A patient who survived total colonic ulcerative colitis surinfected by cytomegalovirus complicated by toxic megacolon and disseminated intravascular coagulation

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Abstract

The authors report the case of a patient aged 60-year-old who survived ulcerative colitis complicated by toxic megacolon and disseminated intravascular coagulation. This patient was not known for this ulcerative colitis and was first hospitalised for a suspicion of diverticulitis. The admission symptoms were fever, abdominal pain and bloody diarrhoea. The evolution was defavorable under antibiotics and sulfasalazine. The patient was readmitted 5 days after he left hospital, and the diagnosis of UC was based on colon biopsy made during the first hospitalisation. A treatment with methylprednisolone was started and the patient worsened day by day with apparition of toxic megacolon and disseminated intravascular coagulation. Subtotal colectomy was performed for degradation of general status and coagulation factors. Pathological findings confirmed ulcerative colitis with toxic megacolon. Cytomegalovirus inclusions were demonstrated on the colonic specimen and confirmed by PCR. In this report the authors discuss the etiology of toxic megacolon and disseminated intravascular coagulation in ulcerative colitis surinfected by cytomegalovirus. Mortality of these pathologies is high necessitating rapid diagnosis of cytomegalovirus infection by sigmoid biopsy. Management requires immunosupression interruption and ganciclovir therapy, or surgery in unsuccessful medical treatment. (Acta gastroenterol. belg., **2005**, 68, **276-279**).

Key words : ulcerative colitis, toxic megacolon, CMV infection, disseminated intarvascular coagulation, surgery.

Introduction

Colon infection due to cytomegalovirus (CMV) may develop in patients with decreased immunity, as in acquired immuno-deficiency syndrome or in transplanted patients receiving immunosuppressive drugs (1). CMV colitis has also been described in patients with inflammatory bowel diseases, especially those taking corticosteroid therapy (2-11). CMV colitis may lead to severe complications, as toxic megacolon (12) or as coagulation disorders as disseminated intravascular coagulation (DIC) (13). Some authors also described DIC associated with ulcerative colitis (UC) (14-17). Herein, we report the case of a patient suffering from UC complicated by CMV infection, toxic megacolon and DIC, and who survived after colectomy.

Case report

A 60-year-old man with a past history of non-insulin-dependant diabetes, arterial hypertension, gastric ulcers, pulmonary tuberculosis and diverticular haemorrhage, was admitted because of frequent episodes of diarrhoea with blood on the stools and fever. The patient has been suffering from this bloody diarrhoea since 3 weeks. He complained from abdominal pain and loss of weight. Eight years before, the patient had been investigated for loss of blood in the stools. Colonoscopy demonstrated bloody diverticulosis and cauterisation resolved the problem. At admission, body temperature was 39°C. Abdominal examination showed tenderness at the palpation of the left and right iliac fosse, with peritoneal irritation. Laboratory examinations revealed high-grade inflammation with C reactive protein (CRP) at 142 mg/l (N : 0-6 mg/l), fibrinogen at 7.32 g/l (N : 2.3-4.3 g/l), and leucocytes at 9430 per mm3. Abdominal computed tomography (CT) was first analysed as uncomplicated acute diverticulitis of the sigmoid. Stool cultures were negative for classic aerobic and anaerobic pathologic germs ; no parasite and no toxin was found. Colonoscopy was performed after few days of intravenous antibiotherapy. The entire colon was demonstrated, revealing the presence of diffuse diverticulitis of the sigmoid, but also showed a continuously oedematous mucosa of the entire colon, with marked bleeding, erosions and ulcers. Proposed diagnoses were infectious or inflammatory colitis. The patient was treated with amoxycillin-clavulanic acid (Augmentin®) and sulfasalazine (Salazopyrine®) for 10 days and was discharged with only a Salazopyrine® treatment. Pathology of the colon biopsy demonstrated colitis with severe neutrophilic infiltration, crypt abscesses, and goblet cell depletion, suggesting UC. Imunohistochemistry search was negative for CMV on histologic specimen.

Five days after discharge, the patient was readmitted at the emergency department for the same symptoms. Physical examination showed fever, asthenia, weight loss and peritoneal irritation. Because of UC pathology diagnosis, 40 mg of methylprednisolone (Solumedrol®) was intravenously administrated during six days without improvement. At the contrary peritoneal irritation signs increased, with right lower quadrant tenderness. Abdominal CT (Figure 1) showed massive dilatation of the colon and pancolitis. The blood tests deteriorated,

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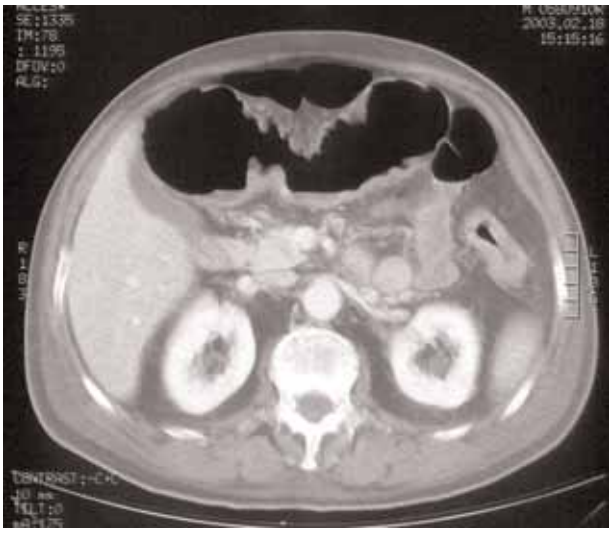

Figure 1. — Abdominal CT scan with contrast showing dilatation of the colon and thickening of the colonic wall.

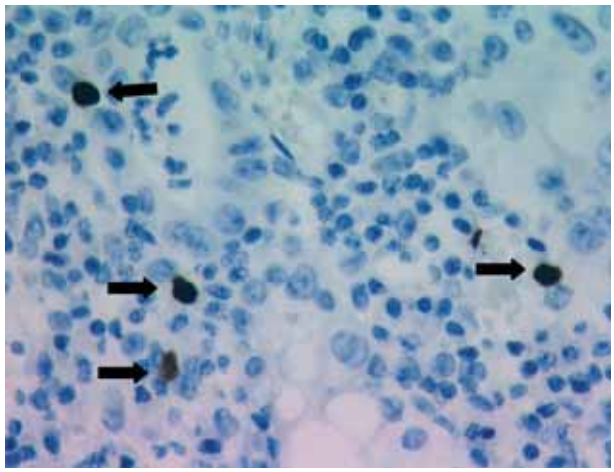

Figure 2. — Representative example of an immunohistochemical section demonstrating the presence of CMV-infected cells (arrows) in the colorectal mucosa (magnification ×200) close to glandular crypts.

revealing progressively decreasing platelet count (54,000 per mm^3 ; N : 170,000-400,000 per mm^3) with increased D dimer level (3,710 microg/l ; N < 200 µg/l) and a low fibrinogen level at 3.05 g/l. Blood and stool cultures were negative. Diagnosis was complicated UC with toxic megacolon and DIC. Antibiotherapy with metronidazole 1500 mg/d (Flagyl®) and ciprofloxacin 400 mg/d (Ciproxine®) was started, with increased doses of Solumedrol® 60 mg/d. No clinical amelioration was noted and emergency surgery was proposed. Subtotal colectomy was performed with terminal ileostomy and sigmoidostomy. Laparotomy revealed massive dilatation of the caecum without perforation, clear ascitis and presence of blood in the left and transverse colon. Transverse, left and sigmoid colons presented severe inflammation with thickness and friability. The postoperative course was first good with a rapid normalisation of platelet count (210,000/mm^3). The patient secondarily developed wound abscess and evisceration necessitating reintervention. Solumedrol® was progressively stopped and replaced by hydrocortisone to avoid a corticosurenal insufficiency. Mesalazine (Pentasa®) enemas were administrated through the anus and the sigmoidostomy with rapid regression of the erosion of this mucosa. The patient developed also a bronchopneumonia due to multiresistant *staphylococcus aureus* and *pseudomonas aeruginosa*. The patient recovered and was discharged after 41 days. Pathological examinations of the surgical specimen demonstrated a dilated colon with a maximal diameter of 13 cm for the caecum and 8.5 cm for the sigmoid. The mucosa was ulcerated with severe continuous inflammation of the colon and a cobble stone aspect on macroscopic examination. Microscopic aspects included goblet cell depletion, monocellular infiltration and crypt abscesses. The ulcers were very deep and the residual mucosa exhibited atypia with regeneration in parts. No dysplasia was found. CMV inclusions were seen (Figure 2) and amplification of DNA by PCR showed CMV on the specimen (Figure 3).

Methods and Results

Amplification of CMV by PCR

Crude DNA was first extracted from the paraffin-embedded biopsy as previously described (18). A PCR was then performed on 5 µl of extracted DNA. We used a pair of primers derived from the sequence coding for the major immediate-early and late antigen of CMV (19). These primers delimit a DNA fragment of 435 bp (Figure 3). The amplification was carried out using a PCR Mix (Eurogentec s.a., Liège, Belgium) in a final volume of 50 µl containing 20 pmoles of each sense and antisense oligonucleotide primer. After initial denaturation of the DNA sample for 3 min at 94°C, the reaction was run for 40 cycles consisting of 2 min at 94°C for denaturation, 9O sec at 65°C for annealing and 1 min at 72°C for extension. In the last cycle, the extension step proceeded for 10 min at 72°C. The amplified product was then electrophoresed on 2% agarose gel in Tris-Acetate-EDTA (TAE) buffer after staining with ethidium bromide. As shown in figure 2, the biopsy specimen of our patient was strongly positive for CMV DNA.

Immunohistological findings

Immunohistology was performed in order to localize the CMV-infected cells. Briefly, paraffin-embedded tissue sections (5-10 µm) were rehydrated and endogenous peroxidase was blocked with 3% H_2O_2 in methanol for 10 min. After permeabilization using citric buffer and PBS-0.15% tween for 5 min in a pressure cooking and 20 min at 20°C, the slides were incubated for one hour with a mouse monoclonal anti-CMV antibody (clone

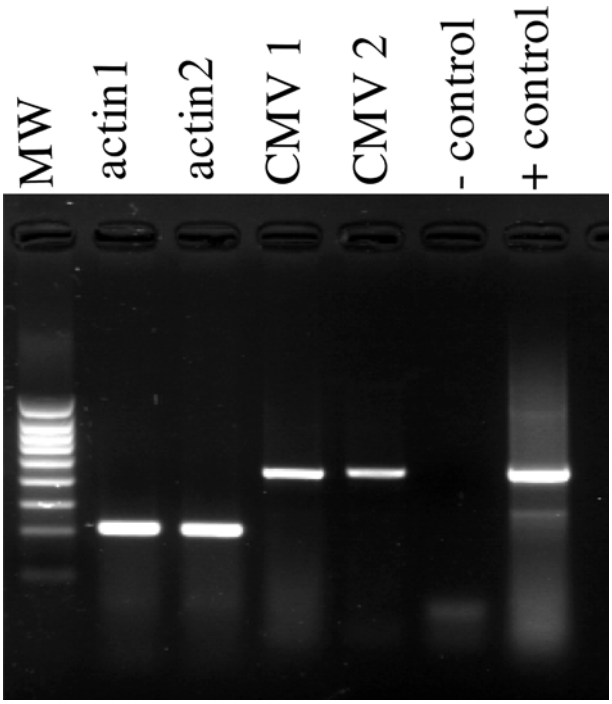

Figure 3. — Agarose gel analysis of polymerase chain reaction (PCR) products visualized by UV light after ethidium-bromide staining. Amplified CMV DNA was detected by PCR at the expected size (435 bp) in the DNA solution obtained from sections of 2 biopsy specimens (CMV 1 and 2). Primers amplifying a 201 base pair fragment in human actin gene sequence were also used to rule out inability to amplify DNA (actin 1 and 2). DNA from an empty paraffin-block was used as negative control. DNA from a previously processed CMV-infected tissue specimen was used as positive control. Lane MW contained DNA molecular weight standards.

CCH2 and DDG9) (Dako, Carpinteria, CA). After washing, the peroxidase-conjugated anti-mouse antibodies (Dako) were incubated for 30 min and visualised using diaminobenzidine (DAB, Dako) for 10 min. The slides were then counterstained using haematoxylin. As shown in Figure 2, the positive cells were mainly observed in the colorectal mucosa.

Two months later, the patient underwent a control endoscopy through the stomies. Rectosimoidoscopy showed residual moderated inflammation and erosions. Ileoscopy was normal. Biopsies confirmed evolutive UC. The UC, diagnosed by clinical, endoscopic and pathologic findings, was confirmed by serologic tests. Antibodies anti cytoplasm of neutrophilic of neutrophilic polynuclear were positive at 1/640.

Once the UC diagnosis was confirmed, a complementary proctosigmoidectomy with mucosectomy of the 2 cm upon the pectinea linea was performed, with confection of a W ileal pouch and a manual ileoanal suture protected by temporary terminal ileostomy. Hepatic biopsy excluded primary sclerosing cholangitis. Postoperative course was quite good and the patient was discharged after two weeks. Pathology confirmed evolutionary UC and immunohistological research of CMV was negative.

Discussion

In this patient the diagnosis of megacolon due to CMV infection of UC was difficult. Finally a surgical procedure was undergone, and the diagnosis was done on pathological findings. The first diagnosis was sigmoiditis or infectious colitis, and the UC diagnosis was not advocated before colonoscopy because of the patient's age and his history of diverticulosis. The UC diagnosis was largely confirmed thereafter.

Association of IBD and CMV colitis was first described by Powell et al in 1961 (10). The role of CMV as an etiologic factor for IBD has been explored in serologic studies (20,21). Cooper *et al.* examined resected UC colons from 46 patients and found CMV infection in six cases (3). Interestingly, five of these six patients had toxic dilatation, whereas only two of the remaining 40 cases without CMV had toxic megacolon. In addition, a review of 19 reported cases of IBD with CMV infection shows that 8 developed toxic megacolon (12). This finding suggested a strong link between the presence of CMV inclusions and toxic megacolon.

In 1985, a review of all cases of CMV colitis in IBD reported in literature noted a mortality of 44% and a colectomy rate of 62% (2). Treatment of CMV colitis with gancyclovir has been reported in patient with compromised immunity (7-9,22-24), but its efficacy in this setting is still unclear.

Concerning the physiopathology of DIC in this case two theories may be proposed. First, DIC may be due to CMV infection. CMV could promote DIC by endothelial injury, as CMV is known to infect and rapidly convert vascular endothelial cells from a non coagulant to a procoagulant phenotype (25,26). DIC was also shown in a rat model of CMV infection (27).The second hypothesis postulates that in patients with severe UC, endotoxin from gram negative bacteria could cause DIC. In our patient, indeed, severe mucosal destruction was recognized histologically but no germ was found in blood culture. It is possible that the destruction of the mucosal barrier enabled bacterial translocation and caused the DIC.

In conclusion, this case shows that the evaluation of patient with severe exacerbation of UC should include sigmoidoscopy with biopsies seeking for CMV infection. Coprocultures should exclude Clostridium difficilae infection. If CMV inclusions are found, the immunosuppressive treatment should be interrupted and an antiviral treatment started if clinical status is still good. If no amelioration occurs, subtotal colectomy should be performed, without intestinal suture. Secondarily complementary surgery could be proposed including proctectomy with ileoanal pouch or ileorectal anastomosis in function of the age and the severity of the disease.

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