Association of Intestinal Malignant Lymphoma and Ulcerative Colitis

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Abstract

A 42-year-old woman with refractory ulcerative colitis (UC) developed ascites, pleural effusion, pretibial edema and severe anemia. Colonofiberscopic examination showed a bulky submucosal tumor in the sigmoid colon, which was histologically diagnosed as malignant lymphoma (diffuse large, B cell type). The lymphoma was resistant to chemotherapy. Autologous peripheral blood stem cell transplantation (PBSCT) was effective; however, she died of severe infection after the second PBSCT. Although the association of intestinal lymphoma with UC is rare, lymphoma should be taken into consideration when the clinical course of UC is atypical or when UC is refractory to therapy. (Internal Medicine 42: 1183-1187, 2003)

Key words: anemia, ascites, muco-bloody stool, peripheral blood stem cell transplantation

Introduction

The association between ulcerative colitis (UC) and intestinal malignant lymphoma is rare. Nugent et al found only 5 cases of malignant lymphoma among 2,500 patients with UC (1). Greenstein et al reported that 5 of 1,156 UC patients had malignant lymphoma (2). In addition, they also reported 4 lymphoma patients among 1,480 patients with Crohn’s disease (2), indicating rare development of intestinal lymphoma in inflammatory bowel diseases. The symptoms of intestinal lymphoma are similar to those of UC (3). Diagnosis of the lymphoma thus tends to be made in advanced stage. In this report, we describe a patient who developed intestinal malignant lymphoma after a long-term course of UC.

Case Report

A 42-year-old woman was admitted to our hospital because of dyspnea, abdominal distension, and pretibial edema. In her past history, she had undergone appendectomy and surgical removal of a right renal tumor at ages 14 and 17 years, respectively. In the 10 years prior to admission she had had muco-bloody stools about 8 times a day, but did not seek any medical examination or care during this time frame. Six months before admission, the muco-bloody stools became more frequent and she was admitted to a hospital in May 1999. A blood test showed severe anemia (hemoglobin concentration 5.5 g/dl). The barium enema examination showed the disappearance of haustra coli and marked pseudopolyposis throughout the colon (Fig. 1). She was diagnosed with ulcerative colitis (UC) based on the findings of the barium enema and colonofiberscopy, and histologic pictures of biopsy specimens. She was given mesalazine (1.5 g/day) orally, but the symptoms did not improve and she visited the outpatient department of gastroenterology in our hospital 2 months later. Colonofiberscopic examination from the rectum to the sigmoid colon disclosed marked ulceration, erosive lesions, many pseudopolyposis, and conspicuous visualization of blood vessels on the mucosa (Fig. 2). Histological picture of the sigmoid colon mucosa demonstrated marked inflammatory cell infiltration in the submucosal region, atrophic crypts, crypt abscess, and dense lymphocyte infiltration in some areas (Fig. 3A, B). The lymphocyte infiltration was most conspicuous in the base of ulcer and less frequent in erosive areas. Based on these findings again a diagnosis of UC was made. Salazosulfapyridine (3,000 mg/day) was administrated (July 1999), and 2 months later (September), prednisolone (30 to 15 mg/day) was combined. However, her condition was unchanged. In October 1999, salazosulfapyridine was replaced with mesalazine without any subsequent improvement of the symptoms. In December 1999, she noticed a decrease in the frequency of urination,
weight gain, abdominal distension, and pretibial edema. She was admitted as an emergency case because of dyspnea and severe malaise on January 8, 2000.

Physically, she had a high fever over 38°C, which continued until the initiation of chemotherapy. Palpebral conjunctivae were severely anemic and the heart rate was as high as 108/min. The abdomen was markedly distended and pitting edema was noted in the legs. Superficial lymph node swelling was not observed. Blood pressure was 86/54 mmHg. Hematological examination revealed a white cell count of 7.1×10⁹/l with 91% neutrophils, 1% basophils, 3% lymphocytes, and 5% monocytes, hemoglobin concentration of 5.6 g/dl, and a platelet count of 577×10⁹/l. Serum total protein and albumin levels were as low as 4.1 and 1.9 g/dl, respectively. C-reactive protein (CRP) was elevated to 7.2 mg/dl.
Serum lactate dehydrogenase (LDH) level was within normal limits (437 IU/l). The concentration of soluble interleukin-2 receptor was also elevated to 3,000 unit/ml (normally below 483). Chest X-ray examination showed bilateral pleural effusion and abdominal ultrasound revealed massive ascites and intrahepatic tumors. Repeated cytological examinations of the ascites (yellowish and not bloody) revealed no malignant cells. Fecal culture for microorganisms was negative. Colonofiberscopic examination revealed a bulky submucosal tumor with ulceration in the sigmoid colon (Fig. 4). A biopsy specimen of the tumor showed infiltration of large atypical lymphocytes, and a histological diagnosis of diffuse large cell type malignant lymphoma was made (Fig. 5A, B). These cells were positive for leukocyte common antigen (CD45) and L-26 (CD20) staining but negative for UCHL-1 (CD45RO) staining, indicating that the lymphoma was of B cell nature. Abdominal CT scanning revealed a bulky mass involving the sigmoid colon and the rectum, multiple metastatic lesions in the liver, and paraaortic lymph node swelling. Galium scintigraphy showed strong uptake in the sigmoid colon, paraaortic lymph nodes, and liver lesions. A bone marrow aspirate did not show any abnormal cells. Although the lymphoma was widely spread in the abdominal cavity, we diagnosed it as sigmoid colon-origin because the tumor was the submucosal type, and because no abdominal tumor lesions were seen on CT scanning performed in May 1999. According to the international prognostic index (4), this patient was classified as high intermediate risk because of stage IV disease and grade 4 performance status.

We started a combination chemotherapy with vincristine, cyclophosphamide, methylprednisolone, and adriamycin (VEPA) on January 20, 2000, and repeated this chemotherapy on February 3. After 2 courses of VEPA chemotherapy, the fever, ascites, and pretibial edema almost disappeared, although the sigmoid colon mass and a number of mesentericum tumors became palpable as the ascites improved. The frequency of the muco-bloody stool markedly decreased after the chemotherapy. On February 14 she developed vesicorectal fistula and underwent a surgical operation to make a colostomy at the descending colon to prevent urinary tract infection on February 25. The third VEPA chemo-

Figure 4. Colonofiberscopic examination performed January 2000. A bulky submucosal tumor with ulceration in the sigmoid colon is seen.

Figure 5. A) Histological picture of the submucosal tumor in the sigmoid colon (January 2000). The tissue is densely infiltrated with abnormal cells and a diagnosis of diffuse large cell type malignant lymphoma was made (HE stain, ×400). B) Pathological findings of the specimen taken near the submucosal tumor. The tissue is granulomatous with neutrophil infiltration. Lymphoma cells are occasionally seen (arrows) (HE stain, ×200).
therapy was postponed until March 24. The lymphoma became active including recurrent ascites during this time lag and the third chemotherapy was less effective than the previous two. The chemotherapy was changed to a weekly regimen including cyclophosphamide, adriamycin, methotrexate, bleomycin, vincristine, etoposide, ifosphamide, and prednisolone (CAMBO-VIP). However, the lymphoma was also resistant to this treatment and we discontinued this after 6 weeks. Then we performed salvage chemotherapy with cisplatin, etoposide, and cytarabine (E-SHAP) with a transient effect. However, we tried to collect peripheral blood stem cells (PBSC) during the recovery phase of the bone marrow function, and obtained 4.26x10^6 CD34-positive (CD34+) cells/kg after 2 courses of E-SHAP. The patient underwent autologous PBSC transplantation with 2.16x10^6 CD34+ cells/kg on August 16, 2000 because of chemotherapy-resistant and rapid-growing disease. The conditioning regimen consisted of high-dose ranimustin, cytarabine, and melphalan. The transplantation was successful without any complications; the tumors almost disappeared except for remaining paraaortic lymph nodes. The muco-bloody stools and diarrhea almost disappeared as previous studies have described (5, 6). Because of residual paraaortic nodes, we proceeded with a second PBSC transplantation with 2.1x10^6 CD34+ cells/kg with the same conditioning regimen on September 11. The patient, however, developed methicillin-resistant staphylococcus aureus (MRSA) pneumonia and septicemia during the neutropenic period and died on September 26.

An autopsy showed generalized pulmonary abscesses with diffuse alveolar damage, focal necrosis of the liver, and so-called shock kidneys and pancreas. No identifiable lymphoma presented in the abdominal cavity or other organs/tissues on either macroscopic or microscopic examinations. Regarding UC, there were a few old ulcers of the recto-sigmoid colon without fresh inflammation, and marked catarrhal inflammation affecting the remaining part of the colon. Neither crypt abscess nor cryptitis was identified.

**Discussion**

In this patient, the interval between the time of diagnosis of UC and that of lymphoma diagnosis was short, and the symptoms of UC were similar to those of intestinal lymphoma (3, 7). The existence of preceding UC should thus be discussed. However, we consider that this case was intestinal lymphoma which developed in the course of preexistent UC for the following reasons. 1. The patient had muco-bloody stools for about 10 years before the diagnosis of lymphoma. A long period of the muco-bloody stools is common in UC but unlikely in intestinal lymphoma. 2. The findings of barium-enema, colonfiberscopy, and histological examination, which were performed in May and July 1999, were all compatible with UC, including the crypt abscess which is a characteristic histological finding of UC. 3. The autopsy showed the disappearance of haustra coli, a few old ulcers in the recto-sigmoid colon, and microscopically, possible chronic inflammation in the same portion.

Regarding the clinicopathological features of UC-associated lymphoma, Abulafi et al reported that 52.4% of the lymphomas originated in the rectum in contrast to 60% in the cecum in case of sole intestinal lymphoma (3). In the present patient, the lymphoma developed in sigmoid colon near the rectum. Lenzen et al reported that the mean duration from the onset of UC to the development of lymphoma is 12 years (8). In our patient, the duration was 10 years. The subtype of lymphoma in the UC-associated intestinal lymphoma was mostly diffuse large, B cell type (7, 9), as with our case.

When did the lymphoma develop in our patient? Abdominal CT scan and ultrasound examination performed in May 1999 did not show any tumoral lesion in the abdominal cavity. We reviewed an H.E. preparation of the biopsy specimen (mucosa of the sigmoid colon) taken at the same time and noted dense infiltration of medium-sized lymphocytes, in addition to chronic inflammation. Colonfiberscopic examination performed in July 1999 showed small nodular lesions in the mucosa of the sigmoid colon (Fig. 2), and microscopically, again dense lymphocyte infiltration was observed (Fig. 3A). On re-examination of this biopsy specimen, these lymphocytes were positive for L-26 but negative for UCHL-1 staining, although these findings did not establish a distinct diagnosis of malignant lymphoma. Cornes et al and Abulafi et al stated that association of lymphoma or future development of lymphoma should be taken into consideration when marked lymphocyte infiltration is observed in the intestinal mucosa of UC patients (3, 8, 10). From this point of view, minute lymphoma might have already developed in the sigmoid colon in our patient in May 1999. This might also be the reason why the histological picture of the mucosa (Fig. 2) was rather atypical as UC.

The mechanism of lymphoma development in UC is unclear. Previous reports, however, showed that intestinal lymphoma tends to arise from areas involved in intense and long-lasting inflammation, such as the rectum (3). As a possible mechanism, therefore, chronic inflammation may cause polyclonal lymphocyte activation and subsequent proliferation. Long-term lymphocyte activation and proliferation may generate mutated lymphocytes and one of them may acquire a growth advantage and ultimately manifest itself as a malignant lymphoma.

In conclusion, although the association of intestinal lymphoma and UC is rare, underlying lymphoma or future development of lymphoma should be taken into consideration when UC is refractory to treatment, the clinical course of UC is atypical, or when lymphocyte infiltration is conspicuous in biopsy specimens from UC patients.

**References**


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