Case Report

A worrying thought—could there be a connection between encapsulating peritoneal sclerosis, tamoxifen and calciphylaxis?

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Introduction

Encapsulating peritoneal sclerosis (EPS) is a serious problem for chronically dialysed patients [1,2]. With an overall prevalence of ~2–3% in patients undergoing peritoneal dialysis (PD), it is now obvious that extended duration of PD therapy increases the incidence and severity of EPS [3]. Mortality rates in patients with EPS remain high—especially after bowel obstruction becomes an overt problem, although success with intra-abdominal surgery is no longer a far-fetched option [2,4]. Pharmacological therapeutic choices are based on anecdotal evidence alone, but a combination of prednisone and tamoxifen has been used in an attempt to reduce both the inflammatory and fibrotic changes associated with this disease [2,5]. Tamoxifen was originally used in desmoid tumours, and since then the drug has proved to be of value in other fibroproliferative disorders, such as retroperitoneal fibrosis and Dupuytren’s contracture [6]. However, tamoxifen produces oestrogenic-like effects on certain tissues, and can lead to an increased incidence of venous thromboembolism [7].

Over the last year, we treated two patients with advanced EPS, with prednisone and tamoxifen. Both developed overwhelming, and ultimately fatal, calciphylaxis. Their case reports follow, together with a discussion on the possible role of tamoxifen in initiating calciphylaxis—a condition characterized by the presence of intraluminal thrombi in small calcified blood vessels of the dermis [8]. Some precautionary measures that can be undertaken before commencing tamoxifen in patients with EPS are given.

Case 1

A 62-year-old man presented with a 4-month history of weight loss of ~10 kg, diffuse abdominal pain, intermittent vomiting and constipation. Relevant medical history included chronic renal disease secondary to focal glomerulosclerosis. A pre-emptive, living-related renal transplant was performed successfully in 1991. In 1999, B-cell gastric lymphoma was treated with a Billroth I partial gastrectomy, six courses of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy and cessation of all immunosuppression. By late 1999, the patient’s renal function had deteriorated to end-stage renal failure and continuous ambulatory peritoneal dialysis (CAPD) was initiated. Peritoneal dialysis was maintained for four consecutive years, until ultrafiltration failure became evident. In March 2003, haemodialysis was commenced.

The patient’s above-mentioned symptoms started in early 2004, ~8 months after starting haemodialysis. Physical examination revealed ascites. Extensive investigations revealed: a normocytic anaemia, hypoalbuminaemia (~3.0 gm/dl), an elevated C-reactive protein (CRP) level: 20 mg/dl (normal: 0.0–0.8 mg/dl) and an exudative lymphocytic ascites, free of infection (including tuberculosis) and malignant cells. Gastroscopy revealed oesophagitis, with no evidence of lymphoma on multiple gastric biopsies. Colonoscopy was normal. Barium examination of the small bowel showed loops of the small bowel pushed high up into the right upper quadrant of the abdomen. Transit time of the barium throughout the small bowel was obviously slow. Computerized tomography (CT) of the abdomen was compatible with a diagnosis of EPS, showing loculated ascites and areas of calcified peritoneum [9]. A CT of the abdomen, performed 15 months previously, showed no evidence of EPS. In July 2004, prednisone (0.5 mg/kg/day: 40 mg) and tamoxifen (40 mg/day) were started. Total parenteral nutrition was commenced in August 2004.
An initial response, with improvement of his vomiting and some weight gain, was soon overshadowed by a gradual clinical deterioration over the next 6 months. Problems at this stage included continuing weight loss, vomiting and recurrent episodes of intradialytic hypotension. Intra-abdominal surgery was considered, but rejected as a therapeutic option by reluctant surgeons. Painless hyperbilirubinaemia caused by extrinsic pressure on the biliary tree was treated, with partial success, by papillotomy.

In January 2005, the patient presented with pain over his penile head and a sterile urethral discharge. Within days, gangrene developed on the patient’s penile head. ‘Tram-like’ calcification of the penile artery was seen on plain radiography. Despite a negative bone scan, the presumptive diagnosis was penile calciphylaxis. Debridement was contemplated, but not undertaken. Worsening pain was treated by narcotics. The patient refused parathyroidectomy (serum parathyroid hormone levels ~1200 pg/ml), and he eventually elected to cease dialysis. He died in February 2005.

On post-mortem, it was found that loops of bowel were bound together in a tight conglomerate. Thick sheets of fibrous tissue had completely covered and partially destroyed the bowel loops. The muscularis of both the vas deferens and the seminal vesicles were heavily calcified.

Case 2

A 51-year-old woman with membranoproliferative glomerulonephritis ‘reached’ end-stage renal disease in 1982. The patient received two cadaveric renal transplants in 1982 and 1984. Both transplants were subsequently removed and the patient began CAPD in 1991. Although ultrafiltration failure was observed initially in 2003, the patient refused transfer to haemodialysis until late 2004. Other relevant medical points included iatrogenic ligation of the left external iliac artery in 1984 and an extensive anterior wall myocardial infarction which resulted in left ventricular failure in 1999.

In February 2005, only a few months after starting haemodialysis, the patient started to complain of intermittent abdominal pain. In April 2005, a bloody ascite was drained for the first time. The ascitic fluid was bacteriologically sterile and contained no malignant cells. Consequently, repeated cultures for tuberculosis were also negative. An abdominal CT scan revealed loculated ascites throughout the peritoneal cavity, together with a calcified and thickened peritoneum. Previous CT examinations were unavailable. CRP was high—10 mg/dl. A diagnosis of encapsulated peritoneal sclerosis was made. In May, prednisone and tamoxifen were started at respective daily doses of 30 and 20 mg. Intradialytic parenteral nutrition was also commenced.

Transiently, improvements were seen in a number of laboratory parameters—including elevations in serum haemoglobin and cholesterol levels and a reduction in CRP. However, abdominal pain remained a constant problem and large volumes (~2 l) of bloody ascitic fluid was drained on three further occasions between May and September 2005. Absolute indications for explorative laparotomy were lacking.

In early September 2005, the patient presented with fever and small, painful ulcers over the anterior aspects of both calves. These ulcers had a necrotic centre and were exquisitely tender. CT of both calves showed calcified arteries and soft-tissue swelling of the subcutaneous fat. Necrotizing fasciitis and myositis were not seen. A three-phase bone scan revealed diffuse uptake in the left calf. Calciphylaxis was diagnosed. Empiric, broad-spectrum antibiotics were commenced. Although serum parathyroid hormone (PTH) levels were ~550 pg/ml, vitamin D was stopped. Intravenous pamidronate was given four times over a 7-day period, but little improvement was seen.

Within weeks the leg ulcers confluented and new ulcers developed over two fingers in the patient’s right hand. She became narcotic-dependent due to severe pain in both legs. A low-grade fever and hypotension did not respond to further antibiotic therapy, intravenous fluids or increased steroid dosages. Severe hypoalbuminaemia and an anaemia, resistant to all therapy, developed. In late October 2005, the patient died as a result of Gram-negative septicaemia. Requests for a post-mortem were refused.

Discussion

Tamoxifen citrate is a unique drug, exhibiting both selective oestrogen receptor modulating (SERM) effects and oestrogen agonistic properties [10]. The drug is an adjuvant agent in treating and preventing breast carcinoma [10,11]. Oestrogen-receptor-negative patients with breast cancer can also benefit from tamoxifen therapy, probably as the drug can modulate the actions of transforming growth factor-β (TGFβ) on a number of cell lines, including on cancerous breast cells [12].

TGFβ plays a role in physiological tissue repair, but with repeated injury its sustained production leads to the development of extracellular matrix fibrosis [13]. Thereafter, it can induce cells within the extracellular matrix to produce more TGFβ, thus leading to an amplification of chronic tissue fibrosis. Tamoxifen was first used in treating desmoid tumours, and thereafter in the treatment of other fibrotic diseases—most notably idiopathic retroperitoneal fibrosis [6]. In both conditions, the initial inflammatory lesion is soon overshadowed by the deposition of collagen in a dense, avascular and, sometimes, calcified mass. TGFβ is one of many cytokines allegedly involved in the pathogenesis of EPS [14], but even before this became known, tamoxifen was used as a possible therapeutic option in EPS—an intra-abdominal inflammatory process which progresses to fibrosis with bowel obstruction, malnutrition and patient death.
Indeed, tamoxifen may benefit patients with EPS, especially if initiated in the early stage of the disease [2,5]. In 2003, del Peso et al. [5] showed that tamoxifen-treated patients with peritoneal sclerosis did not develop EPS. In their control group of 14 patients who did not receive tamoxifen, four went on to develop EPS—three of them died within 6 months. In 2005, Summers et al. [2] described their experience with 27 patients and EPS. Sixteen patients had severe disease requiring surgery, while the other 11 had a ‘milder’ form of EPS. In the group with severe disease, 5/16 patients received tamoxifen and two died. Eight of the 16 patients in this same group received no specific drug therapy. Five of these patients died. In the ‘mild’ EPS group, there was no difference in the patient outcome between those patients who did or did not receive tamoxifen [2]. All these 11 patients remain alive ~1.5–5 years after EPS diagnosis—nine of them on haemodialysis.

On a negative note, tamoxifen is associated with an increased number of deep venous thromboses and superficial thrombophlebitis. This occurs not only in post-menopausal women with breast cancer and in patients receiving combined tamoxifen and chemotherapy [10,15,16], but also in patients with breast carcinoma in full remission and in healthy women enrolled in preventive breast cancer trials [11,16]. The drug can reduce anti-coagulant protein levels, such as antithrombin III, protein C and protein S, and may cause excessive platelet aggregation [15,17,18]. Just recently, Cosman et al. [7] have also shown that tamoxifen is capable of increasing serum levels of factors VIII, IX and vWF—all being known procoagulant proteins [7].

Calciphylaxis occurs nearly exclusively in chronic dialysis patients [8,19]. After open and necrotic ulcers become evident, mortality rates are as high as 60% [19]. The histopathological findings in calciphylaxis are medial calcifications of the dermal arteries and venules, intraluminal thromboses and surrounding soft tissue calcifications [8,19]. Essary et al. [8] found both venous and arteriolar microthrombi in ~25% of cases, often with luminal occlusion. Protein C and protein S deficiencies, acquired abnormalities seen with tamoxifen, have been documented in patients with calciphylaxis and have led some to believe that a thrombotic event superimposed on pre-existing vascular damage ultimately leads to tissue ischaemia and necrosis [20–22]. In 1990, Metha et al. [20] documented a significant reduction in the anticoagulant function of protein C in four dialysed women with calciphylaxis. Budisavijevic et al. [19] added a further eight patients in whom decreased protein C levels were associated with calciphylaxis. Protein S is a cofactor in normal protein C anticoagulant function, and low functional levels of protein S are found in chronic inflammatory processes—much like EPS [21]. Therefore, in the setting of overt and severe EPS with its resulting states of chronic inflammation, malnutrition and a systemic inflammatory response, the addition of tamoxifen may actually be detrimental—leading to the formation of small vessel thrombi, and ultimately to calciphylaxis if these thrombi are present in the skin vasculature [23].

In conclusion, we recommend caution when using tamoxifen in EPS. Firstly, monotherapy with corticosteroids seems to be effective [24]. Furthermore, in 2000, Kawanishi et al. [4] did not routinely use tamoxifen in their patients and even today in 2005, Japanese nephrologists argue that the therapeutic value of tamoxifen in EPS ‘remains unknown’. This is based on two relevant points: first—all reports of tamoxifen in EPS originate from either case reports or small, non-controlled studies, and second—tamoxifen was nearly always given together with corticosteroids [24]. If administered to patients, it should be started at an early stage of the disease, and at a daily dose of 20 mg [2,25], despite the fact that in retroperitoneal fibrosis, a daily dose of 40 mg has been used safely. In the late stages of the disease, when fibrotic changes in the peritoneum are well established, any possible therapeutic value of tamoxifen is unknown. Finally, measuring protein C and protein S levels and their functional activities prior to and during therapy is recommended. Treatment should be withheld in any patient with any deficiency in either of these proteins or in patients with another known hypercoagulable state, such as activated protein C resistance due to factor V Leiden—a common genetic defect in many white European families [15]. Just recently, Eltoum et al. [25] treated four EPS patients successfully with tamoxifen. However, one pulmonary embolus and two thrombosed arteriovenous accesses complicated the tamoxifen therapy [25]. In time, new antagonists of TGFβ may help alleviate the problem of EPS [13], but even now, at least in one experimental model of peritoneal sclerosis, angiotensin II blockade can reduce the expression of TGFβ [14].

Conflict of interest statement. None declared.

**References**


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