Encapsulating Peritoneal Sclerosis in Peritoneal Dialysis Patients After Kidney Transplantation

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ABSTRACT

Objective. Encapsulating peritoneal sclerosis (EPS) is a serious complication for patients with chronic kidney disease (CKD) who were treated with long-term peritoneal dialysis (PD). The risk of EPS was increased after kidney transplantation. In our study we evaluated risk factors for EPS patients after kidney transplantation who were treated before with PD.

Materials and Methods. In our study, between January 2008 and August 2015, 47 PD patients (12 had EPS) who underwent kidney transplantation were analyzed. Age, gender, time of PD treatment, human leukocyte antigen (HLA) matching, cold ischemia time, kidney function (serum urea, creatinine, etc), comorbidities, immunosuppressive therapy, clinical features, and outcomes of PD patients were retrospectively evaluated in both groups.

Results. Mean age was 42 (range, 25–60) years in EPS patients, versus 43 (range, 22–77) years without EPS ($P = .798$). Distribution of gender was similar in both groups ($P = .154$). The C-reactive protein levels ($P < .001$), number of patients with peritonitis ($P = .001$), length of time on PD ($P < .001$), and serum ferritin levels ($P = .020$) were higher in EPS patients. The immunosuppressive therapy was changed; tamoxifen and steroids were used after diagnosis in EPS patients. HLA matching was higher in the non-EPS group ($P = .006$). EPS was more often seen in patients who were treated with continuous ambulatory peritoneal dialysis (CAPD; 75%; $P = .036$). EPS was more often detected in cadaveric transplant recipients (83.3%; $P = .024$). High peritoneal transmittance rate was more identified in EPS (+) patients ($P = .001$). EPS was more often seen in patients who were treated with icodextrin-based regimens in PD before transplantation (91.7%; $P = .037$). The length of time on PD and high ferritin levels increased EPS 1.08 and 1.01, respectively ($P = .036$ and .049, respectively), in multivariate analysis.

Conclusion. The length of time on PD, type of PD, PD regimens with icodextrin, episodes of peritonitis, and peritoneal transmittance in patients with CKD affect the development of EPS after transplantation.

PERITONEAL dialysis (PD) is one of the treatment options for patients with chronic kidney disease (CKD). Encapsulating peritoneal sclerosis (EPS) is one from the major causes of mortality and impairs patients survival and affects quality of life for patients who were treated with PD. EPS is an inflammatory process that induces accumulation of thick fibrous deposits on the peritoneal membrane. Destruction of peritoneal mesothelial cells, interstitial fibrosis, neovascularization, and vascular and morphological changes (thickening of the basement membrane, fibrosis and hyalinization on the vessel wall, and

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Table 1. Clinical Characteristics of Patients Before Transplantation Who Received PD

Variable	EPS (+) Group n = 12	EPS (−) Group n = 35	*P*
Age (y)	42 (25–60)	43 (22–77)	.798
Gender (female/male)	3/9	17/18	.154
The length of time on PD before transplantation (mo)	126.5 (72–168)	46 (3–194)	<.001
Type of PD (CAPD/IPD)	9/3	21/14	.036
PD regimens with Icodextrin (n, %)			.037
Yes	11 (91.70%)	30 (57.10%)	
No	1 (8.30%)	15 (42.90%)	
Number of peritonitis episodes, n	3 (1–7)	1 (0–6)	<.001
Peritoneal transmittance, n (%)			.001
High	8 (66.7)	4 (11.4)	
High-moderate	1 (8.3)	19 (54.3)	
Low	0	1 (2.9)	
Low-moderate	3 (25)	11 (31.4)	
Immunosuppressive regimens			.058
Tac-based	7 (58.30%)	23 (65.70%)	
CsA-based	2 (16.70%)	11 (31.40%)	
mTORi (Eve)-based	3 (25%)	1 (2.90%)	

Abbreviaitons: IPD, instrumental peritoneal dialysis; TAC, tacrolimus; CsA, cyclosporine A; Eve, everolimus.

so on) are seen in EPS. The complication was detected in about 1% of continuous ambulatory peritoneal dialysis (CAPD) patients [1,2]. In addition, recurrent peritonitis, glucose degradation products formed during sterilization (aldehyde, glyoxal, furfural, and so on), genetic factors, characteristics of PD solutions (high-glucose content, low pH, lactate, and so on), and plastic particles in the fluid bags aid the development of EPS. Bowel obstruction, malnutrition, and lack of dialysis symptoms are also more often detected in EPS. Clinical and radiological findings (ultrasonography and computed tomography [CT]) assist the clinicians for diagnosis [3,4].

EPS is seen in 40%–84% of patients after kidney transplantation who were treated with PD before transplantation. EPS was detected after kidney transplantation in 50% of PD patients later than 2007. Studies showed us that the length of time on PD before transplantation and immunosuppression drugs (such as the profibrotic effect of cyclosporine) increase the development of EPS [5,6]. Medical therapy and surgery are treatment options in EPS. Exchanging calcineurin inhibitors (CNIs: tacrolimus and cyclosporine A) with mammalian target of rapamycin inhibitors (mTORi: everolimus, sirolimus) or reducing CNI to initial dose, steroids, tamoxifen, and discontinuing of mycophenolate mofetil (MMF) are medical treatment options. Adhesiolysis operations, peritonectomy and enterolysis, and ileostomy were used as surgery. Surgery must only be applied in specific centers by specialized surgeons because mortality rates are higher. Mortality rates were seen for about 50% despite all of these treatments [6–8]. In our study, we evaluated risk factors that progress to EPS in kidney transplantation patients who were treated before with PD.

MATERIALS AND METHODS

In our study, between January 2008 and August 2015, 47 PD patients (12 had EPS) who underwent kidney transplantation were analyzed. EPS was diagnosed with clinical and radiological findings (CT). CT was performed routinely for all recipients who were on PD to control peritoneal status. Thickening of the peritoneal membrane, calcification on peritoneal membrane, loculated acid, dilatation, thickening, and felting of bowels, intestinal adhesions between bowel lobes, and bowel obstruction symptoms in radiological examination supported our diagnosis with clinical symptoms (bowel obstruction symptoms, such as nausea, vomiting, abdominal distantion, and ileus, abdominal mass, malnutrition, hemoperitoneum, and lack of PD dialysis).

Peritoneal transmittance was evaluated with the peritoneal equilibration test (PET) in our study. PET is a semiquantitative assessment of peritoneal membrane transport function in patients on PD. The solute transport rates are assessed by the rates of their equilibration between the peritoneal capillary blood and dialysate. The ratio of solute concentrations in dialysate and plasma (D/P ratio) at specific times (t) during the dwell signifies the extent of solute equilibration. The standardized test for clinical utility measures dialysate creatinine and glucose levels at 0, 2, and 4 hours of dwell, and serum levels of creatinine and glucose at any time during the test. The ratio of 0.81–1.03 was evaluated as high transmittance, 0.65–0.80 as high-moderate, 0.50–0.64 as low, and 0.34–0.49 as low-moderate [9]. We used 4th hour D/P creatinine levels for peritoneal transmittance. We did not perform peritoneal biopsy. Age, gender, length of time on PD, HLA matching, cold ischemia time, kidney function (serum urea and creatinine), comorbidities, immunosuppressive therapy, clinical characteristics, and outcomes of PD patients were evaluated retrospectively in both groups.

Statistical Analysis

Data were expressed as the median (minimum, maximum) values. For comparison between groups, the Mann-Whitney *U*, chi-square,

Table 2. Laboratuary Findings in Both Groups

Variable	EPS (+) Group n = 12	EPS (−) Group n = 35	*P*
Serum urea, mg/dL	70 (35–99)	67 (19–166)	.634
Creatinine, mg/dL	1.45 (0.8–4)	1.5 (0.7–10.3)	.420
Serum albumin, g/dL	3.55 (2.7–4.4)	3.7 (2–5)	.335
Ferritin, ng/mL	1509 (133–4000)	321 (78–2040)	.020
CRP, mg/dL	11.7 (3.6–19.8)	2.2 (0.8–3.7)	<.001
PTH, pg/mL	104.5 (27–1558)	129 (49–300)	.903
K, mEq/L	4.4 (3.3–5)	4.4 (3.1–5.3)	.713
Ca, mg/dL	9.3 (8–10.5)	9.4 (8–10.6)	.845
P, mg/dL	3 (1.4–5)	3.5 (1.9–6)	.227

Abbreviations: CRP, C-reactive protein; PTH, parathyroid hormone; K, potassium; Ca, calcium; P, phosphorus.

Fisher exact, and Fisher-Freeman-Halton tests were used. A multiple logistic regression analysis with stepwise procedure was performed to determine the independent risk factors that affect EPS development. $P < .05$ was considered significant. Statistical analyses were performed using SPSS v20 software program (SPSS, Chicago, Ill, United States).

RESULTS

EPS developed in 12 patients after 25 (range, 8–42) months from renal transplantation with clinical and radiological findings. Twelve patients, who were diagnosed with EPS, had thickening of the peritoneal membrane, calcification on peritoneal membrane, loculated acid, dilatation, and thickening and felting of bowels when they were examined with radiological with computerized tomography. Seventy-five percent of them had bowel obstruction symptoms (severe abdominal pain, weight loss, nausea, vomiting, abdominal distention, and ileus). Twenty-five of them had deficiency of dialysis and malnutrition. The length of time on PD was longer in the EPS (+) group (126.5 [range, 72–168] months; $P < .001$). CAPD was more used in the EPS (+) patient group (75%; $P = .036$). The number of peritonitis attacks was 3 (range, 1–7) in the EPS (+) group, and was higher than the EPS (−) group ($P < .001$). High peritoneal transport was more seen in the EPS (+) group (66.7%), and high-moderate was more seen in the EPS (−) group (54.3%; $P < .001$). Clinical characteristics of patients before transplantation who were treated with PD are summarized in Table 1. Ferritin and CRP (C-reactive protein) levels were higher in the EPS (+) group. The other laboratory findings were similar in both groups (Table 2). Icodextrin-based PD regimens were more used in PD patients (91.7%) who developed EPS after transplantation ($P = .037$). A tacrolimus, mycophenolate mofetil, and prednisolone regimen was used in 60% of EPS (+) patients and in 58.3% of EPS (−) patients. A cyclosporine-based regimen was used in 31.4% of the EPS (+) patients and in 16.7% of the EPS (−) patients. There was no significant difference between treatment regimens in both groups ($P = .058$).

There were more transplantations from deceased donors in EPS (+) patients (83.3%; $P = .024$). HLA matching was 1.5 (range, 1–3) and was lower in EPS (+) patients ($P = .006$; Table 3). Recurrent hospitalization was 16.7% according to recurrent episodes of ileus and nutritional problems. Twenty-five percent of our EPS (+) patients were supported with parenteral feeding. Survival of patients, graft loss, and functioned graft after transplantation were similar in both groups (Table 4). One recipient died due to malnutrition and sepsis in the EPS (+) group with a functioning graft. Two of the recipients in the EPS (−) group died because of systemic infection and one died due to a cardiovascular cause (myocardial infarction). The causes of graft loss were insufficient immunosuppressive therapy and recurrent peritonitis attacks in the EPS (+) group. Recurrence of primary disease and uncontrolled patients were the main causes of graft loss in the EPS (−) group.

Table 3. Transplantation Features

Variable	EPS (+) Group n = 12	EPS (−) Group n = 35	*P*
Type of donor, cadaveric/living	10/2	16/19	.024
CIT, h	12 (2–16)	5 (1–15)	.137
HLA matching, n	1.5 (1–3)	3 (1–4)	.006
DGF, n (%)	1 (8.3)	3 (8.6)	1.0
Acute rejection, n (%)	4 (33.4)	4 (11.4)	.176

Abbreviations: CIT, cold ischemia time; HLA, human leukocyte antigen; DGF, delayed graft function.

We used tamoxifen (20 mg/d) and prednisolone (0.3–0.5 mg/kg) tapered to a maintenance dose of 5 mg/d in our patients who were diagnosed with EPS after transplantation. Drug levels were adjusted and minimized according to 3–5 ng/mL (C_0) for tacrolimus and 50–75 ng/mL (C_0) for cyclosporine A in 75% of patients diagnosed with EPS. MMF was discontinued in all of our EPS patients. Immunosuppressive therapy was changed to an everolimus-based regimens in 3 patients after clinical suspicion of EPS before the diagnosis. Acute rejection rate was 33.4% in our EPS patients (4 patients) after transplantation. All of them were treated with anti-thymocyte globulin (ATG) and high-dose steroid (250–500 mg/d, 3 days). Two of them (16.7%) had graft loss. One of them (8.3%) died despite all treatment. Our patients with EPS were not treated with surgery. Using multivariate analysis, the length of time on PD and ferritin levels increased development of EPS 1.08-fold ($P = .036$; 95% confidence interval [CI], 1.01–1.17) and 1.01-fold ($P = .049$; 95% CI, 1–1.01), respectively.

DISCUSSION

EPS is a rare but serious complication in patients who were treated with PD. The prevalence of EPS after kidney

Table 4. Graft and Patient Features

Variable	EPS (+) Group n = 12	EPS (−) Group n = 35	*P*
Loss of patient, n (%)	1 (8.3)	3 (8.6)	.628
Graft loss, n (%)	2 (16.7)	4 (11.4)	.155
Functional graft, n (%)	9 (75)	28 (80)	.346

transplantation is reported to be between 1% and 3%. The incidence of EPS in 5th and 8th years varies from 6.4% and 19.4%, respectively, in Australia to 2.1% and 5.9%, respectively, in Japan. EPS could be diagnosed using peritoneal biopsies and clinical, radiological, and laboratory outcomes [8]. EPS seems to occur shortly after kidney transplantation in former PD patients. A Scottish study showed that the contribution of post-transplantation EPS might be even as much as 50% of the total EPS patients [7]. As our study described, EPS was seen in 25.5% of PD patients after transplantation. The rate was similar with other studies.

EPS causes death due to infections and cardiovascular events. EPS was identified as the fourth known cause of death after kidney transplantation and was associated with a decreased survival in these patients. The mortality rate was reported to be around 50% within 12 months of the diagnosis. Graft function was no different in EPS patients after transplantation [5,6,10,11]. Our study showed that there was no difference in mortality rates and graft function between EPS (+) and (−) groups after kidney transplantation. Graft loss and death were independent from EPS in our study.

The episodes of peritonitis, high-glucose concentration in PD solutions and icodextrin- based PD regimens, length of time on PD therapy, and high or high-moderate transport in PET aid the development of EPS [12,13]. Nakao et al [11] reported a large study in which episodes of peritonitis in about 50 months increased the risk of EPS 7.55-fold and biocompatible fluids (containing icodextrin) affected the development of EPS. Habib et al [12] identified EPS more in patients who used icodextrin-based PD solutions (>80%). Some studies reported that EPS was rarely seen in patients who were on PD <3 years. EPS was more often seen after 5 years from transplantation [6,14–16]. In our study, EPS was more detected after 6 years and in PD patients who used icodextrin-based fluids.

The use of CNIs as a part of immunosuppressive regimens also increased the risk of EPS. The CNIs can lead to enhanced expression of transforming growth factor-β (TGF-β), demonstrated in a preconditioned peritoneal membrane, which already demonstrated up-regulation of TGF-β. This results in increased fibrosis and neoangiogenesis on the peritoneal membrane [17]. In our study, there was no difference between immunosuppressive regimens.

Medical therapy and surgery are treatment options in EPS. Changing CNIs with mTORi, reducing CNIs to initial dose, steroids, tamoxifen, and discontinuing MMF are medical treatment options. The effects of medical treatment are TGF-β production, which is stimulated by tamoxifen and might favor mesothelial healing by facilitating the removal of denaturated collagen and stopping the profibrotic influence (facilitated by CNIs) and inflammation. Some studies showed that tamoxifen (20 mg twice a day) with included steroids was useful for EPS and decreased EPS symptoms [18,19]. Messina et al [20] reported that mTORi prevented EPS development after transplantation in 1 patient. In our study all recipients diagnosed with EPS received tamoxifen. Two of 12 (16.7%) had graft loss and 1 died (8.3%). Although immunosuppressive treatments were switched to mTORi-based regimens in EPS recipients, no preventive effect was observed associated with mTORi. We need more studies about the protective effects of mTORi in EPS. Adhesiolysis, peritonectomy and enterolysis, and ileostomy procedures are the surgical approaches for EPS. The complication and mortality rates are high in surgical treatment. Surgery must only be applied in specific centers by specialized surgeons because of high mortality rates. Several approaches are used for EPS patients but mortality rates remain at about 50% despite all of these treatments [6–8].

There were no studies about comparing transplantation features (donor type, HLA matching, and so on) in recipients with EPS who were on PD before transplantation. Our study was the first one that reviewed these findings. Deceased donors and less HLA matching were risk factors for EPS in our study. These findings should be supported by larger studies. Our study showed that long PD vintage and high-glucose solutions affect the development of EPS and these findings were compatible with other studies. The risk of EPS increases after 5 years of PD treatment. We thought that high ferritin levels reflect the ongoing inflammation and automatically correlate with EPS in our study.

However, there are several limitations about the present study. First and the most important one is the absence of peritoneal biopsy. Second, this is a retrospective observational study and prospective, long-term studies could be useful to solve and understand this deleterious process among recipients.

Patients on PD must be evaluated closely and informed about the complications of PD before transplantation. We need more data about the effect of transplantation features in EPS and treatment options. In conclusion, EPS is one of the devastating complications of PD that has deleterious effects in recipients, such as high morbidity and mortality rates and risk of death with a functioning graft. It seems logical to avoid high-glucose solutions in PD patients and to think again carefully for transplantation in candidates with long PD vintage.

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