Encapsulating peritoneal sclerosis in patients on peritoneal dialysis

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ABSTRACT

Encapsulating peritoneal sclerosis (EPS, or abdominal cocooning) is a serious, life-threatening complication in patients on long-term peritoneal dialysis. EPS is characterised by a diffuse thickening and/or sclerosis of the peritoneal membrane which leads to a decreased ultrafiltration and ultimately to bowel obstruction. We present four cases of EPS and discuss the clinical manifestations, multifactorial aetiology, diagnosis, treatment, prognosis, and prevention. We end with a proposal for the development of an EPS prevention guideline.

KEYWORDS

Encapsulating peritoneal sclerosis, peritoneal dialysis, peritonitis, renal failure

INTRODUCTION

Encapsulating peritoneal sclerosis (EPS, or abdominal cocooning) is a serious, life-threatening complication in patients on long-term peritoneal dialysis (PD).1,2 This clinical syndrome was first described by Ghandi et al. in 1980.2 EPS involves thickening and sclerosis of the peritoneal membrane with extensive adhesion of the intraperitoneal organs, which results in decreased ultrafiltration and eventually in bowel obstruction with ileus symptoms. Possible causes of EPS in PD patients are recurrent episodes of peritonitis and exposure of the peritoneum to hypertonic, bioincompatible PD solutions.

CASE REPORTS

Patient A, a 53-year-old man with end-stage renal disease due to Henoch-Schönlein nephritis, underwent a second renal transplantation after a first graft had failed 17 years before. He had been treated with PD for the last 13 years with only three episodes of bacterial peritonitis. For many years he refused a second transplant because he had experienced major problems after the first transplantation. During the second transplantation procedure the surgeon noted a greenish, thickened peritoneum. A biopsy showed extensive fibrosis. From the third day after transplantation, the patient had severe nausea and vomiting. A nasogastric tube produced more than two litres of bilious fluid per day. Computed tomography (CT) of the abdomen showed extensive linear calcification of the thickened visceral peritoneum (figure 1A), fitting with the presence of peritoneal sclerosis. Treatment with tamoxifen was added to the immunosuppressive regimen consisting of tacrolimus, mycophenolate mofetil, and corticosteroids. His abdominal symptoms disappeared, but a severe acute rejection developed, which was unresponsive to treatment with high-dose corticosteroids. Since he refused anti-T cell therapy, the graft was removed and he started haemodialysis. One year later he died after he had decided to stop any further treatment.

Patient B, a 28-year-old man with end-stage renal failure from medullary cystic kidney disease, underwent renal transplantation. During the preceding six years he had been treated with PD, with only two episodes of bacterial peritonitis. Shortly after removal of the PD catheter six months after transplantation, the patient complained of nausea, vomiting, and an increase in abdominal circumference. Physical examination indicated the presence of ascites. Biochemically, this ascites was an exudate, and cultures remained negative. CT showed a
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large amount of ascites with dorsal fixation of the bowel mass, suggestive of EPS (figure 1B). Laparoscopy showed a thick fibrous mass that completely covered the bowel walls. A peritoneal biopsy confirmed the diagnosis of peritoneal sclerosis. Treatment with tamoxifen was started, but eventually complete bowel obstruction necessitated the intravenous administration of fluids, medication, and nutrition. Because of ongoing ascites production a drain was inserted into the abdominal cavity. The ascitic fluid proved to be contaminated with faecal material, which was caused by a perforation of the small bowel wall. Surgical treatment of this perforation was judged impossible. Secondary to the bowel perforation, several episodes of peritonitis occurred. Almost three years after transplantation this patient is alive with a functioning renal graft and in relatively good condition, albeit dependent on total parenteral nutrition and continuous abdominal drainage.

Patient C, a 47-year-old male, received a kidney transplant because of end-stage renal failure due to polycystic kidney disease. Previously, he had been treated with PD for six years with only one episode of bacterial peritonitis. Shortly after transplantation, he developed abdominal discomfort. Initially, this was explained by the use of mycophenolate mofetil, but after discontinuation of this drug, he increasingly complained about a loss of appetite, nausea, vomiting, and swelling of the abdomen with discomfort. He noticed high-pitched bowel sounds and had frequent, watery stools. At six months after transplantation the abdominal discomfort worsened and the patient had lost 17 kg of body weight since transplantation. CT showed a large collection of intraperitoneal fluid, strongly dilated bowel loops, and multiple calcifications of the peritoneum (figure 1C). These findings were compatible with an ileus due to EPS. Cultures of ascites remained negative. Treatment consisted of replacing tacrolimus by azathioprine with continuation of the corticosteroids, addition of tamoxifen, and total parenteral nutrition. He did well until one year after transplantation, when he was admitted because of nausea and vomiting, possibly due to progression of the peritoneal sclerosis. Cultures of the ascitic fluid now grew *E. coli* and *Pseudomonas peruginosa*, for which he was treated with intravenous meropenem. After an initial good response to treatment, the patient developed recurrent infectious episodes, complicated by acute renal failure. At a visit to the clinic he declared that no further treatment should be instituted. Eventually, he died from additional infectious complications.

Patient D, a 41-year-old man with end-stage renal disease due to IgA nephropathy, underwent two renal transplantations. At the age of 34 years, PD was restarted and in the following five years, four episodes of PD peritonitis occurred. Therefore, PD was discontinued and chronic intermittent haemodialysis was started. Six months later, he complained of vomiting without abdominal pain, and loose stools. CT of the abdomen showed a large collection of free fluid (figure 1D). Because EPS was suspected, a laparoscopy was performed. The surgeon noticed a clearly thickened peritoneum as well as a thick fibrinoid layer covering the bowel mass. Peritoneal biopsy showed a thickened connective tissue layer without any signs of acute inflammation, fitting with EPS. Treatment with tamoxifen, prednisone, and total parenteral nutrition was started. The latter could be stopped within a few weeks due to recovery of bowel passage. In the subsequent years he was admitted twice with a mechanical ileus and once with a peritonitis and abscess formation between the bowel loops, for which he was treated with colistin intravenously for several months. Almost three years after the diagnosis of EPS the patient is in a good clinical condition, being treated with haemodialysis and prednisolone, and working several days a week.
DISCUSSION

EPS is a rare but serious, life-threatening complication in patients undergoing long-term PD. Estimates of prevalence range from 0.54 to 7.3%.

Japanese experience suggests that the overall incidence of EPS is 2.5% and a large British single-centre study reported an incidence of 3.3%. It appears that the incidence of EPS in patients on PD has been rising in the last few years.

As demonstrated by three of the cases described above, EPS can also become manifest after kidney transplantation and discontinuation of PD. In addition, EPS is not exclusively a complication of PD, but is also associated with various diseases of the abdominal organs, abdominal surgery, and the use of some drugs (particularly β-blockers).

Aetiology

The aetiology of EPS is poorly understood but is believed to be multifactorial (Table 1).

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<td>Duration of PD</td>
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<td>Poor biocompatibility of dialysate:</td>
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<td>• Antibiotics</td>
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<td>High-transporter membrane</td>
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Table 1. Risk factors for encapsulating peritoneal sclerosis

The latter is associated with an increased number of peritoneal blood vessels, fibrotic alterations, and loss of mesothelium. Continuous exposure of the peritoneum to a fluid with a nonphysiological composition is likely involved in the pathogenesis of these alterations. Glucose and glucose degradation products (GDPs) are toxic to peritoneal cells and induce the formation of advanced glycosylation end-products (AGEs) which are deposited in peritoneal tissue. It has been shown that the use of hypertonic glucose solutions precedes increases in solute transport over the peritoneal membrane, which is associated with ultrafiltration failure.

As a consequence, a further increase in glucose exposure is needed to achieve sufficient fluid removal. This leads to a vicious circle with the risk of progressive peritoneal sclerosis. Other important factors are the buffer that is used in the dialysate (lactate vs bicarbonate) and the acidity of the solution. From in vitro and animal experiments, it can be concluded that biocompatible solutions, characterised by a physiological pH, more bicarbonate vs lactate, and fewer GDPs, are less toxic to the peritoneal membrane.

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So far, the superiority of these solutions with regard to the occurrence of EPS has not been demonstrated in clinical trials. Because of the apparent rise in the incidence of EPS during recent years, an association with the more widespread use of the glucose polymer icodextrin as osmotic agent in PD solutions has been suggested. Although the use of icodextrin has been associated with an increased peritoneal inflammatory response, there are insufficient data to draw a strong conclusion on this subject.

A second risk factor for the development of EPS is the occurrence of refractory and recurrent PD peritonitis. Staphylococcus aureus and coagulase-negative Staphylococcus are the organisms most commonly involved in these episodes of peritonitis. These bacteria have the enzymatic activity to convert fibrinogen to fibrin, which is the major matrix component of intestinal adhesions. Recently, a fulminant form of peritoneal sclerosis was described as a second phase phenomenon immediately following treatment of acute bacterial peritonitis. Treatment with prednisolone appeared to be particularly effective in this setting.

However, EPS also occurs in patients who have never experienced PD peritonitis, and in a recent study of 810 PD patients, no differences in peritonitis rates were found between patients who developed EPS and those who did not.

Histologically, EPS involves proliferation of peritoneal fibroblasts and deposition of extracellular matrix. The latter is stimulated by transforming growth factor-β (TGF-β), and mRNA expression of TGF-β may persist in patients with frequent peritonitis. Interestingly, the calcineurin inhibitors cyclosporine and tacrolimus that are frequently used for immunosuppression after transplantation, have been reported to induce TGF-β production and might contribute to progression of fibrosis.

A Japanese multicentre survey showed that in 68.8% of the most recent EPS patients, EPS became manifest after discontinuation of PD and catheter removal in relation to kidney transplantation. Apparently, besides progression of peritoneal remodelling that happens with long-term PD, additional factors play a role in the progression of EPS. It can be speculated that discontinuation of PD facilitates the progression of peritoneal fibrosis because inflammatory substances and fibrin are no longer efficiently removed from the peritoneal cavity. Furthermore, adhesiolysis by the instilled dialysate might be lost after discontinuation of PD.

Diagnosis

As the prognosis of established EPS is poor, early recognition of preceding symptoms is essential. Features suggestive of early peritoneal sclerosis include the
development of a high transporter state of the peritoneal membrane, a decrease in sodium sieving, a loss of ultrafiltration capacity, and a decrease in mesothelial cell mass as reflected by a low peritoneal fluid CA-125 content. However, these symptoms are not specific, which makes early recognition difficult. As a result, the diagnosis is usually made only when the patient has an established EPS with symptoms of partial or complete intestinal obstruction, as the cases A, B, and C clearly illustrate. At this stage, CT of the abdomen provides a reliable and noninvasive diagnostic tool. Typical CT features of EPS include peritoneal calcification, bowel wall thickening, peritoneal thickening, loculated fluid collections, and tethered bowel loops (figure 1). These findings are diagnostic of EPS in the appropriate clinical setting. Histological findings in a peritoneal biopsy include a very thick sclerosing tissue (1000 to 4000 μm, vs 10 to 70 μm in normal conditions) involving the whole peritoneal wall, often with inflammatory infiltrates, microabscesses, giant cells originating from macrophages, calcifications, and severe vascular alterations.

Treatment
There is no evidence-based therapy available for EPS, so treatment advice is mainly based on anecdotal case reports. Discontinuation of PD is the logical first step of therapy. Additional treatment options include immunosuppressive therapy, surgical treatment, tamoxifen and, if needed, enteric rest with total parenteral nutrition.

Immunosuppressive therapy has been shown to be effective in some cases and has been associated with improved survival. Some patients have markers of acute inflammation such as a high C-reactive protein level in serum or high interleukin-6 levels in the dialysate, and in these cases treatment with corticosteroids, as in patient D, might be useful. Calcineurin inhibitors should be used with caution because they can induce TGF-β production and thus contribute to the progression of tissue fibrosis. Surgical treatment can be considered when symptoms of EPS are not improved by steroid administration or total parenteral nutrition. The surgical procedure consists of total intestinal enterolysis, without damaging the capsule-covered intestine. In one Japanese study of 50 patients with EPS who were treated in this manner, 46 patients experienced complete relief, two patients maintained mild symptoms that could be successfully controlled by diet, and two patients died after perforation of the small intestine. Continuation of PD following successful surgical treatment was reported to be possible in four patients for an average duration of 16 months (range 1 to 32). However, these successful results have not yet been reproduced by non-Japanese groups. In a British single-centre study of 13 patients who underwent surgery for EPS, there were four perioperative deaths, corresponding with a surgical mortality of 31%. After surgery, recurrence of intestinal encapsulation can occur.

In 1999 Allaria et al. reported the first case of EPS successfully treated with tamoxifen. This patient showed a gradual recovery of symptoms as well as a significant reduction in the thickness of peritoneal and intestinal loops. Small case series have confirmed these beneficial findings. One should keep in mind that tamoxifen produces oestrogenic-like effects on certain tissues, and can lead to an increased incidence of venous thromboembolism. Therefore, it has been recommended to withhold this treatment in patients with a known hypercoaguable state, such as activated protein C resistance due to factor V Leiden.

Prognosis and prevention
The cases described above show that the course of EPS is highly variable. In general, the prognosis of EPS is poor and is related to the duration of PD. The incidence (and mortality rate) of EPS was 0%, 0.7% (0%), 2.1% (8.3%), 5.9% (28.6%), 5.8% (61.5%), and 17.2% (100%) in patients who had undergone peritoneal dialysis for 3, 5, 8, 10, 15, and more than 15 years, respectively.

Earlier diagnosis, the use of biocompatible dialysates with nonglucose osmotic agents, and immunosuppressive therapy may improve outcome for such patients in the future. Careful radiological monitoring in patients on PD for more than five years, with early catheter removal if peritoneal thickening is detected, is recommended. To preserve the peritoneum it has been recommended to reduce membrane exposure to the bioincompatible glucose-containing, lactate-buffered solutions. Instead of glucose, amino-acids or icodextrin can be used as osmotic agents. Moreover, the production of dialysis bags with two compartments allows the preparation of dialysis solutions with a higher pH, bicarbonate as buffer, and a reduced concentration of GDPs. Finally, some controversial or experimental measures to prevent the occurrence of EPS are reported: (1) pre-emptive discontinuation of PD after a finite period of PD therapy or when early signs of EPS are evident, (2) prophylactic peritoneal lavage after PD cessation, or (3) medications that may ameliorate inflammation or minimise fibrin deposition.

Based on the currently available literature, including the algorithm described by Kawaguchi et al., we suggest the following guideline (see also figure 2). At any time, the clinician must be aware of the risk of EPS development. Diagnostic evaluation, i.e. CT, should be performed when two or more of the following conditions are present: (1) frequent occurrence of bacterial peritonitis (more than one episode per year), (2) disappearance of sodium sieving or loss of ultrafiltration capacity, (3) development of a high carrier state membrane function, (4) abdominal discomfort.

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When signs compatible with EPS are demonstrated, PD should be discontinued immediately. When CT shows no abnormalities, the decision to replace PD by haemodialysis will also depend on other factors such as the expected near duration of PD, recurrent episodes of PD peritonitis, and exposure to hypertonic glucose-containing peritoneal solutions. EPS should be suspected in PD patients with symptoms suggestive of an ileus. CT can confirm the diagnosis. Although several therapeutic options have been described, an evidence-based therapy is still lacking. The most favoured approach is discontinuation of PD and treatment with corticosteroids and tamoxifen. When symptoms are not alleviated, surgical enterolysis can be considered. The prognosis of EPS is poor and prevention is difficult. Therefore, early recognition of this clinical syndrome followed by proper treatment is essential.

**REFERENCES**


Two balloons in my ruin, why??

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