarged supraclavicular lymph node showed non-caseating granulomatous inflammation with multinucleated giant cells (figure 2). Tissue for acid-fast bacilli (AFB) using Ziehl–Neelsen stain and for fungal organism using methenamine silver and PAS was negative. PCR for tuberculosis was also negative. These findings were suggestive of sarcoidosis. In retrospect, the patient's calcium level was beyond the normal range when corrected for albumin. Additional test results showed ionised calcium of 5.50 mg/dL (4.52–5.28; 1.37 mmol/L), intact parathyroid hormone (PTH) of 50.37 pg/mL (8.0–76.0), 1,25-dihydroxyvitamin D₃ of 22.06 pg/mL (18.7–47.7) and ACE of 139.6 mU/mL (18–55). Radiographic analysis showed no metastatic calcification of the soft tissue although there was some multifocal aortic calcification on CT findings. There was no evidence of heart failure, myocardial ischaemia or conduction abnormalities by electrocardiography and echocardiography. When the patient was referred for ophthalmologic consultation, there was no finding of eye involvement.

Figure 2 Pathological finding of the left supraclavicular lymph node reveals non-caseating granulomas.

OUTCOME AND FOLLOW-UP

In the follow-up of treatment with oral prednisolone for 6 months, the patient no longer showed general or respiratory symptoms, and her ACE levels remained within the normal range.

DISCUSSION

Sarcoidosis often requires a prolonged workup prior to receiving a confirmed diagnosis.¹ In the present case, it took almost 1 year to make the diagnosis of sarcoidosis. There were two main reasons for the delayed diagnosis. First, the presence of recurrent pulmonary symptoms and signs in the current patient was mistaken for more common respiratory diseases like pneumonia. Thoracic involvement occurs in more than 90% of patients with sarcoidosis, manifested by hilar adenopathy, mediastinal lymphadenopathy, obstructive airways disease, pulmonary hypertension and lung parenchymal disease.¹ The history of recurrent pneumonia in the current patient is believed to have been associated with pulmonary involvement of sarcoidosis. Second, hypercalcaemia in the current patient was unappreciated due to the low level of serum albumin. In fact, hypercalcaemia in patients with ESRD has increasingly become a common problem and is usually iatrogenic or has a cause of tertiary hyperparathyroidism or low-turnover bone disease.^{3 5} Although hypercalcaemia is known to be first recognised in patients with sarcoidosis more than five decades ago and has become established as an important manifestation of the disease,⁶ it occurs in only about 11% cases of sarcoidosis.⁷ In addition, clinically significant hypercalcaemia is less frequent and is generally asymptomatic. Re-examination of previous medical records of the current patient proved that the blood calcium level had been slowly elevating for over 1 year. In patients on PD, blood albumin is frequently depressed due to peritoneal protein losses and inflammation.^{4 8} The low plasma albumin level seen in the current patient undergoing PD had caused physicians to underestimate the level of blood calcium. Considering that patients on PD can have systemic disease that will predispose them to hypercalcaemia, a thorough evaluation for malignancies and chronic inflammatory diseases such as sarcoidosis as well as causes related to ESRD should be performed.⁵ Although the mechanism of hypercalcaemia in sarcoidosis is not completely understood, an elevated level of 1,25-dihydroxyvitamin D₃ have been thought to be involved in hypercalcaemia in patients with sarcoidosis.^{1 7} However, serum concentration of 1,25-dihydroxyvitamin D₃ in the current patient, who did not take any vitamin D supplement at that time, was within the normal range. Since intrinsic activation of vitamin D sterols is disturbed in patients with ESRD, their serum levels are usually low or in the lower limit of the normal range.⁶ Therefore, an inappropriately high level of serum 1,25-dihydroxyvitamin D₃ in the current patient suggested that the relatively elevated level of 1,25-dihydroxyvitamin D₃ was due to sarcoidosis.

Despite long duration of unappreciated hypercalcaemia, our patient had no metastatic calcification. Although our patient had some multifocal calcifications in the aorta on CT, circumferential and severe, rather than multifocal, calcification of the aorta such as porcelain aorta was reported to be associated with sarcoidosis according to previous reports.⁹

Because of the confusing clinical presentation in our patient, imaging studies such as FDG-PET CT were vital to the diagnosis of sarcoidosis. Recent studies have demonstrated an emerging role for whole-body FDG-PET CT in investigating sarcoidosis.^{10 11} PET scanning can detect occult or extrapulmonary

disease and may help to determine an accessible site for biopsy.¹ High FDG uptake in the thoracic and abdominal regions including lymph node and spleen in our patient suggested systemic involvement of infectious or inflammatory conditions including sarcoidosis. Considering the physiological FDG uptake by cardiac muscle, other supportive methods should be used to confirm active cardiac granulomatous disease.¹⁰ With no abnormal findings on electrocardiographic and echocardiographic studies and no suggestive symptoms of syncope or heart failure, cardiac involvement of sarcoidosis was carefully excluded in the current case.

Here we described a rare case of systemic sarcoidosis in a patient with ESRD on PD, in which the blood level of calcium was underappreciated and therefore the diagnosis of sarcoidosis was delayed. When treating patients with ESRD undergoing dialysis, physicians need to be careful in interpreting their mineral and electrolyte status.

Learning points

- ▶ Hypercalcaemia in patients with end-stage renal disease (ESRD) on peritoneal dialysis (PD) is frequently related to ESRD and its management, but it can be unrelated to the condition of renal failure and dialysis.
- ▶ Given that serum albumin in patients on PD is frequently depressed due to peritoneal protein losses and inflammation, serum calcium level in these patients on PD can be underestimated.
- ▶ Mineral and electrolyte status in patients during PD should to be carefully interpreted.
- ▶ Sarcoidosis, although relatively rare, should be considered in patients with unexplained hypercalcaemia.

Contributors AK, ESK and SC were involved in the day-to-day patient care. ESK and YKK performed the literature review. AK and SC were major contributors in writing the manuscript. All authors read and approved the final manuscript.

Competing interests None.

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