Case Report

Hypercalcemia and Refractory Peritonitis Alert the Condition of Tuberculous Peritonitis: A Case Report and Review Literature

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Hypercalcemia is commonly encountered in peritoneal dialysis patients with parathyroid hormone abnormalities; however, most of them have faint clinical manifestation and the level usually is less than 13 mg/dL. If severe hypercalcemia exists, granulomatous infection and occult malignancy should be of concern. Tuberculosis, a granulomatous disease associated with hypercalcemia, is commonly prevalent in dialysis patients. Although anti-mycobacterium therapy is highly effective nowadays, the mortality rate is still high because most of the victims have delayed diagnosis. High index of suspiciousness and early diagnosis are mandatory to improve patient outcome. Herein, the authors report a case of TB peritonitis that was suspected because of the disclosure of hypercalcemia and refractoriness to an empirical antibiotic treatment.

***Keywords**: Hypercalcemia, Tuberculous peritonitis, CAPD*

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A 37-year-old-male patient with end-stage renal disease (ESRD)due to diabetic nephropathy had been receiving continuous ambulatory peritoneal dialysis (CAPD) for the past 14 months. Recently, he complained that he had cloudy drained fluid with minimal abdominal discomfort in the past few days. No fever and signs of systemic infection were observed. Peritoneal dialysis cell count revealed leukocyte of 620 cells/mm^3 with 92% neutrophil and 8% mononuclear cells. No organism was found in both gram stain and aerobic culture. He denied any mistakes between connection steps. His nasal swab culture yielded no organism. The empirical antibiotics were initiated with intraperitoneal cefazolin and ceftazidime; however, the PDF leukocyte remained at level higher than 1,000 cells/mm^3 with predominantly neutrophil although his symptom subsided. The PDF cell count and culture were repeated, and the antibiotics were switched to intraperitoneal once-daily netilmycin and twice-weekly vancomycin. PDF cell counts remained high with negative culture results. CT abdomen was performed and the finding revealed moderate amount of ascitic fluid with generalized fat reticulation and thickening parietal peritoneum. There was no detectable source of infection related to bowel pathology, including free air collection, regional bowel inflammation or abnormal positioning of visualized bowel. Two small gallstones without definite cholecystitis and mild to moderate right pleural effusion were also disclosed (Fig. 1). During the period of investigation, the patient developed low grade fever (BT 38°C) and poor appetite. The blood results revealed as follows: Hct 24.5%, WBC count 2,150 cells/mm^3 (14% neutrophil and 56% mononuclear cells), platelets count 466,000/mm^3, ESR 137 mm/hour, BUN 41 mg/dL, creatinine 9.31 mg/dL, Na^+ 131 mmol/L, K^+ 4.2mmol/L, Cl 96 mmol/L, HCO^3 26.8 mmol/L, calcium 13.2 mg/dL, and phosphorus 4.9 mg/dL. Liver function test showed serum albumin 2.7 g/dL, globulin 4.8 g/dL, AST 20 U/L, ALT 13 U/L, alkaline phosphatase 94 U/L, total billirubin 0.45 mg/dL and direct billirubin 0.10 mg/dL. Because of the high level of serum calcium and bicytopenia, in addition to refractory peritonitis with negative organism, the chronic granulomatous

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infection was suspected. Bone marrow aspiration and biopsy were performed. The result revealed negative organism. The anti-tuberculosis medications, including isoniazid, rifampicin and pyrazinamide were started and the Tenckhoff catheter was removed. The patient then underwent hemodialysis via temporary catheter. After aspiration (4-week after presentation), he complained discomfort of upper abdomen and became aware of abnormal bowel movement in RUQ. CT whole abdomen was immediately performed. The finding revealed increased degree of fat reticulation and suspected peritoneal mass in the right side of the abdomen underneath right kidney. The mass was 3.4 x 11.2 cm in size. Moderate amount of ascitic fluid with thickening parietal peritoneum and 1 x 2 cm right subdiaphragmatic lymph node were noted (Fig. 2). Explore-laparotomy was later done to receive tissue diagnosis. The peritoneal fluid leukocyte count decreased to 480/mm^3 with 87% neutrophil. No organism was detected on gram, wright, and AFB stains. The biopsy showed caseousgranulomatous inflammation with negative both of AFB stain and PCR for mycobacterium. No organisms were obtained from both ascitic fluid and tissue, including mycobacterium and fungus. Tuberculous peritonitis was diagnosed, and the anti-tuberculosis treatment was maintained for 18 months. The hypercalcemia was subsided and his clinical abnormalities were improved thereafter.

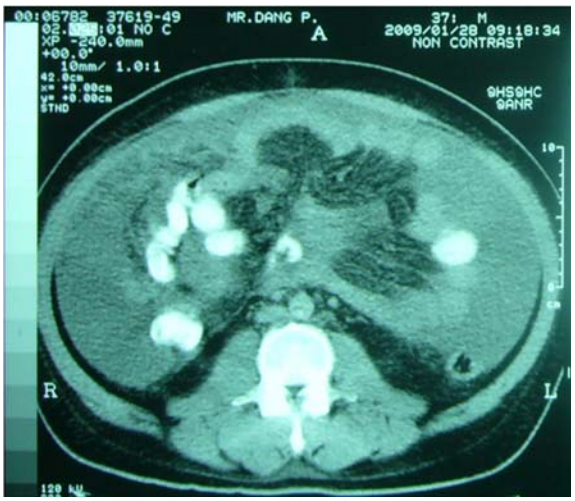

Fig. 1 CT whole abdomen, Jan 28th, 2009, demonstrates moderate amount of ascitic fluid with generalized fat reticulation and thickening parietal peritoneum. No detectable local bowel pathology and abnormal free air is recognized

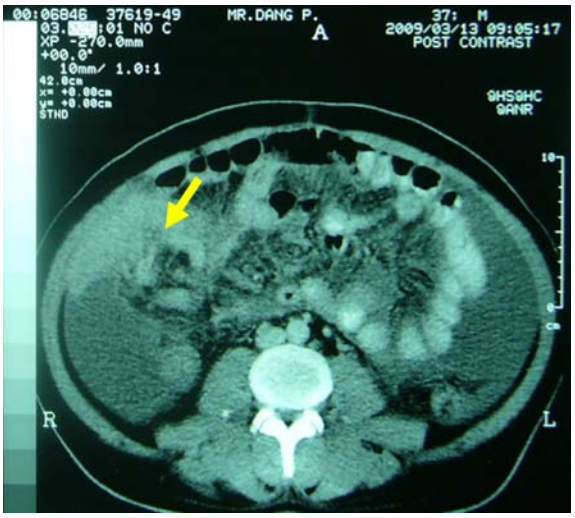

Fig. 2 CT whole abdomen, March 13th, 2009, reveals increased indegree of fat reticulation with suspected peritoneal mass (3.4 x 11.2 cm)at right side abdomen (arrow). Moderate amount of ascites with thickening parietal peritoneum, and right subdiaphragmatic lymph node (size 1 x 2 cm) are depicted

Discussion

Patients with chronic renal failure have an increased risk of developing TB, possibly due to decreased cellular immunity[1-6]. Malnutrition might take responsibility in some cases[7]. However, itscommon occurrence in the peritoneum gives evidence that local alteration ofintraperitoneal immune defense related to the process of CAPD should be the potential factor. Defects of local peritoneal immunity in CAPD; for instances, reductions ofleukocyte phagocytic function, cytokine production, and number of peritoneal lymphocytes[8], occur possibly as results of the high lactate concentration and acidic condition of the dialysate, together with a dilutional effect of the large dialysate volume on peritoneal leukocyte.

Approximately 70 percent of patients have symptoms for more than 4 months before the diagnosis is established[9,10] as indicated in this case. This is due partly to the insidious onset of the disease and because the diagnosis is frequently unsuspected. Symptoms and signs typically develop within the first year after the initiation of CAPD and are usually indistinguishable from bacterial peritonitis[11,12]. TB peritonitis should be alert in any patients presenting with several weeks of abdominal pain, fever, and weight loss. Findings on physical examination were nonspecific in most reports. Many patients had

diffusely abdominal discomfort. The classic doughy abdomen associated with the fibroadhesive form of tuberculous peritonitis is rarely seen in CAPD patients. The salientlyreported findings in decreasing order of frequency, including abdominal tenderness and hepatomegaly, are also not usual manifestation in this population[13]. The most common report of laboratory abnormality is mild to moderate degree of normochromic normocytic anemia. Evidence of pulmonary tuberculosis was obtained in only one thirds of case. Chronic hypercalcemia was described in one case report of a patient on hemodialysis and yet has not been reported in CAPD patient[14].

Although more than 90% of the cases of hypercalcemia are caused by either primary hyperparathyroidism or malignant disease in the general population[15], the situation is quite different among chronic dialysis patients, because of not only their underlying disease but also the derangement of their parathyroid function. Various granulomatous diseases are associated with hypercalcemiain the dialysis population, particularly mycobacterium[16]. Active tuberculosis has a prevalence of hypercalcemia reported varying from 16-51%[17]. A potential explanation for the discrepancy of prevalence might relate to regional differences in vitamin D status and calcium intake. Patients who live in areas with low prevalence of hypercalcemia have either low dietary calcium intake or low vitamin D intake, while those who live in regions with higher rate have relatively high consumptions of calcium and vitamin D. Tuberculosis associated hypercalcemia can occur before or a few-week after the initiation of anti-tuberculous therapy. Hypercalcemia may last for more than a year before the diagnosis of tuberculous infection is made[18]. Few cases of hypercalcemia related to tuberculous peritonitishave been reported from Asian population; however, all of them were hemodialysis patients[19,20]. Of interest, hypercalcemia associated tuberculous peritonitis is also rarely seen in the general population.

The mechanism responsible for the abnormal calcium metabolism has been almost completely evaluated. In normal subjects, the conversion of 25-hydroxyvitamin D (calcidiol) to calcitriol occurs via a 1-hydroxylase in the kidney which is under the physiologic control of parathyroid hormone (PTH) and the serum phosphate concentration. Because of renal failure and phosphate retention, the conversion of 25-hydroxyvitamin D is not possible in the condition of dialysis patient. The production of calcitriol should occur in extra-renal area.Tuberculosis and other granulomatous diseases can activate mononuclear cells, particularly macrophages in the lung and lymph nodes[16,21], to release 1-hydroxylase, resulting in the extra-renal conversionof calcidiol. Extrapulmonary tuberculosis is much more commonly identified in dialysis patients compared to the normal subject. Peritoneal involvement is one of the common reports. Signs and symptoms are confined largely to the abdomen, with abdominal distension, pain, and ascites being most frequently encountered[22-24]. The ascites study mostly demonstrated leukocytosis and exudative in nature. Acid-fast stain and culture for microorganisms not only yield a low incidence (usually less than 3%) but also the culture usually takes a month to yield a result[25]. The faster way is the detection of mycobacterium DNA by PCR; however, the sensitivity and specificity of this technique remains under investigation[12]. The tuberculin skin test also is not the wise choice since high prevalence of anergy in the dialysis population is identified. Tissue pathology obtained by peritoneoscopy has been advocated as a faster and more accurate way to yield the diagnosis; however, many centers have a limitation of access. Moreover, this procedure needs a temporary peritoneal dialysis disruption. The outcome of CAPD patient with tuberculous peritonitis is usually poor, especially in the case of delayed diagnosis. High index of suspiciousness is important. ISPD 2010 stated that the tuberculous peritonitis should take into your consideration in all patients presenting with refractory peritonitis and negative bacterium culture. However, fungus and other rare organisms seldom yield such presentation. Therefore, the existence of hypercalcemia may be helpful in differential diagnosis and promptly alert the clinician.Since the treatment of tuberculous needs long term compliance and the regimen consists of many drugs that needs lower dosage and potentially causes serious side effects in the dialysis patients, the definite diagnosis remains necessary.

In conclusion, peritoneal tuberculosis, an otherwise uncommon entity, is an important manifestation of mycobacterium in patients undergoing CAPD. While can be easily misdiagnosed, it should always be considered when at-risk patients on CAPD develop peritonitis accompanied by hypercalcemia and are unresponsive to conventional antibiotics.

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Potential conflicts of interest

None.

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ภาวะแคลเซียมในเลือดสูงและภาวะการติดเชื้อในช่องท้องที่ไม่ตอบสนองต่อการรักษามาตรฐาน ภาวะชี้บ่งการติดเชื้อวัณโรคในช่องท้อง: รายงานผู้ป่วย

วรพจน์ เตรียมตระการผล, เถลิงศักดิ์ กาญจนบุษย์, สมชาย เอี่ยมอ่อง

ผู้ป่วยล้างไตทางช่องท้องที่มีความผิดปกติของฮอร์โมนพาราไทรอยด์อาจมีภาวะแคลเซียมในเลือดสูง แต่มักมีระดับต่ำกว่า 13 มิลลิกรัม/เดซิลิตร และไม่มีอาการแสดงทางคลินิกหากภาวะแคลเซียมในเลือดสูงยังคงดำรงอยู่ให้สงสัยเนื้องอกร้ายแฝงเร้น และภาวะกรานูโลมาเช่นวัณโรคซึ่งก่อให้เกิดอัตราการเสียชีวิตสูงเนื่องจากการวินิจฉัยล่าช้า

คณะผู้นิพนธ์รายงานผู้ป่วยล้างไตทางช่องท้องที่มีการติดเชื้อวัณโรคในช่องท้องโดยมีลักษณะสำคัญคือมีภาวะแคลเซียมในเลือดสูง และไม่ตอบสนองต่อยาปฏิชีวนะมาตรฐาน