Pathology – Research and Practice 212 (2016) 1174–1178

Contents lists available at ScienceDirect

Pathology – Research and Practice

journal homepage: www.elsevier.com/locate/prp

Original article

Classification chaos in coeliac disease: Does it really matter?

Hilal Özakıncı[a], Ayça Kırmızı[a], Berna Savaş[a], Çağdaş Kalkan[b], İrfan Soykan[b], Hülya Çetinkaya[b], Zarife Kuloğlu[c], Aydan Kansu[c], Ödül Eğritaş Gürkan[d], Buket Dalgıç[d], Zeynep Şentürk[e], Arzu Ensari (MD, Ph.D.)[a,*]

[a] Departments of Pathology, Ankara University Medical School, 06100, Sıhhıye, Ankara, Turkey
[b] Departments of Gastroenterology, Ankara University Medical School, 06100, Sıhhıye, Ankara, Turkey
[c] Departments of Paediatric Gastroenterology, Ankara University Medical School, 06100, Sıhhıye, Ankara, Turkey
[d] Departments of Paediatric Gastroenterology, Gazi University Medical School, 06560, Yenimahalle, Ankara, Turkey
[e] Departments of Biostatistics, Ankara University Medical School, 06100, Sıhhıye, Ankara, Turkey

ARTICLE INFO

Article history:
Received 16 June 2016
Accepted 30 August 2016

Keywords:
Coeliac disease
Mucosal pathology
Classification

ABSTRACT

The spectrum of mucosal pathology in coeliac disease (CD), initially defined by Marsh in 1992 has been subjected to several modifications in the following years by Oberhuber, then by Corazza and Villanaci, and finally by Ensari. The present study, aimed to end the ongoing confusion regarding the classification of mucosal pathology in CD by applying all the classifications proposed so far on a large series of cases. A total of 270 duodenal biopsies taken from the distal duodenum of patients with a diagnosis of CD were included in the study. All biopsies were classified according to Marsh, Oberhuber, Corazza Villanaci, and Ensari classification schemes. For statistical analyses cases were divided into three groups: Group 1 included type 1 lesions in Marsh, Ensari, and Oberhuber and grade A in Corazza Villanaci classifications. Group 2 comprised of type 2 lesions in Marsh and Ensari classifications together with type2, type 3a and 3b lesions in Oberhuber classification and grade B1 lesions in Corazza Villanaci classification. Group 3 included type 3 lesions in Marsh and Ensari classifications, and type 3c lesions in Oberhuber, and grade B2 lesions in Corazza Villanaci classifications. The kappa value was 1.00 (excellent) for group 1, 0.53 (fair) for group 2 and 0.78 (excellent) for group 3 ($p < 0.0001$). These results suggest that any of the above classification system would serve similar purposes in the diagnosis of CD. Therefore, it is advisable that the pathologist should use the simplest reliable scheme.

1. Introduction

Coeliac disease (CD) is an autoimmune disorder of the small intestine precipitated by ingestion of wheat protein, gluten, in genetically susceptible individuals carrying the HLA-DQ2 or HLA-DQ8 genotype. Today, population-based studies indicate that approximately 0.5–1% of the Western European and Northern American populations suffer from CD [1,2].

Diagnosis of CD involves clinical, serological, genetic evaluation of the patient and histological examination of an adequate number of duodenal biopsies [2]. Clinical picture may be extremely variable ranging from classical malabsorption syndrome to cases with subtle and/or atypical symptomatology that are occasionally discovered during serological screening. Serological diagnosis is based on the detection of class IgA anti-tissue transglutaminase (anti-tTG) and anti-endomysial antibodies. In children, when anti-tTG antibody levels are very high (i.e. >10 times above the normal upper limit), and antibody specificity is absolute CD may be diagnosed without performing a duodenal biopsy [3]. In adults, however, biopsy is essential for the diagnosis of CD as seronegative cases have been reported with a prevalence of 6–22% [4].

Mucosal pathology involves a spectrum of abnormalities including intraepithelial lymphocytosis on one end, and completely flat mucosa on the other, none of which are specific for CD as they may be caused by a variety of disorders including autoimmune enteropathy, H.Pylori-associated duodenitis, irritable bowel syndrome, inflammatory bowel disease, bacterial overgrowth, graft-versus-host disease, and, drugs such as olmesartan [5]. Since patients with untreated CD, even if asymptomatic, are still at risk of developing various complications like osteoporosis, infertility, other autoimmune diseases including type 1 diabetes, autoimmune thyroiditis and autoimmune liver disease, and lymphoma [6],

* Corresponding author.
E-mail address: ensariarzu@gmail.com (A. Ensari).

http://dx.doi.org/10.1016/j.prp.2016.08.012
0344-0338/

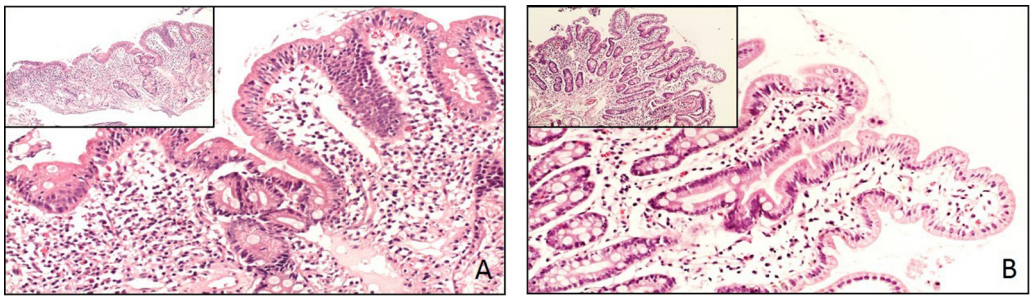

Fig 1. Patchy involvement in the same case. Decreased v/c ratio with increased IEL count in one piece (A) and normal v/c ratio and IEL count in the other piece (B) (H&E; X200, insets: X40, respectively).

pathologists, as members of the diagnostic team, are expected to classify mucosal pathology and make a differential diagnosis.

In 1992, after years of experimental and clinical research and tedious work, Marsh [7] defined the spectrum of mucosal pathology in CD which has received a warm welcome from pathologists worldwide and has been used as the histopathologic classification of CD. In the following years, Marsh's original classification has been subjected to modifications all proposed by pathologists including Oberhuber, Corazza Villanaci, and Ensari [8–10]. Recently, Villanaci suggested to classify CD as "non-atrophic" and "atrophic" in a more descriptive manner since both types of mucosal pathology can be observed in a large variety of conditions other than CD [11]. None of the above, however, became as popular as the original Marsh classification which elegantly illustrated the evolving mucosal pathology in CD. The resulting classification chaos has led to multiple problems for the practicing pathologist: understanding the criteria used for the classification scheme, choosing the most appropriate classification for his/her microscopic approach, and, more importantly, conveying a useful message to the clinician for the diagnosis and follow up of coeliac patients.

Hoping to end the chaos in the classification of CD, we investigated the concordance between the proposed classification schemes in a large cohort of coeliac patients in order to draw useful conclusions for practicing pathologists who deal with coeliac biopsies.

2. Material and methods

A cohort of 270 patients with a diagnosis of CD were collected during a period of ten years between 2000 and 2010 in Ankara University Medical School. There were 192 females and 78 males with a mean age of 38 years ranging from 4 to 82 years. Diagnosis of CD was made by a combination of histological, serological, and genetic criteria. Serologic tests comprised of anti-tissue transglutaminase 2 (tTG2) and/or anti-endomysial (EMA) IgA antibodies, and genotyping involved HLA DQ2-DQ8 haplotypes. All patients had serum anti-tTG2 IgA levels higher than the cutoff provided by the manufacturer and positive EMA. Multiple biopsies were taken from the distal duodenum at upper endoscopy. Biopsy samples fixed in 10% formaline were embedded mucosal surface upwards in paraffin and 4 μm-thick sections were cut at right angles to achieve vertical orientation and stained with H&E. Immunohistochemical staining was performed using anti-CD3 antibody (DAKO, Denmark) and streptavidin biotin-peroxidase for each case to evaluate the number of intraepithelial lymphocytes (IELs). At the time of diagnosis, all duodenal biopsies showed diffuse intraepithelial lymphocytosis (>25/100 enterocytes on CD3-stained slides) accompanied by no/varying degrees of villous abnormalities. Biopsies were re-evaluated by an experienced gastrointestinal pathologist with particular interest in CD (AE) and were classified using the four classification schemes including Marsh, Oberhuber, Corazza-Villanaci and Ensari. A semi-morphometric microscopic approach was employed: villous morphology was defined as "normal" when villous to crypt (v/c) ratio was three or above, as "shortened" when there were still visible villi and hyperplastic crypts with a v/c ratio less than three, and as "flattened" when no visible villi were present and the mucosa was completely flat.

Number of biopsy pieces were also noted to allow evaluation of patchiness of involvement. When there was patchy involvement, the case was classified with respect to the most severe degree of villous abnormality.

With this standardized approach all biopsies were classified according to Marsh, Oberhuber, Corazza Villanaci, and Ensari classification schemes. For statistical analyses cases were divided into three groups: Group 1 comprised of type 1 lesions in Marsh, Oberhuber and Ensari, and grade A in Corazza Villanaci classifications. Group 2 included type 2 lesions in Marsh, Oberhuber and Ensari classifications together with type 3a and 3b lesions in Oberhuber classification and grade B1 lesions in Corazza Villanaci classification. Group 3 consisted of type 3 lesions in Marsh and Ensari classifications, and type 3c lesions in Oberhuber classification and grade B2 lesions in Corazza Villanaci classification (see Table 1).

Statistical analyses were designed to evaluate concordance of the classifications by kappa, Fleiss' kappa statistics [12] using SPSS version 15.0 for Windows and R programme. The strength of agreement for the kappa coefficient was classified as poor when kappa values were <0.40, fair when they ranged from 0.40 to 0.59, good when values were between 0.60 and 0.74, and kappa values between 0.75 and 1.0 were termed as excellent agreement. A p-value of <0.05 was considered statistically significant.

3. Results

Duodenal biopsies consisted of 2–11 pieces with a mean of 3.24 gender or ±1.04 biopsy pieces. Thirty seven percent of the cases had 2 biopsy pieces while 63% of the cases had 3 or more biopsy pieces. Eighty cases (30%) showed a completely normal mucosal architecture with intraepithelial lymphocytosis, while 37 cases (13%) had shortened villi, and 153 cases (57%) presented with flat mucosae. Patchiness was assessed in all cases and was found in 54 specimens (20%) (Fig. 1).

On re-evaluation of the biopsies for classification, if the v/c ratio was normal (i.e.≥3), biopsy was classified as type 1 in Marsh, Oberhuber and Ensari classifications and grade A in Corazza Villanaci classification. A biopsy with normal villi but hyperplastic crypts with no change in v/c ratio was classified as type 2 according to Marsh and Oberhuber classifications. If there was villous shortening and crypt hyperplasia, biopsy was classified as type 3a or 3b in Oberhuber classification and grade B1 in Corazza Villanaci and as type 2 in Ensari classifications while complete flatness of the mucosa with