Peritonitis is a serious and common problem in the peritoneal dialysis (PD) population. Abdominal pain, fever, and cloudy PD fluid usually heralds the onset of infective peritonitis. However, in up to 20% of cases, no organism is identified. In these situations, diagnosis can be made only by excluding a microbiological cause and performing a cytological examination of the PD fluid to determine the cellular or noncellular constituents. This review examines the differential diagnosis of sterile peritonitis and uses cytological examination to facilitate the appropriate diagnosis.


KEY WORDS: Sterile peritonitis; eosinophilic peritonitis.

Peritonitis in the peritoneal dialysis (PD) patient is defined by the International Society for Peritoneal Dialysis (ISPD) as the presence of two of the following three criteria: (1) signs and symptoms such as fever, abdominal pain/tenderness; (2) >100 white blood cells/mL dialysate fluid, of which >50% are neutrophils; and (3) identification of the organism in the PD fluid (1). While it is not required for the diagnosis, the key to management lies in the identification of the organism. In up to 22% of cases, PD fluid cultures prove to be negative and thus the patient with culture-negative cloudy dialysate becomes a diagnostic and management dilemma (2–5). These patients are referred to as having aseptic, culture-negative, or sterile peritonitis.

BACTERIAL INFECTION AS A CAUSE OF STERILE PERITONITIS

Sterile peritonitis often reflects bacterial infection in which the culture may be negative when the patient is on antibiotic therapy unknown to the PD center. Other possible causes for negative cultures include small volume samples and inappropriate microbiological culture techniques (5–7). The causative organism requires specialized culture techniques, including inoculation of blood-culture growth media and concentration of the effluent (Figure 1). This is probably the most important cause of sterile peritonitis of bacterial origin. In any PD program, it is essential that there is good liaison with the microbiology department, who need to understand the peculiarities of PD-associated peritonitis. Szeto et al. (5) found that 45% of cases of sterile peritonitis were associated with technical difficulties in collecting a sample, and 26% had been on an antibiotic within the previous 30 days. Patients who remain repeatedly culture negative despite the presence of cloudy dialysate should be evaluated for other causes.

It is helpful to classify sterile peritonitis by the PD effluent cell count and type into cellular and noncellular causes (Table 1) (8). This topic has been reviewed recently by Rocklin and Teitelbaum (8); the present article represents an update on sterile peritonitis over the past 5 years.
**CELLULAR CAUSES OF STERILE PERITONITIS**

Increased numbers of neutrophils, eosinophils, monocytes, erythrocytes, or malignant cells can all produce a cellular effluent.

**INCREASED NUMBERS OF NEUTROPHILS**

*Atypical Infections:* Tuberculous peritonitis is an uncommon complication in PD patients, occurring in up to 6% of cases, depending on the population studied (3). *Mycobacterium tuberculosis* is the most common pathogen to cause this. However, other atypical mycobacteria, such as *M. kansasii* and *M. fortuitum*, have also been implicated (9). In general, most cases are due to reactivation of latent TB, while some may be due to primary infection. Most patients present with the typical triad of fever, abdominal pain, and a cloudy cellular dialysate. The PD fluid usually contains increased numbers of neutrophils early on, followed by a lymphocytosis. A monocytosis may also be observed (10). The clinical presentation is indistinguishable from more common causes, but is suggested by a history of TB disease, exposure, or risk factors such as an abnormal chest x ray and ethnic background. Smears of PD fluid are insensitive for acid-fast bacilli, thus the diagnosis relies principally on culturing the dialysate, which can take up to 6 weeks. We have reported eight cases in Manchester over the past 13 years. All presented with typical symptoms and signs of peritonitis within 12 months of starting PD (11). Most presented initially as sterile peritonitis. Only two cases were smear positive. There is need for a good index of suspicion (*e.g.*, in high risk and ethnic populations), and more-sensitive tests, such as peritoneal biopsy or fluid polymerase chain reaction, may be necessary to make the diagnosis (12).

Fungal peritonitis has an incidence of up to 4% in PD populations (3). A number of fungi have been identified, but *Candida* species remain the most common cause (13,14). Risk factors include prior antibiotic therapy, immunosuppression, and malnutrition associated with a low albumin. The patient may have severe abdominal pain and may rapidly progress to death if not promptly recognized and treated appropriately. Fluid microscopy may reveal a neutrophilia, while Gram stain is usually negative, and cultures may also be negative.

**Intrapерitoneal Causes:** Any intraperitoneal inflammation may be associated with a cloudy dialysate and abdominal pain. Cholecystitis, appendicitis, abdominal wall hernias with small bowel incarceration, and mesenteric insufficiency resulting in ischemic bowel are all recognized causes of a sterile peritonitis (15,16). Clinically, the patient may have increased abdominal pain, tenderness, and fever. The PD fluid contains increased numbers of neutrophils, often followed by a lymphocytosis. The diagnosis is made by identifying the cause of the peritonitis, usually by culturing the fluid, aspirate, or biopsy. The differential diagnosis of sterile peritonitis is shown in Table 1.

**TABLE 1**

Differential Diagnosis of Sterile Peritonitis

<table>
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<tr>
<th>Cellular causes</th>
<th>Increased eosinophils</th>
<th>Allergic reaction</th>
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<td>Atypical infection</td>
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<td>Strenuous exercise</td>
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<td>Increased malignant cells</td>
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PD = peritoneal dialysis.
these cases are indistinguishable from infectious peritonitis. The mechanism presumably is transmural inflammation of the viscus, resulting in the overlying visceral peritoneum becoming inflamed. Rupture of a sterile intraperitoneal abscess as a result of previous intra-abdominal infection was reported by Alpert et al. as a further cause of sterile peritonitis (17).

**Retroperitoneal Causes**: Retroperitoneal inflammation resulting from acute pancreatitis, splenic infarction, or abscess formation may result in a sterile cloudy dialysate (18,19). Streather et al. reported a case of renal cell carcinoma that resulted in inflammation of the overlying parietal peritoneum, causing a similar presentation (20).

**Drugs**: Both amphotericin B and vancomycin can cause a culture-negative peritonitis (21,22). Freiman et al. reported that the US Food and Drug Administration had received 51 reports in the United States of chemical peritonitis associated with the intraperitoneal administration of sterile vancomycin hydrochloride (23). The clinical presentation of the cases ranged from mild (cloudy dialysate alone) to more severe (severe abdominal pain and fever). In the nine cases that were rechallenged, the sterile peritonitis recurred. It is not known what the underlying mechanism was for this adverse reaction, but two contaminants were isolated in the PD solution produced by Abbott Laboratories.

**Contamination of PD Fluid**: Acetaldehyde is a glucose degradation product derived from the standard heat-sterilization process of lactate-buffered PD solutions. Tuncer et al. reported 21 cases of sterile peritonitis where patients presented with abdominal pain and cloudy bags, without fever (24). Fluid cultures were sterile and the fluid white cell count was markedly elevated, at 1795/mm³. All cases were clustered within 1 month and were associated with a batch of PD fluid with high acetaldehyde levels of 17–20 parts per million (normal: approximately 6 ppm).

Endotoxin-mediated peritonitis with culture-negative peritoneal fluid has been reported (25,26). Contaminated PD solutions were the source in all cases, with endotoxin detected in varying levels. In one report, rabbits were injected with the PD fluid and developed cloudy peritoneal fluid (25).

**INCREASED NUMBERS OF EOSINOPHILS**

First described in 1967 by Lee and Schoen, increased eosinophils in PD effluent is a common phenomenon and may occasionally be associated with a peripheral blood eosinophilia (27). Patients are generally asymptomatic or sometimes have mild symptoms. It occurs most often shortly after peritoneal catheter insertion, where it may be related to an “allergic” reaction. The mechanism is thought to be an irritant effect from plasticizers leached into the peritoneum from solution containers or tubing, resulting in an eosinophilic immune response (28).

Daugirdas et al. also noticed that intraperitoneal air introduced at the time of PD catheter insertion was associated with an eosinophilia (29). To demonstrate this, sterile air was injected into the peritoneal space of 5 volunteers, all of whom developed an eosinophilia to some extent. In general, eosinophilic peritonitis is self-limiting and resolves spontaneously after several weeks. Persistent eosinophilia may require steroid therapy. Eosinophilic peritonitis has also been described with intraperitoneal administration of drugs such as vancomycin, gentamicin, cephalosporins, and streptokinase (23,30,31). There have been several case reports of fungal infection resulting in a raised eosinophil count in the dialysate, such as infection with *Aspergillus niger* (32).

Rarely, peritoneal fluid eosinophilia may occur during treatment of a bacterial peritonitis.

Lastly, retrograde menstruation causing small volumes of blood to leak into the peritoneum may result in an eosinophilic response.

**INCREASED NUMBER OF MONOCYTES**

Icodextrin (Extraneal; Baxter, Castlebar, Ireland) is a glucose polymer used as osmotic agent in patients with decreased ultrafiltration and is a recognized cause of a monocytosis (33). We have reported a series of cases of icodextrin-associated sterile peritonitis where patients who were otherwise asymptomatic developed cloudy bags (34,35). The white cell count varied from 300 to 3500/µL, with a varied number of neutrophils (usually <50%), monocytes, eosinophils, and lymphocytes. Discontinuation of the icodextrin led to resolution of the cloudy bags and, upon rechallenging the patients with icodextrin, it reappeared. In our center, a total of 26 cases were seen and over 50% resolved on discontinuing the icodextrin alone. Following extensive investigation by Baxter, the cause of this sterile peritonitis was established as being secondary to a peptidoglycan. It was determined that batch-related biochemical contaminant(s) in the solution interacted with the hemolymph of the silkworm larva. Silkworm larva plasma (SLP) contains a pro-phenol oxidase-dependent cascade, a self-defense mechanism of insects. The pro-phenol oxidase cascade is activated by cell wall components of bacteria and fungi (36). Results from analyses suggested that the SLP-reactive contaminant in some batches of Extraneal is a peptidoglycan, a non-endotoxin weak py-
rogen capable of inducing an inflammatory reaction in the peritoneum (37). Since this contaminant was removed, no further cases have been reported and the incidence of this phenomenon has declined.

Peritoneal fluid monocytosis may suggest undiagnosed TB peritonitis or may occur in conjunction with increased PD fluid eosinophils.

INCREASED NUMBER OF ERYTHROCYTES

Any cause of a hemoperitoneum may result in a cloudy dialysate. The differential diagnosis is wide and beyond the scope of this article. Frequently encountered causes in females include retrograde menstruation, ovarian cyst rupture, and ovulation, which generally causes mid-cycle bleeding (38). Other causes include catheter-related trauma, hypertonic exchange, strenuous exercise, rupture of a polycystic liver cyst, malignancy, and, lastly, formation of peritoneal adhesions (39).

INCREASED NUMBER OF MALIGNANT CELLS

Malignancy is a rare cause of a cloudy dialysate. Vlahakos et al. reported a case of non-Hodgkin’s lymphoma mimicking peritonitis in a patient on continuous ambulatory PD, with large monomorphic cells in the PD fluid (40). Bargman et al. reported a further case of lymphoma diagnosed by cytological examination of cloudy peritoneal fluid (41). Peritoneal metastases may also mimic peritonitis, such as a case of endometrial carcinoma reported by Bagnis et al. (42).

NONCELLULAR CAUSES OF STERILE PERITONITIS

Increased fibrin and triglyceride levels are primarily responsible for causing a noncellular sterile peritonitis.

INCREASED FIBRIN LEVEL

This is a common finding in patients who are recovering from an episode of infectious peritonitis and in those who are just starting PD. It is recognizable by the presence of filaments in the PD bag, which, when left standing, coalesce to form fibrin clot. It is a nonspecific finding of no clinical significance.

INCREASED TRIGLYCERIDE LEVELS

Like a chylous pleural effusion, PD fluid with high triglyceride levels appears white, although this may vary depending on the fat content of ingested meals (43). Obstruction of peritoneal lymphatics causes increased intra-lymphatic pressure, resulting in leakage of lymph into the peritoneal cavity. Abdominal lymphomas, pancreatitis, and trauma from PD catheters, either during insertion or when in situ, have all been reported to cause increased triglyceride levels in PD fluid, mimicking peritonitis (44,45).

Dihydropyridine calcium channel blockers are associated with reversible, increased, PD-fluid triglyceride levels, the mechanism of which remains unknown (46,47).

CONCLUSION

Sterile peritonitis is a frequently occurring condition with a variety of causes. Most commonly, it results from microbiology methodology problems and resolves with standard infectious peritonitis treatment protocols. Diagnostic yields may be enhanced considerably by reculturing dialysate effluents using appropriate collection methods and optimal laboratory techniques. In patients with persistent culture-negative peritonitis, consideration should be given to the possibilities of unusual or fastidious micro-organisms (especially fungi and mycobacteria) and noninfective causes (especially drug reactions, malignancy, visceral inflammation, and retroperitoneal inflammation).

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