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Cytomegalovirus Colitis—A Severe Complication after Standard Chemotherapy

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We report on a case of cytomegalovirus (CMV) enterocolitis occurring in a 65-year-old patient after a first course of standard chemotherapy for a small cell lung carcinoma (SCLC). Colonic biopsies showed typical inclusion bodies, CMV IgM and IgG antibodies were found in the serum, and polymerase chain reaction for CMV-DNA was positive. Lymphopenia and diminished CD4 T-cell counts were observed. Diarrhoea ceased under ganciclovir treatment, the patient recovered, but died several months later of metastatic lung cancer. Significant immunosuppression leading to severe colitis by CMV infection or reactivation can occur after standard chemotherapy.

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Cytotoxic chemotherapy results in predictable haematological toxicity, and dose escalation is primarily limited by thrombocytopenia and neutropenia, often followed by bacterial infection. Immunosuppression induced by chemotherapy is less well characterized, with opportunistic infections appearing mainly after high-dose treatment or with certain new drugs directly affecting lymphocyte homeostasis (e.g. cladribine) (1). Here we describe the case of a 65-year-old patient presenting an unusual viral complication with cytomegalovirus (CMV) colitis diagnosed 2 weeks after a first course of standard chemotherapy for a small cell lung carcinoma (SCLC).

Case report. A 65-year-old man was admitted because of acute abdominal pain and diarrhoea. He was known for a limited stage small cell lung carcinoma of the right middle lobular bronchus, diagnosed one month earlier. The patient was enrolled in a clinical trial (2) and, accordingly, prophylactic cranial irradiation (total dose 15 Gy, days 1–5) was administered simultaneously with chest radiotherapy (total of 45 Gy: 1.5 Gy, twice daily from day 1 to day 19), and chemotherapy (cisplatin 100 mg/m^2, day 15 and etoposide 100 mg/m^2, day 15 to day 17). Eleven days after the end of chemotherapy, the patient developed fever, asthenia, nausea, vomiting, dysphagia, abdominal discomfort, non-bloody diarrhoea and arthralgia. On physical examination, a marked diffuse tenderness of the abdominal wall was in evidence, but the size of the liver and spleen was within normal limits and no abdominal mass was detected. The blood count showed a haematocrit of 30.8%, 5.5×10^9 white blood cells/L (with 73.0% neutrophils, 6.0% band forms, 4.0% lymphocytes and 11.0% monocytes) and 71×10^9 thrombocytes/L. The lymphopenia (774 lymphocytes/mm^3) was associated with a diminution of CD4-positive cells to 85 cells/mm^3 of blood (normal values >600 cells/mm^3). HIV1 and HIV2 serologies were negative. A CT scan of the abdomen showed a marked circumferential swelling of the entire colon, with relative sparing of the sigmoid (Fig. 1). Four stool cultures and a search for *Clostridium difficile* toxin were negative. The patient was given parenteral nutrition and imipenem, without clinical improvement. A coloscopy was performed, showing multiple ulcerations in the caecum, the right and the transverse colon, with a normal mucosa between the lesions and with normal haustra coli. Histologic examination of the biopsies revealed severe colitis with numerous CMV inclusion bodies present in the epithelial cells (Fig. 2). The patient had not received any CMV-positive blood transfusions, but, at admission, CMV antibodies were positive for IgG (MEIA 516 U Ac/ml) as well as IgM (MEIA 1.4 U Ac/ml) and CMV IgM was still positive one week later at 1.5 U Ac/ml. These tests were carried out using the AxSYM CMV IgG and IgM microparticle enzyme immunoassay (Abbot Laboratories, Diagnostic Divisions, Abbot Park, IL). U stands for antibodies unit (standardized for the test). The 1.4 U IgM/ml titre found in our patient was relatively low in comparison with IgM titres observed in immunocompetent hosts during primary infection.

CMV cultures performed on whole blood using the shell vial assay (3) remained negative, but CMV-DNA polymerase chain reaction (PCR) with frozen serum identified CMV-DNA at 21 copies/ml serum and thus confirmed CMV infection. The PCR was done using the Cobas Amplicor CMV Monitor platform with modifications as described elsewhere (4), whereby positive results correspond either to a systemic CMV reactivation or to a primary infection, and negative PCR results are found in healthy immunocompetent adults.

The patient was given a 2-week course of intravenous ganciclovir (10 mg/kg/day) with marked improvement of the abdominal

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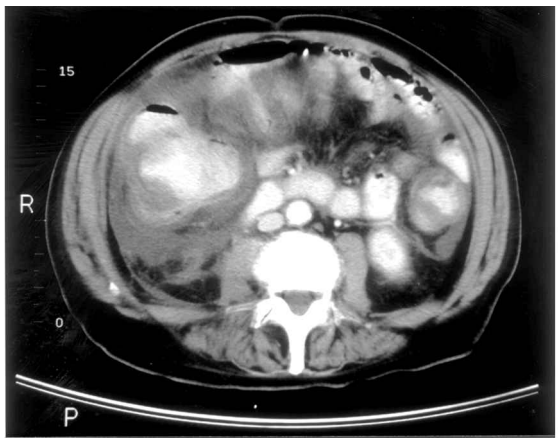

Fig. 1. CT scan showing important circumferential parietal thickening of the entire colon consistent with non-specific colitis.

symptoms and disappearance of fever. Diarrhoea had already ceased one week after initiation of treatment, parenteral nutrition could be discontinued and the patient was discharged. There was no sign of relapse at follow-up one month later.

Discussion. In this report we describe a case of proven CMV colitis following combined chemotherapy with cisplatin and etoposide. CMV colitis occurred in this 65-year-old patient shortly after the first cycle of chemotherapy and was associated with a significant decrease in the level of CD4+ T cells, although neutrophil counts were normal. The low CD4 count probably contributed to CMV infection or reactivation, as confirmed by the serum viraemia. This is consistent with the observation that in AIDS patients CMV complication occurs mainly in patients with a CD4 cell count of 100 or less (5). Interestingly, a recent study showed that the regeneration of CD4+ T cells after chemotherapy is delayed in adults compared with in young patients, which suggests that residual thymic function is helpful for rapid CD4+ T cell regeneration. Indeed, Mackall and co-workers found that, in children, the thymus could become enlarged after chemotherapy, resulting in the production of large numbers of naïve CD4+ T cells with CD45RA phenotype (6). The same group also showed that, after chemotherapy, thymus-independent pathways were able to regenerate substantial numbers of CD8+ but not CD4+ T cells, resulting in a prolonged T-cell subset imbalance in adults

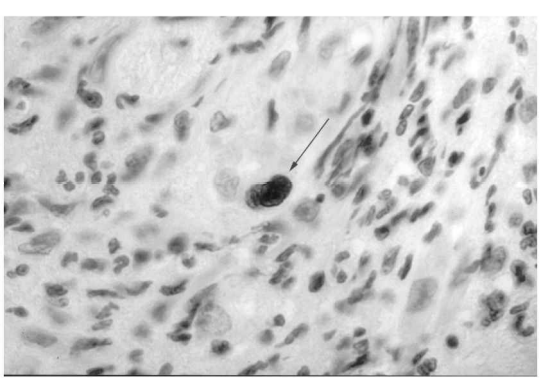

Fig. 2. Biopsy specimen of the right colon mucosa, obtained by colonoscopy. Regenerative colitis with marked ulceration. Several endothelial cells contain inclusion bodies typical of cytomegalovirus (CMV) (arrow) (Haematoxylin & Eosin, 500 ×).

(7). Minimal amounts of functional CD4+ (8) and of CD8+ cells (9) are an absolute requirement for the development of an effective anti-viral response. Certain patients with cancer, particularly elderly subjects, may have an increased sensitivity to chemotherapy with severe and/or prolonged lymphopenia, leading to opportunistic infections including CMV disease. In the case of colitis arising after chemotherapy, the possibility of an active CMV infection should be considered, to avoid severe complications of untreated CMV colitis. Whether in this patient we are dealing with a primary or the reactivation of a chronic persistent infection is not possible to determine, since pretreatment serology was not available and the presence of IgM anti-CMV antibodies has been described in both situations (10). Nevertheless, the relatively low IgM titres as well as the low viraemia indicate the likelihood of a reactivation and not a seroconversion.

Depending upon the clinical context, the manifestations of CMV infection in immunocompromised hosts are diverse, varying from interstitial pneumonia, leucopenia, chorioretinitis to colitis (11). CMV colitis is usually observed as a complication of HIV infection when the CD4+ cell count is low, or in cases of severe immunosuppression after solid organ or bone marrow transplantation (12–14). In these clinical conditions, the diagnosis of CMV is generally considered on the appearance of the first symptoms and signs, and appropriate treatment can be initiated rapidly. In contrast, CMV colitis in immunocompetent patients is rare. A retrospective review of the literature revealed only 14 cases in 1993 (15), and only a few additional cases have been reported until now (12, 13, 16, 17). Tissue injury such as simple erythema or ulcerative lesions can be observed throughout the digestive tract. The right colon is often damaged, leading to watery or bloody diarrhoea, abdominal pain with cramps and fever. Age could be a predisposing factor for CMV disease or colitis, since 10 of the 14 patients were older than 60 years (15). This could be the consequence of the natural decrease in immune competence observed with age, possibly associated with a decreased CD4 T-cell count, although this point was not specifically addressed in this study.

The low incidence of CMV colitis in immunocompetent individuals may explain why this diagnosis is delayed in patients receiving non-intensive chemotherapy. Isolated cases have been described after 5-fluoruracil and interferon-alpha (18) or radiochemotherapy for malignant astrocytoma (19). However, in these case reports no information is provided concerning the number of CD4+ and CD8+ T cells.

In summary, we have presented here the fourth case of CMV colitis appearing after standard chemotherapy. Our observation suggests that CMV colitis can complicate a primary CMV infection or a reactivation of a persistent infection in patients with low CD4+ T-cell counts.

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