Typhlitis as a complication of alemtuzumab therapy

Alemtuzumab is a humanized monoclonal antibody directed against lymphocytes through the CD-52 receptor, an antigen being found on > 95% of peripheral blood lymphocytes and monocytes, and to a smaller extent on granulocytes.[1-7] It is an effective immunotherapeutic agent in patients with malignancies such as non-Hodgkin lymphoma, B cell chronic lymphocytic leukemia and T cell prolymphocytic leukemia.[1-7] Adverse side effects are increasingly recognized in patients receiving alemtuzumab, mainly including fever, rigors, nausea/vomiting, skin rash; other severe alemtuzumab-related reactions have also been described, such as lymphopenia and neutropenia leading to both opportunistic (e.g. cytomegalovirus) and non-opportunistic infections.[7-10] Digestive complications have more rarely been described, i.e.: gastroenteritis and peritonitis.[10] We recently observed a case of particular interest as the patient with T cell prolymphocytic leukaemia treated with alemtuzumab, exhibited symptomatic reactivation of CMV infection and developed subsequently typhlitis

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A 64-year-old woman, with unremarkable previous medical history, was diagnosed with T cell prolymphocytic leukemia in 2006. She received alemtuzumab (30 mg subcutaneously thrice weekly) as first line chemotherapy; combined therapy of valaciclovir and trimethoprim-sulfamethoxazole, for anti-infective prophylaxis, was initiated simultaneously. Before institution of alemtuzumab therapy, full blood cell count disclosed the following: hemoglobin 12.7 g/dL, white blood cell count 88x10^9/L (absolute neutrophil count: 8.5x10^9/L, lymphocyte: 79.5x10^9/L, platelets: 400,000/mm^3). Two days after the 9th alemtuzumab injection, the patient exhibited an asymptomatic reactivation of cytomegalovirus (CMV) infection; she was given valganciclovir therapy for 21 days.

Three days after the 16th alemtuzumab injection, she was admitted with a 2-day history of abdominal pain. On admission, the patient was febrile (38°5C); physical examination showed a tenderness in the appendicular area. Laboratory findings disclosed: erythrocyte sedimentation rate 70 mm/hour, C-reactive protein 172 mg/L, hemoglobin 11.6 g/dL, white blood cell count 1.9x10^9/L (absolute neutrophil count: 0.8x10^9/L, lymphocyte: 0.4x10^9/L); liver and renal tests were normal. Blood cultures, urinalysis and stool cultures yielded negative results. Viral serologies (Epstein-Barr, *Herpes simplex* virus, human immunodeficiency virus) were negative. Abdominal radiograph was normal. Abdominal CT-scan revealed: cecal dilatation, circumferential thickening of the cecal wall as well as inflammatory stranding of the adjacent mesenteric fat. Colonoscopy showed erosions involving the cecum; multiple cecal biopsy specimens of the lesions demonstrated no evidence of CMV infection: 1) cytomegalic cells and *owl's eye* nuclear inclusion bodies were absent; 2) *in situ* DNA hydridization was negative for CMV. Histological analysis of both cecal and colonic biopsy specimens further showed: 1) no malignant cells; and 2) no proliferation of T-cell lymphocytes and pro-lymphocytes. Immunochemistry was also negative for: CD52, CD2, CD3, CD5, CD7 and CD25. A diagnosis of typhlitis related to alemtuzumab therapy was made in our patient, with favorable outcome after institution of antibiotic therapy (ceftriaxon, metronidazole) and hydroelectrolytic rehydratation.

Typhlitis is defined as a necrotizing inflammation of the colon, occurring mainly in neutropenic patients receiving chemotherapy for leukemia.[7,11] Typhlitis has indeed been described in patients treated with various cytotoxic drugs, such as vincristin, adriamycin, cytarabin, 6-mercaptopurin, cyclophosphamide, taxans or camptothecin analogs.[7,12] However, we report, to the best of our knowledge, the first case of alemtuzumab-related typhlitis. In this instance, the diagnosis of alemtuzumab-associated typhlitis could reasonably be made for the following reasons: 1) there was a temporal relationship between alemtuzumab administration and the onset of typhlitis; 2) histological analysis of both cecal and colonic biopsy specimens excluded malignancy, especially intestinal infiltration by T cell prolymphocytes. These latter data indicates that cecal involvement related to T cell prolymphocytic leukemia could be excluded in our patient. Few authors have, in fact, reported previously small intestinal infiltration by T prolymphocytes in a patient with T cell prolymphocytic leukemia;[13] and 3) improvement of typhlitis took place after stopping alemtuzumab therapy.

The exact pathological mechanisms of typhlitis due to alemtuzumab are unknown. However, severe neutropenia is the main underlying factor of typhlitis in patients receiving chemotherapy for acute leukemia.[7,11,12] In essence, alemtuzumab induces prolonged immunosuppresion, leading to lymphopenia and neutropenia.[1-6] In a series of 76 patients with T cell prolymphocytic leukemia receiving alemtuzumab therapy, neutropenia therefore occurred in 52% of cases;[2] severe neutropenia (<0.5x10^9/L) was also encountered in as high as 20 to 30% of these patients, being usually transient.[1,4-6] In this instance, typhlitis could therefore be attributed to the combination of neutropenia and alemtuzumab-induced intestinal mucositis. Nevertheless, other investigators have also speculated that cytotoxic drugs-associated typhlitis may be related to other pathological mechanisms. Firstly, cytotoxic drugs may be responsible for ischemic cecal mucosal injury.[7,11,12] Although rare, vascular impairment (i.e.: myocardial infarction, coronary acute ischemia, congestive heart failure, atrial fibrillation) has, in fact, been described in alemtuzumab-treated patients.[1,3,10,14-16] Interestingly, all cardiovascular events occurred in patients with T-cell malignancies;[1,3,10,14-16] the association between alemtuzumab-induced vascular adverse events and T-cell malignancies has been suggested to be associated by cytokine-release (e.g.: serum tumor necrosis factor, interferon-γ, interleukin 6) syndrome, leading to vasospasm.[3,14,15] Secondly, alemtuzumab-associated immunosuppression create conditions favorable for bacterial overgrowth and translocation, that are further considered to be favoring factors of typhlitis' s onset.[17,18] In our patient, asymptomatic reactivation of CMV infection may have also decreased host defense and increased alemtuzumab-related digestive toxicity. However, no definite conclusion can be drawn for an etiological role of CMV in our patient, as she exhibited concomitantly neutropenia.

Finally, our findings underline that a diagnosis of typhlitis should be considered in alemtuzumab-treated patients with hematologic disorder exhibiting febrile abdominal distress, especially if neutropenia is present, leading to appropriate diagnosis and management at an early stage.

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