Dramatic Improvement with Tamoxifen Plus Everolimus in a Transplant Case with Encapsulated Sclerosing Peritonitis

Kapsüllü Periton Sklerozu Olan Bir Transplant Olgusunda Tamoksifen ve Everolimus ile Belirgin İyileşme

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ABSTRACT A transplant patient was hospitalized due to ileus after six months of renal transplantation. She had the history of continuous ambulatory peritoneal dialysis for 11 years and she defined weight loss about 20 kg at the last 2 months. Encapsulating peritoneal sclerosis was found at laparatomy. She was treated with prednisolon, low dose tacrolimus, everolimus and tamoxifen acetate in monitoring. Her general condition gradually improved and she gained weight 20 kg within 88 weeks after this therapy. In conclusion, encapsulating peritoneal sclerosis can be develop in renal transplant patient. Everolimus plus tamoxifen may be have synergistic effect for this life threatening complication without any negative effect on renal functions.

Key Words: Peritoneal dialysis, continuous ambulatory; peritonitis; tamoxifen; everolimus

ÖZET Altı ay önce renal transplantasyon yapılmış kadın hasta ileus nedeni ile hastaneye yatırıldı. Öyküsünde son 2 aylık süre içinde 20 kg ağırlık kaybı olan hastaya transplant öncesi 11 yıl sürekli ayaktan periton diyalizi uygulanmıştı. Laparatomide kapsüllü periton sklerozu saptandı. Takipte hasta prednisolon, düşük doz takrolimus, everolimus ve tamoksifen asetat ile tedavi edildi. Hastanın durumu giderek düzeldi ve 88 haftalık takip süresince 20 kg ağırlık artışı oldu. Sonuç olarak; kapsüllü periton sklerozu renal transplantasyon sonrası da gelişebilir. Böbrek fonksiyonlarında bozulma olmadan everolimus ve tamoksifen sinerjistik etki göstererek hayatı tehdit eden bu komplikasyonun düzelmesini sağlayabilir.

Anahtar Kelimeler: Periton diyalizi, sürekli ayaktan; peritonit; tamoksifen; everolimus

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35 year old woman was admitted to transplantation unit because of nausea, vomiting and colicky abdominal pain for one month. She was treated with continuous ambulatory peritoneal dialysis (CAPD) for 11 years for chronic renal failure secondary to chronic tubulo-interstitiel nephritis. Peritoneal dialysis solution prescribed as 4 x 2.5 liter per day (3 x 1.36% and 1 x 3.86% BAXTER Co.). Infection developed two times, bacterial peritonitis and exit site enfection during the follow-up period. Peritoneal Equilibration test revealed total KT/V 1.9/week and creatinin clearence 54.8 L/week/1.73 m.[1] Right nephrectomy was performed after control of high blood pressure. She received renal transplant from her sister. Post-transplantation period was uneventful, except hyperglycemia which was controlled by pioglitazone. Immunosupressive medication con-

sisted of methylprednisolone (100 mg daily for 4 days, 64 mg daily for 7 days and dose reduced gradually to 4 mg daily at 2 months), basiliximab (in a standart dose), tacrolimus 10-15 ng/ml at first 2 weeks after that 8-10 first 6 months) and mycophenolate sodium (2 g daily). Amlodipine, doxazosine and propranolol were used for hypertension and oral magnesium and dypridamole for hypomagnesemia and hypophosphatemia, respectively. Mycofenolate sodium was changed with azathiopurine due to elevation of AST and ALT levels. Peritoneal dialysis catheter was removed after a month of renal transplantation. After six months of renal transplantation, she was hospitalized because of severe nausea, vomiting, and abdominal pain. She lost 20 kg weight within 2 months. Physical examination: blood pressure was 110/60 mmHg, there was evidence of hypovolemia and abdominal distension without tenderness. Abdominal X-ray showed multiple intestinal air-fluid levels and mildly dilated small and large intestine bowel loops, without free intraperitoneal gas. Oral feeding was stopped and parenteral alimentation was started. Contrast-enhanced abdominal computed tomography (CT) revealed subileus and ascites (Figure 1). She was followed conservatively by surgery department. The biochemical parameters at this hospitalization were shown at Table 1. Serologically tests for CMV, hepatitis B and C, brusellosis were negative. Her thyroid functions were within normal. Her general condition deteriorated gradually. Renal function tests were

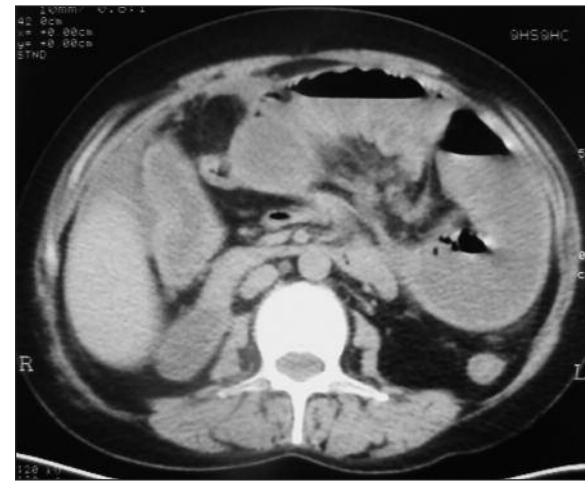

FIGURE 1: Contrast enhanced computed tomography scan taken through the level of the sub-hepatic space shows anterior sub-hepatic fluid collection and distended small bowel loops.

TABLE 1: The biochemical parameters during the abdominal pain and ileus and post-operative period.

Parameters	Post Tx 24. w Hospitalization	Post Tx 28. w Tamoxifen	Post Tx 32. w Tamoxifen 4.w	Post Tx 40. w Tamoxifen12. w	Post Tx 50. w Tamoxifen 22.w	Post Tx 112. w Tamoxifen 84.w
Glucose (mg/dL)	166	83	76	74	83	94
BUN (mg/dL)	16	5	9	15	16	18
Creatinin (mg/dL)	1.1	0.9	0.7	0.8	0.9	1.19
Albumin (g/dL)	3.5	2.4	3	3.6	3.7	4.2
Na mE (q/L)	149	124	138	142	142	141
K mE (q/L)	4.9	3.3	4.3	4.8	4,3	4.69
Ca (mg/dL)	9.7	7.9	9.3	10.2	10.2	9.5
P (mg/dL)	2.4	1.1	2.5	2.9	3.6	2.2
Mg (mg/dL)	1.7	1.3	1.9	2.4	2.4	2.1
WBC (uL)	5300	4900	11850	8000	7900	9900
Hb (g/dL)	10.4	11.9	12.3	11.3	13	11.9
Platelet (uL)	378000	302000	525000	551000	363000	354000
CRP	45.3	86.9	17.8	-	-	6.4
Serum Tac (ng/mL)	5.1	6.4	1.4	2	1.6	2.5
Weight (kg)	60	40	43	48	55	60

Abbreviations: Post Tx: Post-transplantation, w: week, BUN: Blood urea nitrogen, Na: Sodium, K: Potassium, Ca: Calcium, P: Phosphorus, Mg: Magnesium, WBC: White blood cell, Hb: Hemoglobine, Tac: Tacrolimus.

within normal limit, but serum levels of albumin, sodium, potassium, phosphorus magnesium decreased day by day. Exploratory laparatomy showed diffuse adhesive fibrotic bands on small and large intestines. Surgery team conducted multiple biopsies on adhesive bands between small and large intestine loops and intestinal catheter was placed intra-peritoneally for heparin irrigation. Biopsy specimens showed chronic fibrinoid inflamation and these samples were negative for tuberculoses, amyloidosis and malignancy. We did not obtained improvement with heparin irrigation of peritoneal cavity. Rapamycine was began instead of azathiopurine. But liver enzymes increased with Rapamycine. Everolimus (target levels 4-8 ng/ml) and tamoxifen citrate (20 mg daily) were began. Nausea and vomiting decreased and feeding were gradually improved. She recieved the same medication including tacrolimus (target 2-6 ng/ml), everolimus (target 3-8 ng/ml), prednisolone (2 mg/day), tamoxifen (10 mg/day). At the last visit-post Tx 112. week, she was receiving tamoxifen since than 88 weeks and she gained weight 20 kg during this period. Clinical follow-up and treatment were shown on Table 2.

DISCUSSION

Sclerosing peritonitis (SP) is a rare cause of intestinal obstruction due to peritoneal dialysis and is characterized by progressive fibrosis of the peritoneum. Complete intestinal obstruction by SP is known as encapsulating peritoneal sclerosis (EPS) and this entity is the most severe form of SP. Predisposing factors include long duration of peritoneal dialysis, the use of beta-blockers (practolol), acetate in the dialysate, anti-septics used during the bag exchanges, recurrent peritonitis, surgery, neoplasia, intra-peritoneal chemotherapy.[2] In some cases there is no cause and these are named as idiopathic cases and has been reported in young women. Most cases are diagnosed incidentally at laparatomy. Abdominal computed tomography can contribute to the diagnosis with the signs of peritoneal thickening and calcification, localized fluid collections and dilatation of small bowel loops.

In our patient long term peritoneal dialysis and usage of lactate containing dialysis solution were predisposing factors for EPS. Additionally, it can be said that the use of calcineurine inhibitors during post-transplant period can accelerate the development of SP. Because calcineurine inhibitors stimulate fibrosis by enhancing tumor growth factor-β (TGF-β).[1] Diagnosis was confirmed at laparotomy and pathological investigation in our patient. The incidence of SP has been found to be related with the duration of PD in an Australian study: incidence of SP increases from 1.9% for patients on dialysis less than 2 years, to 6.4%, 10.8%, and 19.4% for more than 5, 6 and 8 years, respectively.[2] EPS is extremely rare after renal transplantation. There is no established medical treatment for EPS, however some case reports provide some important points in the management of this life-threatening complication. Surgery has represented variable results. Outcome after surgery may be favorable but mortality may be high especially in patients with renal failure and cirrhosis.[3,4] It has been reported that intra-peritoneal heparin irrigation may diminish the post-operative adhesions in rats.[5] Immunosupression is another therapeutic strategy for amelioration of EPS.[6] In our patient, tacrolimus might be promote fibrosis after renal transplantation. Also it is well known that m-TOR inhibitors have anti-proliferative effects. Tamoxifen has been

TABLE 2: Immunsupressive medication of the patient.

Transplantation (Tx)	Post Tx 2. w	Post Tx 24.w	Post Tx 28	Post Tx 112. w
Tacrolimus	Tacrolimus	Tacrolimus	Low dose Tacrolimus	Low dose Tacrolimus
Methylprednisolone	Methylprednisolone	Methylprednisolone	Methylprednisolone	Methylprednisolone
Mycofenolate mofetil	Azathiopurine	Rapamycine	Everolimus Tamoxifen	Everolimus Tamoxifen
Abnormal AST, ALT levels		Diagnosis of EPS; Abnormal AST, ALT		

successfully used in the treatment of fibrosclerotic disorders including EPS.[7] Dramatic improvement in our patient, may be releated to concominant using of everolimus and tamoxifen and also lower dose of tacrolimus. We did not know exactly how long tamoxifen must be used in these patients but we discontinued the tamoxifen at 88th week of tamoxifen therapy providing that pay attention to thrombotic process. Tamoxifen and other therapeutic strategies did not cause negative effect on renal functions in our patient.

In summary, EPS developed in the patient previously treated with continuous peritoneal dialysis in a short term after renal transplantation. Predisposing factors may be long-term peritoneal dialysis (more than 11 years) and lactate containing dialysate EPS may be manifested or accelerated with standard dose tacrolimus. In our patient with renal transplant, mTOR inhibitors everolimus and tamoxifen may be have synergistic effect for treating EPS and without any negative effect on renal functions.

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