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Case Report

# Cocoon-Like Fibroadhesive Tuberculous Peritonitis in a Peritoneal Dialysis Patient

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## Abstract

**Tuberculous peritonitis is a devastating complication of peritoneal dialysis (PD). Presentations of tuberculous peritonitis range from the common wet ascitic form to the rare fibroadhesive form, which is clinically indistinguishable from encapsulating peritoneal sclerosis. We describe a 76-year-old man on continuous ambulatory PD for three months developing wet ascitic form of tuberculous peritonitis. Three weeks after institution of antituberculous therapy and removal of PD catheter, his abdominal pain recurred and an encapsulating peritoneal sclerosis-like intestinal obstruction was noted. A rare fibroadhesive form of tuberculous peritonitis associated with the paradoxical response to antituberculous therapy was considered by excluding noncompliance, drug resistance and adverse effects, and other concomitant infections. After surgical enterolysis and continuation of antituberculous treatment, he recovered uneventfully. Our case might be the first report regarding paradoxical deterioration to antituberculous treatment in dialysis patients.**

**Key Words: paradoxical response, peritoneal dialysis, tuberculous peritonitis**

## Introduction

Dialysis patients are at higher risks for mycobacterial infection as compared with general population, and tuberculous peritonitis is the most prevalent extrapulmonary tuberculosis in peritoneal dialysis (PD) patients (6). Tuberculous peritonitis manifests from the common wet ascitic form to dry fibroadhesive form, which clinically mimics encapsulating peritoneal sclerosis (10). Paradoxical deterioration in tuberculosis infection which initially responded to antituberculous therapy has been reported in patients of non-renal diseases (3) but not yet been noted in dialysis patients. Herein, to our best knowledge, we report the first case of paradoxical response to antituberculous treatment presenting with the rare fibroadhesive form of tuberculous peritonitis resembling encapsulating peritoneal sclerosis.

## Case Report

A 76-year-old Chinese man receiving continuous ambulatory PD for end-stage renal disease due to hypertensive nephrosclerosis for three months was admitted for diffuse abdominal pain and cloudy peritoneal effluent. He was apyrexial without accompanying nausea, vomiting, or diarrhea. Past history included hypertension and gouty arthritis. Regular medications comprised amlodipine, colchicine, and epoetin-β. Physical examination found a diffusely tender abdomen with rebound tenderness. The catheter exit site and subcutaneous tunnel appeared normal. Peripheral-blood leukocyte count was $5.3 \times 10^3$ cells/μl with 82.6% neutrophils and 8.1% lymphocytes. Leukocyte count in the dialysate effluent was 390 cells/μl (normal range < 100 cells/μl) with 93% neutrophils. A chest radiograph showed no calcifications,

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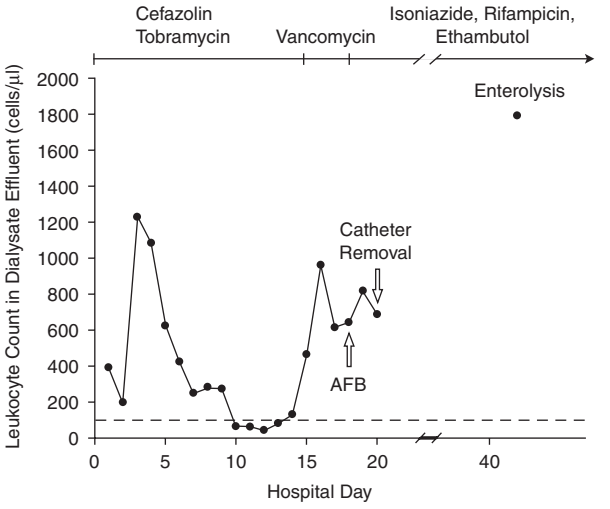


Fig. 1. Hospital course of the tuberculous peritonitis. Abdominal pain and the leukocyte counts in the dialysate effluent fluctuated despite treatment with empiric antibiotics. A mycobacterial staining of dialysate effluent obtained on hospital day 18 was positive for acid-fast bacilli (AFB). Antituberculous therapy was commenced and the peritoneal dialysis catheter was removed on day 20. Abdominal pain and turbid ascites recurred on day 43, for which enterolysis was performed. Dashed line indicated upper limit of normal leukocyte count in dialysate fluid.

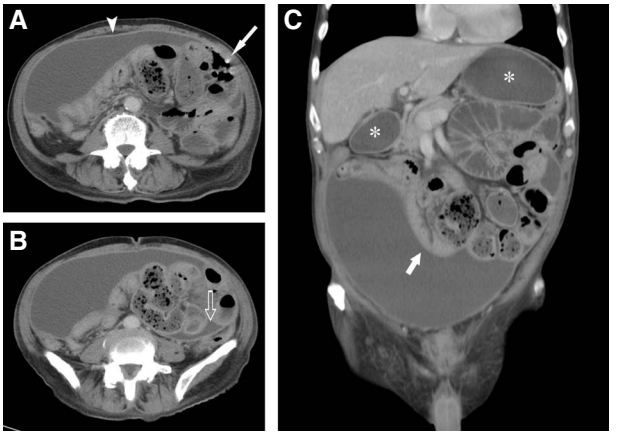


Fig. 2. Abdominal computed tomography of tuberculous peritonitis. (A) Axial view demonstrated loculated ascites with a conspicuous thickened, contrast-enhanced membrane (arrowhead), and focal peritoneal calcification (arrow). Small-bowel loops were encased by the thickened membrane. (B) Loculated fluid collection (open arrow) within the tethered bowel loops and small bowel obstruction were also noted. (C) Coronal view revealed loculated ascites (asterisks) and encapsulated adherent small bowels at the left upper quadrant of abdomen with the characteristic cocoon-like picture (arrow).

cavities, infiltrates or pneumoperitoneum. Intraperitoneal administration of cefazolin and tobramycin was initiated for presumptive bacterial peritonitis. The abdominal pain got partially improved and leukocyte count in dialysate effluent fell with treatment. Nonetheless, on hospital day 15, cloudy dialysate effluent recurred with a dialysate leukocyte count of 462 cells/μ1 (90% neutrophils) and aggravated abdominal pain, which was unresponsive to add-on vancomycin. Purulent discharge at the exit-site developed on day 17 (Fig. 1). Cytological examination revealed no malignant cells. Repeated Gram's stains, bacterial and fungal cultures of the discharge from exit-site and dialysate effluent were also negative. Mycobacterial staining for dialysate effluent revealed a moderate amount of acid-fast bacilli, which was further confirmed by culture positivity for *Mycobacterium tuberculosis* with susceptibility to isoniazide, rifampicin, ethambutol, pyrazinamide and streptomycin. Therefore, PD catheter was removed on hospital day 20 for tuberculous peritonitis and exit site infection. Acid-fast bacilli were also positive for the culture of PD catheter tip. The dialysis modality was shifted to hemodialysis and he received directly observed therapy with isoniazide (300 mg/d), rifampicin (600 mg/d), and ethambutol (800 mg every other day) but not pyrazinamide due to refractory gouty attacks. Abdominal pain, nausea and vomiting gradually resolved one week after anti-tuberculous therapy.

Three weeks after the commencement of antituberculous therapy, he was admitted again for recurrent anorexia and abdominal pain. His vital signs were unremarkable and physical examination disclosed hyperactive bowel sound, a "doughy feeling" on abdominal palpation, and a tender mass over left upper quadrant of the abdomen without guarding rigidity or rebound tenderness. Computed tomography of the abdomen showed loculated ascites, focal peritoneal calcification and the cocoon-like tethered small bowels at the left upper quadrant (Fig. 2). Follow-up peripheral-blood leukocyte count was $3.5 \times 10^3$ cells/μl with 75% neutrophils and 16% lymphocytes. Leukocyte count of the aspirated ascites was $1.79 \times 10^3$ cells/μl with 99% neutrophils. Exploratory laparotomy revealed much turbid ascites and a dense fibrous capsule-like membrane wrapping the adherent small intestines, for which the patient received enterolysis and excision of the thickened fibrous membrane. Pathology of the capsule-like membrane disclosed fibrous tissue infiltrated with inflammatory cells, epithelioid cells and occasional giant cells (Fig. 3). Culture of the encapsulating membrane only yielded *Mycobacterium tuberculosis*. Paradoxical response during antituberculous therapy was considered by excluding noncompliance, drug

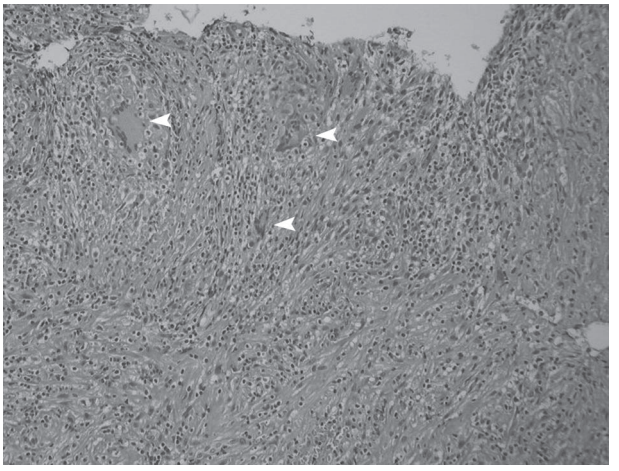

Fig. 3. Histology of the encapsulating membrane disclosed numerous inflammatory cells infiltrated in the fibrous tissue containing many granulomas with multinuclear giant cells (arrowheads). Hematoxylin and eosin stain. Original magnification 400×.

resistance and adverse effects to anti-tuberculous treatment, and other concomitant infections. Postoperatively, the patient responded well to parenteral nutritional support and continuation of the same antituberculous regimens. He recovered uneventfully, but unfortunately died of intracranial hemorrhage two months later.

## Discussion

Patients with chronic kidney disease (CKD) are prone to mycobacterial infection and the incidence of tuberculosis in dialysis patients is 100 folds greater than that in the general population (6). Dialysis patients with tuberculosis have a high percentage (38-80%) of extrapulmonary involvement, among which tuberculous peritonitis is most prevalent in PD patients. CKD patients are known to have defective cellular immunity and are therefore much more susceptible to tuberculous infection. Furthermore, in PD patients, dialysis fluid not only dilutes the concentration of peritoneal macrophages and lymphocytes but also has a direct deleterious effect on the functions of bacterial phagocytosis and cytokine production. Tuberculosis independently associates with a 42% increased mortality rate in dialysis patients based on the report of U.S. Renal Data System (9) and mortality rate might be even up to 75% in PD patients with tuberculous peritonitis (6).

Tuberculous peritonitis is generally clinically categorized as the common (97% of cases) "wet" ascitic form with the features of abdominal pain, fever, and free or loculated cloudy ascites, and the rare "dry" fibroadhesive form with a doughy abdomen (due to omental thickening and matted loops of bowel) and symptoms of intestinal obstruction (10). Less than one third of the cases have extraperitoneal tuberculosis at presentation. Likewise, radiological appearance of tuberculous peritonitis could also be classified as the "wet" type manifesting as large amount of freely distributed or loculated ascites and the less common "fibrotic-fixed" or "dry-plastic" type, characterized by large omental masses, matted and tethered bowel loops, caseous lymphadenopathy, fibrous peritoneal reaction and dense adhesions (15). Most PD patients with tuberculous peritonitis have a predominance of polymorphonuclear neutrophils in the peritoneal fluid analyses (1, 12), which might masquerade bacterial peritonitis. Therefore, a high index of suspicion for tuberculous peritonitis should be raised in patients with culture-negative peritonitis (12). Culture growth from the dialysate effluent or peritoneal biopsy remains the gold standard for diagnosis of tuberculous peritonitis, but it usually takes 4 to 6 weeks to confirm the diagnosis. Targeted biopsy of the peritoneum or omentum by laparoscopy and mini-laparotomy could be safe, promptly diagnostic in most cases (> 90%) and should be considered in suspected cases with non-diagnostic microscopic smear examination of dialysate effluent (2, 12). Detection of mycobacterial DNA amplified by polymerase chain reaction technique can be performed on dialysate effluent but its sensitivity and specificity still require further validation (12). Adenosine deaminase activity of ascites has been proposed as a novel diagnostic tool for tuberculous peritonitis; however, it remains uncertain to apply this concept in PD patients (2).

The clinical and radiological presentations of tuberculous peritonitis should be differentiated from other diseases involving the peritoneum, such as peritoneal carcinomatosis, pseudomyxoma peritonei, and encapsulating peritoneal sclerosis (5, 15). In the present case, lack of malignant cells in ascites or pathognomonic contrast-enhanced nodular, plaque-like peritoneal thickening is against the diagnosis of peritoneal carcinomatosis. Moreover, low-attenuation masses suggesting pseudomyxoma peritonei were not observed within ascites. Encapsulating peritoneal sclerosis (EPS), another infrequent yet dreaded disease in PD patients, has been reported to be caused by abdominal tuberculosis in non-renal disease patients based on the surgical or radiographic findings of the conglomerated small intestines encapsulated in a "cocoon" of thickened peritoneum, and the positive acid-fast smear examination in the excised membrane (4, 7, 8, 11, 14). Nonetheless, typical pathological findings of EPS have not been dictated in these reports. EPS and fibroadhesive tuberculous peritonitis share similar clinical and radiological features but have distinct pathological findings (Table 1) (5). Therefore,

**Table 1. Comparison of encapsulating peritoneal sclerosis and tuberculous peritonitis**

| Encapsulating Peritoneal Sclerosis | Tuberculous Peritonitis |
|---|---|
| **Clinical** | |
| Abdominal pain, insidious onset | Abdominal pain, insidious onset |
| Turbid or blood-tinged ascites | Fever |
| Abdominal mass | Cloudy ascites |
| Nausea/vomiting | Nausea/vomiting |
| Weight loss | Weight loss |
| Culture-negative peritonitis | Positive mycobacterial culture |
| | Abdominal mass (in fibroadhesive form) |
| **Radiological** | |
| ***Similarities*** | |
| Peritoneal thickening with contrast enhancement | |
| Tethering of the small bowels | |
| Loculated peritoneal fluid collections | |
| ***Differences*** | |
| Peritoneal calcification | Fibrin septa in ascites |
| Thickening of the bowel wall | "Smudged" or "caked" appearance of omentum |
| Calcification over liver capsule, spleen and bowel wall | Mesenteric and retroperitoneal lymph nodes with low-density center or calcification |
| | Calcified mesenteric and retroperitoneal lymph nodes |
| | Splenic lesions (low-attenuation mass or parenchymal calcification) |
| **Pathologic** | |
| Loss of mesothelial cell layer | Granulomatous inflammatory reaction |
| Interstitial fibrin deposition and fibroblast swelling | Granuloma comprised from epithelioid macrophages, Langhans giant cells and lymphocytes |
| Capillary angiogenesis | |
| Mononuclear cell infiltration | |
| Presence of immunohistochemical markers for peritoneal fibroblast activation and proliferation | Caseous necrosis at the center of granuloma |
| | Identification of acid-fast bacteria |

whether "cocoon"-like intestinal obstruction is truly triggered by tuberculosis or is merely a rare fibroadhesive form of tuberculous peritonitis remains obscure in previous reports. In our case, tethered small intestines enclosed by a thickened peritoneum were noted by the computed tomography and laparotomy. A typical pathological feature of tuberculosis in the excised encapsulating peritoneum and the culture growth of *Mycobacterium tuberculosis* from the peritoneum corroborate the diagnosis of tuberculous peritonitis evolving from the wet form to the rare fibroadhesive form.

Notably, our case experienced the paradoxical deterioration after antituberculous treatment. Initial abdominal pain resolved completely by antituberculous treatment; however, the abdominal pain recurred three weeks later and a fibroadhesive form of tuberculous peritonitis was confirmed by pathological and microbiological examinations. The recurrent abdominal pain and the matted, encapsulated small intestines responded to surgical enterolysis, stripping of the encapsulating membrane and continuation of the same antituberculous medications. A paradoxical response is defined as either worsening of pre-existing tuberculous lesions or development of new lesions in a patient who initially improves with antituberculous therapy. Establishment of the diagnosis for post-treatment paradoxical response should exclude the other types of infection, suboptimal antituberculous therapy due to drug resistance, poor compliance, and adverse effects of medications. Paradoxical response after antituberculous therapy is originally reported in HIV-positive patients with reduction of viral load and increase in CD4+ lymphocyte count. It is also found in HIV-negative patients with elevated peripheral lymphocyte count (3). Nonetheless, paradoxical response has not yet been described in dialysis patients with tuberculous infection. In our case, culture of the encapsulated membrane only yielded *Mycobacterium tuberculosis*, which was still susceptible to the same

regimen of antituberculous medications. Noncompliance was unlikely because of the implementation of directly observed therapy and adverse effect was not observed. The percentage of lymphocytes in peripheral blood rose from 8.1% to 16% after initiation of antituberculous treatment, implying that an exaggerated immune response might be responsible for the post-treatment paradoxical response. Taken together, our case might be the first report in PD patients developing a fibroadhesive tuberculous peritonitis mimicking encapsulating peritoneal sclerosis and associated with post-treatment paradoxical response.

Quadruple drug treatment with isoniazide, rifampicin, pyrazinamide and ofloxacin are generally recommended for tuberculous peritonitis (12). Nonetheless, a combination of three antituberculous drugs for extended duration of treatment has also been reported to be effective in tuberculous peritonitis (13). The addition of adjunct corticosteroid in treatment of tuberculous peritonitis is controversial and might increase the risk of tuberculous dissemination. Removal of the PD catheter in tuberculous peritonitis is still debatable. Although successful treatment is reported in some cases while maintaining patients on PD, catheter removal would still be necessary should tuberculous peritonitis be persistent and complicated (12). In our case, persistent peritonitis with complication of exit site infection mandated the removal of catheter.

## Conclusion

Tuberculosis remains a disease of high incidence, morbidity and mortality in dialysis patients. Our case highlights the diagnostic perplexity of tuberculous peritonitis in PD patients and firstly illustrates the post-treatment paradoxical response in dialysis patient. Greater awareness of the protean manifestations of tuberculosis will help earlier identify and appropriately manage this dreaded disease.

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