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ENCAPSULATING PERITONEAL SCLEROSIS—A CLINICIAN'S APPROACH TO DIAGNOSIS AND MEDICAL TREATMENT

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Encapsulating peritoneal sclerosis (EPS) is recognized as a serious complication of continuous peritoneal dialysis. A preliminary diagnosis of EPS is usually based on clinical signs and symptoms, which commonly include abdominal pain, nausea, vomiting, anorexia, abdominal fullness, an abdominal mass, bowel obstruction, and radiologic findings, including abdominal roentgenogram, contrast studies, ultrasound studies, and computed tomography. The diagnosis is confirmed by laparoscopy or laparotomy showing the characteristic gross thickening of the peritoneum enclosing some or all of the small intestine in a cocoon of opaque tissue.

A variety of therapeutic approaches to EPS have been reported. This review discusses medical treatment of EPS and includes an overview of the clinical features and diagnostic aspects of the condition.

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KEY WORDS: Encapsulating peritoneal sclerosis; EPS; continuous ambulatory peritoneal dialysis; CAPD; diagnosis; medical treatment; clinical features.

Encapsulating peritoneal sclerosis (EPS) is one of the most serious complications of continuous ambulatory peritoneal dialysis (CAPD), automated peritoneal dialysis, and intermittent peritoneal dialysis. It is characterized by partial or intermittent bowel obstruction, accompanied by marked sclerotic thickening of the peritoneal membrane and subsequent high morbidity and mortality (1–3). Histologically, the peritoneal membrane is found to be greatly thickened and transformed into dense layers of fibro-connective tissue infiltrated by mononuclear and polymorphonuclear cells (4). Bowel loops within the sclerotic peritoneal membrane become adherent and encapsulated, a situation that may ultimately lead to acute bowel obstruction (5).

The pathogenesis of EPS has not yet been elucidated, but several risk factors have been postulated. Early diagnosis is difficult before symptoms develop. Nevertheless, reports of successful outcomes of medical, surgical, and combined treatment have been growing year by year. In the absence of globally accepted, validated guidelines for diagnosis (especially early diagnosis) and medical treatment, the present article provides a clinician's approach to diagnosis and treatment of EPS and a review of the relevant literature.

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CLINICAL FEATURES OF EPS

Encapsulating peritoneal sclerosis can progress slowly and remain asymptomatic for a long period. The first symptoms may appear as early as 1 year after the start of peritoneal dialysis (PD) or years after transplantation or transfer to hemodialysis.

Table 1 lists symptoms and clinical findings observed in patients with EPS. Those symptoms and findings are related primarily to modification of gastrointestinal transit. The most common are abdominal pain, appetite loss, nausea, vomiting, anorexia, an abdominal mass, severe protein loss leading to malnutrition, and incomplete or complete small-bowel obstruction (6–15).

Early symptoms of EPS are bloody ascites, appetite loss, nausea, diarrhea, and abdominal pain (6–12). Sometimes early EPS presents with signs of inflammation, including fever, general fatigue, and slight weight loss (6–8,14,15). The initial presenting signs and symptoms of EPS are often vague and non-localized; they can also be caused by a variety of non EPS disorders.

In the late phase of EPS, abdominal pain, nausea, vomiting, diarrhea, constipation, bloody ascites, and abdominal mass may be seen (6–8,10,11,13,14). The abdominal disorder can induce severe malnutrition and weight loss.

A unique distinguishing feature of EPS may be the intermittent nature of the developing clinical syndrome. Other causes and consequences of alterations in intestinal motility tend to have more acute and permanent manifestations.

TABLE 1
Clinical Findings in Encapsulating Peritoneal Sclerosis

Finding/Clinical features	References
Signs of ileus	6–13
Appetite loss	
Nausea	
Vomiting	
Abdominal fullness	
Abdominal pain	
Absent bowel sound	
Constipation	
Diarrhea	
Anorexia	
Weight loss	
Signs of inflammation	6–8, 13–15
Elevated temperature	
Ascites	
General fatigue	
Weight loss	
Signs of peritoneal adhesions	6–8, 10, 11, 13–15
Bloody dialysate	
Ascites	
Abdominal discomfort	
Abdominal mass	

DIAGNOSTIC PROCEDURES

Clinical Diagnosis of EPS: A preliminary diagnosis of EPS is usually based on a past history of PD and the existence of the previously mentioned clinical signs and symptoms (Table 1). A history of long-term PD is an important risk factor for EPS (16): an EPS incidence of 19.4% after more than 8 years on PD has been reported. Clinically, however, distinguishing obstructive ileus induced by EPS from other causes of disturbed motility is frequently difficult. The clinician also needs to remember that conditions with overlapping clinical symptoms can coexist. Moreover, symptoms related to peritoneal inflammation may be difficult to distinguish from other inflammatory diseases such as bacterial peritonitis.

Laboratory Examinations in Suspected EPS: There is no established laboratory examination to confirm a diagnosis of EPS. However, although erythropoietin-refractory anemia, hypoproteinemia, and elevated plasma levels of C-reactive protein are not specific for EPS, they have been suggested as indicative signs (6,8,17).

Another common clinical finding in EPS is loss of dialysis efficiency. Increases in the mass-transfer area coefficients of creatinine and glucose lead to progressive loss of ultrafiltration volume (10,18). Progression to high peritoneal permeability may indicate the development of a pre-EPS state (19). In patients that are considered to be at high risk for EPS, early detection may be possible if the patients are routinely monitored for changes in fluid removal and peritoneal permeability to small solutes (20).

Peritoneal membrane characteristics are commonly evaluated using the peritoneal equilibration test [PET (21)]. A progression to high peritoneal permeability induces the loss of ultrafiltration volume. Yamamoto *et al.* (19) reported that the development of a high-transport state was observed in patients who later developed EPS after PD withdrawal. That finding may indicate that a high peritoneal membrane transport state is an early marker for EPS.

Morphology analyses of mesothelial cells in peritoneal effluent have shown that not only do giant cells emerge, but mesothelial cells also significantly increase in size as the duration of PD progresses (22–24). If validated, these morphologic indicators may be useful in determining the appropriate timing of PD discontinuation to prevent the development of EPS.

A number of studies have described new markers in peritoneal effluent that can predict the state of the peritoneum.

Cancer antigen 125 (CA125) is a marker produced by mesothelial cells. Whether CA125 can be used as a marker of mesothelial cell mass is still controversial. A study reported that CA125 decreased with PD duration and reached an extremely low value in patients with EPS (25). However, other studies reported no relationship between the level of CA125 and the duration of CAPD (26,27). Some studies also demonstrated that CA125 levels are very low early after the start of CAPD (25).

Other peritoneal markers such as cytokines have been suggested to be possible markers for EPS. Elevated levels of interleukin 1β (IL-1β), IL-6, IL-8, transforming growth factor β1 (TGFβ1), hepatocyte growth factor, and platelet-derived growth factor have all been found in ascites from EPS patients (28). Vascular endothelial growth factor (VEGF) is reported to be a mediator of neoangiogenesis. Increased levels of circulating or intraperitoneal proinflammatory cytokines such as IL-6 and pro-angiogenic VEGF have been speculated to possibly contribute to a high peritoneal small-solute transport rate in CAPD patients (29). Some reports exist of correlations between levels of those markers and levels of inflammation; however, whether those markers can be used as markers of peritoneal sclerosis or fibrosis (or both) is still controversial. Effluent studies have yet to determine their value. No reliable tests currently exist to identify patients at high risk of developing EPS.

Radiologic Diagnosis of EPS: Table 2 summarizes radiology findings in EPS. In early-stage EPS, no specific signs are found in plain roentgenograms, although peritoneal calcifications, signs of ileus (such as dilated small-bowel loops), and air–fluid levels in the small intestine are sometimes seen (9). At a later stage, water-soluble contrast studies of the small bowel may reveal signs of EPS that are more characteristic—for example, varying lengths of intestine tightly enclosed in a "cocoon" of thickened peritoneum, proximal small-bowl dilatation, and an increased transit time (9,30,31).

Abdominal ultrasound examination can demonstrate haustration of the ileum, fixed and rigid bowel loops with ineffective peristaltic contractions, clear-cut separation between the loops involved in the sclerotic process and loops that are still free, dilated fixed loops matted together and tethered posteriorly, intraperitoneal echogenic strands, trilaminar appearance of the bowel wall, and echogenic "sandwich" appearance of the membrane (9,30–34).

Computed tomography (CT) demonstrates findings even more characteristic for EPS, such as adherent bowel loops with increased mesenteric fat density, bowel luminal narrowing, peritoneal calcification, and entrapped fluid collection (35,38–40). Although the number of reports concerning magnetic resonance imaging in EPS are few, the results appear to be similar to those seen in CT (36,37).

Histologic Diagnosis of EPS: Although histologic diagnosis of EPS is reliable, it requires surgery—that is, it is invasive—and it is therefore often made postmortem or at a late stage of the disease. The diagnosis of EPS is confirmed when laparotomy reveals the characteristic gross thickening of the peritoneum, which encloses some or all of the small intestine in a cocoon of opaque tissue. The root of the mesentery may also be sclerotic and retracted (41).

The pathologic changes of EPS are extensively reviewed by Honda in the present supplement. Briefly, a common feature appears to be complete loss of mesothelium, accompanied by gross interstitial thickening within the membrane. Morphologically, peritoneal thickening or sclerosing peritonitis, or both, are observed. In some cases, sclerosing peritonitis indicates peritoneal thickness accompanied by infiltration by inflammatory cells. Newly developed small vessels and existing blood vessels show abnormal morphology. In some cases, remarkable vascular sclerosis has been observed in the subserosal tissue of the peritoneum. However, these changes may be associated with peritoneal fibrosis and sclerosis rather than specifically related to the development of EPS (20,42–44).

Summary of EPS Diagnosis: A preliminary diagnosis of EPS is usually based on a past history of PD and the existence of suggestive clinical signs and symptoms.

Clinical signs of EPS are related to modification of gastrointestinal transit. The most common early signs are bloody ascites, abdominal pain, appetite loss, nausea, vomiting, anorexia, an abdominal mass, severe pro-

TABLE 2
Radiologic Findings in Encapsulating Peritoneal Sclerosis

Investigation	Findings	References
Plain abdominal film	Dilated small-bowel loops Air–fluid level of small bowel Peritoneal calcification	9, 30, 31
Contrast studies	Bowel motility disturbances Separated, rigid, dilated bowel loops Varying degrees of obstruction accompanied by hypermotility	9, 30, 31
Ultrasound	Dilated fixed loops matted together and tethered posteriorly Intraperitoneal echogenic strands Echogenic "sandwich appearance" membrane Trilaminar appearance of the bowel wall	9, 30–34
Computed tomography/magnetic resonance imaging	Variable diameter of bowel segments Adherent, dilated bowel loops Air–fluid level Bowel obstruction with loculated ascites Thickened intestinal wall and peritoneal membrane Increased density of mesenteric fat Entrapped fluid collection Peritoneal calcification	9, 30, 35 36, 37

tein loss leading to malnutrition, and incomplete or complete small-bowel obstruction.

Another common clinical finding in EPS is loss of dialysis efficiency. Progression to high peritoneal permeability may indicate the development of an EPS state.

Radiologic examinations, including plain abdominal X-ray, contrast study, ultrasound study, and CT are helpful for diagnosis. In EPS, the radiologic findings reveal signs of ileus and abdominal mass.

The diagnosis of EPS is confirmed at laparotomy or laproscopy, either of which reveals the characteristic gross thickening of the peritoneum enclosing some or all of the small intestine in a cocoon of opaque tissue.

THERAPEUTIC APPROACHES IN EPS

From a theoretic viewpoint, it may be argued that treatment should be initiated as early as possible. To facilitate early treatment, staging of EPS is proposed (Table 3), based on a retrospective study in Japan obtained from clinical findings in 256 patients with EPS (7). Determining the therapeutic tactics for EPS according to the EPS stage may also be helpful.

Pre-EPS Stage: In the proposed pre-EPS stage, a highly permeable peritoneum, ultrafiltration loss, hypoproteinemia, bloody dialysate, and ascites may be seen, but signs of small-bowel obstruction are absent. Some reports suggest that removal of the PD catheter and cessation of PD may be effective at this stage (6,24,45–48). Furthermore, several reports in the literature describe an association between ultrafiltration failure or reduced small-solute clearance (or both) and EPS (6,13,18, 19,49). Thus, increased peritoneal permeability has been suggested to be a risk factor for EPS development (19).

If the foregoing clinical findings are at hand, especially in long-term PD patients, a noninvasive radiologic work-up should be conducted as an initial screen. If the result of the radiology examinations suggest EPS, treatment should be considered (Table 3). However, cessation of PD and removal of the catheter does not always stop the progression of the condition (6,46,47).

With cessation of PD, the lack of free fluid between the bowel loops brings the bowel surfaces closer together and may hasten adhesion formation and the onset of intestinal obstruction. Under those conditions, EPS may even accelerate after discontinuation of PD (46–48). Dialysis may act to continuously remove fibrin, thus preventing further deposition and organization.

If the diagnosis of pre-EPS has been made, and discontinuation of PD and a switch to hemodialysis seems to be the only option, it has been suggested that, to

TABLE 3
Proposed Staging of Encapsulating Peritoneal Sclerosis

Stage	Clinical findings	Therapeutic approach
Stage 1 (pre-EPS period)	Loss of ultrafiltration capacity Development of a high transport state Hypoproteinemia Bloody dialysate, ascites Calcification of peritoneum	Peritoneal rest Peritoneal lavage Glucocorticoids
Stage 2 (inflammation period)	Increase in C-reactive protein Increase in white blood cells Fever Bloody dialysate Ascites Weight loss Appetite loss Diarrhea	Glucocorticoids
Stage 3 (encapsulating or progressive period)	Disappearance of the signs of inflammation Appearance of symptoms/signs of ileus (nausea, vomiting, abdominal pain, constipation, abdominal mass, ascites)	Glucocorticoids Total parenteral nutrition
Stage 4 (ileus or complete period)	Anorexia Complete ileus Abdominal mass	Surgical intervention

reduce the risks, membrane protective measures such as intra-abdominal lavage (19,21,46–48), corticosteroid treatment (46–48), and administration of other immunosuppressive drugs (48–53) may be useful. Long-term intra-abdominal lavage has been reported to result in improved peritoneal membrane function (24). Based on data presented in this supplement by Breborowicz and Oreopoulos, it appears that a more biocompatible solution than saline should be used if lavage is initiated.

Inflammatory Stage: At the proposed inflammatory stage, clinical findings related to an inflammatory condition—such as fever, general fatigue, appetite and weight loss, ascites, bloody dialysate, and abdominal pain—can be found (Table 3). Non-resolving peritonitis may also be seen (6,8,15,17,54). Clinically, distinguishing the early stage of EPS from other inflammatory conditions such as bacterial peritonitis is difficult.

In the inflammatory stage, peritoneal rest and peritoneal lavage have been prescribed (19,46–48). In cases in which small-bowel obstruction is absent, EPS may improve, and the patient may become asymptomatic following removal of the peritoneal catheter and cessation of PD (6,24,47–49).

If bacterial and fungal peritonitis are ruled out, corticosteroid administration may be considered (8,48–53). Certain reports have suggested the use methylprednisolone pulse therapy [500 – 1000 mg daily for 2 – 3 days (8)], resulting in improvement of inflammation and symptoms including fever, ascites, appetite loss, nausea, and abdominal pain. In other reports, low-dose prednisolone (0.5 – 1.0 mg per kilogram of body weight daily for 2 – 4 weeks), followed by a gradually decreasing dose, has been used (55). However, there is no agreement in the literature regarding the dose of corticosteroids that should be used.

Encapsulating Stage ("Progressive Stage"): In the proposed encapsulating stage of EPS, the clinical picture is characterized by the presence of obstruction of the small intestine (symptoms of ileus). Thus, at this stage, a suspicion of EPS should be raised if symptoms and signs of ileus appear—for example, abdominal pain, nausea, vomiting, and constipation (6–12). These abdominal disorders can induce severe malnutrition (6,15,17).

At our center, the strategy regarding conservative treatment of EPS at this stage is cessation of PD, transfer to hemodialysis, and total parenteral nutrition (TPN)—although the effect of the latter treatment is questionable (2,8,11,16,50,56–61). In addition, administration of corticosteroids, alone or in combination with lysis of the adhesions, has been reported to be beneficial in some patients with EPS (46–51). Thus, in the absence of contraindications, we recommend initiating corticosteroid treatment as soon as possible (48–53). If conservative therapy fails to improve the symptoms of EPS, surgical therapy should be considered (8,27).

Ileus Stage (Complete Stage): The proposed ileus stage is characterized by signs of complete (not intermittent) bowel obstruction. If the patient's condition does not improve or if the symptoms of ileus recur within a few months, the dose of corticosteroids should be reduced, and the patient should be managed with TPN (2,8,11,16, 50,56–61). However, in most cases, this treatment is not sufficient (11,56–61). If ileus symptoms remain despite the absence of inflammatory findings, surgery should be considered.

In the past, surgical treatment for EPS was contraindicated. Although isolated instances of successful outcomes after surgical intervention have been reported, especially in cases related to severe peritonitis, the prognosis after surgery has usually been poor (11,57–61). Serous degeneration of the intestinal wall (commonly seen in long-tern PD patients) increases the risk for anastomotic failure (11,57–61). Because the pathology of EPS was not sufficiently understood, resection of the ileus-producing lesion and intestinal anastomosis were performed to relieve ileus symptoms. Based on a nationwide study, Kawanishi *et al.* (8,56) reported a postoperative mortality rate of 82% for patients with EPS undergoing intestinal anastomosis.

Recently, Kawanishi *et al.* developed a novel surgical technique basically consisting of acute enterolysis (8,56). The surgical treatment of EPS is extensively reviewed by Kawanishi in this supplement, where the most recent data show a mortality rate of only 4%.

THERAPEUTIC MANAGEMENT OF EPS IN JAPAN

The choice of surgical or conservative therapy can be based on the stage of the disease. We retrospectively studied the 256 CAPD patients who developed EPS at 157 CAPD centers in Japan (7). Among those patients, 101 received some kind of therapeutic intervention. Steroids, including low-dose and pulse therapy, were administered to 84 patients (83%), and TPN to 80 patients (79%). Total intestinal enterolysis was performed in 31 patients (31%). Other immunosuppressive agents were used in 8 patients (8%). In addition, surgical viscerolysis was performed in 53 patients (52%). Thus, combination therapy was used in many of the patients.

A total of 100 patients (39.1%) died of various causes. After 2 years, 143 patients (55.9%) were still alive. For 13 patients (5.0%), the outcome was unknown. Among patients treated with steroids, the 2-year survival was

73% (61 of 84 patients). Among patients not receiving such treatment, the 2-year survival was only 48% (82 of 173 patients). Previously, the Japanese Sclerosing Encapsulating Peritonitis Study Group had reported that steroid therapy is effective in 65% of EPS patients in Japan (62).

OTHER THERAPEUTIC APPROACHES TO EPS

A variety of therapeutic approaches to EPS have been reported (Table 4). That variety may reflect the sporadic nature and low incidence of the disease, as well as a lack of clear, widely accepted guidelines for treatment. Evaluations of proposed treatments have been limited to case reports or small-scale studies.

Many reports in the literature describe the beneficial effects of immunosuppressive agents on the progression of EPS (51,53,72). Although most of those reports refer to a combination of corticosteroids and cytotoxic agents, Mori *et al.* (52) reported the first case of a patient with PD-related EPS who responded favorably to corticosteroid therapy alone.

Recently, Allaria *et al.* (71) reported the successful use of tamoxifen in one case of EPS. A 67-year-old woman who developed EPS 8 years after starting CAPD was treated with tamoxifen (10 mg daily) for 3 months. She gradually recovered. Tamoxifen probably interferes with TGFβ1 and may therefore be useful in the treatment of EPS (72,73).

In addition, some reports indicate that renin–angiotensin inhibitors prevent the progress of peritoneal fibrosis and peritoneal adhesions in animal models (63,64) and that phosphatidylcholine exerts a protective effect in patients with peritoneal sclerosis (65). Patients with EPS have also been reported to improve after renal transplantation (15,66), indicating that cyclosporin may have an effect on the condition.

TABLE 4
Therapeutic Agents Used in Encapsulating Peritoneal Sclerosis and Related Disorders

Therapeutic agent	Evidence	References
Corticosteroids	Case reports	48–53
Immunosuppressants	Case reports	51, 53
Tamoxifen	Case report	53
Renin–angiotensin system inhibitors	Animal models	63, 64
Phosphatidylcholine	Case report	65
Antifibrotic agents	Animal models	66–69
Renal transplantation	Case reports	12, 66

CONCLUSIONS

Encapsulating peritoneal sclerosis is a serious, life-threatening complication of PD. The initial clinical symptoms are directly related to disturbances in gastrointestinal transit. The most common findings are abdominal pain, nausea, vomiting, anorexia, abdominal fullness, abdominal mass, severe protein loss leading to malnutrition, and incomplete or complete small-bowel obstruction. Although the observed findings may be strongly indicative of EPS, radiologic examination is required to establish a clinical diagnosis of EPS. Not infrequently, laparotomy or laparoscopy is required to confirm that diagnosis.

The key elements in conservative treatment are early diagnosis, cessation of PD with transfer to hemodialysis, sustained bowel rest with TPN, and corticosteroids. If conservative therapy does not improve the symptoms of EPS, surgical therapy must be considered. By definition, EPS refers only to the encapsulating and ileus stages of the disease. However, from a therapeutic perspective, the diagnosis should be established before the symptoms of ileus occur so that an attempt to cure the disorder with medical treatment can be made.

Because of the sporadic nature and low incidence of the disease, the literature has come to no agreement on the overall management of EPS. Further studies concerning prevention, early detection, and non surgical treatment of EPS are therefore warranted.

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