

Review Article

Peritoneal Sclerosis: From Simple to Encapsulating

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Abstract

Peritoneal sclerosis is a chronic fibro inflammatory condition of the peritoneum which may result from a recurrent subclinical peritonitis with minimal abdominal signs. The mortality of patients with EPS varies between 26-58% with mortality increasing with the length of time on PD. Encapsulating Peritoneal Sclerosis (EPS) is a complex yet rare phenomenon characterized by progressive sclerosis combined with inflammatory infiltrates, calcification, and vascular changes. "Two-Hit theory" best explains the pathogenesis of EPS wherein, the first hit is chronic peritoneal membrane injury, such as resulting from chronic exposure to peritoneal dialysate and followed by a second hit such as an episode of peritonitis, genetic predisposition and/or acute cessation of peritoneal dialysis. Poor biocompatibility of PD is an obvious risk factor for SPS yet peritonitis is the most commonly invoked pathogenetic factor for SPS. Other risk factors suggested to be involved in EPS onset in case of peritoneal dialysis are the composition of dialysis fluid and generation of GDPs, young age, ultra filtration failure and the exposure to PD catheter cleaning reagent, chlorhexidine. Clinical signs of patients developing peritoneal Sclerosis while on peritoneal dialysis therapy are ultra filtration and clearance failure. The clinical picture of EPS being variable poses a diagnostic dilemma for which various investigations are necessary to further evaluate a suspected case. Peritoneal enhancement, peritoneal thickening, calcification, bowel tethering, bowel wall thickening, signs of bowel obstruction, and loculated collections are the most common CT findings of EPS. Surgery (laparoscopy/laparotomy and peritoneal biopsy) therefore may be needed to confirm the diagnosis. Although histological examination is an invasive method, a reliable diagnosis can be obtained by measuring the thickness of the sclerosis. Currently favored surgical techniques are peritonectomy and enterolysis which involves resection of the peritoneum and fibrous tissue together with division of adhesions to release the bowel. Post surgery recurrence rates with advanced disease tend to be as high as around 25%.

INTRODUCTION

Peritoneal sclerosis was first described in 1907 [1] and the term "abdominal cocoon" is in vogue since 1978 [2]. Peritoneal sclerosis is a chronic fibro inflammatory condition of the peritoneum which may result from a recurrent subclinical peritonitis with minimal abdominal signs. Simple Peritoneal Sclerosis (SPS) is a mild, clinically subtle illness that occurs following chronic peritoneal irritation [3]. Encapsulating Peritoneal Sclerosis (EPS) is a complex phenomenon and is not identical with Simple Peritoneal Sclerosis (SPS). While SPS is relatively common, EPS is a rare condition with low incidence of <5/1000/year, [4] but it is dramatic and often fatal. EPS is not simply the advanced and evolved stage of SPS, as some Japanese researchers claim, [5] but a different disease with its own unique characteristics.

ETIOPATHOGENESIS

Peritoneal sclerosis can be both primary where the cause is unknown as well as secondary to conditions that cause

peritoneum inflammation and fibroblastic proliferation, for example peritoneal dialysis (PD)-related conditions or abdominal tuberculosis. Long-term PD is usually incriminated as a cause of peritoneal sclerosis which may range from Simple Peritoneal Sclerosis to Encapsulating Peritoneal Sclerosis. Whereas PD-induced simple fibrosis of the peritoneal membrane is very common in PD-patients, encapsulating form of peritoneal sclerosis with its clinical implications is very rare [6,7].

Pathology

EPS is not simply an evolved stage of SPS [5]. This is because studies have shown lack of intermediate stages which would link SPS to EPS and the unexplained large difference in the incidence of both diseases. Since peritoneal dialysis forms the natural model for peritoneal sclerosis most of our understanding of peritoneal sclerosis has come from it. In the early years of PD, the peritoneal alterations associated include mesothelial modifications which later extend to sub mesothelial tissues. Mesothelial modifications may range from ultra structural alterations to loss of mesothelium

with cuboidal transformation of mesothelial cells in between. Basement membranes of both mesothelium and blood vessels are thickened and may appear reduplicated. With regard to histological features, SPS consists of sclerotic tissue that rarely extends to the whole peritoneum and is devoid of extensive calcifications and severe vasculopathy.

Unlike SPS, EPS [8-10] is characterized by progressive sclerosis combined with inflammatory infiltrates, calcification, and vascular changes. These additional histological features do not favor the hypothesis of evolution of SPS to EPS. Furthermore, unlike SS, inflammation is present in 100% of the EPS cases and manifests both acute and chronic inflammatory cells, including giant cells, granulation tissue, vasculopathy with vascular occlusion, calcification, and perhaps ossification, which contrasts with the pathology of the SPS. Macroscopically, in EPS peritoneal surface is reduced to a rough thickened membrane fixing groups of intestinal loops preventing their movement. Besides intestines

any intra-abdominal organ may be involved in sclerosis forming an encapsulated mass called "abdominal cocoon" [11,12].

The microscopic picture is dominated by sclerosis, with compact sclerotic tissue consisting of dozens of irregular layers (Figure 1). In the matrix, fibroblasts and mesoblasts are prevalent.

Pathogenesis

"Two-Hit theory" so far best explains the pathogenesis of EPS wherein, the first hit is chronic peritoneal membrane injury, such as resulting from chronic exposure to peritoneal dialysate and followed by a second hit such as an episode of peritonitis, genetic predisposition and/or acute cessation of peritoneal dialysis.

Peritoneal dialysis-dependent sclerosing peritonitis

Non-physiologic dialysis solutions may induce a chronic sterile inflammation in the peritoneal cavity with upregulation of several cytokines resulting in collagen synthesis by mesothelial

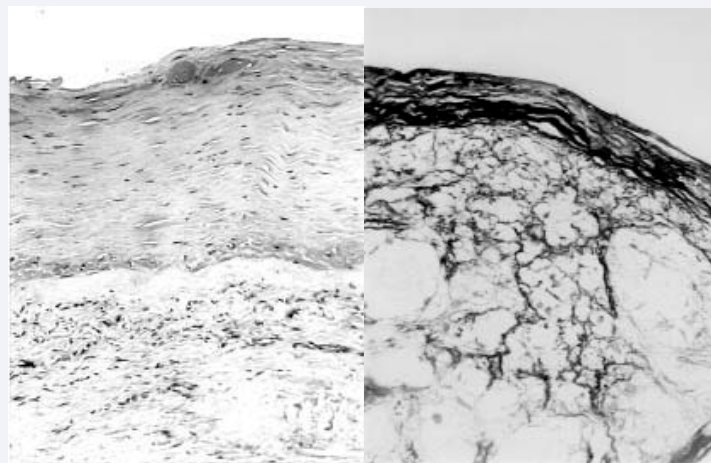
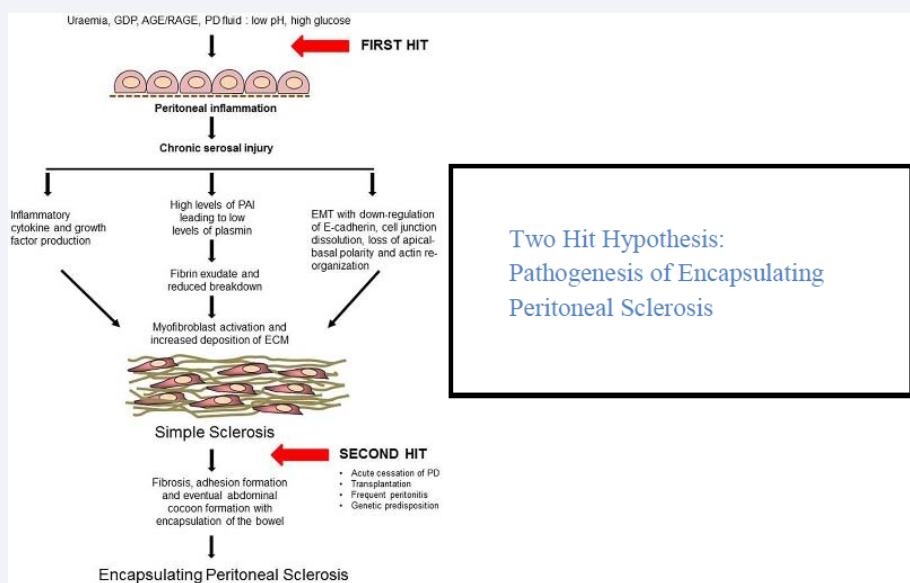


Figure 1 Sclerosing peritonitis. Thick submesothelial sclerotic tissue. Hematoxylin-eosin, ×40.



Two Hit Hypothesis:
Pathogenesis of Encapsulating
Peritoneal Sclerosis

Figure 2 Sclerosing peritonitis. Thick submesothelial sclerotic tissue. Hematoxylin-eosin, ×40.

cells and fibroblasts. Moreover, the high concentrations of glucose and lactate as well as the low pH of the dialysis solutions and bio-incompatible substances directly damage the peritoneal membrane [13]. Peritoneal fibrosis has 2 cooperative parts, the fibrosis process itself and the inflammation. The link between these 2 processes is frequently bidirectional, with each one inducing the other. Long Time on PD leads to peritoneal membrane changes such as mesothelial cell denudation, interstitial fibrosis, vasculopathy and angiogenesis, which may set the stage for the development of EPS. It is proposed that inflammatory stimuli (a "second hit") superimposed on this altered peritoneal membrane may act as the inciting factor to trigger the onset of EPS.

The poor biocompatibility of PDF due to osmotic agents, hyperosmolarity, low pH, and buffer systems result in anatomical alterations of the peritoneum within few years the morphological changes associated with PD have also been reproduced in animal models. The poor biocompatibility of PD solutions is thought to pose chronic irritation to the peritoneum simple sclerosis is a telltale of this chronic irritation what couples chronic irritation to sclerosis is thought to be due to an epithelial to mesenchymal transformation of the mesothelial cells and their further release of cytokines and growth factors (Figure 2). This sets in a cascade of chronic inflammation, angiogenesis and attempt to repair by myofibroblasts leading to fibrosis. Exudation of fibrin from the plasma and its local formation due to up regulation of coagulation cascade and its defective fibrinolysis in an inflammatory milieu contributes to progressive intestinal adhesions and peritoneal thickening. The concept of use of anti-inflammatory and anti-fibrotic drugs in EPS seems logical because of this hypothesis [14,15].

Poor Biocompatibility of PD is an obvious risk factor for SPS but not all cases of simple ps progress to eps and in most cases such a trigger remains unknown. However, Epidemiological studies have elaborated on certain suspected factors. Several factors correlating with poor biocompatibility are incriminated as a trigger for transformation from simple ps to encapsulating ps are as follows: acetate buffer, chlorhexidine, povidone iodine, catheters, in-line bacterial filters, particles of plastics, and plasticizers.

Peritonitis is a common complication of PD and is the most commonly invoked pathogenetic factor for SPS. It plays a complex part in the development of EPS with the number of peritonitis episodes linked to incidence of EPS [16]. Certain etiological agents are also recognized to be more dangerous than others, especially *Staphylococcus aureus*, fungi, *Pseudomonas* species, and *Haemophilus influenzae*. The pathogenesis of peritonitis promoting peritoneal sclerosis has been thoroughly studied [17]. Peritonitis results in loss of mesothelium which besides facilitating damage by bio-incompatible PD solutions results in loss of fibrinolytic capacity by mesothelial cells. The excess fibrin production during bacterial peritonitis and its decreased fibrinolysis results in accumulation and organisation of fibrin on peritoneal surface. These excess fibrins overtime stimulates the ingrowth of fibroblast and blood vessels and thus lead to scarring. Moreover, Intraperitoneal antibiotics instilled during peritonitis may also cause chemical peritonitis [18] thus favoring the development of SPS. The antibiotics suspected

include vancomycin, cephalothin, cefuroxime, tobramycin, sulfamethoxazole, and amphotericin b.

Other risk factors suggested to be involved in EPS onset in case of peritoneal dialysis are the composition of dialysis fluid and generation of GDPs, young age, ultra filtration failure and the exposure to PD catheter cleaning reagent, chlorhexidine [19].

Peritoneal dialysis-independent sclerosing peritonitis

While PD related peritoneal sclerosis serves as a convenient model for peritoneal sclerosis not all cases of Peritoneal Sclerosis are explained by PD-related factors. EPS can also develop in patients with conditions other than peritoneal dialysis such as autoimmune diseases, sarcoidosis, peritoneal and intra-abdominal malignancies, chronic peritoneal ascites, intra-peritoneal chemotherapy, intraperitoneal exposure to particulate matter or disinfectant, abdominal surgery, endometriosis, intra-peritoneal infections (tuberculosis), and beta-blocker administration [16].

Betablockers have been incriminated in the development of peritoneal fibrosis, which was mostly described with practolol, but also metoprolol, propranolol and atenolol. The pathogenesis although not clear, probably relates to the inhibition of surfactant release by betablockers [17]. Studies by Stegmayr and Krediet show that beta-blockers induce a decrease in ultrafiltration, irrespective of peritoneal fibrosis. Sclerosing peritonitis has also been associated with malignancies such as gastric cancer, ovarian thecoma, and ovarian teratoma, carcinoma of the pancreas, multiple polyposis, histiocytic lymphoma, and renal carcinoma.

Many case of Peritoneal Sclerosis have no clear association with any causal factor. In such idiopathic cases extraperitoneal fibrosis (eg: retroperitoneal and mediastinal fibrosis; serosal sclerosis) is a frequent association and many cases appear genetically predisposed.

CLINICAL MANIFESTATIONS

Peritoneal sclerosis in its early stages decreases the capacity of peritoneal membrane to transfer solute and remove fluid. An early and disproportionate reduction in osmotic conductance during the course of PD is an independent predictor of EPS. This functional change is linked to specific alterations of the collagen matrix in the peritoneal membrane of patients with EPS, thereby validating the serial three-pore membrane/fiber matrix and distributed models of peritoneal transport [18].

Clinical signs of patients developing Peritoneal Sclerosis while on peritoneal dialysis therapy are ultra filtration and clearance failure. This decrease in peritoneal dialysis efficiency results in failure of the technique in the meantime.

Patients with more severe anatomical abnormalities usually present insidiously with vague abdominal symptoms like early satiety, anorexia, nausea, vomiting, and altered bowel habit (constipation or diarrhea in the early stages of EPS)). These symptoms may be accompanied by signs of inflammation (fever and raised CRP) and/or blood stained ascites in the early stages. Late stages of EPS are associated with abdominal pain, fullness, overt bowel obstruction and presence of an abdominal mass.

Sometimes onset may be acute, manifesting directly as bowel obstruction. This is caused by the development of a fibrous cocoon that gradually covers the intestines and leads to malnutrition, weight loss, bowel obstruction, ischemia and strangulation, infection and death. Even after the termination of PD treatment, patients with EPS often develop ascites [21].

DIAGNOSIS OF PERITONEAL SCLEROSIS

The clinical picture of EPS being variable poses a diagnostic dilemma for which various investigations are necessary to further evaluate a suspected case [22]. Ultrasonography, water-soluble contrast studies and computed tomography (CT) scanning are the most widely used radiological tests to aid the diagnosis of EPS. CT scanning, however, is the investigation of choice in patients with established EPS and helps monitor disease progression. Peritoneal enhancement, peritoneal thickening, calcification, bowel tethering, bowel wall thickening, signs of bowel obstruction, and loculated collections are the most common CT findings of EPS [23] but, given the rare, complex nature of the disease and with most of the CT scan appearances being non-specific, interpretation and diagnosis can be difficult. Surgery (laparoscopy/laparotomy and peritoneal biopsy) therefore may be needed to confirm the diagnosis [22]. Although histological examination is an invasive method; a reliable diagnosis can be obtained by measuring the thickness of the sclerosis. Histologically, it is often difficult to differentiate simple SPS from EPS as the findings in EPS are indistinguishable from that of simple SPS [24]. In one study following findings were significantly more common in EPS than in patients on PD without EPS: fibroblast like cells (FLC), mesothelial denudation, decreased cellularity, and fibrin deposits [25].

TREATMENT

After the diagnosis of EPS is made, PD should be discontinued and the patient transferred to HD, in most cases [26] these measures are accompanied by improvement in symptoms and anatomical lesions, probably due to removal of this non-physiological stimulus. EPS can lead to severe malnutrition which is a crucial factor in the morbidity and mortality associated with EPS. Dietary referral is of the utmost importance, and parenteral nutrition is recommended for severe cases of EPS. Surgery is usually reserved for the late stages of EPS, in patients that present with absolute bowel obstruction or as surgical emergencies with an acute abdomen. Currently favored surgical techniques are peritonectomy and enterolysis which involves resection of the peritoneum and fibrous tissue together with division of adhesions to release the bowel. Post surgery recurrence rates with advanced disease tend to be as high as around 25%.

Steroid anti-inflammatory and immunosuppressant have been successfully used in early inflammatory stage of disease. Steroids possibly act by suppressing inflammation, preventing fibrin deposition and collagen synthesis and maturation [27] steroids alone, or with cyclophosphamide, azathioprine, or colchicines have been used successfully. A thirty year experience from an Italian center showed that only steroid therapy [hazard ratio (HR) 0.047; 95 % confidence interval (CI) was significantly associated with longer patient survival after EPS diagnosis [28].

Apart from steroids, evidence regarding the efficacy of any other immunosuppressive therapy in EPS remains weak due to lack of robust randomized clinical trials [29]. Other therapies described in the literature include tamoxifen, mTOR inhibitors and novel protein kinase activators. Tamoxifen has successfully been used in treating EPS. The possible antifibrotic effect of tamoxifen is through inhibiting connective tissue growth factor (CTGF) to block collagen synthesis [30]. Although the therapeutic effect of mTOR inhibitors against EPS remains unproven, but for post kidney transplant EPS who do not have any contraindication for mTOR inhibitor administration, converting from CNIs to mTOR inhibitors in addition to other EPS treatments may result in improving EPS in approximately one-third of patients and decreasing patients' mortality [31]. A novel AMP-activated protein kinase (AMPK) activator Namely HL156A has been shown to have beneficial effect on the development and progression of Peritoneal fibrosis by reducing peritoneal membrane thickness and expression of ECM molecules [32].

More efforts are needed to better elucidate the molecular mechanisms of inflammation and fibrosis in peritoneum. Inhibition of main extracellular mediators as well as of specific players in the cascade of events triggered by cytokines (TGF Beta) could become novel targets of drug therapy. Moreover, the possible control of the levels of particular non-coding RNAs (ncRNA), could conceivably guarantee the specific regulation of gene expression for more targeted therapies [33].

While the incidence of EPS in PD patients is around 2.8% , the mortality of patients with EPS varies between 50 ± 20 % with mortality increasing with the length of time on PD [34].

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