

# Tamoxifen Therapy in Kidney-Transplant Patients Presenting With Severe Encapsulating Peritoneal Sclerosis After Treatment for Acute Humoral Rejection

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## Abstract

**Objectives:** Encapsulating peritoneal sclerosis is a rare but serious complication in patients undergoing peritoneal dialysis. Its mortality rate is approximately 30%, despite treatment with total parenteral nutrition, surgery, tamoxifen, or immunosuppressants.

**Materials and Methods:** Of 991 kidney transplants performed at our institution over 9 years, 50 patients were treated for chronic peritoneal dialysis at the time of transplant.

**Results:** Two cases of encapsulating, peritoneal sclerosis occurred in patients receiving pretransplant peritoneal dialysis. Both had received intensive posttransplant treatment for acute humoral rejection. Encapsulating peritoneal sclerosis occurred at 3 months and 4 months after the transplant. Both presented with intestinal pain and gut obstruction. They were given total parenteral nutrition plus tamoxifen (20 mg/d) for 3 months. Outcomes were favorable for 1, though there was no improvement for the second patient, who was then also given sirolimus. He died later from multiorgan failure secondary to digestive-related sepsis, and encapsulating, peritoneal, sclerosis-related symptoms.

**Conclusions:** When encapsulating, peritoneal sclerosis occurs after kidney transplant, tamoxifen therapy could be implemented.

**Key words:** Total parenteral nutrition, Continuous ambulatory peritoneal dialysis, Dialysis, Immunosuppressants

Encapsulating peritoneal sclerosis is a rare but serious complication in patients undergoing continuous ambulatory peritoneal dialysis or automated peritoneal dialysis. Its incidence is reported in up to 4.2 per 1000 patient-years (1, 2, 3). It is characterized by a progressive, intra-abdominal, inflammatory process resulting in sheets of fibrous tissue that cover, bind, and constrict the viscera, thereby compromising the motility and function of the bowel.

Risk factors for developing encapsulating, peritoneal sclerosis include (i) longer duration of peritoneal dialysis modality (4); (ii) possibly the nature of dialysis solution used is clear (2); (iii) cessation of peritoneal dialysis therapy, that is, conversion to hemodialysis or kidney transplant (4); and (iv) kidney transplant in patients with anteriority of peritoneal dialysis therapy (5). Encapsulating peritoneal sclerosis results in a mortality rate of approximately 30%, despite therapies that include total parenteral nutrition, surgery, tamoxifen, or immunosuppressants (such as steroids, cyclosporine, sirolimus, or mycophenolate mofetil (2, 3, 6, 7, 8, 9, 10, 11)).

In the present paper, we report on 2 kidney-transplant patients who received continuous ambulatory peritoneal dialysis at the time of kidney transplant, and who developed severe,

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encapsulating, peritoneal sclerosis following a huge increase in immunosuppression for treatment of acute humoral rejection. An attempt was made to treat encapsulating, peritoneal sclerosis by total parenteral nutrition and tamoxifen therapy, but this was only successful in 1 patient.

### Materials and Methods

Within the last 9 years, 991 kidney transplants have been done at our institution; of these, 50 patients were treated for chronic peritoneal dialysis at the time of transplant. During this time, we reviewed charts of all de novo kidney-transplant patients, and identified development of posttransplant encapsulating, peritoneal sclerosis in 2 patients.

**Patient 1:** A 60-year-old black man received a first kidney transplant from a deceased donor for nephroangiosclerosis in February 2006. He had been treated by continuous ambulatory peritoneal dialysis for the previous 4 years, with 2 episodes of bacterial peritonitis during this period. His initial immunosuppression was based on tacrolimus (targeting trough levels of 8 to 12 ng/mL), sirolimus (2 mg/d), and low doses of steroids without an induction therapy. By 1 month posttransplant, he presented with donor-specific anti-DQ3 alloantibody-mediated acute rejection, which was successfully treated by 3 methylprednisolone pulses, 6 plasmapheresis sessions, 4 rituximab injections (375 mg/m<sup>2</sup> each), and sirolimus was replaced by mycophenolate mofetil (2 g/d).

In May 2006, after the peritoneal catheter had been removed for 3 days, the patient was admitted with fever, abdominal intestinal pain, and gut obstruction. A percutaneous abdominal puncture yielded *Staphylococcus aureus*. He was then placed on parenteral vancomycin, and he underwent an abdominal lavage after an explorative laparotomy (which disclosed encapsulating peritonitis). He then underwent adhesiolysis: a peritoneal biopsy was done. A percutaneous drain was left in the abdomen to allow lavage with vancomycin-containing fluid. The peritoneal biopsy only showed inflamed tissue. At this stage, the patient was placed on a fast and given total parenteral nutrition. A month later, in June, he presented with a peritoneal superinfection of *Aspergillus fumigatus*: he was given intravenous

amphotericin B at 1 mg/kg/d for 6 weeks. After completion of this regimen and because he was still presenting with gut obstruction, we added tamoxifen 20 mg/d in mid-July. His status progressively improved, although he still required total parenteral nutrition. In October 2006, oral nutrition was resumed successfully. Tamoxifen therapy was stopped in April 2007. His serum creatinine was 190  $\mu$ mol/L. Until January 2009, he has not presented with any other complication. His last creatinine reading was 160  $\mu$ mol/L.

**Patient 2:** A 41-year-old white man received a fourth, living-related, kidney transplant for chronic IgA glomerulonephritis in October 2007. He had been treated by continuous ambulatory peritoneal dialysis for the previous 6 years, with 2 episodes of bacterial peritonitis during this period. Initial immunosuppression was based on induction therapy with antithymocyte globulins, followed by a triple sequential, immunosuppressive therapy that included tacrolimus (targeting trough levels of 8 to 12 ng/mL), mycophenolate mofetil, and steroids. At 10 days posttransplant, he presented with donor-specific, antiendothelial, alloantibody-mediated acute rejection, which was successfully treated by 3 methylprednisolone pulses, 6 plasmapheresis sessions, and 4 rituximab injections (375 mg/m<sup>2</sup> each). His serum creatinine level was 150  $\mu$ mol/L. The peritoneal catheter was removed at 6 weeks after transplant.

In February 2008, he was admitted for abdominal intestinal pain and gut obstruction. An abdominal computed tomography scan showed dilatation of the small bowel, thickening of bowel walls, and fluid pockets. He underwent a laparoscopy, which disclosed encapsulating sclerosis and adherent bowel peritoneal thickening. A peritoneal biopsy was not done. Because of persisting gut obstruction, he was placed on fasting and total parenteral nutrition and tamoxifen therapy (20 mg/d). Despite these therapies, the gut obstruction persisted, and his abdominal pain worsened: he required long-term morphine therapy from April 2008 onwards. We therefore increased tamoxifen to 40 mg/d from May 2008. In July 2008, because of persisting encapsulating, peritoneal sclerosis, we added

sirolimus (2 mg/d, aiming for trough levels between 3 and 5 ng/mL) in addition to tacrolimus (aiming for trough levels around 5 ng/mL). This did not lead to any improvement. Two weeks later, he was readmitted for gut-associated *E. coli* sepsis, which was associated with acute renal failure (serum creatinine of 300  $\mu$ mol/L). At this point, we withdrew the immunosuppression. The patient eventually died 10 days later due to multiorgan failure.

## Discussion

The prognosis of encapsulating, peritoneal sclerosis is still poor, despite various therapies, including surgery, total parenteral nutrition, and medications such as tamoxifen. We report 2 patients with posttransplant, encapsulating, peritoneal sclerosis who were placed on tamoxifen therapy: the outcome was favorable in 1 patient, whereas the second patient died from encapsulating, peritoneal sclerosis.

Studies have shown that the incidence of encapsulating, peritoneal sclerosis increases with duration of peritoneal dialysis treatment (1, 4, 5). Our patients had been receiving continuous ambulatory peritoneal dialysis treatment for 4 and 6 years, respectively. In a series of nontransplant patients described by Summers and associates, the overall mortality rate was 29.6%; however, among the 16 patients who had a severe form of encapsulating, peritoneal sclerosis and required a laparotomy, 7 of those patients died, whereas in those patients with only a moderate form of encapsulating, peritoneal sclerosis who did not require a laparotomy, all survived (2).

Herrero and associates found that in those patients with severe forms of encapsulating, peritoneal sclerosis, the mortality rate was as high as 62.5%. Fieren and associates reported on a large series of posttransplant cases of encapsulating, peritoneal sclerosis; in their series, 5 of the 13 encapsulating, peritoneal sclerosis patients died (ie, 38%) (5).

In this series, encapsulating, peritoneal sclerosis developed mostly within 1 to 7 months after the transplant, despite ongoing powerful immunosuppression based on tacrolimus and mycophenolate mofetil. This result suggests a possible link between encapsulating, peritoneal sclerosis and kidney transplant. However, Kawanishi

and associates reported that 68.8% of encapsulating, peritoneal sclerosis cases occurred after stopping peritoneal dialysis, when patients were transferred to hemodialysis therapy after ultrafiltration failure or peritonitis: only a small fraction of these patients underwent kidney transplant with subsequent development of encapsulating, peritoneal sclerosis (4). In contrast, cases of encapsulating, peritoneal sclerosis occurring after kidney transplant have been described (5, 6, 12). These may have been caused by prevention of any fluid exchange in the peritoneal cavity. This could cause concentrations of fibrin, and proinflammatory and profibrotic mediators in the peritoneal cavity to rise, and to bring about acceleration of the inflammatory-fibrosing process (4, 13).

Alternatively, the transplant process itself or some of its related therapies could be implicated in the development or the acceleration of encapsulating, peritoneal sclerosis. De Freitas and associates reported 4 cases of encapsulating, peritoneal sclerosis, 3 of whom occurred after successful treatment of vascular rejection with antithymocyte globulins (14). In contrast, our 2 patients had been treated for acute humoral rejection; that is, vascular rejection before the occurrence of encapsulating, peritoneal sclerosis were not given antithymocyte globulins but received plasmapheresis plus rituximab therapy instead. In addition, the use of anticalcineurin agents (eg, tacrolimus or cyclosporine) may contribute to the development of encapsulating, peritoneal sclerosis.

When it occurs, encapsulating, peritoneal sclerosis therapy is based on enteric rest with total parenteral nutrition. Surgery might be required for adhesiolysis where abdominal symptoms are severe. If symptoms do not improve, one could consider medications such as steroids or immunosuppressants, but this is only based on case reports (2, 6, 15).

Tamoxifen could be given because it has some negative effects on transforming growth factor  $\beta$  (TGF $\beta$ ) (16, 17, 18). When encapsulating, peritoneal sclerosis occurs, the most significant histologic changes are a diffuse loss of mesothelial cells and massive production of that extracellular matrix with proliferation of peritoneal fibroblasts. TGF $\beta$ 1

plays a major role in stimulating extracellular matrix deposition; frequent peritonitis may cause persistent TGF $\beta$ 1 mRNA expression. Moreover, the chronic delivery of anticalcineurin therapy to kidney-transplant patients might contribute to over production of TGF $\beta$ 1 (19, 20). Indeed, tamoxifen has been initially used to successfully treat retroperitoneal fibrosis (21, 22, 23). It has also been used to both prevent (24) and treat encapsulating, peritoneal sclerosis in continuous ambulatory peritoneal dialysis-treated patients (2, 25). Tamoxifen has also been successful in treating 2 patients who presented with posttransplant encapsulating, peritoneal sclerosis (26); in these cases, clinical symptoms improved within 3 and 4 months. In contrast, in our study, this therapy was only effective in 1 patient, whereas in the other, 3 months of tamoxifen therapy, which was then replaced by sirolimus, was unsuccessful. Posttransplant encapsulating, peritoneal sclerosis is not always sensitive to tamoxifen.

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