What is the role of celiac disease in enteropathy-type intestinal lymphoma ? A retrospective study of nine cases

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Abstract

Background and aims : **It is generally accepted that enteropathy-type intestinal lymphoma (EATL) arises against a background of gluten enteropathy. We investigate whether patients with this diagnosis had celiac disease or pre-existing celiac disease, based on gliadin and endomysium antibodies, as well as duodenal biopsies, HLA typing and response to gluten-free diet.**

Methods and results : **Retrospective study of patients with the diagnosis of peripheral T cell lymphoma of the intestine between January 1990 and January 2002 at the university hospital Gasthuisberg Leuven (n = 14). Patients in whom serologic testing was performed or patients known with pre-existing celiac disease (CD) were included (n = 9). Six of these nine patients were tested for endomysium antibodies (AEM), none of them were positive. Of the six patients with biopsies of mucosa uninvolved by lymphoma, all of them had villous atrophy ; five had increased intraepithelial lymphocytes (IEL). In the four patients were HLA typing was performed, the results were compatible with CD. The three patients with initially diagnosed celiac disease all improved on gluten free diet (control biopsies improved as well, but failed to normalise). Of the six other patients, one patient never started GFD, two didn't get better, one initially went better after GFD, and one went better with the concomitantly started chemotherapy.**

Conclusion : **There are two possible explanations : Either these patients with EATL have indeed gluten intolerance but the sensitivity of AEM is overestimated in this patient population ; or these patients don't have gluten intolerance and EATL itself can mimic CD or other factors mimicking CD are at risk for developing EATL** (Acta gastroenterol. belg., **2005**, 68, **419-423**).

Abbreviations

AEM = anti-endomysium antibodies
AGA = anti-gliadin antibodies
CD = celiac disease
EATL = enteropathy-type intestinal lymphoma
GFD = gluten-free diet
IEL = intra-epithelial lymphocytes
MHI = malignant histiocytosis of the intestine
NHL = non-Hodgkin lymphoma
TCL = T-cell lymphoma

Introduction

At present, the best-defined clinicopathologic entity of primary T cell gastro-intestinal lymphoma is the enteropathy-type intestinal lymphoma (EATL), which is a rare condition. It has a high mortality, mostly due to a late diagnosis in patients in already bad general condition. After all, the presenting symptoms are atypical (abdominal pain, anorexia, nausea, vomiting, diarrhoea, weight loss). Symptoms of night sweats, fever or adenopathy are less frequent. Since diagnosis is difficult, patients often present with spontaneous perforation and small bowel obstruction at an advanced stage of illness (1,2,3).

It is generally accepted that this tumour arises against a background of gluten enteropathy. If this is the case, a known or new diagnosis of gluten enteropathy might help to recognize the intestinal T-cell lymphoma. Positive serology for endomysium and gliadin antibodies has a high diagnostic sensitivity and specificity for gluten enteropathy (cfr Table 1). Furthermore, over 95 percent of patients with celiac sprue express the HLA-DQ (α1*501-β1*02) heterodimer (HLA-DQ2). Histologic examination of a biopsy specimen of the small intestine remains the diagnostic gold standard for celiac sprue. In current practice, biopsy specimens are easily obtained from the distal duodenum (second or third part) during upper endoscopy. The classic lesion in patients with untreated celiac sprue is characterized by absent villi, hyperplastic crypts, and increased numbers of intraepithelial lymphocytes, plasma cells and lymphocytes in the lamina propria (15). However, it is unclear whether serology is really positive in the majority of patients with intestinal T-cell lymphoma (16).

The aim of the present study was to review the cases of intestinal T cell lymphoma in our hospital to investigate whether patients with this diagnosis had signs of celiac disease (CD) or pre-existing celiac disease, based on gliadin (AGA) and endomysium (AEM) antibodies, as well as duodenal biopsies, HLA typing and response to gluten-free diet (GFD).

Patients and methods

This is a retrospective study of all patients diagnosed with peripheral T cell lymphoma (TCL) of the intestine between January 1990 and January 2002 at the University Hospital Gasthuisberg Leuven. Cases were identified through pathology reports. We selected cases in which the gliadin and endomysial antibodies had been studied or the cases of patients known with celiac disease.

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Ref	population		AGA IgA Sens/spec %	AGA IgG Sens/spec %	AEM Sens/spec
4	174 pat with suspected or verified CD undergoingbiopsy	median age 1.7 y	89/83		78/99
5	77 pat with suspected or verified CD undergoing biopsy	Mean age 2.7 y	87/93		98/93
6	Group of 688 "untreated CD"	Median age3.8 y	85/85	90/66	94/96
7	95 patients with clinical suspicion of CD	Mean age 5.2 y	83/86	83/85	46-75/96-89#
8	156 adult patients with clinical suspicion or more vague gastro-intestinal symptoms	Mean age females 46 y, males 45y	79/70		74/100
9	Group of 117 patients with " adult CD" (21 untreated)	Mean age 38 y	91/85	76/88	100/99
10	591 pat with biopsy with variety of clinical symptoms	507 adults (median age 39 y) 84 children (median age 6.5 y)		69/71	87/99
11	166 untreated CD patients	Median age 47 y	61/86	87/78	87/85
12	60 untreated adult patients with celiac disease	Median age 41 y			95/100$
13	551 pat with suspected CD undergoing biopsy	Ages from 4 months to 18 y			90/98
14	70 infants with CD	Median age 2.6 y	69/92	89/47	100/97

# monkey esophagus-human umbilical cord
$ monkey esophagus = human umbilical cord

Of the patients known with celiac disease, we noted the serologic test at the time of the diagnosis of celiac disease before starting gluten free diet. We also obtained the initial anatomopathologic reports of small intestinal biopsies.

Results

During the 12 years of the study, 14 eligible cases of peripheral intestinal T cell lymphoma were registered. Serologic testing for celiac disease was available for 7 patients ; two other patients were known with pre-existing celiac disease (5 males and 4 females ; mean age 58 years). Table 2 summarizes the clinical characteristics of these patients. Of the five patients who were excluded from the study, three underwent urgent surgery for acute bowel perforation, with diagnosis on the resection specimen. In the two remaining patients, serologic testing was never performed for unknown reasons.

Three patients (n° 1, 2, 3) were known with pre-existing celiac disease but none of them had been diagnosed more than two years earlier. The presenting symptoms of the intestinal lymphoma were malabsorption, diarrhoea, B symptoms, perforation and subobstruction. The diagnosis of T-cell lymphoma was based on endoscopic biopsies in 3 patients and on surgically obtained biopsies in 6 patients. From the latter, 4 underwent a laparotomy (three for an acute perforation and one for a subobstruction) ; the two other patients underwent a diagnostic laparoscopy.

Of the six patients (n° 4,5,6,7,8,9) with mucosal biopsies uninvolved by lymphoma, five had increased intraepithelial lymphocytes and all of them had villous atrophy. Of these six patients, four showed ulcers on biopsy, the two other patients without ulcers on biopsy had a clinical history of perforation. Of the six patients who were tested for endomysial antibodies, none of them were positive. The four patients in whom HLA were investigated showed results compatible with celiac disease.

The three patients with initially diagnosed celiac disease (n°1, 2, 3) all improved on gluten free diet (control biopsies improved as well, but failed to normalise). Of the six other patients one patient never started GFD (n°4), two did not respond to the diet (n° 7, 8), n°5 initially went better after GFD, and n° 6 went better with concomitantly started chemotherapy.

Only the patients with a general condition allowing chemotherapy survived more than a half year, the general condition of the other patients was too bad to undergo intensive therapy.

Besides their abdominal and general symptoms, six of these 14 patients had skin eruptions (two with the clinical diagnosis of psoriasis, two with biopsy proven cutaneous TCL) and two patients had a history of purulent chronic sinusitis. One had a swollen parotid gland (with negative puncture cytology).

Discussion

Already in 1937, Fairly and Mackie reported the association of malignant lymphoma of the small intestine with steatorrhoea (17). It was not until 1962 before it was suggested that intestinal lymphoma was a complication of celiac disease (18,19). In 1978, Isaacson and Wright reviewed 18 patients with intestinal lymphoma. Only cases in which mucosa uninvolved by lymphoma showed villous atrophy and crypt hyperplasia were included in the study (20). None of these patients had biopsy-proven gluten sensitivity. On the basis of

Patient N°	Sex	Age (y)	Symptoms	AGA IgA	AGA IgG	AEM	HLA	Small Bowel X-ray	Diagnosis of EATL	APO(mucosa uninvolved by tumour)	Internal CD-TCL (y)	Therapy	Survival (y)
1	F	51	Septic shock on bowel perforation	pos	NK	neg	NK	NK	Resection specimen		1	Surgery	0.3
2	M	60	Subobstruction	NK	NK	NK	NK	Multiple places of thickening and stenosis jejunoileal	Endoscopic biopsy		2	chemotherapy	NK
3	F	68	Malabsorption, diarrhoea, B symptoms	NK	NK	NK	NK	Diffuse thickening	Endoscopic biopsy		2	nihil	1.5
4	M	49	Epigastric pain, weightloss	neg	neg	neg	NK	Duodenal stenosis with thickening	Resection specimen	Ulcera, ↑ IEL, atrophy	0	Chemotherapy (CHOP, DHAP) Radiotherapy	>3
5	M	64	B symptoms, malabsorption, diarrhoea	neg	neg	neg	NK	Diffuse thickening	Laparoscopic biopsy	Ulcera, ↑ IEL, atrophy	0	Chemotherapy (CHOP)	>1/2
6	V	57	Malabsorption, B symptoms, posprandial vomitus	neg	neg	neg	DQ2	NK	Laparoscopic biopsy	Ulcera, ↑ IEL, atrophy	0	Chemotherapy (GELA protocol)	>1/2
7	M	55	Diarrhoea, malabsorption, B symptoms, perforation	neg	neg	neg	DQ2	Diffuse nodular thickening jejuno-ileal	Resection specimen	↑ IEL, atrophy	0	steroids	1/2
8	V	59	Epigastric pain, malabsorption, B symptoms	neg	pos	neg	B8-, DR3 +	Multiple segmental stenoses prox ileum	Enteroscopic biopsy ulcera	Atrophy, ↑ IEL,	0	nihil	3/4
9	M	55	Small bowel perforation	pos	neg	NK	B8-, DR3 +	Ileal ulcer	Resection specimen	Atrophy, nl IEL	0	operation	3/4

NK : not known

immune phenotype, the lymphomas were thought to derive from histiocytes, and the term "malignant histiocytosis of the intestine (MHI)" was coined to describe these cases. The same authors noted the association between this condition and ulcerative jejunitis (21).

Subsequent studies have shown MHI to be of T cell origin (22, 23). O'Farrelly used the term enteropathy associated T cell lymphoma" for intestinal lymphoma, associated with abnormal jejunal histology (16). In 1993, the international lymphoma study group (REAL classification) referred to "intestinal T cell lymphoma (with or without enteropathy)" (24). Previous the Kiel, Rappaport and the Luke classification and the working formulation did not list this entity. Intestinal T cell lymphoma is usually found in adults, often with a history of gluten-sensitive enteropathy, but occasionally as the initial event in a patient found to have typical histological feature of sprue in the resected intestine, or less commonly, without evidence of enteropathy. In 1997 the World health Organisation project updated the terminology to "enteropathy-type intestinal lymphoma (EATL)" (25,26).

Thus at the moment, the only defined clinicopathologic entity of primary T cell intestinal lymphoma is EATL, beside of rare forms of nasal type NK T cell lymphoma with intestinal localisation (26). There is an accumulating body of evidence to support the hypothesis that intra-epithelial lymphocytes in many cases of so-called complicated celiac disease (refractory sprue, ulcerative jejunitis) constitute a primary malignant population (27, 28, 29). The demonstration of T cell receptor gamma gene clonality seems to be highly specific and the loss of T cell antigen (CD8) highly sensitive in the diagnosis of EATL (30).

The diagnostic approach to celiac sprue, based on serology, biopsies and response to gluten free diet, is well established. The availability of serologic markers greatly facilitates the diagnosis of celiac sprue. In general it is believed that the endomysium antibodies are highly sensitive and specific. In recent reviews the mentioned sensitivity varies from 75% to 98% and the specificity from 94% to 100%. Tests for IgA en IgG gliadin antibodies have moderate sensitivity but are far less specific than tests for IgA endomysium antibodies (15, 31).

Table 1 summarizes some of these studies. Obviously, there is a great variability between studies, both in children and in the adult population. Moreover, in many of these studies the studied population group is patients referred for endoscopic intestinal biopsy for suspected celiac disease. It is not always clear whether this suspicion was already based on positive antibodies which would induce an important recruitment bias. Moreover, many of these studies are designed to compare gliadin with endomysial antibodies, without the real aim to assess the sensitivity and specificity of each. Based on these considerations, the reported high sensitivity and specificity of serologic markers may be an overestimation. In spite of these limitations, diagnosing celiac sprue could potentially be useful when confronted with a patient who is suspected of intestinal lymphoma.

In 1986, O'Farelly prospectively studied 145 patients with malabsorption and villous atrophy. He found that the subgroup of patients most at risk of developing EATL, predominantly men, responded poorly to gluten withdrawal and were negative for gliadin antibodies (9 patients with EATL of the 16 without gliadin antibodies and no response on gluten free diet) (16). There is no body of literature on the prevalence of endomysium antibodies in patients with complicated CD. Anecdotal reports of the prevalence of AEM in refractory sprue suggest prevalence as low as 57% (32).

In the present study, we identified 9 patients with a primary intestinal T cell lymphoma who were tested for celiac disease. The presenting symptoms of malabsorption, B symptoms, perforation and obstruction are consistent with previous reports (1,2,3,20). Of the six patients who were tested for endomysium antibodies, none of them were positive. Nevertheless, the biopsies taken in mucosa uninvolved by lymphoma, the HLA typing and the response to gluten free diet in four of the six patients are compatible with celiac disease. The maximum time between the diagnosis of celiac disease and T cell lymphoma in our study was 2 years (two of the nine patients). Also in previous reports, patients with a celiac disease diagnosis dating back more than one year constitute a minority (1, 2, 3, 20, 33).

It is clear that the yield of screening for AEM was extremely low in our population of primary intestinal T cell lymphomas. If we accept the high sensitivity and specificity of the AEM for celiac sprue, then celiac disease as a risk factor for EATL is perhaps overestimated. Possibly EATL itself can mimic the histology of celiac disease or some other disease mimicking CD constitutes a risk for developing EATL. This is consistent with the low rate of celiac disease in non-Hodgkin lymphoma (NHL) at any primary site, detected by screening with AEM (33).

An alternative explanation could be that these patients do have gluten intolerance but have lost their capacity to produce endomysium antibodies or form a subgroup of CD patients who never had positive serology. Despite the reported high specificity and sensitivity, Rostami et al found the endomysium antibodies had an excellent sensitivity in total villous atrophy but that the sensitivity in partial villous atrophy was disappointing (34). It seems logical to assume that partial atrophy produces fewer symptoms. Especially in these patients without obvious symptoms, serology is frequently used as the only screening method. Wahnsschaffe et al identified a subgroup of latent/potential CD patients in a group of diarrheic irritable bowel patients, based on HLA-DQ2 positivity and increased CD-associated antibody (against gliadin and /or tissue-transglutaminase) in duodenal aspirate. In this subgroup stool frequency and intestinal IgA decreased significantly under a gluten free diet. None of these patients had elevated CD-associated serum antibodies (35).

Obviously, negative serum CD-associated antibodies do not exclude gluten intolerance. Because of the difficult diagnosis in these patients without serum antibodies and without important symptoms, there is a high risk to be exposed continuously to gluten, resulting is a permanent antigenic drive, which may trigger lymphoproliferative disease (36). It is well conceivable that symptoms only manifest at that moment. Indeed, the histology, the HLA typing and the good response to GFD in some of the patients are in support of this hypothesis Furthermore, the already mentioned small percentage of patients with diagnosed longstanding celiac disease and the reported protective effect of gluten free diet against the development of malignancy are compatible with this hypothesis (37). This would underestimate celiac disease as a risk factor when endomysium antibodies are used for screening (33).

However, in both cases one should have a high index of suspicion in adult patients with a picture of celiac disease with negative endomysium antibodies. The finding that NHL manifestations appear shortly after a period of transitory response to the GFD have previously been reported (3, 33) and may give a false certitude to the physician. Early diagnosis is paramount ; malnutrition, perforation or obstruction is catastrophic in patients facing chemotherapy, and only patients able to receive chemotherapy have a chance for survival (1,3). Especially B symptoms and skin rash should raise suspicion. Only in three of the nine patients was a diagnosis obtained by endoscopic biopsies, the others required a surgical specimen. In suspect cases, one must not rely on a negative endoscopic biopsy and early laparoscopy is recommended. Four of the nine patients had ulcers on the small bowel biopsy, of the five other ; three of them had a perforation. This is compatible with the thought that ulcerative jejunitis may present a continuum with EATL.

In conclusion, out of 9 patients with EATL, none was found to test positive for AEM. Unfortunately, the retrospective nature of the study allowed only incomplete results of history, biopsies, serology and HLA, rendering absolute interpretations very difficult. Either these patients with EATL have indeed gluten intolerance but

the sensitivity of AEM is overestimated in this patient population ; or these patients do not have gluten intolerance and EATL itself can mimic CD or other factors mimicking CD are at risk for developing EATL. Patients with a picture of celiac disease but without AEM should raise suspicion, especially in the presence of associated B symptoms or skin eruptions, and even despite an initial good response on GFD. Even when there are negative endoscopic biopsies, there should be a low threshold to perform a surgical procedure for full-thickness biopsy.

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