Encapsulating peritoneal sclerosis (EPS), previously also referred to as sclerosing peritonitis, is a rare abdominal disease of unknown and multifactorial etiology. Excessive cross-linking of constituents of the basal membrane, i.e. laminin, proteoglycans and collagen IV in the peritoneum results in change of its structure and function. The productive process of fibrosis and hypertrophy of the visceral peritoneum leads to formation of an encapsulating membrane that compresses intestinal loops covered by adhesions. This process can be limited to the small intestine or involve all abdominal organs. Its clinical signs and symptoms include recurrent episodes of bowel obstruction, nausea and vomiting with progressive body weight loss. These signs and symptoms have low specificity, which hampers early diagnosis. In the vast majority of cases, the diagnosis is established intraoperatively during laparotomy performed when bowel obstruction occurs. EPS results in marked cachexia due to bowel obstruction and chronic parenteral nutrition.

Preoperative nutritional treatment and use of intestinal stents results in marked reduction of postoperative complications. Until recently the mortality was very high and reached 50% of patients and resulted from marked preoperative cachexia of the patients. Currently mortality is markedly lower (4-10%) (1, 2, 3), however postoperative recurrences continue to be common, 25% within 2 years after the surgical treatment (4, 5, 6).

Encapsulating peritoneal sclerosis is most commonly observed in patients undergoing peritoneal dialysis due to end-stage renal failure. Other causes of secondary EPS include a history of surgical procedures, subclinical primary peritonitis, recurrent peritonitis, chronic beta-blocker therapy (mainly practolol), and peritoneal-venous fistules. Other, less common causes include: sarcoidosis, tuberculosis, familial Mediterranean fever, intraperitoneal chemotherapy, endometriosis, protein S deficiency, ruptured dermoidal cyst, ovarian thecoma, and cirrhosis and a history of liver transplantation (7, 8). Differential diagnosis should include mainly: internal hernia, extensive intussusceptions, sporadic intestinal adhesions and intestinal pseudoobstruction (7).

Clinical signs and symptoms of EPS include chronic abdominal pain, nausea, vomiting, anorexia, and loss of body weight, slight elevation of body temperature, recurrent subacute signs and symptoms of complete or partial bowel obstruction, often with a solid mass palpable through the abdominal wall. However, some patients remain asymptomatic until bowel obstruction occurs (7, 9). Plain abdominal X-ray may demonstrate dilated intestinal loops with fluid levels. Investigation of intestinal transit time using a contrast agent may demonstrate intestinal loops with vari-
able length, harmonica-like or tightly encapsulated with a cocoon-like thickened peritoneum. This image is characteristic for EPS and is usually referred to as a cauliflower sign. Computed tomography typically demonstrates signs of calcification and thickening of hypertrophic peritoneum, fluid collections, numerous adhesions, ascites with small intestinal loops concentrated in a single region of abdominal cavity and separated from the abdominal wall by fluid (2, 7, 10). Upponi et al. emphasize analogy of this image to a collapsed lung surrounded by an exudate. Fluid collections can be drained percutaneously under tomographic guidance, while demonstration of gas in the abdominal cavity, in particular in the area of fluid collections, should raise a suspicion of sepsis of perforation (11).

Vlijm et al. suggested presence of at least three of six signs in computed tomography as a diagnostic criterion: peritoneal thickening, peritoneal contrast enhancement, presence of calcifications, concentration of intestinal loops, intestinal dilation, presence of fluid collections (or two of five if the imaging was done without contrast administration) with 100% sensitivity and 94% specificity (12). Histopathology reveals increased angiogenesis, fibroblast-like cells, paucity of mesothelial cells, reduced cellularity, numerous fibrin deposits and increased tissue calcification (7, 13). In some cases EPS coexists with embryological abnormalities such as omental hypoplasia or malformation of mesenteric blood vessels (7). Cells positive for podoplanin and myocytes double positive for actin are typical for EPS. Expression of these markers seems more specific for EPS and immunohistochemistry of peritoneal specimens for these markers may facilitate diagnosis (13, 14, 15). Marked correlation was found between degree of angiogenesis in histopathology of peritoneal specimens in patients with EPS and postoperative re-encapsulation of the intestine. Currently proliferation of peritoneal blood vessels is considered the only independent predictor of EPS recurrence (6).

There are many theories attempting to explain factors that induce peritoneal fibrosis in EPS. Kawanishi et al. suggested a commonly accepted “double hit” theory that explains complexity of pathogenesis of this disease. The first hit is a factor that changes the peritoneal structure, among others increasing its permeability. Long standing peritoneal dialysis is the most common of such factors. The second it is proinflammatory stimulation, in particular by exogenous factors such as bacterial endotoxins, chemical agents, uremic toxins or proinflammatory cytokines produced in excess by macrophages activated by RAGE (16). Nakayama’s theory explains this process at the cellular level. It assumes that vascular changes underlie EPS-related processes. These changes result in increased peritoneal permeability for small molecules and accumulation of plasma constituents, mainly of fibrinogen, at the peritoneal surface. Damaged endothelial cells produce cytokines, mainly interleukin 6 and growth factors, including vascular endothelial growth factor (VEGF), connective tissue growth factor (CTGF), transforming growth factor-β1 (TGF-β1), and nitric oxide synthase (NOS), resulting in exacerbation of angiogenesis and further increase of peritoneal permeability. This leads to further extravasation of plasma constituents to the peritoneal cavity and amplification of this process.

Cytokines and growth factors recruit macrophages and fibroblasts and stimulate them to deposit collagen, proteoglycans, laminin and fibrin on the peritoneal surface. At certain point the developed fibrin-collagen network stops further leak of the plasma. Consequently, the inflammatory phase of EPS stops and fibrotic stage begins (17). It must be emphasized that peritoneal fibrosis as a cause of its failure, does not proceed with equal speed and intensity in all patients. EPS is found in 0.7-3.7% of patients undergoing peritoneal dialysis and intensity of these changes closely correlates with the duration of dialysis (90% of EPS patients were treated with peritoneal dialysis for more than 3 years) (4). During the peritoneal dialysis the mesothelial cells are expose to nonphysiological hypertonic environment related to high glucose concentration and low pH of conventional dialysis fluids. Long-term exposure of the peritoneum to the dialysis fluid results in epithelial-mesenchymal transition (EMT) of the mesothelial cells. As a consequence of this phenomenon, the mesothelial cells acquire phenotype of fibroblast-like cells with expression of smooth muscle α-actin and ability to migrate. Concurrently with changes of morphology, the mesothelial cells lose typical markers such as ICAM-1 and cytokeratin. TGF-β1, a growth factor that stimulates fibrosis, plays a major role in EMT (18, 19).
are in vitro reports of rapamycin effect on EMT through partial inhibition of TGF-81 expression in cultures of human mesothelial cells (20). C.M. Hoff demonstrated, in an animal model, EPS-like changes in the peritoneum exposed to chlorhexidine that was used to sterilize certain parts of the dialysis devices (21). Saglam et al. achieved reduction of the fibrotic processes in the mouse model of EPS induced by chlorhexidine through suppression of TGF-81 using pioglitazone (22).

Surgical treatment is mainly used to restore normal gastrointestinal transit, avoiding intestinal resection. The first stage should involve a careful, atraumatic dissection of the membrane from the intestinal surface. If there is a marked calcification that prevents simple dissection, the membrane should be incised longitudinally and subsequently adhesions should be dissected. Surgical treatment in such conditions requires patients and caution, in particular in view of the fact that the risk of perforation is approximately 10-20%. Intestinal perforation is the most common cause of serious postoperative complications, in particular if the perforation is not diagnosed intraoperatively (1, 6). Assuming that the disease recurs after dissection of adhesions, a strategy is adopted to force proper intestinal position during the surgical procedure.

Multiple surgical methods were described that were aimed at prevention of recurrence of adhesions, mainly intestinal plication procedures. Noble procedure aimed at positioning of intestinal loops in a form of an ordered ladder and intestine-to-intestine suuring using mesenteric or antimesenteric margins, is most commonly used surgical procedure (5). Childs-Phillips procedure, a modification of Noble’s method, is used less commonly and involves harmonic-like arrangement of the small intestine by suturing adequately arranged intestinal mesentery laminae with nonabsorbable sutures (2). To avoid intestinal ischemia caused by surgical sutures, Brands et al. recommend intestinal folding procedure utilizing tissue glue (23). Other, currently less commonly utilized method of intestinal folding is internal folding through intestinal intubation using Miller-Abbott probe (2). Currently use of self-expanding intestinal stents that prevent early postoperative stenosis of the small intestine, in particular in patients with advanced lesions and high risk of recurrence, is considered the most effective method of prevention of recurrence of bowel obstruction caused by EPS. Stents are implanted to the small intestine retrogradely through the vermiform appendix and retained until the restoration of normal gastrointestinal function – usually 7-14 days (8, 24, 25). Early postoperative nutritional treatment and small intestinal stenting closely correlates with improved nutritional status of the patient and related lower incidence of postoperative complications (8).

Recently there are suggestions to limit indications to the surgical treatment to irreversible gastrointestinal obstruction and cases nonresponding to medical treatment (5, 7). Corticosteroids and tamoxifen have the best documented efficacy in the medical treatment. Corticosteroids inhibit inflammatory processes in the peritoneum and inhibit synthesis and maturation of collagen. The suggested prednisolone posology is initially 0.5-1.0 mg/kg/day, and subsequently increase of the dose, over six months, to 10 mg daily. The treatment should be maintained for at least one year (4). In Japan corticosteroids are commonly used in an early phase of EPS as a first line therapy (3, 4). Tamoxifen is a non-steroidal estrogen receptor modulator that stimulates metalloprotei
dase 9 to collagen destruction through induction of the TGF-81 release (3, 5). In view of its antifibrotic effects, this drug has been successfully used for many years in the treatment of fibrosing mediastinitis, retroperitoneal fibrosis or Dupuytren’s contracture. There are many reports documenting efficacy of tamoxifen in an early phase of EPS and as a supportive postoperative treatment. Recommended tamoxifen dose is 20 to 40 mg daily for at least one year (4). Angiotensin converting enzyme inhibitors, despite many promising reports documenting their efficacy in animal models, did not produce expected results in humans (26).

REFERENCES


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