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Increased Incidence of Lymphomas and Carcinomas in Patients with Coeliac Disease

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SINCE THE early 1960s, it has been observed that intestinal non-Hodgkin's lymphomas and adenocarcinomas may occur at an unusually high rate in patients with coeliac disease. A high incidence of non-digestive lymphomas and other types of cancer have also been reported [1, 2]. We report here a case of coeliac sprue with Hodgkin's disease.

A 34-year old Caucasian woman was admitted at the Institut Jules Bordet Cancer Centre for staging and treatment of Hodgkin's disease. She had a past history of renal calcic stones, cutaneous naevi requiring surgical removal, and minor digestive problems consisting of eructation and nausea lasting for more than 10 years.

In April 89 she had an exacerbation of the gastrointestinal symptoms with abdominal discomfort and fatigue. Physical examination revealed a cervical lymph node that was firm, fixed and painless and which was not biopsied at that time. Her general status was good with moderate overweight. Liver and renal tests were normal. Haemoglobin was 11.7 gr/dl, MCV 84 fl, WBC 12 000/mm^3 (granulocytes: 74%), iron 43 meq/dl ($n > 60$), TIBC 288 mg/dl, saturation 15% and ferritin 56 ng/ml. An iron stain of a marrow aspiration showed many iron-loaded macrophages. The low serum iron was thus most probably related to the inflammatory syndrome due to the Hodgkin's disease and not to iron depletion. The erythrocyte sedimentation rate was 29 mm after one hour, fibrinogen 551 mg/dl and CRP 3.6 mg/dl.

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Gastrointestinal series and colonoscopy were normal. A duodenal biopsy showed a grade I–II atrophy of the villus and a plasmocytic infiltration of the submucosa. Antigliadin, antireticulin and anti-endomysium antibodies were negative. Based on these findings, the diagnosis of coeliac disease was suggested and the patient was given a gluten-free diet. The digestive symptoms improved but shortly after, fatigue and night sweats increased, she lost 4 kg and the cervical lymph node became bulky. The inflammatory syndrome was still present. A lymph node biopsy was performed and revealed a scleronodular Hodgkin's disease. Clinical staging concluded a stage III B with abdominal and mediastinal lymph nodes and pericardial effusion. She was treated with six cycles of MOPP–ABVD which led to a complete remission.

Coeliac disease that starts during childhood may remain quiescent for many years and become symptomatic again between the third and sixth decade. It involves mainly the jejunum. Grade I–II atrophy of the villus is pathognomonic of the disease and frequently no past history of malabsorption is reported [3]. Tests of malabsorption, antigliadine, anti-reticulin and anti-endomysium antibody are useful for screening the disease and following treated patients, but do not allow a definite diagnosis [4, 5]. Effective treatment is based on the total exclusion of gluten from the diet.

Our case had no past history of malabsorption. The gastrointestinal symptoms, although possibly related to coeliac disease, were not specific. Biology showed a low iron level that was probably related to the inflammatory syndrome associated with Hodgkin's disease. The finding of the typical villus atrophy in asymptomatic relatives of coeliac sprue patients suggest that adults, such as our patient, may have clinically unapparent coeliac sprue for some time [3].

The finding that small intestinal malignant lymphoma may complicate coeliac disease was first suggested in 1962 [1]. A later report established that there was a statistically significant increased incidence of lymphoma in coeliac disease which is most frequently localised in the small intestine, but can also be found in the colon and in the stomach [7]. The histological type most frequently associated with coeliac disease should now be classified as T cell lymphoma [8]. A high occurrence of non-digestive lymphomas has also been reported, the vast majority being, as in our case, Hodgkin's disease [9, 10]. Whether the prognosis of lymphomas related to coeliac disease is different from those without coeliac disease cannot be settled from data published in the literature.

Carcinomas have also been described in patients with coeliac disease: there is a significantly increased incidence of carcinoma of the gastrointestinal tract mainly of the oesophagus. Moreover, cancers of the lung, skin, breast, ovary, testicle, head and neck are also likely to occur [10–12]. Although it cannot be totally excluded that the flat mucosa is a consequence of the cancer itself, a detailed analysis of the data available in the literature supports the hypothesis that coeliac disease is a premalignant disorder. In the majority of the cases, coeliac disease was diagnosed long before the onset of the symptoms attributable to either lymphoma or carcinoma but was sometimes, as in our case, discovered within a short time of each other [9, 10].

There are some data suggesting that although the jejunal mucosa is flat, cell proliferation activity is high, increasing the probability of a malignant mutation to occur [13]. If indeed a gluten-free diet may reverse the flat mucosa to normal, it might also reverse the cancer risk [14]. The reasons for

developing an increased incidence of cancer elsewhere remain speculative: the increased permeability of the intestinal mucosa to carcinogens and the immunological disorders [15–17] often associated with coeliac disease might play an important role.

The prevalence of the disease, which has been estimated at 0.03% of the general population, is not really known, as it may be present in apparently asymptomatic individuals [18]. The incidence appears to vary in different parts of the world: the highest incidence, (1/300), has been reported in West Ireland [19]. As malignancy might develop in as many as 14% of patients with coeliac disease [11], this would justify investigation in order to identify coeliac disease in patients with cancer occurring at an unusual young age, and the evaluation of preventive measures for family members of patients with established coeliac disease.

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Comments on *Costs of Treating Advanced Colorectal Cancer*, *Ross* et al., Eur J Cancer 1996, 32A, 513–517

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Ross and associates [1] presented a detailed analysis of the relative total costs of four different palliative chemotherapy regimens for the treatment of colorectal cancer. They conclude that the pattern of costs is such that high drug costs, for example those associated with raltitrexed therapy, are partially offset by reductions in hospital visits and stays, making it a cost-effective alternative. The De Gramont regimen [2] was shown to be considerably more expensive than any of the other three treatments. A large proportion of the cost was for inpatient stays of 48 h every 2 weeks.

In our department, patients on the De Gramont regimen are all treated as outpatients. The chemotherapy is administered through a Hickman Line with a continuous pump over 48 h and patients attend the chemotherapy day unit for pump connection and to receive their leucovorin and 5-fluorouracil bolus doses. This reduces the staff and fixed costs of this regimen to two attendances with increased pharmacy time for filling the pump. There is, therefore, a considerable cost saving and we would estimate that this brings the De Gramont regime into the cost bracket of the other three treatments. The patient spends less time in hospital.

Our centre now administers several other regimens, as day-case procedures, which previously would have been delivered as an inpatient. For example, cisplatin is delivered as an 8–10 h day-case procedure. This entails problems of bed occupancy in the day unit and also of scheduling of nursing staff. Nevertheless, this has increased our chemotherapy capacity and is a practice that has been undertaken for a decade in the United States where cost pressures have always been more marked [3]. Such treatment delivery has been facilitated by the 5HT3 antagonist anti-emetics. As far as costings in colorectal carcinoma are concerned, this will be one of the major end-points of the MRC CR06 trial which is comparing the De Gramont regimen with continuous 5-fluorouracil and with raltitrexed. The main end-points are survival and quality of life, but a subgroup of patients will have extensive assessment of their costs including drugs, staff (medical, nursing and pharmacy), consumables, investigations and patient borne

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