Panhypogammaglobulinemia associated with bronchiectasis in the present case are classic findings of CVID that explain the repeated episodes of pneumonia. Unresponsiveness to diarrhea was initially thought to be a distal UC, which, unusually, was hard to control; however, the almost normal features on endoscopic (colonoscopy) and histological controls associated with the rapid and sustained positive response after the first gamma globulin infusion, allowing the withdrawal of the steroid and azathioprine, suggest that the gastrointestinal disorders were probably caused by the underlying overlap immunodeficiency process.

Besides the present case, we also have 2 others with CVID among ≈150 patients whose cases we have followed in our IBD outpatient unit. One of them has ileocolitis CD without symptoms of immunodeficiency: the diagnosis was made just by chance during immunological screening. The second patient was initially diagnosed with classic CIVD and was kept on regular gammaglobulin infusions. Later, the investigation of gastrointestinal symptoms resulted in the detection of histological IC. More recently he has developed liver and biliary enzyme elevations (primary sclerosing cholangitis?), as well as splenomegaly and mesenteric lymph nodes (lymphoma?) that are under investigation.

These cases, particularly the 1 described in depth here, highlight the need to be aware of the possibility of immunodeficiency disorders in IBD patients (as the cause or as a consequence, we do not know yet), who may develop unusual responses to common therapeutic applications, or an overlap process of recurrent infections, or any autoimmune disease, or cancer.

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Posttransplant Lymphoproliferative Disorders in Patients with IBD on Immunosuppressive Treatment

To the Editor:

We read with great interest the article by San Roman et al[1] in the *Journal of Crohn's & Colitis* (JCC) reporting on a case of a primary rectal large cell B-lymphoma associated with Epstein–Barr virus (EBV) infection, occurring in a patient with ulcerative colitis (UC) treated with azathioprine and infliximab.

The occurrence of posttransplant lymphoproliferative disorders (PTLDs) in patients with inflammatory bowel disease (IBD) treated with immunosuppressives (IS) has been a matter of great concern to us in the last 5 years, as we managed 3 cases of PTLD in patients with IBD, all on azathioprine. At our department, a referral center for IBD in Portugal, over 700 patients are regularly seen as in- or outpatients. About 56% and 20% of our patients with Crohn's disease (CD) and UC, respectively, are currently on IS, mainly with azathioprine or 6-mercaptopurine (6-MP), with 22% and 2%, in the same order, also being treated with infliximab. We had no other cases of lymphoma, namely, non-Hodgkin's, Hodgkin's, or other rare types.

The first case occurred in 2003 in a 34-year-old female with a 6-year steroid-dependent extensive UC (E3). She was treated with azathioprine (2.0–3.3 mg/kg/day) for 5 years, except for a short period in 1999 when she had a unique infliximab infusion and was on mycophenolate mofetil (20 mg/kg/day)

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for 6 months. In 2003 she was admitted for a severe flare (S3) with concomitant oral candidiasis, herpetic esophagitis, and perirectal abscess related to a previously known rectovaginal fistula. She was first stabilized with medical treatment and then proposed for proctocolectomy. The resection specimen revealed, along with a low-activity ulcerative pancolitis, a monotonous towel-spreading lymphoid population deeply infiltrating the rectal wall up to the perirectal fat. It consisted mainly of pleomorphic B cells (CD20 and CD30+), some marking positively for EBV (LMP1+). The final diagnosis was a diffuse large cell B-lymphoma associated with EBV. The second case emerged in a 35-year-old male with an 18-year left-sided (E2) UC, treated chronically with aminosalicylates (5-ASA, 1.5 g/day) and with azathioprine (1.4 mg/kg/day) for 1 year. The disease had had a generally benign course until 1 year before, when lesions of pioderma gangrenosum appeared on his left leg and azathioprine was started. In 2005 he was admitted for hematochezia, abdominal pain, and low-grade fever (37.5°C) starting the day before (S2). Colonoscopy showed an ulcerated circumferential nonstenosing lesion at the sigmoid colon, with histology showing a lymphoid population similar to that described in the first case. Total proctocolectomy was performed and an EBV-positive diffuse large cell B-lymphoma of the sigmoid colon was confirmed. The third case also occurred in 2005, in a 22-year-old female with a steroid-dependent A1, L3, B2 CD, treated with infliximab (5 mg/kg every 8 weeks) for 2 years and azathioprine (2.0–2.2 mg/kg/day) for 9 years. She had an asymptomatic stenosis at the splenic flexure known for 7 years, regularly evaluated on colonoscopy. In 2005 histological examination of the stenosis revealed an EBV-positive polymorphic polyclonal lympho-plasmacythoid population which was classified as an early PTLD, subtype infectious mononucleosis (IM)-like. This finding prompted suspension of azathioprine. Biopsies taken 2 months later showed only chronic colitis features and PTLD appeared to have suffered regression. However, new sampling taken 8 months after azathioprine stoppage again depicted an EBV-positive polymorphic lymphoid population, now with numerous blast cells suggesting progression to polymorphic lymphoma. Resection of the splenic flexure was undertaken. Surprisingly, the resection specimen did not confirm the latter findings, yet showed features of a more benign early PTLD, subtype plasmacytic hyperplasia. In all 3 cases no spreading disease was found on resected nodes, bone marrow examination, and computed tomography (CT) scanning of the chest, abdomen, and pelvis. All patients are regularly seen on hematology and sustain remission of the disease. None resumed azathioprine. The patient reported last is currently on infliximab and in remission of CD.

The type of lymphoma reported by San Roman et al and in the first 2 cases reported here is one of the malignant PTLDs according to the World Health Organization classification.[2–4] As discussed by San Roman et al, they comprise benign and malignant EBV-driven lymphoid proliferations developing as a consequence of IS treatment in allograft recipients[2–4] that were also described in patients with rheumatoid arthritis (RA) treated with methotrexate.[1] We emphasize that these lesions had been reported in patients with IBD as well, specifically in those treated with azathioprine or 6-MP.[5,6] Moreover, a recent cohort study implicated such medications in the doubling of EBV-associated lymphomas, with an absolute risk of PTLD of 0.5% for patients with IBD treated with azathioprine or 6-MP.[7] Yet even if this figure was reproducible for other populations, it would be of little significance when compared to the benefit obtained with these drugs.[8] PTLDs are poorly understood lesions both in transplant recipients and in RA and IBD patients. Staging and treatment options are mostly adapted from non-Hodgkin's lymphoma, with the major exception being that a reduction on the IS level is the mainstay of treatment, sometimes inducing remission of early PTLD by itself.[2,3] This latter event occurred in the third case reported, although evidence of regression warranted surgery. Indeed, despite the confounding 8-month biopsies suggesting progression to lymphoma, the final diagnosis (plasmacytic hyperplasia PTLD) is believed to be more benign than IM-like PTLD, which may occasionally progress to lymphoma.[3] Likewise, regression of PTLD to a more benign type occurred after IS stoppage on San Roman et al's report. However, we should stress that polymorphic hyperplasia, also termed polymorphic B-lymphoma, does not always have a benign behavior, at least in the transplant setting. They have an intermediate behavior and have a variable response to IS reduction.[3] Thus, although we generally agree that suspension of IS and surgery seemed the most correct approach for the reported case, we diverge for the absolutely benign nature of the lesion found in the resection specimen.

In conclusion, our experience of lymphoma occurring in IBD is limited to 3 (4.5%) cases of PTLD in patients on azathioprine for at least 1 year. PTLDs are poorly understood diseases. Classification, treatment options, and prognostic considerations are still based on limited knowledge obtained in transplant recipients who have major differences compared to patients with IBD. As such, we propose that these patients should not only be *treated* with a multidisciplinary approach as proposed by San Roman et al, but should also be *managed* by a multidisciplinary team. e.g., pathologists, gastroenterologists, surgeons, hematologists/oncologists, and therapeutic radiation experts.

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Infliximab for Severe Gastrointestinal Bleeding in Crohn's Disease

To the Editor:

Severe lower gastrointestinal (GI) bleeding is a rare but potentially life-threatening complication of Crohn's disease (CD), occurring in 0.9% to 6% of cases.[1–4] Although bleeding can occur in a flare-up of the disease, patients with CD sometimes complain of the sudden onset of bloody stool without any deterioration of the other symptoms.[1,2] When the bleeding site can be identified by colonoscopy, bleeding is mostly attributable to colonic ulcers or ulcerated areas.[1] We describe a patient with CD presenting with severe lower GI bleeding in whom infliximab induced rapid mucosal healing and prevented recurrent bleeding.

A 16-year-old girl, who had been suffering from CD involving the colon for 1 year, was referred to our hospital because of bloody stool and lower abdominal pain. CD was well controlled with mesalazine (2250 mg/day) until 1 month before this admission. Physical examination on admission showed slight pain and tenderness at the periumbilical region without muscular guarding. Rectal examination revealed fresh bloody stool. Bowel sounds were normal. Laboratory values were as follows: white blood cell count, 15,400/mm^3; hematocrit, 37.5%; hemoglobin, 12.0 g/dL; albumin, 3.3 g/dL; and C-reactive protein, 5.36 mg/dL. Colonoscopy revealed multiple large and deep ulcers in the colon (Fig. 1a). Small intestinal series showed no abnormalities. We treated her with an increased dose of mesalazine (3000 mg/day) and prednisolone (40 mg/day) on total parenteral nutrition, resulting in rapid improvement of the symptoms.

Eight days later the patient suddenly lapsed into hemorrhagic shock because of the sudden onset of massive bloody stool and her hemoglobin dropped to 5.2 g/dL. Although urgent angiography after 6 units of blood transfusion could not detect a bleeding site, GI bleeding scintigraphy disclosed an uptake at the sigmoid colon. Colonoscopy showed diffuse mucosal inflammation with multiple deep ulcers in the colon. Because we could not discover the definite bleeding site, and colonic mucosa did not improve after therapy, we treated her with a single infusion of infliximab (5 mg/kg) to achieve mucosal healing and to stop and prevent the bleeding. Three days after the infliximab infusion her symptoms disappeared, and colonoscopy showed rapid improvement of mucosal inflammation. One month later mucosal healing was observed without colonic strictures (Fig. 1b). Although the patient refused the maintenance therapy with infliximab, no recurrent bleeding has occurred for 1 year.

The management of severe GI bleeding in CD is a therapeutic challenge.[1–3] Although several approaches such as medical therapy, endoscopic treatment, angiographic intervention, and surgical resection have been attempted to control bleeding, multiple and diffuse bleeding as in our patient does not allow for these approaches, and the recurrence rate of bleeding is high.[1–4] Because most bleeding originates from severe mucosal lesions such as colonic ulcers or ulcerated areas, achieving mucosal healing is the therapeutic goal to prevent recurrent bleeding.[1,3] This goal can be obtained by surgical resection, but medical therapy of CD with conventional drugs such as steroids and immunomodulators does not have a consistent endoscopic improvement.[1]

Recently, several studies reported that the antitumor necrosis factor-alpha antibody, infliximab, is effective for refractory CD.[2,5] Although repeated infliximab infusions can induce rapid and sustained mucosal healing,[1,5,6] there is little evidence on whether infliximab infusion is effective for acute and massive GI bleeding in CD. In our patient, steroids therapy was ineffective, and recurrent bleeding occurred because of persistent mucosal inflammation with multiple ulcers. The infusion of infliximab stopped severe GI bleeding, and promoted rapid mucosal healing resulting in no recurrent bleeding. Because this therapy induces rapid effects, and may avoid surgical resection for uncontrolled bleeding, we believe that infliximab therapy should be considered for acute and massive GI bleeding in CD before surgery.

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