

Pseudoneoplastic Appearance of Cytomegalovirus-Associated Colitis in Nonimmunocompromised Patients: Report of 2 Cases

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Two cases of human cytomegalovirus (HCMV) colitis with pseudoneoplastic appearance are described. Patients presented with abdominal pain, fever, and diarrhea. Colonoscopy revealed a stenosing lesion in one patient and a broad-based, vegetant mass in the other patient, and histopathological examination of colectomy specimens revealed exuberant inflammatory masses with infiltration of mononuclear cells and ulcers with granulation tissue. Typical intranuclear HCMV inclusions were numerous. Peculiar to both patients was the lack of any apparent causes of immunodeficiency, such as human immunodeficiency virus infection or previous organ transplantation.

Human cytomegalovirus (HCMV) can infect different regions of the gastrointestinal tract and can cause a variety of pathological lesions. In the colon, multiple erosions or ulcers, which, at times, cause perforation, are common [1]. Solitary mucosal ulcers have also been described [1]. Pathological patterns that are rarely encountered in HCMV infections of the colon also include hemorrhagic proctocolitis [2], toxic megacolon [3], pseudomembrane formation [4], and, in infants, extensive leiomyolysis [5]. Isolated cases of pseudotumoral appearance of HCMV colitis associated with polypoid masses [6] or strictures [7] are described in the literature, especially among HIV-positive patients. In this report, we describe 2 cases of HCMV

infection of the colon with pseudoneoplastic appearance mimicking carcinoma. Both cases developed in HIV-negative patients that showed no apparent cause of immunosuppression.

Case reports. An 84-year-old woman (patient 1) presented to the emergency department at the University of Modena Medical School complaining of abdominal pain and diarrhea of 1 week duration, with fever (temperature, 38.5°C), which had been present for 5 days. Her medical history included mild hypertension, which had been treated with calcium antagonists. Physical examination revealed tenderness in the right lower quadrant of the abdomen. Blumberg's sign was strongly positive. Laboratory investigations showed an increased WBC count (15,000 cells/mm³), with 90% neutrophil granulocytes, and a hemoglobin level of 9.6 g/dL. Hematocrit was 26%. Occult blood was present in a stool specimen. Other laboratory tests yielded normal results, with findings that were negative for HIV and tumoral markers.

Colonoscopy revealed that the rectum and colon were normal to the middle portion of the ascending colon, where a friable, stenosing lesion was observed. The colonoscope could not be passed beyond the ascending colon. Endoscopic biopsies were performed at the border of the stenotic area and revealed nonneoplastic colonic mucosa with chronic inflammatory infiltrates. A double-contrast barium enema radiograph showed rigidity of the wall of the cecum and proximal ascending colon, with wide disruption of the mucosal pattern. Mucosal borders in this area were irregular and spiculated (figure 1). Exploratory laparotomy was performed on hospital day 12 and revealed an indurated lesion in the cecum and proximal ascending colon, with presence of fibrinous exudate on the serosal surface. Right hemicolectomy was performed.

Gross inspection of a tract (length, 8 cm) that included the cecum and the proximal ascending colon revealed mucosa that appeared markedly swollen and hemorrhagic, as well as 3 oval ulcers, the largest of which measured 1 × 0.6 cm and caused minimal perforation of the intestinal wall. The serosa of the cecum, as well as that of the nearby greater omentum, was covered with fibrinous exudate. Microscopic examination showed chronic inflammatory infiltrates and ulcerations with necrotic material and granulation tissue. Numerous intranuclear inclusions were detected in macrophages, stromal cells, and isolated endothelial cells. Inclusions were eosinophilic and were frequently surrounded by a clear halo (figure 2). Immunohistochemical staining with anti-HCMV monoclonal antibody (clone CCH2; Dako) was positive in intranuclear inclusion bodies. PCR

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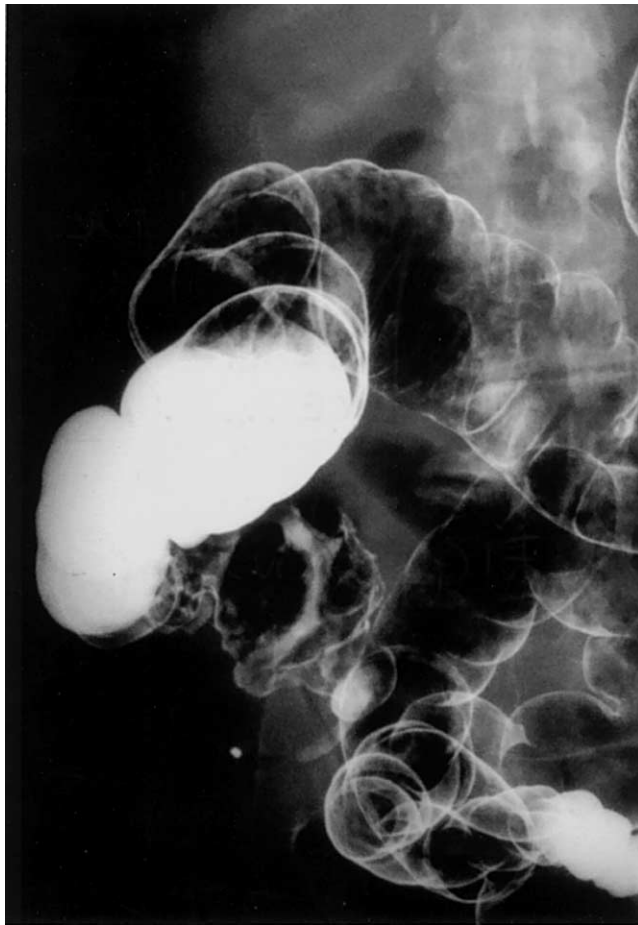


Figure 1. Double-contrast barium enema radiograph of patient 1 showing rigidity of the wall of the cecum and proximal ascending colon with irregular and spiculated mucosal borders.

of DNA extracted from formalin-fixed, paraffin-embedded histological sections was positive for HCMV.

Postoperatively, patient 1 recovered without any recurrence of pain or diarrhea. Antiviral treatment (ganciclovir) was administered for 2 weeks and was tolerated. The patient came to the hospital for postoperative control 2 weeks and 3 months after discharge, then she was lost to follow-up.

A 67-year-old man (patient 2) presented to the hospital with painful abdominal cramps associated with diarrhea and fever (temperature, 38.5°C), all of which had been present for 5 days. He had no history of hematemesis or hematochezia but had a history of hypertension and of depression, which had been treated with fluoxetine. Physical examination revealed a soft, mildly distended abdomen with tenderness in the left quadrants but with no rebound or guarding. No masses were palpable on rectal examination, but a stool specimen was positive for occult blood. The hemoglobin level in patient 2 was 13.1 g/dL, with mild microcytic anemia, and the WBC count was 11,000 cells/mm³. Results of other laboratory tests were within normal lim-

its. Examination of a stool specimen was negative for ova and parasites, performance of a *Clostridium difficile* stool toxin assay yielded normal results, and stool cultures were negative for pathogenic bacteria. Antibiotic therapy was started. An abdominal radiograph series showed a few mildly dilated small bowel loops with no signs of air-fluid levels. Rectosigmoidoscopy showed an intraluminal, polypoid, and ulcerated mass that was strongly suggestive of carcinoma. Analysis of endoscopic biopsy specimens, however, revealed normal-appearing mucosa with inflammatory infiltrates.

Exploratory laparotomy, performed on hospital day 7, showed hyperemia in the serosal surface of the sigmoid colon, which appeared moderately dilated and indurated over a length of 10 cm. Resection of a 30-cm segment of the sigmoid colon was performed. Gross examination of the resected area evidenced edematous and partly hemorrhagic mucosa, with a soft, broad-based, vegetant mass that measured 5 × 2 cm and occupied one-half of the intestinal lumen. The mass showed 2 ulcers, the largest

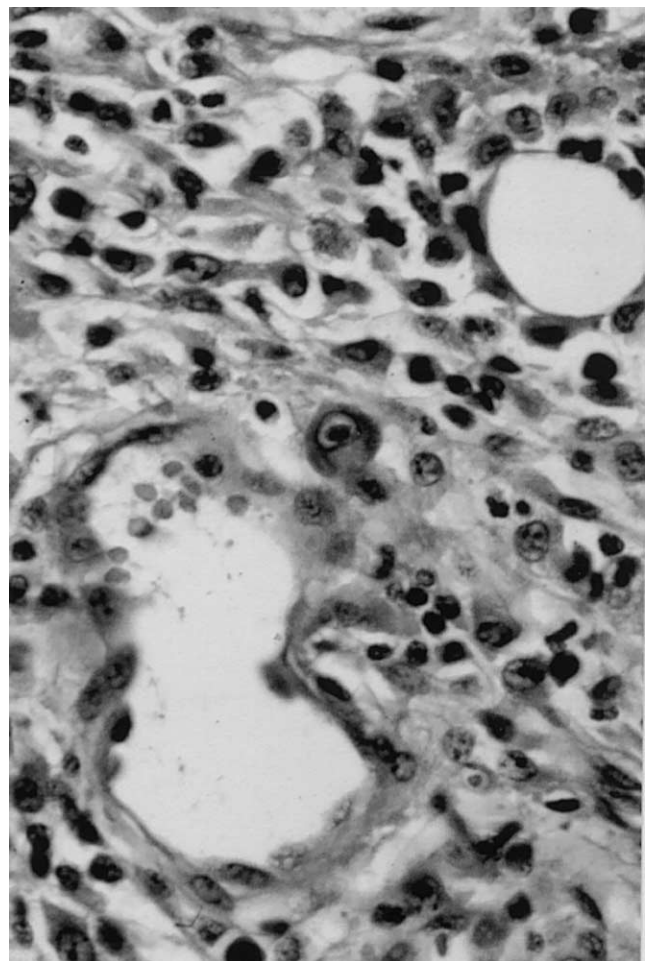


Figure 2. Large intranuclear inclusion of human cytomegalovirus in a macrophage in patient 1 (hematoxylin-eosin stain; original magnification, ×320).

of which measured 2×1.5 cm. Light microscopy revealed no evidence of carcinoma. Abundant granulation tissue and chronic inflammatory infiltrates were present, together with isolated large cells with eosinophilic intranuclear inclusions that had a positive immunohistochemical reaction to anti-HCMV antibody (Dako). Intranuclear inclusions were mainly found in stromal cells and in macrophages, but, occasionally, they were detected also in smooth muscle cells of the muscularis mucosae. PCR of DNA extracted from formalin-fixed, paraffin-embedded blocks was positive for HCMV.

Tests for HIV performed after the histopathological diagnosis of HCMV colitis were rendered negative. The patient was treated for 2 weeks with intravenous ganciclovir and tolerated the treatment. He is now healthy, with no evidence of recurrence of HCMV colitis or of neoplastic disease after a follow-up period of 4 years.

Discussion. Clinically significant HCMV infections usually occur in immunocompromised hosts, such as patients with AIDS, organ or bone marrow transplant recipients, and individuals receiving steroid therapy or undergoing chemotherapy [8]. Nonimmunosuppressed, critically ill patients with severe sepsis, malnourishment, major trauma, or widespread burns also appear to be at risk [8]. In immunocompetent subjects, active infection is rare and can result either from endogenous reactivation of HCMV or from exogenous reinfection with another virus strain.

HCMV infection of the gastrointestinal tract, in which mass lesions were caused that resembled neoplasms (on the basis of endoscopic and radiologic analysis), has been reported. The most commonly affected sites included the esophagus [9], the stomach [6, 9–11], and the large intestine [6]. Pseudotumoral appearance of HCMV infection has been described mainly in patients who have AIDS [6–11] or who have received an organ transplant [7, 12, 13], although occasional cases were detected in patients with common variable immunodeficiency syndrome [14] or chronic renal failure [15].

Patients with pseudotumoral HCMV colitis usually complain of painful abdominal cramps, diarrhea, and fever. Progressive bowel obstruction and vomiting have also been reported [10]. Radiological studies (barium enema radiography or CT scanning) have shown a concentric or eccentric stenotic area, 5–8 cm long, accompanied by irregular mucosal thickening and rigidity of the wall [12–15]. The presence of single or multiple ulcerations is common. Endoscopy usually has detected a friable stenosing lesion or a large intraluminal polypoid mass through which the colonoscope could not be passed, together with ulcers or erosions [9–13]. HCMV infection associated with pseudo-neoplastic appearance has been observed in all sections of the large intestine, but the cecum and the transverse colon appear to be more frequently affected [7, 10, 12, 13]. Endoscopic biopsies have usually revealed either nonneoplastic mucosa with

chronic inflammatory infiltrate or fragments of necrotic material and granulation tissue compatible with the presence of an ulcer. To our knowledge, diagnostic HCMV intranuclear inclusions have not been detected previously in biopsy specimens. In most reported cases, exploratory laparotomy and surgical resection of the affected area were performed [6, 7, 15]. Histopathological examination has revealed exuberant inflammatory masses with infiltration of PBMCs and ulcers with granulation tissue and fibroblastic proliferation.

In this report, 2 patients with HCMV colitis associated with pseudotumors of the colon were described. Peritoneal inflammation secondary to bowel perforation was present in patient 1, whereas patient 2 presented with partial colonic obstruction. Peculiar to both cases was the lack of any apparent cause of immunodeficiency, such as HIV infection, previous organ transplantation, chemotherapy, and malnourishment [8], at the time of surgery. Moreover, although patient 1 was lost to follow-up, no evidence of neoplasia was detected in patient 2 four years after undergoing colonic resection. The possibility that HCMV secondarily colonized bowel mucosa previously affected by another inflammatory process, and, thus, that HCMV behaved like a nonpathogenic bystander, cannot be disregarded [16]; however, no evidence of inflammatory bowel disease or other types of colitis was detected in our patients during histopathological examination.

This unusual presentation of a colonic stricture or mass mimicking carcinoma has, to our knowledge, not been previously reported in nonimmunocompromised individuals. Because serological studies were not performed in our cases, it is not possible to establish whether the HCMV infection occurred as a primary event or as a reactivation. The frequency of HCMV reactivation, however, has been shown to increase linearly with age because of the decline of immunity [17]. As previously suggested by Wisser et al. [10], the occurrence of large-intestinal inflammatory pseudotumors might represent an advanced stage of a previously unidentified HCMV infection.

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