Renal Failure

ISSN: 0886-022X (Print) 1525-6049 (Online) Journal homepage: www.tandfonline.com/journals/irnf20

Additive Effectiveness of Everolimus Plus Tamoxifen Therapy in Treatment of Encapsulating Peritoneal Sclerosis

Bülent Huddam, Alper Azak, Gülay Koçak, Murat Başaran, Nuray Voyvoda & Murat Duranay

To cite this article: Bülent Huddam, Alper Azak, Gülay Koçak, Murat Başaran, Nuray Voyvoda & Murat Duranay (2012) Additive Effectiveness of Everolimus Plus Tamoxifen Therapy in Treatment of Encapsulating Peritoneal Sclerosis, Renal Failure, 34:3, 387-389, DOI: 10.3109/0886022X.2011.647338

To link to this article: https://doi.org/10.3109/0886022X.2011.647338

Published online: 23 Jan 2012.

Renal Failure, 34(3): 387–389, (2012)

ISSN 0886-022X print/1525-6049 online
DOI: 10.3109/0886022X.2011.647338

informa
healthcare

CASE REPORT

Additive Effectiveness of Everolimus Plus Tamoxifen Therapy in Treatment of Encapsulating Peritoneal Sclerosis

Bülent Huddam[1], Alper Azak[1], Gülay Koçak[1], Murat Başaran[1], Nuray Voyvoda[2] and Murat Duranay[1]

[1]*Department of Nephrology, Ankara Education and Research Hospital, Ankara, Turkey;* [2]*Department of Radiology, Faculty of Medicine, Acibadem University, Kocaeli, Turkey*

Abstract

Peritoneal dialysis (PD) is one of the commonly used choices of continuous renal replacement therapies. Peritoneal membrane is damaged by using solutions with lower biocompatibility, peritonitis episodes, and vintage of PD therapy. Encapsulating peritoneal sclerosis (EPS) is a rare complication of PD and is presented by progressive fibrosis of the peritoneum. Fibrous tissue entrapment of the intestine, leading to complete intestinal obstruction, is referred to as EPS, the most severe form of sclerosing peritonitis. EPS is irreversible fibrosis of the peritoneal membrane usually associated with high rates of morbidity and mortality. Preventive strategies are the best choice of treatment. Also there is no proven effective therapy for EPS; there are only small-sized trials. Herein we present a case of EPS who improved with everolimus plus tamoxifen therapy.

Keywords: encapsulating peritoneal sclerosis, tamoxifen, everolimus

INTRODUCTION

Peritoneal dialysis (PD) is one of the commonly used choices of continuous renal replacement therapies (RRTs). These RRTs have many advantages and mostly preferred by young end-stage renal disease (ESRD) patients.

Peritoneal membrane is damaged by using solutions with lower biocompatibility, peritonitis episodes, and vintage of PD therapy.[1] This damage may result with peritoneal fibrosis. Encapsulating peritoneal sclerosis (EPS), a rare complication of PD, is presented by progressive fibrosis of the peritoneum. Fibrous tissue entrapment of the intestine, leading to complete intestinal obstruction, is referred to as EPS, the most severe form of sclerosing peritonitis. The clinical presentation is usually with partial or complete small-bowel obstruction (SBO), ascites, abdominal mass, or impaired peritoneal ultrafiltration.

The incidence of EPS is reported as 0.7–7.3% which increases with the duration of PD.[2] EPS has high rates of mortality.[3] Removal of the PD catheter, total parenteral nutrition, immunosuppression, and surgical treatments have been reported in order to treat EPS.[4,5]

Tamoxifen is a nonsteroidal anti-estrogen agent used to treat breast carcinoma and also fibrosing diseases such as fibrosing mediastinitis and retroperitoneal fibrosis. Everolimus inhibits cytoplasmic growth factor mTOR (mammalian target of rapamycin) and cellular proliferation and cell cycle. Due to these properties we present here the result of an EPS patient who is treated by the combination of tamoxifen and everolimus.

CASE REPORT

To our clinic, a 35-year-old female was admitted with complaints of abdominal tenderness, pain, nausea, and loss of appetite. She had been diagnosed with ESRD for 12 years which was treated with PD for 11.5 years. Her treatment was switched to hemodialysis due to peritoneal dysfunction with ultrafiltration failure for 8 months. In her physical examination blood pressure was measured as 80/40 mmHg and body

Address correspondence to Alper Azak, Department of Nephrology, Ankara Education and Research Hospital, Ulucanlar, Ankara, Turkey. E-mail: dralperazak@gmail.com

Received 5 September 2011; Revised 8 October 2011; Accepted 12 October 2011

temperature 37.5°C. Abdominal tenderness and loss of bowel movement sounds were noted. Laboratory studies showed hemoglobin 8.4 g/dL, C-reactive protein (CRP) 9.6 mg/dL, sedimentation rate 97 mm/h, blood urea nitrogen 46 mg/dL, creatinine 5.7 mg/dL, albumin 3.2 g/dL, and CRP 7.7 mg/dL. Plain abdominal X-ray showed disseminated air–fluid levels and peritoneal calcification focuses. Oral feeding was stopped and parenteral nutrition initiated. Abdominal computerized tomography (CT) showed small-bowel loops congregated to the center of the abdomen encased by a soft tissue density mantle and massive ascites (Figure 1). Peritoneal fluid cytology pointed to chronic inflammation; peritoneal membrane biopsy revealed extended fibrosis (Figure 2). During laparoscopic peritoneal biopsy peritoneal catheter was placed in order to dwell the ascites. About 700–1000 mL of ascite fluid was drained from the PD catheter per 2–3 days. Tamoxifen (10 mg/day, per-oral) and everolimus (0.75 mg/day, per-oral) therapies were started besides parenteral nutrition. In 2 weeks her abdominal pain ceased; liquid and solid intake were started on the 4th and 8th weeks, respectively. The drained ascites volume decreased to 100 mL per 2–3 days. In her abdominal USG (Ultrasonography) minimal fluid has been detected among intestines. Her third month abdominal CT did not show regression in the thickening of peritoneal membrane (Figure 3).

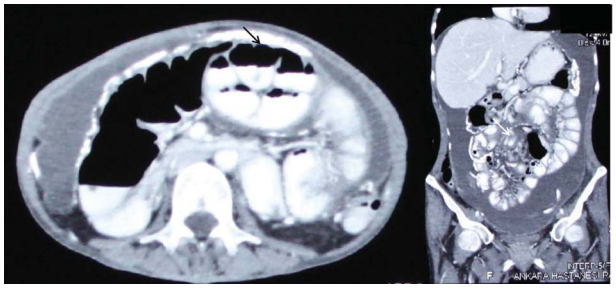

Figure 1. CT scan of lower abdomen shows clustered gas-containing small-bowel loops with thick membrane-like sac (white arrow) and dilated proximal small bowel with air–fluid levels (black arrow) due to intestinal obstruction.

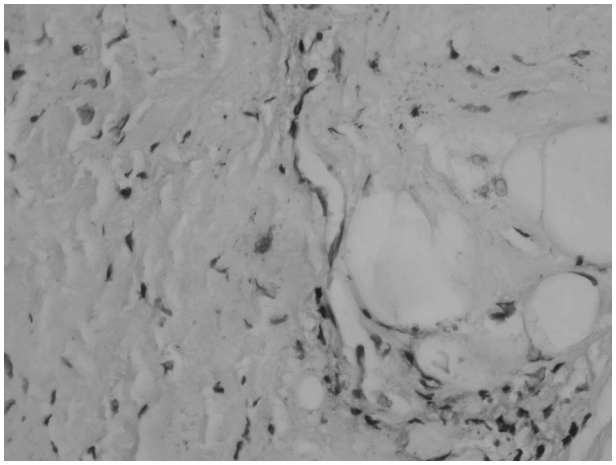

Figure 2. Peritoneal membrane biopsy showing extended fibrosis.

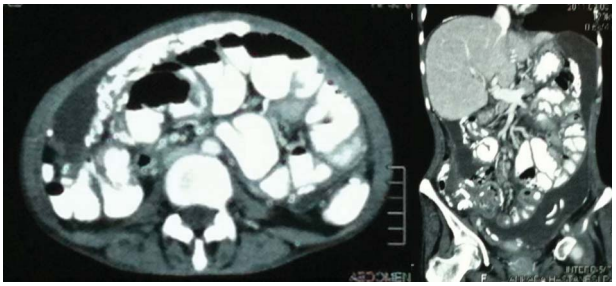

Figure 3. Control examination after 2 months of drug treatment: the clustered small-bowel loop has disappeared.

DISCUSSION

Osmotic active molecules like glucose may damage the peritoneal membrane which results in increased fibrosis, ultrafiltration failure, and intestine dysmotility, which may lead to complete obstruction of the intestines. EPS is irreversible, progressive fibrosis of the peritoneal membrane which is usually associated with high rates of morbidity and mortality. Preventive strategies are the best choice of treatment.[6] Also there is no proven effective therapy for EPS; there are only small-sized trials.

The preoperative diagnosis of abdominal cocoon may be difficult due to its nonspecific imaging findings, and reports are few in the literature on its radiologic imaging findings. The ability of CT to depict the cause of an SBO, with a sensitivity of 73–95% for high-grade SBO, makes it an important diagnostic tool, but few have reported CT findings of abdominal cocoon. Maguire et al.[7] reported that gross ascites with small-bowel intestine loops congregated in a single area in the peritoneal cavity are typical findings of abdominal cocoon on an abdominal CT scan. Wig and Gupta reported that the typical finding of abdominal cocoon on CT is a concentration of the whole small bowel to the center of the abdomen encased by a soft tissue density mantle. Other CT features of abdominal cocoon include signs of obstruction, agglutination and the fixation of intestinal loops, mural thickening, ascites and localized fluid collections, peritoneal thickening and enhancement, peritoneal or mural calcifications, and reactive adenopathy.[8]

Tamoxifen is occasionally used as a therapeutic option for EPS. Moustafellos et al.[9] reported that this agent has improved EPS in two cases who were diagnosed after kidney transplantation. Also it has been reported that tamoxifen therapy was successful in four EPS patients.[10] Tamoxifen therapy may also reduce mortality rates.[11]

Use of tamoxifen plus corticosteroids has also been reported in the literature.[12–14] In a series of 23 patients with peritoneal sclerosis, none of the 9 patients who received tamoxifen developed EPS, but 4 of the 14 patients who were not receiving tamoxifen treatment developed EPS.[15]

According to these results tamoxifen may be an option of treatment accompanying total parenteral nutrition in patients with intestinal occlusion. Duration of the treatment and optimal dosage of tamoxifen has not yet been well determined.

Everolimus inhibits cellular proliferation by blocking mTOR protein, which is commonly used for immunosuppression after kidney transplantation. In a rat model of intraperitoneal chlorhexidine-induced peritoneal fibrosis it has been demonstrated that everolimus reduces the peritoneal thickness.[16] Sirolimus acts through the same mechanism as everolimus. It has been reported that sirolimus plus steroid treatment was successful in an EPS patient.[17]

Even though there are some known factors like more often episodes of peritonitis, low biocompatible peritoneal solutions and catheters, intraperitoneal contamination and beta-blocker use, the exact pathogenesis of ESP has not yet been fully understood. Treatment is still an enigma. There is very limited information in the literature regarding the treatment of EPS. Tamoxifen and mTOR inhibitors, sirolimus and everolimus, are thought to be effective.

In patients who have already developed early symptoms of EPS, initiation of tamoxifen therapy may be useful. In case of intestinal obstruction, it is usually treated conservatively, with bowel rest and total parenteral nutritional support. For severe and persistent intestinal obstruction, surgical enterolysis may be necessary. Tamoxifen or other immunosuppressive agents should be the choices of treatment.

We received improvement in the EPS patient who received tamoxifen plus everolimus therapy. In 2 months we achieved reductions in ascites volume and free air amount but not peritoneal wall thickness. Even though the radiological findings were not significant there was clinical improvement. In order to evaluate the optimal timing and dosage of tamoxifen and everolimus therapies and to confirm our findings, prospective, randomized, and controlled trials are needed.

***Declaration of interest*:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

REFERENCES

[1] Krediet RT. 30 years of peritoneal dialysis development: The past and the future. *Perit Dial Int.* 2007;27(Suppl. 2): S35–S41.

[2] Hirahara I, Inoue M, Okuda K, Ando Y, Muto S, Kusano E. The potential of matrix metalloproteinase–2 as a marker of peritoneal injury increased solute transport, or progression to encapsulating peritoneal sclerosis during peritoneal dialysis—A multicentre study in Japan. *Nephrol Dial Transplant.* 2007;22:560–567.

[3] Sawada T, Ishii Y, Tojimbara T, Nakajima I, Fuchinoue S, Teraoka S. The ACE inhibitor, quinapril, ameliorates peritoneal fibrosis in an encapsulating peritoneal sclerosis model in mice. *Pharmacol Res.* 2002;46:505–510.

[4] Noh H, Ha H, Yu MR, Kim YO, Kim JH, Lee HB. Angiotensin II mediates high glucose-induced TGF-beta1 and fibronectin upregulation in HPMC through reactive oxygen species. *Perit Dial Int.* 2005;25:38–47.

[5] Stegbauer J, Lee DH, Seubert S, et al. Role of the renin-angiotensin system in autoimmune inflammation of the central nervous system. *Proc Natl Acad Sci USA.* 2009;106:14942–14947.

[6] Kawanishi H, Moriishi M. Encapsulating peritoneal sclerosis: Prevention and treatment. *Perit Dial Int.* 2007;27(Suppl. 2):S289–S292.

[7] Maguire D, Srinivasan P, O'Grady J, Rela M, Heaton ND. Sclerosing encapsulating peritonitis after orthotopic liver transplantation. *Am J Surg.* 2001;182(2):151–154.

[8] Wig JD, Gupta SK. Computed tomography in abdominal cocoon. *J Clin Gastroenterol.* 1998;27(3):259–260.

[9] Moustafellos P, Hadjianastassiou V, Roy D, et al. Tamoxifen therapy in encapsulating sclerosing peritonitis in patients after kidney transplantation. *Transplant Proc.* 2006;38(9):2913–2914.

[10] Eltoum MA, Wright S, Atchley J, Mason JC. Four consecutive cases of peritoneal dialysis-related encapsulating peritoneal sclerosis treated successfully with tamoxifen. *Perit Dial Int.* 2006;26:203–206.

[11] Korte MR, Fieren MW, Sampimon DE, Lingsma HF, Weimar W, Betjes MGH, and on behalf of the investigators of the Dutch Multicentre EPS Study. Tamoxifen is associated with lower mortality of encapsulating peritoneal sclerosis: Results of the Dutch Multicentre EPS Study. *Nephrol Dial Transplant.* 2011;26(2):691–697.

[12] Pollock CA. Bloody ascites in a patient after transfer from peritoneal dialysis to hemodialysis. *Semin Dial.* 2003;16:406–410.

[13] Evrenkaya TR, Atasoyu EM, Unver S, Basekim C, Baloglu H, Tulbek MY. Corticosteroid and tamoxifen therapy in sclerosing encapsulating peritonitis in a patient on continuous ambulatory peritoneal dialysis. *Nephrol Dial Transplant.* 2004;19:2423–2424.

[14] Mesquita M, Guillaume MP, Dratwa M. First use of tamoxifen in an HIV patient with encapsulating peritoneal sclerosis. *Clin Drug Invest.* 2007;27:727–729.

[15] del Peso G, Bajo MA, Gil F, et al. Clinical experience with tamoxifen in peritoneal fibrosing syndromes. *Adv Perit Dial.* 2003;19:32–35.

[16] Duman S, Bozkurt D, Sipahi S, et al. The effect of everolimus as an antiproliferative agent on regression of encapsulating peritoneal sclerosis model. *Adv Perit Dial.* 2008;24:104–110.

[17] Rajani R, Smyth J, Koffman CG, Abbs I, Goldsmith DJ. Differential effect of sirolimus vs prednisolone in thetreatment of sclerosing encapsulating peritonitis. *Nephrol Dial Transplant.* 2002;17:2279.