

Screening for Celiac disease in Hodgkin and non-Hodgkin lymphoma patients

Hodgkin ve non-Hodgkin lenfoma olgularında Çölyak hastalığının gösterilmesi

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Background/aims: Celiac disease is an abnormal T cell-mediated immune response against dietary gluten in genetically predisposed individuals. The aim of our prospective study was to evaluate the frequency of Celiac disease in patients with lymphoma and to determine the usefulness of the anti-gliadin and anti-endomysial antibodies (EMA) for diagnosis of Celiac disease in this patient group. **Methods:** We studied 119 patients with previously or newly diagnosed non-Hodgkin's lymphoma and 60 patients with Hodgkin's lymphoma who presented at the hematology and medical oncology divisions of Dicle University Hospital in Turkey between December 2002 and January 2006. Serological screening for Celiac disease was performed in all patients by searching for serum anti-gliadin immunoglobulin A and immunoglobulin G, and EMA immunoglobulin A and immunoglobulin G. **Results:** In the Hodgkin's lymphoma group, anti-gliadin immunoglobulin A was detected in 9 (15%) patients (3 male, 6 female), and anti-gliadin immunoglobulin G was detected in 21 (35%) patients (15 male, 6 female). In the non-Hodgkin's lymphoma group, anti-gliadin immunoglobulin A was detected in 6 (5%) patients (2 M male 4 female), and anti-gliadin immunoglobulin G was detected in 30 (25.2%) patients (18 male, 12 female). EMA immunoglobulin A and immunoglobulin G were not detected in the Hodgkin's lymphoma and non-Hodgkin's lymphoma groups. **Conclusions:** Our report is the first to describe the frequency of Celiac disease in patients with lymphoma in the southeast region of Turkey. In our study, there was no evidence that Celiac disease is a pre-malignant condition for lymphoma. Serological screening for Celiac disease in lymphoma patients does not seem to be necessary.

Key words: Celiac disease, anti-endomysium antibody, anti-gliadin antibody, lymphoma

INTRODUCTION

Celiac disease (CD) is an abnormal T cell-mediated immune response against ingested gluten in genetically predisposed individuals, which leads to a typical inflammatory response in the small bowel mucosa. This inflammatory response is characterized by the clinical features of malabsorption. The prevalence of CD in the general population

Amaç: Çölyak hastalığı (ÇH) genetik olarak yatkın kişilerde diyetle alınan glutene karşı anormal T hücreli immünite ile oluşmaktadır. Bizim bu prospektif çalışmamızda amacımız lenfoma hastalarımızda Çölyak hastalığı sıklığını değerlendirmek ve bu grup hastalarda anti-gliadin ve anti-endomysyum antikorlarının Çölyak hastalığı tanısında kullanılabilirliğini saptamaktır. **Yöntem:** Dicle üniversitesi Tıp Fakültesi Hastanesi Medikal Onkoloji ve Hematoloji Kliniklerinde Aralık 2002-Ocak 2006 yılları arasında takipleri yapılmış 119 non-Hodgkin ve 60 Hodgkin lenfoma olgusu çalışmaya dahil edildi. Tüm olgulara Çölyak hastalığı'nın serolojik görüntülenmesi için serum anti-gliadin immunoglobulin A and immunoglobulin G, ve anti-endomysyum immunoglobulin A (EMA IgA), immunoglobulin G'e bakıldı. **Bulgular:** Hodgkin lenfoma grubundaki hastalarda; anti-gliadin immunoglobulin A 9 (15%) hastada (3 erkek ve 6 kadın), ve anti-gliadin immunoglobulin G 21 (35%) hastada (15 erkek ve 6 kadın) saptandı. Non-Hodgkin lenfoma grubundaki hastalarda; anti-gliadin immunoglobulin A 6 (5%) hastada (2 erkek ve 4 kadın), ve anti-gliadin immunoglobulin G 30 (25.2%) hastada (18 erkek ve 12 kadın) saptandı. EMA immunoglobulin A ve immunoglobulin G Hodgkin lenfoma and non-Hodgkin lenfoma gruplarında saptanmadı. **Sonuç:** Bu çalışma Türkiye'nin güneydoğu Anadolu bölgesinde lenfoma hastalarında çölyak hastalığı sıklığını araştıran ilk çalışmadır. Bizim çalışmamızda Çölyak hastalığı'nın lenfoma için premalign bir hastalık olduğuna dair bir bulgu saptanamamıştır. Lenfoma hastalarında Çölyak hastalığı için serolojik tarama gerekmediği saptanmıştır.

Anahtar kelimeler: Çölyak hastalığı, anti-endomysyum antikor, anti-gliadin antikor, lenfoma

is estimated to be about 1 in 200 subjects (1). Nonetheless, limited studies have been conducted in Turkey. In Ertekin et al.'s (2) studies, the prevalence rate of CD was detected 1 in 115-158 in the Turkish population. It is now clear that CD can present in adults of all ages, and that the clinical features are often subtle, leading to problems

such as mild anemia or fatigue (3,4). There are several clinical presentations of CD and patients usually present with diarrhea, weight loss, or symptoms suggesting malabsorption or anemia, whereas some of the patients remain asymptomatic or experience non-specific symptoms. The current diagnostic criterion for CD is the characteristic small-intestinal histology showing villous atrophy (5). The invasiveness of small intestinal biopsy has motivated the search for simpler and more acceptable screening tests for CD. Today, several serological tests of different sensitivity and specificity are used for the diagnosis of CD (6). The most sensitive and specific tests are IgA anti tissue transglutaminase (tTG) and IgA endomysial antibody (EMA), which have equivalent diagnostic accuracy. By contrast, antigliadin antibody (AGA) tests are no longer used routinely because of their lower sensitivity and specificity. IgA EMA had a positive predictive value of 100%; comparable values for IgG and IgA AGA were only 2 and 12% (7). The positive and negative predictive value of combining the measurement of IgA antibodies with tTG and IgA EMA levels has been reported to be 96-100% for diagnosis of CD (8-13).

Malignancy has been observed in 8-21% of CD patients, and about 50% of these were lymphomas (14). The most frequent malignancy associated with CD is a high grade T-cell non-Hodgkin's lymphoma (NHL) of the upper small intestine, currently defined as enteropathy-associated T-cell lymphoma, which peaks in the sixth or seventh decade of life (15). Additionally CD may be associated with other NHL types (16,17). The high rates of lymphoma observed in CD patients have been shown in several studies. However, there are limited case reports and studies reporting the rates of CD in lymphoma patients, and the exact incidence of CD in lymphomas is unknown (18-20). There are no large scale studies concerning the incidence of CD in lymphoma patients in the southeast region of Turkey. Therefore, we designed this present study at Dicle University Hospital to assess the incidence of CD in patients with HL and NHL.

MATERIALS AND METHODS

We studied 119 patients with previously or newly diagnosed NHL and 60 patients with HL who presented at the hematology and medical oncology divisions of Dicle University Hospital in Turkey between December 2002 and January 2006. The diagnosis of lymphoma was verified by histopathologi-

cal examination. Cases were categorized according to the World Health Organization (WHO) classification for lymphoma (21). Patients were assessed with regard to their characteristics including age, gender, histological distribution, and stage of the disease. The latter was determined using the Ann Arbor staging system. Patients were asked specific questions about the presence of signs or symptoms of CD, and any malabsorption, iron deficiency anemia, weight loss, and diarrhea was recorded. All of these patients were treated with chemotherapy and/or radiotherapy between December 2002 and January 2006, according to patient's characteristics and histopathology.

Serological screening was performed to determine the levels of autoimmune markers including AGA IgA, IgG and EMA IgA, IgG. Antibodies were detected in all lymphoma patients by fluorescence patterns as autoimmune markers with Euroimmun (Medizinische Labordiagnostika AG) immune fluorescence autoantibody determination kits. Total IgA levels were determined from the serum samples of all lymphoma patients. Patients who had known CD and had also undergone a complete serological evaluation for the diagnosis of CD as well as patients who had IgA deficiency were excluded from the study. All blood samples were taken before treatments. From the study inception, we excluded patients who were already receiving chemotherapy. Patients treated with chemotherapy or radiotherapy in the 6-12 months before blood samples for serological tests were excluded from the study because the treatments could affect the immunological response and reliability of the serological screening tests.

We had planned to perform endoscopic examination in all of our patients in order to confirm the diagnosis of CD, but some patients refused the procedure and others were unable to tolerate the process. Gastroduodenoscopic examination and intestinal biopsy were performed in 129 (72%) of all HL and NHL patients. Nonetheless, intestinal biopsy to confirm the diagnosis of suspected CD was used in 66 (36.8%) lymphoma patients with antibody positivity or clinical suspicion. In the intestinal histopathological analysis, more than three biopsy specimens were taken from the second part of the duodenum during gastroduodenoscopy. Hematoxylin-eosin staining was used in these specimens. Slides were graded by conventional histology as normal, with partial villous atrophy, and with subtotal villous atrophy.

Statistical Analysis

Mean variation, standard deviation (SD), and minimum and maximum values were calculated. Independent t test was used to determine the mean values of the variables. The relation of categorical variables was analyzed with the chi-square test. A p value <0.05 was accepted as statistically significant.

RESULTS

The NHL group consisted of 119 patients (71 M, 48 F), with a median age of 43 years (range: 17-79 years) in males and 39 years in females (range: 17-76 years). The HL group consisted of 60 patients (39 M, 21 F), with a median age of 41 years (range: 15-73 years) in males and 38 years (range: 16-77 years) in females. The study population for NHL included 20 patients (16.8%) with small lymphocytic lymphoma, 49 (41.1%) with diffuse large B-cell lymphoma, 25 (21%) with mantle cell lymphoma, 14 (11.8%) with mucosa associated lymphoid tissue (MALT) lymphoma, 4 (3.3%) with follicular lymphoma, and 7 (5.8%) with T cell lymphoma. The distribution of the 60 HL patients was as follows: 2 patients (3.3%) with lymphocyte-depletion lymphoma, 6 (10%) with lymphocyte-rich lymphoma, 19 (31.6%) with nodular sclerosis type lymphoma, and 33 (55%) with mixed cellularity subtype lymphoma. Ann Arbor clinical staging revealed that 23 patients (19.3%) had stage IV, 49 (41.1%) stage III, 31 (26%) stage II and 16 (13.4%) stage I disease in the NHL group. Clinical staging of the patients in the HL group revealed

that 13 patients (21.6%) had stage IV, 32 (53.3%) stage III and 15 (25%) stage II disease. The distribution of patients according to patient characteristics, subtypes and clinical staging of HL and NHL is shown in Table 1.

AGA IgA positivity was found in 9 (15%) patients (3 M, 6 F) and AGA IgG positivity was found in 21 (35%) patients (15 M, 6 F) in the HL group. In patients with NHL, AGA IgA positivity was found in 6 (5%) patients (2 M, 4 F) and AGA IgG in 30 (25.2%) patients (18 M, 12 F). There was a statistically significant difference in terms of AGA IgA positivity between patients with NHL and HL ($p=0.023$). EMA IgA and IgG positivity were not detected in any of the patients with HL or NHL. Antibody positivities in patient groups are presented in Table 2. Total serum IgA concentration was found to be within normal ranges in all patients. The most frequently observed symptoms were fatigue in 156 (75.9%), weight loss in 42 (23.4%), and anemia in 72 (40%) patients. B symptoms were detected in 58 (32.4%) patients. Diarrhea was determined in 22 (12.2%) patients with lymphoma. However, we were unable to detect any EMA or AGA positivity in these patients. In addition, we did not find any CD-related findings on endoscopic and histopathological examination in these 22 patients with diarrhea. Endoscopic and histopathological examinations were performed in all 66 (36.8%) patients who had AGA positivity. However, there were no positive findings related with CD in gastroduodenoscopic and histopathological examination of AGA IgA- or IgG-positive patients.

Table 1. Distribution of subtypes and stages of Hodgkin's lymphoma and non-Hodgkin's lymphoma

Characteristics of patients, subtypes and stages of disease	Hodgkin's Lymphoma (n:60)	Non-Hodgkin's Lymphoma (n:119)
Median age (years)		
Male	41	43
Female	38	39
Male/female	39/21	71/48
Lymphocyte depletion	2 (3.3%)	--
Lymphocyte rich	6 (10%)	--
Nodular sclerosis	19 (31.6%)	--
Mixed cellularity	33 (55%)	--
Small lymphocytic lymphoma	--	20 (16.8%)
Diffuse large B-cell lymphoma	--	49 (41.1%)
Mantle cell lymphoma	--	25 (21%)
MALT lymphoma	--	14 (11.8%)
Follicular lymphoma	--	4 (3.3%)
T cell lymphoma	--	7 (5.8%)
Ann Arbor Stages		
Stage I	--	16 (13.4%)
Stage II	15 (25%)	31 (26%)
Stage III	32 (53.3%)	49 (41.1%)
Stage IV	13 (21.6%)	23 (19.3%)

Table 2. Distribution of autoantibodies in patients with Hodgkin lymphoma and non-Hodgkin lymphoma autoantibodies

	Hodgkin Lymphoma (n:60) (%)	Non-Hodgkin Lymphoma (n=119) (%)	P value
AGA IgA	9 (15)	6 (5)	0.023*
AGA IgG	21 (35)	30 (25.2)	0.111
EMA IgA	0	0	
EMA IgG	0	0	

* P value is statistically significant.

DISCUSSION

Celiac disease is a chronic inflammatory disorder of the small intestines characterized by the clinical features of malabsorption in response to dietary gluten in genetically predisposed individuals. In clinical practice, CD can present in adults of all ages and the clinical features are heterogeneous and often subtle, giving rise to problems such as anemia and tiredness (3,4). The classical signs of diarrhea and malabsorption are indeed present in only a minority of cases. Increased risk of malignancies related to CD has been suggested in studies which showed that the proportion of CD patients with several neoplasms was higher than expected. Nielsen *et al.* (22) showed that CD patients had an increased incidence of malignancies, predominantly malignant lymphomas and carcinomas of the gastrointestinal tract. Askling *et al.*'s (23) study evaluated cancer risk in CD and dermatitis herpetiformis in the Swedish population, and they found that adults with CD had an elevated overall risk for cancer. Elevated risks were found for malignant lymphomas, small intestinal, oropharyngeal, esophageal, large intestinal, hepatobiliary, and pancreatic carcinomas. In this sense, NHL has been recognized as a frequent complication in CD patients (24). In addition, case reports on Hodgkin disease associated with CD have also been described (25,26). Although the same symptoms such as anemia and fatigue are often seen in lymphoma patients, physicians generally do not suspect CD in lymphoma patients with these symptoms. This makes it difficult to detect CD in lymphoma patients. In the present study, we investigated the frequency of CD-related autoantibodies in patients with lymphomas. We studied the prevalence of CD-related autoantibodies, i.e., AGA IgA, IgG and EMA IgA, IgG in HL and NHL patients. In this series of 119 NHL and 60 HL patients, AGA IgA positivity was found in 9 (15%) patients with HL and in 6 (5%) patients with NHL and AGA IgG positivity was found in 21 (35%) patients in the HL group and in 30 (25.2%) patients in the NHL group. No EMA IgA or IgG positivity

was determined in any of the patients with HL or NHL. In our study, we were unable to determine any positive findings associated with CD in the gastroduodenoscopic and histopathological examination of AGA IgA- or IgG-positive patients.

The variable clinical presentation of CD, increased awareness of subclinical disease in primary care and the invasive nature of small intestinal biopsy have motivated the search for simpler, less invasive and more acceptable screening tests for CD (6). However, small intestinal biopsy remains the gold standard for diagnosis (27), with the characteristic small-intestinal histology being villous atrophy (5). Several tests were used for diagnosis of CD in the last decade. The first serological test to be used was the determination of AGA, followed by EMA, and more recently, by the anti tTG assays. Although the diagnosis of CD relies on intestinal biopsy, serum AGA determination is also well-known to have a role in the diagnosis of this condition. The reported sensitivity of AGA assay for clinically suspected cases of CD is very high, ranging between 95 and 100%. In two large scale, multi-centered European studies, 100% of children with active CD had serum IgG-AGA positivity, while IgA-AGA was detected in 89-90.5%. IgG-AGA was also detected in 21% of subjects with other gastrointestinal disorders, whereas IgA-AGA was only found in 3%. Because IgG-AGA is more sensitive but less specific, and IgA-AGA is more specific but less sensitive, determination of both IgG-AGA and IgA-AGA is usually recommended (6).

The EMA are autoantibodies directed against the endomysium and are found in subjects with active CD. EMA are usually searched for as IgA-class autoantibodies, which are more sensitive than those of IgG class. In contrast, IgA-EMA is a highly sensitive (93-98%) and specific (99-100%) test, with a high predictive value (28,29). Since IgA-EMA test has a high sensitivity and specificity, histopathological confirmation is not indicated in its positivity for definitive diagnosis of CD (30, 31).

Several studies have shown the presence of an association between CD and lymphoma. Farré et al. (1) investigated serological markers, and personal interviews were obtained from 298 consecutive lymphoma cases and 251 matched controls recruited in four Spanish hospitals. CD was detected in two cases and in three controls. The authors suggested that there was no evidence that CD was a risk factor for lymphoma, and they did not recommend serological screening for CD in people with lymphoma. In Catassi et al.'s (20) study, CD was diagnosed in six (0.92%) of 653 patients with NHL. Of the six cases, three were of B-cell and three were of T-cell origin. Four of the six cases had lymphoma primarily located in the gut. In these patients, AGA IgA and IgG and EMA IgA were evaluated. AGA IgA was detected in four, AGA IgG in four and EMA IgA in four patients who had lymphoma and CD. The authors concluded that association does not represent a great enough risk to justify early mass screening for CD. Carroccio et al. (18) evaluated the usefulness of the serum anti-tTG antibody assay in screening for CD in consecutive NHL patients. Biopsy specimens were obtained for histological examination from subjects with positive serum EMA and/or anti-tTG. Eight out of 80 (10%) NHL patients were found to be positive for anti-tTG and none of the 80 patients was positive for serum EMA. There was atrophy of the intestinal mucosa in only one anti-tTG-positive NHL patient, and follow-up confirmed the diagnosis of CD. A normal intestinal mucosa was present in the remaining seven anti-tTG-positive NHL patients. In the conclusion of that study, the authors showed that in patients with NHL, anti-tTG assay often gives results that are discordant with the EMA assay, with a high frequency of anti-tTG false-positive results. All of the similar studies in the literature evaluated CD in serological screening test-positive lymphoma patients, but in our study we evaluated CD in serological screening test-po-

sitive patients and also the patients who had CD symptoms in the HL and NHL groups.

Some authors have postulated that specific treatment of lymphoma induces cellular lysis leading to the production of different autoantibodies. In our study, however, we encountered no false positivity for EMA IgA and IgG in any of the lymphoma cases despite the fact that we had seen AGA IgA and IgG-positive cases of HL and NHL. AGA IgA and IgG positivity were also detectable with other gastroenterological disorders. In our patients, AGA IgA and IgG positivities would be associated with other gastroenterological disorders such as irritable bowel disease (32). We thus conclude that EMA IgA and IgG are reliable diagnostic tests for the diagnosis of CD in lymphoma patients.

One limitation of our study was the lack of information from a healthy control group and evaluation of the incidence of serological markers such as EMA of CD in lymphoma patients. Additionally, in our study, the proportion of T-cell lymphomas was 7 (5.7%) of those with NHL, and in Catassi et al.'s (20) study 8%, well within the range (6%-12%) expected from previous European (33) and North American studies (34,35). In these studies, most CD cases were detected in T-cell lymphoma patients. However, the aim of our study was not only to evaluate the frequency of CD in patients with lymphomas, but to evaluate the usefulness of EMA assay in screening for CD in patients suffering from lymphoma.

In conclusion, to the best of our knowledge, our report is the first to describe the frequency of CD and CD-related auto-antibodies in patients with HL and NHL in a southeastern Turkish population. There is no evidence that CD is a premalignant condition for HL and NHL. Serological screening for CD in lymphoma patients does not seem to be necessary. Further large-scale studies should be performed to confirm this conclusion.

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