Primary Herpetic Peritonitis Causing Intestinal Perforation: Case Report and Review of the Literature

Theodoros Katsivas,1,2 Richard Sokolov,2 Marjorie Miller,3 Aviv Hever1 and Bing Hu1
1Department of Pathology and 2Division of Infectious Diseases, Cedars-Sinai Medical Center, 3Infectious Diseases Section, Greater Los Angeles Veterans Affairs Medical Center, and 4University of California Los Angeles Medical Center Clinical Laboratories, Los Angeles

Peritonitis of viral etiology is rarely reported in the literature; a prior report described a patient undergoing continuous ambulatory peritoneal dialysis who had the disease. We report a case of primary herpetic peritonitis (the agent of which was typed by polymerase chain reaction as herpes simplex virus biotype 1), which caused intestinal perforation, and we review the current literature and provide possible pathophysiologic mechanisms.

There are many etiologic classifications of peritonitis; in primary peritonitis, there is no gastrointestinal tract perforation or spillage of intestinal flora into the peritoneal cavity; spontaneous bacterial peritonitis, granulomatous peritonitis (including tuberculous peritonitis), and, sometimes, continuous ambulatory peritoneal dialysis (CAPD)–related peritonitis are in this category. Secondary peritonitis involves gastrointestinal content spillage caused by an acute perforation or an anastomotic leak or trauma. The category of tertiary peritonitis includes culture-negative peritonitis, fungal peritonitis, and low-virulence bacterial peritonitis. Finally, other separate categories include drug-related, periodic, hyperlipidemic, porphyric, and foreign-body–, lead–, and talc-induced peritonitis. Viral peritonitis is rarely reported in the literature. We report a case of primary herpetic peritonitis due to infection with herpes simplex virus (HSV) biotype 1, which caused intestinal perforation.

Materials and methods. Previously reported data from a computerized search of the MEDLINE and Ovid databases from 1966 to the present were abstracted and summarized.

Tissue for histological examination was fixed in 10% formalin, embedded in paraffin, stained with hematoxylin-eosin, and tested with peroxidase-linked monoclonal antibodies to HSV types 1 and 2. DNA was extracted from paraffin-embedded tissue using the QIAMP DNA MINI Kit tissue protocol (Qiagen). The DNA yield was 27.5 µg/mL by measuring absorbance at 260 nm; the purity was 1.75 (A260/A280). Real-time PCR was performed using the LightCycler (Roche Molecular Diagnostics) and HSV 1/2 Primer/Hybridization Probes, which amplify a region of the HSV DNA polymerase gene (GenBank accession numbers M12356 and M16321); the resulting amplicon is detected by fluorescence. For the assay, 5 µL of extracted nucleic acid was added to 15 µL of master mix (HSV 1/2 Primer/Hybridization Probes, 2 µL; FastStart DNA Master Mix, 2 µL; HSV 1/2 Internal Control, 2 µL; MgCl2 (3 mmol/L), 1.6 µL; and sterile water, 7.4 µL). A negative control (water) and a positive control (HSV 1/2 Template DNA) were included in each amplification run, which were performed as follows: 1 cycle of 95°C for 10 min and 45 cycles altogether of 95°C for 10 s (denaturation), of 55°C for 15 s (annealing), and of 72°C for 15 s (extension).

Melting curve analysis was performed after amplification. The temperature was increased to 95°C, decreased to 40°C for 60 s, and then increased to 80°C, and the fluorescence was measured continuously. HSV types 1 (HSV-1) and 2 (HSV-2)
can be distinguished by their melting peak temperatures \( T_m \). According to the manufacturer, HSV-1 has a \( T_m \) of 54.0°C ± 2.5°C, whereas the \( T_m \) of HSV-2 is 66.5°C ± 2.5°C.

**Case report.** The patient was a 46-year-old woman who had multiple myeloma with skeletal involvement for 4 years and who elected to undergo laparoscopic bilateral oophorectomy, oocyte harvest, and fallopian tube ligation before scheduled spinal radiation sessions. She had undergone an uncomplicated laparoscopy 6 days before her presentation. On the third day after the operation, she developed mild, bilateral, lower-quadrant abdominal pain, which progressively worsened over 3 days, at which time she visited the emergency department. At presentation, the patient’s abdominal pain was constant and of moderate intensity; she admitted she never had such pain before; she denied experiencing any fever, nausea, vomiting, diarrhea, or any other acute concerns.

Her past medical history was significant for an appendectomy, history of herpes labialis and genital herpes (with no recurrences within the prior year), chronic constipation, and IgG lambda multiple myeloma with skeletal and renal involvement. She was a lifetime nonsmoker, did not drink alcohol, and did not use illicit drugs. She was not sexually active at the time. Medications she used included erythropoietin, hydrocortisone suppositories, oral nystatin, and ranitidine. She denied having any known drug allergies.

Physical examination revealed that the patient appeared anxious and fatigued, had a temperature of 36.6°C (97.8°F), blood pressure of 173/91 mm Hg, pulse rate of 108 beats/min, and respiratory rate of 20 breaths/min. The rest of the examination was notable for a minimally distended abdomen, which was diffusely tender, with rebound sign and voluntary guarding in all 4 quadrants. Notable laboratory values were as follows: serum sodium level, 129 mmol/mL; potassium level, 5.7 mmol/mL; hemoglobin level, 11.7 g/dL; hematocrit, 34.5%; and WBC count, 13,600 cells/mm³, with 97% neutrophils and 2% band cells. The total protein level was 7 g/dL, the albumin level was 1.1 g/dL, the total γ-globulin level was 3.8 g/dL, and the IgG level was 3.12 g/dL. Abdominal studies showed free air underneath the diaphragm; the patient received 2 g of cefotetan intravenously and was admitted to the hospital with a diagnosis of acute abdomen and viscus perforation.

Intraoperative findings included fibrinous adhesions in the peritoneal cavity, a perforation of the terminal ileum, and mild spillage of fecal material into the pelvis. The perforation site was resected, and an end-to-end anastomosis was performed. The patient was treated with antibiotics and, after the results of the pathology report, with acyclovir (10 mg/kg iv every 8 h for 10 days). Her postoperative recovery was slow, but she eventually felt healthy.

The resected small bowel serosa was rough and dull, with diffuse fibrinopurulent exudate and a 1.2 × 0.9–cm defect. The mucosa surrounding the open defect was granular but otherwise had normal folds, whereas examination of adipose tissue revealed no enlarged lymph nodes.

Hematoxylin-eosin staining revealed a normal mucosal surface (figure 1). However, the serosa was covered with a thick layer of fibrinopurulent exudate (figure 2), in which multiple intranuclear viral inclusions consistent with herpetic infection were evident (figure 3). Immunoperoxidase stains were reactive for both HSV-1 (figure 4) and HSV-2 (figure 5) biotypes; however, many intranuclear viral inclusions within the serosal inflammatory exudate stained intensely for HSV-1 (figure 6).
have observed this shift in $T_m$ for this specific assay, from 54.0°C (± 2.5°C) to 60.0°C for rare HSV-1 isolates confirmed by culture and monoclonal antibody staining. The manufacturer states that, in this case, the HSV type cannot be determined with this assay and suggests culture for confirmation of type, which was not possible, because the tissue specimen was already paraffin embedded.

**Discussion.** HSVs have increased transmissibility on contact with warm and moist mucosal layers, where they achieve attachment to and penetration of the host cell [2, 3]. In vitro, herpes viruses can infect most types of mammalian cells; the in vivo pathogenicity of the feline infectious peritonitis virus [4, 5] and the bovine herpesvirus type 4 [6] and its association with endometritis and abortion in cows are known examples. In humans, the in vivo pathogenicity of HSV is host specific, causing lytic infection of fibroblasts and epithelial cells and establishing latent infection in neurons. The mechanisms by which various stimuli (UV light, immunosuppression, and trauma to the skin or ganglia) cause the reactivation of HSV infection are largely unknown. Cellular immunity is critical in controlling infection; infants and patients who are immunocompromised because of HIV infection or organ transplantation can manifest extensive viremic spread to visceral organs; however, agammaglobulinemic patients appear to handle HSV infection well.

Infections of the digestive tract mucosa with HSV are extensively described in the literature. In occasional cases, multinucleated intranuclear inclusion–bearing cells are present in the lamina propria; antiviral therapy speeds healing. Sporadic reports of the viral etiology of peritonitis in patients with CAPD have been appearing in the nephrology literature since 1986 [7, 8]. In an intriguing study from 1989 [9], peritoneal dialysis effluent was cultured for detection of HSV and other herpesviruses and enteroviruses, with no evidence of viral growth in cell culture lines; the authors speculated that an antiviral factor was present in the effluent.

There has been a report [10] of a patient with CAPD who received a clinical diagnosis of peritonitis and who had undergone an exploratory laparotomy and excision of a portion of the omentum. The findings of routine and immunoperoxidase stains, as well as electron microscopy, were consistent with HSV infection of the stromal cells of the peritoneum. Reactivation of a previously acquired HSV infection that has established latency, likely in the sacral ganglia, to the peritoneal/omental stroma is possible. A previously performed hysterectomy and the presence of the CAPD catheter might have acted as irritants, because HSV infection reactivation is common in areas of trauma, inflammation, or other type of tissue irritation.

Our patient has had latent infection with HSV, and the sections obtained for pathological examination documented the diagnosis of HSV infection of the serosal surface, without mucosal involvement. There were also positive results of immunoperoxidase staining with anti-HSV antibodies to both biotypes because of cross-reactivity, which was not helpful for typing. The LightCycler PCR was shown to be more sensitive than isolation by tissue culture (sensitivity of culture vs. sensitivity of PCR, 78%) and HSV antigen detection (sensitivity of EIA vs. sensitivity of PCR, 56%) [1, 11]. The amplified DNA from the tissue specimen had a $T_m$ of 60.0°C, which strongly suggests HSV-1.

To our knowledge, reinfection with HSV of the same biotype in a previously infected individual is not reported in the literature. We speculate reactivation of infection from the sacral
ganglia to the serosal surfaces of the lower abdomen and pelvis; the previous procedure could have acted as an irritant, as noted previously. Both HSV-1 and HSV-2 have been shown to be rare causes of pelvic inflammatory disease [12] and to cause extension of HSV infection into the uterine cavity; laparoscopic evidence of vesicular lesions on the fallopian tube from which HSV has been isolated has been reported [13].

It should be emphasized that the clinical course before the perforation was extremely insidious; bilateral, lower, intermittent abdominal pain predominated, without other local symptoms (e.g., ileus, guarding, nausea, vomiting, and tenesmus) or major systemic symptoms (e.g., fever, chills, hypotension, and shock). Spontaneous bacterial peritonitis in cirrhotic patients can also be insidious, but the presence of ascites is a sine qua non, in contrast to herpetic peritonitis.

This case demonstrates that herpetic peritonitis can be an underestimated cause of morbidity and mortality in immunocompromised patients, in women, and in patients who have undergone any procedure causing irritation or trauma to the serosal surfaces of the intra-abdominal organs.

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