Encapsulating peritoneal sclerosis: The abdominal cocoon

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ABSTRACT

Encapsulating Peritoneal Sclerosis (EPS) is a rare but serious complication of long-term peritoneal dialysis (PD) that is associated with a high morbidity and mortality. EPS has been previously referred to as sclerosing peritonitis, sclerosing encapsulating peritonitis or the 'abdominal cocoon'. EPS is characterised by diffuse thickening and sclerosis of the peritoneal membrane which leads to a decrease in ultrafiltration, ascites and ultimately partial or complete small bowel obstruction. The aetiology of EPS is unknown but it has been reported to be closely associated with the duration on PD, recurrent peritonitis, high transporter status and use of high concentration of glucose dialysis solutions. Stopping or switching from PD seems to be another trigger factor. Several treatment options including oestrogen and immunosuppressive therapy have been tried, but the mortality remains high at approximately 50%. In some cases, surgery has been attempted but this is associated with high morbidity and mortality. Supportive therapy includes nutritional support with total parenteral nutrition. EPS needs to be diagnosed early and one has to have a high index of suspicion. We report three cases of EPS in patients on PD with different presentation of EPS, their treatment and a brief literature review.

Keywords: Encapsulating peritoneal sclerosis, high transporters, membrane failure, peritoneal dialysis, sclerosing peritonitis

INTRODUCTION

Encapsulating Peritoneal Sclerosis (EPS) is a rare but serious complication of long term peritoneal dialysis (PD) which was first described by Gandhi *et al*. [1] EPS has been previously referred to as sclerosing peritonitis, sclerosing encapsulating peritonitis or the 'abdominal cocoon'. Prevalence varies from 0.54% to 3.3%. EPS is characterised by diffuse thickening and sclerosis of the peritoneal membrane resulting in a decrease in ultrafiltration, ascites and ultimately partial or complete small bowel obstruction. The aetiology of EPS is unknown but it has been reported to be closely associated with duration on PD, recurrent peritonitis, high transporter status, the use of high glucose concentrated solutions and changing modality from PD. [2] The incidence increases with the duration of PD. A study from Japan demonstrated an incidence of 0.7% at five years on PD increasing to 2.1% at eight years and 5.9% after 10 years.

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However, an Australian study showed higher incidence of 1.9% at two years, 6.4% at five years, 10.8% at six years and 19.4% at eight years of PD. [3] Clinical features of EPS are variable and include abdominal pain, nausea, vomiting, weight loss, ascites, blood-stained dialysate and loss of ultrafiltration. EPS is associated with a high morbidity related to malnutrition and sepsis and a high mortality. Fifty-three per cent of 111 patients died in the Pan-Thames EPS study. [4]

We report three cases of EPS in PD patients, their clinical presentation, possible factors associated with the development of EPS, treatment received and a review of the literature on EPS.

CASE REPORT

CASE 1: A 51-year-old Indian lady presented in 2002 with end stage renal disease (ESRD) secondary to hypertension. She was started on continuous ambulatory peritoneal dialysis (CAPD) with four exchanges per day using 1.5% glucose dialysate. During the first year, she had no problems, but over the subsequent years, she developed fluid overload despite good ultrafiltration. Her prescription was changed to once daily 2.3% glucose dialysate until 2005 when she required frequent use of 4.25% glucose dialysate to improve her ultrafiltration. Her dialysis adequacy was good with Kt/V >1.7/week during this period. As the patient declined to switch over completely to haemodialysis, she received hybrid therapy with CAPD (4 exchanges/day) and once weekly haemodialysis. There was no change in her solute transport status and she remained a low average transporter throughout her duration on peritoneal dialysis (PD).

In November 2009, she presented with abdominal pain secondary to peritonitis and was treated with antibiotics for PD peritonitis. She was converted to regular haemodialysis (3 sessions x 4hrs/week). Four months later, she presented with recurrent admissions for refractory anaemia, persistent blood stained ascites, unresolved fever and loss of appetite and weight loss. She had ascites with no hepatosplenomegaly. There was no lymphadenopathy and examinations of other systems were unremarkable. She was worked up for reactivation of tuberculosis and malignancy but all investigations were negative. She was started on anti-tuberculous therapy in view of history of chronic unresolved blood stained ascites and fever with a previous history of pulmonary tuberculosis. Peritoneal fluids culture for bacteria, fungal and tuberculosis was negative.

Her condition did not improve despite anti-tuberculous therapy and she later developed signs and symptoms of sub-acute intestinal obstruction. A computed tomography (CT) scan of her abdomen and pelvis demonstrated thickening of the peritoneal wall and multi-septate ascites (Figure 1) but without

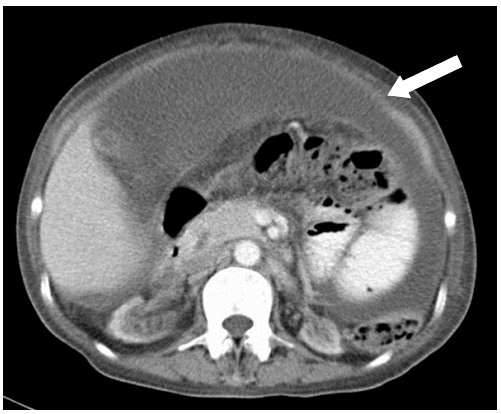

Fig. 1: Axial CT abdomen demonstrating thickened peritoneum (arrow) with ascites and tethering of the bowel.

any peritoneal calcification or bowel thickening. A diagnosis of EPS was made and she was started on tamoxifen.

She received intra-dialytic parenteral nutrition and oral nutritional supplements. Over the next eight months, her weight increased, she was able to tolerate a normal diet and was weaned off parenteral nutrition. Two years after the diagnosis of EPS, the patient's weight remains stable.

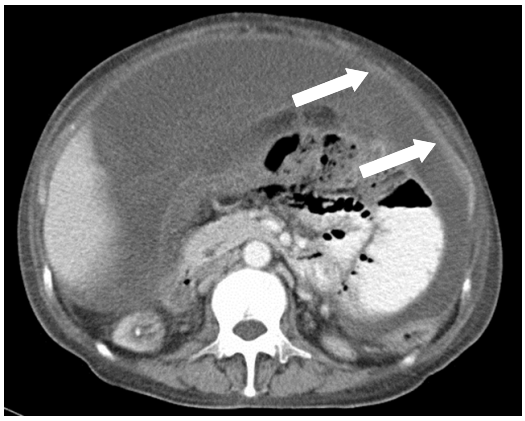

Fig. 2: Axial CT abdomen of Case 2 also demonstrating enhancing thickened peritoneum (arrows) with ascites.

CASE 2: A 56-year-old Chinese man presented with ESRD in early 2006. He was commenced on CAPD with four exchanges per day with 1.5% glucose dialysate. He was well dialysed with a Kt/V of >1.7/week during the three monthly follow up until the end of 2010 when he started to lose his residual renal function and developed membrane failure resulting in chronic fluid overload. His PD prescription was tailored to maintain his target dry weight and he needed a combination of 1.5% and 2.3% glucose dialysate daily and an occasional 4.25%. His remained a low average solute transporter throughout the intervening years.

In 2006, he was treated for secondary hyperparathyroidism with paracalcitol and had a persistent renal anaemia despite an increased dose of erythropoietin. He also developed one episode of peritonitis in 2009 but recovered well with antibiotic treatment. He developed recurrent episodes of fluid overload in May 2011 despite adjusting his PD prescription and increasing frequency of exchanges. He was finally converted to regular haemodialysis in June 2011.

Seven months after being on haemodialysis, he presented with a one month history of dyspepsia and weight loss. Examination of the abdomen revealed a distended abdomen. Examination of other systems was unremarkable. CT scan of the abdomen revealed gross ascites without septations or loculations, small bowel tethering and small bowel thickening which were consistent with EPS. He was treated with tamoxifen and intra-dialytic parenteral nutrition and 8 months later, he remains on tamoxifen with a stable weight and no further episodes of bowel obstruction.

CASE 3: A 47-year-old Chinese lady presented with ESRD secondary to glomerulonephritis in July 2004 and was started on CAPD with four exchanges/day of 1.5% glucose concentration. She was well dialysed with a good Kt/V of >1.7 during regular follow up until late 2005, when she became fluid overloaded despite good ultrafiltration and needed 2.3% glucose dialysate. This was subsequently increased to two exchanges of 2.3% glucose dialysate and an occasional 4.25% to maintain her target dry weight. She was a high average solute transporter but with time became a high transporter. She had no episodes of peri–

tonitis but had been troubled with candida infection of the exit site intermittently for which she received prolonged courses of treatment. In 2008, she lost all residual renal function and her prescription had to include at least one 4.25% glucose dialysate solution. She eventually agreed to removal of Tenchkoff catheter and conversion to haemodialysis in March 2009.

Two years later she presented with a history of 25kg weight loss over 6 to 9 months, abdominal pain and dyspepsia and was diagnosed with EPS. CT scan demonstrated loculated ascites, thickened peritoneum, small bowel dilatation and calcification. She was treated with intra-dialytic parenteral nutrition and tamoxifen and one year on, she is still alive, has gained some weight and is off intra-dialytic parenteral nutrition.

DISCUSSION

EPS is a rare but serious complication of long-term PD. EPS presents with a broad clinical spectrum and clinicians must have a high index of suspicion. Clinical features are variable and non-specific: abdominal pain, nausea, vomiting, weight loss, loss of ultrafiltration, ascites and blood stained dialysate. There are no specific laboratory findings to diagnose EPS. Nevertheless, there are a few features which may suggest EPS such as erythropoietin refractory anaemia, hypoproteinaemia, elevated C-reactive protein and progression to high transporter status.

In our first case (Case 1), there was a delay in diagnosing EPS. We initially investigated for TB as some of the presenting features are similar especially in this part of the world where TB is still prevalent. Our other two cases presented with weight loss and dyspepsia and were both patients who had previously been on PD. The International Society of Peritoneal Dialysis (ISPD) recently produced a consensus statement on the diagnosis of EPS based on the presence of clinical symptoms of obstructive ileus, with or without various degrees of systemic inflammatory reaction, AND the presence of peritoneal thickening and encapsulation, peritoneal calcification, bowel wall thickening, tethered bowel loops (cocoon) and loculated fluid collections. [5]

The aetiology of EPS is believed to be multi-factorial and has been reported to be closely associated with factors such as duration of PD, recurrent peritonitis, high solute transport status, the use of high glucose concentrated solutions and switching treatment modality to PD. [2] The pathogenesis is not well

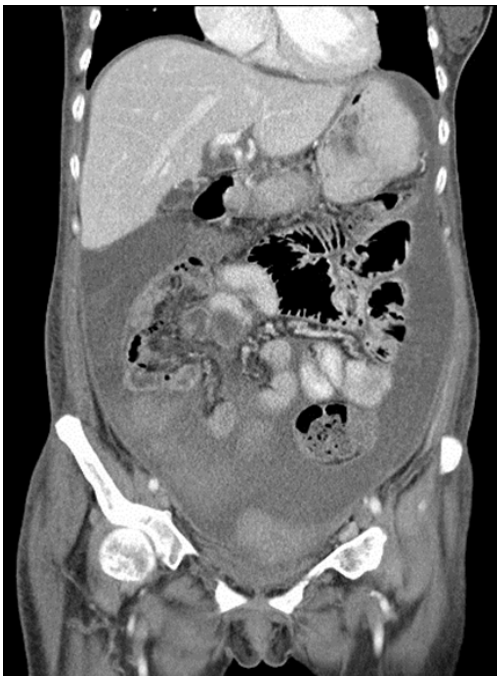

Fig. 3: Sagittal CT abdomen showing thickened peritoneum, ascites with bowel located in the mid abdomen.

understood. EPS is not exclusive to PD and can also occur in non-dialysis patients. [6, 7] However, EPS can sometimes occur in patients who have not had any episodes of peritonitis or in low solute transporters.

There is a strong correlation between the duration of PD and developing EPS especially if this is more than five to six years as demonstrated by several studies. [3, 8] Long-term PD is associated with an increase in number of peritoneal blood vessels, fibrotic alterations and loss of mesothelium resulting in peritoneal membrane failure and loss of ultrafiltration. [9] Based on the 'two hit theory', where the first 'hit' is peritoneal deterioration caused by long-term PD, there is usually a second 'hit' (intra-peritoneal inflammation) that occurs to accelerate this process and includes factors like peritonitis or terminating PD. [10] In our case series, all patients had been on CAPD for more than five years. In our first patient, it was difficult to switch the patient to haemodialysis earlier due to patient choice. Some nephrologists would routinely consider changing patients from PD after 5 years, although there is no strong evidence for this practice at present.

Another important risk factor for the development of EPS is the occurrence of peritonitis. In our case series, only one patient developed peritonitis prior to the onset of EPS. EPS can occur in patients who have never experienced PD peritonitis.

EPS has also been associated with the use of hypertonic glucose dialysate. Continuous exposure of the peritoneum to a non-physiological fluid is likely to be involved in the pathogenesis of peritoneal deterioration. Glucose and glucose degradation product (GDPs) are toxic to peritoneal cells and induce the formation of advanced glycosylation end products which are deposited in peritoneal tissue. [11] The use of hypertonic glucose solutions precedes an increase in solute transport, 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 cycle with the risk of progressive peritoneal sclerosis.

All our three cases developed EPS after changing treatment modality. Discontinuation of PD is the logical first step in the event of membrane failure. Several studies have noted that discontinuation of PD may accelerate the development of EPS with 59% to 68% of cases developing EPS after termination of PD. [4] It is speculated that discontinuation of PD facilitates the progression of peritoneal fibrosis because of the loss of removal of inflammatory mediators and fibrin from the peritoneal cavity. [8] Studies suggest that the average time to developing EPS after changing modality was 5.5 months with 75% developing it within six months. [4]

There is currently no compelling evidence based therapy for EPS at present. The treatment advice is mainly based on anecdotal case reports. Although most cases develop after terminating PD, discontinuation of PD in the event of membrane failure is still the most logical step. Other treatment options that have been tried with various success rates include anti-fibrotic therapy with tamoxifen, immunosuppressive therapy, surgical treatment and enteric rest with total parenteral nutrition in certain cases.

The first case of EPS successfully treated with tamoxifen was reported in 1999. [12] Tamoxifen, a non-steroidal anti-oestrogen used to treat breast carcinoma has been used in fibrosing medianitis and retroperitoneal fibrosis. Tamoxifen has anti-fibrotic properties by up regulating transforming growth factor$_{\beta}$1 and stimulating degradation of denatured collagen. Small studies have shown benefit with tamoxifen at doses of 20 - 40 mg/day. [13]

Steroids have been commonly used in Japan to reduce the inflammation in EPS. In a prospective cohort, 15 of 42 cases (35.7%) treated with prednisolone alone experienced clinical improvement. [8] There are isolated reports of improvement after steroids used in combination with immunosuppressive agents such azathioprine or mycophenolate mofetil. However, there are also many cases of EPS developing after renal transplantation despite being on immunosuppressive therapy. The evidence for immunosuppressants other than steroids is not compelling and more data is needed. The introduction of EPS registries in several countries will provide more information in the future. In our case series, none of our patients were treated with steroids or immunosuppression.

Surgical treatment can be considered when symptoms of EPS do not improve with steroids and administration of total parenteral nutrition. Adhesiolysis is one of the popular surgical methods in Japan. However, it is difficult to perform with a high mortality and morbidity even in highly selected cases. [13]

Total parenteral nutrition (TPN) is sometimes needed in patients with small bowel obstruction who are unable to tolerate oral feeding. However, TPN alone will not improve the outcome in EPS, rather it is a supportive therapy. There are risks with long term TPN use including catheter related infections.

EPS is a serious complication in patients receiving long-term PD. The prognosis of EPS is poor and is related to the duration of PD. [4] The mortality rate in one study increased to 8.3%, 28.6%, 61.5% and 100% respectively after 8, 10, 15 and more than 15 years of PD. [8] As the prognosis of EPS is poor, early recognition is of utmost importance. At present, there is no evidence for routine screening using CT scans in asymptomatic PD patients. [15] More data is needed to consider CA-125 as a screening tool for EPS. Once EPS has developed, progress should be monitored by use of inflammatory parameters, nutritional status and weight gain, reduction of ascites and episodes of small bowel obstruction.

In conclusion, EPS is a rare but serious complication of long-term PD and has high mortality and morbidity rates. Prevention perhaps is important as the treatment remains undefined. Some nephrologists advocate changing from PD after five years, however the majority of cases of EPS occur after stopping PD. Therefore, if one is considering changing a patient to HD pre-emptively due to the risk of EPS, it may be appropriate to consider the high risk patients i.e. patients with multiple episodes of peritonitis, high use of glucose concentration dialysate and high solute transporters. Other prevention strategies include the avoidance of high glucose concentration dialysate and the use of biocompatible dialysate solutions.

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