Malignant lymphoma complicating ulcerative colitis

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Abstract

Carcinoma of the colon as a complication of chronic ulcerative colitis is relatively common, whereas malignant lymphoma is apparently rare. We report two cases of patients with malignant lymphoma complicating ulcerative colitis, a CD 30 + T-cell lymphoma of the intestine and a low grade B-cell non-Hodgkin's lymphoma of MALT type. It is important to be aware of the possibility of malignant lymphoma in ulcerative colitis in order to evaluate correctly any lymphoid infiltrate seen in a biopsy, expecially when anti-inflammatory treatment seems to be ineffective or when symptoms change.
Key words: Malignant lymphoma, ulcerative colitis.

Introduction

Although colonic carcinoma is the major longterm complication of ulcerative colitis, primary lymphoma of the small and large intestine has also been shown to be associated with long-standing ulcerative colitis. Diagnosis can be masked and correct treatment may be delayed, because clinical symptoms of chronic inflammatory bowel disease and malignant lymphoma can be very similar with an alteration in bowel habit, passage of blood rectally or an abdominal-rectal mass. Surgical excision of lymphoma, either alone or in combination with radiotherapy, remains the mainstay of treatment, at stage I and II. Radiotherapy or chemotherapy, or both may also be of use, as adjuvant treatment, for cases with advanced stage and high grade lymphomas; often, after chemotherapy, clinical symptoms improve and lymphocitic infiltrates disappeas. We report two cases of patients suffering of ulcerative colitis, in which diagnosis of associated malignant lymphoma was made after operation.

Patients and methods

Case 1: A 67 year old woman presented in 1996 with abdominal pain associated with bloody diarrhoea. Laboratory examinations showed only anaemia (10,5 mg/dl) while blood cell count, immunoglobulin values and other parameters of inflammatory activity were normal. Chest x-ray, abdominal ultrasound and repeat stool cultures were negative.

Endoscopy with histological examination showed chronic inflammatory bowel disease of the whole colon with tipical signs of ulcerative colitis moderatly active. She discarged from hospital in good conditions after nine days of total parenteral therapy associated with corticosteroids and azathioprine. During the following period she remained well with specific therapy and underwent regular endoscopy with biopsy which did not show aggravation of ulcerative colitis. In december 1998 the patient was readmitted because of weight loss (-8 kg), high fever (> 38 °C), nausea with vomiting and important rectal bleeding; the exams showed important anemia (7,8 g/dl), high inflammatory activity (white blood cells count of 23500/ul, fibrinogenous 740 mg/dl, VES 41 mm), mild hypoproteinemia (total protein 5,2 g/dl, albumin 3,1 g/dl), and marked elevation of LDH (716 U/L). A new endoscopy showed a progressive worsening of the ulcerative colitis; histological examination showed acute ulcerative colitis with ulcers of mucosa, reactive macrofages, polymorphonuclear inflammatory infiltration of basalis lamina and thrombosis of vascular vessels; also T-lymphocytic infiltration of mucosa and submucosa was evident with presence of blastes. After five days stercoral peritonitis recurred with massive melena and shock; the patient underwent emergency laparotomy, which disclosed hemorrhage from colonic ulcers and multiple perforations

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of colon-rectum. An ileostomy was performed after total proctocolectomy; no abnormality of liver, spleen or abdominal lymph nodes was seen. Histological examination of colon-rectum identified high grade angiocentric T-cell lymphoma of the intestine with atipical cells CD 30 +; extensive ulcerations of colon-rectum were present and Peyer's patch involvement was confirmed microscopically. The patient was admitted in Intensive Care in poor general conditions; after four days she underwent new laparotomy for ileal perforation and an ileal resection of 7 centimeters was performed. However the patient died after 11 days for acute myocardiac infarct. Histologic examination showed foci of lymphomatous infiltration into the mucosa and submucosa of the whole ileum and into regional lymph nodes. No systemic infiltration of the atypical T-cells were seen.

Case 2: A 54 year old woman suffering from ulcerative colitis of the whole colon from 1979, presented in 1991 for ineffective longterm treatment with corticosteroids, azathioprine, and sulphasalazine and persistent bloody diarrhoea from one month (7-8 stools). Abdomen was aching to palpation with normal peristalsis, no hepatosplenomegaly; rectal examination revealed thickening of the rectal wall and presence of blood. Laboratoy examinations showed important anemia (7,4 g/dl), and inflammatory activity (white blood cells count of 22000/ul, fibrinogenous 695 mg/dl, and VES 38 mm). Endoscopy showed features of an acute ulcerative colitis of the whole colon. She underwent colectomy with ileostomy; she discarged after 12 days in good general conditions. Histological examination showed lymphocytic infiltration forming lymphoepitelial lesions, evidence for the presence of low grade non-Hodgkin's lymphoma of MALT-type, with infiltration of regional lymph nodes. Further immunocytochemistry confirmed this to be a B-cell lymphoma Histological examination of the bone marrow did not show infiltration; plasma cells containg IgM, IgG, IgA, and lambda light chains, while the immunological typing of peripheral lymphocitic cells showed CD 3 +, (+ 60,5%), CD 4 + (+ 39,9%), CD 8 + (+ 26.1%), CD 19+ (+ 13.1%), CD 25 + (+ 16.6%), and CD4/CD8 = 1,53. Chest x-ray, contrast radiography of the small intestine, thoracic and abdominal computed tomography and scintigraphy of the skeleton were normal. After the patient received six chemotherapeutic courses according to the CVP protocol: cyclophosphamide 400 mg/m2, vincristine 1,4 mg/m2, and prednisone 60 mg/m2. After chemotherapy a rectal biopsy confirmed the presence of malignant lymphoma into the rectum, while no systemic infiltration was seen; abdominal computed tomography showed normal size of spleen and normal lymph nodes. The histological examination of bone marrow did not show infiltration. The patient underwent proctectomy one year later after first operation. Follow-up after 6 years is regular. No further treatment has been given and the patient shows no evidence of lymphoma.

Discussion

Colonic adenocarcinoma is recognised complication of chronic ulcerative colitis with a 9% risk at 25 years in an extensive colitis (1). Less is known about the association between this disease and primary gastrointestinal lymphoma, a rare condition constituting only 1-4% of all gastrointestinal malignancies (2). The gastrointestinal tract is the commonest site of extranodal lymphomas (3). The stomach is the most commonly involved, while colorectal lymphoma comprises between 10 and 20% of primary gut lymphoma in the larger publisher series (4-7,2). The small number of reported cases makes it difficult to prove a definite association between ulcerative colitis and colonic lymphoma, although various mechanisms of pathogenesis have been postuled; these include repeated episodes of lymphoid hyperplasia with neoplastic growth factors of mucosal lymphocites (8) and abnormalities of the reticuloendothelial system with prolonged stimuli of the MALT tissue (9, 10). Another factor to be considered in these patients is the prolonged use of corticosteriod or azathioprine; a relation has been established between immunosoppressive drug treatment and an increased incidence of malignant tumours in patients with acquired immune deficiency syndrome or after organ transplantation (11-13). These patients tended to have multiple long-standing colitis (38% v 10%, except for malignant lymphomatous polyposis), left sided (compared with the caecal predominance in sporadic lymphoma), high grade (80% v 35%) in an advanced stage at diagnosis, being modified Dukes B and C (14). Many of such primary gastrointestinal lymphomas express B cell surface phenotypes (15-17, 14), while T-cells lymphomas of the intestine are infrequently encountered. Only a few reports of T-cell lymphoma complicanting Chron's disease have been documented so far (18, 14). The B-cell tumours are composed of a polymorphic population of centrocytic like cells, plasmacytoid cells, and blast cells. Isaacson defined these neoplasm as "malignant lymphomas arising in mucosa associated lymphoid tissue-MALToma" (19, 20). An important and distinctive feature of these lymphoma cells is the tendency to invade mucosal epithelium and form characteristic lymphoepitelial lesions. Often these centrocyte like cells are present as clusters, both intraepithelially and intraluminally and obliterate partially mucosal glands (21). T-cell malignancy associated with inflammatory bowel disease is extremely rare; Isaacson and all. in 1985 proposed a new high-grade small bowel malignancy, "enteropathy-associated T-cell lymphoma (EATCL)" (21). It is histologically equivalent to so-called malignant histiocytosis of the intestine. Chott et all. classified peripheral T-cell lymphomas of the intestine into three types; EATCL, EATCL-like lymphoma without enteropathy, and non-EATCL (18). The phenotypes of EATCL are tipically CD 3 +/-, CD 4-, CD 5-, CD 7 +, and CD 8- (21) and the highly malignant tumor cells are reactive with a monoclonal antibody HML-1 to human mucosal lymphocytes. These fin-

dings suggest neoplastic proliferation of the double negative subclass of IEL (22). EATCL may express CD 8 + and HML-1- phenotypes (18). Furtermore EATCL-like lymphoma without enteropathy showed phenotypes similar to EATCL but was devoid of both lateral mucosal spread of lymphoma cells and increase of IEL (18). Large cells anaplastic lymphomas, the so-called Ki-1 (CD 30) lymphomas frequently showing T-cell phenotypes (23), may involve the gastrointestinal tract (24, 15), even if the commonly occurs in the lymph nodes. The majority of malignant histiocytosis coexpress CD 30, EMA and CD 25 and thus can be included in the concept of Ki-1 lymphoma (25). Even a close association of infection with Ebstein-Barr virus (EBV) and EATCL (26), and with CD 30+ intestinal T-cell malignancy (27), has been reported. To distinguish between primary and secondary gastrointestinal lymphoma, the definiti-on of primary gastrointestinal lymphoma by Dawson (28) is quite applicable, which consists of a normal chest x-ray, no evidence of hepatosplenomegaly or superficial lymphoadenopathy, a normal white blood count cells count (that is, no evident of leukaemia), and a predominant tumour mass in the bowel with only local lymphadenopathy. Diagnostic problems may occur, however, to discriminate between primary gastrointestinal lymphoma, which has generalised and nodal lymphoma, with secondary gastrointestinal manifestation: this case fulfils these criteria, except for the mild splenomegaly and bone marrow infiltration which was caused by distant spread. Profound staging is required; this includes upper and lower endoscopy with multiple biopsy which usually confirms the diagnosis, contrast radiography of the small intestine, cervical, thoracic and abdominal computed tomography, bone marrow cytology and histology, scintigraphy of the skeleton, endosonography, and in addition liver biopsy. Treatment of inflammatory bowel disease combined with gastrointestinal lymphoma follows primarily the guidelines of lymphoma treatment at stage I and II surgery either alone or in combination with radioteraphy should be performed. Radiotherapy or chemotherapy, or both may also be of use for cases with advanced stage and high grade lymphomas (29). Prognosis in cases of lymphoma associated with inflammatory bowel disease generally is poor; infact it is demonstrated that adenocarcinoma combined with chronic inflammatory bowel disease has a better survival than colorectal lymphoma (30, 31, 29). Any presence of lymphocytic infiltrate, expecially when symptoms change or when treatment is not effective should be accurately valute to exclude the presence of lymphoma of gastrointrestinal tract, which is a rare but important complication of inflammatory bowel disease, expecially in patients with long-stading ulcerative colitis. It is even important to underline the possibility of association between T-cell lymphoma and ulcerative colitis, because this type of lymphoma is more agressive and can interest all intestine with more complications and a worse prognosis as to B-cell lymphoma.

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Commento Commentary

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Adani and coll. present two interesting cases of malignant lymphoma associated with ulcerative colitis. Indeed, the association between primary malignant lymphoma and ulcerative colitis is extremely rare. Primary lymphoma itself is quite uncommon, as the authors pointed out, representing 1-4% of all gastrointestinal malignancies but only 0.5% of colonic cancers and 0.1% of rectal ones. (1, 2) Clinically, the lymphoma can mimic ulcerative colitis therefore the diagnosis can be difficult and, as the authors remarked, it is important to be aware of such association for correct diagnosis. The tumor can appear as a poly - poid or ulcerated mass resembling carcinoma or a process involving a long segment of bowel. Altematively, nonulcerated, sub - mucosal lesions of the rectal wall can occur. Thus, endoscopy with biopsy and histologic examination are crucial to establish the diagnosis.

In the first case presented by the authors, deep colorectal ulceration and perforation occurred. However, in contrast to small bowel lymphoma, they are uncommon in the colorectal site.

Interestingly, in both cases the chronic inflammatory disease seemed to affect the whole colon but not the rectum. The lymphoma, however, was present both in the colon and rectum. In fact, in case 1, preoperative endoscopy had shown no proctitis but the patient underwent a total proctocolectomy with ileostomy for colorectal lymphoma complicated with blee - ding ulcers and multiple perforations. In case 2, preoperative colonoscopy showed ulcerative disease extending only to the colon biopsies showed colonic lymphoma, and the patient underwent colectomy with ileostomy. Rectal lymphoma, howe - ver, was disclosed at follow-up endoscopy after adjuvant chemotherapy.

In conclusion, as underlined by the authors, it is important to evaluate any lymphocitic infiltrate in patients with inflammatory bowel disease, particularly in the presence of long standing disease or no benefit with medical the- ra py.

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Adani e coll. presentano due casi interessanti di linfoma maligno associato a rettocolite ulcerosa. L'associazione tra linfoma maligno primitivo e rettocolite ulcerosa è veramente rara. Lo stesso linfoma primitivo è piuttosto raro, come segnalato dagli autori, rappresentando l'1-4% di tutte le neoplasie gastrointestinali ma solo lo 0.5% dei cancri del colon e lo 0.1% di quelli rettali (1, 2). Dal punto di vista clinico, il linfoma può mimare la rettocolite ulcerosa, rendendone difficile la diagnosi e, come indicato dagli autori, è importante essere a conoscenza di tale associazione per stabilire una diagnosi corretta. Il tumore può apparire come polipo o massa ulcerata simile a un carcinoma o come processo che coinvolge un lungo segmento d'intestino. Per contro, vi sono forme non ulcerate, sottomucose della parete rettale. L'endoscopia con biopsia ed esame istologico sono, quindi, cruciali ai fini diagnostici.
Nel primo caso presentato dagli autori, vi erano ulcerazioni profonde e perforazioni del colon-retto. Tuttavia, contrariamente a quanto avviene nel linfoma dell'intestino tenue, tali complicanze sono rare in sede colorettale.
È interessante notare che in entrambi i casi, la malattia infiammatoria cronica avrebbe coinvolto l'intero colon, risparmiando però il retto. Il linfoma, in ogni modo, era presente sia nel colon sia nel retto. Nel caso 1, infatti, l'endoscopia preoperatoria non aveva mostrato proctite ma il paziente fu sottoposto a proctocolectomia totale con ileostomia per un linfoma colorettale complicato da ulcerazioni sanguinanti e perforazioni multiple. Nel caso 2, la colonscopia preoperatoria mostrò la malattia solo nel colon, le biopsie evidenziarono linfoma colico e il paziente fu sottoposto a colectomia con ileostomia. Un linfoma rettale fu tuttavia scoperto al follow-up endoscopico, dopo la chemioterapia adiuvante. In conclusione, come rilevato dagli autori, è importante valutare attentamente qualsiasi infitrato linfocitico nei pazienti con malattia infiammatoria cronica dell'intestino, particolarmente in presenza di affezione di lunga durata e mancata risposta alla terapia medica.

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