

Encapsulating peritoneal sclerosis in patients on peritoneal dialysis. A single centre experience

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Received for publication: 30/07/2009

Accepted in revised form: 29/09/2009

ABSTRACT

Encapsulating peritoneal sclerosis is a rare but extremely serious complication of peritoneal dialysis. There is no established medical treatment and surgery has been reported with variable success. Some reports have suggested that management with immunosuppression and steroids might be effective. Since the first case reported by Allaria in 1999 suggesting the benefits of tamoxifen in treating encapsulating peritoneal sclerosis, other cases of successful treatment have been described.

We identified 4 cases in 110 patients treated in our PD unit since 1993. The incidence of EPS was 1.67% per year (1 episode/719 months/patient). Three patients were treated with tamoxifen. A female 20-year-old African patient developed small bowel obstruction after 5 years on peritoneal dialysis. Adhesions were lysed during laparotomy and the patient was switched to haemodialysis. Tamoxifen was recommenced and there was steady improvement with no further bowel obstruction. A 41-year-old man on peritoneal dialysis for 5 years presented impaired peritoneal ultrafiltration, and abdominal CT scan demonstrated adherencies and loculated collection in November 2004. A renal transplant was performed one month later and in October 2006 he presented small bowel obstruction. The patient started treatment with tamoxifen and currently remains free of symptoms. A 40-year-old woman on peritoneal dialysis for 8 years presented ultrafiltration failure and was switched to haemodialysis. She

presented fever, refractory haemorrhagic ascites, intolerance to any oral intake and cachexia. TC scan revealed sclerosing peritonitis. She was treated with prednisone and tamoxifen for eighteen months and her gastrointestinal symptoms and nutrition improved markedly. She was maintained successfully on haemodialysis for 2 years in a stable condition.

In our experience tamoxifen has been effective in treating encapsulating peritoneal sclerosis, even in severe and advanced cases. It seems that treatment with tamoxifen prolongs patient survival, at least in the short- to mid-term.

Key-Words:

Peritoneal dialysis; peritoneal sclerosis; tamoxifen.

INTRODUCTION

Encapsulating peritoneal sclerosis (EPS) related to peritoneal dialysis (PD) was first described by Gandhi¹ in 1980. It is a clinical syndrome characterised by symptoms caused by the persistent, intermittent or recurring obstruction of the intestine, sometimes associated with haematic peritoneal effluent or ascites, with constriction of the small bowel by the thickened fibrotic membrane. This is a severe but rare complication and is associated to a high mortality rate. EPS was regarded for a long time as an advanced stage of peritoneal fibrosis, but a number of studies have shown that EPS and peritoneal

fibrosis are separate entities, with different pathogeneses. The mechanisms involved in the development of EPS are complex and include mesothelial denudation, capillary angiogenesis and fibrin deposition². It has still not been possible to establish the direct causes of the disorder, although a set of risk factors has been identified that could predispose to its appearance. These factors may or may not be PD-related. Severe peritonitis may precede the diagnosis, but this condition may be established after changing to haemodialysis (HD). Abdominal CT scan can be used to reliably make the diagnosis of EPS. Laparotomy may reveal parietal thickening, intestinal obstruction by encapsulation or dense adhesions and biopsy of the peritoneum shows replacement of the mesothelium by acellular material³.

Treatment of EPS is extremely difficult. Corticosteroids have been used in the inflammatory stage of the disease, but once intestinal obstruction has been established laparotomy with enterolysis is necessary. Even though surgery removes the intestinal obstruction, this does not prevent peritoneal deterioration, sometimes with recurrence of the disease⁴. Immunosuppressors have been tried, with varying success. The use of tamoxifen, a drug with antifibrotic properties, has been reported with an improved clinical course⁵.

We present four cases of EPS occurring in a population of patients undergoing PD in the Nephrology Unit of Hospital Garcia de Horta, from the start of the programme in June 1993 to December 2007. We treated 110 patients during this period, and the average time on PD was 26.15 months. The incidence of EPS was 1.67% per year (1 episode/719 months/patient).

■ CASE REPORTS

Case 1: A 50-year-old woman developed end-stage renal disease (ESRD) caused by chronic pyelonephritis in July 1994 and was started on HD immediately. She was transferred to continuous ambulatory peritoneal dialysis (CAPD) three months later due to vascular access exhaustion. She had five episodes of bacterial peritonitis caused by *Coagulase-negative Staphylococcus*, *Acinetobacter baumannii*, *Staphylococcus epidermidis* and *Staphylococcus aureus*. In one case, cultures of peritoneal effluent showed no growth of bacteria or

fungus. In November 2001 she presented with abdominal pain, nausea, vomiting, fever, dyspnoea and malaise. The peritoneal effluent was normal and she was initially followed conservatively with antibiotics and total parenteral nutrition (TPN). After that, her symptoms worsened and she underwent laparotomy which revealed multiple thick leathery adhesions with an encapsulated small bowel. Biopsies were taken from the peritoneum and pathological examination revealed EPS. The patient was transferred to HD but recurrent bowel obstruction continued. In April 2002 she was switched back to PD due to vascular access exhaustion. Eight months later, she presented with recurrent small bowel obstruction (SBO) which became complete. Intraoperatively, strangulation of the ileus by a thick sclerotic membrane was detected and enterectomy was performed. Bowel function did not recover. The probable cause of patient death was ongoing sepsis.

Case 2: An African female patient aged 20 years developed SBO in July 2002 after five years on CAPD (she had been on HD for two years and had been switched to DP due to vascular access exhaustion). During this period there had been four episodes of peritonitis (three episodes of *Staphylococcus aureus* peritonitis and one episode of *Streptococcus B hemolyticus*) that settled rapidly with appropriate antibiotics. The patient was admitted to hospital with abdominal pain and repeated vomiting. Abdominal CT scan revealed marked thickening of the peritoneum, calcification and dilatation of the small bowel with tethering. Adhesions were lysed at laparotomy. Tamoxifen treatment (10mg once a day) and prednisone (50mg once a day) were started and the patient was switched to HD. Tamoxifen treatment was discontinued four months later due to hepatic toxicity. In January 2003 she developed symptoms of recurrent partial SBO, anaemia, hypoalbuminaemia and haemorrhagic ascites, requiring several therapeutic paracenteses. TPN was given for three weeks. The patient received oral prednisone 40mg once a day for two months and tamoxifen 10mg twice a day for six months. Her symptoms improved with an increase of albuminaemia and haemoglobin. Three years later, she was symptom-free on HD.

Case 3: A 41-year-old man who had been treated with HD for end-stage renal failure secondary to nephroangiosclerosis since May 1996 due to vascular access exhaustion was transferred to CAPD in August 1999. In December 2002 the patient underwent deceased-related

donor kidney transplantation complicated by venous thrombosis and early graft failure. He developed a pulmonary embolism during hospitalisation. Over five years there had been only two episodes of peritonitis caused by *Staphylococcus aureus*, one of these with particular severity. In November 2004 he presented impaired peritoneal ultrafiltration and CT scan demonstrated adherencies and loculated collection. A second renal transplant was performed in December 2004. He was maintained on MMF, ciclosporin and prednisone therapy. Two years later the patient was admitted to hospital complaining of abdominal pain and fever. Exploratory laparotomy revealed haemoperitoneum and thick opaque visceral peritoneum and peritoneal *toilette* was performed. Failure to improve after 48h of appropriate antibiotic therapy led to repeat CT scanning which revealed localised fluid collection. The patient required several CT-guided percutaneous drainages for recurrent haemoperitoneum. He developed sepsis related to bowel perforation and received the appropriate antibiotics and TPN with improvement. Tamoxifen 10mg once a day was started after 20 days and he developed a femoral venous thrombosis. He started oral anticoagulation with no recurrence of symptoms. Currently the patient remains symptom free, medicated with tamoxifen 10mg once a day.

Case 4: A 40-year-old woman developed ESRD at the age of 15 years old (1982) and was maintained on HD for five years. Two renal transplants were performed (June 1987 and March 1991). She reinitiated HD in October 1993 and was transferred to PD in August 1998 (personal choice).

The patient experienced one episode of peritonitis during the second year of peritoneal dialysis. In October 2006 she presented ultrafiltration failure and was switched to HD. Two months later she was hospitalised with a one month history of abdominal pain, fever, vomiting, blood-stained ascites and malnutrition. She presented anaemia, hypoalbuminaemia and elevated C-reactive protein (CRP). Because the patient was intolerant of any oral intake, TPN was commenced and a broad spectrum antibiotic was prescribed. Abdominal CT scan revealed large ascites and dilatation of small bowel. Ascitic fluid aspirate did not show malignant cells. Extensive microbiological cultures, including culture of peritoneal fluid, were negative.

Emergency surgery was performed due to worsening symptoms. At laparotomy the peritoneum was described

as thickened, sclerosed and adherent to viscera. A biopsy of the peritoneum revealed dense fibrous tissue. The patient continued to lose weight and fever persisted. Her condition deteriorated and her survival was uncertain. Oral prednisone at a dose of 20mg daily was commenced. Over the next month she had recurrent episodes of tense ascites and required several therapeutic paracenteses. Her diet was advanced slowly but she remained seriously ill with cachexia. The patient was treated with prednisone and tamoxifen 10mg twice per day for eighteen months. Her gastrointestinal symptoms and nutrition improved markedly. There was recovery of inflammatory state and a fall in CRP was observed. She was maintained successfully on HD for two years with no further complications. However, after this time, the patient developed fever, cachexia and bowel obstruction and died.

We briefly describe four cases of laparotomy-confirmed EPS with biopsy of the peritoneum in one case. They were characterised by long duration of PD (mean duration 76 months). All but one received tamoxifen and only that patient died early.

■ DISCUSSION

EPS is a potentially fatal entity if not diagnosed in the early stages. A diagnosis of EPS should be considered in patients who are or have been undergoing PD and who exhibit nonspecific gastrointestinal symptoms or intestinal obstruction in advanced disease, as was found in the first three cases described. In patients no longer undergoing PD the most common clinical presentation involves gastrointestinal symptoms and recurring ascites, usually haematic⁶. Loss of ultrafiltration through the membrane may be an early sign, and a sudden fall in peritoneal effluent CA-125 may indicate a reduction of mesothelial cells and the development of sclerosis⁷. The clinical presentation in the fourth patient was dominated by a persistent inflammatory state associated with severe malnutrition, with a clear risk of death, and the diagnosis may not be immediately obvious in these cases. Malnutrition progresses steadily in these patients, to the point of cachexia. Nonspecific analytical changes may be present, such as hypoalbuminaemia, elevated CRP and erythropoietin-resistant anaemia. Changes to the peritoneum found on ultrasound and CT have been used as indicators of the disease⁶. Abdominal

ultrasound often shows altered peristalsis, and 36% of patients show the formation of bridges between the loops and the presence of a membrane anterior to the small intestine. CT may reveal parietal thickening in 44-100% of cases, loculated fluid collections in 44-99% and peritoneal calcification in 11-70%⁸. Calcification seems to be related more to the time under PD. Definitive diagnosis is confirmed by laparotomy.

Aetiology seems to be multifactorial. According to some published reports⁹ in which there was no prior history of peritonitis, a direct relation between peritonitis and the development of EPS cannot be established. But even though none of our patients presented with the disorder in the wake of peritonitis, all of them had developed bacterial peritonitis during treatment, caused by particularly virulent pathogens such as *Staphylococcus aureus*. The severity and recurrence of peritonitis appears to be a risk factor in that it facilitates peritoneal deterioration through loss of the mesothelium, thereby favouring the development of the disease.

Although the rate of peritonitis in patients undergoing PD has been declining in recent years, the incidence of EPS has risen, which is partly explained by prolonged PD. Several studies have confirmed treatment duration as an important risk factor, with greater likelihood of the disease developing in patients undergoing treatment for more than 4-5 years. The only prospective study, by Kawanishi, shows a clear association between the rate of incidence of the disorder and the duration of PD, with an incidence rate of 2.5%, varying from 0.7% in patients undergoing PD for three to five years and 17.2% when treatment lasts over 15 years¹⁰. No patient whose treatment lasted less than three years developed the disorder. The four cases described above had been undergoing PD for longer than five years (average 6.3 years). Long-term PD is probably the most important risk factor for EPS. If peritoneal biopsy demonstrates sclerosis in these patients, PD should be discontinued.

The poor biocompatibility of the dialysate and the use of chlorhexidine have also been implicated. The presence of glucose, of AGEs (advanced glycation end-products) resulting from the heat sterilisation of dialysate with glucose, lactate and acid pH may have a role in overproduction of TGF β 1 and VEGF by mesothelial cells, resulting in adhesion formation, angiogenesis and ultrafiltration failure^{11,12}. Genetic predisposition

and the use of beta-blockers remain controversial issues. Acquisition of a high-transporter profile could be an early marker of patients at high risk of developing the disease¹³. All our patients presented with this profile on manifestation of the disease.

Once EPS has been diagnosed PD must be stopped and HD instituted. In these cases, it has been suggested that maintaining the catheter and peritoneal lavage for a year may help to eliminate factors implicated in the progression of the disease¹⁴, but this is still controversial.

At first, mortality after surgery was quite high due to intestinal perforation and sepsis. In patients who fail to respond to conservative measures such as TPN, the treatment of choice is enterolysis, avoiding intestinal resection¹⁵. Corticosteroid monotherapy has been effective in some cases¹⁶⁻¹⁸, but its use is not consensual¹⁰. There seems to be some benefit when corticosteroids are administered in the early stages of the disease or when the presentation is predominantly one of inflammation^{19,20}.

Since the first case described by Junor *et al.*²¹ in 1993 there have been reports of the apparent benefit of kidney transplantation and/or the use of immunosuppression (azathioprine and ciclosporin) in EPS patients²². On the other hand, our third patient developed the disorder despite having received a transplant and being under immunosuppression, and this has been described in other cases, too⁹. Recently ciclosporin has been associated with greater risk of developing EPS²³. The role of immunosuppression is not clear, since there are reports of variable success with the use of different regimes.

It was in 1999 that Allaria²⁴ described the first case of EPS treated with tamoxifen, an anti-oestrogen, effective in other fibrosing diseases^{25,26}. It has been used in other patients since then, improving short- to medium-term survival rates²⁷. The mechanism of action of tamoxifen in this type of disorder is unknown, but it is thought that it could be related to the modulation of TGF β 1, an important factor in stimulating the deposition of extracellular matrix²⁸. The development of thromboembolic disease, as observed in the third patient, is a known side effect of tamoxifen.

Even though the four cases described presented with severe EPS and high mortality was expected, rapid

progression to septic shock and death only occurred in the first patient. This is a common outcome of the disease and has been reported in many cases¹⁰.

In the remaining three cases, clinical improvement related to the use of tamoxifen in association with corticotherapy in the initial treatment phase seems to show the benefit of tamoxifen in these cases. Despite death, the fourth patient had a marked improvement in symptoms and was in stable condition for two years. It is probable that this patient had extremely severe disease at time of diagnosis. Among patients treated with tamoxifen, one-year mortality after the diagnosis of EPS was 0%, an excellent result compared with the high mortality rate observed in other centres²⁹.

No therapy of choice has been established for patients with EPS. It seems that treatment with tamoxifen prolongs patient survival, at least the short- to mid-term. Controlled, randomised studies are needed, however, in order to establish the appropriate duration of treatment.

Conflict of interest statement. None declared.

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