INTERNAL MEDICINE

□ CASE REPORT □

Continuous Inflammation and Ascites 10 Months after the Initiation of Peritoneal Dialysis

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Abstract

A 38-year-old man underwent peritoneal dialysis (PD) in May 2011 due to chronic renal failure with chronic glomerulonephritis. In early February 2012, he underwent laparoscopy to salvage and correct a mal-positioned PD catheter. The laparoscopic intra-abdominal findings revealed turbid ascites and multiple fibrin lumps, despite the patient's lack of history of peritonitis. Based on these findings, in addition to the presence of continuous inflammation and ascites, a diagnosis of pre-encapsulating peritoneal sclerosis was suspected, and the treatment was switched from PD to hemodialysis. The administration of prednisolone at a dose of 20 mg/day and peritoneal lavage resulted in a decrease in the ascites and fibrin lumps.

Key words: peritoneal dialysis, continuous inflammation, ascites, pre-encapsulating peritoneal sclerosis

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Introduction

In patients undergoing peritoneal dialysis (PD), the general causes of ascites formation include an increased net ultrafiltration pressure in the peritoneal capillaries, increased permeability of the peritoneal membrane to macromolecules and decreased peritoneal lymphatic absorption. In addition, specific factors involved in the pathogenesis of dialysis ascites include fluid overload, impaired lymphatic drainage, heart failure, constrictive pericarditis, hypoalbuminemia, hyperparathyroidism, pancreatitis and hepatitis (1).

Encapsulating peritoneal sclerosis (EPS) was first reported as a serious complication of PD in 1980 by Gandhi et al. (2). EPS involves the symptoms of ileus and the development of progressive, inflammatory lesions with thick fibrous tissue replacing and covering the peritoneum and increasing the pressure in the intestinal tract (3). EPS is classified into four stages (4): stage 1 (the pre-EPS period) exhibits ascites retention, a highly permeable peritoneum, hypoproteinemia and calcification of the peritoneum; stage 2 (the inflammatory period) presents with fever, weight loss, an increased white blood cell (WBC) count and an increased C-reactive protein (CRP) level; stage 3 (the encapsulating or progressive period) marks the appearance of ileus symptoms and the disappearance of inflammation; and stage 4 (the ileus or complete period) presents with abdominal masses and complete ileus. Therefore, EPS should be considered a cause of ascites formation in PD patients.

We herein report a patient who developed continuous inflammation and ascites despite undergoing PD for 10 months and having no history of peritonitis.

Case Report

The patient was a 38-year-old man with chronic glomerulonephritis diagnosed at 12 years of age. The patient had a history of hypertension starting in 2007; however, his family

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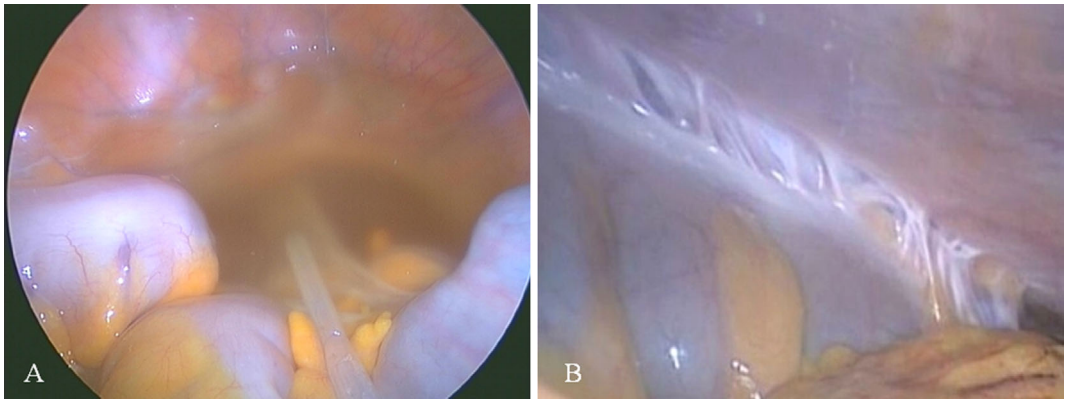

Figure 1. Laparoscopic findings. (A) Turbid ascites, fibrin lumps and fibrin adhering to the abdominal wall. (B) Digestive tract adhesion with edema in some areas.

medical history was unremarkable. He had no history of smoking and consumed alcohol only occasionally. His kidney function suddenly worsened during a bout of the common cold in March 2011; hence, emergency hemodialysis (HD) was initiated in April. A decreased heart function (ejection fraction [EF], 36%) was observed at the start of dialysis, and we suspected myocarditis. In early May, a β-blocker (carvedilol) was administered to protect the patient's heart function and PD was initiated (the mode of PD was continuous ambulatory PD). The patient continued to exhibit a slightly elevated CRP level. Large quantities of intraperitoneal fluid (1,200-1,300 mL/day) were eliminated by PD; however, no reduction in urinary output was observed. In addition, the patient's weight remained constant. Furthermore, no occurrence of PD-related peritonitis was encountered. In late January 2012, a bout of common cold led to a decrease in urinary output and an increase in body weight. In early February, the patient presented with poor drainage and fibrin deposition and was admitted to our hospital for an examination and treatment.

On admission, the patient was 173 cm tall and weighed 66 kg, which increased by 3 kg within two weeks. He had no fever, abdominal pain or symptoms of ileus. His body temperature was 36.3℃, his blood pressure was 118/73 mmHg and his SpO_2 was 99% (room air). Auscultation revealed normal heart and respiratory sounds, and a physical examination demonstrated no other abnormal abdominal findings. No lymphadenopathy was present. Mild edema of the legs was observed.

The blood and urine examination results showed the following values: WBCs, 8,300/μL; red blood cells, 326×10^4/μL; hemoglobin, 10.0 g/dL; platelets, 20.1×10^4/μL, indicating anemia; and Na, 121 mEq/L, indicating marked hyponatremia. After contracting a common cold in late January, the patient exhibited a total protein content of 5.4 g/dL, an albumin level of 2.5 g/dL and a CRP level of 1.64 mg/dL, indicating hypoproteinemia and an increased inflammatory reaction. Furthermore, the blood urea nitrogen level was 52 mg/dL, the serum creatinine level was 11.6 mg/dL and the blood β_2-microglobulin level was 18.6 mg/dL.

Under medication with an active metabolite of vitamin D and phosphate binders, the following values were obtained: Ca, 8.5 mg/dL; P, 6.0 mg/dL; and intact parathyroid hormone, 119.3 pg/mL. The liver function was normal, and test results were negative for hepatitis B surface antigen and hepatitis C virus antibodies. The thyroid function was normal. An increased ferritin level (559 ng/mL) was observed, and the *N*-terminal-pro-B-type natriuretic peptide level was above 35,000 pg/mL, which was higher than that observed when PD was initiated. The urinary protein level of 0.72 g/day had not increased, although the urinary output decreased from 1,200-1,500 to 880 mL/day. Pleural fluid was not observed on chest radiographic images, and a cardiothoracic ratio (CTR) of 44% was noted. Cardiac ultrasound showed an improvement in the patient's contractions, with an EF of 50%. PD catheter malposition was observed on an abdominal radiograph. However, adjusting the displaced peritoneal catheter using the alpha-replacement method proved difficult. Therefore, laparoscopy was performed on the day of admission to salvage the PD catheter. During the operation, the macroscopic findings of the abdominal cavity showed turbid ascites, multiple fibrin lumps, fibrin adhering to the abdominal wall and adhesion and edema of the digestive tract wall (Fig. 1), despite the patient having no history or signs of peritonitis.

The increased CRP level and hypoalbuminemia noted after the patient contracted a cold further worsened after he underwent laparoscopic therapy to salvage the PD catheter. In addition, the daily ultrafiltration volume increased compared with that observed before admission, with the patient exhibiting a tendency toward excessive fluid elimination of 2 L/day. In the absence of retained dialysate, ascites formation was confirmed at a rate of 1,000 mL/9 h. The ascites appeared clear and contained no WBCs, and the serum ascites albumin gradient (SAAG) was 2.1 g/dL. The results of bacterial, fungal and acid-fast bacilli cultures of the ascites were negative. A computed tomography (CT) scan showed no thickening or calcification of the digestive tract. The transport rate, as determined using a peritoneal equilibration test (PET), was in the low average range when PD was initi-

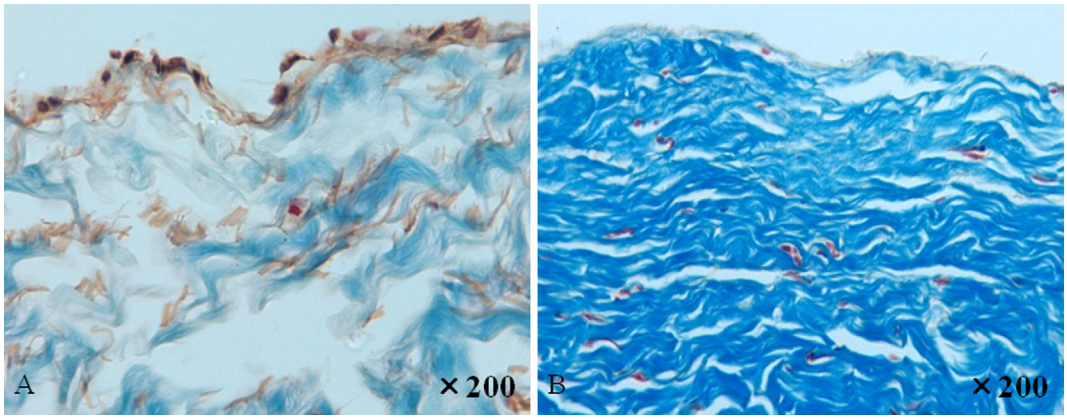

Figure 2. **Peritoneal tissue findings. (A) Mesothelial cells in the peritoneal tissue at the initiation of peritoneal dialysis (Masson trichrome staining, original magnification ×400). (B) Detachment of mesothelial cells and marked collagen accumulation in the peritoneal tissue 10 months after the initiation of peritoneal dialysis (Masson trichrome staining, original magnification ×400).**

ated, then increased to the high average range 10 months later, suggesting a change in the peritoneal function. The Kt/V and creatinine clearance values obtained after admission were 1.49/week and 47 L/week, respectively. Mesothelial cells exhibited enlarged cell areas of 346.5 μm^2 (normal, 200-300 μm^2). The CA 125 and IL-6 levels in the dialysate were 35.8 U/mL and 253.0 pg/mL, respectively. In the microscopic findings of the peritoneum harvested during the laparoscopic surgery, mesothelial cell shedding, a marked increase in the number of collagen fibers and scattered calcification were observed (Fig. 2). However, luminal narrowing of the venules, which has been reported to be a characteristic of EPS, was not detected on periodic acid-Schiff (PAS) staining. Although there were no clinical findings of symptoms of ileus or peritoneal pathohistological findings characteristic of EPS, we could not completely exclude the possibility of pre-EPS due to the presence of a continuous inflammatory response and ascites.

Thereafter, the patient was treated with 20 mg of oral prednisolone (PSL) orally (0.3 mg/kg), in accordance with the pre-EPS therapy, and the treatment was switched from PD to HD. The peritoneal lavage was continued. After 21 days of steroid therapy, the CA125 level in the dialysate increased to 51.9 U/mL, whereas the IL-6 in the dialysate declined to 42.5 pg/mL. The dose of PSL was reduced to 15 mg three months after the initiation of therapy, when a decrease in the amount of drainage was observed during outpatient care.

Discussion

We experienced a patient presenting with continuous inflammation and ascites 10 months after the initiation of PD. In a review by Glück and Nolph (1), 69% of dialysis ascites cases occurred in patients who had been undergoing PD. The pathogenesis of PD-associated ascites is multifactorial, involving underlying diseases (heart failure or liver cirrhosis), peritonitis and/or EPS. Therefore, we considered the pathogenesis of the ascites in the present case to be intricately interrelated to heart failure, stimuli induced by PD catheter malposition, systemic inflammation induced by viral infection, uremia and intraperitoneal inflammation. Among these factors, we were unable to exclude the possibility of stage 1 EPS (pre-EPS stage) as a cause of the continuous inflammation and ascites, despite the absence of fever, an increased leukocyte level or symptoms of ileus.

The diagnosis of EPS is generally based on the clinical manifestations of obstructive ileus symptoms and a systemic inflammatory reaction combined with imaging findings, such as peritoneal thickening, encapsulation of the digestive tract and peritoneal calcification (5). However, the mechanisms underlying the development of EPS remain unclear. Given the reported EPS cases with mild peritoneal deterioration and strong inflammation, as well as a history of long-term PD with advanced abdominal deterioration and only mild inflammation, the balance between peritoneal deterioration and inflammation is thought to contribute to the occurrence of the disease. The “two hit theory” suggests that EPS occurs when peritoneal deterioration is accompanied by inflammation (6).

The reported risk factors for EPS include the use of long-term continuous PD, repeated bouts of peritonitis, biocompatibility of the dialysate, the formation of advanced glycosylation end products, the presence of intra-abdominal foreign bodies, abdominal surgery and the administration of β-blockers (7). Our patient had no history of peritonitis or long-term PD; however, the use of β-blockers and laparoscopic therapy to salvage the PD catheter may have caused the EPS. Korte et al. (8) reported that the initiation of PD at a young age is an independent risk factor for EPS. In the current case, the presence of continuous inflammation and ascites, hypoalbuminemia, calcification of peritoneal tissue and changes in the peritoneal function from low to high average within 10 months suggested the possibility of pre-EPS. Kawanishi et al. reported that, before the development of the pre-EPS state, permeability to high-molecular-weight

solutes is enhanced and the effluent level of IL-6 is increased (9). The level of effluent FDP was not elevated in the pre-EPS stage, although it subsequently increased. These findings suggest that inflammation, the associated enhancement of peritoneal permeability and the formation of fibrin comprise the mechanisms underlying the development of EPS. In the present case, the effluent level of IL-6 was increased, although the effluent FDP level was not measured. Honda et al. compared the grade of four histologic parameters for the biopsy categories EPS and pre-EPS (10), classifying patients suspected to have EPS without later clinical onset into the pre-EPS group. The grade of both fibrin deposition and peritoneal fibroblast swelling was significantly higher in the EPS group than in the pre-EPS group. However, the characteristic histologic parameters for pre-EPS remain unclear.

The recommended treatment for each stage of EPS includes the following: stage 1=peritoneal rest, peritoneal lavage and the administration of glucocorticoids; stage 2=the administration of glucocorticoids; stage 3=the administration of glucocorticoids and total parenteral nutrition; and stage 4=the administration of total parenteral nutrition and surgical intervention (4). In our case, although a definitive diagnosis of pre-EPS could not be made based on these findings, PD was discontinued, peritoneal lavage was performed once per day and 20 mg of PSL was administered orally in accordance with the therapy for pre-EPS due to the presence of continuous inflammation and ascites consistent with a diagnosis of pre-EPS. Steroids have been shown to aid in the recuperation of the digestive tract function in various ways and to have an effect on the prognosis (11). Many studies have demonstrated the usefulness of steroids in stage 1 (pre-EPS period) and 2 (inflammation period) EPS (5, 12). In the present case, after 21 days of steroid therapy, the CA125 level in the dialysate increased, whereas the IL-6 in the dialysate declined. Hence, we considered that steroid treatment may improve the mesothelial cell status and intraperitoneal inflammation.

Although there is still no clear evidence, peritoneal lavage is considered to be a risk factor for EPS, as many EPS cases have occurred after discontinuing PD (7, 12-14). Many recent articles have reported the importance of peritoneal lavage, recommending the procedure for six months or more following the discontinuation of PD (5, 12-14). Patients with a history of PD of six years or longer are recommended to undergo peritoneal lavage for at least six months, especially when presenting with high PET results (15). In our case, peritoneal lavage was useful for suppressing the digestive tract adhesion associated with EPS, delaying its occurrence.

In conclusion, we herein reported the case of a patient with continuous inflammation and ascites despite undergoing PD for 10 months and having no history of peritonitis. In this case, we were unable to exclude a diagnosis of pre-EPS. Even in patients without subjective symptoms, we recommend investigating the possibility of EPS based on the presence of continuous inflammation and ascites, as EPS is thought to be the most severe complication associated with PD. Furthermore, in order to differentiate the pathogenesis of ascites in PD patients, future studies should be conducted to establish specific markers for EPS.

The authors state that they have no Conflict of Interest (COI).

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