CASE REPORT

Discovering implicit associations in a case of encapsulating peritoneal sclerosis complicated by severe mineral imbalance

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SUMMARY

We describe the case of a 42-year-old woman who developed encapsulating peritoneal sclerosis (EPS) after 7 years on peritoneal dialysis, with clinical relief by enterolysis associated to treatment with tamoxifen, corticosteroids and parenteral nutrition in haemodialysis. During the next 7 months, she was also conservatively stabilised for mild hyperparathyroidism until she was admitted with calciphylaxis, associated with massive extraosseous calcification. Despite parathyroidectomy and sodium thiosulfate treatment, which resulted in a successful resolution of calciphylaxis, she died 1 year later due to a gross calcified peritoneum. In view of controlled hyperparathyroidism, the massive extraosseous calcification beginning after EPS diagnosis furthermore corroborates a recently suggested role for calcium-regulatory factors associated with poor outcome in EPS.

BACKGROUND

Encapsulating peritoneal sclerosis (EPS) is a rare but increasingly life-threatening cause of bowel obstruction,¹ which is most importantly and frequently associated with peritoneal dialysis (PD).² Even though mesothelial denudation and fibroblasts proliferation first suggest that EPS is, at the beginning, a simple sclerosis,³ the inflammation and calcification present in EPS, in conjunction with vasculopathy, can situate EPS pathologically near to calciphylaxis.^{3–4} Indeed, like the severe forms of dialysis-associated calcification, the EPS origin is still ill defined.⁵ Recently, the role of calcium-regulatory factors in the pathogenesis of dialysis-associated calcification has been discussed.^{6–7} We report a unique case of a patient with EPS during long-term PD, followed by uncontrolled tissue calcification, who ultimately died from bowel obstruction associated with unmanageable peritoneal calcification. Since the hyperthyroidism was transitory, the calcium-regulatory factors are probably the most important pathogenic cause that could justify the poor outcome in certain cases of EPS.

CASE PRESENTATION

A 42-year-old Caucasian woman undergoing continuous ambulatory PD for 7 years due to IgA nephropathy presented with an insidious onset of abdominal pain, anorexia and nausea between regular bimonthly follow-up evaluations. She had no previous complications except in four simple episodes of bacterial peritonitis easily treated with

antibiotics. Additionally, she was found to be infected with HIV just before beginning dialysis. She was placed under several antiretroviral strategies, remaining with an undetectable viral load.

During the initial physical examination, a palpable abdominal mass and decreased bowel sounds were found. A cloudy peritoneal effluent showed 2100 leucocytes/mm³ (89% neutrophils), but the cultures were negative. Blood tests revealed elevated inflammatory parameters (white cell count 11 260/ $\times 10^3/\mu\text{L}$ and C reactive protein (CRP) 33 mg/dL [normal <1 mg/dL]), degradation of nutritional parameters (albumin 2 g/dL), hyperparathyroidism (intact parathormone (iPTH) 900 pg/mL) and normocytic anaemia (haemoglobin 9.1 g/dL). The abdominal CT was compatible with a diagnosis of EPS, showing bowel loops incorporated in a cocoon-like mass and loculated peritoneal fluid (figure 1). After the failure of conservative management, an exploratory laparotomy was performed with enterolysis and removal of the Tenckhoff catheter. The patient was switched to haemodialysis and oral prednisolone was initiated at 40 mg/day with tamoxifen 20 mg twice daily, as well as cinacalcet in increasing doses. She also received total parenteral nutrition for 3 months, after which tamoxifen was stopped and prednisolone was tapered off. Despite improvement of bowel obstruction symptoms, the patient maintained anorexia and developed signs of marked malnutrition. Regular monitoring of blood tests revealed no considerable recover of CRP

Figure 1 A transverse CT scan showed parietal peritoneal calcification and thickening, encasement of the dilated bowel loops, with tethering and luminal narrowing and a loculated intra-abdominal collection.

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neither albuminaemia. Anaemia trended to improve and it was observed a gradual decreasing of iPTH with control of phosphorus-calcium serum levels.

The HIV viral load remained undetectable, with special concern to potential interactions between tamoxifen and antiretrovirals.

Seven months later, she presented with a painful cyanotic plaque—like subcutaneous nodular lesion in the lower left leg that progressed to a skin ulcer. A Doppler ultrasound ruled out significant arterial and venous diseases. An X-ray of her pelvis and lower limbs (figure 2A) and skin biopsy demonstrated typical changes of calciphylaxis (small arteriolar intima proliferation and medial deposits of calcium). Consequently, she underwent a successful total parathyroidectomy, followed by intravenous sodium thiosulfate for 3 months. After 2 months, she had a remarkable clinical response with complete healing of the skin ulcer. At that time, the levels of phosphorus, calcium and iPTH were kept within the normal range, though the control CT scan demonstrated persistent extensive calcifications of the peritoneum and metastatic calcifications (figure 2B).

Two years after the original EPS, she was again admitted with abdominal pain, vomiting and severe weight loss despite parenteral nutrition and in relation to recurrent bowel obstruction. The reintroduction of immunosuppression and intra-abdominal surgery was deemed unsafe. Owing to an unmanageable bowel obstruction associated with severe calcification, her clinical condition deteriorated further, and she eventually died 6 months later.

DISCUSSION

The diagnosis of EPS was reliably based on clinical and radiological grounds. To the best of our knowledge, this is a unique case of EPS with a transient recovery due to enterolysis and dual antifibrotic and anti-inflammatory therapeutics, but one that is constrained by severe metastatic calcification, including calciphylaxis and gross peritoneal calcification.

Cox *et al*⁸ reported the first case of EPS with gross peritoneal calcification, and after the report of two cases of EPS followed by calciphylaxis⁹ the theory emerged that EPS could be a spectrum of metastatic calcification. In view of the fact that peritoneal calcification is considered as an early sign of EPS¹⁰ and the extent of the peritoneal calcification correlates with its clinical severity,¹¹ this hypothesis makes good sense. Furthermore, it recently

described a case of calcifying sclerosing peritonitis, a year and half after an established diagnosis of EPS, that encouraging the role of metastatic calcification in poor outcome of EPS, pointing deficiency of calcium-regulatory factors as cause.¹²

Peritoneal calcification and calciphylaxis have been reported in patients without any evidence of alteration in the phosphate-calcium-parathyroid hormone axis or even after parathyroidectomy.¹³ Hyperphosphataemia, hypercalcaemia and hyperparathyroidism play a well-documented pathological role in vascular calcification, but their effects on the genesis of calciphylaxis are not as well established.⁵ The vast majority of dialysis patients with comparable degrees of phosphate-calcium-parathyroid derangement never develop calciphylaxis, and often patients with calciphylaxis do not show uncontrolled values of mineral metabolism at the time of diagnosis.¹⁴ For the development of calciphylaxis, the total calcium load and maintained hyperphosphataemia seem much more relevant than the isolated measurement of high calcium or high phosphate serum levels, with rapid control by treating non-calcium-containing phosphate binders and cinacalcet, such as in the present case.¹⁵

In view of the transient hyperparathyroidism and isolated measurement of high calcium-phosphorus serum levels, the accelerated and severe metastatic calcifications, including calciphylaxis, highlight the role of calcium-regulatory factors, in particular the deficiency of inhibitors of calcification, such as fetuin-A and matrix Gla protein (MGP). MGP acts locally, preventing media calcification of the elastic lamellae of arteries, while fetuin-A acts systemically by formation of calciprotein particles. Greatly stabilised by albumin, these particles serve as a transport form of otherwise insoluble mineral debris. As a result, the deficiency of fetuin-A, a liver-derived plasma protein-like albumin, induced the precipitation of calcium-hydroxyphosphate-apatite crystals.⁷ High inflammation levels associated with EPS determine the combined deficiency in fetuin-A and albumin. Moreover, our patient had severe malnutrition, which may further increase her higher risk of calcification.^{7 16} Indeed, the highest reductions of fetuin-A were found in patients with calciphylaxis on haemodialysis.⁷ Furthermore, there is an important deficiency of MGP in calciphylaxis, which was first described after the description of a strong association between calciphylaxis and use of warfarin.⁷

Figure 2 (A) A plan X-ray of the pelvis and lower limbs revealed 'tram-like' calcifications of the arterioles; (B) A three-dimensional reconstruction of the CT scan showed severe diffuse parietal and visceral peritoneal calcifications, as well as extraosseous calcium deposition in the heart, spleen, liver, small bowel and uterus.

Therefore, the management of this case may be limited by the absence of determination regarding variations of fetuin-A and MGP, as it was approached with all three proved treatments, including enterolysis, steroids and tamoxifen. Indeed, there is no certitude about the therapy of choice for EPS. Enterolysis tries to solve the fibrotic and calcified cocoon already established and its success is highly dependent on surgery expertise.¹⁷ In order to control the fibrosis and inflammatory activities, many cases of EPS have been treated with tamoxifen, steroids and immunosuppressants.^{1 2 15-17} Nevertheless, the mortality rate remains as high as 24% to 38%.² Regarding the ectopic calcification of the peritoneum, there is no specific management and the calcium phosphate nanocrystals are themselves powerful proinflammatory agents.¹⁷

Learning points

- ▶ The poor prognosis of severe calcified encapsulating peritoneal sclerosis (EPS) emphasises the need for enhancing the understanding of its aetiopathogenesis.
- ▶ Deficiency of calcium regulatory factors, already demonstrated in calciphylaxis, may also be involved in the more severe forms of calcified EPS, determining its negative long-term outcome.
- ▶ Urgent research needs to be undertaken to clarify the role of calcium-regulatory factors in EPS aetiopathogenesis, especially regarding severe peritoneal calcifications.

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Competing interests None.

Patient consent Obtained.

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