

Tamoxifen as the possible cause of severe thromboembolic complications in a patient with a history of renal transplantation and encapsulating peritoneal sclerosis

In the latest issue of the *Polish Archives of Internal Medicine* and in the first ever edition of the “Clinical Image” section of this journal, Jakimowicz et al.¹ presented the case of a rare but not unusual complication of long-term peritoneal dialysis, namely, encapsulating peritoneal sclerosis (EPS). In the last paragraph, the authors mentioned that tamoxifen, a drug approved for the treatment of breast cancer, is used as one of the conservative treatment options. Although this was not confirmed by any prospective randomized trial, tamoxifen seems to improve the survival of patients with EPS, especially when combined with another drug (usually with immunosuppressive and antifibrotic properties, excluding calcineurin inhibitors; see below).^{2,3}

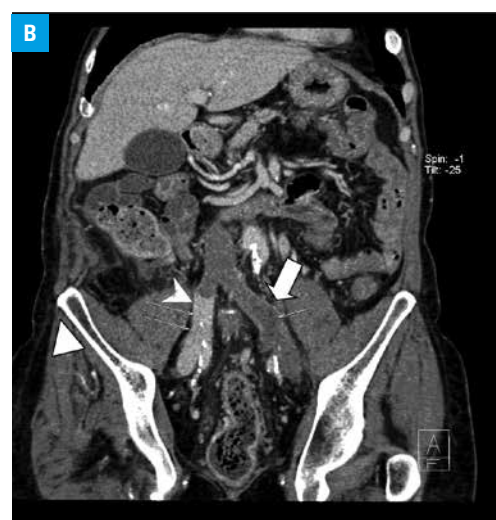
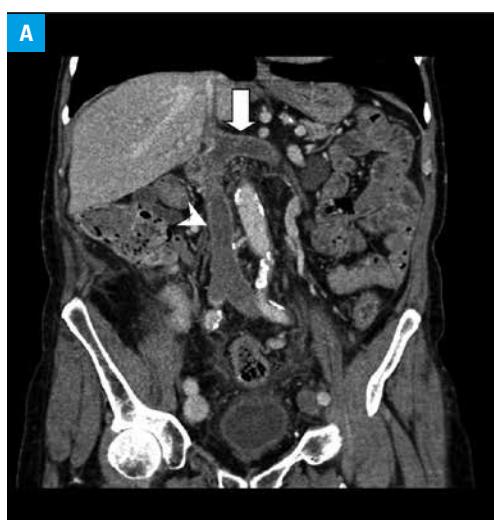
One of the major side effects of tamoxifen includes an increased risk of thromboembolic complications. Unfortunately, no data on long-term use of tamoxifen are available in patients with EPS (especially given the short life expectancy in this complication). However, some of these patients undergo kidney transplantation and their survival significantly improves. In addition, in many cases, EPS does not develop on peritoneal

dialysis but rather after its discontinuation (including successful kidney transplantation).

Calcineurin inhibitors (such as cyclosporine and tacrolimus) used in immunosuppressive protocols are potent inducers of tumor growth factor β (a growth factor with a strong profibrotic potential) and are considered as factors that contribute to the development of EPS after transplantation.⁴⁻⁶

In the present paper, we would like to present the case involving a patient who suffered from end-stage renal disease due to autosomal dominant polycystic disease and renal cell cancer and who underwent unilateral right side nephrectomy followed by peritoneal dialysis. He was treated with dialysis for 5 years and then underwent successful transplantation. A few weeks after transplant surgery, he developed nonspecific abdominal pain and symptoms of subileus. Explorative laparotomy (performed also to remove a Tenckhoff catheter) revealed peritoneal membrane thickening, which is consistent with the diagnosis of EPS. Massive peritoneal fibrosis was also seen in a histopathological specimen of the peritoneum. Tamoxifen was introduced

FIGURE Multiplanar reconstruction of abdominal computed tomography scan – venous phase;
A – thrombosis of the renal vein of autosomal dominant polycystic disease in the left kidney (arrow) and inferior vena cava (arrowhead);
B – thrombosis of the left common and external iliac veins (arrow) with patent right common iliac vein (arrowhead)



and EPS responded well to therapy. On February 4, 2013, approximately 6 years after otherwise uncomplicated clinical course following kidney transplantation, he was admitted to our center. We observed elevated serum creatinine (it increased from 1.1 mg/dl [97.7 μ mol/l] noted 6 weeks before present admission to 3.3 mg/dl [293.0 μ mol/l]), decreased urine volume, nonspecific pain located in the abdomen and renal graft, and asymmetric edema of the lower left extremity. A Doppler ultrasound showed massive thrombi within the left-sided saphenous and common iliac veins and in the lower segment of the inferior vena cava. Subsequently, computed tomography angiography was performed (FIGURE), which demonstrated massive embolus of the inferior vena cava, left renal vein of native polycystic kidney, and left common and external iliac veins. Our careful evaluation failed to show any other cause of impaired renal graft function (including cytomegaly virus infection, calcineurin toxicity, acute rejection, etc.; no major pathology was found in transplant biopsy specimen, except for discrete lesions related to chronic allograft nephropathy).

Treatment with high-dose enoxaparin with subsequent switch to warfarin was administered and tamoxifen was immediately discontinued, which resulted in a spectacular improvement (within 6 days) of graft function and normalization of creatinine (back to 1.2 mg/dl [10.6 μ mol/l]). A history showed an uninterrupted use of tamoxifen for more than 6 years (since the diagnosis of EPS). We searched for other common causes of an increased risk of thrombosis, including factor V Leiden mutation, but no other risk factors have been identified so far.

It is tempting to speculate that long-term tamoxifen given to treat EPS and to prevent its recurrence may lead to disseminated thrombosis of the venous system of the lower extremity, inferior vena cava, and left renal vein (renal graft artery and vein were connected to the respective right-side vessels of the recipient and were thrombus-free). An impaired function of renal graft might be secondary to the resistance of venous outflow from the graft due to thrombosis (although no signs of passive hyperemia could be noticed in biopsy specimen). Standards of treatment and best practice guidelines available in peritoneal dialysis do not provide any recommendations concerning the duration of treatment with tamoxifen following the diagnosis of EPS.

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Authors' reply We want to thank Dr Pawłowska et al.¹ for their interest in our paper and raising an important issue which is the role of tamoxifen in the management of encapsulating peritoneal sclerosis (EPS). The case presented by Pawłowska et al.¹ is interesting and adds an important message to the literature about the benefits and risks of long-term use of tamoxifen.

Indeed, tamoxifen may have some survival benefit in patients with EPS, especially in certain circumstances: earlier stages of the disease, in post-transplantation EPS (which is suggested to have a better outcome), after successful surgery, or even in the prevention of EPS as reported by del Peso et al.²⁻⁴ However, the available literature is mostly limited to case reports and case series, which always implies a selective bias. Moreover, the two largest retrospective analyses have shown divergent results with a substantial mortality decrease in the Dutch EPS study, and no improvement in the survival rate in the Pan-Thames study.^{5,6} In most reports, tamoxifen has been given for 3 to 12 months, and data from longer treatment is anecdotal.^{2,7}

Due to limited data and potential adverse effects of tamoxifen associated with the risk of thromboembolic disease,^{8,9} caution is needed until the results from long-term follow-up become available. Until then, it seems wise not to prolong the treatment over the period of 12 to 36 months. It has also been suggested that the dose should not exceed 20 to 40 mg/d, which is similar to that used in retroperitoneal fibrosis. Additionally, before the decision on prolonged treatment with tamoxifen is made, common thrombotic risk factors, including protein C and S deficiency and factor V Leiden mutation, should be excluded. Also, a possibility of other adverse effects of tamoxifen such as strokes, hot flushes, and

endometrial carcinoma has to be considered in each individual case.

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