Encapsulating Peritoneal Sclerosis

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Summary: Encapsulating peritoneal sclerosis (EPS) is a rare but serious complication of peritoneal dialysis. In this review, we describe the clinical picture and histologic changes to the peritoneal membrane that are associated with EPS and provide an update on current diagnosis and management. We also discuss the recent studies that have suggested that the use of more biocompatible solutions containing lower concentrations of glucose degradation product that often are pH neutral in combination with a change in clinical practice (reducing glucose exposure and monitoring peritoneal membrane function) might ameliorate peritoneal degeneration, reduce the incidence of EPS, and minimize the severity of the disease.

Keywords: Encapsulating peritoneal sclerosis, peritoneal membrane, peritoneal dialysis, EPS

Peritoneal dialysis (PD) was started in North America in 1978, and now is established as a standard renal-replacement therapy for end-stage renal disease. Cumulative data have confirmed the clinical benefits of PD as part of an integrated model of care for patients with end-stage renal disease; patients starting on PD have similar survival rates compared with those starting hemodialysis (HD) in the early phase of their disease but perhaps with better social rehabilitation and cost effectiveness with respect to patient quality of life.[1] However, encapsulating peritoneal sclerosis (EPS) has emerged as an issue of serious concern, and is affecting the penetration of PD therapy and causing early withdrawal of PD in some countries, including Japan.

EPS, first described in 1980,[2] is a rare but serious complication of peritoneal dialysis, characterized by recurrent small-bowel obstruction and sclerotic thickening of the peritoneal membrane. It historically has carried high mortality and extreme morbidity to the extent that fear of this condition may be partly to blame for the decrease in the adoption of PD in many countries. Diagnosis requires both clinical features of intestinal obstruction or disturbed gastrointestinal function, and evidence of bowel encapsulation either radiologically or pathologically.[3,4] The exact incidence of EPS is difficult to ascertain because the clinical picture can be variable and onset can be insidious. However, there are now several large-scale registry and cohort studies showing incidence rates between 0.5% and 4.4%,[5-11] with length of time on PD being an important risk factor.[6,12-15]

CLINICAL PICTURE

The original article describing EPS was a case series of five peritoneal dialysis patients who, upon undergoing laparotomy for unrelated reasons, were found to have marked thickening, opacity, and sclerosis of the entire peritoneal surface "resembling icing on a cake."[2] The loops of bowel were bound together and shortened by this casing.

Since then, numerous centers have reported a very wide range of symptoms associated with what now is termed *Encapsulating Peritoneal Sclerosis* (previously referred to as *sclerosing peritonitis*). EPS has been defined by the International Society for Peritoneal Dialysis (ISPD) as "a syndrome continuously, intermittently, or repeatedly presenting with symptoms of intestinal obstruction caused by adhesions of a diffusely thickened peritoneum, and is a purely clinical diagnosis."[16] Pathologically, this condition is a progressive intra-abdominal inflammatory process resulting in sheets of fibrous tissue that constrict the viscera, compromising the motility and function of the bowel and eventually forming a dense cocoon. Symptoms include loss of appetite; GI disturbances such as nausea, vomiting, constipation, and diarrhea; weight loss resulting from both reduced oral intake and poor gut absorption; and symptoms of complete or partial small-bowel obstruction such as abdominal fullness and pain.[17] There also may be evidence of inflammation such as pyrexia, increased C-reactive protein level, anemia, bloody dialysate, and ascites.[18] Perforation caused by bowel obstruction also has been reported.[19]

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Interestingly, although much less common, similar cases also have been described in patients with end-stage renal failure never receiving PD, and in patients without end-stage renal failure (particularly young adolescent females from tropical and subtropical countries, but it also has been associated with a range of conditions, including autoimmune diseases, after abdominal or gynecologic surgery or malignancies, and after β-blocker administration).[20-22]

A CONTINUUM WITH PERITONEAL SCLEROSIS?

Many of the histologic and radiologic changes associated with EPS are echoed in the chronic changes to the peritoneal membrane seen in long-term peritoneal dialysis. This has led to the suggestion that EPS may be part of a spectrum of inflammatory diseases affecting the peritoneal membrane.

According to the "two-hit" theory of EPS pathogenesis,[23] there is chronic deterioration of the peritoneum as a result of peritoneal dialysis (the first "hit"), while a subsequent proinflammatory stimulation constitutes a second “hit.” Triggering insults may include bacterial/fungal peritonitis, endotoxin, chemical agents, uremic toxins, and endogenous advanced glycation end-product (AGE)-receptor–mediated oxidative stimuli.[24] Given that two thirds of EPS cases develop after stopping PD, production of proinflammatory and fibrogenic cytokines and mediators is thought to be balanced by their removal while on PD. A disruption of the balance and/or a dysregulated membrane regeneration process is proposed to result in EPS. Of note, the reported incidence of EPS varies depending on patients’ genetic background such as the genotype for receptor of AGE.[25]

CLINICAL PROGRESSION

Several large-scale registry studies have been performed,[10,19,26] as well as one large prospective observational study.[9] Patients who went on to develop EPS generally were faster transporters on standard peritoneal equilibration tests (PETs), with lower ultrafiltration (UF) volumes during the PET and over 24 hours. EPS patients also had more episodes of peritonitis or had episodes that were more severe, and were exposed to greater volumes of peritoneal dialysates compared with control patients on PD. A longer time on peritoneal dialysis was also a strong risk factor for EPS—in the Italian pediatric registry study[26] the incidence of EPS was 0.45% in patients with a PD exposure shorter than 5 years compared with 21.1% in patients with a PD exposure of 5 years or longer.

Cases of EPS can develop after discontinuation of PD (many years later in some instances), including after transplantation.[27,28] In the Pan Thames retrospective cohort, 58% of EPS cases developed after discontinuation of PD.[19] In the prospective study by Kawanishi et al,[9] the figure was 68%. Progression of symptoms after diagnosis can be rapid, with some studies suggesting that time from mild symptoms to ful-blown EPS with bowel obstruction may be as short as 3 months.[29]

It is important to retain perspective. EPS is not an inevitable consequence of PD; thankfully it remains rare. Although the peritoneal mesothelium is subjected to a variety of insults during PD, it retains a degree of regenerative capacity; mesothelium activation can result in both apoptosis and reactive proliferation. If the injury is limited in both time and extent, the injured peritoneum can recover to a healthy state. Recent scientific progress has shown the critical role of macrophages and monocytes in orchestrating the wound-healing process.[30] In short, the wound-healing process can be summarized as comprising three phases: inflammation, granulation, and healing/remodeling. In response to tissue injury, M1-type macrophages play a proinflammatory role, followed by switching to M2-type macrophages, which play a profibrotic role for granulation. Thereafter, another form of M2-type macrophage with an anti-inflammatory role completes the whole wound-healing process. A recently published report has shown an increase in M2-type macrophages in the encapsulating membrane of EPS,[31] which may indicate that the encapsulating membrane is a reactive structure that forms during a dysregulated final step of wound healing.

Originally thought to be associated with very high mortality, more recent studies have shown that average survival may vary between 6 and 48 months.[6,19,32] It should be noted that these patients often have high comorbidity (eg, long dialysis vintage), and therefore life expectancy even without a diagnosis of EPS would not be high. Indeed, when determined, causes of death frequently were unrelated to EPS itself. Johnson et al[32] showed that a diagnosis of EPS was not an independent risk factor once PD vintage, loss of residual renal function, and high transporter status were included in a multivariate analysis comparing EPS patients with matched dialysis control patients.

In a position statement on behalf of the International Society of Peritoneal Dialysis, Brown et al[33] argued that “There is no evidence to withhold PD as a treatment option because of fear of development of EPS.” EPS is extremely rare in patients who are on peritoneal dialysis for fewer than 3 years (and still fairly rare in those on PD for <5 years). This small risk of EPS must be weighed against the significantly better quality of life seen in patients on home therapies given the short average life expectancy on dialysis, particularly in older frailer patients.