Patients With Celiac Disease and B-Cell Lymphoma Have a Better Prognosis Than Those With T-Cell Lymphoma

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BACKGROUND & AIMS: Celiac disease (CD) is associated with an increased risk of lymphoma. However, relatively few studies have assessed the outcome of patients diagnosed with both CD and lymphoma. We evaluated the temporal association between lymphoma and CD, along with clinical presentation, response to therapy, and prognosis. **METHODS:** Patients diagnosed with both CD and lymphoma were identified retrospectively in a tertiary referral center. Clinical characteristics and survival were analyzed. **RESULTS:** Sixty-three patients (36 men) were identified who had been diagnosed with lymphoma and CD. Thirty-six (57%) were diagnosed with CD before they were diagnosed with lymphoma. The most common histologic entity was diffuse, large, B-cell lymphoma, which affected 18 (29%) patients. Complete information for staging was available in 59 patients; 24 (38%) had stage IV disease. Only chemotherapy or only radiation therapy was used for 43 (68%) and 11 (17%) patients, respectively. The 5- and 10-year cumulative survival rates for the entire cohort were 58% and 39%, respectively. Survival of patients with T-cell lymphoma was shorter than for all other lymphomas (119.4 vs 22.8 mo; $P = .02$). **CONCLUSIONS: CD is associated with B- and T-cell lymphomas. Patients with B-cell lymphomas had a better prognosis than those with T-cell lymphoma. Therapy is unsatisfactory for enteropathy-type T-cell lymphoma.**

Keywords: Cancer; Enteropathy; GI Disease; Gluten.

Celiac disease (CD) is a common autoimmune systemic disorder resulting from ingestion of gluten-containing foods, a major storage protein of wheat, barley, and rye.[1] CD may affect as many as 1% of the general population, and the prevalence appears to be increasing over time.[2–4] Most intestinal and extraintestinal manifestations of CD are reversible after treatment with a gluten-free diet.[1] Severe complications and increased mortality may develop in the absence of treatment of symptomatic CD.[5] Indeed, untreated CD has been associated with various hematologic complications, including lymphoma.[6]

The association of CD and lymphoma has been known for decades, and earlier studies suggested the risk of contracting lymphoma was high.[6–13] The risk of lymphoma in the setting of CD likely is lower than previously thought because of the inclusion of high-risk patients in the historical estimates (eg, patients with refractory sprue) and a higher background prevalence of subclinical CD.[11] Recent studies using large databases have suggested the risk of lymphoma in patients with clinically diagnosed CD may be as high as 5 times what is seen in the general population, and this risk seems to have diminished over the past decades.[8,9] The association of CD (especially refractory CD type 2) with enteropathy-type T-cell lymphoma (ETL) appears particularly strong with standardized incidence ratios being as high as 24 and odds ratios of 28.[9,10,14] ETL is a very rare disease,[15] thus, despite the strong association of CD with ETL, the majority of lymphomas associated with CD are of the non-ETL type.[7,9,10] Other types of lymphomas observed in patients with CD include B-cell lymphomas (eg, diffuse large B-cell lymphoma, DLBCL) and non-ETL T-cell lymphomas (eg, peripheral T-cell lymphoma).[10,11] About 35% of ETL patients are associated with a previous clinical history of adult-onset CD.[16] In more than 90% of ETL there is histologic evidence of enteropathy-like alterations in the gastrointestinal mucosa adjacent to the invasive tumor.[12,16] Strict adherence to a gluten-free diet may decrease the risk of lymphomagenesis and development of other cancers associated with untreated CD.[17,18] Finally, lymphomagenesis can occur in a minority of patients with CD and persistent villous atrophy despite treatment with a gluten-free diet, even in the absence of symptoms related to CD.[19,20]

The mechanisms of lymphomagenesis in CD are poorly understood but likely multifactorial. Change to a monoclonal phenotype, clonal expansion, and increased survival of intraepithelial lymphocytes induced at least in part by the uncontrolled overexpression of interleukin-15 by enterocytes in patients with refractory CD type 2, may promote the emergence of T-cell clonal proliferations and lymphoma.[21] Thus, refractory CD associated with clonal intraepithelial lymphocytes is associated with a high risk for T-cell lymphoma over time.[22–24] Indeed, lymphomagenesis (eg, ETL) may occur in 60% to 80% of patients with refractory CD type 2 (characterized by clonal intraepithelial lymphocytes) and occasionally in patients with refractory CD type 1.[14,25–27] There is no established therapy to prevent progression to lymphoma in refractory CD type 2.[28,29] Allelic imbalances with complex chromosomal gains at 9q or losses at 16q are present in most cases of ETL.[30] Partial trisomy of the 1q region (1q22-q44) is strongly associated with refractory CD and can be present in 16% of patients with ETL.[31,32] Homozygosity for HLA-DQ2 and myosin IXB gene (MYO9B) polymorphism (rs7259292) are associated with increased risk of ETL in European patients with CD.[33,34] The mechanisms underlying extraintestinal lymphomagenesis in CD are unknown.

Abbreviations used in this paper: CD, celiac disease; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; DLBCL, diffuse large B-cell lymphoma; ETL, enteropathy-type T-cell lymphoma; IPI, International Prognostic Index.

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Although the literature on the epidemiology of CD-associated lymphomas is ample, relatively few studies have assessed the outcome of individual patients.[11,16,35] The clinical course of ETL is highly aggressive, with most patients dying of the disease within months of diagnosis.[14,16] The results of chemotherapy alone or chemotherapy and autologous stem cell transplantation for ETL are very poor with few long-term survivors.[16,36]

The aim of our study was to retrospectively review all cases of lymphoma in patients who also carried the diagnosis of CD and determine the temporal association of the lymphoma with CD, the clinical presentation, response to therapy, and prognosis.

Materials and Methods

Patients

Patients carrying the diagnosis of both CD and lymphoma were identified through the Mayo Clinic patient registry and the Mayo Clinic Lymphoma Database. Patients diagnosed with lymphoma in the period from 1970 to 2005 who also had a diagnosis of CD were included. Details of presenting history, physical examination, staging investigations, treatment, and clinical outcome were extracted from patient records. We collected information necessary to perform accurate lymphoma staging and to apply the International Prognostic Index (IPI) to all patients.[37] Lymphoma staging was performed according to the Ann Arbor staging system.[38] Information on therapy and to assess response was also collected where available. Complete remission was defined as a return to normal by all documented tumor sites. Partial remission was defined as a more than 50% reduction in disease bulk for at least 1 month. All other patients were regarded as nonresponders.

Statistical Analysis

Data were summarized using descriptive statistics. Overall survival was used as the primary outcome. Overall survival was defined as the number of months between the date of diagnosis of lymphoma and date of death (if the patient had died) or last follow-up evaluation. The date of death was obtained from the Mayo Clinic records. Survival was estimated using the Kaplan–Meier method, and log-rank statistics were computed to detect differences between survival curves for various prognostic factors. The χ^2 test was used for comparing categoric variables where appropriate. The nonparametric Wilcoxon rank-sum test was used for comparing the median of continuous variables between groups. All statistical analyses were performed using JMP 8.0.2 (SAS Institute, Cary, NC).

Results

Patients and Clinical Presentation

Sixty-three patients carrying both a diagnosis of lymphoma and CD were identified. Thirty-six (57%) were men, and 27 (43%) were women. The median age at the time of diagnosis of lymphoma was 62 years (range, 11–91 y). The lymphoma diagnosis was confirmed from 1975 to 1985 in 16 (25%), from 1986 to 1996 in 22 (35%), and from 1997 to 2005 in 25 (40%) patients. Thirty-six (57%) patients had CD diagnosed before being diagnosed with lymphoma. Four (6%) patients were diagnosed with CD and lymphoma simultaneously. The remaining 23 patients (37%) were diagnosed with CD after being diagnosed with lymphoma. The median time from diagnosis of CD to the diagnosis of lymphoma in those patients in whom CD preceded the lymphoma was 8.6 years (range, 0.1–45 y). All 8 patients with ETL either had a pre-existing diagnosis of CD or were diagnosed with CD at the time of the lymphoma diagnosis (median time from CD diagnosis to ETL diagnosis, 3 y; range, 0–22 y). In the 23 patients in whom the lymphoma preceded the CD, the median time from the diagnosis of lymphoma to the diagnosis of CD was 2.7 years (range, 0.1–32.9 y). The diagnosis of CD was confirmed to be biopsy-proven in 53 (84%) patients. Subtotal or total villous atrophy were present in 49 (92%) patients, but partial villous atrophy was present in another 4 patients. An increased number of intraepithelial lymphocytes were described in 23 of 24 patients for whom this information was available in the pathology report. Positive tissue transglutaminase antibody or endomysial antibodies were documented in 9 patients at the time of CD diagnosis. HLA genotyping was available in 8 patients (DQ2 heterozygous, n = 6; DQ2/DQ8, n = 1; and DQ8, n = 1). Seven patients had biopsy-proven dermatitis herpetiformis, including 3 with small-bowel biopsy compatible with CD and 4 without small-bowel biopsy. Lymphoma was diagnosed either after the diagnosis of dermatitis herpetiformis in 5 patients or before the diagnosis of dermatitis herpetiformis in 2 patients. Three were B-cell lymphomas (2 nodal, axilla and retroperitoneal nodes; and 1 small intestine), 2 were T-cell lymphomas (located in the colon and the liver), and 2 were unclassified lymphomas (located in the stomach and soft tissue).

Twenty-three (38%) patients presented with gastrointestinal lymphoma, 21 (33%) had nodal disease, and 18 (29%) had nongastrointestinal extranodal disease. The gastrointestinal lymphomas were located in the small bowel in 15 (65%) patients. Other gastrointestinal locations were the large intestine (n = 4), the liver (n = 3), and the stomach (n = 1). The pathology of small-bowel lymphomas included ETL (n = 8), B-cell lymphomas (n = 4), and unclassified lymphomas (n = 3). Ten (16%) patients presented with gastrointestinal emergencies, including 2 of the 8 patients with ETL. One of these patients presented with severe abdominal pain and possibly bowel perforation, and the other had severe gastrointestinal hemorrhage. Sixteen (25%) patients had B symptoms at the time of diagnosis (Table 1).

Pathology

The lymphoma histology varied among patients. The most common histologic entity was diffuse, large, B-cell lymphoma affecting 18 (29%) patients. Twelve (19%) patients had T-cell lymphoma other than ETL, 8 (13%) patients had ETL, and other histologies were less common (Table 2).

Staging and Prognostic Indicators

Sufficient information for staging was available for 59 (94%) patients. Fifteen (24%) patients presented with stage I disease, 18 (31%) presented with stage II, 2 (3%) presented with stage III, and 24 (41%) presented with stage IV according to the Ann Arbor criteria. B symptoms (fever, weight loss, and night sweats) were seen in 16 (25%) patients. Histologic type did not seem to affect the stage at diagnosis (data not shown). Thirty-two (54%) patients presented with IPI 0 to 1, 16 (27%) presented with IPI of 2, and 11 (19%) presented with IPI of 3 or higher. Patients with T-cell lymphoma had higher IPI and higher East-