CASE REPORT

Encapsulating peritoneal sclerosis: surgery, sustained drug therapy and treatment of recurrence at 1 year

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Accepted 26 October 2015

SUMMARY

A 74-year-old woman with end-stage renal disease presented with clinical symptoms of encapsulating peritoneal sclerosis 2 years after switching from peritoneal dialysis to haemodialysis. Imaging revealed a large cystic structure in her abdomen and her final diagnosis was made by exploratory laparotomy. A 10 cm×15 cm fibrous rind was excised from the peritoneum and the patient was subsequently started on tamoxifen 20 mg daily and prednisone 20 mg daily. Given her reduction in clinical symptoms and concerns about the long-term effects of corticosteroids, prednisone was tapered and she remained on tamoxifen monotherapy. 1 year postsurgery, she presented with symptoms of nausea, vomiting and anorexia. A repeat CT of the abdomen confirmed a recurrence of encapsulating peritoneal sclerosis. Prednisone and tamoxifen were restarted at increased dosages of 25 and 40 mg daily, respectively. The patient's symptoms were ameliorated within 2 weeks of drug therapy modification.

BACKGROUND

Encapsulating peritoneal sclerosis (EPS) is a serious complication of peritoneal dialysis, characterised by fibrotic changes of the peritoneum.¹ Although the aetiology of fibrosis has not been fully elucidated, Kawanishi's two-hit hypothesis is widely acknowledged.^{1–3} This hypothesis suggests that the dialysate used in peritoneal dialysis is a bioincompatible solution that contributes to the breakdown of the peritoneum—also known as the 'first hit'.^{1–2} The 'first hit' leaves the peritoneum vulnerable to a variety of insults, which are collectively referred to as the 'second hit'.^{1–2} The 'second hit' then results in accelerated fibrosis of the peritoneum and formation of a fibrin capsule.^{1–2} The manifestations of EPS are abdominal pain, nausea, vomiting, anorexia, malnutrition and bowel obstruction, which are consequences of fibrin encapsulating the intestines.^{1–4}

Given the variable incidence and high mortality rate of this condition, the treatment of EPS warrants attention from those caring for peritoneal dialysis patients. The incidence of EPS ranges from 1% to 17%.⁵ It has been found that a longer duration of peritoneal dialysis is associated with an increased risk of developing EPS.⁵ The mortality associated with EPS is between 19% and 55%.^{1–6}

Although we are continually learning about EPS, a number of gaps still remain in our knowledge. This case seeks to solidify our prior understanding of EPS and aims to add to the literature by

exploring the management of a complication that is not well established: EPS recurrence.

CASE PRESENTATION AND INVESTIGATIONS

A 74-year-old South Asian woman was initiated on peritoneal dialysis for end-stage renal disease secondary to hypertension, in December 2004. She remained on peritoneal dialysis for over 6 years. Over her course of treatment, she developed three episodes of bacterial peritonitis—all of which were successfully treated with intraperitoneal antibiotics. In January 2010, she experienced reduced ultrafiltration capacity with peritoneal dialysis, and haemodialysis was initiated to supplement her peritoneal dialysis and ensure adequate ultrafiltration. In July 2011, the patient was switched exclusively to conventional haemodialysis.

The patient's comorbidities included hypertension, aortic sclerosis and hypothyroidism. In addition, she had a remote history of transient ischaemic attack. Previous examinations had found a benign liver mass as well as stable bilateral pulmonary nodules. Her surgical history consisted of a cholecystectomy and parathyroidectomy, completed in 2006 and 2010, respectively.

In July 2012, the patient presented to haemodialysis, reporting a 3-day history of nausea and vomiting. She was referred to the emergency room. A history and physical examination revealed that she had been experiencing intermittent abdominal pain, abdominal distension and postprandial fullness for approximately 12 months. In 2011, she weighed 66 kg and her serum albumin was in the range of 24–31 g/L. However, by July 2012, her weight had decreased by 5 kg, to 61 kg, over the most recent 2-month period, and her albumin had dropped as low as 21 g/L; this prompted further investigation.

Further laboratory investigations were performed, and the patient's C reactive protein was found to be mildly elevated at 52 mg/L. CT of the abdomen revealed a large amount of ascitic fluid in her peritoneal cavity, thickening of the adjacent jejunum, and dilated small bowel loops suggestive of a developing obstruction. However, a repeat scan found that thickening of the jejunal wall was less evident. Following an extensive work up of our patient's clinical presentation, the ascitic fluid was drained, her symptoms improved and she was discharged.

Investigations resumed in April 2013, when the patient reported right upper quadrant pain, abdominal distension and decreased appetite. An ultrasound of the abdomen found a large fluid collection encapsulated in the abdominal wall. A subsequent

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To cite: Cho R, Ghag D, Karim MA, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-211490

CT of the abdomen and pelvis established the presence of a thin-walled cystic structure containing visible septations that inferiorly displaced the bowel inferiorly and transverse colon superiorly. The structure measured 26 cm in diameter on axial images and, in coronal images, up to 24 cm in maximal diameter. Moreover, a lesion occupying the inferior aspect of the liver had developed since the investigations in July 2012. An extensive malignancy work up was performed, the results of which were negative. Our patient was managed symptomatically and discharged.

In October 2013, the patient was noted to be cachectic, and a review of her history revealed weight loss of 9 kg over the past year. In addition, her symptoms of decreased appetite, nausea, abdominal distension and abdominal pain had worsened compared to a year prior. C reactive protein levels were now in the range of 30–37 mg/L. Her malignancy work up was once again negative. No hepatic abnormalities were noted, with the exception of the benign mass that had been previously visualised. However, the large abdominal cystic structure with a thin enhancing capsule was noted once again.

At this time, the fluid in the patient's cystic structure was drained and an exploratory midline laparotomy performed due to her cachexia. During laparotomy, 4 L of clear serous fluid were suctioned out of the cavity and sent for cytology; the ascitic fluid and peritoneal fluid were both negative for malignant cells. A large capsule consistent with the macroscopic description of type III EPS was found adhering to the internal organs and abdominal walls, and a 10cm×15 cm rind was excised and sent for pathology.⁷ It was composed of dense lamellated connective tissue, which displayed features of chronic inflammation. The remainder of the rind was dissected free towards the retroperitoneum to allow the cavity to drain. Further dissection was not performed due to the significant risk of bowel injury. There were no complications associated with the procedure. A diagnosis of EPS was confirmed based on the previous imaging studies, the encapsulation of the bowel loops and the patient's clinical symptoms.

Diagnosis and partial excision of the rind prompted the initiation of pharmacotherapy with tamoxifen 20 mg daily and prednisone 20 mg daily for 6 weeks. Prednisone was subsequently decreased to 10 mg daily for 6 weeks and then tapered over a course of 8 weeks. The patient's medications were assessed for contributing factors and metoprolol 100 mg twice daily, which she had been taking for several years, was identified. Some of the literature suggests an association between β -blockers and EPS; thus, given her lack of a compelling indication for this agent, it was discontinued.¹

In December of 2013, the patient was hospitalised for a severe gastrointestinal bleed. She was treated with an intravenous proton-pump inhibitor. An oesophagoduodenoscopy identified gastrointestinal ulcerations, which were cauterised. The ulceration was thought to be secondary to the initiation of prednisone and concomitant acetylsalicylic acid (ASA) use for secondary stroke prophylaxis. ASA was withheld and the patient was transitioned to an oral proton-pump inhibitor.

In July 2014, the patient reported fullness of the anterior abdomen and was sent for an abdominal ultrasound. At this time, no fluid was identified, and there was no obvious mass or acute pathology. Assessment of liver parenchyma was also unremarkable.

In October 2014, the patient once again reported abdominal pain, nausea, vomiting and anorexia, which lasted for approximately 2 weeks. She was sent for a CT of the abdomen and pelvis. This identified a sheet of minimally enhancing soft tissue

that contained a small collection of fluid overlying the hepatic flexure. Although there was no evidence of frank bowel obstruction, a tethered loop of bowel was noted and there were also findings to suggest abnormal transit. These results, together with her symptoms, confirmed the recurrence of EPS.

TREATMENT

The re-emergence of EPS prompted the reinitiation of prednisone at a dose of 25 mg/day, and tamoxifen was increased from 20 mg once daily to 20 mg two times per day.

OUTCOME AND FOLLOW-UP

After 2 weeks of therapy, the patient endorsed resolution of her gastrointestinal symptoms. She continues to be monitored for gastrointestinal symptoms and signs of bowel obstruction.

DISCUSSION

EPS is characterised by pathological fibrotic changes of the peritoneum and progressive gastrointestinal symptoms.¹ The two-hit hypothesis suggests that the 'first hit' causes pathological changes secondary to chronic exposure to a bioincompatible dialysate.^{1 2} This in turn causes a breakdown of the peritoneum due to increased fibroblast activity, mononuclear infiltration, and upregulation of profibrotic modulators such as vascular endothelial growth factor and transforming growth factor (TGF- β).¹ The 'second hit' is the result of exposure to a precipitating factor, which stimulates fibrotic changes and leads to the formation of a thick, adherent fibrin capsule.^{1 2} Possible precipitating factors include peritonitis, cumulative exposure to glucose-based dialysate solution, genetics and discontinuation of peritoneal dialysis.^{1 2} Certain medications have also been implicated in EPS, such as calcineurin inhibitors and β -blockers.¹ Prior to this patient's diagnosis of EPS, her ultrafiltration capacity on peritoneal dialysis had decreased; this is thought to be among the earliest signs of EPS as the fibrotic changes result in decreased exchange capacity.¹

Some experts argue that discontinuation of peritoneal dialysis is considered a risk factor for EPS. It has been postulated that peritoneal dialysis decreases the concentration of profibrotic modulators in the peritoneal cavity and that stopping it may lead to an accumulation of these modulators and might accelerate fibrosis.¹ Peritonitis is another risk factor that this patient experienced, as the resulting inflammation may precipitate EPS.¹ Furthermore, the use of β -blockers may have been an additional risk factor for this patient.¹ Thus, this patient's second hit may have been the chronic use of metoprolol, peritonitis episodes, discontinuation of peritoneal dialysis, or a combination of all three of these factors.

A diagnosis of EPS requires detection of fibrin encapsulation of bowel loops, which results in clinical symptoms of nausea, vomiting, anorexia, weight loss and malnutrition. Gastrointestinal symptoms are typically present before EPS is diagnosed. Diagnostic challenges are typical of EPS, as it usually presents as non-specific gastrointestinal features until frank bowel obstruction occurs.¹ Moreover, despite the large number of patients presenting with ascites as their first symptom, ascitic fluid in the capsules does not appear to be a reliable indicator of diagnosis.^{1 8}

Encapsulation of the bowel loops may be assessed through CT, ultrasound, laparoscopy or laparotomy.¹ Although CT scan is one of the least invasive methods of diagnosing encapsulation, it is not without its limitations. In addition to limitations in detecting the degree of peritoneal thickening,^{3 8} CT is not a reliable marker of changes associated with EPS in the prediagnostic period.⁸ Moreover, the Pan-Thames EPS study found that CT

was not adequate at diagnosing EPS in some of their patients,³ and in these cases, laparotomy was the diagnostic method used.³ It was postulated that a lack of experience with EPS by radiologists may have affected the diagnostic ability of scans for these patients.³ This may explain why, despite numerous CT scans, EPS was not diagnosed in this patient until she presented with severe gastrointestinal symptoms and cachexia.

Depending on the severity, the management of EPS usually consists of the following: discontinuing peritoneal dialysis, and initiating haemodialysis, bowel rest, total parenteral nutrition and treatment.⁹ Two treatment modalities exist for EPS, surgical intervention and drug therapy; however, these are frequently used in combination.⁹ The most well-established surgery is enterolysis, which involves separation of the fibrin capsule from the bowel loops and the parietal perineum.⁹ Enterolysis can restore bowel function in 96% of cases where the bowel is encapsulated.¹⁰ Since only a portion of the fibrin capsule was excised in this patient, in an effort to avoid potential bowel injury, the nephrology team chose to initiate drug therapy. One could argue that perhaps the drugs with the most published use in the treatment of EPS are tamoxifen and corticosteroids.

Tamoxifen, a selective oestrogen-receptor modulator, is proposed to exhibit antifibrotic activity by inhibiting the actions of TGF- β .¹¹ Some also believe that tamoxifen may block the stimulation of oestrogen receptors on fibroblasts in the peritoneum and therefore lead to decreased action of these cells, although this theory is refuted by the findings of Braun *et al.*¹² Tamoxifen was selected for this patient's initial presentation of EPS based on the Dutch Multicentre EPS Study, which demonstrated decreased mortality in those treated with tamoxifen.¹¹ The mortality rate of patients treated with tamoxifen was 46% versus 74% for those not treated with tamoxifen ($p=0.03$).¹¹ The dosing regimens in this study varied from tamoxifen 10 mg daily to 20 mg two times per day for at least 4 weeks.¹¹ In the presented case, tamoxifen 20 mg daily was initiated after the initial diagnosis of EPS in October 2013, with a plan to reassess the therapy after 1 year.

Corticosteroids are thought to elicit anti-inflammatory activity in EPS.^{10 13} Korte *et al.*¹¹ reported that use of prednisone was associated with improved survival. Kawanishi *et al.*⁵ reported that 15 of 39 patients treated with corticosteroids recovered from EPS and 9 of 39 displayed signs of symptomatic improvement. Corticosteroids are thought to be most beneficial in the initial stages of EPS, when inflammatory changes are most active.³ This concept guided the relatively short duration of prednisone treatment in this patient. The decision to choose a shorter course of prednisone was also supported by the occurrence of her gastrointestinal bleed after initiating prednisone.

To the best of our knowledge, EPS recurrence has only been reported in two studies. Kawanishi *et al.*¹⁴ reported a recurrence rate of 23.4% within 2 years of surgical enterolysis. Ten out of the eleven patients with recurrent EPS in the study were managed surgically and some received up to six surgical interventions.¹⁴ Another study by Latus *et al.*⁶ found that 3 of 29 patients experienced a recurrence of EPS when treated with peritonectomy and enterolysis (PEEL). These patients were successfully re-treated with PEEL and were alive at study follow-up, which averaged 41.6 months.⁶ Patients in this study also received concomitant drug therapy, such as corticosteroids, tamoxifen, or other immunosuppressive agents.⁶ However, the management of the patient in this case report differed from the aforementioned populations, as she received a sustained course of tamoxifen therapy and was likely not a candidate for further surgical intervention based on the risk of bowel injury.

With the recurrence of EPS in this patient, prednisone was reinitiated and her dose of tamoxifen was increased. Although there are no data to suggest that the antifibrotic activity of tamoxifen is dose dependent, the dose increase was guided by previous studies and case reports that demonstrated resolution, improvement or survival at 3 months with tamoxifen 40 mg daily.¹¹ Prednisone was reinitiated, as inflammation is thought to be a component of EPS.³ Therapy will be reassessed following sustained symptomatic resolution. Despite concerns about the feasibility of further surgical intervention, a surgical consult was requested to confirm our patient's non-candidacy.

Two weeks following the increase in tamoxifen dose and the initiation of prednisone, the patient endorsed resolution of abdominal pain, nausea and vomiting, as well as return of appetite. Perhaps it could be argued that this response to therapy may have been sooner than one would expect. However, we do not have an alternative explanation for the patient's clinical response. This case suggests that therapy with tamoxifen and prednisone may serve as a viable treatment option in patients with recurrent EPS. The patient will be vigilantly monitored for signs and symptoms of EPS recurrence.

Patient's perspective

English is our patient's second language and she is unable to read or write. Thus, a translator communicated her perspective to us.

Owing to the challenges in diagnosing my condition, I am agreeable to having my experience shared for the benefit of other patients who may experience this condition. Despite experiencing a recurrence of my condition, I am in bright spirits following the resolution of my abdominal pain, nausea and vomiting only 2 weeks after reinitiating prednisone and increasing my dose of tamoxifen.

Learning points

- Unexplained ascites in haemodialysis patients who have previously undergone peritoneal dialysis should prompt clinicians to consider EPS in the differential.
- Despite symptomatic resolution of encapsulating peritoneal sclerosis (EPS) following treatment, healthcare providers should remain vigilant for signs of EPS recurrence, as early treatment likely increases the chance of successful treatment.
- Dual treatment with prednisone and tamoxifen may be effective at managing EPS recurrence and is a less invasive approach to surgery, particularly in those who are not good surgical candidates.

Acknowledgements The authors would like to acknowledge Dr Priti Flanagan, PharmD, for reviewing the final draft of this article.

Contributors RC, MAK and CL conceptualised the writing of this case report. RC and DG acquired the necessary data and produced the draft article. All the authors were involved in reviewing and revising the draft article and approval of the final version.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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