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Apoptotic colopathy in a pediatric autologous bone marrow transplantation patient with spontaneous colonic cast excretion: Is it due to GVHD or rotavirus infection?

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Informed Consent
The authors stated that the written consent was obtained from the parents of the patient presented with images in the study.

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Abstract

Spontaneous colonic cast excretion per anus is a very rare entity. Colonic ischemia and severe infections are the most common etiologic factors. It is mostly seen in adults. Only one pediatric patient with colonic cast excretion was reported in the literature. We present a three-year-old male patient with the diagnosis of neuroblastoma who had undergone autologous BMT. After suffering a prolonged rotavirus infection, on the 25th the post-transplantation day, he presented with nausea, vomiting, abdominal pain, and spontaneous excretion of colonic mucosa-like material via defecation. The histopathological interpretation of the excreted material revealed acellular material composed of fibrin and neutrophils. The patient's colonoscopic biopsy specimen revealed crypt distortion, regeneration, and numerous apoptotic bodies within the crypt epithelium. Apoptotic colopathy and colonic cast excretion per anus is a sign of ischemia, which may be caused by severe intestinal infections or rarely, graft-versus-host disease. Therefore, a clinicopathological correlation was performed to reach a definitive diagnosis. The patient's symptoms were attributed to severe, prolonged rotavirus infection.

Keywords: Allogeneic, Bone marrow transplantation, Colonic cast, Rotavirus, GvHD

Introduction

Passage of intestinal casts per anus is an extremely rare entity. Severe ischemia, inflammation, bacterial and viral infections, and graft-versus-host disease are the etiological factors reported in the literature [1, 2]. Apoptotic bodies in crypt epithelium may be a sign of ischemic crypt damage, viral infections (mostly CMV), chemotherapy, and/or radiation exposure. It is also the characteristic form of cell death in gastrointestinal GVHD [3].

Although CMV is the most common microorganism associated with enterocyte apoptosis, other viral or bacterial infections may also be involved. We present an exceedingly rare entity of colonic cast excretion per anus in a pediatric bone marrow transplantation (BMT) patient with a review of the literature, discussing the differential diagnoses, and stressing the importance of clinicopathological correlation in reaching a definitive diagnosis.

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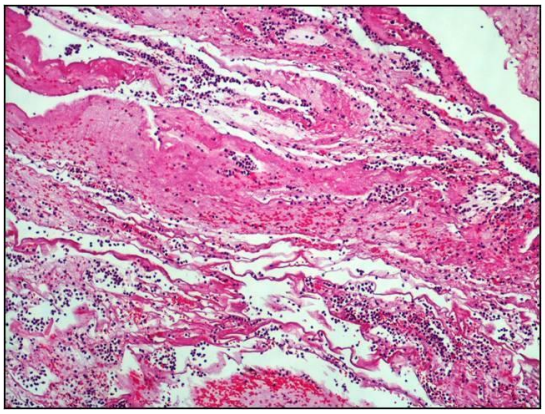
Case presentation

A three-year-old male neuroblastoma patient who had undergone autologous BMT 25 days prior presented with nausea, vomiting, abdominal pain, and spontaneous excretion of colonic mucosa-like material via defecation (Figure 1). His stool culture was positive for rotavirus one month ago when diarrhea began, and negative for clostridium difficile. The macroscopic pathological interpretation of the material was compatible with a colonic cast. The microscopic evaluation revealed casts composed of fibrin, neutrophils, sparse histiocytes, and mucus. Normal intestinal mucosal tissue was not observed (Figure 2). As the patient continued to excrete similar colonic casts, a colonoscopy was performed. Colonoscopic examination revealed edematous, granular, and hyperemic mucosa in the distal and prominent exudates and hyperemia in the proximal colonic segments. Endoscopic diagnosis was compatible with widespread colitis. The differential diagnoses included infectious, pseudomembranous, and ischemic colitis.

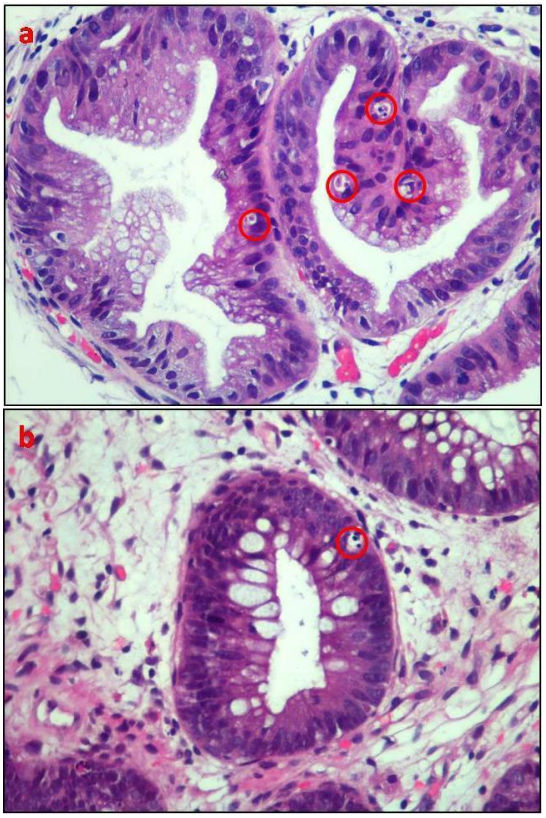
Figure 1: Spontaneously excreted colonic mucosa-like material

Figure 2: Casts composed of fibrin, numerous neutrophils, sparse histiocytes and mucus. Note that there is no normal intestinal mucosal tissue, (H&E, 200X).



The histopathological examination of the colonoscopic biopsy revealed crypt distortion, regeneration, and numerous apoptotic bodies within the crypt epithelium (Figure 3). Viral inclusions were not present and anti-CMV immunohistochemical antibody revealed negative immunoreaction. The pathological diagnosis was compatible with an “apoptotic colopathy.” GVHD and infections were included in the differential diagnoses. To avoid any potential diagnostic bias, we performed a clinicopathological correlation. Since the patient had received autologous BMT and the clinical symptoms were not compatible with GVHD, the patient’s prolonged rotavirus infection was considered the etiological factor.

Figure 3: Numerous apoptotic bodies within the distorted crypt epithelium (circles), (H&E, 400 X).



The patient received fluid and electrolyte therapy. A diarrhea diet was started, and intravenous immunoglobulin was administered every 10 days. The patient's complaints improved during the follow-ups.

Informed consent was received from the primary caregivers of the patient.

Discussion

Only 26 cases of colonic cast excretion per anus were reported in the literature. Most patients with colonic cast excretion (88%) were diagnosed with ischemic colitis.

In most cases (50%), the cause of colonic cast passage is colorectal cancer surgery or surgery for an abdominal aortic aneurysm. Ischemia secondary to operations was attributed to ligation of the inferior mesenteric artery or other bowel arteries [4]. The remaining patients developed colonic ischemia due to prior circulatory disorders.

Most previously reported cases were adult patients. In 2017, Nambu et al. [5] reported a 6-year-old pediatric patient with colonic cast excretion who had a fever, abdominal pain, and refractory diarrhea. The patient had neutropenia (<100 neutrophils/μl), as did our patient. The authors assumed that the patient might have had an autoimmune disorder mimicking inflammatory bowel disease but the exact etiological factor causing colonic cast excretion was not determined [5].

Similarly, Samee et al. reported a neutropenic adult patient with enteropathy and sepsis presenting with the excretion of intestinal casts. The casts contained numerous fungal elements that pointed out a fungal infection [1].

In the literature, the casts excreted by patients with ischemic colitis were composed of necrotic colonic mucosa, sometimes including the muscularis propria and serosal layers. In the present case, the casts were not histopathologically

compatible with colonic tissue or necrosis. They were composed solely of fibrin, large amounts of neutrophils, and scattered histiocytes, i.e., "fibrinopurulent casts."

In one of the reported cases, gastrointestinal GVHD was considered the etiological factor associated with excretion of the colonic casts [6].

GVHD is an immune-mediated complication of allogeneic BMT where graft T lymphocytes attack the tissues of the host [7]. Clinical symptoms of gastrointestinal GVHD are diarrhea, nausea, vomiting, and abdominal pain. Since many of these symptoms are nonspecific, confirmation by an endoscopic biopsy is often needed for both evaluation of the endoscopic findings and a clinicopathological correlation.

Although GVHD is considered a disease of allogeneic BMT patients, GVHD after autologous BMT has also been reported very rarely [7]. It has been reported after cyclosporine administration to patients who have received autologous BMT [8].

Because of the preceding prolonged rotavirus infection, the lack of GVHD findings in gastroscopy, and the fact that the patient was an autologous BMT recipient, apoptotic colopathy due to severe rotavirus infection was considered the pathological mechanism in the formation of colonic casts.

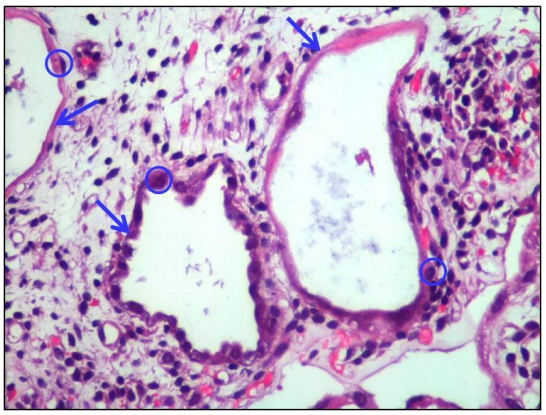
Acute diarrhea after BMT is generally due to GVHD or infection. The incidence of infection-related diarrhea in BMT patients is 40%-50%, mostly occurring in allogeneic BMT patients [9]. Viruses are the most common etiological factor of enteritis [10]. Rotavirus displays prominent tropism for the intestinal enterocytes and is accepted to be the major cause of viral gastroenteritis in pediatric patients [11]. The incidence of rotavirus in stool samples of BMT patients has been reported as high as 10%. In a series of 94 BMT patients with diarrhea, adenovirus, rotavirus, and echovirus were isolated from 20% of the BMT patients. In other case reports and smaller series, severe enteritis in BMT patients due to rotavirus have also been reported [10].

The mechanism of apoptosis due to rotavirus infection has been explained in many studies. The pathophysiology underlying apoptosis is explained by the increase in the concentration of intracellular calcium caused by the rotaviral enterotoxin nonstructural protein-4. Calcium induces the transition in mitochondrial permeability, leading to the release of cytochrome C from the mitochondria, an important condition during apoptosis [12]. SA-11 strain of rotavirus was reported to induce apoptosis in numerous cell types. Chaibi et al. [12] demonstrated that rotavirus infection caused apoptosis in intestinal caco-2 cells via an immune assay. In the present case, we also detected apoptotic bodies in the epithelial cells of cystically dilated and distorted crypts.

Alfajaro et al. [13] demonstrated villous epithelial desquamation, villus atrophy, and crypt hyperplasia in the later stages of rotavirus infections. Boshuizen et al. [14] described irregular nuclei in the enterocytes of the patients infected by rotavirus.

In the present case, histopathological findings other than apoptotic bodies included crypt hyperplasia, crypt distortion, dilatation, and irregularly located nuclei in the crypt epithelium, in line with the literature (Figure 4). In the literature, apoptotic colopathy cases due to mycophenolate use were also reported.

Figure 4: Irregularly located nuclei (circle) in the epithelium of the distorted and dilated crypts (arrows), (H&E, 400 X).



Patients with mycophenolate-related gastrointestinal toxicity typically present with afebrile, watery diarrhea with mostly insignificant or mild endoscopic findings. The histopathological changes in crypt epithelium in patients with a history of mycophenolate use included apoptosis in crypt bases, cystically dilated atrophic crypts, surface epithelium erosion, crypt architectural distortion, and eosinophils in lamina propria [15]. Our patient did not have a history of mycophenolate use.

Conclusion

We present the case of the first pediatric autologous BMT patient with apoptotic colopathy following prolonged diarrhea and resulting in the excretion of fibrinopurulent colonic casts per anus. This is a rare complication of colonic ischemia, severe enteritis, and very rarely, GVHD. In the present case, the etiological factor was a severe and prolonged rotavirus infection. The histopathological findings in the present case coincide with the findings described in the previous studies and case reports. If diarrhea is present in BMT patients, it is crucial to make a clinicopathological correlation and differentiate GVHD, because it requires a completely different treatment regimen, and if left untreated, it may result in mortality.

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