Etiology and Management of Toxic Megacolon in Patients With Human Immunodeficiency Virus Infection

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We report six cases of toxic megacolon in patients with human immunodeficiency virus (HIV). One case, at an early stage of HIV infection, mimicked a severe attack of Crohn's disease, with a negative search for infectious agents. Subtotal colectomy was successfully performed with an uneventful postoperative course. The five other cases concerned patients with acquired immunodeficiency syndrome at a late stage of immunodeficiency. They were related to *Clostridium difficile* or cytomegalovirus (CMV) intestinal infection in two and three patients, respectively. One case of CMV colitis presented macroscopically and histologically as pseudomembranous colitis. Emergency subtotal colectomy, performed in the first four patients with acquired immunodeficiency syndrome was followed by a fatal postoperative outcome. The last patient treated conservatively by colonoscopic decompression, in association with anti-CMV therapy, had a favorable short-term outcome. From the experience of our series and data from the literature, we discuss the best diagnostic and therapeutic approach to toxic megacolon in patients with HIV.

Toxic megacolon is defined as a severe attack of colitis with total or segmental dilatation of the colon.[1] In immunocompetent patients, toxic megacolon can occur as a complication of inflammatory bowel disease, antineoplastic chemotherapy,[2] or infectious colitis caused by *Clostridium difficile*,[3] *Salmonella*,[4] *Shigella*,[5] *Campylobacter jejuni*,[6] or *Yersinia enterocolitica*.[7] In patients with human immunodeficiency virus (HIV), toxic megacolon has been reported as a complication of cytomegalovirus (CMV) colitis[8–10] or colonic Kaposi's sarcoma[11] and in all cases has been treated by emergency colectomy. We report here six cases of toxic megacolon in patients with HIV mimicking a severe attack of Crohn's colitis in one patient and being caused by *C. difficile* or CMV colitis in two and three patients, respectively. Five of the six patients underwent emergency colectomy with a fatal postoperative outcome in the four immunocompromised patients. In the most recent case of CMV colitis with toxic megacolon, we opted for nonsurgical treatment of colonic decompression and anti-CMV treatment with a favorable short-term outcome.

Case Report

All of the cases of toxic megacolon in patients with HIV seen at Rothschild Hospital between 1988 and 1992 were reviewed. During this period, 2430 patients were seen in the hospital for HIV infection. Diagnostic criteria for toxic megacolon were defined as follows: (1) histologically proven colitis; (2) radiological dilatation of the transverse colon on x-ray film of the abdomen with a colonic diameter above 6 cm at the point of maximum dilatation[12]; and (3) evidence of at least two of these following signs[1]: tachycardia greater than 100 beats per minute, body temperature >38.6°C, leukocytosis $>10.5 \times 10^9$/L, and hypoalbuminemia <30 g/L. Six patients met these criteria. The main features of patients' past history are listed in Table 1. All of the patients were homosexual men ranging in age from 27 to 46 years. Patient 1 was at an early stage of HIV infection with a CD4 cell count of 290/mm^3 at the time of diagnosis, and he had no past history of opportunistic infection or wasting syndrome. All of the other patients (patients 2–6) were at a late stage of HIV infection, having experienced from one to four previous or still active opportunistic infections, and they had a CD4 cell count < 50/mm^3 in peripheral blood.

Results

Clinical Background of the Patients at the Time of Diagnosis of Toxic Megacolon

Diarrhea had lasted for 1–4 months before the diagnosis of toxic megacolon (Table 2). At the onset of diarrhea, stool specimens were negative by culture for the most common pathogenic bacteria (i.e., *Salmonella, Shigella, Yersinia,* and *Campylobacter* species) in all patients. Direct microscopy for ova and parasites was positive for *Cryptosporidium* organisms in three patients. At

Abbreviations used in this paper: CMV, cytomegalovirus; HIV, human immunodeficiency virus.

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Table 1. Past History and Main Features of HIV Infection in the Six Patients With Toxic Megacolon

	Patient no.					
	1	2	3	4	5	6
Age (*yr*)/sex	29/M	27/M	44/M	43/M	38/M	46/M
Risk factors for HIV	Homosexual	Homosexual	Homosexual	Homosexual	Homosexual	Homosexual
CD4 cell count at the time of diagnosis of toxic megacolon (*/mm³*)	297	5	7	6	2	5
History of opportunistic infection	No	PCP, Cryptosporidiosis	TB, CNS toxo, PCP, CMV retinitis	PCP, CNS toxo, TB	MAI	Cryptosporidiosis
Time between the occurrence of the first opportunistic infection and the diagnosis of toxic megacolon (*mo*)		14	29	31	6	14
Symptomatic opportunistic infection at the time of the diagnosis of toxic megacolon		Cryptosporidiosis	Cryptosporidiosis			Cryptosporidiosis

CNS toxo, central nervous system toxoplasmosis; MAI, *Mycobacterium Avium-Intracellulare;* PCP, *Pneumocystis carinii* pneumonia; TB, tuberculosis.

the time of the diagnosis, one patient was receiving clindamycin, and one additional patient had been recently treated by this antibiotic. All of the patients with acquired immunodeficiency syndrome were receiving antidiarrheals. No patient was treated by antineoplastic chemotherapy.

Clinical, Biological, and Radiological Features of Toxic Megacolon

The main data are listed in Table 3. All patients presented watery diarrhea, painful abdominal distension, fever, and tachycardia. Diffuse abdominal tenderness was noted at the physical examination in one (patient 6). Severe neutropenia was present in two patients. The platelet count ranged between 35 and 183 10^9/L. Hypoalbuminemia was encountered in five cases. The plain radiograph of the abdomen showed extensive dilatation of the colonic lumen in all cases with a maximal diameter of the tranverse colon ranging from 8 to 15 cm. Presence of air in the small intestine, without frank dilatation, was noted in all of the patients. The upright film of the abdomen showed the presence of fluid levels in patients 1, 4, and 6.

Etiology and Treatment of Toxic Megacolon

Left colonoscopy was performed within the preoperative state in 3 of the 5 patients who underwent the operation (Table 4), and the left colonoscopy showed mucosal lesions in all cases. In patient 6, the endoscopic procedure not only showed mucosal lesions but was also therapeutic. Patients 1–5 underwent emergency subtotal colectomy with ileostomy and sigmoidostomy. Perioperatively, dilatation of the whole colon was noted in all of the patients. Terminal ileum was mildly dilated in patients 2 and 3. One case of sealed perforation of the transverse colon was observed in patient 3. Patient 6 underwent colonic decompression using a fenestrated

Table 2. Clinical Background at the Time of the Diagnosis of Toxic Megacolon

	Patient no.					
	1	2	3	4	5	6
Current cutaneous Kaposi's sarcoma	No	Yes	No	Yes	Yes	No
Duration of diarrhea (*mo*)	1	12	3	5	1	14
Previously diagnosed intestinal pathogen		Cryptosporidiosis	Cryptosporidiosis	Cryptosporidiosis	*Giardia intestinalis*	Cryptosporidiosis
Number of antibiotic agents	0	1	3, including Clindamycin	4 + recent treatment by Clindamycin	1	1
Antidiarrheals	No	Loperamide	Loperamide	Paregoric tincture of opium	Codeine	Loperamide, diphenoxylate

Table 3. Clinical, Biological, and Radiological Features of Toxic Megacolon

	Patient no.						
	1	2	3	4	5	6	Mean (range)
Clinical data							
No. of liquid stools per day	10	6	10	6	3	8	7.2 (3–10)
Temperature (°C)	39	40	39	37	40	37	38.6 (37–40)
Pulse rate (*beats/min*)	120	120	110	110	120	105	114 (105–120)
Biological data							
Leukocyte count (10^9/L)	7.3	1.0	1.6	0.4	4.0	4.4	3.1 (1.0–7.3)
Neutrophil count (10^9/L)	6.4	0.9	1.4	0.3	3.2	3.6	2.6 (0.3–6.4)
Albuminemia (g/L)	28	31	29	25	27	28	28 (25–31)
Radiological data							
Maximal transverse diameter at the radiograph of the abdomen (*cm*)	11	8	8	15	8	10	10 (8–15)

tube positioned over a colonoscopically inserted guide wire (Figure 1).[13] Etiologic conclusions were based on histological findings of colonoscopic biopsy specimens and/or colectomy specimens and on the results of cultures for enteric pathogens. Culture for bacteria (*Salmonella, Shigella, Campylobacter,* and *Yersinia* species), from stools in all of the patients, and from colonic biopsy specimens (patients 1, 2, 4, and 6) or colonic specimen (patient 5), was always negative. *C. difficile* toxin assay, performed in the stools from all of the patients, was positive in patients 3 and 5. Histological search for mycobacteria from colonic biopsy specimens and from colonic specimens was negative in all the patients. Histological search for CMV inclusions, including routine histological lecture and immunostaining, was positive in patients 2, 5, and 6. The main diagnostic conclusions are listed in Table 4. In patient 1, final diagnosis was severe colitis mimicking Crohn's disease without any identifiable intestinal pathogen. Of the 3 cases of CMV colitis (patients 2, 5, and 6), one was associated with colonic Kaposi's sarcoma (patient 5), and one presented macroscopically and histologically (Figure 2) as a pseudomembranous colitis (patient 2). Finally, *C. difficile*–induced pseudomembranous colitis was the definite diagnosis in the two remaining cases and was associated with a concurrent or recent treatment by clindamycin in patients 4 and 5, respectively.

Outcome

Patient 1 recovered from colectomy without any postoperative complications. Intestinal continuity was reestablished 1 year later. At that time, the CD4 cell count was 325/mm^3. *P. carinii* pneumonia occurred as the first

Table 4. Etiology, Treatment, and Outcome of the Six Cases of Toxic Megacolon

	Patient no.					
	1	2	3	4	5	6
Endoscopic pretherapeutic procedure	Left colonoscopy	Left colonoscopy	Not done	Left colonoscopy	Not done	Total colonoscopy
Endoscopic findings	Deep ulcerations	Pseudomembranes overlying superficial ulcerations		Superficial ulcerations		Superficial ulcerations
Therapeutic procedure	Subtotal colectomy	Subtotal colectomy	Subtotal colectomy	Subtotal colectomy	Subtotal colectomy	Colonic decompression
Associated treatment		Vancomycin, ganciclovir	Vancomycin, ganciclovir	Metronidazole	Ganciclovir	Ganciclovir
Histological findings	Pancolitis, cobblestone mucosa, deep fissures	Pancolitis, pseudomembranes overlying ulcerations	Pancolitis, pseudomembranes overlying ulcerations	Pancolitis, pseudomembranes overlying ulcerations	Pancolitis, ulcerations, colonic Kaposi's sarcoma	Pancolitis, ulcerations
Final diagnosis	Crohn's-like colitis	CMV colitis presenting as pseudomembranous colitis	*C. difficile*–induced pseudomembranous colitis	*C. difficile*–induced pseudomembranous colitis	CMV colitis associated with colonic Kaposi's sarcoma	CMV colitis
Postoperative outcome	Uneventful, alive at 5 yr	Died on day 3	Died on day 8	Died on day 12	Died on day 14	Died after 3 mo

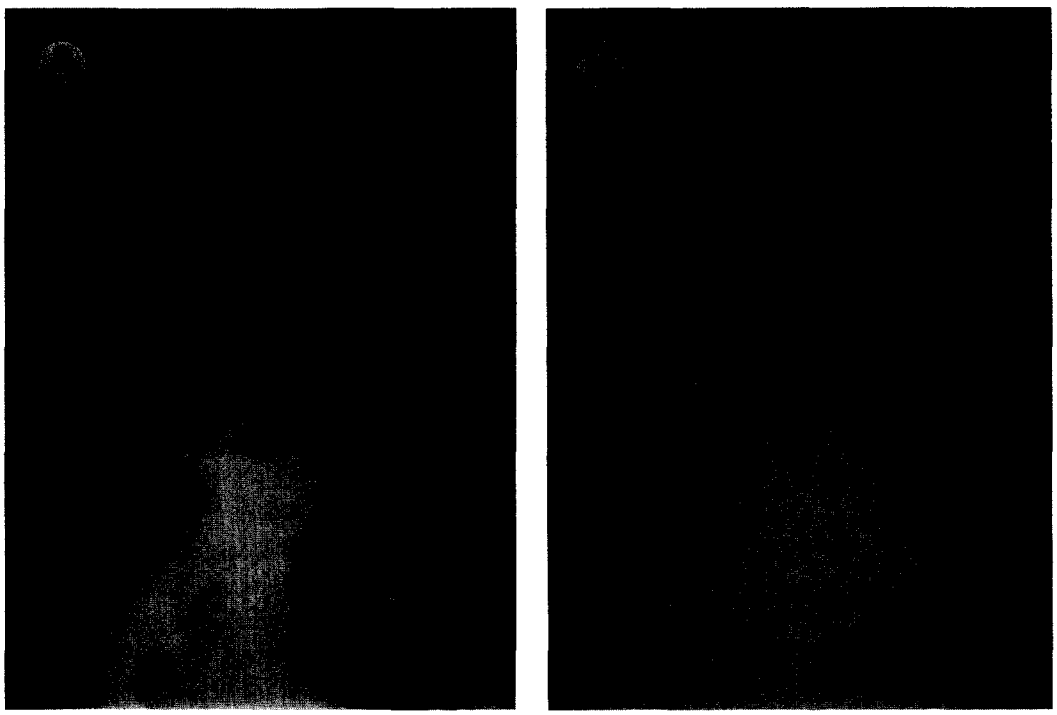

Figure 1. (*A*) Radiograph of the abdomen of patient 6 in the supine position at the time of the diagnosis of toxic megacolon, showing a marked dilatation of the colon. (*B*) Radiograph of the abdomen of patient 6 in the upright position 12 hours after colonoscopic insertion of a fenestrated tube.

opportunistic infection 2 years after colectomy. The patient is still alive 5 years after colectomy. He has had no recurrence of diarrhea during this period. Patients 2–5, who underwent colectomy at a late stage of HIV infection, died in the postoperative course from multiple organ failure within 3–21 days, despite the absence of mechanical or infectious intestinal complications. Patient 6, who underwent colonic decompression for CMV colitis with toxic megacolon, was treated during a 1-month period by ganciclovir (5 mg/kg every 12 hours). At the end of this induction treatment, total colonoscopy showed a complete healing of the colonic CMV-induced mucosal ulcerations. A maintenance treatment of ganciclovir (5 $mg \cdot kg^{-1} \cdot day^{-1}$) was then initiated. The patient died 2 months later from septicemia. During the 3-month period between colonic decompression and death, no further episode of colitis or megacolon was observed.

Discussion

This study attempts to analyze the etiology and prognosis of toxic megacolon in patients with HIV. A clinically significant finding is that in immunocompromised patients, emergency colectomy is a very hazardous procedure and that an alternative medical approach, which we successfully attempted in the last case, should be considered.

Patient 1, at an early stage of HIV infection, presented as a severe attack of Crohn's colitis with a negative workup for infectious agents. *C. jejuni* infection that mimics Crohn's disease has been reported during HIV infection,[14] but both stool and colonic biopsy cultures for *Campylobacter* were negative in patient 1. Colonic mucosal inflammation has been recently described as a consequence of HIV replication.[15,16] In these studies, the histological changes were found to be very pronounced in the early stages of HIV infection.[16] Nevertheless, no severe attack of colitis was observed. Finally, although remission of Crohn's disease after HIV infection has been reported,[17] the hypothesis of a first frank exacerbation of Crohn's disease without any recurrence cannot be excluded.

Patients 2–6 were all at a late stage of HIV infection because they had experienced from 1 to 4 opportunistic infections and they had a CD4 cell count below 50×10^9/L. They all had a megacolon, histologically proven colitis, and at least 2 of the 4 diagnostic criteria of toxicity proposed by Fazio.[1] Nevertheless, none of the patients met the last criterion, i.e., leukocytosis $>10.5 \times 10^9$/L. This feature is very unlikely at the advanced stages of HIV infection and could be considered as an inappropriate diagnostic criterion of toxicity in patients with HIV. *C. difficile* and CMV were the two causative agents identified among the five patients with acquired immunodeficiency syndrome.

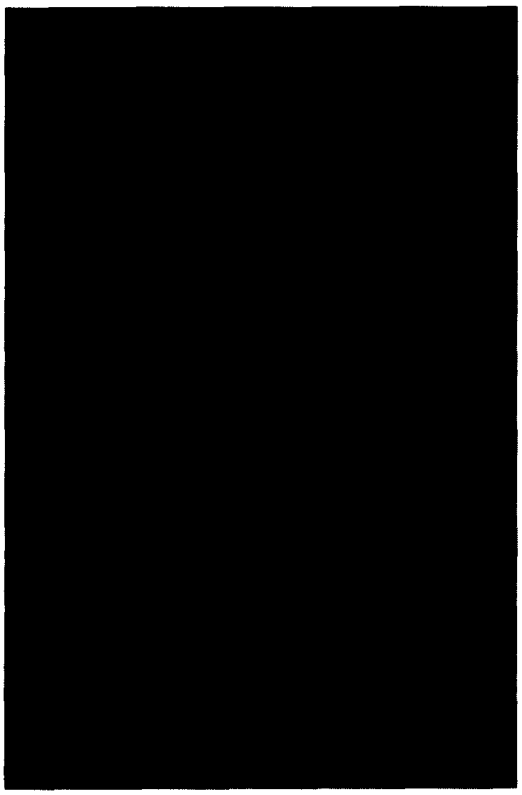

Figure 2. CMV colitis with pseudomembrane in patient 2. The *small arrow* shows a pseudomembrane lying on submucosa (the mucosa has disappeared). The *large arrow* shows an intranuclear CMV inclusion in a submucosa cell (original magnification 51×).

Severe neutropenia with a neutrophil count below 10^9/L was present in 2 of the 5 immunocompromised patients. These patients presented with pseudomembranous colitis that was related to CMV infection (patient 2) or *C. difficile* infection (patient 4). Ulcerative colitis complicated by toxic megacolon has been described in patients with low neutrophil count who are receiving antineoplastic drugs, such as cytosine arabinoside or methotrexate.[2] Pseudomembranous colitis leading to toxic megacolon, related in some cases to *C. difficile* infection, has been also reported in association with antineoplastic chemotherapy.[18] Neutropenic enterocolitis, also called typhlitis, appears as a distinct entity that is characterized by necrosis of various layers of the bowel wall, involving predilection for the cecum and the terminal ileum.[19] This syndrome, which is usually not related to a specific pathogen, has been recently evocated in two patients with HIV.[20] In the two patients with infectious colitis and low neutrophil count, we believe that neutropenia was not more than an adjuvant factor.

It is noteworthy that all of the patients with acquired immunodeficiency virus were receiving antimotility drugs at the time of the diagnosis of toxic megacolon. Loperamide has been suspected of precipitating the occurrence of toxic megacolon in patients with ulcerative colitis[21] or *C. difficile* colitis.[22] In our patients, such an unfavorable effect of antimotility drugs cannot be excluded. Antimotility drugs should be used with caution in patients with HIV with diarrhea and should be withdrawn as soon as a painful meteorism occurs.

In the literature, a few cases of CMV-induced toxic megacolon have been reported in patients with HIV.[8–10] There is no theoretical reason why, in addition to CMV and *C. difficile,* the other etiologic agents of toxic megacolon that are reported in immunocompetent patients, such as *Salmonella* and *Shigella,* could not also be isolated in patients with HIV. Because a potentially efficient medical therapy is available for all of these infectious agents, the timing of diagnosis is crucial. In patients with chronic diarrhea, the occurrence of a painful meteorism should be considered as an alarming clinical feature. At this point, the antidiarrheal agents should be stopped. The diagnostic procedure should then include an x ray of the abdomen; a stool examination to find bacteria, *C. difficile,* and its toxin; and colonoscopy with biopsies for histology and culture for bacteria. Colonoscopy with mucosal biopsies for histology is essential for the diagnosis of CMV colitis and should always be performed. Left colonoscopy can be sufficient to reach the lesions of colitis. However, if left colonoscopy appears as normal, total colonoscopy should be attempted, particularly because up to 39% of the lesions of CMV colitis are present in only the right colon.[23] Cultures of biopsy specimens can increase the probability of the identification of bacteria such as *Salmonella* or *Shigella.* As noted in patient 2, CMV colitis can mimic endoscopically and histologically a *C. difficile*–induced colitis, perhaps because of underlying vasculitis. Therefore, we suggest that a treatment using agents active against different infectious etiologies of toxic megacolon should be initiated after the colonoscopy and should be adapted to histology and culture results.

A review of the literature shows that subtotal colectomy has been performed in all of the cases of CMV colitis with toxic megacolon in patients with HIV.[8–10] Among the six observations reported, one case of early postoperative death by multiorgan failure was described.[9] In the five other cases, death, when it occurred, was not directly related to the operative procedure. By contrast, the postoperative outcome was very poor in our series, except in the previously asymptomatic patient. One explanation could be that all of the patients who died from multiorgan failure in the early postoperative state were at a very late stage of HIV infection. Furthermore, it can be suggested that diagnosis of toxic megacolon was more delayed in our critically ill patients as compared with

cases described in the literature. In patient 6, who presented with CMV colitis with toxic megacolon, we opted for the conservative treatment of colonoscopic decompression as proposed for pseudomembranous colitis in immunocompetent patients.[3] Ganciclovir was associated with the endoscopic procedure to treat the underlying cause of the toxic megacolon. Such an approach needs constant clinical and radiological monitoring because a risk of colonic perforation remains constant throughout the early stage of the treatment.

In conclusion, this study shows that toxic megacolon has multiple etiologies in patients with HIV. In the late stages of HIV disease especially, toxic megacolon occurs as a potentially curable complication of infectious colitis. Colonoscopy with biopsies should be performed early in the patient's management and before the development of colonic perforation. Colonic decompression in conjunction with appropriate anti-infective therapy should be considered as an alternative to emergency colectomy, particularly in critically ill patients.

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