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Evaluation of the role of CD3 and CD8 immunostaining in the diagnosis of mild enteropathy celiac disease

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Celiac disease is a chronic, immune-mediated inflammatory disorder of the small intestine, triggered by gluten ingestion in genetically predisposed individuals. This study aims to investigate the role of CD3 and CD8 immunohistochemical stains in the detection of increased intraepithelial lymphocytes in patients diagnosed with mild enteropathy celiac disease. A cross-sectional study was conducted at Basrah/Al-Sader Teaching Hospital from April 2018 to July 2019. Patients with mild enteropathy celiac disease were selected, and intraepithelial lymphocytosis in duodenal biopsies was histologically evaluated before and after the application of CD3 and CD8 immunostains. A total of 57 patients participated in the study, with a median age of 30 years. Of these, 37 (64.9%) were female, and 20 (35.1%) were male, with a male-to-female ratio of 1:1.8. Routine hematoxylin and eosin staining revealed that 31 cases (54.4%) were classified as Marsh type 0, 19 cases (33.3%) as Marsh type 1, and 7 cases (12.3%) as Marsh type 2. However, the application of CD3 and CD8 immunohistochemical stains led to a reclassification in 27 out of 57 cases (47.4%). Specifically, 17 of the 31 cases (54.8%) initially classified as Marsh type 0 were reclassified as Marsh type 1, while 6 of the 19 cases (31.6%) initially classified as Marsh type 1 were reclassified as Marsh type 0, and 4 of the 7 cases (57.1%) initially classified as Marsh type 2 were reclassified as Marsh type 0. Immunohistochemical staining with CD3 and CD8 plays a crucial role in the evaluation of intestinal biopsies for celiac disease.

Keywords: celiac disease; immunohistochemistry; CD3; CD8; intraepithelial lymphocytes; marsh classification.

Introduction

Celiac disease is defined as a chronic inflammatory disorder of the small intestine, precipitated by ingestion of gluten in genetically predisposed individuals (Losowsky et al., 2008; Elli et al., 2015). It is the major cause of malabsorption and because of its wide range of clinical presentation and multi-systemic involvement it might be considered as a syndrome (Parzanese et al., 2017).

It has unique features compared to other autoimmune diseases, including complete recovery of mucosal damage after gluten-free diet (GFD). On the other hand, undiagnosed subjects might have severe complications that may be a life threatening condition (Mubarak et al., 2015). Both genetic and environmental factors play role in its pathogenesis (Hudacko et al., 2013).

Genetic components have a fundamental role in celiac disease as it is highly associated with human leukocyte antigen (HLA) of major histocompatibility complex (MHC) (Gutiérrez et al., 2017).

Over 90% of celiac patients express the HLA-DQ2 molecule, the rest 10% express HLA-DQ8. Although HLA DQ2 and HLA DQ8 molecules are frequent among the general population (30%), only 1–3% of them develop celiac disease. This disproportion together with less than 100% involvement of monozygotic twins suggest that there are additional genetic and environmental factors involved in the developing of the disease (Scanlon et al., 2011). Several environmental factors are involved in celiac disease pathogenesis, however the most important one is dietary gluten (Lionetti et al., 2015). Gluten is broken down into smaller peptides and amino acids by the action of proteolytic enzymes derived from stomach, pancreas and intestinal brush border, yielding a large peptide (mer-33) that cannot be completely digested. Mer-33 fragments will bind vigorously to HLA-DQ2 and HLA-DQ8 heterodimers that are expressed on the surface of antigen presenting cells like macrophages and lymphocytes causing amplification of gluten specific T-cell responses (Bożena et al., 2017; Sollid et al., 2012).

Celiac disease can occur at any age from childhood to old age. It is more common in women with male to female ratio 1:2 to 1:3 (Kumar et al., 2017; Caio et al., 2019). Clinical presentation of celiac disease is variable, most patients present with weight loss, chronic diarrhea, abdominal pain and vomiting, while others presented with extra intestinal features like iron deficiency anemia (IDA) which did not respond to iron therapy (about 40%), macrocytic anemia (due to folate or B_{12} deficiency), osteopenia and osteoporosis (due to calcium and vitamin D_3 deficiency), neurological abnormalities like headache, paresthesia, anxiety and depression have been reported in some cases (Troncone et al., 2011). Endoscopic duodenal biopsy has a crucial role in the diagnosis of celiac disease, multiple endoscopic biopsies are required, it is recommended that two biopsies from the first part and four biopsies from the second part of the duodenum must be taken (Barker et al., 2008; Marietta et al., 2013). Histological features which should be evaluated in the duodenal biopsies from patients suspected to have celiac disease include increased IELs, crypt hyperplasia and villous atrophy (Mocan et al., 2016).

Intraepithelial lymphocytoses (IELs) are regarded as a normal component of intestinal mucosa, however, the number of IELs is greatly variable, Hayat et al. (2002), and Veress et al (2004), regarded the count of IELs between 25 and 29 cells per 100 enterocytes as a borderline. Increase in IELs more than 30 cells/100 enterocytes is considered the most important histological feature for the disease since it represents the earliest mucosal abnormalities related to the disease. Recent randomized studies showed that patients with mild enteropathy celiac disease can get benefit from a GFD with subsequent reduction in the complications of the disease like nutritional deficiency and small bowel malignancies (Brown et al., 2006; Pellegrino et al., 2011). IELs is usually evaluated on hematoxylin and eosin stained sections, however, nuclear overlapping and variability of nuclear shape make it difficult to differentiate lymphocytes from enterocytes and other inflammatory cells (Dickson et al., 2006).

Matherials and methods

The study was approved by the Human Ethics Committee of Department of Histopathology in Al-Sader Teaching Hospital, Basrah, Iraq. Everyone who took part in the study was told about it and asked to sign a consent form. Each patient was also guaranteed that his

information would be kept private. A cross-sectional study was conducted from April 2018 to July 2019, collecting all duodenal biopsies submitted to the histopathology department at Al-Sader Teaching Hospital in Basrah. Among these, 57 cases of mild enteropathy celiac disease were selected based on specific criteria, including patient age (18–60 years), clinical features, serological tests (anti-tTG), endoscopic findings, and histopathological examination. Only cases classified as Marsh type 0, 1, or 2 were included. Duodenal biopsies were assessed by an expert pathologist, with hematoxylin and eosin staining used to evaluate intraepithelial lymphocytes, counting only supranuclear and perinuclear lymphocytes above the basement membrane along the entire villous length. Immunohistochemical evaluation of IELs was performed using CD3 and CD8 immunostains. Biopsy samples were fixed in 10% neutral buffered formalin, processed routinely, and embedded in paraffin. Three sections of 4-micrometer thickness were obtained from each paraffin block, with one stained using hematoxylin and eosin and the other two stained with CD3 and CD8 immunostains for further analysis.

Statistical analysis is often used to analyze quantitative data, and provides methods for data description, simple inference for continuous and categorical data. The procedure involves the collection of data leading to test of the relationship between two statistical data sets. In this study, all data are presented as frequency and percentage. We used SPSS (version 26) and the dependent t-test (two-tailed) and independent t-test (two-tailed) for variables that had a normally distributed distribution. For variables that did not have a normally distributed distribution, we used the Mann-Whitney U test, the Wilcoxon test, and the Chi-square test. $P < 0.05$ was seen as statistically significant.

Results

Immunohistochemical examination results for both CD3 and CD8 across different stages of Marsh classification showed statistically significant differences between groups ($P < 0.001$). Looking at the overall results, 42.1% of all samples were CD3 positive, 52.6% were CD8 positive, and 5.3% of cases were classified as Marsh 2. These results reflect the differential distribution of immune cell types across different Marsh stages, suggesting their potential role in the development of histological changes associated with the disease state.

The results of the immunohistochemical examination of anti-tTG across the different stages of the Marsh classification showed no statistically significant differences between groups ($P = 0.936$). In Marsh stage 0, 64.5% of samples were negative for anti-tTG, while 35.5% were positive. In Marsh stage 1, 63.2% of samples were negative, while 36.8% were positive. For Marsh stage 2, 57.1% of samples were negative and 42.9% were positive. When looking at the overall results, 63.2% of samples were negative, while 36.8% of samples were positive for anti-tTG. These results suggest that there is no clear relationship between anti-tTG expression and the different Marsh stages, which may reflect that this marker is not directly related to the development of histological changes in this disease.

The results of the immunological distribution of CD3 and CD8 in relation to Anti-tTG across different Marsh stages showed highly significant differences ($P < 0.001$). In Marsh stage 0, the vast majority of samples were negative for Anti-tTG (91.7%), while only 8.3% were positive. In Marsh stage 1, the proportion of negative samples decreased to 46.7%, while the proportion of positive samples increased to 53.3%. In Marsh stage 2, all samples were 100% positive for Anti-tTG. When looking at the overall distribution, samples negative for Anti-tTG accounted for 63.2% of the total samples, while 36.8% of samples were positive. These results reflect the strong relationship between CD3 and CD8 expression and Anti-tTG level, especially in the advanced stages of Marsh changes, indicating the role of cellular immunity in the development of the disease.

Table 1
Immunostaining for CD3 and CD8 across different Marsh stages

Immunostaining (CD3 & CD8)	Marsh 0	Marsh 1	Marsh 2	Total
No. (% within immunostain)	No. (%)	No. (%)	No. (%)	No. (%)
Negative	14 (45.2%)	17 (54.8%)	0 (0.0%)	31 (100%)
Positive	6 (31.6%)	13 (68.4%)	0 (0.0%)	19 (100%)
Strong positive	4 (57.1%)	0 (0.0%)	3 (42.9%)	7 (100%)
Total	24 (42.1%)	30 (52.6%)	3 (5.3%)	57 (100%)

Notes: statistical test: chi-square test (χ^2), P-value < 0.001 (significant).

Table 2
Anti-tTG Immunostaining across different Marsh stages

Anti-tTG Result	Marsh 0 (n = 31)	Marsh 1 (n = 19)	Marsh 2 (n = 7)	Total (n = 57)
Negative	20 (64.5%)	12 (63.2%)	4 (57.1%)	36 (63.2%)
Positive	11 (35.5%)	7 (36.8%)	3 (42.9%)	21 (36.8%)
Total	31 (100%)	19 (100%)	7 (100%)	57 (100%)

Notes: P-value = 0.936 (by chi-square test).

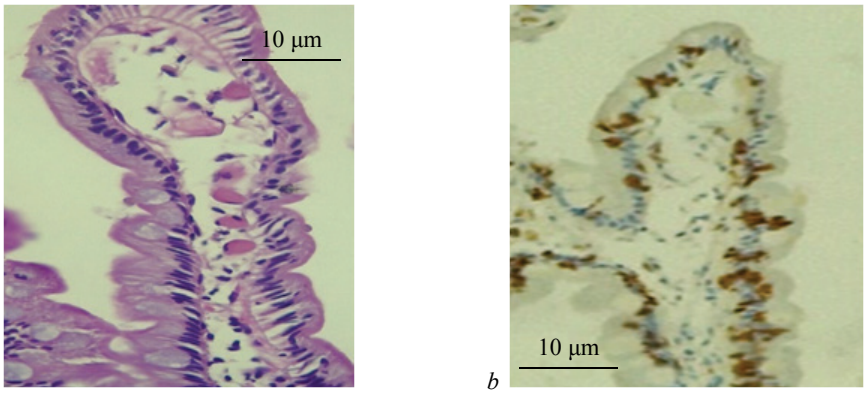
Table 3
Distribution of Immunostaining for CD3 and CD8 in relation to anti-tTG across different Marsh stages

Anti-tTG Result	Marsh 0 (n = 24)	Marsh 1 (n = 30)	Marsh 2 (n = 3)	Total (n = 57)
Negative	22 (91.7%)	14 (46.7%)	0 (0.0%)	36 (63.2%)
Positive	2 (8.3%)	16 (53.3%)	3 (100.0%)	21 (36.8%)
Total	24 (100%)	30 (100%)	3 (100%)	57 (100%)

Notes: P-value < 0.001 (chi-square test).

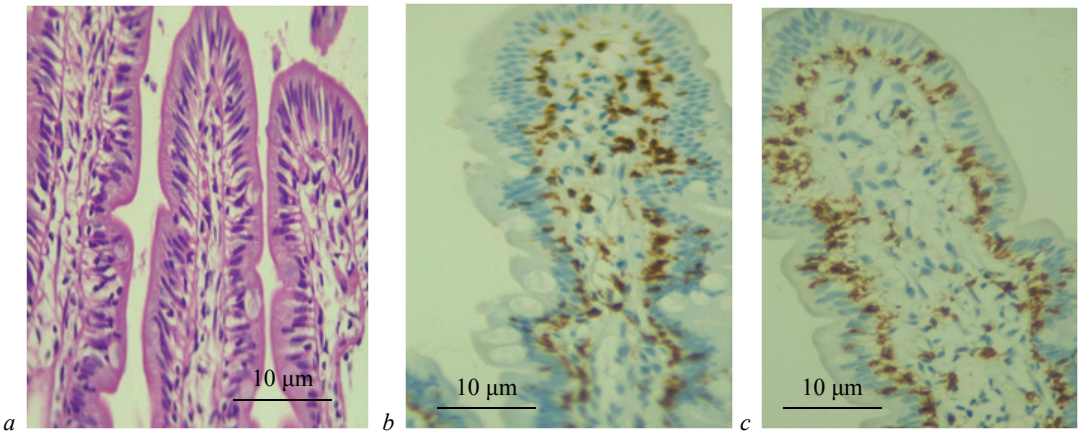
Discussion

Celiac disease is a chronic, immune-mediated inflammatory disorder of the small intestine triggered by a combination of genetic and environmental factors. The hallmark histological features for diagnosing celiac disease include villous atrophy, crypt hyperplasia, and increased intraepithelial lymphocytes (IELs). Fry et al. (1972), highlighted the diagnostic significance of increased IELs in patients with celiac disease over three decades ago.



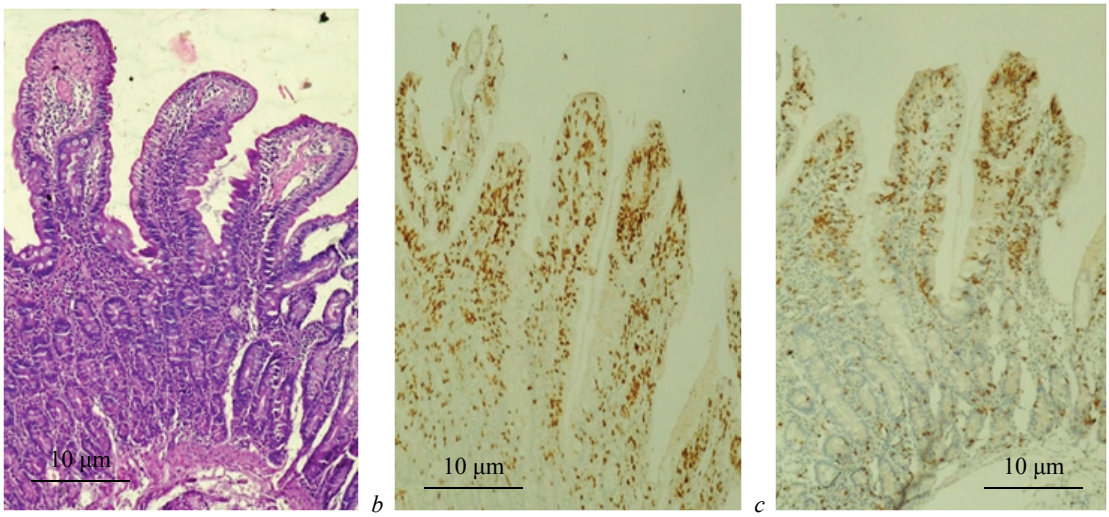
a *b*

Fig. 1. Duodenal biopsy – Marsh type 0: *a* – stained with hematoxylin and eosin sections show no evidence of increased intraepithelial lymphocytes (IELs); *b* – the same figure demonstrates strong immunoreactivity for CD8 in IELs at high-power view



a b c

Fig. 2. Duodenal biopsy – Marsh type 1: *a* – stained with hematoxylin and eosin sections show increased intraepithelial lymphocytes (IELs) >30 cells/100 enterocytes; *b* – CD3- and CD8-stained sections demonstrate immunoreactive IELs; *c* – CD3-stained sections of Marsh type 1 reveal negative immunoreactivity of IELs



a b c

Fig. 3. Duodenal biopsy – Marsh type 2: *a* – stained with hematoxylin and eosin section shows preserved villous architecture with crypt hyperplasia; *b*, *c* – CD3- and CD8-stained sections reveal positive immunoreactivity of IELs

Mubarak et al. (2015) emphasized the important role of immunohistochemistry for CD3 in evaluating IELs in patients with celiac disease. In this study, the median age of patients was 30 years, ranging from 18 to 54 years. This finding is consistent with a study conducted in Malaysia in 2014 (Iftikhar et al., 2016), which showed that celiac disease is more common in the 21–30 age group. However, it contrasts with a study conducted in Canada in 2008 (Freeman, 2008), which reported that the burden of the disease is higher in individuals aged over 60. The sex distribution of celiac disease varies globally, with some geographic regions showing equal distribution between males and females (Ciclitira, 2001).

Our study revealed a clear female predominance, with a male-to-female ratio of 1:1.8. This finding aligns with a study in the United Kingdom in 2015 (Zingone et al., 2015) but contrasts with a study in China (Jiang et al., 2009), which reported a higher prevalence in males. In this study, most patients (56.2%) presented with unexplained iron deficiency anemia, which is consistent with a study conducted in Basra in 2017 (Hashim et al., 2017), where 43.4% of patients had unexplained iron deficiency anemia. Histologically, both CD3 and CD8 immunostains yielded similar results. They led to different assessments of Marsh classification in 27 out of 57 cases (47.4%), which was statistically significant (P-value < 0.001). Therefore, CD3 and CD8 immunohistochemistry stains are considered to have an additional role in the histological diagnosis of celiac disease. This finding is consistent with a study conducted in the Netherlands in 2015, which found that CD3 immunostaining resulted in a different assessment in 12.6% of patients. Similarly, Mino et al. (2003) and Hudacko et al. (2013) noted that CD3 immunostaining detected more IELs than routine hematoxylin and eosin (H&E) staining. Tissue transglutaminase (tTG) is an intracellular enzyme found in various tissues, and serum tTG levels are often elevated in patients with celiac disease (D'Argenio et al., 1989). In the current study, 21 out of 57 cases (36.8%) tested positive for anti-tTG antibodies, while 36 out of 57 cases (63.2%) tested negative. Statistically, there was no significant correlation (P-value = 0.963) between serology and Marsh classification on routine H&E staining.

However, after applying CD3 and CD8 immunostains, there was a highly significant correlation (P-value < 0.001) between serology and Marsh classification. In Marsh type 0, anti-tTG antibodies were positive in 2 out of 24 cases (8.3%) and negative in 22 out of 24 cases (91.7%). Positive serology despite normal duodenal mucosa may indicate that the mucosal abnormalities are patchy or that mucosal lesions have not yet developed (Hammer et al., 2013).

This is consistent with Freeman's (2004) study, which showed that 20% of patients with positive anti-tTG antibodies had normal duodenal mucosa. Ludvigsson et al. (2009) suggested that not all patients with positive serology will develop celiac disease, and that positive results might be transient (Collin et al., 1993; Ludvigsson et al., 2009). In contrast, other studies suggest that individuals with normal mucosa and positive serological tests often progress to Marsh type 1–3, and follow-up is necessary for such patients (Iltanen et al., 1999).

On the other hand, anti-tTG antibodies were negative in 14 out of 30 cases (46.7%) with Marsh type 1 lesions, while positive in 16 out of 30 cases (53.3%). This finding is supported by Lewis and Scott (2010), who reported that 5–16% of cases diagnosed with celiac disease had negative anti-tTG serology. Mucosal abnormalities asso-

ciated with negative serology could be explained by IgA deficiency or seronegative celiac disease (Abrams et al., 2004). All three cases with Marsh type 2 lesions had positive serological tests.

Conclusion

Immunohistochemical staining of CD3 and CD8 plays a significant role in evaluating intestinal biopsies for the diagnosis of celiac disease, providing deeper insights compared to routine H&E staining. The application of CD3 and CD8 immunostains allows for the detection of additional cases with Marsh type 1 lesions that may have been misdiagnosed as Marsh type 0 in standard hematoxylin and eosin examinations. Additionally, cases over-diagnosed as Marsh type 1 and type 2 lesions were accurately reclassified as Marsh type 0 after immunostaining. Furthermore, the correlation between the serological test for anti-tTG antibodies and Marsh classification showed significant improvement with the application of immunohistochemistry, indicating that the combination of these methods enhances the diagnostic accuracy and classification of celiac disease.

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