

Encapsulating peritoneal sclerosis successfully treated with corticosteroids and Tamoxifen

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■ ABSTRACT

Encapsulating peritoneal sclerosis is a rare but serious complication of long-term peritoneal dialysis characterised by abnormal deposition of fibrous tissue involving intra-abdominal organs and resulting in symptoms of obstructive ileus accompanied or not by various degrees of systemic inflammation.

We describe a case of encapsulating peritoneal sclerosis in a patient four years on peritoneal dialysis with multiple previous episodes of peritonitis and evidence of recent peritoneal membrane dysfunction with decreased ultrafiltration ability. He presented with a consumptive disease with signs of ongoing systemic inflammation and malnutrition associated with slight ileus and recurrent bloody ascites after recent transfer to haemodialysis. Peritoneal membrane thickening suggestive of a desmoid-like lesion was seen in radiology imaging. A diagnosis of encapsulating peritoneal sclerosis at an inflammatory stage was suggested. Influenced by several published reports, prednisolone and tamoxifen treatment was initiated. In a few weeks the patient's symptoms gradually improved with total resolution of bloody peritoneal effluent.

We conclude that corticosteroid and tamoxifen treatment can be effective in early inflammatory

stages of encapsulating peritoneal sclerosis, possibly avoiding progression to late stages of the disease.

Key-Words:

Bloody ascites; encapsulating peritoneal sclerosis; peritoneal dialysis; tamoxifen.

■ INTRODUCTION

Patients on peritoneal dialysis (PD) are exposed to some particular conditions and are prone to specific complications related to this type of renal replacement therapy. The peritoneal membrane (PM) of PD patients is exposed to some non-physiological factors that go towards modifying the PM's initial morphological and functional properties. It is recognised that peritoneal sclerosis, a mild fibrosing condition affecting the PM, occurs in most PD patients over time¹. A small minority of PD patients see magnified PM sclerotic changes. The full expression of this is known as encapsulating peritoneal sclerosis (EPS). This is a rare but serious condition whose incidence increases with time on PD²⁻⁴ and whose aetiology is believed to be multifactorial. Why only some patients, despite all patients being exposed to similar risk factors, develop EPS remains unknown.

Treatment strategies are not well defined and are frequently unsuccessful.

■ CASE REPORT

We report the case of a 68 year-old Caucasian man with end-stage renal disease secondary to chronic glomerulonephritis on automated PD (continuous cycling peritoneal dialysis) since May 2003 with total dwell infusion volumes of 13.6 L/day. He had no residual renal function and generally used 2.27% dextrose, lactate buffered and low glucose degradation products (GDPs) dialysis solutions. By February 2007 he had had five episodes of peritonitis, two caused by *Staphylococcus epidermidis* and three caused by Gram-negative organisms. Over time the peritoneal equilibration test (PET) results showed a progressive evolution towards a high-average transporter status (D/P ratio for creatinine =0.75). This was accompanied by a moderate loss of net ultrafiltration and an increasing need for high osmolality dextrose solutions for adequate body fluid and blood pressure management. Prescribed drug treatment included vitamin B complex, folic acid, sevelamer, statin, omeprazol, allopurinol and captopril. Beta blockers were never used while on PD.

On February 2007 he was admitted to hospital with headache, fever, chills and prostration. Physical examination revealed a sleepy and confused state, hypertension (179/115 mmHg), tachycardia (116 bps), fever (38.8 °C) and diffuse pain on deep abdominal palpation without evidence of abdominal organ enlargement. Bloody peritoneal effluent was visible. Laboratory data revealed leucocytosis (19400/μL), thrombocytopenia (80000/μL) and elevated C-Reactive Protein (CRP) (17.59 mg/dL). Hepatic function, serum amylase and lipase levels were within their reference intervals. Cerebrospinal fluid (CSF) analysis excluded meningitis and a non-contrast brain computed tomographic (CT) scan did not show acute vascular lesions. Peritoneal effluent analysis was misleading due to the massive presence of blood and abdomen CT scan revealed intraperitoneal liquid without evidence of adhesions in the peritoneal cavity or bowel distension. At that time a diagnosis of peritonitis complicated with sepsis was made and intraperitoneal antibiotic therapy (vancomycin and ceftazidime) started. Intravenous vancomycin and piperacillin/tazobactam were then administered with clinical and laboratory improvement. During a short stay in the Intensive Care Unit PD was temporarily suspended and haemodialysis (HD) initiated. Peritoneal dialysate, blood and CSF cultures were always

sterile. Haemoperitoneum was attributed to possible catheter trauma with progressive resolution in the following days. After recovery patient opted to switch permanently to HD but the Tenckhoff catheter was left in place. In the following months a recurrent presence of bloody effluent on peritoneal exchanges performed at weekly intervals was seen.

Approximately three months after starting HD he presented with diffuse abdominal pain, melaena, constipation and bloody ascites. On physical examination he was extremely malnourished, had hypotension (76/53 mmHg), mucosa and skin discoloration and diminished bowel sounds. On laboratory evaluation, peripheral white blood cell count was 12000/μL, haemoglobin 9.6 g/dl, albumin 32 g/l and CRP 2.2 mg/dl. Culture of peritoneal effluent was sterile and negative for carcinoma cells. Esophagogastroduodenoscopy did not show haemorrhagic lesions and colonoscopy revealed only presence of digested blood and excluded tumoral lesions of the observed mucosa. CT scan of the abdomen revealed only massive ascites, without evidence of bowel distension or gross adhesions wrapping bowel loops. Magnetic resonance imaging (MRI) scan (without gadolinium) revealed peritoneal thickening on right parieto-colic gutter suggestive of a desmoid-like lesion and a star-shaped appearance of the mesentery (Fig. 1).

A diagnosis of EPS was suggested and prednisolone (0.5 mg/Kg daily – 20 mg/day) and tamoxifen (20 mg/day) were prescribed. The patient's symptoms improved gradually over the next few weeks with recovery of lost weight and three months later abdominal ultrasound demonstrated no evidence of ascites.

■ DISCUSSION

One of the most serious complications of PD is EPS, a particular type of fibrosis that is being increasingly recognised, with an estimated incidence of 0.6 to 3.3% in PD populations⁵⁻⁷. It is characterised by the development of an inflammatory process resulting in the appearance of increased sheets of fibrous tissue in the peritoneum with possible encasement of abdominal viscera and mechanical compromise of its normal function. Incidence and severity are increased with time on PD⁷.

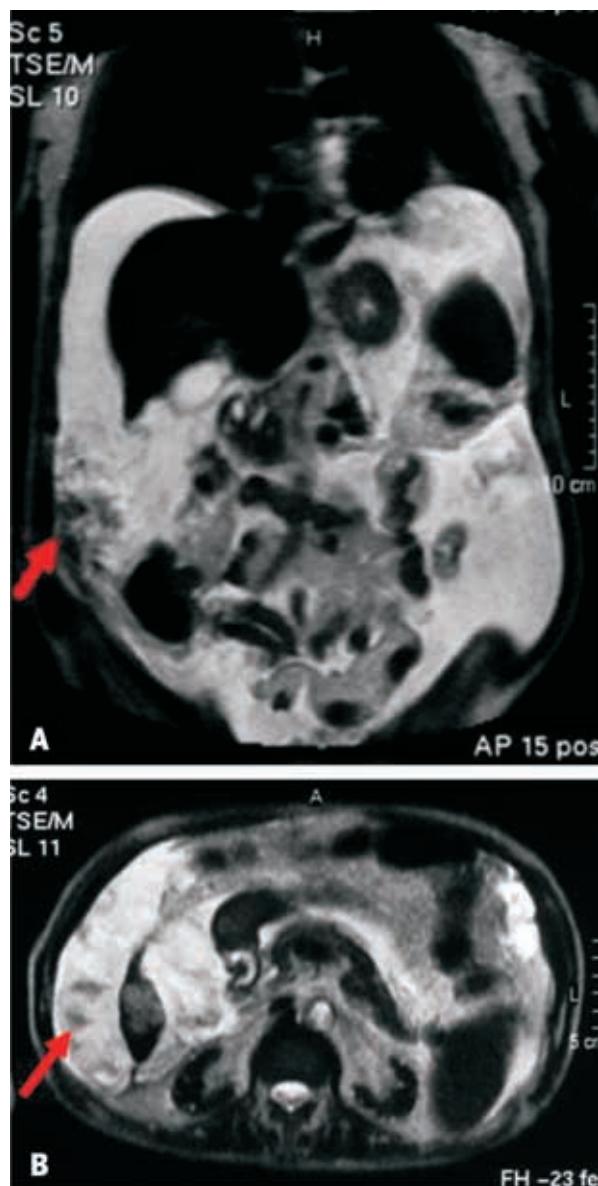


Figure 1

Abdominal MRI image showing a heterogeneous peritoneal thickening on right parieto-colic gutter

A) Coronal section (arrow)

B) Transverse section (arrow)

It seems that peritoneal fibrosis is of multifactorial pathogenesis. Contributing factors can be related to the bioincompatible nature of PD solutions^{8,9}; uraemia itself²; previous episodes of peritonitis^{1,10}; chronic inflammatory states^{8,11}; previous

abdominal surgeries for PD related problems¹; inadvertent PM exposure to chlorhexidine¹²; chronic use of beta blockers. All of these factors can adversely contribute to changes in the morphological and functional properties of resident cellular populations and recruitment of foreign cells at a peritoneal level¹²⁻¹⁴. Some final consequences are variable degrees of inflammatory cell infiltration, submesothelial fibrosis¹³, neoangiogenesis¹⁴, mesothelial disintegration, disturbance of membrane permeability^{1,15} and ultrafiltration failure.

The clinical picture associated with EPS has substantial variability and may include signs of inflammation, peritoneal adhesions or ileus. Nakamoto *et al.*¹⁶ state that the variability of the clinical picture of EPS is due to the fact that the disease progresses over four stages, with different clinical pictures seen at the different stages.

According to this author, the first stage is the pre-EPS stage, characterised by loss of ultrafiltration capacity, development of a high transport state, hypoproteinaemia, and calcification of the peritoneum. The second stage is the inflammatory stage characterised by fever, weight loss, appetite loss, diarrhoea, increased levels of CRP and white blood cell count. Ascites and bloody dialysate are common features of these early stages. The third stage is the encapsulating or progressive stage, characterised by disappearance of inflammation, and appearance of symptoms/signs of ileus (nausea, vomiting, abdominal pain, constipation, abdominal mass, ascites). The fourth stage is the ileus stage, characterised by anorexia, complete ileus, and abdominal mass.

Radiology examinations, including plain abdominal X-ray, contrast study, ultrasound study, and CT are helpful for diagnosis. Plain abdominal X-ray shows calcifications and signs of bowel obstruction (dilated small bowel loops with gas-fluid levels), ultrasonography can show loculated ascites, abnormal intestinal peristaltic activity, echogenic strands and trilaminar echogenic bowel wall thickening and CT scan can reveal adhesions, calcifications, increase PM thickness and cocoon formation^{3,16,17}.

Although the number of reports with data on magnetic resonance imaging is scarce, the results appear to be similar to those seen in CT¹⁶.

At laparotomy, at later stages of the disease, patients are typically found to have a thick-walled PM and clumped intestine cocooned with a dense sclerotic membrane¹⁸.

In our case report, the clinical picture was compatible with EPS at the inflammatory stage. Identified risk factors for EPS development were five previous episodes of peritonitis. Increased need for high osmolality solutions with high glucose content to attain ultrafiltration needs was a sign of PM deterioration and possibly a contributing factor too for peritoneal sclerosis development.

Our patient had been on PD for 48 months. The initial presenting sign of EPS was recurrent bloody ascites and occurred after PD withdrawal. Abdominal pain, malnutrition and symptoms of intestinal dysmotility appeared thereafter.

In our patient CT scan showed only massive ascites and did not reveal adhesions or small bowel distension but MRI scan was useful as it detected a marked peritoneal thickening on right parieto-colic gutter and mesentery.

Recommendations on the management of EPS in Japan were published in 2005 by Kawaguchi *et al.*¹⁷ According to these authors, therapy should depend on the stage of the disease^{16,18}. In the pre-EPS stage the use of preventive measures such as the use of more biocompatible solutions (free of glucose and with low-GDPs) is recommended. Here icodextrin-containing solutions may confer some theoretical advantage. In the inflammatory stage treatment with prednisolone 20 to 30 mg per day with or without initial methylprednisolone pulse therapy is recommended. If the EPS is not relieved with corticosteroid treatment or if it recurs within 1 month (encapsulation stage) the steroid dose should be decreased and the patient should be managed by total parenteral nutrition. In the ileus stage, laparotomy and ablation of intestinal capsules by enterolysis is the surgical approach recommended¹⁸ with a 94% of success rate (relief from bowel obstruction symptoms) instead of other reported techniques associated with a high postoperative mortality related to bowel perforation and recurrent sepsis. In all stages consider transfer to HD if patient has been on PD for more than 8 years or earlier if PET shows an increase in D/P Creatinine ratio with development of

a high transport status or severe and recurrent peritonitis occurs¹⁷.

Immunosuppression alone or in combination with corticosteroids has been reported in some case reports and small retrospective studies with apparent benefit. In this context azathioprine was the immunosuppressant most frequently used^{3,19-21}.

Tamoxifen is a drug that competitively binds to oestrogen receptors on tumours and other tissue targets. To date, there are some data that support its use in diseases that are accompanied by increased production and deposition of fibrotic tissue. In 1999 Allaria *et al.*²² reported the first case of EPS successfully managed with tamoxifen. Since then, other case reports and small studies suggest its usefulness in the prevention and treatment of EPS in doses ranging from 10 to 40 mg/day^{5,6,22-25}. Under these conditions efficacy can be related to an anti-proliferative activity on fibroblasts that is believed to be mediated in part by altered regulation in the expression of transforming growth factor beta isoforms.

Inhibitors of mammalian target of rapamycin (mTOR) are immunosuppressive agents that also inhibit proliferation of smooth muscle cells and theoretically can be useful in treatment of fibrotic processes similar to EPS. Although a study in a rat model suggested a therapeutic value for the mTOR everolimus in EPS²⁶ clinical benefit in this disease is to be proven so far.

These favourable reports supported the rationale for the use of corticosteroids and tamoxifen in the treatment schedule of this patient. The disappearance of recurrent bloody ascites, restoration of normal bowel function and progressive improvement of nutritional status were good clinical markers of response to treatment.

■ CONCLUSION

EPS is not an intractable disease^{6,18} but in the appropriate clinical setting a high index of clinical suspicion, active and early diagnosis and treatment is mandatory. Immunosuppression is a logical approach to suppressing inflammation in order to

prevent encapsulation and progression to an ileus stage of the disease. At present most reports advocate the use of corticosteroids as the immunosuppressive agent, above all in early stages of EPS. The clinical value of tamoxifen *per se* remains to be proven.

Here we describe a picture of an EPS case at a typical inflammatory stage of the disease. Early treatment with corticosteroids and tamoxifen was extremely effective in controlling disease activity and possibly avoiding evolution to an encapsulation stage.

Conflict of interest statement. None declared.

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