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Encapsulating Peritoneal Sclerosis: A Case Report and Literature Review

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Conflict of interest: None declared

Patient: Male, 26-year-old
Final Diagnosis: Encapsulating peritoneal dialysis
Symptoms: Abdominal distension • abdominal pain • constipation • vomiting
Medication: —
Clinical Procedure: —
Specialty: Nephrology • Surgery • Transplantology

Objective: Rare disease

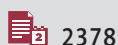
Background: Encapsulating peritoneal sclerosis (EPS) is a rare, life-threatening, and serious complication of long-term peritoneal dialysis (PD). No evidence-based management strategy has been established until now. Surgical management, including enterolysis and excision of the sclerotic and obstructing adhesions, should be considered as soon as conservative management fails to work. We report a case of EPS soon after transplantation in a patient with end-stage kidney disease who had been on long-term PD.

Case Report: A 26-year-old man had been found to have advanced chronic kidney disease secondary to glomerulonephritis on pre-employment investigation. He was on continuous ambulatory PD for 5 years, after which he underwent a living donor renal transplant from his full HLA-matched sibling. He did well postoperatively, with excellent graft function. One month after transplantation, he repeatedly presented to our Emergency Department with signs and symptoms of complete small-bowel obstruction. Computed tomography of the abdomen showed features of small-bowel obstruction secondary to interloop adhesions. The patient was initially managed conservatively; however, as his condition continued to deteriorate, an exploratory laparotomy was carried out. Operative findings were suggestive of early EPS localized to the terminal ileum. Total enterolysis along with peritonectomy was performed along with resection of the diseased and obstructing terminal ileum. The patient did well, and he was discharged home day 10 postoperatively.

Conclusions: EPS remains a serious and fatal complication of long-term PD. Early definitive diagnosis, treatment, and ultimately surgical intervention may be required to prevent the morbidity and mortality associated with this condition.

MeSH Keywords: Kidney Transplantation • Peritoneal Dialysis • Peritoneal Fibrosis • Tissue Adhesions

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Background

Encapsulating peritoneal sclerosis (EPS) was first described in 1907 and linked to peritoneal dialysis (PD) only in 1978 [1]. EPS can be classified as primary, if the underlying cause is unknown, or secondary. Secondary EPS has many etiologies, the most common being PD. EPS is a rare clinical syndrome characterized by an acquired, inflammatory fibrocollagenous membrane encasing or cocooning the abdominal contents, mainly the small intestine, resulting in signs and symptoms of bowel obstruction and malnutrition. EPS is defined by the International Society for Peritoneal Dialysis [2] as “a syndrome in which adhesions of a diffusely thickened peritoneum causes repetitive and intermittent signs and symptoms of intestinal obstruction.” The incidence of EPS in PD patients has been reported to range from 0.7% to 7.3% [3]. Studies have shown a direct relation between the incidence of EPS and the duration of PD. The preoperative diagnosis of EPS remains challenging and requires a high index of suspicion, and in many cases a definitive diagnosis is made at the time of the surgical procedure. Medical treatment of EPS includes the use of tamoxifen, steroids, or immunosuppressants. The failure of medical treatment to effect improvement is an indication for surgery. Owing to the rarity of the disease and high morbidity, we report a case of EPS in a patient with end-stage kidney disease who was on PD before undergoing kidney transplantation.

Case Report

A 26-year-old man had been found to have advanced renal impairment on pre-employment investigations and commenced dialysis soon after. A renal biopsy showed evidence of C3 glomerulonephritis with severe interstitial fibrosis and tubular atrophy. Further work-up based on serological and genetic testing confirmed complement dysregulation (factor H mutation).

The patient was on continuous ambulatory PD for 5 years (April 2014–April 2019), without any episodes of peritonitis. He had severe hyperparathyroidism with parathyroid hormone levels reaching 450 pmol/L (normal 1.6–6.9), for which he underwent subtotal parathyroidectomy in October 2018 with improvement in his parathyroid hormone levels to around 80 mmol/L pretransplant.

He underwent a living donor renal transplant in April 2019 from his full HLA-matched sibling. The transplant was done with a standard retroperitoneal approach, and no assessment of intra-abdominal findings was done because all the work was extra-peritoneal. The patient initially had delayed graft function and needed dialysis for a few days, but he subsequently started to produce urine and his creatinine gradually improved to completely normal (60–70 $\mu\text{mol/L}$). The PD catheter was removed 2 weeks after the transplant.

Postoperatively, the principles of enhanced recovery after surgery were applied. The patient was started on a normal diet on day 1 postoperatively in addition to early mobilization and physiotherapy. He tolerated his diet well up until his 10th day after receiving the transplant, when he developed acute abdominal distension, nausea, and vomiting, with generalized tenderness and absent bowel sounds. An X-ray of the abdomen showed an element of small-bowel obstruction. Computed tomography (CT) with oral contrast showed generalized dilatation of the small-bowel loops, suggesting subacute small-bowel obstruction.

The patient was managed conservatively with nasogastric decompression, and he recovered fully within a few days and was subsequently discharged home. After discharge, he had persistent abdominal distension, anorexia, and nausea associated with decreasing weight. He was on a normal diet during this time but tolerating it poorly. He was readmitted in May 2019 with abdominal distension, prerenal acute kidney injury (AKI, creatinine 149 $\mu\text{mol/L}$), and significant elevation in C-reactive protein (CRP) without a focus of infection and negative cultures. Abdominal ultrasound was done, and it showed moderate ascites. The patient had no signs of bowel obstruction on that presentation; however, based on the constellation of his symptoms, as well as elevated CRP of 177 (normal 0–5) and the finding of ascites, EPS in an inflammatory phase was suspected. The patient’s prednisolone dose was increased to 25 mg once daily (0.5 mg/kg) and tamoxifen was added. He was discharged home a few days later in a stable condition. His creatinine completely normalized with intravenous (IV) volume replacement (70 $\mu\text{mol/L}$).

Despite medical treatment for possible EPS, the patient presented to our Emergency Department approximately a week later with worsening abdominal distension and further increases in his CRP (250) and AKI (creatinine 110 $\mu\text{mol/L}$) but without signs of obstruction. His ultrasound showed worsening ascites and hence paracentesis was carried out, which revealed a lymphocytic, culture-negative fluid and no malignant cells on cytology. CT with IV contrast showed angulation, tethering, and kinking of the small-bowel loops suggestive of interloop adhesions with persistent fecalization of the small bowel, suggestive of slow transit. The peritoneal membrane surrounding the loops had slight thickening, but there was no element of peritoneal calcification (Figure 1). His creatinine remained above his baseline despite IV fluids, hence a graft biopsy was performed, which showed no signs of rejection or recurrent disease.

Medical therapy with prednisolone and tamoxifen was continued. Based on data suggesting that mTOR inhibitors may be of benefit due to their antifibrotic properties [4], tacrolimus was switched to sirolimus. The patient had significant weight

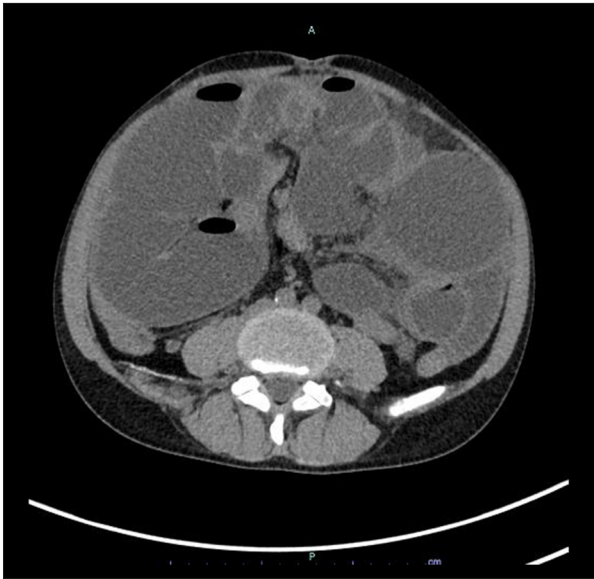


Figure 1. Computed tomography of the abdomen showing the features of early encapsulating peritoneal sclerosis: thickened peritoneum and angulation, tethering, and kinking of the small-bowel loops, suggestive of interloop adhesions.

loss, requiring the administration of dietary supplements. A few weeks later, he developed a second bout of bowel obstruction, which was again managed conservatively with total parenteral nutrition for a few days. After clinical improvement, he was again discharged, although he continued to have air-fluid levels on abdominal X-rays. Within 48 hours of discharge he was readmitted with his third episode of obstruction and high inflammatory markers. Conservative management worked again, the radiologic signs resolved, and the patient was discharged in relatively good health.

In June 2019, the patient presented with overt bowel obstruction, confirmed on abdominal X-ray. This was managed conservatively with nasogastric decompression and total parenteral nutrition. During that admission, due to the recurrent obstructions without any clinical improvement, surgical intervention was considered. The patient was initially reluctant to undergo surgery. However, due to his continued clinical deterioration, he eventually underwent surgery 2 months after admission. Due to persistent bowel obstruction, as well as clinical evidence of malnutrition, total parenteral nutrition was started 1 month prior to his surgery through a peripherally inserted central catheter. No further small-bowel imaging was done at that point, as the diagnosis was clear. At laparotomy, there was grossly distended small bowel from the mid-jejunum to the distal ileum with a closed loop obstruction. Thirty centimeters of distal terminal ileum approximately 20 cm from the ileocolic junction was diseased with partial cocooning (Figure 2), sclerosis, contraction, and gross features

in keeping with early localized EPS. Total enterolysis was performed from the duodenojejunal flexure to the ileocecal junction, and the diseased obstructed distal ileum was resected and re-anastomosed with a side-to-side ileocolic anastomosis. The abdomen was managed as a laparostomy with negative-pressure therapy using a homemade VAC system with a continuous negative pressure of -40 mmHg. After 48 h, the patient underwent a planned re-exploration, and the anastomosis was found to be intact and the abdomen was clean. It was closed in the midline in a standard fashion with 2 drains.

Postoperatively, the patient was managed with continuous nasogastric suction, deep vein thrombosis prophylaxis, and total parenteral nutrition. Over the next 14 days, there was a gradual return of gut function, oral feeds were introduced, and the patient was weaned off parenteral nutrition. His postoperative course was complicated by an episode of multi-drug-resistant *Pseudomonas aeruginosa* bacteremia for which a 10-day course of piperacillin-tazobactam and fosfomycin was given, with subsequent negative blood cultures. The patient was discharged home 2 weeks after surgery on tacrolimus, prednisolone (tapered dose), and tamoxifen. Sirolimus had been stopped 1 month prior to surgery because it is known to impair wound healing. The patient remains very well 9 months after surgery, with no signs of recurrent disease, and he has gained more than 10 kg. Tamoxifen, which he was on for 6 months, was recently stopped.

Discussion

EPS results in peritoneal thickening and bowel encapsulation leading to intestinal obstruction secondary to an exaggerated fibrogenic response of the peritoneal membrane [5]. Many factors have been implicated in its pathogenesis, including exposure to hypertonic glucose-containing solutions, long duration of PD therapy (more than 5 years), and repeated episodes of peritonitis [6]. The 2-hit hypothesis highlights the balance between 2 factors: peritoneal damage due to chronic exposure to toxic PD fluids, which disrupts the natural peritoneal and mesothelial physiology (the first hit), and a major inflammation stimulus (the second hit). Our patient was on PD for more than 5 years, which likely resulted in long-term changes to his peritoneal membrane (i.e., first hit). Moreover, he was exposed to multiple potential inflammatory stimuli, which included renal transplant, removal of the PD catheter, and immunosuppressive medications, all of which may have potentially served as the second hit, leading to the development of EPS [7].

The relationship between long-term exposure to PD and increased risk of EPS is not well understood. Animal models have shown that the secretion of different cytokines, including transforming growth factor $\beta 1$ and vascular endothelial

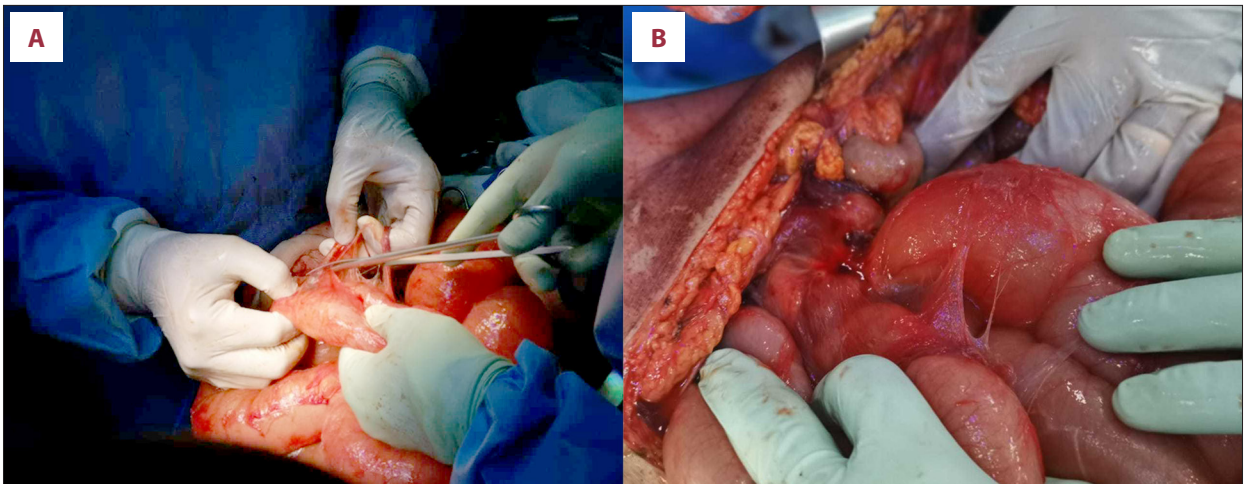


Figure 2. Macroscopic appearance of encapsulating peritoneal sclerosis. (A) Partial cocooning of the terminal ileum. (B) Adhesiolysis.

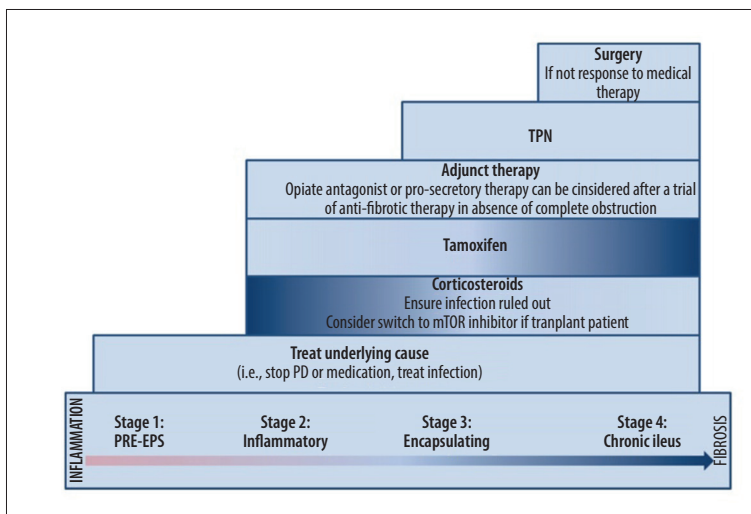


Figure 3. Therapeutic and management approach for encapsulating peritoneal sclerosis (EPS) [2]. EPS is classified into 4 stages: pre-EPS, inflammatory, encapsulating, and chronic. Depending on the stage of the disease, the management and therapeutic approach differs [2].

growth factor, by the macrophages and fibroblasts leads to mesothelial cell damage [8]. However, EPS is a dynamic process in which fibrosis and neovascularization progress even after the triggering agent has been removed [6]. For example, EPS can occur in kidney transplant patients who were previously on PD, as in our case. A recent study has shown that kidney transplantation itself and the usage of calcineurin inhibitors in immunosuppressive regimens also increase the risk of EPS [6]. Early EPS manifests with nonspecific symptoms, including nausea, diarrhea, and abdominal pain. These symptoms may wax and wane and progress to more severe symptoms, such as constipation, malnutrition, and weight loss. Our patient exhibited all the classical EPS signs and symptoms of gastrointestinal dysfunction, leading to obstruction.

Due to the rarity of the disease, the diagnosis of EPS on imaging can be challenging and depends on underlying suspicion of the condition by the radiologist. According to recent literature, an abdominal CT scan is the main imaging modality used

to diagnose EPS [9], and it was the main diagnostic method in our case. CT images often show thickened or calcified peritoneum enveloping tethered small-bowel loops. Other radiographic features include loculated ascites, increased density of mesenteric fat, and localized or diffuse peritoneal calcification [2]. In our patient, diagnostic features on CT included peritoneal thickening, proximal bowel loop dilation, and distal small-bowel intestinal obstruction.

EPS has been classified into 4 stages: pre-EPS, inflammatory, encapsulating, and chronic stages [2]. Depending on the stage of the disease, the management and therapeutic approach differ (Figure 3). For example, during the earlier stages (stages 1–2), the pathophysiology tends to be more inflammatory and the degree of sclerosis tends to be minimal. In the later stages (stages 3–4), more advanced sclerosis may be present, and patients may start exhibiting signs and symptoms of partial or complete bowel obstruction [2]. Medical treatment options for EPS include corticosteroids followed by immunosuppressive

drugs such as azathioprine, sirolimus, tacrolimus, and anti-fibrotic drugs such as tamoxifen [10].

Surgical intervention is important if the medical treatment does not improve the clinical condition, and it should be considered before the patient's condition deteriorates while on medical therapy [9]. Surgical techniques vary depending on the patient presentation. Some are done with curative intent, such as enterolysis (ablation of fibrotic tissue and lysis of adhesions), while others address a specific complication, such as resection of perforated or ischemic bowel and limited lysis of adhesions. Although most cases respond to surgical treatment, poor surgical outcomes have been reported. The literature provides varying outcomes with regard to the surgical management of EPS. In a large case series from Japan, 181 of 239 patients underwent adhesiolysis with no complications in their long-term follow-up. In another case series, 45 EPS patients showed no response and partial deterioration to decapsulation; moreover, 3 of the 45 patients died [11]. Outcome data are even more limited in posttransplant patients.

The need for an enterectomy and anastomosis may be associated with a very high mortality rate. In a retrospective study of 106 patients with EPS in Japan, 9 out of 11 patients (82%) died after enterectomy and anastomosis. Conversely, only 2 of 15 cases (13%) died after enterolysis alone [11]. These results suggest that enterolysis is preferred over enterectomy and anastomosis in EPS patients. Kawanishi [12] has also suggested that combining Noble plication (suturing the intestines to each other) with enterolysis reduces the rate of EPS recurrence to 12.3%. During enterolysis, it is advised to tackle obstructing areas at the end and to begin with segments where adhesiolysis can be performed easily [12].

An important factor that determines the surgical outcome of EPS patients is the duration of PD, which correlates with the severity of peritoneal deterioration. It is technically less challenging to operate on patients who have undergone PD for less than 10 years. Peritoneal calcification, especially visceral, is another factor that may increase the risk of intestinal perforation and complicate the postoperative course [12].

Small-bowel obstruction is an early postoperative complication that usually happens secondary to prolonged bowel dissection, and it frequently results in edema and fibrinous adhesions. These patients improve with conservative management, which includes bowel rest and parenteral nutrition. Steroids, somatostatin, and postoperative stenting of the intestinal loops may reduce the rate of postoperative bowel obstruction [13]. In a single-center review of 65 cases with abdominal cocoon, intestinal stenting was performed for 46 out of 65 patients using a tube that entered the intestine through the root of the appendix. These patients had a lower incidence of intestinal obstruction compared with those without stenting ($P=0.005$) [14]. Surgical mortality, which was as high as 50% in the past, can be significantly reduced in experienced centers managing a high case load [10]. Our patient demonstrated a classical posttransplant EPS in which medical therapy failed, but surgical intervention was successful. Nine months after surgery, the patient remains well.

Conclusions

EPS is a rare but serious complication of long-term PD, with high morbidity and mortality rates if not diagnosed early and managed properly. It is especially unfortunate when patients who were on PD for a long time develop EPS after a successful transplantation. Therefore, timely surgical management should always be provided as soon as the patient fails to respond to medical treatment.

Institution where work was done

Sultan Qaboos University Hospital, Muscat, Oman.

Conflict of interest

None.

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