Incidence of lymphoproliferative disorders in patients with celiac disease

Lori A. Leslie,[1] Benjamin Lebwohl,[2] Alfred I. Neugut,[3,4] John Gregory Mears,[3] Govind Bhagat,[5] and Peter H.R. Green[6]*

Prior studies describe an increased incidence of lymphoma in celiac disease. However, few studies differentiate among lymphoproliferative disorders (LPDs). Our aim was to determine incidences of LPD subtypes in celiac disease patients, describe patterns of celiac disease presentation in patients who develop LPD, and compare survival in patients with various LPD subtypes. We conducted a retrospective cohort study of adults with biopsy-proven celiac disease seen at a US referral center from 1981 to 2010, identified patients with comorbid LPD, and calculated standardized incidence ratios (SIR) for each LPD subtype. In our cohort of 1,285 patients with celiac disease, there were 40 patients with LPD [SIR = 6.48, 95% confidence interval (CI) = 4.62–8.64] including 33 with non-Hodgkin lymphoma (NHL, SIR = 6.91, 95% CI = 4.26–8.28). The incidences of NHL subtypes including enteropathy-associated T-cell (EATL, *n* = 12), non-EATL T-cell (SIR = 22.43, 95% CI = 7.08–46.41), diffuse large B-cell (SIR = 5.37, 95% CI = 1.93–10.52), mantle cell (SIR = 32.21, 95% CI = 6.07–78.97), and marginal zone (SIR = 37.17, 11.73–76.89) lymphoma remained significantly elevated when only those diagnosed with celiac before LPD were considered (*n* = 24, NHL SIR = 4.47, 95% CI = 2.86–6.44). Patients who developed LPD were older at time of celiac disease diagnosis (57.9 ± 15.5 versus 42.5 ± 17.4 years, *P* < 0.0001) and more likely to present with diarrhea (60.0% versus 39.8% *P* = 0.016), abdominal pain (17.5% versus 5.5% *P* = 0.0046), and/or weight loss (12.5% versus 4.0%, *P* = 0.028). EATL patients had a shorter average survival than non-EATL NHL patients (3.2 versus 15.0 years, *P* = 0.016). The incidence of LPD is increased in celiac disease patients. Those diagnosed later in life who present with symptoms of malabsorption are more likely to be diagnosed with LPD. Am. J. Hematol. 87:754–759, 2012. © 2012 Wiley Periodicals, Inc.

Introduction

Celiac disease is an autoimmune disorder that occurs in genetically susceptible individuals due to an immune mediated inflammatory reaction to dietary gluten [1]. It is common, occurring in 1% of the population worldwide. Celiac disease is considered an emerging disorder as the prevalence has increased ~ fivefold over the past 50 years [2]. Despite improved diagnostic techniques and increased awareness, it is considered that those diagnosed with celiac disease represent only a fraction of the true prevalence [3]. With the rising prevalence, there has been a growing interest in studying the complications of longstanding disease, particularly the observed increased mortality in patients with celiac disease compared with that of the general population. This increased mortality has been mainly attributed to the elevated incidence of malignancy, including lymphoma [4–7].

Lymphoproliferative disorder (LPD) is a general term that includes lymphoma, chronic lymphocytic leukemia (CLL), and plasma cell dyscrasias such as multiple myeloma. Within LPD, lymphoma is typically classified as Hodgkin lymphoma or non-Hodgkin lymphoma (NHL). NHL can be further divided into B-cell NHL or T-cell NHL. B-cell NHL includes subtypes such as diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, marginal zone lymphoma, and follicular lymphoma. T-cell NHL includes subtypes such as cutaneous T-cell lymphoma, peripheral T-cell lymphoma, and enteropathy-associated T-cell lymphoma (EATL). It is clinically important to distinguish among the various subtypes of LPD due to the differences in natural history, prognosis, and approach to treatment.

Prior studies on the incidence of lymphomas in celiac disease commonly distinguish between Hodgkin and non-Hodgkin lymphoma as well as B-cell and T-cell NHL. However, only a small number of studies further differentiate among NHL subtypes and even fewer studies include other LPD subtypes such as CLL and multiple myeloma [8–16]. Additionally, how to identify celiac disease patients with an increased risk of developing LPD remains unclear.

Our aim was to determine the incidences of LPD subtypes in a large cohort of patients with celiac disease seen at a single outpatient, tertiary referral center compared with the expected population based frequency in the United States. In addition, we determined the pattern of celiac disease presentation in patients who were diagnosed with concurrent LPD compared with those who were not and compared survival in celiac disease patients diagnosed with various LPD subtypes.

Methods

We conducted a retrospective cohort study of patients seen at the Celiac Disease Center at Columbia University Medical Center, a tertiary outpatient referral center, from 1981 to 2010. A list of patients with celiac disease was obtained from a preexisting institutional review board (IRB)-approved database. All patients had biopsy-proven celiac disease and were age 18 or older at time of evaluation at the Celiac Disease Center. We obtained prospectively collected data on gender, age at celiac disease diagnosis, presenting symptoms at time of celiac disease diagnosis, and survival for each patient in the cohort. Patients with comorbid LPD were identified by performing a manual search of the database as well as performing an ICD-9 search of the electronic medical record used at Columbia University Medical Center. For those with LPD, we also determined age at LPD diagnosis and time elapsed between celiac disease and LPD diagnoses.

[1]Department of Medicine, Columbia University Medical Center, New York, NY (CUMC); [2]Division of Gastroenterology, CUMC; [3]Division of Hematology and Oncology, CUMC; [4]Department of Epidemiology, CUMC; [5]Department of Pathology, CUMC; [6]Division of Gastroenterology, Celiac Center at CUMC, CUMC

Conflict of interest: Nothing to report.

*Correspondence to: Peter H.R. Green, 180 Fort Washington Ave, Suite 936, New York, NY 10032. E-mail: pg11@columbia.edu

Received for publication 18 November 2011; Revised 10 April 2012; Accepted 13 April 2012

Am. J. Hematol. 87:754–759, 2012.

Published online 26 April 2012 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/ajh.23237

TABLE I. Patient Characteristics

	Celiac only	Celiac and LPD	Total
N	1,245	40	1,285
Proportion of CD patients with LPD		40/1,285 (0.031)	
Total men (% of cohort)	364 (29.2%)	16 (40.0%)	380 (29.6%)
Proportion of CD men with LPD		16/380 (0.042)	
Total women (% of cohort)	881 (70.8%)	24 (60.0%)	905 (70.4%)
Proportion CD women with LPD		24/905 (0.027)	
Age at CD diagnosis			
Total (SD) years	42.5 (17.4)	57.8 (15.5)	43.0 (17.5)
Men (SD) years	45.4 (18.1)	55.0 (16.6)	45.8 (18.1)
Women (SD) years	41.4 (16.9)	59.7 (14.7)	41.8 (17.1)

LPD, lymphoproliferative disorder; CD, celiac disease; SD, standard deviation.

TABLE II. SIRs and 95% Confidence Intervals, all LPD Patients (*N*=40)

Category	*N*	SIR	95% CI
LPD overall	40	6.48	4.62–8.64
LPD men	16	6.01	3.42–9.31
LPD women	24	6.84	4.37–9.84
NHL overall (B-cell and T-cell)	33	6.91	4.26–8.28
NHL: excluding EATL	21	3.91	2.42–5.76
NHL: B-cell overall	16	3.41	1.94–5.29
DLBCL	6	5.37	1.93–10.52
Mantle cell	3	32.21	6.07–78.97
Marginal zone	5	37.17	11.73–76.89
Follicular	1	n/a	n/a
Post-transplant LPD	1	n/a	n/a
NHL: T-cell (non-EATL)	5	22.43	7.08–46.41
EATL	12	n/a	n/a
Hodgkin lymphoma	1	n/a	n/a
CLL	6	4.85	1.75–9.51
Multiple myeloma	0	n/a	n/a

SIRs, standardized incidence ratios; LPD, lymphoproliferative disorder; NHL, non-Hodgkin lymphoma; EATL, enteropathy-associated T-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; CLL, chronic lymphocytic leukemia.

LPD was defined as Hodgkin lymphoma, NHL, CLL, or multiple myeloma. NHL was further classified as EATL, non-EATL T-cell NHL, or B-cell NHL. Cases of B-cell NHL were subclassified as marginal zone lymphoma, mantle cell lymphoma, follicular lymphoma, DLBCL, or post-transplant LPD. All cases of LPD were confirmed by histopathology, immunophenotype, cytogenetics, and radiographic data as available; then staged according to the Ann Arbor staging system for Hodgkin and NHL or Rai classification system for CLL.

We calculated age and sex-adjusted standardized incidence ratios (SIR) and correlating 95% confidence intervals (95% CI) using the Surveillance, Epidemiology, and End Result (SEER) database to estimate the expected incidences of LPD subtypes in the general U.S. population. The SEER database is a resource established by the National Cancer Institute that collects cancer statistics from specific geographic areas representing 28% of the U.S. population [17]. The SIR was not calculated for a LPD subtype if the observed incidence was less than two or if the expected incidence was zero. In addition, we calculated the number of person-years at risk for each age group starting from diagnosis of celiac disease and ending with the diagnosis of LPD, death, or the last follow-up date in this analysis. Because patients who were diagnosed with LPD before diagnosis of celiac disease contributed no person-years at risk, we performed a sensitivity analysis, repeating the calculation of SIRs while excluding this group of individuals.

Throughout the analysis, a two-tailed *P*-value less than 0.05 was considered significant. For the survival analysis, SAS software (version 9.2, Cary, NC) was used to create Kaplan Meier curves, and equality testing was performed using log rank test with alpha cutoff of 0.05.

Results

There were 1,285 celiac disease patients in our cohort with a total of 12,693 person-years of observation (Table I). There were 46 patients (3.5%) diagnosed with celiac disease before 1980, 62 patients (4.8%) diagnosed in the 1980s, 365 patients (28.4%) diagnosed in the 1990s, and 812 patients (63.2%) diagnosed in the 2000s. Of the 40 patients with celiac disease and LPD, two (5%) were diagnosed with celiac disease before 1980, one (2.5%) was diagnosed in the 1980s, 17 (42%) were diagnosed in the 1990s, and 20 (50%) were diagnosed in the 2000s. The mean duration of follow-up for patients with celiac only was 10.6 ± 8.2 years versus 6.6 ± 7.5 years in patients with celiac and LPD.

Of the 1,285 patients with celiac disease, 40 patients with LPD (SIR 6.48, 95% CI 4.62–8.64) were identified. There were 33 patients with NHL, one with Hodgkin lymphoma, and six with CLL, but no patient with multiple myeloma was identified. The SIRs for each LPD subtype are shown in Table II. Of the 33 patients with NHL, there were 16 cases of B-cell NHL, five cases of non-EATL T-cell lymphoma, and 12 cases of EATL. Due to the rarity of EATL cases in the SEER database, the expected incidence of EATL is listed as zero, and therefore, we were unable to calculate the SIR of EATL. Non-EATL T-cell lymphoma included one patient with cutaneous T-cell lymphoma, two patients with peripheral T-cell lymphoma, and two patients with NK-T cell leukemia/lymphoma. Of the 16 cases of B-cell NHL, there were six cases of DLBCL, three cases of mantle cell lymphoma, five cases of marginal zone lymphoma, one case of follicular lymphoma, and one case of post-transplant LPD.

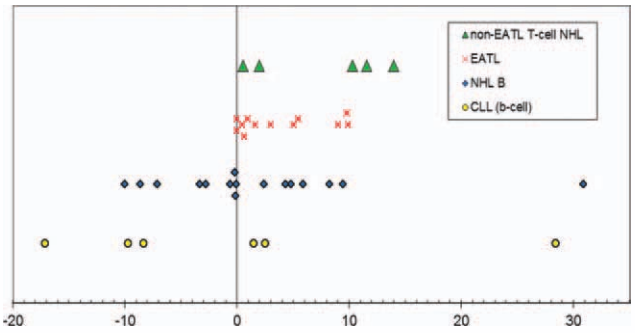

Figure 1. Timing of LPD development in relationship to celiac disease diagnosis. Each horizontal line on the *y*-axis represents a different category of LPD and each point represents one patient (green triangle = T-cell NHL, red x = EATL, blue diamond = B-cell NHL, yellow circle = CLL). The *x*-axis represents time between celiac disease diagnosis and LPD diagnosis, with $x = 0$ representing time of celiac disease diagnosis. Points to the right of the *y*-axis represent patients diagnosed with LPD after celiac disease and points to the left of the *y*-axis represent patients diagnosed with LPD before celiac disease. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Of the 1,285 patients with celiac disease, 905 (70%) were women and 380 (30%) were men. Twenty-four (60%) of the 40 patients diagnosed with LPD were women, 16 (40%) were men. The proportion of women with celiac disease diagnosed with concurrent LPD was 0.027, the proportion of males with celiac disease and concurrent LPD was 0.042 (Table I). The SIRs of LPD overall in men (SIR 6.01, 95% CI 3.42–9.31) and women (SIR 6.84, 95% CI 4.37–9.84) were similar (Table II).

The timing of the diagnosis of lymphoma in relationship to the timing of the diagnosis of celiac disease is shown in Fig. 1. Twenty-four patients were diagnosed with celiac disease before LPD, six patients were diagnosed with celiac disease and LPD concurrently (defined as ± 6 months), and 10 patients were diagnosed with celiac disease after LPD. No T-cell lymphoma was diagnosed before the diagnosis of celiac disease, whereas B-cell lymphoma was diagnosed both before and after the diagnosis of celiac disease. Of the patients with T-cell NHL (EATL and non-EATL), 14 were diagnosed with celiac disease before LPD, while three were diagnosed with celiac and LPD concur-

TABLE III. SIRs and 95% Confidence Intervals for Patients Diagnosed with Celiac Disease Before LPD (*N*=24)

Category	*N*	SIR	95% CI
LPD overall	24	3.89	2.48–5.60
LPD men	10	3.75	1.79–6.44
LPD women	14	3.99	2.17–6.35
NHL overall (B-cell and T-cell)	21	4.47	2.86–6.44
NHL: excluding EATL	12	2.79	1.56–4.39
NHL: B-cell	7	1.49	0.59–2.80
DLBCL	2	1.79	0.17–5.13
Mantle	2	21.47	2.02–61.54
Marginal	3	22.30	4.20–54.68
Follicular	0	n/a	n/a
Post-transplant LPD	0	n/a	n/a
NHL: T-cell (non-EATL)	5	22.43	7.08–46.41
EATL	9	n/a	n/a
Hodgkin	0	n/a	n/a
CLL	3	2.43	0.46–5.95
Multiple myeloma	0	n/a	n/a

SIRs, standardized incidence ratios; LPD, lymphoproliferative disorder; NHL, non-Hodgkin lymphoma; EATL, enteropathy-associated T-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; CLL, chronic lymphocytic leukemia.

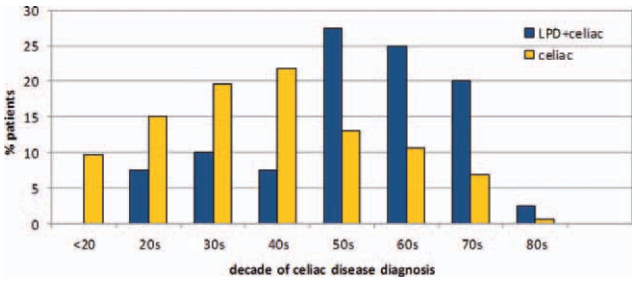

Figure 2. Age at celiac disease diagnosis in patients with and without LPD. The decade of life during which celiac disease was diagnosed is on the *x*-axis and the percentage of patients diagnosed during each decade of life is on the *y*-axis. The yellow bars represent patients with celiac disease only and the blue bars represent patients with celiac disease and LPD. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

rently. Of those with B-cell NHL, seven were diagnosed with celiac disease before LPD, three were diagnosed with celiac disease and LPD concurrently, and six were diagnosed with celiac disease after LPD. Half of the six patients with CLL were diagnosed with celiac disease before LPD and half were diagnosed with celiac disease after LPD (Fig. 1). When only those patients diagnosed with celiac disease before LPD were considered ($N = 24$, Table III), the SIR results were similar to those calculated using all 40 cases of LPD. The SIRs of LPD overall, NHL overall, mantle cell lymphoma, marginal zone lymphoma, and non-EATL T-cell NHL remained significantly elevated. The prevalence of EATL remained high in this cohort, and the SIRs of LPD in men and women remained similarly elevated. However, the SIRs of DLBCL and CLL were no longer significantly elevated (Table III).

The mean age at celiac disease diagnosis in the cohort was 43.0 ± 17.5 years. The mean age at celiac diagnosis was later in men compared with women (average age in men 45.8 ± 18.1 years versus 41.8 ± 17.1 years in women, *P*-value = 0.0002, Table I). Patients who were diagnosed with LPD were diagnosed with celiac disease at a later age than patients who were not diagnosed with LPD (average age 57.8 ± 15.5 years versus 42.5 ± 17.4 years, *P*-value <0.0001, Table I, Fig. 2).

Patients with celiac disease and LPD were more likely to present with diarrhea (60.0% versus 39.8%, *P*-value 0.016), abdominal pain (17.5% versus 5.5%, *P*-value 0.0046), and/or weight loss (12.5% versus 4.0%, *P*-value

TABLE IV. Symptoms at Time of Celiac Disease Diagnosis in Patients with and without LPD

Symptom	Celiac only *N* (%)	Celiac and LPD *N* (%)	Celiac and LPD (Excluding patients diagnosed concurrently)
Diarrhea	492 (39.8%)	24 (60.0%)	21 (61.8%)
		$P = 0.016$	$P = 0.010$
Abdominal pain	68 (5.5%)	7 (17.5%)	7 (20.6%)
		$P = 0.0046$	$P < 0.0001$
Weight loss	50 (4.0%)	5 (12.5%)	5 (14.7%)
		$P = 0.028$	$P = 0.0026$
Anemia	169 (13.7%)	8 (20.0%)	8 (23.5%)
		$P = 0.36$	$P = 0.10$
Screening	193 (15.6%)	3 (7.5%)	2 (5.9%)
		$P = 0.24$	$P = 0.12$
Incidental	58 (4.7%)	1 (2.5%)	1 (2.9%)
		$P = 0.79$	$P = 0.63$
Bone disease	68 (5.5%)	2 (5.0%)	2 (5.9%)
		$P = 0.83$	$P = 0.92$
Dermatitis herpetiformis	20 (1.6%)	1 (2.5%)	0 (0.0%)
		$P = 0.84$	$P = 0.46$

LPD, lymphoproliferative disorder.

TABLE V. Characteristics and Symptoms of Patients with EATL versus All Other Types of LPD

	EATL	Other LPD
N	12	28
Characteristics		
Age at CD dx (SD) years	48.6 (14.7)	59.2 (15.8)
Age at LPD dx (SD) years	58.3 (15.0)	61.5 (12.7)
Number of women (%)	6 (50.0)	18 (64.3)
Number of men (%)	6 (50.0)	10 (35.7)
Preceding RCD2 (%)	2 (16.7)	0 (0.0)
Symptoms		
Diarrhea (%)	75.0	53.6
Incidental (%)	0.0	3.6
Screen (%)	0.0	10.7
Bone disease (%)	0.0	7.1
Anemia (%)	8.3	25.0
Weight loss (%)	8.3	14.3
Abdominal pain (%)	8.3	21.4
Lymphoma (%)	8.3	17.9
Dermatitis herpetiformis (%)	0.0	3.6
Neuropathy (%)	0.0	0.0

EATL, enteropathy associated T-cell lymphoma; LPD, lymphoproliferative disorder; CD, celiac disease; SD, standard deviation; RCD2, refractory celiac disease Type 2.

0.028) at time of celiac disease diagnosis than patients who did not develop LPD. There was no difference in the frequency of anemia, bone disease, or dermatitis herpetiformis at time of celiac disease presentation. The frequencies of diagnosis by screening in patients with a positive family history if celiac disease and incidental diagnosis of celiac disease during endoscopy performed for other indications were similar in the two groups. These results did not significantly change when those diagnosed with celiac disease and LPD concurrently were excluded (Table IV).

Patients with EATL were diagnosed with celiac disease at a younger average age than those with other types of LPD (48.6 ± 14.7 versus 59.2 ± 15.8 years, $P = 0.06$) and were also diagnosed with EATL at a younger average age than celiac disease patients with other subtypes of LPD (58.3 ± 15.0 versus 61.5 ± 12.7 years, $P = 0.55$), but these trends were not statistically significant. Seventy-five percentage of patients with EATL presented with diarrhea at time of initial celiac disease diagnosis (Table V).

The pattern of DLBCL presentation in our cohort of celiac disease patients was atypical compared with the pattern of presentation of DLBCL in the general population. All six

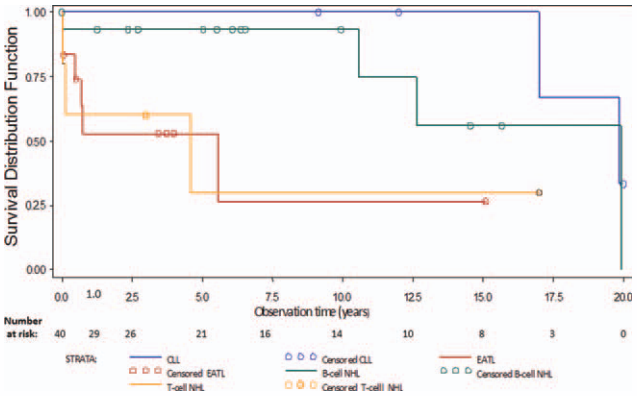

Figure 3. Survival by LPD subtype. The observation time is on the *x*-axis, with $t = 0$ representing time at LPD diagnosis. The proportion of patients living is on the *y*-axis. Open circles represent the time point at which data was right-censored for a single patient. Right-censoring was necessary due to staggered entry and loss to follow-up. The number at risk at each time point is listed below the *x*-axis. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

DLBCL patients had extranodal disease with DLBCL confined to the GI tract in four of the six patients; one with jejunal DLBCL, two with gastric DLBCL, and one with DLBCL of the transverse colon. The fifth patient presented with a malignant pleural effusion and a jejunal mass; however, an intestinal biopsy was not obtained to determine the etiology of the jejunal abnormality. The sixth patient also had extranodal DLBCL with isolated long bone involvement. All five patients with marginal zone lymphoma had typical presentations. There were two cases of splenic marginal zone in patients who presented with splenomegaly, one case of nodal marginal zone in a patient who presented with lymphadenopathy, and two cases of localized extranodal marginal zone lymphoma of the mucosa associated lymphoid tissue (MALT) type. Both cases of MALT lymphoma were gastric MALT in *Helicobacter pylori* negative patients. All three patients with mantle cell lymphoma presented with Stage IV disease; no case of mantle cell involved the gastrointestinal tract. All patients with EATL has gastrointestinal tract involvement; six of the 12 patients with EATL presented with Stage I disease, four with Stage II disease, and two with Stage IV disease. All six patients with CLL presented classically with asymptomatic lymphocytosis with or without lymphadenopathy, splenomegaly, anemia, and/or thrombocytopenia.

Fifteen of the 40 patients with celiac disease and LPD died during the study period. The mean survival for patients with EATL or non-EATL T-cell NHL was short (mean survival 3.2 ± 0.9 years and 2.8 ± 1.2 years, respectively) compared with patients with B-cell NHL or CLL (mean survival 15.5 ± 2.3 years and 18.9 ± 1.1 years, respectively, $P = 0.033$; Fig. 3).

Discussion

We describe an increased incidence of LPD, particularly various types of NHL, in patients with celiac disease seen at a tertiary care referral center compared with that of the general U.S. population. Although the increased risk of T-cell lymphoma is generally appreciated in this population [13–16,18], in this study, the incidence of T-cell NHL ($N = 17$) and B-cell NHL ($N = 16$) were equally elevated in individuals with biopsy proven celiac disease. For B-cell NHL subtypes, similar to prior studies, an increased incidence of DLBCL was noted. We also found an increased incidence of marginal zone and mantle cell lymphoma, subtypes that frequently involve the gastrointestinal tract but have not previously been thought to be strongly associated with celiac disease. Marginal zone lymphoma is classically associated with conditions that cause chronic inflammation, such as *H. pylori* infection or Sjogren's disease [19,20]. Therefore, the high prevalence of marginal zone lymphoma in patients with celiac disease, a chronic inflammatory disorder of the bowel, is not surprising and has been suggested but not quantified previously. The majority of mantle cell lymphomas are thought to arise from naïve B-cell precursors or B-cells that have not been antigenically stimulated [21]. However, recent studies have shown that ~20% of mantle cell lymphomas exhibit evidence of somatic hypermutation suggesting an origin from B-cells that have transited the germinal center [22,23]. If it is determined that patients with celiac disease develop mantle cell lymphomas with mutated immunoglobulin variable region genes, a common pathophysiologic mechanism between mantle cell and marginal zone lymphoma may be uncovered. On the other hand, no cases of multiple myeloma were detected with 1.23 cases expected. This may either represent an absence of increased risk or possibly a decreased risk of multiple myeloma in patients with celiac disease. Although there is a paucity of data on the incidence of multiple myeloma in patient with celiac disease, this finding is consistent with the absence of increased risk recently described by Elfström et al. [15].

The increased incidence of DLBCL in our cohort was similar to that described in previous studies [16]; however, the mode of DLBCL presentation in our cohort of celiac disease patients was atypical. In the general population nodal, DLBCL is more common than extranodal DLBCL, which accounts for ~25%–30% of DLBCL cases. The most common primary sites of extranodal DLBCL include the gastrointestinal tract, skin, bones, central nervous system, and testes [24]. In our cohort, all six patients with DLBCL had extranodal disease. Additionally, four of the six patients had isolated primary gastrointestinal disease. Although screening for celiac disease in all patients with lymphoma has not been shown to be of value [25,26], celiac disease screening may be indicated in those diagnosed with extranodal DLBCL of the gastrointestinal tract.

It is generally accepted that the incidence of LPD is higher in males than females [27–29]. The fact that autoimmune conditions are more common in females than males has also been well described [30–32]. The 3:7 male to female ratio in our cohort is similar to the gender distribution reported in prior studies of celiac disease patients. Similar to LPD overall, the prevalence of LPD in males with celiac disease was higher than females with celiac disease. However, comparable SIRs of LPD in males and females in our cohort argues against gender as an independent risk factor for development of LPD in celiac disease.

Silano et al. [33] suggest that the risk of malignancy is increased in patients who are diagnosed with celiac disease later in life. Similarly, we found that patients diagnosed with celiac disease after age 50 were more likely to develop LPD than those diagnosed with celiac disease before age 50. This suggests that a prolonged period of continued gluten ingestion before celiac disease diagnosis may be a risk factor for developing LPD and, therefore, age at celiac disease diagnosis should be considered when trying to identify celiac disease patients at increased risk of developing LPD.

Corrao et al. [34] reported increased mortality in celiac disease patients who initially present with a malabsorption syndrome compared with celiac disease patients who present with mild or absent symptoms. The increased mortality was attributed to malignant complications, most commonly lymphoma. In our cohort, patients who presented with diarrhea, abdominal pain, and/or weight loss were more likely to develop LPD than those without these symptoms. To

ensure these symptoms were not due to an underlying LPD rather than celiac disease, a second comparison was performed excluding patients diagnosed with celiac disease and LPD concurrently with unchanged results (Table IV). The presence of anemia, bone disease, dermatitis herpetiformis, and a family history of celiac disease were similar in celiac disease patients with and without LPD. The presence of diarrhea or a malabsorption syndrome at time of celiac disease diagnosis may indicate a higher degree of local intestinal inflammation, may correlate with intensity of the systemic inflammatory response, and could be used to help identify patients at increased risk of developing complications of chronic inflammation such as LPD.

Although prognosis varies greatly among the various subtypes of T-cell and B-cell lymphoma, in general patients with T-cell NHL have a poorer prognosis than those with B-cell NHL. Halfdanarson et al. [35] recently reported a decreased 5-year and 10-year survival in celiac disease patients with T-cell lymphoma compared with celiac disease patients with B-cell lymphoma. We also found that, similar to the general population, the mean survival of celiac disease patients with T-cell NHL, including EATL and non-EATL T-cell NHL, is decreased compared with celiac disease patients with B-cell NHL, including B-cell NHL and CLL. Considering the difference in survival among patients with various LPD subtypes, we suggest that it is crucial to differentiate among LPD subtypes when determining prognosis in patients with LPD and underlying autoimmune or chronic inflammatory conditions. We are not aware as to whether LPD patients with celiac disease have different survival rates compared with LPD patients without celiac disease.

The risk for EATL was increased markedly because it is so rare in the general population that it is not represented as a NHL subtype in the SEER database. Sharaiha et al. [36] estimated that the incidence of EATL was 0.016 to 0.024 per 100,000 in the United States during the study period. All EATL cases occurred either concurrently or up to 10 years after the diagnosis of celiac disease. The prognosis for these patients was poor.

Elfström et al. reported an increased risk of lymphoma in patients with chronic intestinal inflammation and histopathologically diagnosed celiac disease. However, patients with latent celiac disease, or positive serology without evidence of intestinal inflammation, were not at risk [15]. One major strength of our study was that the cohort only included cases of biopsy proven celiac disease, which is the presumed at risk population. Other strengths included the large size of the cohort and long follow-up period, which included over 12,000 person-years of observation. The vast majority of patients were seen as nonhospitalized patients. Conducting the study in an outpatient setting was another strength because, unlike studies that solely include hospitalized patients, the results of an outpatient study are more applicable to the general celiac disease population. The detailed clinical description of a relatively large number of celiac disease patients with concurrent LPD and subsequent comparison between these patients and celiac disease patients without LPD within the same referral cohort were the major strengths of the study.

Patients seen at a tertiary care celiac disease referral center may be referred due to the presence of complicated or severe disease, and the prevalence of LPD may be overestimated in our cohort due to referral bias. On the other hand, considering that many patients presented for a second or third opinion and then were lost to follow-up the prevalence of LPD may also have been underestimated. Since approximately one-third of patients were lost to follow-up and, therefore, were presumed to be living, mortality may have been underestimated in our study. Additionally, it is possible that patients seen at a tertiary care center receive more aggressive screening for LPD and therefore survival may be overestimated in this cohort. The absence of population-based data on EATL in the SEER database was another limitation of the study. Finally, we did not have detailed information regarding adherence to the gluten-free diet so as to assess the relationship between dietary adherence and LPD risk [37].

The pathophysiologic mechanism linking chronic inflammation to LPD is poorly understood and likely multifactorial. Loss of epithelial barrier function, systemic migration of aberrant small intestinal T-cells, inhibition of DNA repair mechanisms, and dysfunctional immune surveillance all may contribute to the increased incidence of LPD in patients with celiac disease. The inflammatory microenvironment includes cytokines and growth factors that lead to migration or accumulation of inflammatory cells, cell proliferation, and angiogenesis all fostering tumor development [38,39]. Further studies are needed to elucidate the underlying mechanisms of both local and distant tumorigenesis in celiac disease.

In conclusion, we found an elevated incidence of multiple LPD subtypes among patients with celiac disease. In the future, the association between celiac disease and various LPD subtypes could be further analyzed to identify common molecules in the inflammatory and lymphoproliferative pathways as promising targets for drug design. These findings could then be studied to risk stratify patients with regard to lymphoma, devise surveillance protocols, and propose preventative strategies in celiac disease patients with increased risk of developing LPD.

References

1. Green PH, Cellier C. Celiac disease. N Engl J Med 2007;357:1731–1743.
2. Rubio-Tapia A, Kyle RA, Kaplan EL, et al. Increased prevalence and mortality in undiagnosed celiac disease. Gastroenterology 2009;137:88–93.
3. Murray JA, Van Dyke C, Plevak MF, et al. Trends in the identification and clinical features of celiac disease in a North American community, 1950–2001. Clin Gastroenterol Hepatol 2003;1:19–27.
4. Ludvigsson JF, Montgomery SM, Ekbom A, et al. Small-intestinal histopathology and mortality risk in celiac disease. JAMA 2009;302:1171–1178.
5. Metzger MH, Heier M, Maki M, et al. Mortality excess in individuals with elevated IgA anti-transglutaminase antibodies: The KORA/MONICA Augsburg cohort study 1989–1998. Eur J Epidemiol 2006;21:359–365.
6. West J, Logan RF, Smith CJ, et al. Malignancy and mortality in people with celiac disease: Population based cohort study. BMJ 2004;329:716–719.
7. Peters U, Askling J, Gridley G, et al. Causes of death in patients with celiac disease in a population-based Swedish cohort. Arch Intern Med 2003;163: 1566–1572.
8. Green PH, Fleischauer AT, Bhagat G, et al. Risk of malignancy in patients with celiac disease. Am J Med 2003;115:191–195.
9. Freeman HJ. Lymphoproliferative and intestinal malignancies in 214 patients with biopsy-defined celiac disease. J Clin Gastroenterol 2004;38:429–434.
10. Gao Y, Kristinsson SY, Goldin LR, et al. Increased risk for non-Hodgkin lymphoma in individuals with celiac disease and potential family association. Gastroenterology 2009;136:91–98.
11. Smedby KE, Hjalgrim H, Askling J, et al. Autoimmune and chronic inflammatory disorders and risk of non-Hodgkin lymphoma by subtype. J Natl Cancer Inst 2006;98:51–60.
12. Smedby KE, Akerman M, Hildebrand H, et al. Malignant lymphomas in coeliac disease: Evidence of increased risks for lymphoma types other than enteropathy-type T cell lymphoma. Gut 2005;54:54–59.
13. Anderson LA, Gadalla S, Morton LM, et al. Population-based study of autoimmune conditions and the risk of specific lymphoid malignancies. Int J Cancer 200915;125:398–405.
14. Catassi C, Fabiani E, Corrao G, et al; Italian Working Group on Coeliac Disease and Non-Hodgkin's-Lymphoma. Risk of non-Hodgkin lymphoma in celiac disease. JAMA 2002;287:1413–1419.
15. Elfström P, Granath F, Ekström Smedby K, et al. Risk of lymphoproliferative malignancy in relation to small intestinal histopathology among patients with celiac disease. J Natl Cancer Inst 2011;103:436–444.
16. Kane EV, Newton R, Roman E. Non-Hodgkin lymphoma and gluten sensitive enteropathy: Estimate of risk using meta-analyses. Cancer Causes Control 2011;22:1435–1444.
17. Available at: http://www.seer.cancer.gov/seerstat. National Cancer Institute, accessed on September, 2011.

18. Smedby KE, Vajdic CM, Falster M, et al. Autoimmune disorders and risk of non-Hodgkin lymphoma subtypes: A pooled analysis within the InterLymph Consortium. Blood 2008;111:4029.
19. Martin DN, Mikhail IS, Landgren O. Autoimmunity and hematologic malignancies: Associations and mechanisms. Leuk Lymphoma 2009;50:541–550.
20. Suarez F, Lortholary O, Hermine O, Lecuit M. Infection-associated lymphomas derived from marginal zone B cells: A model of antigen-driven lymphoproliferation. Blood 2006;107:3034–3044.
21. Lenz G, Staudt LM. Aggressive lymphomas. N Engl J Med 2010;362: 1417–1429.
22. Walsh SH, Thorsélius M, Johnson A, et al. Mutated VH genes and preferential VH3-21 use define new subsets of mantle cell lymphoma. Blood 2003; 101:4047.
23. Kienle D, Kröber A, Katzenberger T, et al. VH mutation status and VDJ rearrangement structure in mantle cell lymphoma: Correlation with genomic aberrations, clinical characteristics, and outcome. Blood 2003;102:3003.
24. López-Guillermo A, Colomo L, Jiménez M, et al. Diffuse large B-cell lymphoma: Clinical and biological characterization and outcome according to the nodal or extranodal primary origin. J Clin Oncol 2005;23:2797–2804.
25. Carroccio A, Iannitto E, Di Prima L, et al. Screening for celiac disease in non-Hodgkin's lymphoma patients: A serum anti-transglutaminase-based approach. Dig Dis Sci 2003;48:1530–1536.
26. Cil T, Altintaş A, Işikdogan A, et al. Screening for celiac disease in Hodgkin and non-Hodgkin lymphoma patients. Turk J Gastroenterol 2009;20:87–92.
27. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010;60:277–300.
28. Smith A, Roman E, Howell D, et al. The Haematoligical Malignancy Research Network (NHRN): A new information strategy for population based epidemiology and health service research. Br J Haematol 2010;148:739–753.
29. Roman E, Smith AG. Epidemiology of lymphomas. Histopathology 2011;58:4–14.
30. Gleicher N, Barad DH. Gender as risk factor for autoimmune diseases. J Autoimmun 2007;28:1–6.
31. Fairweather D, Frisancho-Kiss S, Rose NR. Sex differences in autoimmune disease from a pathological perspective. Am J Pathol 2008;173:600–609.
32. Invernizzi P, Pasini S, Selmi C, et al. Female predominance and X chromosome defects in autoimmune diseases. J Autoimmun 2009;33:12–16.
33. Silano M, Volta U, Mecchia AM, et al. Delayed diagnosis of coeliac disease increases cancer risk. BMC Gastroenterol 2007;7:8.
34. Corrao G, Corazza GR, Bagnardi V, et al. Mortality in patients with celiac disease and their relatives: A cohort study. Lancet 2001;358:356–361.
35. Halfdanarson TR, Rubio-Tapia A, Ristow KM, et al. Patients with celiac disease and B-cell lymphoma have a better prognosis than those with T-cell lymphoma. Clin Gastroenterol Hepatol 2010;8:1042–1047.
36. Sharaiha RZ, Lebwohl B, Reimers L, et al. Increasing incidence of enteropathy-associated T-cell lymphoma in the United States, 1973–2008. Cancer 2011 Dec 13. [Epub ahead of print].
37. Olén O, Askling J, Ludvigsson JF, et al. Coeliac disease characteristics, compliance to a gluten free diet and risk of lymphoma by subtype. Dig Liver Dis 2011;43:862–868.
38. Westbrook AM, Szakmary A, Schiestl RH. Mechanisms of intestinal inflammation and development of associated cancers: Lessons learned from mouse models. Mutat Res 2010;705:40–59.
39. Verbeek WHM, von Blomberg BM, Coupe VM, et al. Aberrant T-lymphocytes in refractory coeliac disease are not strictly confined to a small intestinal intraepithelial location. Cytometry Part B 2009;76B:367–374.