Malt lymphoma as first clinical presentation of a celiac disease

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Abstract

We report a case of a 35 year-old-woman who suffered from abdominal pain and weight loss. Asymptomatic celiac disease was discovered and complicated with a MALT Lymphoma in the jejunum. This is an uncommon combination because lymphoma that arises in the presence of enteropathy is commonly from T lymphocytes. Also because it normally appears in patients with long standing celiac disease who report a recrudescence of the abdominal symptoms. (Acta gastroenterol. belg., **1998**, 61, **479-482**).

Introduction

Celiac disease is characterized by an intolerance to gluten caused by hypersensitivity to a component of gliadin. Exposure to gluten causes an increase in intraepithelial lymphocytes, villous atrophy, and increases titres of systemic antigliadin antibody. Removal of gluten reverses the histological features and leads to a decrease in the antigliadin antibodies. Patients with celiac disease have an increased risk of epithelial malignancy of the oropharynx, small and large intestine and the breast (1-4). They also have an increased risk of development of primary small bowell lymphoma, in particular the so-called enteropathy associated T-cell lymphoma (5). The clinical presentation of celiac disease is quite variable and the diagnosis is often delayed. Early diagnosis is important since treatment with a gluten-free diet seems to reduce the risk of subsequent gastrointestinal malignancy (6). We report a case of a lymphoma MALT discovered with changes in the small intestine consistent with the presence of enteropathy.

Case report

A 35-year-old woman was admitted to the hospital because of abdominal colic pain and weight loss. The patient had been well until a year earlier when epigastric pain developed. Four months before entry, abdominal pain worsened, and the patient began to lose weight. The patient did not have diarrhoea.There was a history of tobacco use and of cholecystectomy. The patient's temperature was 36 C, the pulse was 75, and the respirations were 17. Her blood pressure was 120/80 mm Hg. *On physical examination* the patient was thin. There was an absence of palpable peripherical lymphadenopathy. The abdomen exam revealed a palpable mass of 4-5 cm of diameter in the mesogastric area. *Laboratory tests* were performed. Hematologic laboratory values, blood chemical values, prothrombin and partial-thromboplastin times were all normal. Xylose tolerance test was normal. Stool examination had normal fat content in the Van de Kamer chemical method. IgA antigliadin antibodies were 173 uA (normal to 25 uA) and IgA antiendomysium antibodies were 1/1280 (normal to 1/5). The class I histocompatibility antigen revealed HLAB8, and the class II histocompatibility antigen HLADR3, HLADQw2.

Upper gastrointestinal endoscopy was normal and six biopsies were taken from the distal duodenum. All biopsies taken revealed moderately increased lymphomatous infiltrate and eosinophils in the lamina propria and subtotal atrophy. Interepithelial lymphocytes and subtotal atrophy are features suggestive for a diagnosis of celiac disease.

Barium small bowell study noted a stenotic jejunum loop with loss of the normal mucosal fold pattern. Ileum was normal (fig. 1).

Abdominal scan revealed a mesenteric lymphoid nodular mass (fig. 2).

Laparotomy was performed. A loop of jejunum of 21 × 9 cm was removed and ten lymph nodes of 0,5-1,2 cm was also removed.

Lymphoid tumor was focally ulcerative and infiltrated to the serosa. *Histologically*, the neoplastic infiltrates which sometimes formed well-defined nodules, were distributed in the mucosa and submucosa, and sometimes extend through the muscularis propia. *Cytologically*, the tumor cells were centrocyte-like cells, small lymphoid cells with slightly irregular nuclei, fine chromatin, non-prominent nucleoli and sparse cytoplasm. Mitosis were infrequent. Lymphoepithelial lesion was also present, the centrocyte-like cells invading the crypts and often partly destroying them. Phenotyping reveals that tumor cells express monoclonal surface immunoglobulin (IgM, IgG, IgA) and not IgD. PanB cells antigens were expressed without CD5, CD10 or CD23 coexpression. (fig. 3, A, B). *By immunohistochemistry*, the centrocyte-like cells were stained by a variety of pan B cell antibodies (CD20, CD45RA and MB2).

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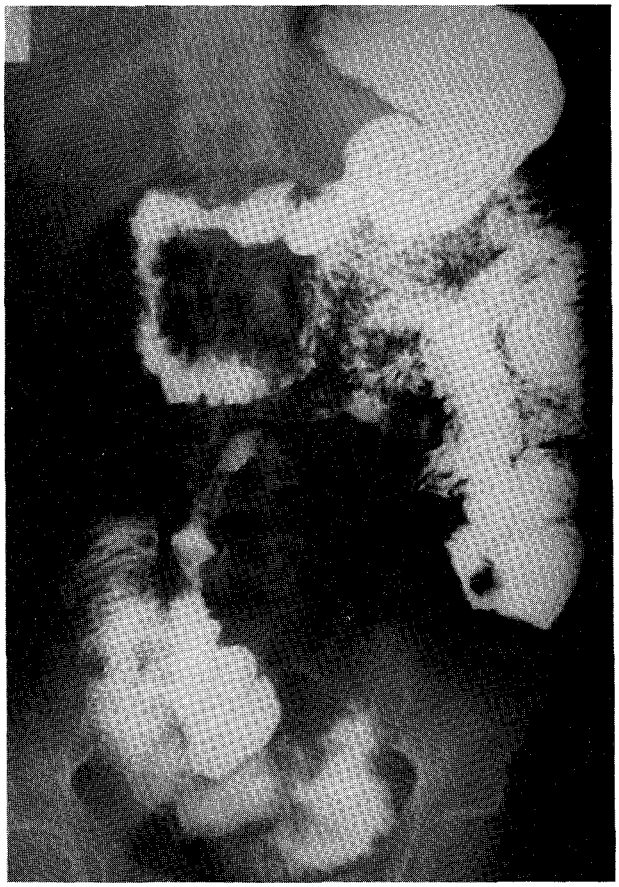

Fig. 1. — Barium small bowel study : jejunum loop with loss of the normal mucosa fold pattern and mass effect.

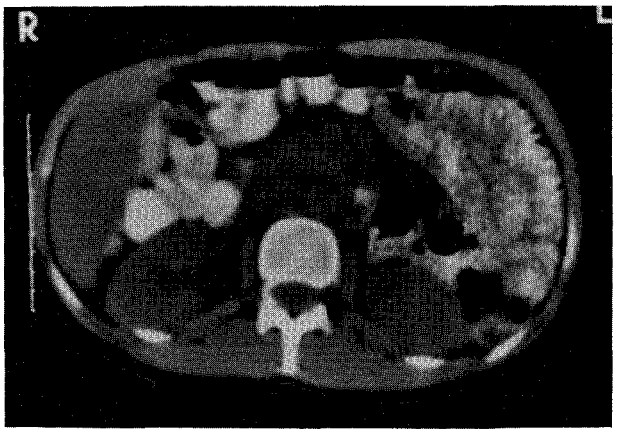

Fig. 2. — Abdominal CT scan : Mesenteric Lymphoid nodular mass.

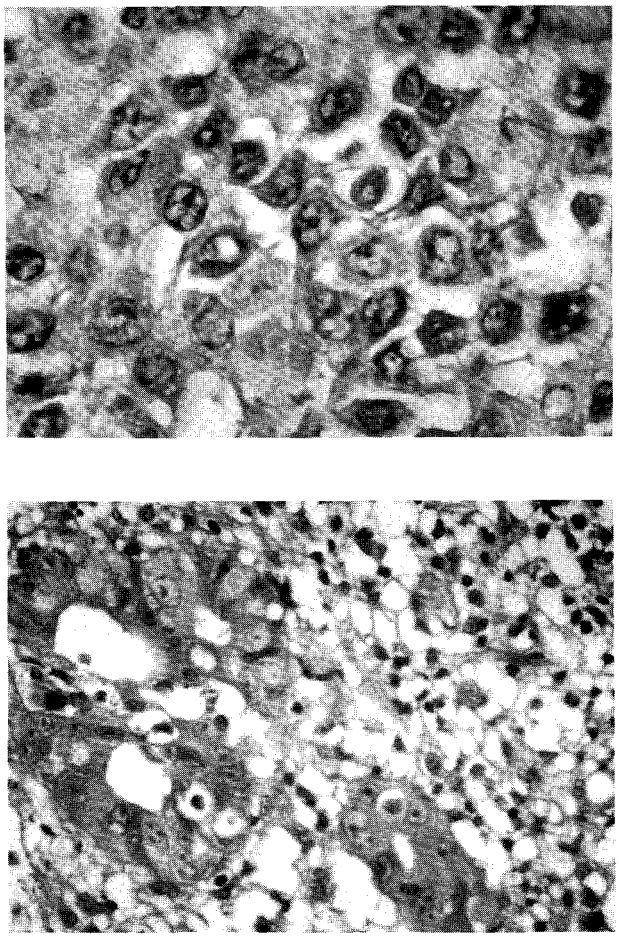

Fig. 3. — A : Lymphomatous infiltrate admixed with mature and immature appearing lymphocytes (HE, × 1 000) ; B : High power magnification of a lymphoepitelial lesion showing a intestinal node infiltrated by atypical lymphocytes and causing its destruction (HE, × 400).

There were restrictions for lambda chains and negative antigens for specific markers of T cells (CD3, CD43, CD45RO). Immunohistochemical analysis was performed on formalin-fixed, paraffin-embedded tissues by using microwave-oven heating and streptolidin-biotin complex method. The origin and dilutions of antibodies used were as follows : CD19 Dako ; 1:50. CD23 Dako ; 1:100. CD20 Dako ; 1:100. CD79alpha Dako ; 1:50. CD10 Immunotech ; 1:50. CD5 Novocastra ; 1:50. IgA Dako ; 1:500. IgG dako ; 1:100. IgM Dako : 1:150. IgD Dako ; 1:50. CD3 Dako ; 1:100. CD43 Biogenex ; prediluted. Bcl-2 Dako ; 1:50. Ki-67 Immunotech ; 1:30. p53 Dako ; 1:100. Broad Spectrum Keratin Biogenex ; prediluted. 3-3' diamocrobenzidine was used as chromogen and the sections were counterstained with Meyer's hematoxylin.There was a mutation of p53 gene (less than 1%). A know p-53 positive tumor and normal tonsil were used as positive controls for p53 gene and lymphoid population, respectively. Cellular proliferation index ki-67 (MIB-1) was 50%-60%. There was no expression of the oncogen Bcl-2, no dendritic follicular cells (CD21, CD35) were found.

After surgical resection, adjuvant chemotherapy was indicated. A chemotherapeutic regime of vincristine, procarbazine, chlorambucil and cyclophosphamide was given during six months. A favourable response to surgery and chemotherapy was observed and the patient remains asymptomatic with normal laboratory parameters (lactate dehydrogenase, beta-2-microglobulin) and normal chest-abdominal scanner.

Discussion

An increased risk of malignant tumors has long been noted in patients with celiac disease (1,2). The most striking incidence occurs in intestinal lymphomas (3-17). Recent studies indicate that most intestinal lymphomas associated with celiac disease are derived from T lymphocytes (7). In the large series of 119 cases of small intestinal lymphoma recently reported by Domizio *et al.* (15), none of the 78 B cells lymphomas were associated with enteropathy, in contrast to 20 enteropathy of 41 T cell tumors. Also, Ilyas *et al.* followed a group of 166 patients with celiac disease for a period of up to 25 years. During this time 17 patients developed intestinal lymphoma and only two were of the B cell type. Our case report is a very rare case of a MALT Lymphoma (B cell type) arised in the presence of enteropathy.

Mucosa Associated Lymphoid Tissue (MALT) Lymphomas are mostly of B cell lineage and histologically consist of three different components : follicles, plasma cells, and centrocyte-like cells (11). The hallmark of the MALT lymphoma is the lymphoepithelial lesion, formed by invasion of the mucosa by the centrocyte-like cells (12). This is shown in Fig. 3 (A, B). By immunohistochemistry, the centrocyte like cells are stained by a variety of pan-B cell antibodies and these cells exhibit variably weak perinuclear staining for immunoglobulin (17). In our case report, centrocyte like cells stained by a variety of pan B cell antibodies (CD20, CD45RA and MB2) with restrictions for lamba chains and negative antigens for specific markers of T cells (CD3, CD43, CD45RO). The p53 gene encodes a 53-Kda protein with an antiproliferative activity (18). Normally, the protein cannot be detected by immunohistochemical techniques. Mutations of the gene produce alterations in the protein structure that inhibit function and also produce a prolonged half-life, thus allowing detection of the protein by immunohistochemical analysis. P53 mutation and protein overexpression have been shown in numerous malignancies and lymphomas (19). In our case the p53 mutation was approximately 1% in relation with the low grade of the lesion. The Ki-67 protein is reprted to be present in nearly every phase of the cell cycle except G0 (20). The protein overexpression (over 80%) has been shown in high grade lymphomas. An expression of about 50% has a significance of low-intermedium grade of malignancy.

All these immunohistological studies reflect the low grade malignancy of our case report. Also, MALT lymphomas are typically localized disease (about 70% of MALTOMAS are stage I or II) at the time of diagnosis, and it may be cured by local therapy. In contrast with this expected prognosis for MALT lymphomas, enteropathy associated T cell lymphomas are distinguished by an aggresive clinical course and a poor response to current modes of therapy (16). In our patient, a benign clinical course and good response of surgery and chemotherapy was observed and the patient remains well a year after diagnosis.

Finally, it is important to note that our patient did not have a previous diagnosis of celiac disease but had abdominal symptoms and a lymphoma was discovered. In our case report, a loop of jejunum was the site of localized involvement of MALT lymphoma and caused the main clinical symptoms of intestinal pseudobstruction. Patients with documented celiac sprue merit a careful search for a gastrointestinal malignancy if, after initially improving with gluten withdrawal, they subsequently develop symptoms such as weight loss, malabsorption, abdominal pain, or intestinal bleeding despite of strict adherence to a gluten free diet. A single study provides evidence that strict adherence to a gluten free diet reduces the incidence of malignant disease in patients with celiac sprue, strengthening the case for a lifetime commitment to gluten withdrawal once celiac sprue is diagnosed (3). Not knowing of the existence of celiac disease in our patient impeded the possible prevention of the appearance of a lymphoma or at least an earlier diagnosis. However, the fact that it was the B cell lymphoma present and not the T cell, that offered our patient a better prognosis.

In our case a benign clinical course was observed and the patient remains well a year after surgery and chemotherapy.

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