Herpes Simplex Peritonitis: Case Report

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It has been previously reported that the most common cause of peritonitis in patients undergoing chronic ambulatory peritoneal dialysis (CAPD) is infection by a single gram-positive bacterial species. Polymicrobial bacterial infections are identified that may be secondary to bowel perforation. In 20% of cases bacterial cultures are negative. Although cultures may be negative when infection is due to a fastidious organism, when antibiotic therapy has been administered, and in cases of chemical peritonitis, a viral etiology should also be considered. We report the first documented case of herpes simplex peritonitis, which involved a 60-year-old female undergoing CAPD. Viral peritonitis may be an important form of peritonitis that has been previously unrecognized and should be considered in the differential diagnosis.

Chronic ambulatory peritoneal dialysis (CAPD) has been used as a form of therapy for chronic renal failure since the 1940s [1]. This technique has been increasingly utilized in the past 15 years by clinicians interested in curbing medical costs. One of the major complications of CAPD is infection. It has been reported that polymicrobial infections involving gram-negative aerobic and anaerobic bacilli are common in cases of surgical peritonitis, but infections due to a single gram-positive bacterial species are the rule in CAPD-related peritonitis [1]. When polymicrobial infections develop in patients undergoing CAPD (CAPD patients), bowel perforation should be suspected [1]. For ~20% of patients with peritonitis, cultures are negative [2]; possible explanations include infection with fastidious organisms, infection localized to the indwelling peritoneal catheter, recent antibiotic treatment, and inflammation caused by phlogistic substances [1, 3].

The role of viruses as a cause of culture-negative peritonitis in CAPD patients is not known. It may be that viral peritonitis is a more common occurrence than is clinically suspected and it remains unrecognized because the appropriate testing for viruses and viral antibodies is not performed. In this report, a CAPD patient with recurrent bacterial culture-negative peritonitis is described. The omental biopsy specimen obtained from this patient showed histologic, immunohistochemical, and electron microscopic evidence of herpes simplex peritonitis.

Materials and Methods

Previously reported cases of herpes simplex and cytomegalovirus peritonitis were sought by means of a computerized search (via MEDLINE) of the medical literature from 1966 to the present. All pertinent clinical data were abstracted from these reports and summarized.

Tissue for histology was fixed in 10% formalin, embedded in paraffin, and stained with hematoxylin and eosin. Immunohistochemical evaluation was performed with use of commercial antibodies against cytomegalovirus and herpes simplex virus 1 and 2 (Dako, Carpinteria, CA). Immunohistochemical reactions were evaluated by means of an avidin-biotin complex–based methodology, with aminoethylcarbazole as the chromogen, and the method of Hsu et al. [4].

Formalin-fixed tissue was selected from the paraffin block for electron microscopy. The tissue was deparaffinized in xylene and graded alcohols, rehydrated in PBS, and fixed in glutaraldehyde. The specimen was embedded in epon. “Thick” (1 μ) sections were screened by light microscopy. From these sections, “thin” sections were prepared. The specimens were stained with uranyl acetate and lead citrate and examined with an electron microscope.

Case Report

The patient, a 60-year-old woman, was admitted to the hospital because of crampy abdominal pain associated with nonbloody diarrhea, nausea, and chills, all of 48 hours’ duration. The abdominal pain was localized in the lower quadrants without radiation. The patient had never experienced pain in this area before this admission. The patient had no complaints of fever, chest pain, shortness of breath, or hematochezia. The previous week, the patient had experienced cough, sneezing, and diarrhea.

Physical examination findings were significant in that the elderly woman was not in acute distress and had no fever or chills. The abdomen was diffusely tender, soft, and with normal bowel sounds. An abdominal peritoneal catheter for continuous ambulatory dialysis was in place and appeared clean, without erythema or drainage at the insertion site.
An abdominal radiograph showed a nonspecific gas pattern with no free air or air-fluid levels. The peripheral WBC count was 9,400/mm³, with a differential count of 41% neutrophils, 29% bands, 18% lymphocytes, and 12% monocytes. Other laboratory values included the following: hemoglobin, 9.4 g/dL; hematocrit, 28.5%; serum blood urea nitrogen, 55 mg/dL; creatinine, 13.7 mg/dL; amylase, 144 U/L; and lipase, 376 U/L. Serum electrolyte values were within normal limits.

The medical history was significant for end-stage renal disease secondary to hypertension, which had been treated with hemodialysis for 6 years and then with continuous ambulatory dialysis for the past 9 months. The patient had undergone a hysterectomy and bilateral salpingo-oophorectomy for malignant mixed mesodermal tumor of the uterus 6 months previously. The postoperative period was complicated by rectovaginal hematoma, which was secondary to dehiscence of the sutures at the vaginal apex, which was drained transvaginally. The patient also had a postoperative myocardial infarction that was treated by percutaneous transluminal coronary angioplasty.

The patient was an insulin-independent diabetic and had been hypothyroid for the past 30 years. Social history was negative for alcohol abuse or smoking. Medications included nifedipine, clonidine hydrochloride, levothyroxine sodium, and dialysis vitamin supplements. There was no history of cold sores. The clinical impression was probable viral gastroenteritis, but the prolonged course and severity of symptoms were of concern. The patient was admitted to the hospital for evaluation. CT scan of the abdomen was negative for diverticulitis or abscess. Sigmoidoscopy showed external hemorrhoids and normal colonic mucosa to 60 cm. A colon biopsy was normal and showed no viral inclusions. Abdominal flat-plate suggested possible small-bowel obstruction. Urine culture, stool culture for enteric pathogens, three sets of blood cultures, and three sets of peritoneal fluid cultures were all negative.

The peritoneal fluid was cloudy. A peritoneal fluid aspirate contained 25 WBCs/mm³, with 8% neutrophils, 48% lymphocytes, 36% monocytes, and 8% eosinophils. Dialysate fluid contained 100 WBCs/mm³, with 2% neutrophils, 64% lymphocytes, 32% monocytes, and 2% eosinophils. The peripheral WBC count increased to 23,800/mm³, with 80% neutrophils, 16% bands, and 4% lymphocytes.

During her hospitalization, the patient developed more severe abdominal pain and became febrile (temperatures to 39°C). A second abdominal CT scan showed severity-bowel obstruction, and stool was positive for *Clostridium difficile* toxin on the seventh hospital day. Therapy with metronidazole was started at a dosage of 250 mg po every 8 hours, and vancomycin (30 mg/L) and gentamicin (20 mg/L) were used in peritoneal exchange fluids. Exploratory laparotomy on hospital day 16 showed friable and grossly necrotic omental tissue. A 9 × 5.5 × 3-cm portion of omentum was excised and submitted for histologic examination.

The patient was treated with acyclovir at a dosage of 150 mg intravenously every day, starting on hospital day 26, but this was increased to 400 mg on day 27. The patient became afebrile but continued to do poorly, with no response to verbal stimuli and no eye contact. Following the cessation of peritoneal dialysis, she died on hospital day 30. A test for HIV was not done. Serum titers of antibodies to herpes simplex virus included an IgG titer of 1:640 and an IgM titer of <1:10. An autopsy was not performed.

**Gross findings.** An elongated 9 × 5.5 × 3–cm portion of firm, hemorrhagic tan and red tissue was surgically removed from the patient. Representative portions of the tissue were submitted for histologic analysis.

**Microscopic findings.** Microscopic examination of sections showed severe acute inflammation involving the fibroadipose tissue, with the most intense inflammation involving the septal portions of the specimen. The inflammatory infiltrate was accompanied by karyorrhexis, necrosis, and thrombosis of the adjacent blood vessels. Readily identifiable nuclei with a ground-glass appearance were present in the areas of acute inflammation and necrosis (figure 1). The entire nucleoplasm in these virus-affected cells was homogeneous and blended without a halo into the nuclear membrane. Occasional multinucleated cells with nuclear molding and intranuclear inclusion bodies were also present (figure 2). Immunoperoxidase stains of the tissue section with use of an antibody for herpes simplex virus types 1 and 2 showed strong positive staining of numerous cells throughout the specimen (figure 3). Immunoperoxidase staining for cytomegalovirus was negative.

**Electron microscopy.** Electron microscopy showed intranuclear viral particles with diameters of 100–120 nm (figure 4) in many of the cells, consistent with the herpes group of viruses.

**Discussion**

Peritonitis remains the most frequent complication of chronic peritoneal dialysis, occurring at a rate of about one episode per
patient per year [1]. In up to 30% of patients, peritonitis is recurrent, often leading to the discontinuation of CAPD [5]. Gram-positive organisms commonly found on the skin can be isolated in 60%–80% of cases, and gram-negative organisms thought to originate from the enteric flora can be isolated in 15%–30%; negative cultures account for 5%–10% of cases. These negative cultures are variously ascribed to poor culture technique, prior antimicrobial therapy, or fastidious organisms [2]. Viral cultures are not routinely performed, and special cultures for fungal, mycobacterial, and anaerobic pathogens are often performed only after aerobic bacterial cultures are found to be negative.

The incidence of viral peritonitis reported in the literature is very low. In 1986, a case of viral peritonitis in the Netherlands was reported by Struijk et al. [6]. Echovirus type 2 was cultured repeatedly from the dialysate and feces, and there was a rise and fall in serum titers of antibodies to enterovirus. Abraham et al. reported a case of a CAPD peritonitis involving a 50-year-old woman with a mononucleosis-like illness and persistently cloudy effluent with many reactive and atypical lymphocytes [7]. Repeated dialysis-effluent cultures for bacteria, mycobacteria, and fungi were negative. Serum assays for hepatitis B surface antigen, heterophil antibody, and antibodies to cytomegalovirus and hepatitis A were negative. Serum was positive for both herpesvirus 2 and *Toxoplasma* IgG. It was concluded that this was a case consistent with viral peritonitis because of the continued benign course 6 months after the episode and persistently negative cultures.

Cytomegalovirus has been the most frequently isolated virus of the herpes group. In 1991, Lewis reported a case of recurrent peritonitis involving a patient undergoing CAPD that was characterized by cloudy effluent, elevated WBC counts (predominantly lymphocytic), and negative bacterial cultures [8]. Viral cultures of the peritoneal fluid were positive for cytomegalovirus. The patient had recurrent episodes of peritonitis and eventually died of pulmonary edema secondary to interstitial lung disease and congestive heart failure, ~1 year after the initial diagnosis of peritonitis. There have also been reports of cytomegalovirus peritonitis occurring with AIDS, both with and without evidence of bowel perforation [9, 10]. As a known pathogen of the gastrointestinal system, cytomegalovirus is likely to have mechanisms of infection similar to those of other enteric flora.

Herpes simplex virus infects cells of epithelial origin most readily, but fibroblasts also are susceptible. Clinically, this results in the common primary and secondary cutaneous manifestations of herpes simplex, with systemic and deep organ involvement occurring much less frequently. In our reported case, repeated cultures for bacterial pathogens were negative, prompting laparotomy. It was only after the pathological evi-
dence of viral infection was present that this possibility was considered in the differential diagnosis. The cessation of dialysis following surgery and the institution of comfort measures precluded any further viral cultures. However, light microscopy, immunohistochemical studies, and electron microscopy all support the diagnosis of herpes simplex peritonitis.

The patient in this case report was severely immunocompromised by diabetes, age of 60 years, a history of a recent malignant uterine neoplasm, and chronic renal failure (for almost 7 years) requiring dialysis. All of these factors contributed to a decrease in immunity, but at an unquantifiable level. She was not a normal host, and it is not surprising that she did not have a predictable IgM response to acute, fulminant herpes simplex peritonitis.

Although the number of cases of viral peritonitis reported in the literature has increased in recent years, viral peritonitis remains a rare entity. It is unclear whether this is a consequence of the low incidence of the disease or the fact that viral peritonitis is not considered in the differential diagnosis and is therefore underdiagnosed. An interesting finding is that of Pomeranz et al., who have demonstrated that there is an antiviral substance present in the peritoneal dialysis effluent that may be responsible for the difficulty in documenting peritonitis of viral origin [11]. It is possible that this noninterferon factor may play a role in the conversion of an active infection into an abortive infection in the peritoneal cavity.

To our knowledge this is the first case of herpes simplex virus–caused CAPD peritonitis. On the basis of our experience with this case, we would recommend that for patients with peritonitis characterized by cloudy, predominantly lymphocytic dialysis effluent and negative bacterial cultures, a search for possible viral pathogens be instituted.

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References