Encapsulating Peritoneal Sclerosis

A study on pathophysiology, clinical aspects and management

Meelad Habib

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Encapsulating Peritoneal Sclerosis

A study on pathophysiology, clinical aspects and management

Encapsulating peritoneal sclerosis

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تقدیم به دو بزرگوارزنده گی ام
والدین عزیزام

Dedicated to my beloved parents

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Chapter 1

General introduction

INTRODUCTION

The kidneys are essential life sustaining organs as they remove potential toxic water soluble waste products, called uremic toxins, and excessive fluid from the body. Chronic kidney disease (CKD) leading to a loss of kidney function over time is an increasing worldwide public health concern.[1,2] Common risk factors of CKD include diabetes mellitus, hypertension, and glomerulonephritis.[1] Patients with CKD progressing to end-stage renal disease (ESRD) are in need of medical support. Kidney transplantation is the optimal treatment option improving the quality of life of these patients and extending survival.[3] Unfortunately, not all patients with ESRD will undergo a transplantation due to the limited availability of donor kidneys and/or medical contraindications. For these patients, renal replacement therapy (RRT) by dialysis is the therapeutic option of choice. The two major and well-known types of dialysis include hemodialysis (HD) and peritoneal dialysis (PD).[4]

PERITONEAL DIALYSIS

Continuous ambulatory peritoneal dialysis (CAPD) was introduced in 1976 by Robert Popovich and Jack Moncrief as a renal replacement therapy modality.[5] In 2008, approximately 196,000 patients worldwide were on PD, representing 11% of all patients treated with dialysis.[6] In PD, the peritoneal membrane is used as a natural filter via which the exchange of excess water and solutes from the peritoneal blood capillaries into the dialysis solution is accomplished. The peritoneum is divided into the visceral and the parietal peritoneum.[7] The parietal peritoneum lines the wall of the abdominal cavity and the pelvic cavity. The visceral peritoneum covers the inner surface of the abdominal cavity and the external surface of the abdominal organs. The peritoneum is a delicate semipermeable membrane that consists of a monolayer of mesothelial cells covering the interstitial tissue. The submesothelial layer contains connective tissue fibers, fibroblasts, lymphatic vessels, and numerous essential capillaries.[8]

During PD, a sterile and hyperosmolar dialysis solution is introduced inside the peritoneal cavity through an intraperitoneal catheter. During a typical CAPD scheme, the total volume of dialysis fluid (dwell) is left in the abdomen for 4-6 hours and afterwards replaced with fresh dialysis fluid. An important element of dialysis fluids includes glucose, resulting in an osmotic gradient and enabling ultrafiltration.[7] During each PD cycle, transport of solutes and water from the peritoneal capillaries into the dialysate occurs through the processes of diffusion and convection.[9,10] In CAPD, the process of dialysis fluid exchange is at least repeated four times throughout the day, seven days a week. This makes PD a therapy that filters the blood continuously, similar to a healthy kidney, in contrast with conventional HD, which filters the blood usually three times[11] a week.

A major benefit of PD includes the possibility for patients to dialyze at home or at work. This results in greater flexibility in lifestyle activities, as patients do not need to visit the dialysis centers for treatment regularly. Several studies have also reported a higher rate of satisfaction in PD as compared to HD patients.[12,13] Other benefits associated with PD as compared to HD include the greater preservation of residual renal function, the needle-free treatment sessions, preservation of vascular access, lower costs, and less dietary restrictions.[14] Studies in the past have also reported a survival advantage on PD as compared to HD, at least after the first two years of dialysis onset.[14,15] However, the results of studies on this topic are contradictory and different in subgroups of patients with regard to age or other co-morbidities, such as diabetes.[16,17] Furthermore, studies also exist reporting equivalent outcomes between PD and HD patients.[17,18]

Many developments have occurred in the past decades, advancing both our knowledge and the clinical practice of PD. Some of these include the laparoscopic PD catheter insertion technique, the usage of automated peritoneal dialysis (APD), the introduction of the flush before fill Y-system, and the development of "biocompatible" PD solutions.[19]

A major element of conventional dialysis solutions is a high glucose content serving as an osmotic agent. Alongside with other elements such as lactate, the low pH, and formation of glucose degradation products (GDP's) after heat sterilization, the PD solutions are considered bio-incompatible and therefore may have damaging effects on the peritoneal membrane.[20] The bio-incompatibility of the conventional dialysis solutions causes morphological changes of the peritoneal membrane. Important changes include loss of peritoneal mesothelial cells, epithelial to mesenchymal transdifferentiation, submesothelial fibrosis, and an increase in the number of peritoneal blood vessels resulting in ultrafiltration problems.[21,22] In recent years, more biocompatible dialysis solutions with neutral pH and lower levels of glucose and GDP's have been developed and found their way into clinical practice. Furthermore, alternative osmotic agents such as amino acids and glucosepolymers are also included in some of the biocompatible solutions.[23] With respect to the latter one, icodextrin was introduced in dialysis solutions instead of glucose with the advantage of maintaining an ultrafiltration gradient for a prolonged period of time. This has particularly been proven to be useful in patients developing ultrafiltration failure.[24] Although a large variability exists in the current literature, several clinically relevant benefits after the use of the biocompatible dialysis solutions have been reported. These benefits include a better peritoneal membrane function, less therapy failure, and less alterations of the peritoneal membrane with the use of the new solutions.[23,25] In the balANZ trial, which was an open-label randomized controlled trial, 185 adult PD patients were assigned to use either a biocompatible or a conventional dialysis solution for 2 years.[26] In this study, use of a biocompatible dialysis solution was not associated with preservation of renal function in patients as compared with the use of a conventional dialysis solution. However, as part of the secondary outcomes of interest,

the investigators reported a reduced incidence of peritonitis and a longer time until onset of anuria in patients who were treated with the biocompatible solution as compared to patients who were on a conventional dialysis solution during PD.

But despite many remarkable advances in the field of PD, a decline in the proportion of dialysis patients that are treated with PD as renal replacement therapy has been observed in previous years. This decreasing trend especially seems to be an ongoing issue in developed countries, such as the Netherlands.[6,27] Whereas 30.4% of dialysis patients were on PD in 2000, 25.6% in 2005, only 15.8% of dialysis patients in the Netherlands were on PD in 2012 (www.renine.nl). There is not an obvious or single reason for this decline, and many possible factors have been suggested. The major factors include the increase in the use of HD in the ageing ESRD patient population, the relative increase of kidney transplantations as RRT, and economic influences including physician reimbursement.[6,27] A rare, but feared complication of PD that has also been pointed out as a barrier to the implementation of (long-term) PD therapy is encapsulating peritoneal sclerosis (EPS).[28,29]

ENCAPSULATING PERITONEAL SCLEROSIS (EPS)

Definition, epidemiology and pathophysiology of EPS

Encapsulating peritoneal sclerosis (EPS) is a severe complication of PD (Figure 1). One of the first descriptions of EPS in patients with a history of PD dates back to the early eighties. In 1980, Ghandi *et al.*[30] published a paper on an abnormality looking like " a layer of icing on a cake" in five patients receiving PD treatment. During surgical exploration, a thickened and sclerotic peritoneal surface accompanied by adhesions between the bowel loops was observed**.** However, the macroscopic findings of EPS are not only limited to PD patients who may develop this entity. In 1978, Foo *et al.*[31] introduced the term "abdominal cocoon" which parallels EPS with regard to the macroscopic findings and clinical presentation. Similar to EPS, the intestinal obstruction in patients with abdominal cocoon is reported to be secondary to encapsulation of the bowels by a fibrotic and thick membrane. However, the differentiation of EPS and abdominal cocoon seems to be on the basis of etiology. Abdominal cocoon has been described as a rare idiopathic condition, described in adolescent girls from the tropical and subtropical countries while EPS is associated with a variety of other factors of which PD treatment is a well-reported one.[32,33]

Numerous definitions have been offered and used in the literature to describe EPS including sclerosing peritonitis[34], sclerosing obstructive peritonitis[35], sclerosing encapsulating peritonitis[36], and progressive calcifying peritonitis[37]. In particular, encapsulating peritoneal sclerosis (EPS) is currently a common nomenclature that is used in the nephrology literature and also

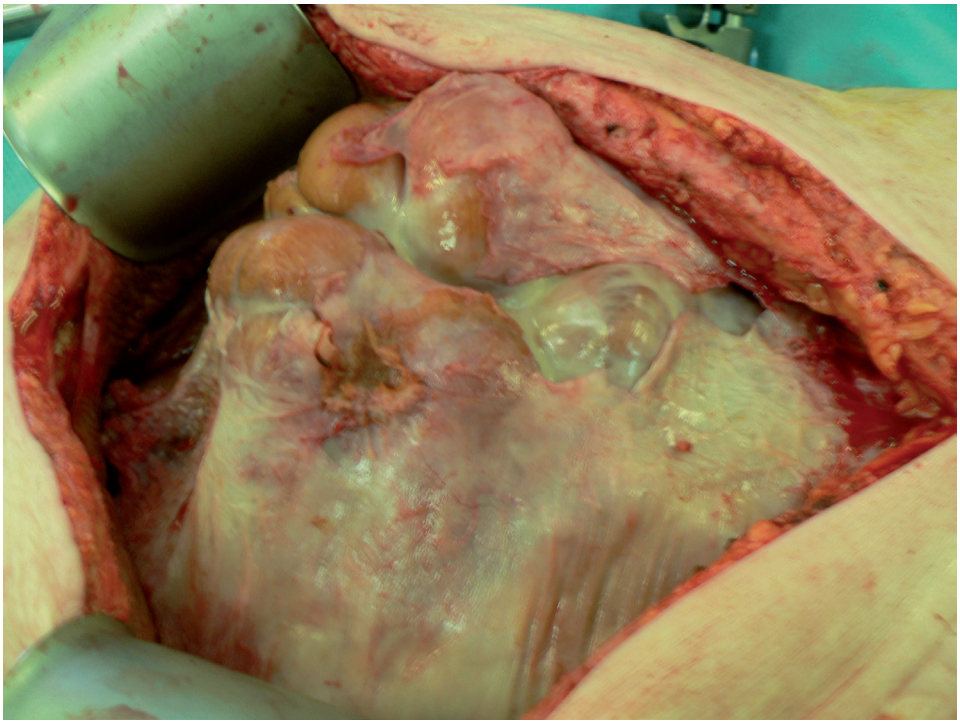

Figure 1. Macroscopic appearance of EPS.
At laparatomy, there is a fibrotic and cocoon-like membrane covering the bowels.

recommended by the Ad Hoc Committee of the International Society of Peritoneal Dialysis (ISPD).[38]

The estimates around the epidemiology of EPS vary widely around the world. However, EPS is recognized as a rare condition with a prevalence ranging between 0.7% and 3.7%.[39] Most reports on the topic of EPS are from Asian countries, such as Japan where transplantation rates are low and dialysis patients are on PD for a long time.[40] However, in the last decade, EPS has also gained growing interest from European countries resulting in the establishment of several EPS registries. The Dutch EPS registry has been designed in 2009 as a web-based database and has been extended to a European EPS registry since 2011.[29,41] An important goal of this registry is to achieve a greater understanding of EPS and extend the knowledge with regard to its epidemiology, pathophysiology, and management.

Although a large number of factors have been implicated in the development of EPS, a major and consistently reported risk factor includes long-term PD therapy.[42,43] During the first years on PD, the risk of EPS seems to be low. However, the risk of developing EPS increases after 3-4

years on PD.[39] Additional risk factors contributing to the development of EPS in patients with a history of PD include age at start of PD, the number of peritonitis episodes, a high transporter membrane state, and kidney transplantation.[43,44] The primary underlying pathophysiological mechanisms of EPS are yet not fully understood. Developmental pathways have been studied in several animal models of EPS that were based on intraperitoneal administration of chemical irritants such as chlorhexidine gluconate.[45] But although the macroscopic and microscopic findings in these animal models may correlate well with EPS, no firm conclusions can be drawn on the clinical relevance of these models. In recent years, several theories of EPS pathophysiology have been proposed with the two-hit theory of Kawanishi being the generally accepted one.[46,47] This two-hit theory is centered around two "hits" that are at least required for the onset of EPS (Figure 2). According to the two-hit theory, the damaging effects of long-term PD on the peritoneal membrane serve as a first hit, increasing a patient's risk of EPS. In addition to the first hit that preconditions the peritoneal membrane, a second hit is considered to be an important requirement for triggering inflammation and the excessive fibrosis of the peritoneal membrane. The proposed second hits are infections (e.g. peritonitis), medication (e.g. calcineurin inhibitors), genetic factors (e.g. Alport syndrome), or cessation of PD.[46,48,49] Particularly, the latter seems to be important as a majority of EPS patients are diagnosed after discontinuing PD treatment, e.g. after switching to HD or undergoing kidney transplantation.[43,50,51]

EPS following kidney transplantation, known as post-transplantation EPS, has gained attention in recent years. Previously, a study from the Netherlands reported an increase in the number of observed EPS cases manifesting after kidney transplantation in the years 2004 and 2005 in two university hospitals.[52] This clinical presentation of EPS tends to appear in former PD patients shortly after undergoing a successful kidney transplantation.[53-60] Currently, the exact mechanisms for the development of EPS after cessation of PD are not completely elucidated. However, an increased expression of pro-fibrotic, angiogenic, and inflammatory mediators due to the lack of peritoneal lavage, resulting in EPS manifestation are suggested as a possible explanation.[48,61] Numerous profibrotic and angiogenic mediators are important in the development of EPS. Transforming growth factor beta (TGF-β) is considered as an essential pro-fibrotic protein in the molecular basis of both EPS and several other fibrotic diseases.[62,63] Prolonged exposure to the bio-incompatible elements of dialysis fluids, such as glucose is an important factor stimulating the production of TGF-β.[64] Expression of TGF-β in turn appears to initiate peritoneal damage and eventually the formation of peritoneal fibrosis.[65,66] Liu *et al.*[67] have previously shown the importance of prolonged TGF-β expression as a contributing factor in EPS. By injecting mice with a helper-dependent adenovirus vector that expresses active TGF-β, the investigators have in their animal model shown the development of EPS like changes of the peritoneal membrane and encapsulation of the bowels. In addition to fibrotic changes, vascular changes of the peritoneal membrane are also a hallmark of EPS pathology. Vascular endothelial growth factor (VEGF) has

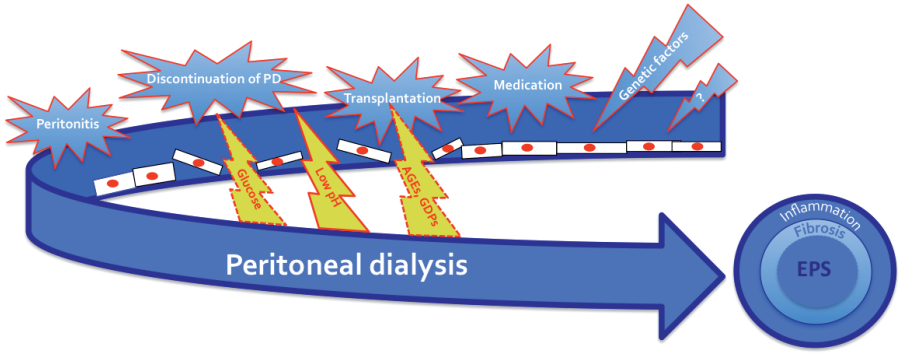

Figure 2. A schematic presentation of the two-hit theory of EPS. The first hit is represented by the damaging effects of long-term PD on the peritoneal membrane. The second hit can be an inflammatory stimulus (e.g. peritonitis), discontinuation of PD, kidney transplantation, medication (e.g. calcineurin inhibitors), or genetic factors. Additional, yet unknown second hits, may also exist.

been implicated as a key molecule via its effect on new vessel formation.[68] Some additional relevant factors that are proposed in the literature for EPS development include connective tissue growth factor (CTGF) and platelet derived growth factor (PDGF).[69]

Clinical spectrum and diagnosis of EPS

The clinical spectrum of EPS is nonspecific. Due to the insidious onset of EPS, most patients are diagnosed in the advanced stages of the disease. Patients commonly present with varying signs and symptoms of bowel obstruction such as abdominal pain, abdominal fullness, nausea, and vomiting. A decreased nutritional status and weight loss are additional important elements because patients have a poor appetite and difficulty with taking solid foods.[39,70] Japanese investigators have categorized the clinical course of EPS into four stages; (1) pre-EPS period, (2) inflammatory period, (3) encapsulating period, and (4) ileus stage (Table 1).[70] The pre-EPS period is characterized by a loss in ultrafiltration capacity, the development of an altered solute transport status, (bloody) dialysate and/or ascites. During the inflammatory stage, manifestations of inflammation, such as fever, increased levels of C-reactive protein (CRP), and bloody ascites may be present. The inflammatory stage is followed by a progressive encapsulating stage that is mainly characterized by the appearance of symptoms related to intestinal obstruction. Finally, the ileus stage may occur and is characterized by bowel obstruction and the presence of a palpable abdominal mass at physical examination. Additionally, inflammatory findings and changes in effluent markers are important to consider in the diagnostic work-up. Sampimon *et al.*[71] have

Table 1. Proposed clinical stages of EPS.

Stage	Clinical characteristics
(1) Pre-EPS period	Loss of ultrafiltration capacity
	Fast transporter status
	(Bloody) dialysate, ascites
(2) Inflammation period	Loss of appetite, weight loss
	Diarrhea
	Fever
	Increase in C-reactive protein levels
	Leukocytosis
	Ascites
(3) Progressive or encapsulating period	Disappearance of signs of inflammation
	Appearance of symptoms/signs of ileus
	(nausea, vomiting, abdominal pain, obstipation)
(4) Ileus period	Anorexia
	Complete ileus
	Abdominal mass

Adapted from Korte *et al.*[68] and Nakamoto *et al.*[69]

focused on investigating early diagnostic markers for EPS and reported on the potential use of effluent cancer antigen-125 (CA-125) and interleukin-6 (IL-6) as possible diagnostic markers for EPS. Especially in combination with the presence of ultrafiltration failure, the appearance rate of CA-125 and IL-6 in their study had a sensitivity of 70% and specificity of 100% for the development of EPS.

Getting an accurate clinical diagnosis of EPS can be difficult, however, abdominal imaging is important in confirming a pre-operative diagnosis. There are reports on the use of ultrasonography or magnetic resonance imaging (MRI) as diagnostic imaging modalities for EPS.[72] However, the abdominal computed tomography (CT) scan is the most frequent used and well-reported imaging modality visualizing several changes specific for EPS, such as peritoneal thickening, peritoneal calcifications, and loculated ascites. Other findings may be bowel wall thickening, bowel tethering, or bowel dilatation.[73] In the past, two large studies have been performed emphasizing the benefits of the CT scan as the diagnostic modality of choice in patients who are suspected of having EPS.[73,74] However, there is also a study reporting a lack of the diagnostic ability of the CT scan in asymptomatic patients in the months prior to the diagnosis of EPS.[75] Furthermore, the CT scan in EPS might be operator dependent and reported to be reviewed differently by radiologists who are experienced with PD and EPS as compared to the radiologist without PD experience.[74]

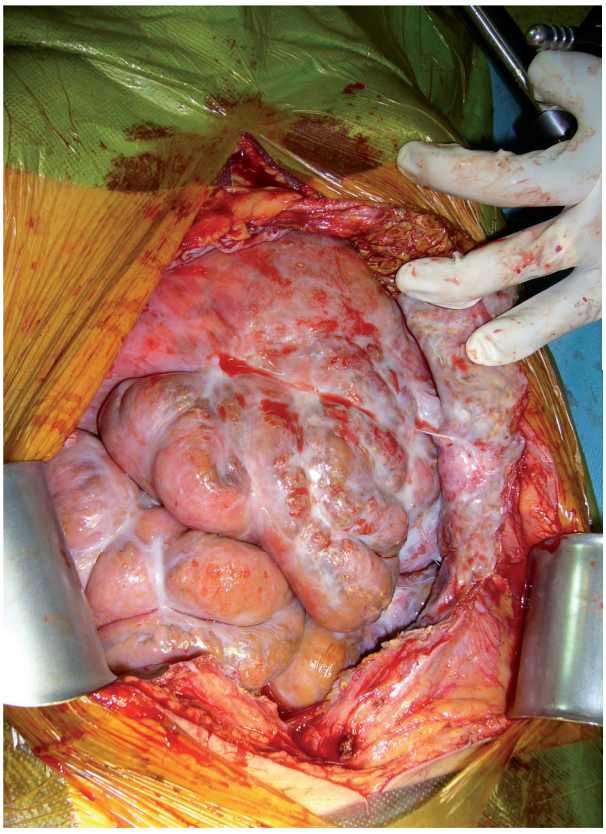

Figure 3. Macroscopic appearance of EPS at laparotomy. The pictures of EPS in this chapter are kindly provided by Dr. T. Augustine (Surgeon, referral center for EPS surgery, Manchester Royal Infirmary, United Kingdom).

Whenever the clinical diagnosis of EPS is unclear, it is essential to consider exploratory surgery to confirm or exclude a diagnosis of EPS. The macroscopic appearance of EPS is characterized by a fibrotic, adhesive, and cocoon-like membrane encasing the bowels (Figure 1 and Figure 3). The extent of the process and the macroscopic appearance, however, may vary in patients.[76,77] Although surgical exploration for diagnostic purposes may be hazardous in some cases, it has additional benefits, such as offering the possibility to provide surgical treatment or to obtain peritoneal biopsies**.** There are several differences between the morphology of peritoneal biopsies of EPS patients as compared to PD patients without EPS. In a recent study, Braun *et al.*[78] aimed to define standardized histological criteria for EPS. Histological predictors for EPS in this study were reported to be mesothelial denudation, calcifications, acellular areas, fibrin deposits, positive staining for vascular or avascular podoplanin, and the presence of fibroblast like cells. A study by Garosi *et al.*[79] have also added on vasculopathy and the presence of inflammation as significant findings in EPS.

Management of EPS

Unfortunately, due to the rarity of EPS disease, no randomized controlled trials have been performed until now in order to guide treatment. As a result, there are currently no widely accepted pharmacological options for the treatment of EPS. EPS is, however, not an incurable disease as Kawanishi reported.[80] A large number of published case reports, case series, and observational studies have in recent years highlighted the value of parenteral nutrition and several drugs in the management of EPS. Although the successful use of immunosuppressive medication in the management of EPS was indicated earlier[81], Mori *et al.*[82] in 1997 were one of the first who reported a case of EPS who responded to monotherapy with a corticosteroid (prednisolone). Since then, several other reports have followed and in the same year, corticosteroids were also launched as first line drugs for EPS in Japan.[83] Steroids are especially reported to be of value in the early stages of EPS.[59,84] The benefit of steroids in the management of EPS is thought to be due the immunosuppressive effects of these drugs on the inflammatory state of EPS patients.[53,59,80]

Tamoxifen on the other hand is an anti-estrogenic drug that is clinically used in the management of patients with estrogen positive breast cancer.[85] However, studies have also shown the benefits and value of tamoxifen in the management of several fibrotic disorders[86,87], including EPS[88-90]. In particular for the treatment of retroperitoneal fibrosis (RPF), which is characterized by the development of a fibrotic tissue in the retroperitoneum, tamoxifen has been reported to be an effective and safe treatment option.[91] In patients with RPF, tamoxifen seems to reduce symptoms, lower the level of inflammatory markers, and result in fibrotic mass reduction.[91,92] Since the recovery of one of the first female EPS patients on tamoxifen therapy in 1999[93], who showed a reduction of peritoneal thickness on the CT scan, several others have reported their experience with tamoxifen therapy in EPS.[89,94-96] The exact pathways by which tamoxifen acts is not completely understood, however, it has been proposed to be mainly related to the ability of tamoxifen to balance the release of TGF-β.[62,97] Reported effects of tamoxifen in EPS patients include improvement in symptoms, reduction in the level of CRP, changes in peritoneal thickness and prolonged survival.[89,90,98] Although the risk of severe adverse effects after tamoxifen therapy is rare, thrombotic events[90,96] and endometrial carcinoma[95] have been described in the literature. Some other adverse effects of tamoxifen described in EPS cases include thrombopenia[98] and calciphylaxis[99].

Surgery is the final and an essential therapeutic option in EPS. Peritonectomy and enterolysis (PEEL) are the commonly used surgical techniques and include resection of the EPS membrane off the bowels and separation of the adhesions by repetitive lysis.[100,101] Most reports on the benefits of EPS surgery are from Japan, where successful surgical outcomes have been reported due to advances in surgical techniques and EPS referral centers.[46,102,103] Also in Europe, the surgical experience has progressed and has led to the establishment of well-known EPS surgical referral centers in the United Kingdom (Manchester and Cambridge) and Germany (Stuttgart).[61,100]

CONCLUDING REMARKS

Despite improvements in our current understanding of EPS, there are several aspects of the disease, particularly in clinical practice, which need more clarification. The role and presence of systemic and local inflammation in EPS for example needs to be investigated in more detail in order to improve our understanding of the mechanisms and cells involved in the development of EPS. Furthermore, the presentation of EPS after cessation of PD has gained interest in recent years. In this respect, the clinical and pathophysiological aspects of post-transplantation EPS have not been studied in detail yet. Currently, the prognosis of EPS is still poor and patients are diagnosed in the late stages of the disease. This can be partly attributed to a lack of both diagnostic tools and therapeutic options. However, in some cases, clinician's delay in recognizing the clinical spectrum of EPS may also be an important factor. Specifically, there are no recommendations for the diagnosis and management of EPS in the Netherlands directed at nephrologists who may encounter these patients and deal with them in clinical practice. In this thesis, these clinically significant topics are addressed by clinical and basic science studies.

EPS

Chapter 1.1

Aim and outline of the thesis

AIM AND OUTLINE OF THE THESIS

The principle **aim of this thesis** is to expand the current knowledge of EPS by providing novel insights into its pathophysiology, clinical aspects, and management. An important part of the thesis is focused on a more recently described entity, post-transplantation EPS.

In **chapter 1**, a general introduction on the topic, the aim, and outline of the thesis are given. The macroscopic appearance of EPS is characterized by a fibrotic sheet covering and compressing the bowel loops. Many EPS patients present with signs and symptoms related to inflammation and bowel obstruction. For several years, a major role of inflammation in the pathogenesis of EPS has been implicated. However, little is known about the presence of local inflammation and the specific nature of the inflammatory process in the peritoneal membrane of patients with EPS. In the study described in **chapter 2,** we focus on the peritoneal inflammatory process and aim to characterize the inflammatory cells, in particular T cell and macrophage subsets, in the peritoneal membrane of patients with EPS. Importantly, the findings in the peritoneal membrane of EPS patients are compared to those in the peritoneal membrane of PD patients without EPS. In addition, we investigate whether the composition of the cell infiltrate is related to clinical outcome of EPS patients.

A majority of EPS patients have a poor overall clinical outcome with a high morbidity and mortality. Although EPS is recognized as a complication of PD, a considerable proportion of EPS patients present after undergoing kidney transplantation. EPS occurring after kidney transplantation (post-transplantation EPS) has emerged in recent years as a novel presentation of EPS, as opposed to EPS diagnosed in patients without having received a kidney transplantation that are or have been treated with PD therapy (classical EPS). In chapter 3, 4, and 5, several aspects of post-transplantation EPS are outlined.

Chapter 3 delineates the clinical course of post-transplantation EPS in more detail. The study described in this chapter explores the possible differences between post-transplantation EPS and classical EPS with regard to clinical presentation, baseline CT scan findings, and outcome of patients. Additionally, the systemic inflammatory response has been documented in both post-transplantation and classical EPS patients in the year before, at the time of, and in the year after the diagnosis of EPS.

In **chapter 4** we hypothesize that post-transplantation EPS may have a possible contribution to mortality after kidney transplantation. By using the RENINE (Registratie Nierfunctievervanging Nederland) and nationwide transplantation database, we have performed a multicenter retrospective study to investigate the impact of post-transplantation EPS on mortality of transplanted PD patients in the Netherlands in the period 1996-2007.

Chapter 5 is devoted to an unusual clinical presentation of post-transplantation EPS that can be encountered in clinical transplantation practice. In this case study, we also discuss the benefits of surgery in the diagnosis and management of EPS.

The CT scan is currently considered as an important radiologic tool in the diagnosis of EPS. However, it may not always be conclusive. In some cases, surgical exploration may be necessary to allow an early identification and definite diagnosis of EPS. During surgical exploration, which may include a diagnostic laparoscopy or laparotomy, encapsulation of the bowels by a fibrotic membrane and adhesion between the bowel loops can be observed. However, some patients may have localized involvement of the bowel and local encapsulation in the abdominal cavity. Therefore, in **chapter 6**, we performed a single-center retrospective study, including all EPS patients who were referred for a diagnostic laparotomy over a 9-year period, with the objective to investigate and report on patients with localized EPS.

In **chapter 7**, a consensus guideline for clinical practice in the Netherlands has been developed regarding both diagnosis and management of EPS. The recommendations were based on the results of a review of the published literature on the topic of EPS and were extended with the experience of the members of the steering committee of the EPS registry.

In **chapter 8**, the main findings of the studies described in this thesis are summarized and discussed. Moreover, conclusions following from this thesis are provided. In **chapter 9**, recommendations for future research on the topic of EPS are outlined. **Chapter 10** includes the summary and general discussion of the thesis in Dutch.

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EPS

Chapter 2

CD4-positive T cells and M2 macrophages dominate the peritoneal infiltrate of patients with encapsulating peritoneal sclerosis

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ABSTRACT

Background

Encapsulating peritoneal sclerosis (EPS) is a severe complication of peritoneal dialysis (PD). Previously, it has been shown that infiltrating CD4-positive T cells and M2 macrophages are associated with several fibrotic conditions. Therefore, the characteristics of the peritoneal cell infiltrate in EPS may be of interest to understand EPS pathogenesis. In this study, we aim to elucidate the composition of the peritoneal cell infiltrate in EPS patients and relate the findings to clinical outcome.

Study design, setting, and participants

We studied peritoneal membrane biopsies of 23 EPS patients and compared them to biopsies of 15 PD patients without EPS. The cellular infiltrate was characterized by immunohistochemistry to detect T cells(CD3-positive), CD4-positive (CD4+) and CD8-positive T cell subsets, B cells(CD20-positive), granulocytes(CD15-positive), macrophages(CD68-positive), M1(CD80-positive), and M2(CD163-positive) macrophages. Tissues were analysed using digital image analysis. Kaplan-Meier survival analysis was performed to investigate the survival in the different staining groups.

Results

The cellular infiltrate in EPS biopsies was dominated by mononuclear cells. For both CD3 and CD68, the median percentage of area stained was higher in biopsies of EPS as opposed to non-EPS patients ($p < 0.001$). EPS biopsies showed a higher percentage of area stained for CD4 (1.29%(0.61-3.20)) compared to CD8 (0.71%(0.46-1.01), $p = 0.04$), while in the non-EPS group these cells were almost equally represented (respectively 0.28%(0.05-0.83) versus 0.22%(0.17-0.43), $p = 0.97$). The percentage of area stained for both CD80 and CD163 was higher in EPS than in non-EPS biopsies ($p < 0.001$), with CD163+ cells being the most abundant phenotype. Virtually no CD20-positive and CD15-positive cells were present in biopsies of a subgroup of EPS patients. No relation was found between the composition of the mononuclear cell infiltrate and clinical outcome.

Conclusions

A characteristic mononuclear cell infiltrate consisting of CD4+ and CD163+ cells dominates the peritoneum of EPS patients. These findings suggest a prominent role for both CD4+ T cells and M2 macrophages in the pathogenesis of EPS.

INTRODUCTION

Encapsulating peritoneal sclerosis (EPS) is a rare and severe complication of peritoneal dialysis (PD).[1,2] EPS is characterized by fibrotic and sclerotic thickening of the peritoneal membrane (PM), covering and constricting the intestines.[3-5] Although an interplay between chemical irritation of the PM, chronic inflammation, and excessive extracellular matrix deposition may be important, the exact pathogenesis of EPS remains poorly understood.[6,7] Early studies have provided evidence to the hypothesis that inflammation precedes the development of EPS[8,9], offering a window of opportunity to use immunosuppressive therapy in the management of these patients. Declining cancer antigen 125 effluent concentrations (reflecting loss of mesothelial cell mass) and increasing effluent interleukin-6 concentrations have also been linked to EPS development.[10] Recently, increasing C-reactive protein levels have been reported in the months preceding the diagnosis of EPS, with a maximum at time of clinical diagnosis.[9] These findings indicate the presence of an inflammatory response at the level of the PM, which in turn may drive the progression to excessive fibrotic tissue formation characteristic for EPS.

Although it has been suggested that mononuclear immune cell infiltration is an important hallmark of EPS pathology[11,12], the peritoneal inflammatory cell population in EPS has been poorly defined. This is relevant, as several studies have shown the importance of T cells in regulating inflammatory host responses in fibrotic tissue disorders such as pulmonary fibrosis[13], systemic sclerosis[14], and hepatic fibrosis[15]. In an experimental model, Chung *et al.*[16] have reported an increase of activated T cells homing to the peritoneal cavity shortly after peritoneal injury and proposed a central role for CD4 positive (CD4+) T cells in peritoneal adhesion formation. Furthermore, macrophages are believed to be key cells linking inflammation and fibrosis. Macrophages can be divided into the pro-inflammatory M1 or pro-fibrotic M2 phenotype.[17] Particularly, M2 macrophages have gained interest in recent years as main regulators of fibrosis through secretion of pro-fibrotic mediators and subsequent activation of collagen producing cells.[18]

The main objective of the present study was to characterize the inflammatory cells, in particular T cell and macrophage subsets, in the PM of patients with established EPS in comparison to PD patients without EPS. In addition, we investigated whether the composition of the cell infiltrate was related to clinical outcome of patients.

METHODS

Study population

We studied PM biopsies of 23 EPS patients and compared them with biopsies of a reference group that consisted of 15 patients who were on PD, but had no EPS (non-EPS). The PM biopsies of EPS patients were obtained during abdominal surgery for diagnostic purposes. All biopsies were collected from the participating centers and stored in the bio-bank of the Dutch EPS registry.[19] PM biopsies in the non-EPS group were performed in PD patients prior to kidney transplantation procedure at the University Medical Center Utrecht, Utrecht, The Netherlands. Patients who had peritoneal infections at time of PM biopsy were excluded from further study.

The diagnosis of EPS was made according to the criteria developed by the Ad Hoc Committee of the International Society for Peritoneal Dialysis.[20] EPS was defined as a clinical syndrome with symptoms of intestinal obstruction, with or without elevated inflammation parameters, and the presence of compatible radiological or macroscopic findings such as peritoneal thickening, calcifications, and encapsulation. Clinical information of patients was gathered by reviewing the medical records. The study was performed with the approval of the Medical Ethics Committee (METC) of the Erasmus Medical Center, Rotterdam, The Netherlands. Approval for performing PM biopsies in PD patients without EPS was obtained from the METC of the University Medical Center Utrecht, Utrecht, The Netherlands. All PD patients gave written informed consent for participation in this study.

Immunohistochemistry and analysis

Four micrometer sections were cut from the formalin fixed paraffin-embedded tissue. Initially, we performed a haematoxylin-eosin staining on all tissue sections. To determine the type of the mononuclear immune cells, immunohistochemistry was performed on serial sections of the PM biopsies by routine diagnostics on the Benchmark Ultra stainer (Ventana), using antibodies validated for diagnostics and buffers provided by Ventana. Antibodies against cell surface antigens of interest were used to identify mononuclear cells including T cells, macrophages, and their subtypes.

Antibodies against CD3 (1:150 dilution, DAKO, Glostrup, Denmark), CD4 (ready to use, Ventana, Tucson, USA), and CD8 (1:50, DAKO, Glostrup, Denmark) were used to detect all pan-T lymphocytes and T-cell subsets. Antibody against CD68 (1:1600, KP-1, DAKO, Glostrup, Denmark) was used to detect pan-macrophages. In order to determine the subtype of macrophages, we stained biopsies with antibodies against M1 or M2 macrophages. The CD80 antigen has been used as a marker for the detection of M1 macrophages (1:400, R&D, Minneapolis, USA).[17,21] The CD163 antigen, which is known as a haemoglobin scavenger receptor and strongly expressed on M2 macrophages has been used as a marker for the detection of M2 macrophages (1:200, Leica, Wetzlar, Germany).[17,22]

The biopsies were stained simultaneously to reduce inter-staining variation. Incubation with

antibodies was done for 32 minutes and anti-rabbit or anti-mouse amplifiers were used. As positive controls, tonsil sections (for CD3, CD4, CD8, CD68, and CD80) and tonsil and lung sections (for CD163) were used. In a subpopulation of seven EPS patients, granulocytes and B cell infiltrates were investigated by staining tissue sections with antibodies against CD15 and CD20 respectively. However, our preliminary findings showed a minute numbers of these cells present, if even any at all, in EPS biopsies. Our focus was therefore only on the presence of T-cells and macrophages.

After staining, the overall histomorphological quality of the tissues was evaluated by two observers who were unaware of the group to which the peritoneal biopsies belonged. All slides were scanned and digitalized on a NDP Nanozoomer virtual microscopy system (Hamamutsu Photonics, Japan). Five random microscopic fields of the submesothelial compact zone in each slide were selected for immunohistochemical analysis using the 40 times power objective (original magnification x400). The submesothelial compact zone was defined as the zone between the basal mesothelial layer and the upper margin of the peritoneal adipose tissue.

Immunohistochemical quantification was performed in a blinded manner using automatic digital image analysis of the slides (KS-400 version 3, 1997, Carl Zeiss Vision GmbH) as previously described and validated.[23] To analyze the immunohistochemical staining for each marker, the amount of staining area was measured across the fields and expressed as a percentage of area stained.

Statistical analysis

The SPSS software version 20.0 was used for all statistical analysis. Medians (25^{th}-75^{th} percentile) are presented of continuous variables and compared using the non-parametric Mann-Whitney test. Categorical variables are presented as numbers and/or percentages, and proportions were tested using the χ^2-test. The Spearman's rank correlation test was used to assess correlation coefficients. Univariate Kaplan-Meier survival analysis was used to investigate the survival in the different staining groups. All probabilities were two tailed. P-values of less than or equal to 0.05 were considered statistically significant.

RESULTS

Patient characteristics

The clinical characteristics of the study population are summarized in table 1. The median age in the EPS group was 42.6 (31.8-61.5) years (versus 56.0 (46.0-62.0) years in the non-EPS group, $p = 0.11$), and the majority of EPS patients were male. EPS patients had a longer cumulative duration of PD as compared to non-EPS patients (58.2 (34.1-77.2) versus 30.0 (15.0-41.0) months, $p < 0.001$). The two groups did not significantly differ regarding the incidence of peritonitis or

time between last peritonitis and biopsy. Eight EPS patients had a functioning kidney transplant, five EPS patients were on PD, and 10 patients were on hemodialysis (HD) at time of diagnosis.

Table 1. Patient characteristics.

	EPS (23)	Non-EPS (15)	P-value
Age (years)	42.6 (31.8-61.5)	56.0 (46.0-62.0)	0.11
Gender (male/female)	15/8	6/9	0.13
Cause of renal disease			-
Glomerulonephritis	8 (34.8)	4 (26.7)	
Interstitial nephritis	4 (17.4)	0 (0.0)	
Renal vascular disease	5 (21.7)	2 (13.3)	
Diabetic nephropathy	2 (8.7)	0 (0.0)	
Cystic kidney diseases	0 (0.0)	4 (26.7)	
Congenital/Hereditary kidney disease	2 (8.7)	0 (0.0)	
Other	2 (8.7)	2 (13.3)	
Unknown	0 (0.0)	3 (20.0)	
Cumulative peritoneal dialysis (months)	58.2 (34.1-77.2)	30.0 (15.0-41.0)	< 0.001
History of peritonitis (yes)	17 (73.9)	8 (53.3)	0.13
Peritonitis episodes per patient year	0.42 (0.1-1.4)	0.21 (0.0-1.4)	0.32
Time since last peritonitis until biopsy (months)	6.8 (4.6-27.4)	11.3 (7.6-22.7)	0.51

Values are median (25^{th}-75^{th} percentile) or n (%). Medians were compared using the non-parametric Mann-Whitney test. Proportions were compared using the χ^2 test.

Immunohistochemical analysis

Immunohistochemical staining was adequate in all biopsies and quantification could be performed for all markers. The cellular infiltration in EPS biopsies was predominated by a mononuclear cell infiltrate that was mainly found scattered and at times patchy throughout the fibrotic submesothelial area. Figure 1 shows the results of immunohistochemistry in both groups for the T cell markers. In patients with EPS, there was an increased percentage of area stained for CD3, as compared to the non-EPS group (1.48% (0.96-2.49) versus 0.26% (0.19-0.41), $p < 0.001$) (Figure 1A3). The percentage of area stained for CD4 (EPS 1.29% (0.61-3.20) versus non-EPS 0.28% (0.05-0.83), $p = 0.001$) (Figure 1B3) and CD8 (EPS 0.71% (0.46-1.01) versus non-EPS 0.22% (0.17-0.43), $p < 0.001$) (Figure 1C3) were also increased in biopsy specimens of EPS patients, as compared to the non-EPS group. Additionally, the difference in percentage of area stained between CD4 and CD8 was analyzed, and an increased percentage of area stained for CD4 in comparison to CD8 (Figure 2) in EPS biopsies was observed. Interestingly, while the difference in CD4 and CD8 percentage of area stained was significant in biopsies of EPS patients (1.29% (0.61-3.20) versus 0.71% (0.46-1.01), $p = 0.04$) this was not the seen in biopsies of the non-EPS group where these cell types were equally represented (0.28% (0.05-0.83) versus 0.22% (0.17-0.43), $p = 0.97$).

Figure 3 shows the distribution of CD68 staining in both EPS and non-EPS group. CD68+ cells were diffusely distributed along the submesothelial area. We observed a significantly higher percentage of area stained for CD68 in EPS biopsies when compared to the non-EPS group (3.94% (2.35-5.08) versus 0.37% (0.23-1.16), $p < 0.001$) (Figure 3A3). With respect to M1 macrophages, CD80+ staining was sparsely present in EPS biopsies and rarely detected in tissues of the non-EPS group (0.22% (0.14-0.85) versus 0.04% (0.00-0.07), $p < 0.001$) (Figure 3B3). In contrast, M2 macrophages, as assessed by CD163+ staining, were the most abundant macrophage phenotype

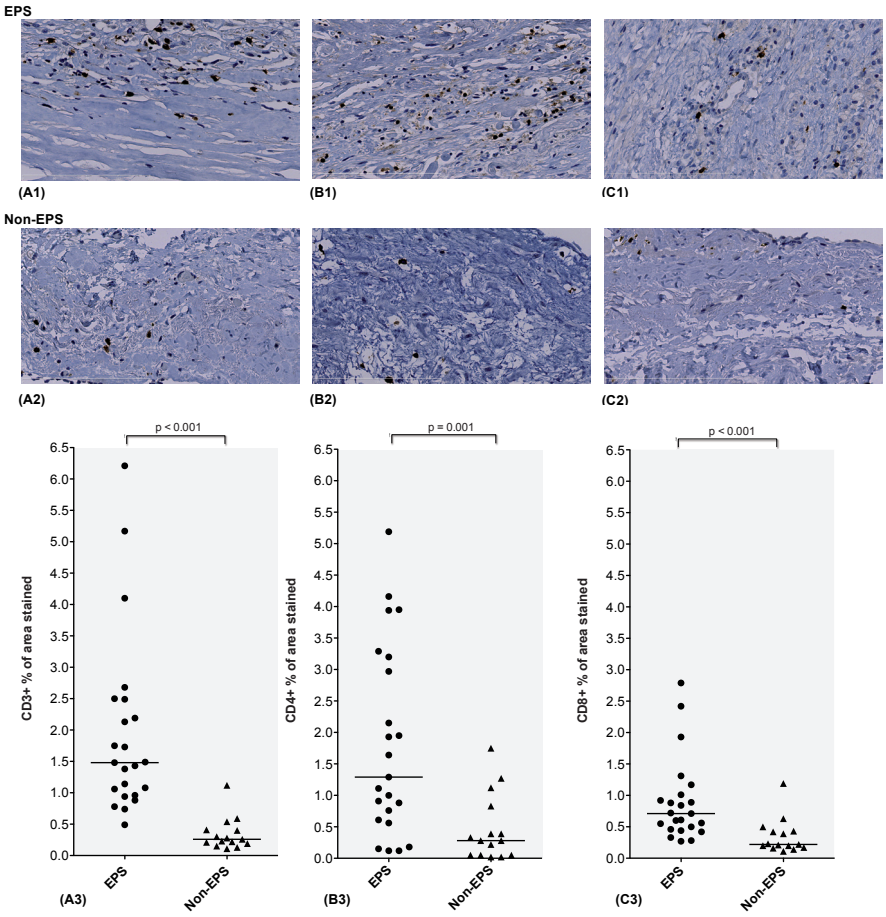
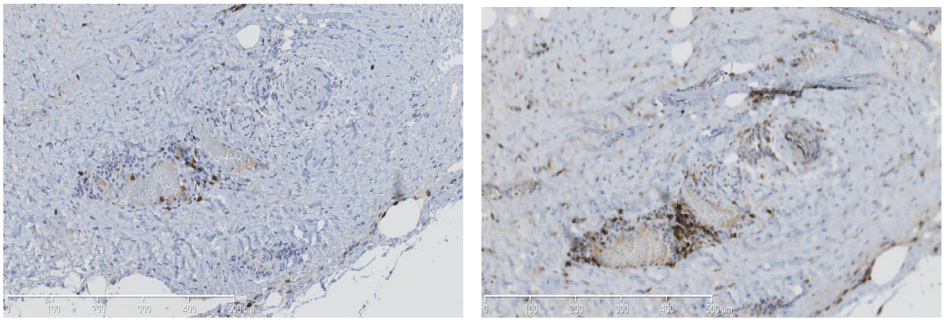


Figure 1. Immunohistological features of the infiltrating T lymphocyte population. Representative peritoneal findings are shown for both groups: **(A1-2)** CD3+ cell fields **(B1-2)** CD4+ cell fields **(C1-2)** CD8+ cell fields. Magnification x400. A quantitative comparison of the percentage of area stained for all markers in the peritoneal membrane of EPS and non-EPS patients is shown in A3, B3, and C3. Medians (25^{th}-75^{th} percentile) are presented and compared using the non-parametric Mann-Whitney test. Scale bar shows 200uM length.



(A) (B)

Figure 2. Staining of peritoneum of a patient with antibodies against CD4 and CD8. In 2A a few CD8+ (brown) cells are present in a mononuclear cell infiltrate while in 2B a substantial number of CD4+ cells are identified in the same infiltrate and scattered throughout the thickened and sclerosed submesothelial tissue. Magnification x150. Scale bar shows 500uM length.

and almost 5 times higher in extent in EPS tissues as compared to the non-EPS group (3.74% (0.20-5.13) versus 0.77% (0.32-1.86), $p < 0.001$) (Figure 3C3). In the eight post-transplantation EPS patients who were on steroids, no significant differences in the percentage of area stained for pan-T cells (CD3+ staining: 1.61% (1.20-2.04) versus 1.43% (0.88-2.68), $p = 0.88$) or pan-macrophages (CD68+ staining: 3.89% (2.42-4.48) versus 4.09% (2.02-5.84), $p = 0.59$) were noted as compared to the fifteen patients who were not receiving steroids.

Peritoneal cellular infiltrate and clinical outcome

During follow up (median 52.6 (11.9-85.0) months), 17 (73.9%) out of 23 EPS patients died, with a median time of death of 24.2 (4.76-55.77) months after diagnosis. In order to evaluate a possible influence of T cells and macrophages on the clinical outcome of EPS patients, we divided patients into two staining groups. A group with a percentage of area stained below the corresponding median (low staining) and a group with a percentage of area stained equal or above to the corresponding median (high staining) for CD3 or CD68 staining. As it is shown in figure 4A, we did not find a significant difference in survival between the low and high staining group for CD3. Similarly, no significant difference in survival was observed in the two groups with regard to the presence of CD68 (Figure 4B).

Separate analysis after stratification by the diagnostic subgroup to which the patients belonged to (post-transplantation or classical (being on HD or PD) EPS) did not change these results (data not shown).

For further analysis, we also assessed the correlation between the percentage of area stained and PD duration for each one of the markers in both groups, and calculated Spearman's rank correlation coefficients. Subsequently, a negative correlation between PD duration and percentage of area stained for CD3 ($r= -0.27$, $p = 0.21$) and CD68 ($r=-0.22$, $p = 0.31$) over time was

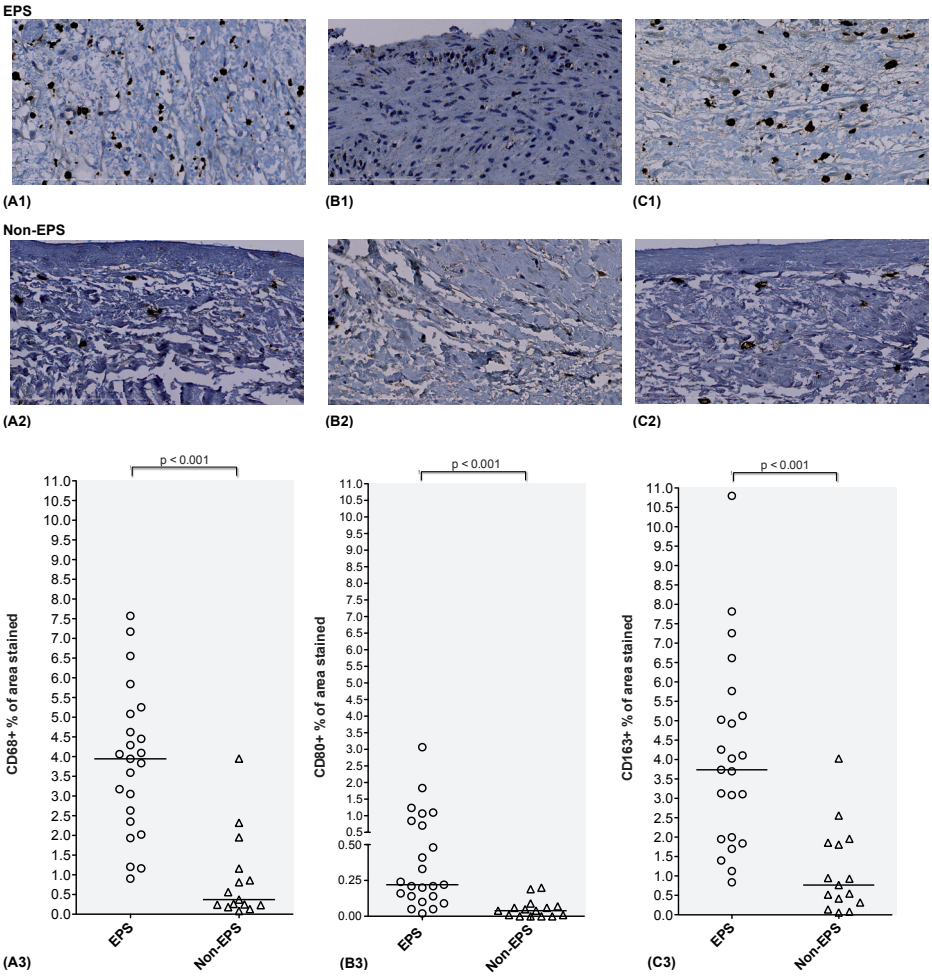


Figure 3. Immunohistological features of infiltrating macrophages. Representative peritoneal findings are shown for both groups: (**A1-2**) CD68+ cell fields (**B1-2**) CD80+ cell fields, (**C1-2**) CD163+ cell fields. Magnification x400. A quantitative comparison of the percentage of area stained for all macrophage markers in the peritoneal membrane of EPS patients and PD controls is shown in A3, B3, and C3. Medians (25^{th}-75^{th} percentile) are presented and compared using the non-parametric Mann-Whitney test. Scale bar shows 200uM length.

observed in the EPS group (Figure 5A and 5C), though not statistically significant. In addition, no significant correlations between PD duration and percentage of area stained for CD3 (r= 0.12, p = 0.67) or CD68 (r=0.25, p = 0.36) was found in the non-EPS group (Figure 5B and 5D).

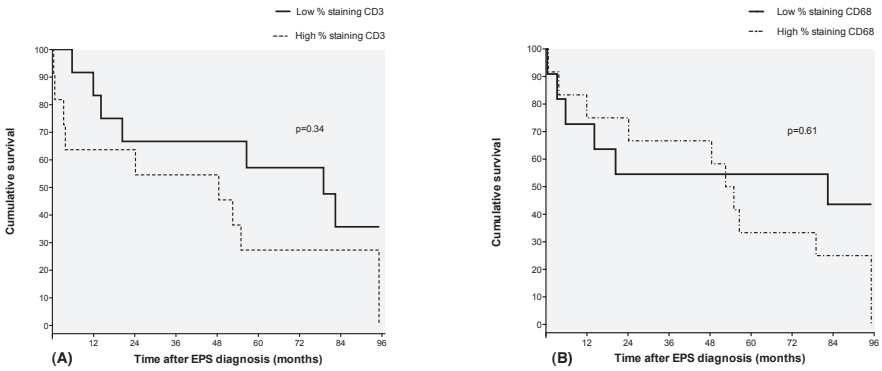


Figure 4. Kaplan-Meier curves showing overall survival comparison between high (dotted line) and low (solid line) staining groups for CD3 **(4A)** and CD68 **(4B)**. P values are based on the log-rank test.

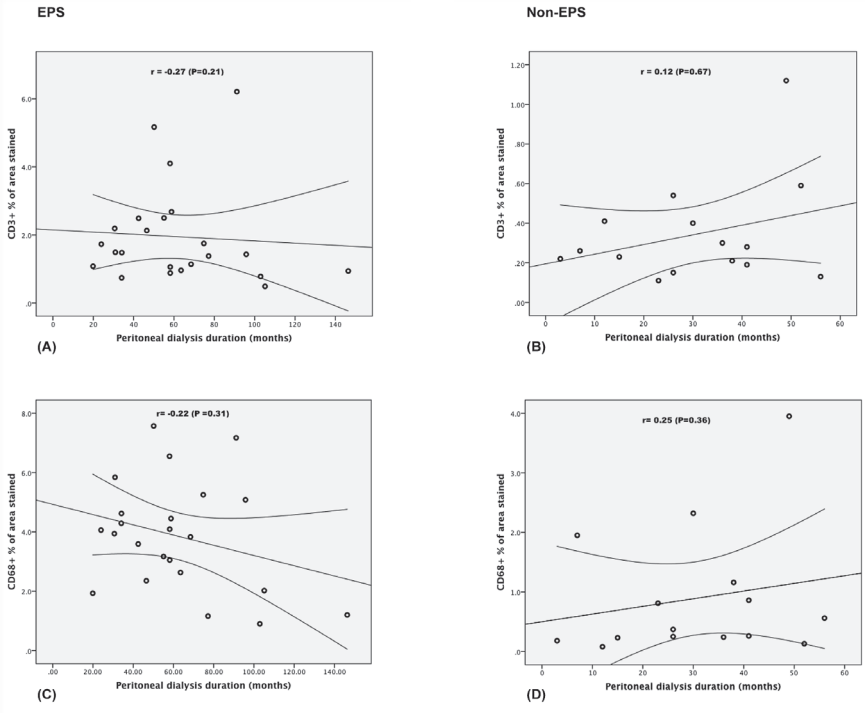


Figure 5. Correlation between PD duration and percentage of area stained for CD3 and CD68 in the EPS (**5A** and **5C**) and the non-EPS group (**5B** and **5D**). In all graphs, the regression line and the 95% confidence interval are plotted.

DISCUSSION

In this study, we found a more intense mononuclear cell infiltration, predominantly consisting of CD4+ cells and CD163+ cells, in the PM of patients with EPS as compared to the presence of these cells in the PM of PD patients without EPS. These findings provide evidence for a local peritoneal inflammatory response in EPS and support the concept of immune cell-mediated excessive fibrosis in the pathogenesis of this condition.

The results of our study are in agreement with previous studies reporting on the presence of chronic inflammation in the PM of patients with EPS. In this context, a study by Honda *et al*.[11] revealed an increased frequency of mononuclear cell infiltration in the EPS group as compared to a non EPS group. The presence of a mononuclear cell infiltrate has also been proposed as one of the histomorphologic criteria for EPS.[11,12] Furthermore, in a mouse model of EPS, histological evaluation of sections from the abdominal cocoon revealed fibrotic thickening of the intestinal serosa with an infiltrate of mononuclear cells and only a few polymorph nuclear leukocytes.[24] However, although these studies underscore the inflammatory nature of EPS, they do not report on the presence of specific subsets of T cells and macrophages, which are known to be involved in profibrotic responses.

In the present study we found an increased extent of staining for both CD4+ and CD8+ cells in EPS tissues in comparison to the non-EPS group tissues. However, the increase in CD4+ cells in EPS tissues was relatively more pronounced as compared to CD8+ cells. Normally, the CD4/CD8 ratio of T cells within the peritoneal effluent of stable PD patients is reported to be decreased (below 1.5)[25], which is not in accordance with the distribution of these cell subsets in the PM of our EPS patients. Therefore, our observations contribute to the hypothesis that recruitment of CD4+ T cells in the PM is of possible importance in the pathogenesis of EPS. CD4+ T cells have a pivotal effect on collagen synthesis by their production of pro-fibrotic cytokines.[26] The production of T-helper-2 (Th-2) cytokines, such as IL-4 and IL-13, may enhance fibrosis formation through activation of M2 macrophages or stimulation of fibroblast proliferation.[13,26] In a mouse model, Zampell *et al.*[27] have reported on the importance of CD4+ cells in the regulation of fibrosis. In this study, CD4+ cell depleted animals showed a decrease in dermal fibrosis as reflected by a decline in type I collagen deposition and dermal scar index. In contrast, non-significant decreases in scar index and no decreases in type I collagen deposition were noted in CD8+ cell depleted mice as compared to controls.

In our study, we have demonstrated an increased presence of macrophages in the PM biopsies of EPS patients. Macrophages play a crucial role in chronic inflammation-induced fibrosis by their production of pro-fibrotic cytokines and ability to regulate extracellular matrix turnover via controlling the balance of several matrix metalloproteases.[28] With their capacity to act pro-fibrotic, M2 macrophages are thought to promote fibrosis through production of transforming growth factor-beta (TGF-β) and stimulation of fibroblasts.[18,28] Consistent with findings in biopsies from

patients with other fibrotic diseases, such as pulmonary fibrosis[29], we found a predominance of M2 macrophages in the peritoneal tissue of EPS patients, highlighting their importance. Bellón *et al.*[30] have previously reported on the phenotype of peritoneal effluent macrophages and demonstrated the capacity of CD163+CD14+ cells to stimulate proliferation of human fibroblasts. The capacity of peritoneal macrophages to stimulate fibroblast proliferation correlated strongly with chemokine ligand 18 (CCL18) mRNA levels. Additionally, they showed that an increased concentration of CCL18, a pro-fibrotic chemokine produced by M2 macrophages, was found in the peritoneal effluent of patients who later developed EPS. In support of this finding, a prospective observational study by Ahmad *et al.*[31] has reported higher baseline dialysate and serum levels of CCL18 in patients who developed EPS as compared to a stable PD group.

In the present study, both T cell and macrophage infiltration were not significantly associated with clinical outcome of EPS patients. In addition, we did not observe a difference in immunohistochemical staining between EPS patients who received steroids as part of transplantation immunosuppressive protocol as compared to those patients who were on PD or HD at time of biopsy. With regard to this, the low number of patients in the subgroups could have been of influence in demonstrating significant differences.

One limitation of our study is the difference in PD duration between the two groups, which may have influenced the amount of cell infiltration in the biopsies. Hence, we have focused on the influence of PD duration on the percentage of area stained for CD3 and CD68 in each of the groups and did not observe significant correlations between these two variables. Importantly, other studies have reported a decrease in both lymphocytes in the peripheral blood of PD patients[32,33], and macrophages in the PD effluent of PD patients[25] during the course of PD treatment. Due to the descriptive nature of our study, the exact mechanisms responsible for the increased cellular response that was observed in EPS patients could not be studied and remain uncertain. Yáñez-Mó *et al.*[34] have reported on alterations of the PM and transdifferentiation of peritoneal mesothelial cells into myofibroblasts in PD patients. Considering this, we can speculate that when severe, these alterations of the PM may induce immune activation and serve as a trigger for the cascade of events ending in peritoneal inflammation and fibrosis. Most EPS patients have had a long history of PD. The bio-incompatible elements in PD fluids to which the PM mesothelial cells are exposed may increase oxidative stress and induce the production and release of pro-inflammatory mediators that can enhance a CD4+ T helper-2 cell response. CD4+ T helper-2 cell subsets along with the pro-fibrotic cytokine microenvironment in the peritoneal cavity may in turn promote the infiltration of macrophages or polarization of resident macrophages that would be activated towards an M2 type. Finally, these M2 macrophages may further contribute to the fibrotic process development through the secretion of TGF-β or other fibrogenic factors ending in fibroblast proliferation and excessive collagen synthesis. However, additional experimental studies are required to further examine this concept and determine a possible crosslink between CD4+ T cells, M2 macrophages, and fibroblasts in the development of the fibrotic-inflammatory tissue in EPS.

In conclusion, a characteristic mononuclear infiltrate consisting of CD4+ cells and CD163+ cells dominates the peritoneum of EPS patients and probably drives the excessive fibrosis. These findings may suggest a prominent role for both CD4+ T cells and pro-fibrotic M2 macrophages in the pathogenesis of EPS.

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EPS

Chapter 4

Lower mortality and inflammation from post-transplantation encapsulating peritoneal sclerosis compared to the classical form

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ABSTRACT

Background

Encapsulating peritoneal sclerosis (EPS) may occur after kidney transplantation (post-transplantation EPS) or may be diagnosed during or after peritoneal dialysis treatment (classical EPS). The aim of the present study was to investigate to what extent both EPS entities differ in clinical presentation, radiological findings, outcome, and the systemic inflammatory response, as measured by plasma C-reactive protein (CRP) levels both prior and after EPS diagnosis.

Methods

We performed a retrospective analysis of 15 post-transplantation EPS and 19 classical EPS patients who were diagnosed at seven hospitals in the Netherlands between January 1, 2000, and January 1, 2011.

Results

There were no inter-group differences in age, duration of peritoneal dialysis, clinical presentation, or radiology findings at diagnosis. Post-transplantation patients had experienced a lower number of peritonitis episodes per patient year (0.2 (0.0-0.4) versus 0.7 (0.3-1.2), $p = 0.01$) with a longer interval between the last peritonitis and EPS diagnosis (18.1 (4.6-34.3) versus 4.4 (0.89-13.78) months, $p = 0.01$). Post-transplantation EPS patients showed a remarkably lower mortality rate (40.0 versus 84.2%, $p < 0.05$). In both groups a pattern of elevated CRP values was observed, increasing within the year before EPS diagnosis. In the post-transplantation group the median CRP level at diagnosis was lower (56.0 versus 144.50 mg/l, $p < 0.05$) than in the classical EPS group.

Conclusion

Post-transplantation EPS has a similar clinical presentation as classical EPS but with a lower systemic inflammatory response and better outcome.

INTRODUCTION

Encapsulating peritoneal sclerosis (EPS) is a dreaded complication of peritoneal dialysis (PD).[1] EPS is characterized by fibrotic thickening of the peritoneal membrane with encapsulation of the intestines.[2,3] This leads to symptoms related to bowel movement impairment such as abdominal pain, vomiting, and weight loss. Parenteral feeding may be necessary and bacterial peritonitis can occur because of (micro)blow-outs of the guts.[4,5] The mortality rate among EPS patients is high and found to be almost 50% in most studies.[6,7] The single most important risk factor for EPS is the total duration of PD.[6,8] There is a rise in the incidence of EPS after 3-4 years of PD treatment.[6] Therefore, EPS is a serious complication to consider when patients are treated with PD for a prolonged time and as such limits long-term treatment with PD.

It is currently not known what causes the excessive peritoneal fibrosis in EPS patients, but peritoneal neoangiogenesis with an influx of mononuclear cells and fibrin deposition have been described as hallmarks of active disease.[9,10] This underscores the inflammatory nature of EPS, which is reflected by the observation that both steroids[11-13] and tamoxifen[14,15] are able to favorably attenuate the clinical course of disease. At the time of EPS diagnosis the peritoneal inflammation is usually at its most active. This probably represents the final stage of an inflammatory process, which may have been smoldering for many months to years. Recognizing the early stage of peritoneal inflammation and closely following the suspected cases may have a major impact on patient outcome and survival. To date, however, no study has been published that has documented the presence of inflammation prior and at the time of EPS diagnosis in a cohort of well-defined EPS patients. In addition, current data suggest that EPS is not a homogenous entity. Cases may substantially differ in clinical severity[1], degree of inflammation[5,14], and the extent to which the intestines are encapsulated.[3] In this respect, EPS occurring after kidney transplantation (coined post-transplantation EPS) is of interest.[3,11,16-23]

On average 3% of PD patients develop post-transplantation EPS and it is the fourth known cause of mortality in this group of patients.[24] At least in Europe, this presentation of EPS seems to be increasing and has been reported to account for almost 50% of cases in the Netherlands.[25] However, a detailed description of post-transplantation EPS is lacking. For instance, it is not known whether the clinical presentation and prognosis of post-transplantation EPS is similar to that of EPS occurring in patients without previous kidney transplantation that are or have been treated with PD.

In this study, we have addressed the question whether clinical presentation, baseline imaging findings, and outcome of post-transplantation EPS differ from classical EPS by comparing well-defined groups of both types of EPS. In addition, we have documented the systemic inflammatory response, as measured by plasma C-reactive protein (CRP) concentration, in both groups the year before, at the time, and the year after the diagnosis of EPS.

SUBJECTS AND METHODS

Study population

In this observational retrospective study we reviewed the medical records of EPS patients who were diagnosed at five university hospitals and two large teaching hospitals in the Netherlands between January 1, 2000**,** and January 1**,** 2011. Following the recommendations of the ad hoc committee of the International Society for Peritoneal Dialysis, EPS was defined as a clinical syndrome with symptoms of gastrointestinal disturbance due to intestinal encapsulation confirmed by compatible CT scan findings or macroscopic inspection of the peritoneal cavity.[26] We selected patients for two defined groups: post-transplantation EPS and classical EPS. Post-transplantation EPS cases were defined as patients who had been treated solely with PD as renal replacement therapy, subsequently received a kidney transplantation after which they developed EPS while having a functioning kidney graft. Classical EPS was defined as EPS diagnosed in patients who had been or were treated with PD at the time of diagnosis, but without previous kidney transplantation. The study protocol was approved by the medical ethics committee of the Erasmus Medical Center.

Patient characteristics

Patient characteristics were divided into demographic information, dialysis related data, and transplantation-related information. In all cases of classical EPS, it was recorded whether patients were on PD or hemodialysis (HD) at the time of diagnosis and, when appropriate, the reason of changing from PD to HD. We computed the number of peritonitis episodes per patient year by dividing the total number of peritonitis episodes per patient by the total number of years on PD. The time since peritonitis until EPS was defined as the time from the occurrence of the last peritonitis episode until EPS diagnosis date. Ultrafiltration failure was defined as a net ultrafiltration <400 mL using 3.86%/4.25% glucose during a 4-hour exchange.[27] Transplantation-related variables were only collected for post-transplantation EPS cases.

Clinical features

Clinical signs and symptoms at baseline that led to a diagnosis of EPS were recorded. Laboratory data have been extracted from the laboratory files and include blood levels of albumin, hemoglobin, and CRP. In order to evaluate the degree of inflammation over time, we focused on CRP values prior to, during, and after disease onset. CRP was assayed serially over the study period by standard commercial laboratory methods as part of routine clinical practice. CRP values obtained at periods of infection or defined inflammatory conditions other than EPS were excluded from the analysis. Serum CRP concentrations from 86 stable PD patients (median PD duration 23.4 (12.0–36.0) months) were used for comparison. CT scan findings were scored by review of the radiology reports. According to a combination of CT scan findings that have been

validated by Tarzi *et al.*[28] and Vlijm *et al.*[29], the following CT scan findings at EPS diagnosis were collected: bowel dilatation, fluid pockets, peritoneal calcification, peritoneal thickening, and adhesions of bowel loops.

Treatment and survival

All medical therapies for EPS were tabulated after reviewing of the medication list. The use of total parenteral nutrition was recorded only if it was used as supportive care for EPS management. Furthermore, we studied the influence of EPS development on patient survival and compared the groups. EPS-related death was defined as death due to (abdominal) sepsis, bowel perforation, or other EPS-related causes (e.g. malnutrition, complicated peritonitis, infection).

Statistical analysis

The SPSS software version 18.0 was used for all statistical tests. Descriptive statistics were used to summarize baseline characteristics. Continuous variables are presented as medians (interquartile range) and compared using the non-parametric Mann-Whitney test. Categorical variables are presented as numbers and/or percentages. For comparison between two group proportions, the $\chi 2$ test was used. Survival was analyzed with the Kaplan-Meier method. $p < 0.05$ was considered to be significant; all probabilities were two-tailed.

RESULTS

Patient characteristics

During the study period a total of 15 post-transplantation and 19 classical EPS patients were included in the analysis. Table 1 shows the comparison of patient characteristics between the groups. In both groups the majority of patients were men. Post-transplantation EPS patients tended to be younger than classical EPS patients (42.1 (31.0–53.9) versus 49.4 (41.5–69.0) years, $p > 0.05$). Post-transplantation EPS patients were younger at start PD (36.1 (26.5–48.7) versus 42.6 (36.0–65.7) years) with a longer duration on PD (64.4 (55.9-68.5) versus 58.8 (42.5-76.9) months), however these values did not reach statistical significance. Ultrafiltration failure prior to diagnosis was recorded in 6 (40.0%) post-transplantation versus 11 (57.9%) classical EPS patients ($p > 0.05$).

Potential second hits

Peritonitis, stopping of PD treatment and use of calcineurin inhibitors are considered as potential triggers of EPS[30] and therefore documented in both groups. A significant difference in the rate of peritonitis episodes prior to EPS diagnosis was noted; post-transplantation EPS patients experienced less peritonitis episodes per patient-year compared with classical EPS patients (0.2 (0.0-0.4) versus 0.7 (0.3-1.2), $p = 0.01$).

Ten post-transplantation EPS patients (66.7%) experienced at least one peritonitis episode versus 17 (89.5%) classical EPS patients ($p > 0.05$). However, the time since last peritonitis until diagnosis of EPS was significantly different among the groups: 18.1 (4.6-34.3) months in the post-transplantation versus 4.4 (0.89-13.78) months in the classical EPS group ($p = 0.01$).

In the group of classical EPS patients, EPS was diagnosed with certainty in 12 after they were transferred from PD to HD (63.2%). Within this group, 7 (58.3%) were switched to HD due to recurrent/non-resolving peritonitis, 4 (33.3%) due to suspected EPS, and 1 (8.3%) due to

Table 1. Patient characteristics.

Variable	Post-transplantation EPS	Classical EPS	P-value
Number of patients	15	19	
Gender			NS
Female (%)	6 (40.0)	4 (21.1)	
Male (%)	9 (60.0)	15 (78.9)	
Age at diagnosis EPS, years	42.1 (31.0 – 53.9)	49.4 (41.5-69.0)	NS
Underlying kidney disease			NS
Glomerulonephritis	4 (26.7)	5 (26.3)	
Congenital and hereditary kidney disease	2 (13.3)	1 (5.3)	
Interstitial nephritis and pyelonephritis	2 (13.3)	4 (21.1)	
Cystic kidney diseases	1 (6.7)	0 (0.0)	
Renal vascular disease	3 (20.0)	4 (21.1)	
Diabetes mellitus	1 (6.7)	0 (0.0)	
Other	0 (0.0)	4 (21.1)	
Unknown	2 (13.3)	1 (5.3)	
Dialysis related			
Age at start of PD, years	36.1 (26.5 – 48.7)	42.6 (36.0 – 65.7)	NS
Time on PD, months	64.4 (55.9-68.5)	58.8 (42.5-76.9)	NS
Ultrafiltration failure during PD	6 (40.0)	11 (57.9)	NS
Peritonitis	10 (66.7)	17 (89.5)	NS
Peritonitis episodes per patient-year	0.2 (0.0-0.4)	0.7 (0.3-1.2)	0.01
Time since last peritonitis until EPS, months	18.1 (4.6-34.3)	4.4 (0.89-13.78)	0.01
Switch to HD prior to final diagnosis of EPS		12 (63.2)	
Due to recurrent/non-resolving peritonitis		7 (58.3)	
Due to suspected EPS		4 (33.3)	
Due to ultrafiltration problems		1 (8.3)	
Time since switch to HD until final EPS diagnosis, months		2.4 (0.8-6.5)	
Transplantation-related			
Age at transplantation	41.9 (30.6 – 53.7)		
Use of Calcineurin Inhibitor	13 (86.7)		
Time since transplantation until EPS, months	6.4 (3.5-7.9)		

Values are median (range) or n (%). Medians were compared using the non-parametric Mann-Whitney test. Proportions were compared using the $\chi 2$ test. NS=not significant.

ultrafiltration problems. The median time since switch to HD until EPS diagnosis in this group was 2.4 (0.8-6.5) months. Post-transplantation EPS patients had a mean age of 41.9 (30.6–53.7) years at transplantation and 13 (86.7%) received a calcineurin inhibitor. Most post-transplantation EPS patients (80.0%) were diagnosed within 1 year after transplantation. Median time since last transplantation until EPS was 6.4 (3.5-7.9) months.

Clinical features

Table 2 shows the clinical features at presentation of both groups. Common presenting symptoms in the post-transplantation group included abdominal pain (93.3%), nausea (73.3%) and vomiting (80.0%). Classical EPS patients had similar signs and symptoms without any inter-group differences.

Decreased albumin and hemoglobin levels at the time of diagnosis were evident in most patients. Median albumin levels were respectively 32.0 g/l (27.7-37.2) for post-transplantation versus 24.5 g/l (18.3-30.8) for classical EPS patients ($p < 0.05$). Median hemoglobin levels were 6.8 mmol/l (6.1-7.3) for post-transplantation versus 6.1 mmol/l (5.3-7.4) for classical EPS patients ($p > 0.05$).

Table 2. Comparison of clinical features at presentation.

	Post-transplantation EPS (15)	Classical EPS (19)
Signs and symptoms at presentation		
Any sign or symptom at presentation	15/15 (100)	19/19 (100)
Abdominal pain	14/15 (93.3)	15/19 (78.9)
Nausea	11/15 (73.3)	11/19 (57.9)
Vomiting	12/15 (80.0)	10/19 (52.6)
Ileus/Obstruction	8/15 (53.3)	4/19 (21.1)
Appetite loss	6/15 (40.0)	8/19 (42.1)
Weight loss	8/15 (53.3)	9/19 (47.4)
Laboratory data		
Albumin, g/l	32.0 (27.7-37.2)*	24.5 (18.3-30.8)
Hemoglobin, mmol/l	6.8 (6.1-7.3)	6.1 (5.3-7.4)
C-reactive protein, mg/l	56.0 (21.5-85.0)*	144.5 (63-166.5)
Baseline imaging findings		
Bowel dilatation	11 (73.3)	9 (47.4)
Fluid pockets	12 (80.0)	16 (84.2)
Peritoneal calcification	2 (13.3)	2 (10.5)
Peritoneal thickening	4 (26.7)	9 (47.4)
Adhesions/fixed bowel	3 (20.0)	2 (10.5)

Except for laboratory data, values are the number (percentage) of patients. At diagnosis, albumin was measured in 12 out of 15 post-transplantation EPS and 12 out of 19 classical EPS patients. At admission, hemoglobin was measured in 10 out of 15 post-transplantation and 15 out of 19 classical EPS patients. Proportions were compared using the $\chi 2$ test. Laboratory data are presented as medians (interquartile range) and compared using the non-parametric Mann-Whitney test. * $p < 0.05$.

Significantly lower CRP levels at the time of diagnosis were detected for post-transplantation patients in comparison to classical EPS patients (56.0 mg/l (21.5-85.0) versus 144.5 mg/l (63.0-166.5), $p < 0.05$). Three classical EPS patients and 1 post-transplantation EPS patient presented with peritonitis in addition to their EPS at time of diagnosis. The CRP values of these patients were excluded from the analysis. CRP levels before and after the diagnosis of EPS are shown in Figure 1. One year prior to EPS diagnosis, an increasing pattern of elevated CRP values was observed in both EPS groups until the diagnosis was established. A similar decrease was shown over the following 12 months after EPS diagnosis. The total group of EPS patients showed statistically significantly higher CRP values (post-transplantation EPS 8 mg/l (7-15.5), classical EPS 15.5 mg/l (8.5-24.8)) already at 12 months before the diagnosis of EPS, compared with the control group of stable PD patients (3.5 mg/l (2-8.3), $p < 0.05$). A CT scan of the abdomen was performed in all patients. Common findings on the CT scan in both groups included fluid pockets, bowel dilatation and peritoneal thickening. The frequency and severity of EPS-related findings on abdominal CT scans in the post-transplantation EPS group did not differ significantly from the classical EPS group (Table 2).

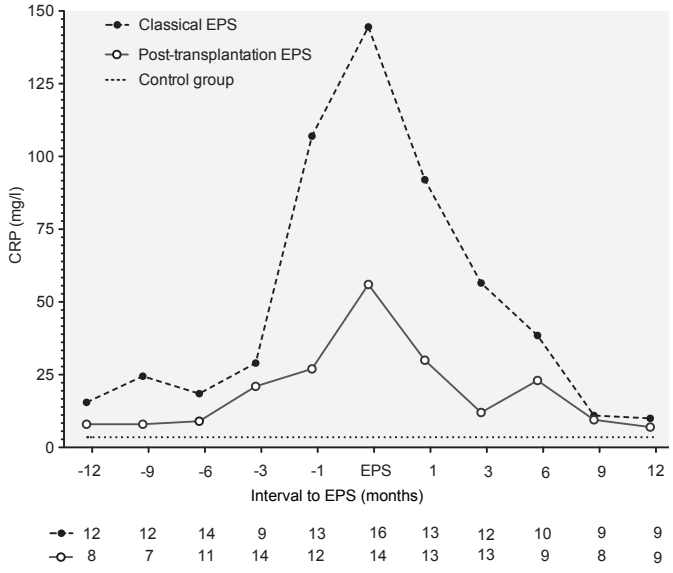

Figure 1. Time course of CRP levels from 1 year prior to, at the time of, and until 1 year after EPS diagnosis in patients with post-transplantation and classical EPS. The filled and open circles indicate median values of classical and post-transplantation EPS patients, respectively. The dotted line indicates the median CRP value of 86 stable PD patients that was used for comparison with EPS data.

Table 3. Type of intervention used.

Intervention	Post-transplantation EPS (15)	Classical EPS (19)	P-value
Medical intervention[a]			
Prednisone	11 (73.3)	6 (31.6)	0.02
Tamoxifen	9 (60.0)	6 (31.6)	NS
Surgery (adhesiolysis/peritonectomy)	4 (26.7)	1 (5.3)	0.08
Supportive care Total parenteral nutrition	9 (60.0)	11 (57.9)	NS

Proportions were compared using the χ^2 test. NS=not significant. [a]Some patients received >1 medication.

Treatment and survival

Medical intervention was used in the management of both post-transplantation and classical EPS patients (Table 3). The initial EPS treatment consisted of prednisone, tamoxifen or the combination. Post-transplantation EPS patients were more frequently treated with prednisone (73.3% versus 31.6%, p = 0.02) and tamoxifen (60.0% versus 31.6%, p > 0.05). Initiation of prednisone in the post-transplantation group, intended as EPS therapy, occurred in 7 out of 11 cases. Surgical treatment was used in 4 post-transplantation EPS patients and 1 classical EPS patient. Total parenteral nutrition was initiated as supportive care for 9 post-transplantation and

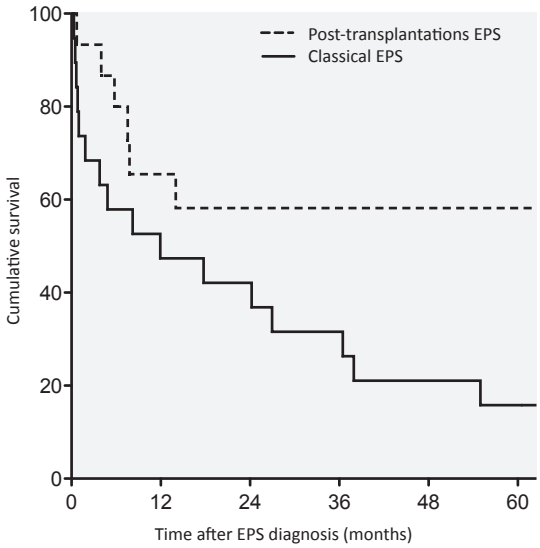

Figure 2. Kaplan-Meier survival curve showing overall survival. Post-transplantation EPS patients appear to have a better overall outcome than classical EPS patients. Log rank test: p < 0.05.

11 classical EPS patients. There were 3 post-transplantation and 9 classical EPS cases who did not receive any specific treatment. Ten of these untreated patients died within a mean time of 6.9 months after diagnosis.

Figure 2 shows the estimated survival. One year after diagnosis, 5 (33.3%) patients died in the post-transplantation EPS group, and 10 (52.6%) in the classical EPS group. The overall mortality rate was significantly different between the groups: 6 (40.0%) out of 15 post-transplantation EPS and 16 (84.2%) out of 19 classical EPS patients died during the study period ($p < 0.05$). 19 out of 22 (86.4%) deaths were EPS related, 2 out of 22 (9.1%) deaths were not EPS related deaths, and 1 out of 22 (4.5%) deaths was due to an unknown cause.

DISCUSSION

In this study, we have analyzed the clinical presentation, baseline imaging findings, and outcome of post-transplantation EPS cases and compared these findings with cases of classical EPS. The results indicate that clinical presentation and imaging findings between the two types of EPS do not significantly differ. In agreement with previous studies, the duration of PD before EPS developed was relatively long and strikingly similar for both groups. This supports the notion that duration of exposure to dialysis fluids is a predominant risk factor for EPS to develop. Apart from the detrimental effects of PD fluids on the peritoneal membrane, it has been hypothesized that a second hit is necessary to start the excessive formation of collagen in the peritoneal membrane.[30,31] Interpretation of our results according to this second-hit model yields interesting, though hypothetical, insights.

First, we have documented for the first time that at least 1 year before the onset of EPS a systemic inflammatory response as measured by CRP levels could be detected. Although the median CRP level was only modestly and variably elevated, it was significantly higher when compared to a control group of stable PD patients. Serum CRP levels are the result of increased levels of pro-inflammatory cytokines, in particular interleukin-6.[32] Therefore, it is of interest that a retrospective study showed elevated peritoneal interleukin-6 concentrations in EPS patients in the years before they became symptomatic.[33] In addition, an increase in effluent interleukin-6 prior to EPS diagnosis was shown after the use of icodextrin.[34] Therefore, the increased CRP levels found before the diagnosis of EPS is established may be indicative of increased peritoneal inflammation, resulting in progressive peritoneal sclerosis and finally impairment of bowel movements leading to the clinical diagnosis of EPS. This scenario and time frame fits with the radiological data of Goodlad *et al.*[20] who found that the hallmarks of EPS on a CT scan develop rather rapidly but late and are not found within a median time of 7.7 months before EPS diagnosis is established.

Second, the findings of this study identify several potential second hits in both groups: cessation

of PD and/or kidney transplantation in the post-transplantation EPS group and peritonitis in the classical EPS group. The mere discontinuation of PD is believed to be a major second hit for the development of EPS, as most studies have shown that the diagnosis of EPS is usually made in patients after cessation of PD.[4,8] Our results are in accordance with this finding as all post-transplantation EPS patients and the majority of classical EPS patients were off PD at the time of diagnosis. Therefore, we cannot dismiss the hypothesis that cessation of PD contributed to the development of EPS. However, the timeframe from cessation of PD to the diagnosis of EPS is substantially different in both patient groups arguing against a dominant role of cessation of PD in the pathogenesis. In addition, most of the classical EPS patients were switched to HD due to suspected EPS, a recurrent/non-resolving peritonitis or ultrafiltration problems, confirming some previous findings in a Japanese study.[4] This observation indicates that cessation of PD in the classical group may have accelerated the process of EPS development but by itself is not a cause of EPS. In support of this view is the finding that within the registered cases in the Dutch EPS registry only few cases are present of EPS developing in PD patients transferred to HD for other reasons than treatment-related complications [unpubl. observations].

It is significant to note that the average time from the second hits until the development of clinical overt EPS was remarkably similar in both groups. Our results with regard to peritonitis preceding EPS in patients on PD are in accordance with observations from other studies that have suggested that peritonitis is an important factor in the development of EPS.[4,35,36] A Japanese study observed a history of peritonitis in 90.6% of EPS patients who were diagnosed during the course of PD. Moreover, the average frequency of peritonitis episodes were reported to be 3.3 times higher in EPS patients compared to a group of control PD patients.[37] In contrast, there are studies that did not find a relation with peritonitis episodes and EPS when compared to a control group of PD patients.[1,8,38] This variation might be partially explained by patient-case mix, as none of these studies have analyzed the relationship between peritonitis episodes and EPS development while taking the etiology of EPS into account. However, there is an alternative explanation for lack of consensus on peritonitis as a risk factor for EPS. Our data suggest that peritonitis in a patient at risk for EPS, that is a patient with a pre-existent low-grade inflammation of the peritoneum, may be a trigger for EPS to develop. This implies that peritonitis incidence or number of peritonitis episodes may sometimes relate with EPS incidence, but that it is not the only factor that is of direct relevance. Along the same line of reasoning, kidney transplantation is the key secondary event for EPS to develop in the post-transplantation EPS group but predominantly in patients with a "peritoneum at risk". The additional role of the use of calcineurin inhibitors in the pathogenesis of EPS remains hypothetical and cannot be inferred from this study.

At present it is not known which PD patients are susceptible to mount a local inflammatory peritoneal response to dialysis fluids that puts them at risk for development of EPS. In previous studies it has been reported that young age at the start of PD was an independent risk factor for EPS.[6,8] This may be explained by the hypothesis that a less aged immune system is more likely to

react with peritoneal inflammation to the exposure to PD fluids.[39]

It was obvious that post-transplantation patients had significantly lower CRP concentrations at presentation. This may be related to their use of immunosuppressive medication, which partially suppresses the inflammatory response. The survival was also markedly better in post-transplantation EPS as compared to classical EPS patients. These results are in accordance with the Pan-Thames EPS study which showed that survival was better in post-transplantation EPS patients compared with patients who were diagnosed while on PD.[16] In our study, the observed better survival in the post-transplantation EPS group may be in part due to the younger age of post-transplantation EPS patients and a better overall condition of patients with a functioning kidney allograft. In addition, in the group of post-transplantation EPS patients, prednisone or tamoxifen for the treatment of EPS were also more frequently used. The higher survival in medically treated EPS patients, irrespective of etiology, once again underscores the potential benefit of prednisone or tamoxifen for inflammatory EPS patients.

For clinical practice, an unexplained increasing pattern of CRP values in a PD patient developing vague abdominal symptoms after kidney transplantation or a after a severe peritonitis episode should increase clinicians' awareness of EPS. These early signs could reflect the inflammatory reaction in the peritoneum being in a pre-EPS state. Recognition of this early stage of peritoneal inflammation, that can eventually worsen and lead to EPS after a second hit, may be pivotal in the prevention and early treatment of EPS

In conclusion, the novel described entity of post-transplantation EPS has very similar clinical characteristics as classical EPS. Low-grade inflammation preceded the development of clinically overt EPS, irrespective of its etiology. Post-transplantation EPS patients, however, do not manifest as prominent an inflammatory response as reflected by lower CRP levels, and have a better survival in comparison to the classic form of EPS.

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EPS

Chapter 4

Post-transplantation encapsulating peritoneal sclerosis contributes significantly to mortality after kidney transplantation

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ABSTRACT

Background

Encapsulating peritoneal sclerosis (EPS) is a severe complication of peritoneal dialysis (PD) and may present after kidney transplantation, a condition known as post-transplantation EPS. The prevalence and impact of post-transplantation EPS on survival after kidney transplantation is unknown.

Methods

From January 1, 1996 until July 1, 2007, 1241 PD patients were transplanted in participating centers. Thirty-eight cases of post-transplantation EPS (3%) were identified from the Dutch multicenter EPS study.

Results

In EPS patients the mean pre-transplant dialysis duration was longer than in the controls (65.8 ± 30.7 versus 31.1 ± 22.6 months, p=0.0001). The majority of EPS cases were observed within the first two years after transplantation, but some cases appeared many years after transplantation. Two-hundred-and-one (16.2%) patients died after transplantation, of which seventeen EPS patients. After infection (23.9%), cardiovascular disease (21.9%) and malignancy (10.9%), EPS (8.5%) was the fourth known cause of death after transplantation. Kaplan-Meier analysis showed a significant decreased survival for transplanted patients with post-transplantation EPS compared to transplanted patients without EPS.

Conclusions

Post-transplantation EPS is rare but carries a high mortality. A prolonged clinical vigilance and a high index of suspicion for the diagnosis are warranted, specifically in PD patients with a relatively long cumulative pre-transplant duration of PD.

INTRODUCTION

Peritoneal dialysis (PD) is a well-established renal replacement therapy, preferred by many young patients with end-stage renal disease in good clinical condition. Most PD patients are eligible for kidney transplantation and there is no apparent difference in rate of infections or patient survival between transplanted PD and hemodialysis (HD) patients.[1,2] Early transplant function may even be improved in former PD patients receiving a deceased donor kidney transplantation.[3,4]

Common identified causes for death after kidney transplantation are primarily cardiovascular events followed by infections and malignancy.[5,6]

Encapsulating peritoneal sclerosis (EPS) is a clinical syndrome characterized by intestinal encapsulating and subsequent obstruction of the intestinal tract by formation of excessive peritoneal fibrosis tissue.[7] EPS is most frequently seen in patients treated with or having a history of PD. EPS has come to be recognized as a serious complication of PD with a high morbidity and a mortality of approximately 50%.[8]

A substantial proportion of EPS cases present after renal transplantation, an entity known as post-transplantation EPS. The pathophysiology of EPS is probably influenced by multiple factors. The widely accepted second hit theory assumes a progressively damaged peritoneum by prolonged use of dialysis fluids, which may be complicated by factors that aggravate the peritoneal sclerosis.[9] In support of this theory is the finding that EPS is related to longer PD duration.[10,11] The use of calcineurin-inhibitors after transplantation may promote EPS, as these drugs are considered profibrotic.

Recently, we showed an increasing incidence of EPS in the last decade with a surprisingly high frequency of EPS in the first years after renal transplantation.[12,13] The prevalence and impact of post-transplantation EPS on survival after kidney transplantation is unknown. We hypothesized that post-transplantation EPS may have a significantly contribution to the mortality after kidney transplantation, which has previously gone unrecognized. To test this hypothesis we analyzed the mortality due to EPS of transplanted PD patients in The Netherlands in the period 1996 to 2007.

MATERIALS AND METHODS

Design and setting

The design of the study was a retrospective multicenter study in the period January 1, 1996, until July 1, 2007. All data analyzed are from patients transplanted in the four participating university hospitals in The Netherlands; Erasmus Medical Center Rotterdam, University Medical Center Utrecht, University Medical Center Nijmegen and the Academic Medical Center, Amsterdam. The study protocol was approved by the medical ethics committee of the Erasmus Medical Center, Rotterdam.

Participants

All post-transplantation EPS cases in the study period January 1, 1996, until July 1, 2007 were previously identified by investigating the medical records and were described in the Dutch multicenter EPS study.[13] Medical records of patients with EPS were reviewed in detail by the investigating nephrologist, who was not the primary treating physician. The date of diagnosis of EPS was retrospectively set at the date at which the diagnosis fulfilled the definition of EPS and confirmed by two separate nephrologists. All EPS patients underwent abdominal CT scanning.

Variables

Two compatible national registries were used for collecting the additional data. Information regarding renal replacement therapy in the Netherlands was retrieved from RENINE. This is a clearly defined cohort of all patients with renal replacement in The Netherlands (RENINE, Registratie Nierfunctievervanging Nederland).[14] Information regarding the kidney transplantation was retrieved from the Dutch Transplantation Foundation, a registry for all transplanted patients in the Netherlands. From these two databases all transplanted PD patients were identified. All demographic, dialysis and transplantation-related variables were investigated using these databases and the medical records of patients. Pre-transplant PD period is calculated by adding all separate PD periods prior to the last transplantation for each patient.

Death due to EPS is defined as any cause related to the underlying EPS, for instance: ileus, abdominal infection and catheter (in case of parenteral nutrition)-related sepsis.

Immunosuppressive medication is reported in the transplantation database as induction therapy, at three months, 1 year and 2 years after kidney transplantation. For the statistical analysis the use of immunosuppressive medication at three months after the last kidney transplantation was used when part of the maintenance therapy. Tacrolimus and cyclosporin were grouped as calcineurin inhibitors (CNI's).

Classification and diagnosis of EPS

EPS was defined according the criteria developed by the Ad Hoc Committee of the International Society of Peritoneal Dialysis (ISPD).[15] It is defined as a clinical syndrome with persistent or recurrent presence of intestinal obstruction with or without the existence of inflammation parameters and the existence of peritoneal thickening, sclerosis, calcifications and encapsulation confirmed by macroscopic inspection or radiological findings.

Using this definition of EPS the studied population was limited to severe forms of intestinal obstruction that lead to persistent clinical problems, the necessity of surgical intervention, immunosuppressive therapy and/or the necessary use of total parental nutrition (TPN).

Statistical Methods

Data were entered and statistical tests were done in SPSS 17.0.1 datamanager (Chicago, USA). Means were compared using unpaired t-tests. Medians were compared with non-parametric tests (Mann Whitney). Proportions were compared with the chi-square test. A two sided p-value of less than 0.05 was considered to be statistical significant. Survival was further analyzed with Kaplan-Meier statistics.

RESULTS

Demographics

In the period January 1st 1996 - July 1st 2007 1241 PD patients were transplanted. Thirty-eight (3%) patients developed a severe EPS after kidney transplantation. All EPS patients had abdominal complaints of intestinal obstruction and were diagnosed with EPS according the ISPD guidelines. EPS patients were previously described in the Dutch multicenter EPS study.[13]

Table 1. Patient characteristics.

Variable	Controls	EPS patients	P-Value
Number of patients	1203	38	
Gender			
Female (%)	474 (39.4)	15 (39.5)	NS
Male (%)	729 (60.6)	23 (60.5)	NS
Cause of renal disease			
Glomerulonephritis	299 (24.9)	9 (23.7)	
Interstitial nephritis and pyelonephritis	125 (10.4)	5 (13.2)	
Cystic kidney diseases	129 (10.7)	2 (5.3)	
Congenital and hereditary kidney diseases	48 (4.0)	5 (13.2)	
Renal vascular disease, excluding vasculitis	165 (13.7)	5 (13.2)	
Diabetes mellitus	70 (5.8)	1 (2.6)	
Other multisystem disease	109 (9.1)	5 (13.2)	
Others	31 (2.6)	1 (2.6)	
Unknown	161 (13.4)	4 (10.5)	
Missing	66 (5.5)	1 (2.6)	
Time on pre-transplant peritoneal dialysis (months)	31.1 ± 22.6	65.8 ± 30.7	0.0001
Deceased patients (%)	184 (15.3)	17 (44.7)	< 0.0001

Months on pre-transplant dialysis as mean ± SD. Means were compared using t-test. Proportions were compared with chi-square test. NS=not significant.

Patient's characteristics and the transplantation related variables are shown in table 1 and table 2, respectively. In EPS patients, the pre-transplant PD duration was significantly longer than in the controls and they tended to be younger at last kidney transplantation. Ten EPS patients (26.3%) had a total PD duration shorter than 48 months. EPS patients had more kidney transplantations and more overall transplant failures compared to non-EPS patients. There was no significant difference in cause of transplant failure of the last kidney transplantation between the EPS and non-EPS group.

Table 2. Transplantation characteristics.

Variables	Control patients (1203)	EPS patients (38)	P-Value
Number of transplantations	1.20 ± 0.5	1.50 ± 0.8	< 0.0001
Donor last transplantation	Deceased: 767 (63.8%) Living: 436 (36.2%)	Deceased: 32 (84.2%) Living: 6 (15.8%)	< 0.0001
Mean age at last transplantation (years)	46.1 ± 14.7	42.0 ± 14.2	0.09
Overall transplant failure	0.32 ± 0.6	1.05 ± 1.1	< 0.0001
Transplant failure last transplantation	yes 139 (11.6%)	yes 21 (55.3%)	< 0.0001

Data as means ± SD, except for transplant failures of last transplant which are reported as number of patients. Means were compared using t-test, proportions were compared with chi-square test.

Figure 1 shows the prevalence of EPS patients in time after the last kidney transplantation. EPS patients were diagnosed with EPS with a median time of 12.4 months (IQR 6.2 – 45.6) after transplantation. Sixty percent of the patients were diagnosed with EPS in the first 2 years after the last kidney transplantation. Three patients developed EPS more than 6 years after the last transplantation. The mean PD duration of these three patients was not significantly different (mean 56.2 ± 18.2 months) from patients with post-transplantation EPS within 6 years after transplantation (67.6 ± 32.6 months, p-value 0.6). There was no difference in number of transplants and graft failures between these groups.

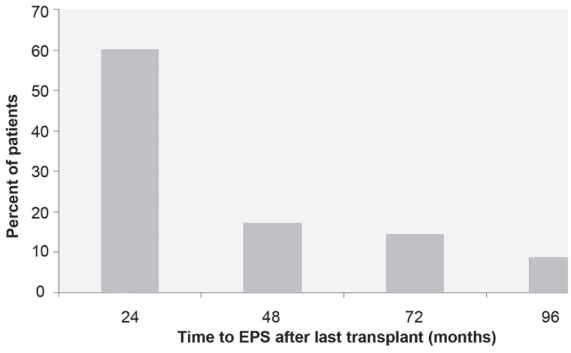


Figure 1. EPS after kidney transplantation.

CNI's were the mainstay of immune suppressive therapy in both EPS and non-EPS patients (respectively 85% and 95% of patients at 3 months after transplantation, p-value > 0.1). There was no significant difference in use of corticosteroids, azathioprine, mycophenolate mofetil, or sirolimus as maintenance therapy between EPS patients and the non-EPS group (data not shown).

Mortality

During the ten-years follow-up 201 patients died after transplantation. Infections and cardiovascular events are the most important causes of death after kidney transplantation. Seventeen EPS patients died due to EPS related causes, 184 non-EPS patients died due to other reasons. EPS patients died with a median time of 15.2 months, (IQR 7.6 – 35.0), after the EPS diagnosis. Specific details about causes of death in the first two years after kidney transplantations are shown in table 3. Overall EPS related mortality after kidney transplantation is 8.5%, which results in the fourth known cause of mortality after kidney transplantation (Figure 2). There remains a large group of death due to unknown cause. Kaplan-Meier analysis showed that patients with post-transplantation EPS had a significantly decreased survival after transplantation compared to patients without EPS (Figure 3).

Table 3. Diagnosis of death after kidney transplantation.

Cause of death	Overall	Percentage occurring within one year of transplantation	Percentage occurring within two years of transplantation
Infections	48 (23.9%)	15 (31.3%)	19 (39.6%)
Cardiovascular disease	44 (21.9%)	24 (54.5%)	26 (59.1%)
Malignancy	22 (10.9%)	4 (18.2%)	5 (22.7%)
Encapsulating Peritoneal Sclerosis	17 (8.5%)	6 (35.3%)	8 (47.1%)
Gastrointestinal	11 (5.5%)	7 (63.6%)	7 (63.6%)
Cerebrovascular accident	6 (3.0%)	-	2 (33.3%)
Social	6 (3.0%)	2 (33.3%)	2 (33.3%)
Pulmonary embolus	5 (2.5%)	3 (60.0%)	3 (60.0%)
Haemorrhage	3 (1.5%)	1 (33.3%)	1 (33.3%)
Other	8 (4.0%)	1 (12.5%)	3 (37.5%)
Unknown	31 (15.4%)	4 (12.9%)	7 (22.6%)
Total number	201 (16.2%)	67 (33.3%)	83 (41.3%)

Data in numbers of patients (%). One and two-years post-transplantation represents deaths at one and two years after kidney transplantation (% of total of each cause of death).

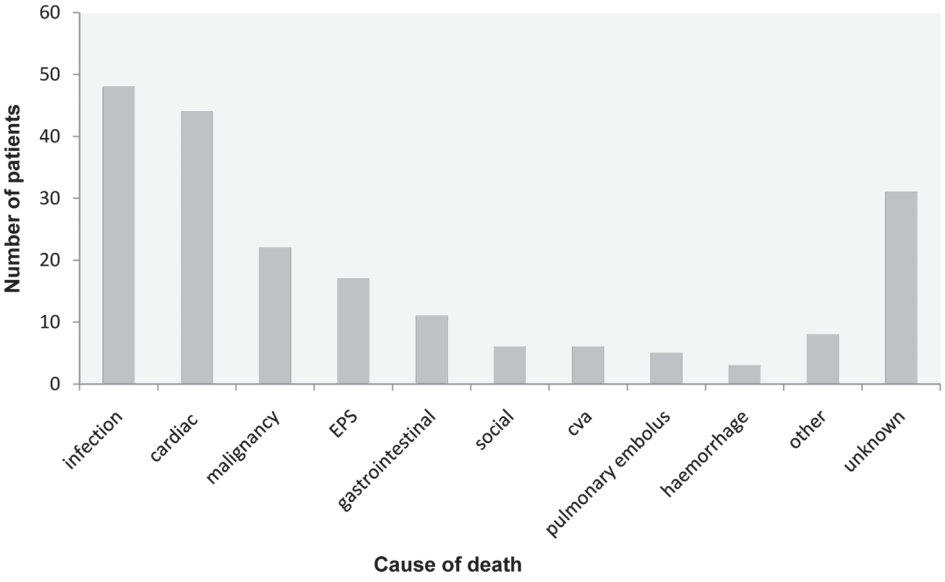
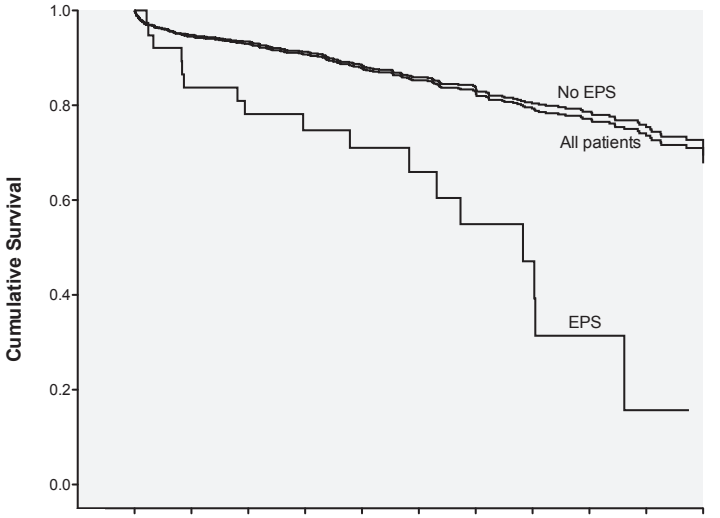


Figure 2. Overall causes of death after kidney transplantation.

DISCUSSION

Post-transplantation EPS is a rare but severe complication in transplanted PD patients. Next to already known causes of death, like 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 contribution of EPS to mortality after kidney transplantation was previously not investigated and our findings can therefore not be compared to other studies. However, our general results, showing the various proportions of different causes of death after kidney transplantation, are comparable to other reports.[16] In accordance with other studies, there remains a large group of unknown causes of death.[5] In the past the EPS-related mortality was possibly included in this group or in a group with gastro-intestinal causes.

Post-transplantation EPS appears to be a new phenomenon in transplantation practice. A recent Scottish study showed that the contribution of post-transplantation EPS might be even as much as 50% of the total EPS patients.[17] It differs from the classic form of EPS, which is predominantly associated with long term PD (longer than 5 years) and changed peritoneal membrane function, resulting in ultrafiltration failure. This latter form is extensively described in Japan, where patients tend to stay on PD longer, because kidney transplantation is limited.[10] In contrast,



Number at risk											
No EPS	1203	1019	898	766	644	510	413	323	236	153	87
EPS	38	30	27	22	17	13	8	6	3	1	0
Cumulative number of events											
No EPS	0	61	75	95	118	134	145	161	167	175	184
EPS	0	6	8	9	10	11	13	14	16	17	17

Figure 3. Influence of EPS on ten-years survival of PD transplanted patients. Kaplan-Meier analysis with time after last transplantation, with analysis censored for ´time until end of study or death´. Data presented as univariate analysis, P-value < 0.001

post-transplantation EPS patients tend to be younger when initiating PD and do not necessarily have a prolonged PD duration.[13,18] In this study, patients with post-transplantation EPS had a significantly longer PD duration compared to transplanted patients without EPS. The longer cumulative duration of PD may be partly explained by a higher frequency of transplant failure in this group. As pre-transplant PD duration is implicated as a risk factor for post-transplantation EPS, this information should be part of the informed consent procedure before transplantation. However, one must realize that there is a large variation in PD duration. This is shown in the current study, where a considerable number of EPS patients (26%) had a PD duration shorter than 48 months. The study design did not allow for a reliable multivariate analysis of this large variation and/or the impact on the incidence of post-transplantation EPS.

The post-transplantation EPS patients usually become symptomatic shortly after kidney transplantation, as was also shown in a recent study from the United Kingdom.[19] In this study, 21 post-transplantation EPS patients (identified from a total of 111 EPS patients) were diagnosed

with a mean time from transplantation of only 5.4 months (1-19 months). In the current study the majority of EPS cases were also observed within the first two years after transplantation. However, in some patients the diagnosis was even made after a number of years after transplantation. The clinical implication is that a prolonged clinical vigilance and a high index of suspicion for the diagnosis are warranted. Furthermore, our findings contribute to the ongoing discussion whether young PD patients should prematurely be transferred to HD after a few years of PD while awaiting transplantation or after transplant failure.[20,21]

The etiology of post-transplantation EPS is yet unknown. But there are several hypotheses. The current accepted pathophysiological theory on EPS in general, is that the peritoneal membrane is preconditioned by damaging PD solutions. In reaction to this a repair process develops with an increased inflammation. After a second hit, such as a fungal peritonitis, this might result in an uncontrolled fibrosing process with an encapsulating of the intestines.
In post-transplantation EPS the relationship with the moment of transplantation is striking, suggesting that transplantation might impose the second hit. A possible explanation of the association with transplantation might be the discontinuation of peritoneal lavage of profibrotic factors after successful kidney transplantation. Another hypothesis is that post-transplantation EPS might be related to the concomitant use of profibrotic CNI's. In the damaged peritoneum there is already an upregulation of TGF-β, which leads to fibrosis and neoangiogenesis.[22] Both tacrolimus and cyclosporin also lead to enhanced TGF-β expression and subsequent fibrosis.[23] The additional administration of cyclosporin to an experimental rat model of chronic peritoneal exposure to dialysis solutions indeed leads to EPS like abnormalities.[24]
Furthermore, the introduction of CNI's has led to a trend to lower corticosteroids after kidney transplantation. Corticosteroids may, however, have a beneficial effect on the inflammatory state during the development of EPS. The role of CNI's in post-transplantation EPS remains unclear and given the evidence it is premature to conclude that the use or absence of CNI's are associated with EPS development.

The current study has a retrospective design with its obvious limitations. One might argue that this design could lead to an underestimation of diagnoses, other than EPS. This is partially diminished because the used registries collect their data at the actual time of treatment with only a slight delay. There were some missing values in the use of maintenance immunosuppressive medication. These were equally distributed among both groups and it mainly concerned patients with kidney transplantation in the early nineties.

Once EPS has been diagnosed the therapeutical options are limited. Surgical treatment with extensive enterolysis might be successful, but it requires an experienced surgeon and has a high risk of recurrence and complications.[25] Successful treatment of EPS with immunosuppressive

medication such as high dose steroids, azathioprine and mycophenolate mophetil has been described[10,26,27], but these reports are anecdotal. Finally, we recently showed that tamoxifen treatment of EPS is associated with an increased patient survival.[28]

In conclusion, post-transplantation EPS occurs infrequently but contributes significantly to a decreased survival in transplanted PD patients. A prolonged clinical vigilance and a high index of suspicion for the diagnosis is warranted, specifically in PD patients with a relatively long cumulative pre-transplant duration of PD.

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EPS

Chapter 5

Post-transplantation encapsulating peritoneal sclerosis without inflammation or radiological abnormalities

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BMC Nephrology. 2013;14:203

ABSTRACT

Background

Post-transplantation encapsulating peritoneal sclerosis (EPS) causing bowel obstruction has been identified as a serious complication after kidney transplantation in patients previously treated with peritoneal dialysis. Systemic inflammation and abnormalities on an abdominal computed tomography (CT) scan are important hallmarks of EPS. To our knowledge, this is the first report of a case being diagnosed with late-onset post-transplantation EPS without systemic inflammation or abnormalities on a CT scan which could only be diagnosed by laparotomy.

Case presentation

A 59-year old female presented because of symptoms of bowel obstruction 33 months after kidney transplantation. The patient had a 26-month history of peritoneal dialysis before her first kidney transplantation and was treated with peritoneal dialysis for 4 years before undergoing a second kidney transplantation. Physical examination was unremarkable and laboratory tests showed no signs of systemic inflammation (C-reactive protein <1mg/L). An abdominal CT scan did not reveal any abnormalities fitting the diagnosis of EPS, except a "feces sign". Given the severity of the progressive symptoms, a diagnostic laparotomy was performed, visualizing a classical EPS. Total peritonectomy and enterolysis were performed, leading to restoration of peristalsis.

Conclusion

EPS may occur several years after kidney transplantation in the absence of inflammation and typical radiological abnormalities. Obtaining a diagnosis of post-transplantation EPS is challenging, however, a low threshold for surgical exploration in case of high clinical suspicion and negative findings on the CT scan is mandatory.

BACKGROUND

Encapsulating peritoneal (EPS) sclerosis is a rare but potentially lethal complication of peritoneal dialysis (PD) treatment, characterized by excessive sclerotic and fibrotic thickening of the peritoneal membrane, which may eventually lead to bowel obstruction.[1,2] In recent years, EPS occurring after kidney transplantation (KTx) in patients who were previously being treated with PD (coined post-transplantation EPS) is increasingly observed.[3,4] The prevalence of post-transplantation EPS is reported to be 1-3% in PD patients undergoing KTx and is associated with significant mortality.[4-6] The prognosis of EPS can be substantially improved by treating with tamoxifen, anti-inflammatory drugs, and timely surgical intervention.[7,8]

The time from KTx until development of post-transplantation EPS is typically short with the vast majority occurring within the first year after transplantation.[4,9,10] In most cases, EPS is accompanied by systemic inflammation.[11] The presence of symptoms of obstructed bowel movements and characteristic findings on computed tomography (CT) scan of the abdomen are mandatory for the clinical diagnosis of EPS.[1,12] We here report a unique case of post-transplantation EPS presenting 33 months after KTx in a patient with progressive symptoms of intestinal obstruction without systemic inflammation and absence of typical radiological abnormalities. This unusual presentation emphasizes the value of considering a diagnosis of EPS even several years after KTx. Whenever there is a high degree of suspicion for this condition in former PD patients undergoing KTx, a laparotomy by a surgeon with EPS experience is recommended.

CASE PRESENTATION

A 59-year old female was referred to our EPS center outpatient clinic because of progressive symptoms of bowel obstruction almost 33 months after KTx. The nausea, vomiting and abdominal pain predominantly occurred shortly after eating solid meals. The patient's medical history included end stage renal disease secondary to polycystic kidney disease. She had a 26-month history of PD before her first KTx and was treated with PD for almost 4 years before undergoing her second transplantation with a kidney from a living donor. During PD treatment she had no signs of ultrafiltration failure and had experienced one uncomplicated peritonitis episode with Staphylococcus aureus.

Her symptoms had started insidiously one year after transplantation while she received a tacrolimus-based immunosuppressive regimen. Diagnostic work-up did not show any signs of inflammation with normal radiological imaging of the abdomen. Almost 23 months after her last transplantation a diagnostic laparoscopy was performed elsewhere, but no macroscopic abnormalities were reported.

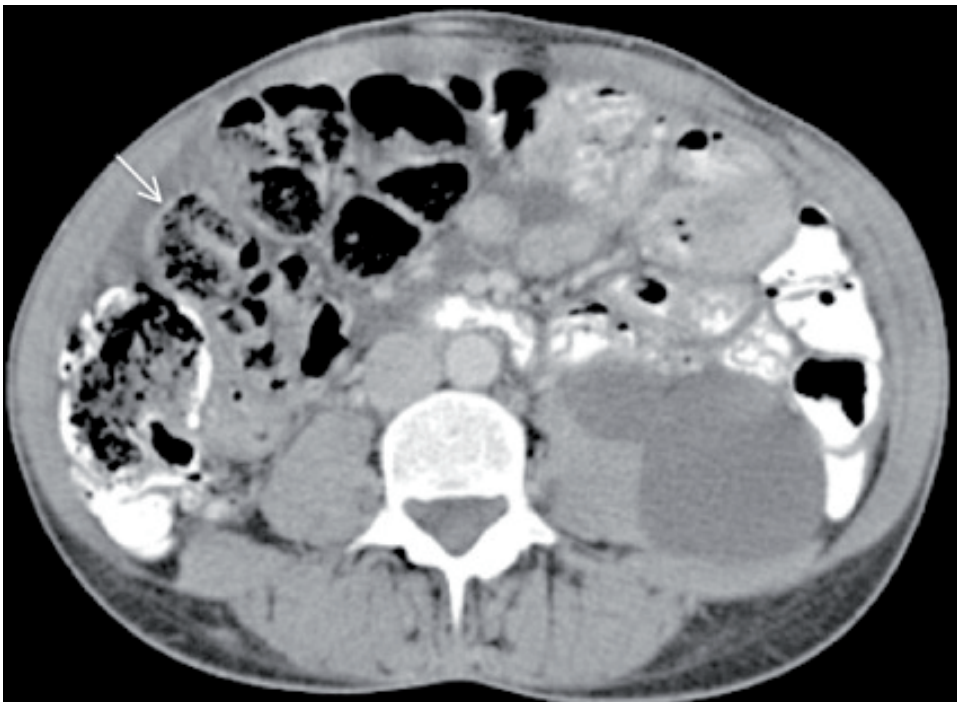

Figure 1. Abdominal computed tomography scan demonstrating the presence of feculent material in the small bowel (arrow) and a small amount of localized ascites.

However, peritoneal biopsies were taken and showed signs of fibrosis without active or chronic infiltration. As the symptoms and weight loss persisted, she was referred to our clinic for a second opinion.

At presentation she had lost 5 kilograms of weight over the last year (BMI 19kg/m^2) and was unable to tolerate solid foods. No abnormalities were found at physical examination, and laboratory tests showed no signs of systemic inflammation (C-reactive protein (CRP) < 1 mg/L, albumin 40 g/L) and adequate graft function (serum creatinine 91 umol/L). A recent abdominal CT scan did not reveal any abnormalities compatible with the diagnosis of EPS although a "feces sign", consisting of intraluminal feculent material in the small bowel, was observed (Figure 1). Additionally, the CT scan showed a small amount of localized ascites in the abdomen but no other diagnostic signs of EPS like bowel tethering, calcifications, or peritoneal thickening. Despite the absence of typical findings, but the severity of the progressive symptoms we considered the possibility of localized EPS, a condition in which the peritoneum shows encapsulating sclerosis predominantly at the level of the terminal ileum.[13,14]

Surgical exploration was considered as a final diagnostic procedure. During the operation, a classical picture of EPS was found characterized by a thin cocoon-like sclerotic membrane encasing the small bowel (Figure 2A). A complete resection of the encapsulating sclerotic membrane and total enterolysis were performed, combined with complete removal of the thickened visceral peritoneal membrane (Figure 2B), which lead to restoration of peristalsis durante operationem. Histologic evaluation of the visceral peritoneal membrane was performed, supporting the diagnosis of EPS, and showed dense sclerosis with patchy mononuclear cell infiltration (Figure 3). On the fifth postoperative day, an emergency ileocecal resection with protective loop ileostomy was necessary because of a perforation at the level of the ileocecal junction where a serosal injury had been made during the first operation. The patient recovered soon after surgery, and in an attempt to prevent further recurrences, was prescribed 10 mg twice-daily tamoxifen and 10 mg once daily prednisolone. After five weeks the loop ileostomy was closed and bowel continuity restored, with an uneventful postoperative course. One year after EPS surgery, the patient has gained almost 20 kilograms in body weight and is doing well with a stable graft function and without clinical signs of EPS recurrence.

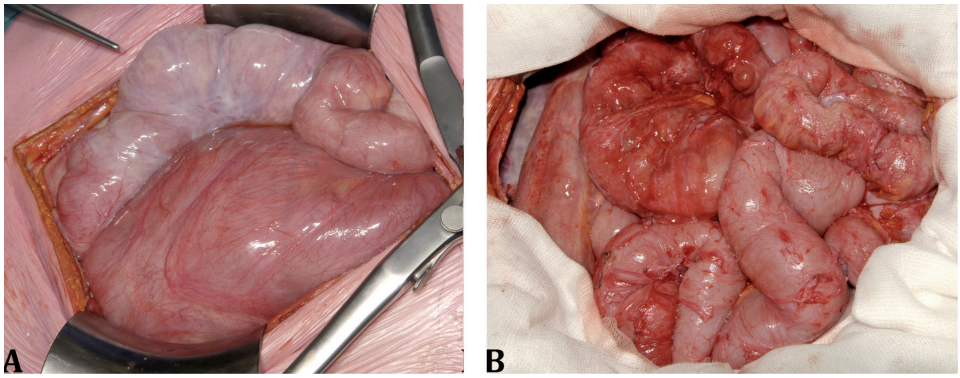

Figure 2. Macroscopic appearance of EPS before and after surgery. During the laparotomy, a classical picture of EPS was observed characterized by a thin cocoon-like sclerotic membrane encasing the small bowel **(A)**. A complete resection of the encapsulating sclerotic membrane and total enterolysis were performed, combined with removal of the thickened visceral peritoneal membrane **(B)**.

DISCUSSION

We report a case of late-onset EPS in a patient presenting 33 months after KTx, with the diagnosis being suspected only on basis of her history of PD and progressive symptoms of intestinal obstruction.

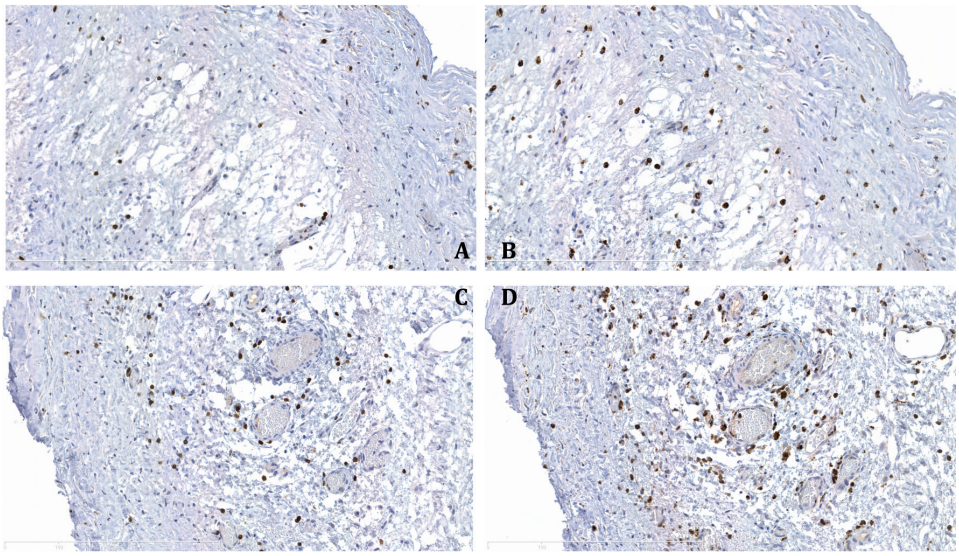

Figure 3. Microscopic evaluation of the visceral peritoneal membrane revealed dense sclerosis with patchy mononuclear cell infiltration. Immunostaining with anti-CD3 antibody **(A,C)** and anti-CD68 antibody **(B,D)**. Original magnification X 200. Scale bar represents 400 µm.

The risk of developing EPS primarily depends on the duration of PD, however, EPS occurs more frequently in patients discontinuing PD treatment.[9,15] In this respect, post-transplantation EPS has gained attention in recent years. The timeline from KTx until diagnosis of EPS varies widely from just a few months to over 2 years. However, most cases of post-transplantation EPS develop within the relatively short time period of one year after transplantation.[4,5,9,10]

The current leading theory of EPS pathophysiology assumes that a second hit on an inflamed peritoneal membrane may play an important role in the development of EPS.[2] In line with this theory, cessation of PD treatment causing accumulation of inflammatory and fibrotic mediators[16] may serve as a "second hit" in the development of post-transplantation EPS. In addition, the time from KTx until final EPS diagnosis in our patient was relatively long while patient received tacrolimus monotherapy, and therefore in support of the concept that transplantation per se or exposure to a profibrotic calcineurin inhibitor may have played a role in the development of EPS.

Reaching a definite diagnosis of post-transplantation EPS can be difficult, as is illustrated by our patient, due to aspecific symptoms of bowel obstruction and absence of typical radiological findings. Classically, EPS has an initial inflammatory phase with elevated markers of inflammation, such as CRP.[2,11,17] In this case, the patient presented with a non-elevated CRP level. This finding may be explained by the fact that EPS in this patient was detected in its final stage in which the process of inflammation subsided and only a cocoon-like thickened peritoneal membrane remained.

The CT scan aids in the diagnosis of EPS, and according to Tarzi and colleagues may reveal characteristic findings such as peritoneal calcifications, peritoneal thickening, bowel tethering and ascites.[12] In our patient, only a "feces sign[18]" was detected, which may indicate a stenosis in the small bowel, but no classic signs of EPS were found. The thin nature of the sclerotic membrane that covered the bowels apparently prevented detection by CT scan and could only be detected during surgical exploration. The final diagnosis in our patient was made during an exploratory laparotomy, indicating that a low threshold for surgical exploration is needed in case of high clinical suspicion and negative findings on the CT scan. Additionally, surgical exploration can offer a therapeutic benefit as soon as EPS is confirmed, as peritonectomy and enterolysis can be performed during the same operation.

Although steroids and tamoxifen have shown to be of benefit in the treatment of EPS, this may only be the case in the early stage of active disease that is characterized by elevated markers of inflammation.[11] The ultimate treatment of EPS is surgery, involving resection of the sclerotic membrane. Our patient developed a peritonitis on the fifth day after surgery due to a perforation at the ileocecal junction, based on a single serosal injury that was made during the initial operation, and which was sutured straight away. This underscores the hazards of EPS surgery, which is a challenging and time consuming procedure, and preferably should be performed in a specialized center.[19] In experienced hands, elective EPS surgery has a mortality rate <10 %[20], however, this may be much higher in patients with an acute indication. Recurrence rates after surgery are high and reported to be 25% in some studies.[21] Our patient received tamoxifen and prednisolone until one year after surgery. Although the benefits of tamoxifen have not been clearly determined, it is believed to have antifibrotic properties[1] and therefore may be useful in preventing recurrences.

CONCLUSION

In conclusion, EPS may occur several years after transplantation in the absence of systemic inflammation and typical radiological abnormalities. Obtaining an accurate diagnosis of post-transplantation EPS is challenging, however, a low threshold for surgical exploration in case of high clinical suspicion and without positive findings on the CT scan is mandatory. Surgical treatment for EPS by an experienced surgeon may be indicated to restore bowel movement, improve nutritional status, and alleviate symptoms. Furthermore, surgical exploration in a specialized center should be considered earlier rather than later when EPS is suspected. Finally, this case underscores the important value of considering a possible diagnosis of late-onset EPS even several years after KTx in patients with a long duration of pre-transplant PD.

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EPS

Chapter 9

Localized encapsulating peritoneal sclerosis constricting the terminal ileum-an unusual appearance requiring surgical intervention

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Peritoneal Dialysis International. 2013;33(5):503-6

ABSTRACT

Background

Encapsulating peritoneal sclerosis (EPS) is a rare complication of peritoneal dialysis (PD). It is characterized by encapsulation of the bowel, causing symptoms of intestinal obstruction. Exclusive involvement of parts of the bowel may occur and may be more common than previously thought. Our main objective was to investigate and report on patients with localized EPS.

Methods

Between July 2002 and December 2011, 9 of 17 EPS patients were referred to our department of surgery for a diagnostic laparotomy. Three of the 9 cases showed localized encapsulation of the small bowel and were selected for the purpose of this study.

Results

All 3 patients presented with an acute inflammatory state and symptoms of bowel obstruction. In 2 patients, EPS became clinically overt after kidney transplantation; the third patient was diagnosed while on hemodialysis. All shared a history of PD ranging from 31 to 101 months. In none of the patients was radiologic examination conclusive, although 2 showed peritoneal thickening and ascites. Each patient underwent laparotomy, confirming EPS. In all cases, a thickened peritoneal membrane became apparent, predominantly covering the ileocecal region of the intestine. In addition, a constrictive membrane at the level of the terminal ileum was noted. In 2 cases, the patients underwent enterolysis and dissection of the constricting fibrotic peritoneal membrane (peritonectomy) without bowel resection. The 3rd patient was managed with parenteral nutrition and tamoxifen. The postoperative course in 1 patient was complicated by infected ascites that resolved with antibiotic treatment. Eventually, all patients were doing well, with adequate oral intake and without the need for repeat surgery.

Conclusions

Localized EPS may be more common than previously thought. It has a predilection for the level of the terminal ileum. We believe that an elective diagnostic laparotomy should be considered early, because this procedure offers both diagnostic opportunities and therapeutic options. Localized EPS cases may benefit most from enterolysis and peritonectomy.

INTRODUCTION

Encapsulating peritoneal sclerosis (EPS), a rare complication of peritoneal dialysis (PD), can become manifest in the course of PD treatment or in former PD patients after transfer to hemodialysis (HD) or receipt of a kidney graft. The single most important risk factor for EPS is the cumulative time on PD.[1] It is postulated that the disease is the consequence of an inflammatory healing response of a peritoneum that has been exposed to bioincompatible dialysis fluids. The result is excessive thickening of the peritoneal membrane surrounding the bowel, which may eventually cause symptoms of intestinal obstruction.

A diagnosis of EPS can be made when symptoms of obstructed bowel passage are present in combination with characteristic computed tomography (CT) findings.[2] In some cases, though, a definite diagnosis of EPS requires surgical exploration. The classical macroscopic appearance of EPS is total encapsulation of the bowel by a fibrotic membrane.[3] However, exclusive involvement of parts of the bowel may occur and could be more common than previously reported. Our main objective was to investigate and report on patients with localized EPS.

METHODS

Between July 2002 and December 2011, 17 EPS cases of EPS were diagnosed at our center. Of the affected patients, 9 were referred to the department of surgery for diagnostic laparotomy. Patient histories were analyzed in reference to the renal replacement therapy, clinical picture, radiologic findings, surgical findings, and treatment. When surgical exploration showed localized encapsulation in the abdominal cavity, the presentation was defined as localized EPS, and the patient was selected for the purpose of this study. The study was approved by the institutional board of the medical ethics committee of the Erasmus Medical Center.

RESULTS

In this group of 9 patients referred for diagnostic laparotomy, 3 were classified as having localized EPS. The case histories of those patients are described next.

CASE 1

A 28-year-old male was admitted to our hospital 1 week after removal of his PD catheter because of ileus and elevated serum C-reactive protein [CRP (152 mg/L)]. Nine months earlier, he had undergone an uncomplicated second kidney transplantation (KTx), with serum creatinine of 131 µmol/L. Plain radiography showed multiple dilated small bowel loops with fluid levels. Imaging of the abdomen by CT revealed mesenteric infiltration that was focused mainly in the right lower quadrant, ascites, and a marginally thickened peritoneum. Those findings were not considered diagnostic for EPS.

The patient's medical history included end-stage renal disease secondary to tubulointerstitial nephropathy. He had a 15-month history of PD before his first KTx and 86 months before his second KTx. The clinical course during his second PD period was complicated by 3 episodes of peritonitis. His immunosuppressive regimen included prednisone, tacrolimus, and mycophenolate mofetil. He had experienced intermittent attacks of abdominal pain 3 weeks before admission.

The patient's condition did not improve with a conservative approach (intravenous fluids, bowel rest, and a nasogastric suction), and a diagnostic laparotomy was performed. Inspection of the small bowel identified proximal dilatation. Specifically, about 20 cm of the terminal ileum was covered by thickened and fibrotic peritoneal membrane, with an additional overlying adhesion band. The constricting adhesion band was cleaved, thereby releasing the contained part of the bowel and restoring normal peristaltic movement. Parenteral nutrition was instituted for 10 days, and the patient was discharged 21 days postoperatively in good clinical condition.

Symptoms of obstructive bowel passage recurred at 5, 11, and 21 months after the initial diagnosis. During all episodes, strict dietary regulation using a liquid diet or total parenteral nutrition resulted in quick resolution of symptoms. The patient was started on 10 mg tamoxifen twice daily, which may have contributed to the prevention of further recurrences. After 8 years of follow-up, the patient is doing well, with adequate oral intake.

CASE 2

A 37-year-old man was admitted to our hospital because of a fourth episode of recurrent ileus. The patient's medical history revealed end-stage renal disease secondary to focal segmental glomerulosclerosis. He was successfully transplanted after being treated with PD for 26 months without any infectious complications. Immunosuppressive therapy consisted of prednisone, tacrolimus, and mycophenolate mofetil. At 2.5 years after KTx, this patient experienced progressive loss of graft function because of recurrent focal segmental glomerulosclerosis, necessitating re-initiation of PD treatment. A transplantectomy was performed 5 months later, incurring peritoneal damage that necessitated HD treatment thereafter.

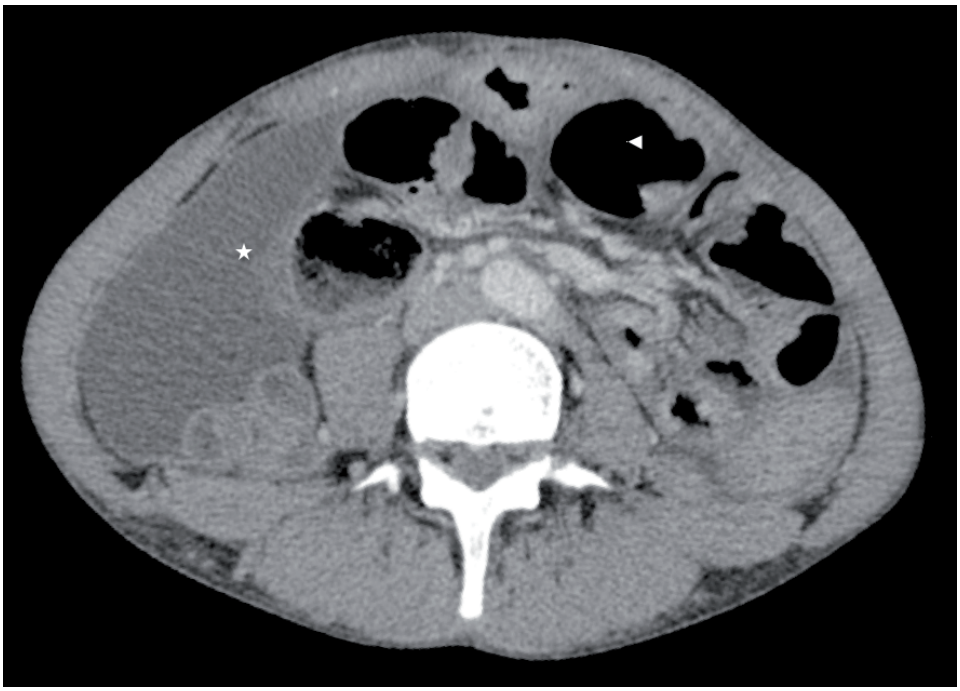

Figure 1. Computed tomography imaging of the abdomen in case 2 showed dilated small-bowel loops (arrowhead) and ascites (star), but no classical signs of encapsulating peritoneal sclerosis

At 2.5 months after the switch to HD, the patient presented with symptoms of bowel obstruction. This complaint initially responded to conservative management, but eventually persisted. The patient's serum CRP was elevated, reaching a maximum of 238 mg/L. Imaging of the abdomen by CT showed dilated small bowel loops, but no classical signs of EPS (Figure 1).

The history of this patient's recurrent obstructive symptoms and multiple admissions led to an exploratory laparotomy, during which a white and slightly thickened peritoneum was observed covering the small intestine (Figure 2), liver, and spleen. In particular, an obvious sclerotic layer was noted, encasing a loop of the terminal ileum. Enterolysis and stripping of the sclerotic layer were performed, releasing the encased bowel loop, which regained motility. The post-operative course was uneventful and total parenteral nutrition was instituted until bowel movements returned. The patient was discharged after 17 days, thereafter started a normal diet, and continued on tamoxifen therapy (20 mg once daily).

CASE 3

A 52-year-old male renal graft recipient was admitted to our hospital with a 2.5-month history of diarrhea, subacute abdominal pain, nausea, and vomiting. This patient had a history of diabetic end-stage renal disease, for which he was treated with PD for 32 months without experiencing any peritonitis episodes. He had undergone a living-donor KTx 6 months before the current admission and received a triple immunosuppressive regimen of prednisone, tacrolimus and mycophenolate mofetil.

Abdominal examination revealed ascites, right upper quadrant tenderness, and right lower quadrant pain on palpation. Laboratory tests showed signs of systemic inflammation (CRP 40 mg/L) and a serum creatinine of 129 µmol/L. Ascitic fluid examination was negative on bacterial culture.

Abdominal radiography showed dilated loops of jejunum with small-bowel air–fluid levels. Abdominal CT imaging showed massive ascites, small-bowel ileus, and a slightly thickened peritoneal membrane.

In a planned diagnostic laparotomy**,** thickened peritoneum covered by a whitish membrane was found to be encasing the part of the jejunum proximal to the ileocecal area. In particular,

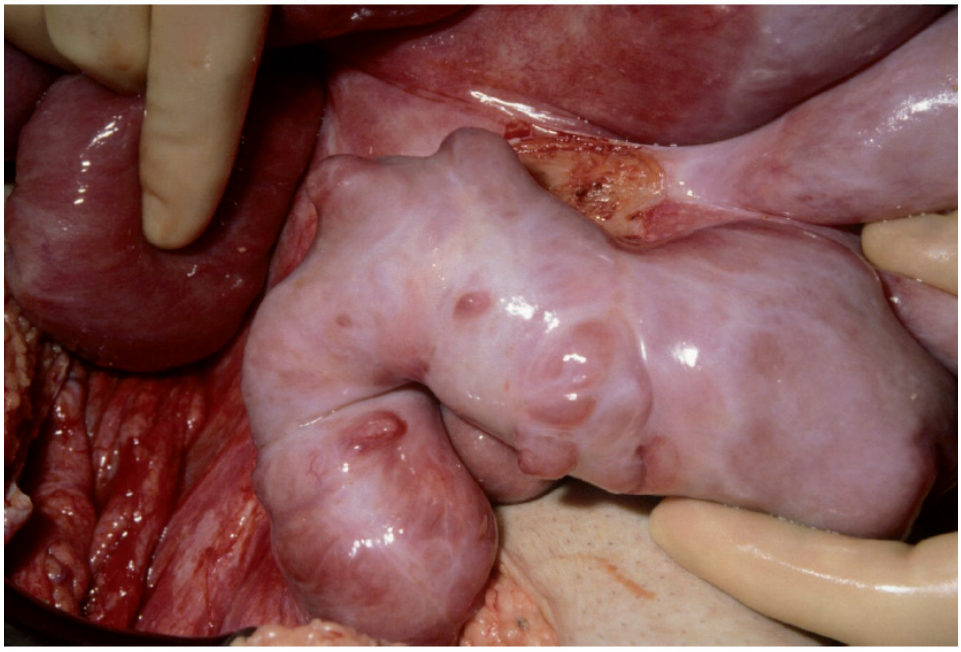

Figure 2. Localized appearance of encapsulating peritoneal sclerosis at laparotomy.

constrictive stenosis of the terminal ileum because of the thickened peritoneum was noted. The patient's postoperative period was complicated by infected ascites, successfully treated with antibiotics. Conservative treatment was continued, with the addition of total parenteral nutrition. The patient's serum CRP returned to normal in 5 weeks, and the patient was discharged from hospital with restored bowel passage and adequate oral intake. Because of recurrent symptoms of bowel obstruction, this patient was given tamoxifen therapy (20 mg twice daily). Thereafter, the number and severity of recurrent episodes of bowel obstruction markedly decreased, and he died of untreatable ischemic cardiac disease 8 years after the initial diagnosis of EPS.

DISCUSSION

In the cases presented, an intraoperative diagnosis of localized EPS was made in 3 patients who presented with an acute inflammatory state and symptoms of bowel obstruction. In 2 patients, EPS became clinically overt after KTx; the third patient was diagnosed while on HD. They all shared a history of PD, with cumulative exposures of 101, 31, and 32 months respectively. In none of the patients was radiologic examination conclusive, and the final diagnosis of EPS was made during laparotomy. In all 3 cases, an obviously sclerotic and thickened peritoneal membrane was observed, predominantly covering and constricting the terminal ileum. The number of localized EPS cases in our series is relatively small, but the condition is clearly not a rare finding and should be considered when a patient suspected for EPS shows few abnormalities on CT imaging. Classically, the macroscopic feature of EPS is a cocooning condition that involves nearly all parts of the small bowel.[3]

The specific findings in our cases may add interesting clues to the understanding of this rare disease. First, the appearance was unusual in that the ileocecal region was particularly involved. Only one other study has considered this localized pathology of EPS, reporting surgical exploration in a transplanted patient with a 5-year history of PD.[4] Second, the findings in our cases also demonstrate that it may be extremely difficult to establish a diagnosis of EPS preoperatively, especially when the process of fibrosis has not extended to the entire peritoneal surface of the abdominal cavity. Imaging of the abdomen by CT in cases 1 and 3 alerted us to a slightly thickened peritoneum and the presence of ascites. However, the exact nature of the lesion was not revealed. Tarzi *et al.* validated CT scoring parameters-including peritoneal calcification, bowel tethering, bowel wall thickening, dilated bowel loops, peritoneal thickening, and ascites-to assist in the diagnosis of EPS.[5] However, the same authors also suggested that CT imaging may not be conclusive in the early detection of EPS. The localized pathology in our patients adds another level of complexity, because it appears to be difficult to identify the condition by CT imaging. Our patients therefore highlight the need to consider a diagnostic laparotomy early as a definitive

diagnostic tool.

Immunosuppressive drugs and tamoxifen are reported to be of value in the management of EPS, especially in the inflammatory stage.[6] Tamoxifen is an antagonist of the estrogen receptor, and previous work suggests that its antifibrotic mechanisms of action could be be a result of inhibition of transforming growth factor β production.[7] This agent has also been used in the management of other fibrosing disorders, such as retroperitoneal fibrosis.[8] Eltoum *et al*.[9] previously reported resolution of peritoneal thickening 6 months after tamoxifen therapy in 1 patient. In addition, Korte *et al.*[10] reported mortality rates that were lower in EPS patients who were treated with tamoxifen than in those who were not. Unfortunately, the optimal medical treatment regime or the optimum dose of tamoxifen for EPS has not been established because no randomized controlled trials have been performed yet.

Surgical enterolysis is the recommended treatment when features of intestinal obstruction occur. In an observational retrospective study, Kawanishi *et al.*[11] outlined their experience with EPS surgery in 181 patients. Those authors presented favorable surgical outcomes with a postsurgical mortality of 7.7% and overall mortality of 35.4%. In agreement with them and with other authors, we believe that early surgical treatment should be undertaken in cases that present with severe and recurrent symptoms of intestinal obstruction, not resolving with conservative treatment. In 2 of our 3 cases, release of the constricting fibrous membrane and enterolysis were all that was required to free the bowel. In case 3, no surgery for the purpose of EPS relief was performed, although there seemed to be a clear indication for it during the laparotomy. The decision not to pursue surgery was taken because EPS surgery was considered to be a high-risk procedure, indicated only in selected cases of irreversible and complicated bowel obstruction.

CONCLUSIONS

Our cases highlight an unusual appearance of EPS. Localized EPS may be more common than previously thought and has a predilection for the level of the terminal ileum. We believe that an elective diagnostic laparotomy, preferably performed by a surgeon familiar with EPS surgery, should be considered early**,** because that approach offers both diagnostic opportunities and therapeutic options. Localized EPS cases may benefit most from enterolysis and a peritonectomy.

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EPS

Chapter 7

Management of encapsulating peritoneal sclerosis: a guideline on optimal and uniform treatment

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ABSTRACT

Encapsulating peritoneal sclerosis (EPS) represents a rare complication of long-term peritoneal dialysis (PD). It is characterized by diffuse peritoneal membrane fibrosis, progressive intestinal encapsulation and the clinical spectrum of intestinal obstruction. The pathogenesis is yet not well understood but includes inflammation, angiogenesis and fibrosis. The current diagnosis of EPS lacks specificity and relies on clinical, radiographic or macroscopic evaluation. There is no general agreement on managing EPS although accumulating clinical data suggest drug treatment (steroids, tamoxifen), surgery (enterolysis) or a combination of both. Here, we provide a short overview on the current knowledge of EPS, with a focus on treatment. Moreover, we present a diagnostic and a therapeutic algorithm for EPS based on the best available published data and our combined experience.

INTRODUCTION

Encapsulating peritoneal sclerosis (EPS) complicating peritoneal dialysis (PD) is a rare disease of the peritoneum characterized by the presence of an inflammatory and fibrotic peritoneal capsule, which partially or completely entraps the bowel.[1] The reported prevalence of EPS within the PD patient population ranges worldwide from 0.7 to 3.7%.[2-5] The time on PD is the most important risk factor for EPS, possibly because it represents the time the peritoneum is exposed to the potential harmful effects of dialysis fluids.[4] Other possible factors associated with the development of EPS include age at start PD, number of peritonitis episodes, fast peritoneal membrane transporter status, loss of ultrafiltration, and kidney transplantation.[6,7] Within the first few years of PD treatment, the incidence of EPS is usually less than 1%, but rises significantly after 2-3 years exceeding 15% in the group of patients on PD for 10 years or more (Figure 1). The overall number of patients on PD rapidly decreases within the first years after starting PD and after three years only 25% of the original cohort is treated with PD (Figure 2). Still, over 90% of all EPS cases have been treated with PD for more than three years (Figure 2). Unfortunately, the early stages of EPS are difficult to recognize although progressive loss of ultrafiltration is frequently

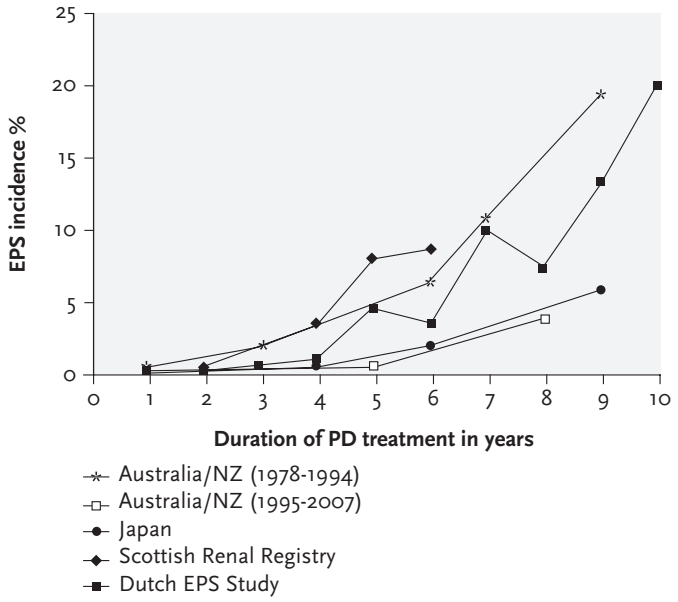

Figure 1. The incidence of encapsulating peritoneal sclerosis (EPS) in relation to duration of peritoneal dialysis (PD) treatment. The EPS incidence is not cumulatively shown and should be interpreted as the percentage of patients diagnosed with EPS within the population of patients treated with PD for a given number of years (shown on the x-axis). Data from Australia/New Zealand for two time periods (Rigby, 1998 and Johnson, 2010)[2,5], Japan (Kawanishi, 2004)[3], Scotland (Brown, 2009)[32], The Netherlands (Korte, 2011)[7] are shown.

observed in patients that go on to develop EPS.[8,9] The consequences of EPS are devastating and mortality rates exceed 50%, most commonly because of complications related to persistent bowel obstruction (e.g. perforation) and prolonged parenteral feeding.[2,5,10] Most cases of EPS (>50%) are reported after PD treatment has been stopped either because of symptoms of EPS, a non-resolving peritonitis, or kidney transplantation.[3,7] The last-mentioned condition is coined post-transplantation EPS and has been described as a novel entity.[11,12] Post-transplantation EPS has a major negative impact on patient survival after kidney transplantation and EPS-related mortality is the fourth known cause of death in this patient population.[13]

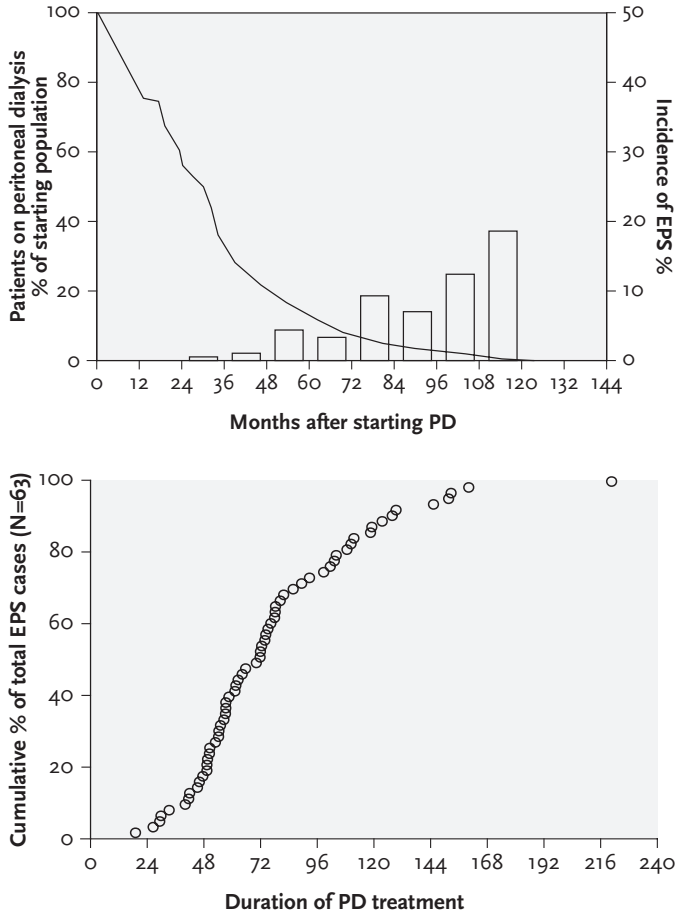

Figure 2. The top figure shows the percentage of patients who remain on peritoneal dialysis (PD) after starting treatment (black line, total number patients 126). The bars show the incidence of encapsulating peritoneal sclerosis (EPS) as the percentage of patients diagnosed with EPS within the population of patients treated with PD for a given number of months (shown on the x-axis). The bottom figure shows the cumulative percentage of EPS patients in relation to their time of treatment with PD. All data were obtained from the Dutch EPS study (Korte, 2011)[7]

Timely diagnosis and treatment of EPS seems warranted as it may offer the opportunity for resolving the bowel obstruction at an early stage, before complete encapsulation has occurred. Unfortunately, there is much uncertainty and delay in establishing the diagnosis of EPS. Furthermore, there is a lack of consensus on best therapeutic options to guide the management of EPS.

The Dutch EPS registry has been successfully launched in June 2009 and is currently collecting clinical data as well as related biological patient material of cases with a possible or definite diagnosis of EPS. It is a collaboration of the Dutch kidney centers and the Hans Mak Institute.[14] Also an expanding international collaboration with the UK registry and other European countries has been established recently.[15] The main goal of the registry is to track the routine clinical outcomes of patients with EPS and contribute to a better medical understanding of the disease.

The present article provides a short overview of the current knowledge on EPS, with a focus on treatment. We outline a rational strategy that can be used to guide the diagnosis and treatment of patients with EPS.

PATHOGENESIS

Appreciating the current knowledge on the mechanisms that lead to EPS is essential for the development of a management approach. EPS can be considered as an inflammatory repairing response of the peritoneum that has been damaged by chronic exposure to bio-incompatible dialysis fluids.[16,17] In an attempt to create a comprehensive overview of the disease, Kawanishi classified the disease into different stages.[18] In the early stages of EPS, the thin encapsulating membrane shows active inflammation. This is followed by elaboration of a thickened fibrotic membrane that progressively impairs normal bowel movement. Eventually the inflammation subsides and a thick acellular fibrotic membrane remains that encloses the intestines.[19] During PD treatment the peritoneal changes include submesothelial thickening and fibrosis, accompanied with neoangiogenesis.[20] A key pathological mechanism may be the epithelial to mesenchymal transition (EMT) of mesothelial cells (MC). In this process, new fibroblast cells arise from local conversion of MC by EMT.[21,22] Although it is as yet unclear to what extent EMT is also present in EPS development, TGF-beta (TGF-β) is one of the central regulators.[23] Other growth factors and molecules may also play a role in the development of EPS. In an experimental model of EPS, it was for instance noted that vascular endothelial growth factor is important in the EPS like changes of the peritoneal membrane.[24]

EPS usually develops after long-term PD, but not all long-term PD patients will necessarily develop EPS. Which factors cause or allow its development is not exactly known but a second hit may be an important trigger. The 'two-hit theory' hypothesizes that the preconditioned thickened and transformed peritoneum undergoes a second hit triggering symptomatic EPS.[25] This second event may be peritonitis, transplantation, or discontinuation of PD.[1,26]

DIAGNOSIS

The diagnosis of EPS lacks specificity but should include the clinical spectrum of intestinal obstruction with or without the existence of inflammation parameters and the presence of peritoneal sclerosis confirmed by macroscopic inspection or radiological findings.[27] The appearance of ultrafiltration failure, bloody ascites, and elevated markers of inflammation such as C-reactive protein (CRP) may express the early inflammatory nature of the disease.[18] Unfortunately, in most cases EPS is diagnosed when abdominal pain due to recurrent or chronic bowel obstruction becomes clinical manifest.[28,29] Physical examination may indicate the presence of ascites or ileus in the abdomen. In some instances a palpable abdominal mass is found.[30] As none of these findings is specific, other diagnoses such as infections, tuberculosis, pancreatitis and malignancies (e.g. lymphoma) should be ruled out.

The provisional diagnosis of EPS is usually made after radiographic evaluation by CT scan showing a characteristic picture of a thickened peritoneum encapsulating the intestines.[31-33]

In case of clinical suspicion and a negative CT scan, diagnostic surgery (laparoscopy or laparotomy) can provide the diagnosis.[25,34] It also facilitates taking peritoneal biopsies to detect early EPS or exclude other causes.[35] However, surgical exploration is a challenging decision as extensive peritoneal fibrosis and bowel loops adherent to one other may exist.[1] Therefore, we advocate performing diagnostic surgery timely to establish the diagnosis of EPS with certainty.

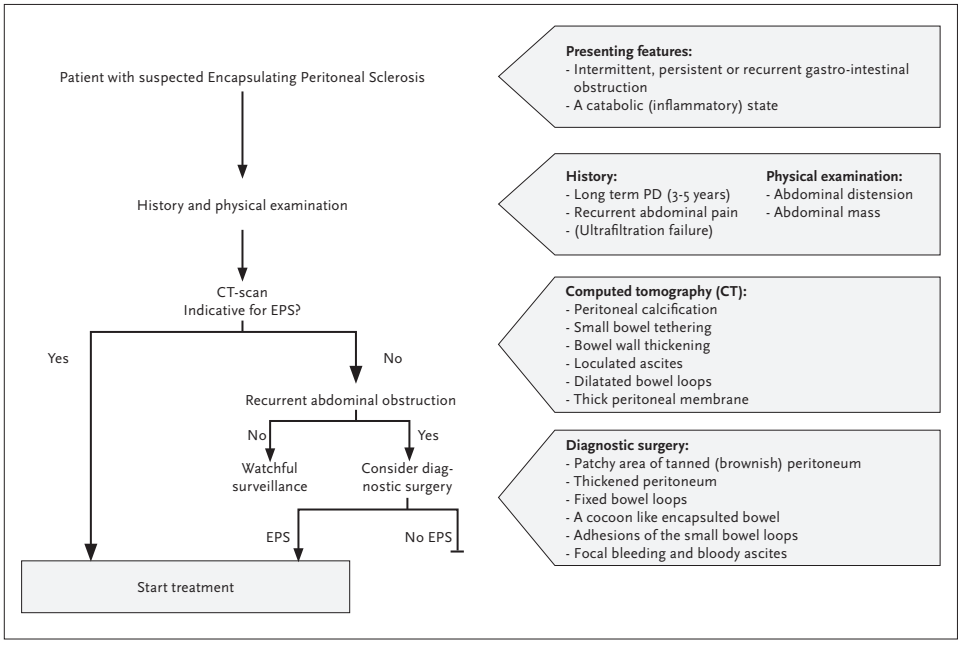

Figure 3. Proposed algorithm for the diagnosis of encapsulating peritoneal sclerosis.

TREATMENT

Cessation of PD treatment

An important initial step in the management of EPS is cessation of PD to prevent further peritoneal damage.[27,36,37] Although this approach seems reasonable, it is a matter of debate as this approach does not always reverse the progression of peritoneal fibrosis.[38] A logical explanation might be the absence of peritoneal lavage to remove fibrin, profibrotic factors and cytokines. Studies show that more than half of EPS cases are often diagnosed two years after stopping peritoneal dialysis and less severe cases of EPS may even worsen after discontinuation of PD.[3,32,39] Leaving the catheter in situ and performing regular peritoneal lavage in patients who have discontinued PD has been tried in Japan. However, no convincing evidence of a beneficial effect on the course of EPS has been reported yet.[3,40,41]

A clear statement on withdrawing patients from PD after the diagnosis of EPS has been established may be difficult. But given the association between PD duration and progression of EPS we propose a switch from PD to hemodialysis with removal of the PD catheter.

Immune suppressive medication

There is no agreement on the use of immune suppressive drugs to treat EPS. This is largely due to a lack of targeted pharmacologic therapies and absence of trials with a significant number of patients. Immunosuppressants like azathioprine, myocophenolate mofetil, and sirolimus have been used in patients with EPS, usually coadministered with corticosteroids.[42-44] But the available data are limited to anecdotal reports and the superiority of these drugs to corticosteroids alone is not proven. Here we summarize the two best-documented management strategies for EPS: corticosteroids and tamoxifen. We propose an algorithm, which is based on a critical appraisal of published data and our combined experience.

Corticosteroids

Corticosteroids are the most reported and successfully used drugs in treating EPS. Steroids are thought to be effective in suppressing the inflammatory process of the peritoneal membrane and inhibiting collagen synthesis and maturation.[45] Thickening of the peritoneal membrane may even disappear. In Japan, the use of corticosteroids as first line therapy has gained widespread acceptance. In a report by Kuriyama *et al*. all patients treated with corticosteroids maintained good prognosis after the diagnosis of EPS. Patients who did not receive corticosteroid therapy died within eight months of diagnosis.[46] Similarly, others have reported lifesaving treatment with corticosteroid therapy.[40,44,47-49] Only one series has reported a clinical improvement rate of 38.5% in patients treated with corticosteroids alone.[3]

Importantly, the use of immune suppressive medication seems only appropriate in case of ongoing inflammation. Albeit aspecific, this can only be assessed by clinical observation of

patient's status and laboratory measurements of levels of inflammatory biomarkers, such as CRP.[18,48,50] In the late stages of EPS, surgery may be more effective as the inflammatory tissue seems to be gradually replaced by fibrosis and is less likely to shrink with medical therapy.[18] However, there are no data to support this view and in our experience almost all patients are inflammatory to some degree.

Although the optimum dose and duration of steroid therapy have not been established by a controlled trial, most publications support a regimen of prednisolone 0.5-1.0 mg/kg/day or a pulse dose of 500–1000 mg methylprednisolone for two to three days.[3,25,46,47,51,52] The dose of prednisolone needs to be approximately 0.5-1.0 mg/kg/day during the first month, 0.25-0.5 mg at months 2 and 3, and thereafter tapered to 10 mg a day at six months. Treatment with steroids must be continued for at least one year. It is important to prolong the period of high dose steroids in a responding patient with a persistently elevated CRP level as dose reduction may result in recurrence of intestinal obstruction and inflammation, responding to retreatment with prednisolone.[48] Of course the well-known potential adverse effects of prednisolone should be taken into account but the high mortality of EPS tips the balance in most cases in favor of treatment. Peritonitis, particularly caused by tuberculosis, should be ruled out as much as possible.[53] Any sudden rise in CRP level not adequately responding to steroids should raise the suspicion of a bacterial peritonitis because of spontaneous small bowel perforation.

Tamoxifen

Tamoxifen is a selective estrogen receptor modulator (SERM), which has been successfully used in fibrosclerotic disorders such as fibrosing mediastinitis, sclerosing cervicitis, desmoid tumours, retroperitoneal fibrosis, and Dupuytren's contracture.[54-57] In recent years, the use of tamoxifen in the treatment EPS patients has gained more interest. Allaria *et al*. were the first to describe the successful use of tamoxifen in an EPS patient.[58] The therapeutic potential of tamoxifen therapy is also confirmed in a significant proportion of reported cases. Most reports show improvement of the intestinal function and a decrease in inflammation and fibrosis.[59-61] The largest controlled series by the Dutch EPS study, showed a decreased mortality in a group of EPS patients treated with tamoxifen (45.8% versus 74.4%, p=0.03) compared to a group who were not.[62] Remarkably, a large case series from the UK showed no improvement in survival rate when tamoxifen was used.[63] This discrepancy in survival outcomes may be the result of including more severe cases in the Dutch study.

Although the specific working mechanism of tamoxifen remains to be defined, it appears different from the treatment of breast cancer. In the latter, its main action is through binding of active metabolites to the estrogen receptor (ER).[64] Inhibition and modulation of TGF-β, which are ER-independent pathways, might be the rationale behind the positive results in fibrotic diseases.[65] Interestingly, this was underlined by findings from a recent study by Braun *et al*. showing almost no ER expression in the peritoneal tissue of EPS patients.[66]

Tamoxifen is an alternative to the (long-term) use of corticosteroids as its side effects are mild compared to prednisolone. When remission on corticosteroids is absent, additional tamoxifen can be considered. Alternatively, when there is doubt of an underlying inflammatory EPS, tamoxifen may be considered as first choice. Unfortunately no data exists supporting this view as there are no comparative studies for tamoxifen and corticosteroids, and tamoxifen is nearly always given in combination with steroids. In the Dutch EPS study, the multivariate analysis with adjustment for concomitant prednisone use in the tamoxifen-treated group confirmed the trend of improved survival.

Most studies in EPS report a tamoxifen dose between 20 and 40 mg/day.[59,60,67-70] This is similar to that used in retroperitoneal fibrosis.[56,71] After the introduction of tamoxifen therapy, favourable clinical outcomes are often seen within two to six months.[51,58,67,69] When there is clinical improvement the treatment with tamoxifen is probably maintained for a longer period analogous to recommendations on retroperitoneal fibrosis.[56] We recommend an initial dose of 20 mg twice daily for at least one year. The CT scan can be used to monitor resolution of peritoneal thickening and fluid collection after tamoxifen therapy.[59] Tamoxifen may have beneficial effects in the management of EPS, but caution is warranted and more studies are needed to confirm its (adverse) effects. In addition, the adverse effects of tamoxifen such as strokes, thromboembolic events, hot flushes, and endometrial carcinoma have to be considered carefully for each patient.[72,73] Reported adverse effects of tamoxifen in the EPS literature include arteriovenous access thrombosis, pulmonary embolism, thrombopenia, and calciphylaxis.[59,52,60]

Surgery

Surgical treatment has created exciting possibilities in the management of EPS. New surgical techniques have gained broad attention and nowadays even specialized referral centers for surgery are established in the UK.[74]

In the past, mortality rate as a result of surgical complications was high and prognosis post-surgery was poor.[75,76] The new performed surgical technique of enterolysis has shown to be successful in treating more than 92% out of 130 EPS patients with a postsurgical mortality of 6.9%.[77] The procedure of enterolysis implies the ablation of fibrotic tissue and lysis of the adhesions.[25] Of note, a peritonectomy as part of the surgical approach in EPS has been used in Manchester, but no large-scale studies have been published yet.[74]

The surgical procedure to remove the adhesive lesion may be extremely time consuming, demanding, and very hazardous. It is proposed that surgery should be performed if the patient does not get better with conservative or medical therapies.[78] Surgery is indicated after the inflammation has subsided and if ileus symptoms become pervasive.[18] Sometimes the encapsulation is very localized and in these cases, it tends to be at the ileocecal part of the intestines.[79,80] These EPS patients benefit most from a relatively easy to perform localized peritonectomy.

Some complications after surgical intervention include recurrent intestinal obstruction, formation of fistulas, or sepsis due to a perforated intestinal wall.[30] In addition, surgery may not exclude the recurrence of adhesions or symptoms of bowel obstruction. In a report by Kawanishi *et al*. 33 (25%) of the 130 patients required re-surgery.[81] In order to prevent re-obstruction, suturing intestine to intestine as part of the Noble procedure has been described and also postoperative prophylaxis with steroids or tamoxifen might be useful.[77]

Nutritional management: total parenteral nutrition

The decision on planning patients for nutritional support is necessary to prevent malnutrition as this is a major problem in EPS.[39] A study from the UK has highlighted the importance of total parenteral nutrition (TPN) and dietary counseling in the integral approach of EPS. In a group of EPS patients undergoing surgery, improved surgical outcomes were reported when TPN was used as part of the preoperative care.[82] The authors recommend careful monitoring of the nutritional status by use of markers such as albumin. With regard to this statement, we would like to underline the negative correlation between inflammation and markers such as albumin.[83] However, TPN is not a curative therapy as low recovery rates are observed when it is used alone.[3,78]

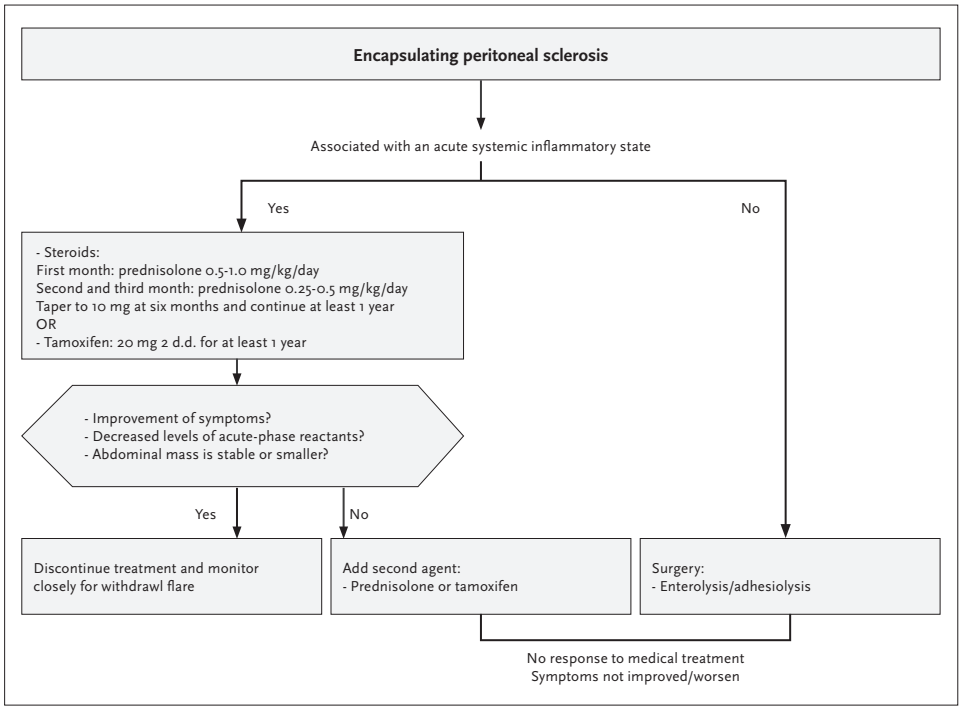

Figure 4. Proposed algorithm for the treatment of encapsulating peritoneal sclerosis.

The Pan Thames study also observed shorter time to death (10 months, range 0 to 101) in the TPN treatment group compared with patients maintained on oral nutrition (15 months, range 0 to 119).[63] Although there was no information on the initial nutritional status or clinical condition of patients, the difference in survival could be due to TPN-related complications such as infections.[84]

CONCLUDING REMARKS

EPS is an infrequent but severe complication of PD with the incidence increasing progressively with the duration of dialysis. A high degree of suspicion for EPS in any (former) PD patient with signs of bowel obstruction is warranted. Given the current published data and our experience with EPS cases, there is a rationale for corticosteroids, tamoxifen, and surgery in the treatment of EPS. Integrating the available data, we have developed algorithms for the diagnosis and treatment of EPS (Figure 3 and 4). A multidisciplinary approach to the patient with EPS is needed and should at least involve a nephrologist, dietician, and surgeon. In addition, a specialized surgical center or surgeon is needed in The Netherlands to ensure a high standard of quality for this challenging and time-consuming abdominal surgery in EPS patients. Studies on the complex pathogenesis and the role of inflammatory-mediated mechanisms are needed and may provide new clues for treatment. Finally, the optimum dose and duration of steroid therapy and the benefits of tamoxifen need to be further investigated. We encourage physicians to submit every suspected or proven case of EPS to the Dutch EPS registry at www. epsregistry.eu.

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Chapter
7

EPS

Chapter 8

Summary and general discussion

INTRODUCTION

In this thesis, the results of studies investigating pathophysiological aspects, clinical aspects, and management of encapsulating peritoneal sclerosis (EPS) are described. A particular focus has been set on research regarding the condition of post-transplantation EPS. The studies performed are intended to increase the understanding of EPS by the nephrologist. In this chapter, the main findings of the studies described in the thesis will be summarized and discussed.
Chapter 1 is the introduction to the thesis and provides an overview on the topic of EPS.

ENCAPSULATING PERITONEAL SCLEROSIS

The EPS paradox; not a rare disease, but rarely seen

Since its first description in peritoneal dialysis (PD) patients, EPS has been recognized as a serious complication of PD treatment. A common used word in the first sentence of several publications related to EPS is the word "rare".[1-3] Given the low reported prevalence and incidence of EPS in the literature, the use of this word may seem justified. However, a closer look at the cumulative incidence reveals a paradox as EPS is actually not a rare complication of PD but is rarely seen. In the Netherlands, for example, the prevalence of EPS has been estimated to be around 2.7%.[4] However, it is important to note that the occurrence of EPS varies globally and is mainly dependent on the duration of PD in individual patients. Within the first 3 years of PD treatment the EPS incidence is well below 1%, but rises thereafter with every additional year of PD treatment.[5,6] For instance, in a study from Scotland, it has been reported that the incidence of EPS is at least 8.1% in patients who continue PD treatment beyond 4 years.[7] Therefore, EPS is actually not an infrequent complication of treatment in patients who continue PD for a long time. However, the majority of patients do not continue PD beyond 3-4 years, which significantly reduces the population at risk and thereby the overall incidence of EPS. As most dialysis centers do not treat a large number of patients (with only a few continue on PD ≥ 5 years)[8,9] the individual nephrologist will rarely diagnose a patient with EPS.

Besides duration of PD, additional risk factors have been identified for EPS development. Furthermore, many studies exist reporting on the development of EPS after cessation of PD.[10] In a study by Brown *et al.*[7], 33 (71.7%) out of 46 patients were diagnosed within two years after cessation of PD. Some other factors that have been identified in association with an increased risk for EPS development include younger age, a high transporter state, ultrafiltration failure, the use of icodextrin, high peritonitis rates, and kidney transplantation.[4,11]

It is important to diagnose EPS patients in the early stages of disease and start treatment immediately. EPS carries a poor prognosis due to the high risk of patients becoming malnourished or developing bowel perforations.[12-14] Particularly, the disease may also strongly affect the quality of life of patients. Although several studies have contributed to our current knowledge of EPS, the reported mortality rate in EPS patients is still high, with a large number of patients dying within the first year after diagnosis.[6,15] Furthermore, there are some aspects of the disease, both regarding its pathophysiology, clinical presentation, and management that still need more exploration.

PATHOPHYSIOLOGY OF EPS

Inflammation and EPS

Currently, the mechanisms for EPS development and the exact pathophysiological aspects of EPS remain incompletely understood. Two important hallmarks of EPS include inflammation and fibrosis.[16,17] In the past, a large number of studies have focused on the fibrotic and morphological changes in the peritoneal membrane of patients with EPS.[18-22] However, there still remain some unanswered questions regarding the presence of inflammation in EPS. In **chapter 2** of this thesis, the results of a multicenter study focusing on the immunohistological changes in EPS peritoneal biopsies are described. In this study, we investigated the cellular infiltrate in the peritoneal membrane of EPS patients with a focus on T cells, macrophages and their subsets. Peritoneal membrane biopsies of 23 EPS patients were studied and their findings were compared with those in the peritoneum of a reference group, consisting of 15 PD patients without EPS. The results of the study showed an increased area percentage (%) of staining for both CD3-positive (CD3+), CD4-positive (CD4+), and CD8-positive (CD8+) cells in the peritoneal membrane of patients with EPS as compared to the non-EPS group. Furthermore, EPS biopsies predominantly contained CD4+ cells rather than CD8+ cells, while in the non-EPS group these cell types were almost equally represented. EPS peritoneal biopsies also contained a higher area % of staining for all macrophage markers with particularly CD163+ cells being a major cell type. Additionally, immunohistochemical findings were related to clinical outcome of EPS patients. However, no relation was found between the area % of staining of CD3+ and CD68+ cells and clinical outcome. In summary, in this study we have reported on a characteristic mononuclear infiltrate, mainly consisting of CD4+ cells and CD163+ cells, in the peritoneal membrane of patients with EPS. These findings suggest a prominent role for both CD4+ T cells and pro-fibrotic M2 macrophages in the pathogenesis of EPS. But given the descriptive nature of the study, further studies are required to investigate the exact role of inflammation in EPS. Preferably, future studies should focus on the properties of immune cells influencing the pathways of fibrosis and sclerosis ending in EPS.

CLINICAL ASPECTS OF EPS

Post-transplantation EPS

Chapter 3, 4, and 5 mainly focus on the clinical aspects of post-transplantation EPS. This presentation of EPS occurs in PD patients undergoing kidney transplantation.[23-25] In contrast to studies on the epidemiology, pathophysiology, and management of EPS that are mainly reported from Japan, a majority of studies on the topic of post-transplantation EPS are reported from European countries.[15,24,26] This may be due to the higher transplantation rates in Europe as compared to Asian countries. In the Dutch multicenter EPS study, multivariate regression analysis showed that besides other known risk factors for EPS, kidney transplantation was strongly associated with EPS development.[4] The development of post-transplantation EPS, however, is remarkable as these patients develop the disease while being off PD and while treated with immunosuppressive medication as part of the post-transplant immunosuppressive regimen. To date, no studies have been performed unraveling the exact mechanisms responsible for the development of post-transplantation EPS. However, three possible explanations have been put forward in the literature. The first explanation is within the concept of the "two-hit theory" in which the procedure of kidney transplantation itself may act as a second hit in triggering EPS manifestation.[27,28] This may in particular be the case in former PD patients who had a pre-conditioned peritoneum and are at high risk of EPS. The second explanation is related to the pathogenic role of calcineurin inhibitors that are used in current immunosuppressive transplant protocols. Calcineurin inhibitors, such as tacrolimus and cyclosporin, have been reported to have profibrotic effects by upregulating TGF-beta expression and consequently enhancing fibrosis.[29,30] The pro-fibrotic effects of calcineurin inhibitors have been mainly observed in kidney transplant recipients developing kidney fibrosis.[31,32] Additionally, an experimental study has shown fibrotic changes of the peritoneal membrane in an experimental animal of EPS due to cyclosporin administration.[33] Finally, the development of post-transplantation EPS may be unrelated to kidney transplantation itself but instead may be caused by an abrupt discontinuation of PD, which results in a lack of peritoneal lavage. The latter, on its turn, may cause an acceleration of profibrotic and pro-inflammatory mediators in the peritoneal cavity and function as a second hit triggering a fibrotic and inflammatory reaction resulting fibrin deposition.[28,34] Finally, a fibrous sheet develops and covers the intestines.

In the study described in **chapter 3**, we have focused on the clinical course of post-transplantation EPS in more detail and addressed the question whether the clinical presentation, computed tomography (CT) scan findings, and outcome of post-transplantation EPS patients differ from EPS occurring in patients without previous kidney transplantation that are or have been treated with PD (classical EPS). A second aim of this study was to investigate the systemic inflammatory response, as measured by plasma C-reactive protein (CRP) concentration, in the two groups in the

year before, at the time, and in the year after the diagnosis of EPS. The results showed no significant differences in age or duration of PD between the two groups. However, in contrast to the classical EPS patients, post-transplantation EPS patients had a lower incidence of peritonitis with a longer time between the last peritonitis episode and EPS diagnosis. This observation led us to suggest and hypothesize that peritonitis may be a second hit trigger for (classical) EPS to develop, but that kidney transplantation could have been a secondary hit for post-transplantation EPS to develop. Another finding in the study was that within the year before EPS was diagnosed in both groups, a pattern of increasing CRP values was observed. However, in the post-transplantation group the CRP levels at presentation were significantly lower. In this study, we did not find any differences in clinical presentation between post-transplantation and classical EPS patients. Both patient groups presented with signs and symptoms of intestinal obstruction without significant differences in the EPS related findings on the abdominal CT scan. With regard to outcome, one year after diagnosis 33.3% of post-transplantation EPS patients and 52.6% of classical EPS patients had died. The overall mortality rate was significantly lower in the post-transplantation EPS (40.0%) as compared to the classical EPS (84.2%) group. Additionally, Kaplan Meier analysis showed a better survival outcome in the post-transplantation EPS group as compared to the classical EPS group. However, it should be taken into account that post-transplantation EPS patients in this study were younger than the classical group. Although this difference did not reach statistical significance, it could have been of influence on the survival outcome between the two groups. Given the low number of patients in this study, no COX regression analysis was undertaken to investigate this issue. In summary, in this study it has been shown that patients with post-transplantation EPS have a similar clinical presentation as classical EPS but present with a lower systemic inflammatory response and a better survival outcome.

In **chapter 4**, the results of a study investigating the impact of post-transplantation EPS on mortality after kidney transplantation are reported. We hypothesized that a possible contribution of post-transplantation EPS on mortality may exist, but has not been recognized previously. The design of this study was a retrospective multicenter study. We compared the survival of 1203 PD patients who were transplanted in four participating university hospitals in the Netherlands in the period of January 1st 1996 until July 1st 2007, with the survival of 38 (3.0%) identified cases of post-transplantation EPS. In this study, the cases were diagnosed within the first two years after kidney transplantation. Next to known causes of death in the transplanted group, such as infections, cardiovascular disease and malignancies, we identified EPS as the fourth cause of death after kidney transplantation in this group of transplanted PD patients. Using Kaplan-Meier survival analysis, we have also shown a significantly lower long-term survival for post-transplantation EPS patients as compared to transplanted PD patients without EPS. In conclusion, post-transplantation EPS may be rare, however, is a clinical relevant entity. In clinical practice, a high index of suspicion for the diagnosis of post-transplantation EPS is recommended in patients with a long cumulative

pre-transplant duration of PD.

In the case study in **chapter 5,** we describe the case of a 59-year old female with late-onset post-transplantation EPS without systemic inflammation and typical CT imaging findings. This patient, with a long-term history of PD, presented 33 months after undergoing her second kidney transplantation. Her symptoms had started insidiously one year after kidney transplantation and she was referred to our EPS center outpatient clinic due to progressive symptoms of bowel obstruction. The patient had no abnormalities on physical examination and laboratory results showed no signs of systemic inflammation. Although a recent CT scan did not reveal any findings characteristic for EPS, there was a high clinical suspicion for EPS due to the severity of the progressive symptoms of intestinal obstruction. Therefore, the patient was referred for exploratory surgery and a laparotomy was performed, revealing EPS. In an attempt to free the bowel loops, a total enterolysis and peritonectomy were performed. In conclusion, this case illustrated the value of considering a diagnosis of EPS several years after kidney transplantation and underscored the clinical benefit of a diagnostic laparotomy whenever there is a suspicion for this condition in former PD patients.

Localized EPS

In the macroscopic appearance of the case described in chapter 5 and in a majority of EPS patients described in the literature, EPS is characterized by generalized encapsulation of the bowels causing symptoms of severe obstruction. However, it has been reported that several anatomical variants and phenotypes can be recognized at the intraoperative situs of EPS.[16,35,36] The main objective of the study described in **chapter 6** was to investigate and report on patients with localized EPS. Out of 9 patients who were referred for a diagnostic laparotomy to the department of surgery of the Erasmus Medical Center, 3 cases showed localized encapsulation of the bowel particularly involving the ileocecal region, and defined as having localized EPS. The specific findings in these cases highlight an unusual appearance of EPS in which it was difficult to establish the diagnosis pre-operatively on the CT scan. A possible explanation for this may be because localized disease, in which the process of cocooning and fibrosis had not extended to the whole surface of the bowels and abdominal cavity, has prevented the detection on radiological imaging. Therefore, we recommend that an elective diagnostic laparotomy should be considered early in cases of high clinical suspicion of EPS and negative CT scan findings. This approach offers both diagnostic opportunities as well as therapeutic options. Preferably, future studies should also focus on reporting on the varying phenotypes (localized versus generalized EPS) of EPS during surgical exploration.

MANAGEMENT OF EPS

To date, no trials have been performed comparing diagnostic tools or treatment options for EPS. This may be particularly the case due to the rarity of EPS. As a result, an area of uncertainty remains among nephrologists in choosing the best approach in the management of these patients. On the other hand, a substantial number of small-based studies have been published in previous years reporting the benefits of several diagnostic and therapeutic options. Furthermore, EPS surgical referral centers[37,38] and EPS registries[39,40] have been established to manage these patients in specialized centers and contribute to a greater understanding of this condition. In the Netherlands, the Dutch EPS registry was established in 2009.[40] One of the aims of the registry was to establish a rational strategy to guide the management of EPS. In an attempt to provide recommendations for both diagnosis and treatment of EPS, we have outlined a consensus guideline in **chapter 7**. The recommendations were based on a review of the literature and extended with the experience of the members of the EPS registry.

First of all, a degree of suspicion for EPS in any (former) PD patient with signs of bowel obstruction in a catabolic inflammatory state is recommended. The CT scan is considered as the diagnostic modality of choice. However, a low threshold for surgical exploration is recommended in case of clinical suspicion, as both the absence of inflammation or typical signs on a CT scan should not defer the clinician from the diagnosis of EPS. This is for example well illustrated by the case described in chapter 5 and the patients described in chapter 6. Given the current published studies and the experience of the EPS registry working group, the use of coticosteroids and/or tamoxifen is recommended, dependent on the presence of systemic inflammation. In recent years, however, also a number of children diagnosed with EPS have been reported.[41-47] With regard to these group of patients, it is important to use tamoxifen with caution due to the anti-estrogenic effects of this drug.

As a final treatment of choice in EPS, surgical treatment is preferred. Particularly, in patients with severe intestinal obstruction without elevated parameters of inflammation or when patients do not respond to medical treatment sufficiently, surgery might be considered as a final option. As the process of adhesiolysis and peritonectomy are technically difficult and hazardous, it is recommended to perform surgery in an EPS surgical referral center. Recurrence of EPS after surgery may occur for which additional surgical interventions are needed. Therefore, future intervention trials are required and should also focus on the prevention of recurrence after EPS surgery by, for example, use of post-operative tamoxifen therapy.

CONCLUSIONS

Based on the results of the studies described in this thesis, the following conclusions are drawn:

1. **The mononuclear cell infiltrate in the peritoneal membrane of patients with EPS is dominated by CD4-positive T cells and M2 macrophages.**
2. **Despite similarities in clinical presentation and radiological findings, post-transplantation EPS patients have a better outcome as compared to classical EPS patients.**
3. **Low-grade systemic inflammation precedes the development of clinically overt EPS, however, post-transplantation EPS is associated with a lower systemic inflammatory response as compared to classical EPS.**
4. **Post-transplantation EPS contributes significantly to a decreased survival of transplanted PD patients.**
5. **Localized EPS has a predilection to appear at the level of the terminal ileum and may benefit most from surgery, preferably performed in an experienced surgical center.**
6. **There is a rationale for the application of corticosteroids, tamoxifen, and surgery in the treatment of EPS dependent on the presence of inflammation and response to medical therapy.**

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Chapter 6

Future perspectives and recommendations

INTRODUCTION

This thesis describes the results of studies focusing on the pathophysiology, clinical aspects, and management of encapsulating peritoneal sclerosis (EPS). We have reported on the presence of inflammation in EPS, described several clinical aspects, and focused on the entity of post-transplantation EPS. Furthermore, recommendations for both diagnosis and management of patients with EPS have been provided. However, more research on the topic of EPS is certainly needed as several challenges have not been met and questions remain to be answered. In this chapter, recommendations for future research on the topic of EPS will be outlined.

PATHOPHYSIOLOGY OF EPS

In chapter 1 of this thesis, we report an increased presence of mononuclear immune cells in the peritoneal membrane of patients with EPS as compared to a group of PD patients without EPS. However, we are currently in need of additional integrated research efforts in order to shed light on the pathogenesis and pathophysiology of EPS and turn this knowledge into the development of biomarkers indicative of ongoing inflammation and peritoneal fibrosis that may end in EPS. This will guide clinical decision making, such as changing some patients who have been on PD for a long time to HD before development of EPS symptoms.

Additional to the findings of the study in chapter 1, it is important to better understand the role and significance of immune cells and their functional properties in the development of EPS. To reach this objective, a knockout mouse model of EPS, by selectively depleting different cell populations, should be established. This will not only yield valuable information of the immune cell subsets involved, but also on their relative importance, and their mode of action in the development of EPS. In recent years, the importance of T lymphocytes in fibrotic disease development, such as in pulmonary fibrosis, has been increasingly reported.[1] In particular, the production of T-helper-2 (Th-2) cytokines, such as IL-4 and IL-13, are reported to enhance fibrosis formation through activation of M2 macrophages or stimulation of fibroblast proliferation.[2] Following this, it may be interesting to look at signs of T cell involvement in EPS. After the establishment of an EPS mouse model, the influence of different T cell populations on peritoneal fibrosis can be studied. Key questions should be to what extent CD4+ T cells are involved in peritoneal fibrosis and sclerosis, which T cell subpopulation is involved (as judged by chemokine receptor expression and cytokine production) and whether intraperitoneal administration of anti-T cell reagents will enable to block/modulate peritoneal fibrosis and sclerosis.

CLINICAL ASPECTS OF EPS

As the incidence of EPS is largely dependent on the duration of PD treatment and exposure to the bio-incompatible elements in PD fluids, EPS limits the long-time use of PD in patients. In recent years, however, several changes in PD practice have occurred including the introduction of the new biocompatible dialysis solutions.[3] It may therefore be of interest to investigate the influence of these new biocompatible dialysis solutions on the incidence of EPS. Giving the rarity of EPS, a multicenter study examining this issue is needed.

EPS is a multi-factorial condition. Besides duration of exposure to bio-incompatible dialysis solutions, several other factors have been proposed to be associated with EPS development. From a clinical point of view, a nephrologist should be able to determine a patient's risk of developing EPS and provide information to the patient on this. For this reason, a prognostic model for EPS will allow clinicians to inform patients and classify patients according to their risk of developing EPS. Indirectly, a prognostic model will yield valuable information in managing long-term PD patients with the aim of preventing EPS. A study with the objective to develop a prognostic model for EPS should preferably include variables that until now have been associated with EPS development. Some of these variables include age of the patient, duration of PD, number of peritonitis episodes, development of ultrafiltration failure during PD, the transporter status during PD, discontinuation of PD, kidney transplantations, use of glucose based dialysis solutions and the use of icodextrin.

MANAGEMENT OF EPS

Although several breakthroughs have occurred in recent years, the prognosis of EPS patients is still poor due to late diagnosis and lack of effective treatment options. An additional goal of future research should be improving the management of EPS by developing and validating new and effective treatment strategies.

A novel therapy with a potential benefit in the management of EPS may include intraperitoneal mesenchymal stem cell (MSC) therapy. It is known that mesenchymal stem cells are able to differentiate into several cell lineages.[4] Ueno *et al.*[5] have recently demonstrated that intraperitoneal MSC therapy in a chlorhexidine gluconate rat peritoneal fibrosis model resulted in a reduction of collagen deposition, reduced functional impairments of the peritoneal membrane, and resulted in a reduction of peritoneal thickening. Additionally, MSC therapy suppressed transforming growth factor-beta1 (TGF-β1) signaling and TGF-β1 induced epithelial to mesenchymal transition responses. It was also demonstrated that treatment with MSC therapy inhibited infiltration of the

submesothelial layer of the peritoneal membrane with macrophages/monocytes. The authors suggested that, after infusion, mesenchymal stem cells migrate to the site of peritoneal injury. The use of mesenchymal stem cells in EPS may therefore have several benefits as this therapeutic approach may exert both anti-inflammatory and antifibrotic effects. Whether MSC therapy may serve as a therapeutic target against the process of peritoneal inflammation fibrosis, as observed in EPS, therefore requires further investigation.

A second strategy with a potential benefit in the management of EPS may include the use of thalidomide. Thalidomide is a drug with immunomodulatory, anti-inflammatory and anti-angiogenic properties. The use of this drug has been in the past associated with serious birth effects after its use in pregnant woman.[6] However, the drug has also been successfully used for effectively treating patients with several inflammatory and autoimmune diseases.[7] As thalidomide is able to inhibit the production of several inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), vascular endothelial growth factor (VEGF), and transforming growth factor-beta (TGF-β) it may have a potential benefit in the management of EPS.[8,9] Previously, Mondello *et al.*[10] established a peritoneal fibrosis model by injecting rats with chlorhexidine gluconate. The investigators showed a significant lower rate in the extent of peritoneal injury in mice orally treated with thalidomide. Additionally, a substantial reduction of TNF-α, interleukin-1beta (IL-1β), TGF-β, and VEGF expression was shown in the injured peritoneal membrane. But whether thalidomide is also able to exert beneficial effects and suppress inflammation and fibrosis in patients with EPS is not clear yet. Therefore, additional studies reporting the use of thalidomide in patients with EPS are required. Unfortunately, the development of large-scale studies, such as randomized controlled trials, for the treatment of EPS is hampered due to the rarity of the condition. However, several registries have been developed in recent years and may facilitate collaboration between countries. Future multi-country collaborative approaches should also focus on developing general accepted treatment guidelines in order to improve both quality of care and quality of life of EPS patients.

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Chapter 10

Nederlandse samenvatting en bespreking

INTRODUCTIE

In dit proefschrift zijn de resultaten van onderzoeken beschreven waarin aspecten rondom de pathofysiologie, kliniek en behandeling van EPS zijn onderzocht. Er is met name nadruk gelegd op onderzoek naar post-transplantatie EPS. De uitgevoerde onderzoeken zijn bedoeld om het begrip en kennis van de nefroloog over EPS te vergroten. In dit hoofdstuk worden de voornaamste bevindingen van de studies samengevat en besproken.

Hoofdstuk 1 is de inleiding van het proefschrift en geeft een overzicht over het onderwerp EPS.

ENCAPSULATING PERITONEAL SCLEROSIS

De paradox van EPS; niet een zeldzame ziekte, maar zelden gezien

Sinds de eerste beschrijving van EPS bij peritoneale dialyse (PD) patiënten wordt EPS erkend als een serieuze complicatie van PD. Een veel gebruikte term in de eerst zin van diverse publicaties over EPS is het woord "zeldzaam". Gezien de laag gerapporteerde prevalentie en incidentie van EPS in de literatuur lijkt het gebruik van dit woord correct. Echter, een gerichte blik op de cumulatieve incidentie van EPS leidt tot de paradox dat EPS eigenlijk niet zo zeldzaam is, maar zelden wordt gezien. In Nederland is de prevalentie van EPS geschat op ongeveer 2.7%. Echter, het is belangrijk op te merken dat het voorkomen van EPS wereldwijd varieert en voornamelijk afhankelijk is van de duur van PD bij individuele patiënten. Gedurende de eerste drie jaren PD is de incidentie van EPS lager dan 1%, maar stijgt daarna na ieder bijkomend jaar op PD. In een studie vanuit Schotland is bijvoorbeeld gerapporteerd dat de incidentie van EPS op zijn minst 8.1% is bij patiënten die langer dan 4 jaar doorgaan met PD. Hierdoor zouden we kunnen veronderstellen dat EPS vaker wordt gezien bij patiënten die voor een lange tijd op PD zitten. Echter, de meerderheid van de patiënten gaan niet langer dan 3-4 jaar door met PD wat leidt tot een significante vermindering van de populatie die risico loopt op EPS en hierdoor ook een invloed heeft op het aantal nieuwe patiënten met EPS. Verder wordt in de meeste dialyse centra een beperkt aantal patiënten behandeld met PD (waarbij slechts een klein aantal patiënten ≥ 5 jaar nog aan PD doet), waardoor een gemiddelde nefroloog zelden een patiënt zal diagnosticeren met EPS.

Behalve de duur van PD zijn tevens andere risicofactoren vastgesteld voor het ontwikkelen van EPS. Bovendien zijn er studies die het ontstaan van EPS hebben gerapporteerd bij patiënten na het stoppen van PD. In een studie door Brown *et al.* werden 33 (71.7%) van de 46 patiënten gediagnosticeerd met EPS na het stoppen van PD. Enkele andere factoren die zijn geassocieerd met een verhoogd risico op EPS zijn jonge leeftijd, hoge transport status, ultrafiltratie falen, gebruik van icodextrin, een frequent aantal peritonitis episodes en niertransplantatie.

Het is belangrijk om EPS patiënten in een vroeg stadium te diagnosticeren en behandeling onmiddellijk te starten. EPS gaat gepaard met een slechte prognose doordat EPS patiënten een hoog risico hebben op ondervoeding en het ontwikkelen van darmperforaties. Het ziektebeeld heeft daarnaast grote impact op de kwaliteit van leven van patiënten. Hoewel diverse studies hebben bijgedragen aan onze huidige kennis over EPS blijft de mortaliteit onder EPS patiënten nog steeds hoog en overlijdt een groot aantal patiënten binnen het eerste jaar nadat de diagnose is gesteld. Verder zijn er een aantal aspecten van het ziektebeeld, zowel met betrekking tot de pathofysiologie, klinische presentatie als behandeling die verder onderzoek vergen.

PATHOFYSIOLOGIE VAN EPS

Inflammatie en EPS

Op dit moment zijn de mechanismen achter de ontwikkeling van EPS en de exacte pathofysiologische aspecten van EPS niet volledig opgehelderd. Twee belangrijke kenmerken van EPS betreffen inflammatie en fibrose. In het verleden hebben een groot aantal studies zich gericht op de fibrotische en morfologische veranderingen in het peritoneale membraan van EPS patiënten. Er zijn echter nog steeds een aantal onbeantwoorde vragen met betrekking tot de aanwezigheid van inflammatie in EPS. In **hoofdstuk 2** van dit proefschrift worden de resultaten van een multicenter studie beschreven waarin wij ons hebben gericht op de immunohistologische veranderingen in het peritoneum van EPS patiënten. In deze studie hebben wij het cellulair infiltraat in het peritoneum van EPS patiënten onderzocht met een focus op T cellen, macrofagen en hun subsets. Peritoneum biopten van 23 EPS patiënten werden bestudeerd en de bevindingen werden vergeleken met die in het peritoneum van een referentie groep, welke werd gevormd door 15 PD patiënten zonder EPS. Uit de resultaten van dit onderzoek kwam naar voren dat het percentage (%) oppervlakte aankleuring van zowel CD3-positieve (CD3+), CD4-positieve (CD4+), en CD8-positieve (CD8+) cellen verhoogd was binnen de EPS groep, in vergelijking met de niet-EPS groep. Verder bevatten EPS biopten voornamelijk CD4+ cellen in tegenstelling tot CD8+ cellen, terwijl deze twee celtypes in de niet-EPS groep gelijkmatig waren verdeeld. In de biopten van EPS patiënten werd tevens een verhoogde oppervlakte % gevonden van alle macrofagen markers, waarbij voornamelijk CD163+ cellen het dominante cel type bleken te zijn. In deze studie werd tevens onderzocht of de immunohistologische bevindingen een invloed hadden op de klinische uitkomst van patiënten. Echter, werd er geen relatie werd gevonden tussen het oppervlakte % aankleuring van CD3+ en CD68+ cellen en overleving van patiënten. Kort samengevat hebben wij in deze studie gerapporteerd over de aanwezigheid van een karakteristiek mononucleair celinfiltraat in het peritoneum van EPS patiënten, welke voornamelijk bestond uit CD4+ cellen en CD163+ cellen. Deze bevindingen suggereren een belangrijke rol voor zowel CD4+ T cellen en pro-fibrotische M2 macrofagen in de pathogenese van EPS. Gezien het beschrijvende karakter

van deze studie zijn er aanvullende onderzoeken nodig die de exacte rol van inflammatie in EPS nader onderzoeken. Bij voorkeur dienen toekomstige studies zich te richten op de eigenschappen van immuuncellen waardoor fibrotische paden worden geactiveerd, wat uiteindelijk zouden kunnen leiden tot fibrose en sclerose, zoals wordt waargenomen bij EPS.

KLINISCHE ASPECTEN VAN EPS

Post-transplantatie EPS

De **hoofdstukken 3, 4 en 5** richten zich voornamelijk op de klinische aspecten van post-transplantatie EPS. Deze presentatie van EPS komt voor bij sommige PD patiënten die een niertransplantatie hebben ondergaan. In tegenstelling tot studies over de epidemiologie, pathofysiologie en behandeling van EPS, die voornamelijk vanuit Japan afkomstig zijn, zijn de meeste studies over het onderwerp post-transplantatie EPS afkomstig uit Europese landen. Dit zou verklaard kunnen worden door een hoger aantal transplantaties in Europese landen in vergelijking tot Japan. In de Nederlandse multicenter EPS studie werd door middel van multivariate regressie analyse aangetoond dat ook een niertransplantatie sterk geassocieerd was met het ontstaan van EPS. Het ontstaan van EPS na een succesvolle niertransplantatie is echter opmerkelijk aangezien deze patiënten ten tijde van de diagnose gestopt zijn met PD en behandeld worden met immunosuppressieve medicijnen in het kader van het immunosuppressieve regime na transplantatie. Tot op heden zijn er nog geen onderzoeken verricht die de exacte mechanismen ontrafelen die verantwoordelijk zijn voor het ontstaan van post-transplantatie EPS. In de literatuur zijn er echter drie mogelijke verklaringen gegeven. De eerste verklaring is binnen het concept van de “two-hit theory” waarbij een niertransplantatie kan bijdragen aan het ontstaan van EPS door te functioneren als een stimulerende factor. Dit zou voornamelijk het geval kunnen zijn bij patiënten die in het verleden zijn behandeld met PD en een pre-geconditioneerd peritoneum hebben en daardoor een grotere kans hebben op het ontwikkelen van EPS. De tweede verklaring is gerelateerd aan het gebruik van calcineurin inhibitoren die in het huidige immunosuppressieve regime na niertransplantatie zijn opgenomen en worden toegepast. Calcineurin inhibitoren, zoals tacrolimus en cyclosprine hebben pro-fibrotische eigenschappen doordat deze de expressie van TGF-beta verhogen en daardoor aanzetten tot fibrose ontwikkeling. De pro-fibrotische effecten van calcineurin inhibitoren zijn voornamelijk geobserveerd in gefibroseerde nieren van getransplanteerde patiënten. Tevens zijn in een experimentele studie fibrotische veranderingen in het peritoneale membraan geobserveerd als gevolg van het gebruik van cyclosporine. De derde en laatste verklaring voor het ontwikkelen van post-transplantatie EPS lijkt niet gerelateerd te zijn aan de niertransplantatie maar aan het plotseling stoppen van peritoneale dialyse, wat resulteert in een gebrek aan peritoneale spoeling. Het stoppen van PD na een lange tijd zou namelijk kunnen zorgen voor de stapeling

van pro-fibrotische en pro-inflammatoire mediatoren in de peritoneale holte en fungeren als een stimulerende factor. Hierdoor zou een mogelijke fibrotische en inflammatoire reactie kunnen ontstaan die leiden tot fibrine neerslag. Uiteindelijk ontwikkelt zich een fibrotisch kapsel en bedekt deze de darmen.

In **hoofdstuk 3** hebben wij ons gericht op het klinische beloop van post-transplantatie EPS en onderzocht of er een verschil is in klinische presentatie, CT scan bevindingen, en overleving van post-transplantatie patiënten in vergelijking tot EPS patiënten die geen niertransplantatie hadden ondergaan en met dialyse werden behandeld ten tijde van diagnose (klassieke EPS). Een tweede doel van deze studie was om de systemisch inflammatoire respons in beide EPS groepen nader te onderzoeken in het jaar voor, ten tijde van en in het jaar na de diagnose van EPS. Uit de resultaten volgde geen significante verschillen tussen de twee groepen met betrekking tot leeftijd of duur van PD. Echter, in tegenstelling tot klassieke EPS patiënten hadden post-transplantatie EPS patiënten een significant lagere incidentie van peritonitis en een langere duur tussen de laatste peritonitis en de diagnose van EPS. Mede door deze bevindingen stellen wij de hypothese dat een peritonitis de uitlokkende factor zou kunnen zijn voor het ontwikkelen van klassieke EPS, maar dat een niertransplantatie een uitlokkende factor zou kunnen vormen voor het ontwikkelen van post-transplantatie EPS. Een andere bevinding in deze studie was dat in het jaar voor de diagnose EPS in beide groepen stijgende CRP waarden werden gevonden. Echter, de CRP waarden ten tijde van klinische presentatie waren significant lager in de post-transplantatie groep. Wij hebben in deze studie geen verschillen gevonden tussen post-transplantatie en klassieke EPS met betrekking tot de klinische presentatie. Beide patiëntgroepen presenteerden zich met symptomen van darmobstructie zonder verschillen in de bevindingen op de CT scan. Een jaar na de diagnose EPS bedroeg de mortaliteit 33.3% in de post-transplantatie groep en 52.6% in de klassieke EPS groep. De totale mortaliteit was significant lager in de post-transplantatie groep (40.0%) in vergelijking tot de klassieke EPS groep (84.2%). Bovendien toonde Kaplan Meier analyse een betere overleving over de tijd in de post-transplantatie groep in vergelijking tot de klassieke EPS groep. Echter, de post-transplantatie EPS patiënten in deze studie waren jonger dan de klassieke EPS patiënten. Alhoewel dit verschil geen statistische significantie bereikte, zou het toch invloed kunnen hebben gehad op de overleving binnen de patiëntgroepen. Gezien het kleine aantal patiënten in deze studie is er geen COX regressie analyse uitgevoerd om te corrigeren voor leeftijd. Samenvattend hebben wij in deze studie aangetoond dat post-transplantatie EPS patiënten klinische symptomen hebben die niet te onderscheiden zijn van klassieke EPS, maar zich presenteren met een lagere mate van systemische inflammatie en een betere overleving hebben.

Hoofdstuk 4 beschrijft een studie waarin de invloed van post-transplantatie EPS op mortaliteit na niertransplantatie is onderzocht. Onze hypothese luidde dat post-transplantatie EPS een

mogelijke bijdrage levert aan de mortaliteit na niertransplantatie welke voorheen niet was herkend. De opzet van de studie betrof een retrospectieve multicenter studie. De overleving van 1203 PD patiënten die waren getransplanteerd in vier deelnemende academische medische centra in Nederland in de periode van 1 januari 1996 tot 1 juli 2007, werd vergeleken met de overleving van 38 (3.0%) patiënten met post-transplantatie EPS. In deze studie werd de meerderheid van EPS patiënten gediagnosticeerd gedurende de eerste twee jaren na niertransplantatie. Naast de reeds bekende doodsoorzaken bij getransplanteerde patiënten zoals infecties, cardiovasculaire ziektes en maligniteiten werd EPS in deze groep van patiënten vastgesteld als de vierde doodsoorzaak. Met behulp van Kaplan Meier analyse werd tevens aangetoond dat de overleving van de post-transplantatie EPS patiënten op lange termijn lager was in vergelijking tot de overleving van getransplanteerde PD patiënten zonder EPS. Concluderend, EPS zou dan wel zeldzaam kunnen zijn, maar is daarnaast ook een klinisch relevant ziektebeeld. Voor de klinische praktijk is een verhoogde verdenking op de diagnose post-transplantatie EPS aangewezen in patiënten met een lange PD duur voor de niertransplantatie.

In **hoofdstuk 5** wordt de casus beschreven van een 59 jarige patiënte die werd gediagnosticeerd met een late presentatie van post-transplantatie EPS en zich zonder tekenen van systemische inflammatie of karakteristieke CT scan bevindingen presenteerde. Deze patiënte, met een lange PD duur in de voorgeschiedenis, presenteerde zich 33 maanden nadat ze een tweede niertransplantatie had ondergaan. Haar symptomen waren een jaar na de niertransplantatie ontstaan en patiënte werd als gevolg van haar toenemende symptomen van darmobstructie doorverwezen naar ons EPS expertise centrum. Het lichamelijk onderzoek leverde geen bijzonderheden op en in het laboratorium onderzoek werden geen tekenen van systemische inflammatie gevonden. Ondanks de afwezigheid van karakteristieke EPS bevindingen op een eerder uitgevoerde CT scan, bestond er een hoge klinische verdenking van EPS bij deze patiënte als gevolg van de toenemende symptomen van darmobstructie. Daarom werd de patiënte doorverwezen voor een diagnostische operatie en werd een laparotomie verricht, waarbij het beeld van EPS werd gezien. Een enterolyse en peritonectomie werden verricht om de darmen vrij te maken uit het fibrotische kapsel. Concluderend, deze casus illustreert de waarde van het overwegen van de diagnose EPS enkele jaren na een niertransplantatie en onderstreept het klinische voordeel van een diagnostische laparotomie in de diagnostiek van (voormalige) PD patiënten waarbij een verdenking bestaat op EPS.

GELOKALISEERDE EPS

Het macroscopisch beeld van EPS zoals beschreven in hoofdstuk 5 en in een meerderheid van de patiënten in de literatuur wordt gekenmerkt door inkapseling van de darmen, resulterend

in symptomen van darmobstructie. Echter, er zijn rapporten waarin diverse macroscopische beelden worden beschreven. Het doel van de studie in **hoofdstuk 6** was om onderzoek te doen naar patiënten met gelokaliseerde EPS. Van de 9 patiënten die werden doorverwezen naar de afdeling chirurgie in het Erasmus Medisch Centrum voor een diagnostische laparotomie, werd bij 3 patiënten een gelokaliseerde inkapseling van de darmen geobserveerd. Dit betrof voornamelijk het gebied van het terminale ileum waarbij het beeld werd gedefinieerd als gelokaliseerde EPS. Door het beschrijven van de specifieke bevindingen in deze patiënten wordt een ongewone presentatie van EPS onderkend, waarbij het lastig is om de diagnose preoperatief te stellen middels het gebruik van een CT scan. Een mogelijke verklaring hiervoor zou kunnen zijn dat gelokaliseerde ziekte, waarbij de cocon vorming en het proces van fibrose zich niet hebben uitgebreid tot de gehele oppervlakte van de darm, zich lastig laat opsporen op de CT scan. Daarom bevelen wij aan om een diagnostische laparotomie te verrichten wanneer een hoge verdenking op EPS bestaat, ondanks niet-karakteristieke CT scan bevindingen. Deze aanpak zou zowel diagnostische mogelijkheden als therapeutische opties kunnen bieden. Bij voorkeur zouden toekomstige studies zich moeten richten op het beschrijven van de diverse fenotypes (gelokaliseerd versus gegeneraliseerde EPS) van EPS die wordt geobserveerd gedurende chirurgische exploratie.

BEHANDELING VAN EPS

Tot op heden zijn er nog geen klinische onderzoeken verricht waarbij diagnostische of therapeutische opties voor EPS zijn vergeleken. Dit zou vooral kunnen komen door de zeldzaamheid van EPS. Als gevolg hiervan bestaat er op dit moment onduidelijkheid onder nefrologen over het toepassen en uitkiezen van de beste strategie in de aanpak van EPS patiënten. Aan de andere kant zijn er in de afgelopen jaren een aantal kleinschalige studies gepubliceerd over de voordelen van diverse diagnostische en therapeutische opties. Verder zijn er chirurgische refereer centra voor EPS en EPS registraties opgericht om deze patiënten te behandelen in expertise centra en om een bijdrage te leveren aan de kennis over dit ziektebeeld. In Nederland is de Nederlandse EPS registratie opgericht in 2009. Een van de doelen van de registratie was om een strategie te ontwikkelen voor de aanpak van EPS. In **hoofdstuk 7** hebben wij een consensus richtlijn voor de diagnose en behandeling van EPS uiteengezet. De aanbevelingen waren gebaseerd op een review van de literatuur en werden uitgebreid met de medische expertise van de leden van de Nederlandse EPS registratie.

Allereerst is enige verdenking op EPS aangewezen in iedere (voormalige) PD patiënt die zich presenteert met symptomen van darmobstructie en zich verkeert in een systemisch inflammatoire

staat. De CT scan wordt beschouwd als de diagnostische modaliteit van keuze. Echter, het laagdrempelig verrichten van chirurgische exploratie wordt aanbevolen in patiënten waarbij een klinische verdenking bestaat op EPS, aangezien zowel de afwezigheid van inflammatie en typische CT scan bevindingen de clinicus niet moeten weerhouden om de diagnose EPS te stellen. Dit wordt bijvoorbeeld geïllustreerd door de casus zoals beschreven in hoofdstuk 5 en de patiënten in hoofdstuk 6. Gezien de huidige gerapporteerde studies en de ervaring van de leden van de EPS registratie wordt het gebruik van corticosteroïden en/of tamoxifen aanbevolen, afhankelijk van de aanwezigheid van systemische inflammatie bij patiënten. In de afgelopen jaren zijn er echter ook een aantal kinderen met de diagnose EPS gerapporteerd. Met betrekking tot deze groep patiënten is voorzichtigheid geboden in het gebruik van tamoxifen gezien de antioestrogene werking van dit middel.

Chirurgische interventie wordt aanbevolen als definitieve optie in de behandeling van EPS. Vooral bij patiënten die zich presenteren met ernstige symptomen van darmobstructie zonder verhoogde inflammatie parameters, of als patiënten niet voldoende reageren op medicamenteuze behandeling zou chirurgie beschouwd kunnen worden als een uiteindelijke behandeloptie. Aangezien adhesiolyse en peritonectomie ingewikkelde en gevaarlijke operatietechnieken zijn, wordt aanbevolen om EPS patiënten te opereren in een chirurgisch expertise centrum voor EPS. Recidief van EPS na chirurgie kan ontstaan en dit vergt bijkomende chirurgische interventies. Daarom zijn toekomstige onderzoeken vereist die zich richten op maatregelen ter preventie van recidief van EPS na chirurgische interventie, bijvoorbeeld door het postoperatief toedienen van tamoxifen.

CONCLUSIES

Op basis van de onderzoeken die zijn beschreven in dit proefschrift zijn de volgende conclusies getrokken:

1. **Het mononucleair cel infiltraat in het peritoneum van EPS patiënten wordt gedomineerd door CD4-positieve T cellen en M2 macrofagen.**
2. **Ondanks de overeenkomsten in klinische presentatie en radiologische bevindingen hebben patiënten met post-transplantatie EPS een betere overleving vergeleken met klassieke EPS patiënten.**
3. **Een lage graad van systemische inflammatie bestaat al voor de klinische presentatie met EPS, maar post-transplantatie EPS is in vergelijking tot klassieke EPS geassocieerd met een lagere mate van systemische inflammatie.**
4. **Post-transplantatie EPS leidt tot een significant verminderde overleving van getransplanteerde PD patiënten.**
5. **Gelokaliseerde EPS heeft een voorkeur voor het terminale ileum en leent zich goed voor chirurgische behandeling, bij voorkeur uitgevoerd in een EPS gespecialiseerd chirurgisch centrum.**
6. **Er is een rationale voor de toepassing van corticosteroïden, tamoxifen, of chirurgische interventie in de behandeling van EPS afhankelijk van de aanwezigheid van inflammatie en respons op medicamenteuze behandeling.**

EPS

Chapter 11

APPENDICES

List of abbreviations

PhD portfolio

List of publications

Dankwoord/Acknowledgements

About the author

LIST OF ABBREVIATIONS

APD	Automated peritoneal dialysis
CA-125	Cancer antigen-125
CAPD	Continuous ambulatory peritoneal dialysis
CCL18	Chemokine ligand 18
CKD	Chronic kidney disease
CNI's	Calcineurin inhibitors
CRP	C-reactive protein
CT	Computed tomography
CTGF	Connective tissue growth factor
EMT	Epithelial to mesenchymal transition
EPS	Encapsulating peritoneal sclerosis
ER	Estrogen receptor
ESRD	End-stage renal disease
GDP's	Glucose degradation products
HD	Hemodialysis
IL-6	Interleukin-6
ISPD	International Society of Peritoneal Dialysis
KTx	Kidney transplantation
MC	Mesothelial cells
METC	Medical Ethics Committee
MRI	Magnetic resonance imaging
MSC	Mesenchymal stem cell
PD	Peritoneal dialysis
PDGF	Platelet derived growth factor
PEEL	Peritonectomy and enterolysis
PM	Peritoneal membrane
RENINE	Registratie Nierfunctievervanging Nederland
RPF	Retroperitoneal fibrosis
RRT	Renal replacement therapy
SERM	Selective estrogen receptor modulator
TGF-β	Transforming growth factor beta
TGF-β1	Transforming growth factor beta1
Th-2	T-helper-2
TNF-α	Tumor necrosis factor-alpha
TPN	Total parenteral nutrition
VEGF	Vascular endothelial growth factor

PhD portfolio

Summary of PhD training

Name PhD student:	S.M. Habib
Erasmus MC department:	Internal Medicine, Division of Nephrology and Transplantation
Research school:	Netherlands Institute for Health Sciences (NIHES)
Start research period:	July 2009
Title thesis:	Encapsulating Peritoneal Sclerosis; A study on pathophysiology, clinical aspects and management
Date of defense thesis:	May 14th, 2014
Promotor:	Prof.dr. R. Zietse
Copromotors:	Dr. M.G.H.Betjes
	Dr. M.R.Korte

Master of Science in Health Sciences (ECTS 118.4)

Netherlands Institute for Health Sciences, Rotterdam, The Netherlands
Erasmus Summer programme

2010 Principles of research in medicine and epidemiology
2010 Clinical decision analysis
2010 Methods of public health research
2010 Clinical trials
2010 Social epidemiology
2010 Markers and prognostic research

University of Cambridge, Cambridge, United Kingdom

Feb 2012 Environmental epidemiology
Apr 2012 Nutrition & physical activity
Feb 2013 Chronic disease

Harvard University, Boston, Massachusetts, United States of America

Aug 2012 Summercourses at the Harvard School of Public Health
Global nutrition
Elements of epidemiologic research

Netherlands Institute for Health Sciences

Core courses

2010 Study design

2010 Biostatistical methods I: basic principles

Programme specific courses

2012 Biostatistical methods II: classical regression models

Advanced courses

2011 Pharmaco-epidemiology

2011 Conceptual foundation of epidemiologic study design

2011 Principles of genetic epidemiology

2011 History of epidemiologic ideas

2011 The practice of epidemiologic analysis

2011 Research seminars 1

2012 Ethnicity, health and health care

2012 Clinical epidemiology

2013 Pharmaco-epidemiology and drug safety

2013 Advanced topics in clinical trials

2013 Advanced analysis of prognosis studies

2013 Research seminars 2

2013 Principles of epidemiologic data-analysis

2013 Quality of life measurement

Skills courses

2012 Scientific writing in english for publication

2013 PhD day Erasmus MC -"Network your way through your career"

(INTER)NATIONAL CONFERENCES OR MEETINGS

Oral presentations

2010 Nederlandse Transplantatie Congres. Rotterdam, The Netherlands. "Encapsulating peritoneal sclerosis contributes significantly to mortality after kidney transplantation"

2011 Nederlandse Nefrologie Dagen. Veldhoven, The Netherlands. "Post-transplantation encapsulating peritoneal sclerosis contributes significantly to mortality after kidney transplantation"

2011 Dutch EPS Registry board meeting. Veldhoven, The Netherlands. "Managing Encapsulating Peritoneal Sclerosis (EPS): towards a Dutch guideline"

2012 European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Congress. Paris, France. "A Dutch Guideline for the management of encapsulating peritoneal sclerosis"

2012 14th Congress of the International Society of Peritoneal Dialysis (ISPD). Kuala Lumpur, Malaysia. "Clinical features of post-transplantation encapsulating peritoneal sclerosis (EPS); less inflammation, lower mortality and a different second hit compared to classical EPS"

2012 Nederlandse Nefrologie Dagen. Veldhoven, The Netherlands. "Encapsulating peritoneal sclerosis may evolve without systemic inflammation and absence of radiological abnormalities"

2012 Minisymposium MSc Health Sciences & Clinical Research. NIHES, Rotterdam, The Netherlands. "Encapsulating peritoneal sclerosis"

2013 Dutch EPS Registry board meeting, Hans Mak Instituut, Utrecht, The Netherlands. "The research initiative on immune cells involved in encapsulating peritoneal sclerosis (TriCeps)"

2013 Nederlandse Nefrologie Dagen. Veldhoven, The Netherlands. "T-helper cells and fibrosis-associated macrophages dominate the peritoneal inflammatory infiltrate in EPS patients"

2013 European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Congress. Istanbul, Turkey. "T-helper cells and fibrosis-associated macrophages dominate the peritoneal inflammatory infiltrate in EPS patients"

2013 Nefrologie lunch bespreking, Erasmus Medical Center, The Netherlands. "Unraveling the abdominal cocoon; studies on pathophysiology, clinical aspects, and management of EPS"

2014 Department of Surgery, Reinier de Graaf Gasthuis, Delft, The Netherlands. "Encapsulating peritoneal sclerosis; surgical aspects"

Invited lectures

2012 European training & Research in Peritoneal Dialysis. Winterschool. Amsterdam, The Netherlands. "Post-transplantation encapsulating peritoneal sclerosis; a new kid on the block?"

2012 Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA. "Post-transplantation encapsulating peritoneal sclerosis"

2013 Personalized Dialysis Initiatives "Inflammation and EPS." De Lutte, The Netherlands. Invited by Baxter Healthcare B.V.

Poster presentations

2010 American Society of Nephrology. Denver, USA

2012 Nederlandse Nefrologie Dagen. Veldhoven, The Netherlands

2012 European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Congress. Paris, France

2012 14th Congress of the International Society of Peritoneal Dialysis (ISPD). Kuala Lumpur, Malaysia

2013 Nederlandse Nefrologie Dagen. Veldhoven, The Netherlands

2013 European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Congress. Istanbul,Turkey

Other attended scientific symposia or meetings

2010 De toekomst van Peritoneale Dialyse. Rotterdam, The Netherlands

2012 Regionale nierbiopsieavond, Rotterdam, The Netherlands

2012 Regionale nierbiopsieavond, Rotterdam, The Netherlands

2013 Regionale nierbiopsieavond, Rotterdam, The Netherlands

2013 Tweede regionale nascholing (day 1). Niertransplantatie Anno 2013. "Nog Steeds Innovatieve Geneeskunde". Rotterdam, The Netherlands

2013 PLAN (Platform AIO's Nefrologie) day-"The Rotterdam Experience". Rotterdam, The Netherlands

TEACHING ACTIVITIES

2012 Teaching nurses on the topic of Encapsulating peritoneal sclerosis. Bijscholingsdagen LievensBerg ziekenhuis. Lievensberg Hospital, Bergen op Zoom, The Netherlands

2012-present Assessing practical/lab reports written by first and second year medical students during practical classes. Erasmus University Rotterdam, The Netherlands

2013- present Supervising a medical student with master thesis/keuzeonderzoek. Erasmus University Rotterdam, The Netherlands

OTHER ACTIVITIES RELATED TO EPS

2012 Visiting the referral center for EPS surgery. Addenbrooke's Hospital, Cambridge, United Kingdom

2012-2013 Data collector Dutch EPS registry. Responsible for the data collection of all incident EPS cases in the Netherlands. Hans Mak Institute, Utrecht, The Netherlands

PEER REVIEWER FOR SCIENTIFIC JOURNALS

2011-present Erasmus Journal of Medicine

2013-present Peritoneal Dialysis International

2013-present PLOS ONE

AWARDS AND GRANTS

2010-2011	Programma student Assistenten Onderzoek (PSO) laureate. Granted by the Dutch foundation of social partners in the academic sector (SoFoKleS)
2012	Award best scientific abstract category and Travel Grant Winner. European Renal Association-European Dialysis and Transplant Association (EDTA) congress. Paris, France
2012	Gerrit Jan Mulder Travel grant. Erasmus Medical Center, Rotterdam, The Netherlands
2012	Young Investigator Award. 14th Congress of the International Society of Peritoneal Dialysis (ISPD). Kuala Lumpur, Malaysia
2012	Kolff Studenten Beurs 2012. Granted by the Dutch Kidney Foundation
2013	Kolff Studenten Beurs 2013. Granted by the Dutch Kidney Foundation
2013	Award best scientific abstract category and Travel Grant Winner. European Renal Association-European Dialysis and Transplant Association (EDTA) congress. Istanbul, Turkey

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1. Korte MR, **Habib SM**, Lingsma H, Weimar W, Betjes MG. Posttransplantation encapsulating peritoneal sclerosis contributes significantly to mortality after kidney transplantation. (Am J Transplant. 2011;11(3):599-605)
2. **Habib SM**, Betjes MG, Fieren MW, Boeschoten EW, Abrahams AC, Boer WH, Struijk DG, Ruger W, Krikke C, Westerhuis R, de Sévaux RG, van der Sande FM, Gaasbeek A, Korte MR–on behalf of the EPS registry. Management of encapsulating peritoneal sclerosis: a guideline on optimal and uniform treatment. (Neth J Med. 2011;69(11):500-7))
3. **Habib SM**, Korte MR. Encapsulating peritoneal sclerosis: een ingekapselde diagnose. (Dialyse & Nefrologie Magazine. Invited. 2012;30(1):10-13)
4. **Habib SM**, Korte MR. Encapsulating peritoneal sclerosis: een ingekapselde diagnose. (Forum. Invited. 2012;12(2):9-12)
5. **Habib SM**, Korte MR, Betjes MG. Lower mortality and inflammation from post-transplantation encapsulating peritoneal sclerosis compared to the classical form. (Am J Nephrol. 2013;37(3):223-30)
6. **Habib SM**, Hagen SM, Korte MR, Zietse R, Dor FJ, Betjes MG. Localized encapsulating peritoneal sclerosis constricting the terminal ileum-an unusual appearance requiring surgical intervention. (Perit Dial Int. 2013;33(5):503-6)
7. **Habib SM**, Dor FJ, Korte MR, Hagen SM, Betjes MG. Post-transplantation encapsulating peritoneal sclerosis without inflammation or radiological abnormalities. (BMC Nephrol. 2013;14:203)
8. **Habib SM**, Abrahams AC, Korte MR, Zietse R, De Vogel LL, Boer WH, Dendooven A, Van Groningen MC, Betjes MGH. CD4-positive T cells and M2 macrophages dominate the peritoneal infiltrate of patients with encapsulating peritoneal sclerosis. (Submitted)
9. **Habib SM**, de Jonge LCW, Carels RA, Verveer C, Zandbergen AAM. A patient with weight loss and fatigue; remarkable findings upon imaging. (To be submitted)
10. Latus J**, **Habib SM****, Kitterer D, Korte MR, Ulmer C, Fritz P, Davies S, Lambie M, Alscher D, Betjes MGH, Segerer S, Braun N- on behalf of the European EPS study group. Histological findings do not discriminate between post-transplantation and classical EPS: a European multicenter study **contributed equally (Submitted)

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Zonder ouders en broertjes, geen Meelad

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Meelad

About the author

Meelad is our oldest son and was born on May 4th, 1989 in Kabul, Afghanistan. He was at the age of 9 when our family immigrated to the Netherlands. After graduating from secondary school (Atheneum, Groene Hart, Barendrecht), he started medical school in 2008 at the Erasmus University Rotterdam. At the end of his first year in medical school, Meelad started to work as a student assistant at the dialysis unit, Erasmus Medical Center, Rotterdam. At the same time, he started conducting research on the topic of EPS at the division of Nephrology and Transplantation under supervision of Dr. M.G.H.Betjes and Dr. M.R.Korte. In 2010, Meelad was nominated to participate in the "Programma Studentassistenten Onderzoek" project, supported by the Dutch foundation of social partners in the academic sector. He received his Bachelor of Science degree in Medicine in 2011.

During medical school, he was selected to participate in the Master of Science (MSc) program in Health Sciences at the Netherlands Institute for Health Sciences. He broadened his educational horizons by spending part of his MSc training at the Harvard School of Public Health, Boston, Massachusetts, USA, during the Summer Program in 2012. Furthermore, he spent several weeks in the enchanting city of Cambridge and performed three MSc electives (2012/2013) at the Institute of Public Health, Cambridge University, UK. Reflecting back at the years that have passed, Meelad has been fully engaged in conducting clinical research. He kept continuing his research projects since 2009, postponed his Master program in Medicine since 2012, and has throughout the years been working on his PhD thesis, which is lying before you (Promotor: Prof. dr. R. Zietse, Copromotors: Dr. M.G.H.Betjes and Dr. M.R.Korte). He has explored the boundaries of science by participating actively in conferences and shared his research findings at (inter) national level. During several international conferences, he has been granted abstract awards, including a Young Investigator Award at the 14th ISPD conference in Kuala Lumpur, Malaysia.

Currently, Meelad is working towards his Master's degree in Medicine and is performing his medical internships. He has developed a keen interest in Nephrology and will continue his educational journey by undertaking a clinical observership (Internal Medicine and Nephrology) at the Beth Israel Deaconess Medical Center, a teaching hospital of Harvard Medical School in Boston, Massachusetts, USA, starting on May 19th, 2014 (Clinical sponsor: Dr. S. Lecker). He expects to complete his medical studies and will become a medical doctor in the second half of 2015. Meelad enjoys traveling, spending time with his family, friends, and his little brothers Haris (23) and Yousef (16).

Moheb and Gulalai Habib
(*Meelad's parents)*

Chapter 11