Colitis ulcerosa complicated by malignant lymphoma: case report and analysis of published works

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Abstract
A 51 year old woman with a two year history of ulcerative colitis developed a widespread gastrointestinal non-Hodgkin's lymphoma of low grade malignancy (MALT-lymphoma) involving upper and lower gastrointestinal tract, spleen, and bone marrow. After chemotherapy, clinical symptoms improved and lymphocytic infiltrates disappeared. Thirty nine cases of ulcerative colitis and 22 cases of Crohn's disease complicated by gastrointestinal lymphomas reported in published works are reviewed. In inflammatory bowel diseases any dense lymphocytic infiltrates seen in biopsy specimens obtained from ulcerative colitis or Crohn's disease should be assessed to exclude gastrointestinal lymphoma.

Keywords: colitis ulcerosa, non-Hodgkin's lymphoma.

Although colonic carcinoma is the major long term complication of ulcerative colitis, primary colonic lymphoma has also been shown to be associated with ulcerative colitis. As the clinical symptoms of chronic inflammatory bowel disease and malignant lymphoma of the large bowel can be rather similar, diagnosis of lymphoma can be masked and correct treatment may be delayed. We report a case of a patient suffering from ulcerative colitis for more than two years when malignant lymphoma of the colon developed. The diagnosis was made after treatment failure of the colitis with corticosteroids, azathioprine, and sulphasalazine.

Case report
A 51 year old woman suffering from ulcerative colitis since 1989 was transferred to our hospital in 1991 because of ineffective longterm treatment with corticosteroids, azathioprine, and sulphasalazine. First endoscopy of the colon and histological examination in 1989 showed chronic inflammatory bowel disease with typical signs of ulcerative colitis (Figs 1 and 2) involving the entire colon and the terminal ileum. Different therapeutic strategies including total parenteral or enteral nutrition had not improved the symptoms, which were dominated by 10–15 bloody stools a day.

When we saw the patient in 1991, she presented with a slightly painful abdomen with normal peristalsis, no superficial lymphadenopathy, no hepatosplenomegaly. Laboratory examinations showed mild inflammatory
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Colonoscopy showed a mild form of acute ulcerative colitis. Histological examination of the stomach and duodenal biopsy specimens showed not only typical polymorphonuclear inflammatory infiltration, but also distinct lymphocytic infiltration (Figs 3 and 4), which was even more evident in the colonic biopsy specimens (Fig 5A). In all sections the lymphocytic infiltration invaded the mucosa forming lymphoepithelial lesions and destroying the mucosal glands, typical evidence for the presence of primary gastrointestinal malignant lymphoma of MALT type (Fig 5B). Cells showed typical cleaved nuclei reminiscent of centrocytic cells (Fig 5C). Characteristic signs for acute ulcerative colitis were no longer detectable. Further immunocytochemistry confirmed this to be a B cell lymphoma (Fig 6). Histological examination of the bone marrow showed invasion of the malignant lymphoma, which had already led to a 40% suppression of bone marrow cells (Fig 7).

Summarising the results, our patient had developed a low grade B cell non-Hodgkin’s lymphoma involving the upper and lower gastrointestinal tract and the bone marrow – that is, stage IV. The enlargement of abdominal lymph nodes and spleen was probably also caused by distant lymphoma spread.

activity, anaemia, normal total and differential white blood cell counts, and normal immunoglobulin values. Repeated stool cultures were negative. A chest x ray showed no evidence of lymphadenopathy. Abdominal ultrasonography and computed tomography showed slightly enlarged spleen and multiple lymph nodes up to 1 cm diameter. In upper endoscopy we only saw a small duodenal ulcer and mild inflammation of the gastric mucosa.

Figure 3: Dense, sharply limited lymphocytic infiltrate in the upper half of an otherwise normal gastric body mucosa. Haematoxylin and eosin, original magnification ×95.

TREATMENT
The patient received chemotherapy according to the CVP protocol: cyclophosphamide 400 mg/m², vincristine 1.4 mg/m², prednisone 60 mg/m². After three courses, there was a decrease in diarrhoea from 10 to 5 stools daily with no blood contamination. Continuation of the chemotherapy for another three courses did not result in any further decrease in stool frequency. Repeated colonoscopy and bone marrow investigation, however, showed a progressive reduction of the lymphocytic infiltration. After chemotherapy had ended, the colon endoscopically showed typical changes as seen after long standing chronic inflammation of the colon with reduced haustration, but no evidence for acute disorder. Histologically, the malignant lymphoma was no longer present. Bone marrow was also free of lymphocytic infiltration. Abdominal computed tomography showed normal size of spleen and normal lymph nodes.

Discussion
Primary gastrointestinal lymphomas occur between 1 and 4% of all gastrointestinal malignancies. The gastrointestinal tract is the commonest site of extranodal lymphomas. In western populations, the stomach is most commonly involved, while colorectal lymphoma comprises between 10 and 20% of primary gut lymphomas in the larger published series. This fraction, however, may be reduced to 3% if ileocaecal tumours are excluded. Most of the tumours show characteristic histological and immunohistochemical features: the B cell tumours are composed of a polymorphic population of centrocytic like
Figure 5: Colonic involvement by the lymphoma. (A) Replacement of the crypts by the aggressive lymphoid infiltrate. Haematoxylin and eosin, original magnification ×95. (B) Inset: enlargement of the group of crypts shows two glands invaded by lymphoid cells (so called lymphoepithelial lesions). Haematoxylin and eosin, original magnification ×230. (C) High power enlargement of the lymphoma cells: small lymphocytic cells with partly cleaved, centrocytoid nucleus. Haematoxylin and eosin, original magnification ×600.

cells, plasmacytoid cells, and blast cells. Isaacson defined these neoplasmas as ‘malignant lymphomas arising in mucosa associated lymphoid tissue – MALToma’. An important and distinctive feature of these lymphoma cells is the tendency to invade mucosal epithelium and form characteristic lymphoepithelial lesions. Often these centrocyte like cells are present as clusters, both intraepithelially and intraluminally and obliterate partially the mucosal glands.

To distinguish between primary and secondary gastrointestinal lymphoma, the definition of primary gastrointestinal lymphoma by Dawson is quite applicable, which consists of a normal chest x-ray, no evidence of hepatosplenomegaly or superficial lymphadenopathy, a normal white blood cell count (that is, no evidence for 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.

The combination of gastrointestinal malignancy and chronic inflammatory bowel disease is of increasing interest. It is already well known that, after 25–30 years of ulcerative colitis, the cumulative risk of developing cancer is about 10%. Adenocarcinoma complicating Crohn’s disease is increasingly recognised, especially in the small intestine.

The nature of the relation between inflammatory bowel disease and intestinal lymphoma, however, is less certain. The first instance of this association is Barken in 1927 who reported two cases in ulcerative colitis with malignant lymphoma. To date, there are 26 publications reporting 39 cases of non-Hodgkin’s lymphoma (35 cases) or Hodgkin’s lymphoma (four cases) complicating ulcerative colitis. Four of these case reports even describe the additional occurrence of...
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...homogenates have been reported to induce B cell lymphomas in athymic mice suggesting, at least in experimental animals, that a link between Crohn’s disease, immunosuppression, and malignant lymphoma exists.60 61 Another factor to be considered is the prolonged use of corticosteroids and azathioprine. A convincing relation has been established between immunosuppressive drug treatment and an increased incidence of malignant tumours in patients after organ transplantation.62 Recently, an increasing number of cases have been reported in homosexuals in association with the acquired immune deficiency syndrome (AIDS).63 64

Before starting any treatment, profound staging is required. This includes upper and lower endoscopy with multiple biopsy specimens from all different parts, 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 radiotherapy should be performed. Chemotherapy should be the primary treatment for cases of malignant lymphomatous polyposis as this type of lymphoma is usually widespread throughout the gastrointestinal tract. Radiotherapy or chemotherapy, or both may also be of use for cases with advanced stage and high grade lymphomas.33 Yet, prognosis seems to be poor.32 33 Adenocarcinoma combined with chronic inflammatory bowel disease obviously has a better survival than colorectal lymphoma.33

In conclusion, malignant lymphoma of the bowel is a rare but significant complication of inflammatory bowel disease, apparently being more common in chronic ulcerative colitis than in Crohn’s disease. It is quite conceivable that the changed lymphoid populations in inflammatory bowel disease represents the clones in which lymphoma arises. Therefore, it is important to evaluate any lymphocytic infiltrate seen in a biopsy specimen, especially when anti-inflammatory treatment seems to be ineffective.

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