Cytomegalovirus colitis in an apparently immunecompetent host after biliopancreatic diversion for obesity

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Abstract

CMV colitis in an immunocompetent host is a rare occurrence. We report a case of CMV colitis after biliopancreatic diversion surgery. The diagnosis of primary CMV infection with CMV colitis was based on histological examination of tissues biopsies obtained at colonoscopy, serology positive for CMV-IgM and CMV-IgG antibodies and a good response to systemic gancyclovir treatment. Malnutrition and colonic mucosal damage, both consequences of biliopancreatic diversion surgery, were thought to be predisposing factors.

To our knowledge this is the first report in the English language literature of an association between CMV colitis and status following biliopancreatic diversion surgery. (Acta gastroenterol. belg., **2008**, 71, **423-426**).

Introduction

Cytomegalovirus (CMV) is a member of the herpesvirus family, and is a common viral infection in humans. Seroprevalence in the general population is reported to be between 40-100% (1-6). There is a bimodal peak of infection, with the first in early childhood due to vertical and horizontal transmission, and the second occurring in young adults mainly due to sexual transmission (3,6). CMV is excreted in body fluids, including saliva, respiratory secretions, urine, blood, breast milk and semen, and transmitted through close personal contact (6).

Most primary CMV infections in immunocompetent adults are asymptomatic or associated with a mild mononucleosis-like syndrome of fever, myalgia, cervical lymphadenopathy and elevated liver enzymes (3,4). Primary infection resolves and is followed by viral latency (1,3-6). Fibroblasts, myeloid cells and endothelial cells are the principal reservoirs of CMV (4). A lifelong carrier state with intermittent reactivation is well described (6).

Severe CMV infections are rare in immunocompetent patients but can affect almost every system. In a recent review severe organ involvement included, in a decrescendo order of frequency : the gastrointestinal tract (colitis), the central nervous system (meningitis, encephalitis, myelitis, nerve palsies, myeloradiculopathy), haematological manifestations (haemolytic anaemia and thrombocytopenia), the eye (uveitis, retinitis), liver (hepatitis), lung (pneumonitis), and thrombosis of the arterial and venous system (deep venous thrombosis, portal vein thrombosis, pulmonary embolism) (7).

CMV colitis is a well-know entity in immunocompromised patients, such as those with human immunodeficiency virus (HIV) infection, organ transplant recipients and patients receiving immunosuppressive therapy (5,6). CMV colitis is rare in immunocompetent hosts (2).

This case report describes CMV colitis in a patient who had undergone a biliopancreatic diversion operation, for obesity.

Case report

A 33-year woman presented to the emergency room with a several week history of loss of appetite, vomiting and malaise. She had undergone a number of surgical procedures in the past. These included laparoscopic sterilisation and resection of endometriosis, vaginal hysterectomy, laparoscopic adnexectomy and most recently, biliopancreatic bypass surgery for obesity, seven months earlier.

Her vital signs were normal, as was examination of her cardiovascular and respiratory systems. Abdominal examination revealed only epigastric tenderness. Her weight on admission was 53.3 kilograms (kg) [body mass index (BMI) 21], a marked reduction from before her operation when her weight was 91 kg (BMI 36).

Laboratory results revealed a normal C-reactive protein (CRP) of 0.43 mg/dl (0-0.6), a normal white blood cell count (WBC) of $7.6 \times 10^*3/\mu L$ (4.0-11.0) and mildly deranged liver function tests [total bilirubin 1.86 mg/dl (0.2-1.1), direct bilirubin 1.09 mg/dl (0.0-0.3), aspartate aminotransferase (AST) 56 U/l (10-32), alanine aminotransferase (ALT) 47 U/l (10-31), gamma glutamyl transpeptidase (GGT) 49 U/l (5-39), alkaline phosphatase (ALP) 118 U/l (35-104)]. Renal indices and electrolytes were normal. Computerized tomography (CT) of the abdomen showed wall thickening of the left

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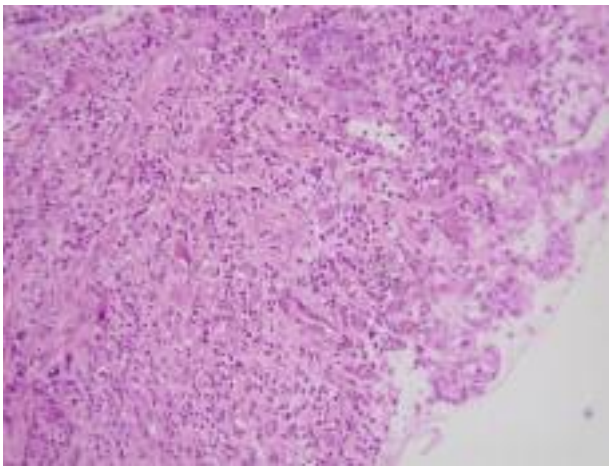

Fig. 1. — Biopsy of terminal ileum, haematoxylin and eosin stain, magnification ×200. The ileal mucosa is ulcerated with loss of villi and the presence of a mixed inflammatory infiltrate of moderate density in the underlying lamina propria.

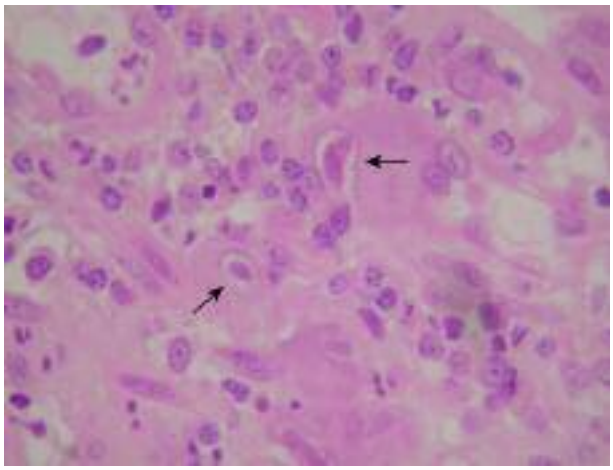

Fig. 2. — Biopsy of terminal ileum, haematoxylin and eosin stain, magnification ×400. Multiple endothelial and stromal cells show nuclear inclusions typical of CMV-infection, often described as 'owl's eye' (arrows).

hemi-colon. Colonoscopy with ileoscopy showed small patches of hyperaemia throughout the entire colon. Histological examination of mucosal biopsies reported only mild, non-specific inflammation. In the absence of any other diagnosis, the patient was presumed to have intermittent intestinal sub-obstruction, due to adhesions consequent to previous surgery. She was discharged after 3 days in hospital.

One week later the patient was readmitted with complaints of crampy abdominal pain, anorexia, vomiting and diarrhoea. Physical examination revealed a tachycardia of 100 beats per minute and epigastric tenderness on deep palpation.

Blood tests revealed a slightly raised CRP (0.8 mg/dl), further derangement of liver function tests (total bilirubin 1.66 mg/dl, direct bilirubin 1.08 mg/dl, AST 80 U/l, ALT 76 U/l, GGT 73 U/l, ALP 126 U/l) and low serum albumin [1.96 g/dl (3.4-4.8)] and total protein [4.34 g/dl (6.4-8.3)]. A plain abdominal X-ray was normal, with no distended bowel loops or air-fluid levels to suggest bowel (sub-)obstruction. A CT scan of the abdomen was repeated, now showing wall thickening of the entire colon and the terminal ileum, from the ileocaecal valve to the enteroenteric anastomosis. An upper gastro-intestinal (GI) endoscopy and a repeat colonoscopy with ileoscopy were performed. Upper GI endoscopy with visualisation of the alimentary limb of small bowel, using a paediatric colonoscope, was normal. Colonoscopy and ileoscopy confirmed the results of the initial examination, with patchy hyperaemia throughout the colon and mild associated mucosal oedema. The terminal ileum was visualised up to a retrograde distance of 50 cm and was normal. Histology of gastric, colonic and ileal biopsies reported only focal, non-specific inflammation with superficial ulceration at the anastomosis between the stomach and jejunum. The patient was presumed to have an infectious colitis and empiric therapy with a quinolone antibiotics initiated.

Despite therapy the patient showed no clinical improvement. Serial laboratory tests revealed a progressive rise in CRP and liver function tests. Cultures of urine and blood were negative. Empirical antibiotic therapy for the presumed infectious colitis was switched to piperacillin/tazobactam. At that time faeces sent for analysis was positive for Clostridium difficile toxin. Clostridium difficile infection, secondary to antibiotic therapy with quinolone, was diagnosed. Metronidazole was added to therapy.

A CT scan of the abdomen was repeated eight days after admission showing progression of the diffuse bowel wall thickening and decreased expansion of the diseased bowel segments, the presence of ascites and pleural effusions. Despite antibiotic therapy and supportive measures the patient's clinical condition deteriorated further.

At this point the case was referred for discussion at the multidisciplinary meeting. On review of biopsies taken in the ileum at the initial ileoscopy, the pathologist noticed eosinophilic intranuclear inclusions surrounded by a clear halo. This was suggestive of cytomegalovirus infection. Subsequent serological tests were positive for CMV immunoglobulin (Ig) M- and IgG-antibodies, a finding compatible with primary CMV infection. Polymerase chain reaction (PCR) performed on a blood sample was positive for CMV with a viral load of 1800 copies/ml. A human immunodeficiency virus (HIV) test was negative.

The diagnosis of CMV-colitis was made and therapy with gancyclovir started. Gradual clinical and biochemical improvement ensued and after two weeks no further fever was documented. The patient made a full recovery and was discharged one month after her second hospital admission.

Discussion

CMV colitis rarely occurs in an immunocompetent host (2). Immunocompetence is assumed in the absence of primary immunodeficiency, HIV-infection, organ transplantation, prior chemotherapy or immunosuppressive therapy (8).

A recent meta-analysis of case reports of CMV in immunocompetent hosts, published in the English language literature from 1980-2003, found only 44 such cases (6). The most common presentations were diarrhoea, gastrointestinal haemorrhage, fever and abdominal pain (2,8).

Endoscopic features in CMV colitis are non-specific and include patchy erythema, exudates, microerosions, diffusely oedematous mucosa, multiple mucosal erosions, pseudomembranes or deep ulcers and pseudotumors (1,4,5). Histological examination of tissue samples is considered the "gold standard" for diagnosis of organ involvement (1,4). On conventional haematoxylin and eosin-stained tissue, eosinophilic intranuclear inclusions, sometimes surrounded by a clear halo (the so called "owl's eye" inclusion) and smaller cytoplasmic inclusions in enlarged cells, are typical of CMV (1-4). Sensitivity varies due to sampling error (4). Immunohistochemistry with monoclonal antibodies directed against CMV immediate early antigen increases the diagnostic yield (1,4).

Positive serology, CMV-detection with culture (standard or shell vial) or any of the newer diagnostic techniques (PCR, antigen detection) only indicates CMV-infection and are not sufficient for the diagnosis of CMV organ involvement or CMV related disease (3,9). Within the transplant literature 'CMV-gastrointestinal disease' is defined as a combination of upper or lower gastrointestinal symptoms, mucosal lesions seen on endoscopy and compatible histological results on biopsy specimens from the gastrointestinal tract (9).

Both local mucosal damage and systemic conditions may predispose to, and are reported in association with CMV-colitis. As predisposition to CMV colitis, mucosal damage plays a role in inflammatory bowel disease (4,10,11), cow's milk allergy in infants (12) and Shigella colitis (13). A systemic predisposition is reported in several conditions including diabetes mellitus, lymphoproliferative and non-haematological malignancies, renal failure, autoimmune diseases and pregnancy (6).

In an immunocompetent host, spontaneous resolution of CMV-colitis is more likely, if the patient is younger then 55 years in the absence of other diseases. The rate of spontaneous remission is reported as 31.8% overall, but > 50% for patients less than 55 years of age (2,6). Severe complications including colonic haemorrhage necessitating resection, toxic mega- colon and colonic perforation have been described (8). A mortality rate of 31.8% is reported in patients older than 55 years (2,6). This suggests that selected patients who are young and otherwise healthy may not require antiviral therapy (6). In contrast, antiviral therapy with gancyclovir or foscarnet is mandatory in older patients and in patients with certain co-morbidities (2).

Our patient presented with non-specific gastrointestinal symptoms and was initially thought to have partial bowel obstruction due to adhesions. Endoscopic examination revealed patchy hyperaemia of colonic mucosa, throughout the colon. The diagnosis of CMV-colitis was suspected after review of the initial biopsies, with visualisation of typical cellular inclusions. She met the criteria for diagnosis of organ involvement (in this case the colon) with added evidence of a positive CMV-PCR on blood and the presence of IgM- and IgG-antibodies suggestive of primary infection. Despite her young age and the absence of any co-morbidity, her clinical condition deteriorated until antiviral therapy with gancyclovir, was initiated.

She had none of the known risk factors for CMV-colitis in an immunocompetent host. Biliopancreatic diversion surgery, with subsequent malnutrition and altered colonic mucosal integrity may have resulted in the development of CMV colitis in this case. This has not previously been reported.

In the seven months following the operation our patient lost 37.7 kilograms in weight. Admission values of albumin [1.96 g/dl (3.4-4.8)] and transferrin [36 mg/dl (200-360)], indicate a pronounced state of malnutrition. It is well known that malnutrition predisposes to a greater incidence of clinically apparent infection with increased morbidity and mortality (14,15). A wide range of immune defects are associated with malnutrition including cutaneous anergy, diminished T cell mitogen responses, decreased phagocytic cell function, impaired specific antibody responses (14,15).

Several consequences of biliopancreatic diversion may compromise colonic mucosal integrity. Malabsorption with malnutrition, exposure of colonic mucosa to excessive bile salts and bile acids and bacterial overgrowth, can all cause mucosal damage (16-18). These mucosal alterations can predispose to CMV infection of the colon.

In summary, CMV colitis in immunocompetent individuals, is rare but needs to be excluded in patients presenting with abdominal pain, diarrhoea, gastrointestinal haemorrhage or fever, in whom investigations are inconclusive. To our knowledge this report is the first in the English language literature, of CMV colitis following biliopancreatic diversion for obesity, in an otherwise healthy individual.

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