HISTOLOGICAL OUTCOME OF DUODENAL BIOPSIES IN PATIENTS WITH CLINICALLY SUSPECTED CELIAC DISEASE - A STUDY OF 100 CASES

Tariq Sarfraz, Muhammad Matloob Ur Rehman*, Hina Tariq, Saleem Ahmed Khan, Humaira Tariq, Samina Waqar, Aiza Sadia, Motia Kanwal, Faryal Zafar, Amna Hanif**

Army Medical College/ National University of Medical Sciences (NUMS) Rawalpindi Pakistan, *Combined Military Hospital/ National University of Medical Sciences (NUMS) Rawalpindi Pakistan, **Military Hospital/ National University of Medical Sciences (NUMS) Rawalpindi Pakistan

ABSTRACT

Objective: To see the histological outcome of duodenal biopsies done in patients clinically suspected of celiac disease.

Study Design: Prospective descriptive study.

Place and Duration of Study: Histopathology Department, Army Medical College Rawalpindi, from 1 Jan 2017 to 30 Jun 2017.

Material and Methods: One hundred (100) cases were included in the study. Duodenal biopsies done in patients clinically suspected of celiac disease were included in the study. Inadequate biopsies were excluded from the study. All the normal and abnormal histological features were noted to make the diagnosis. Data was entered and analyzed by using SPSS version 17.

Results: Duodenal biopsies of 100 patients, done in clinically suspected cases of celiac disease were analyzed histologically. Out of these 100 cases, 46 cases (46%) showed histological features consistent with celiac disease, while 38 cases (38%) revealed chronic non specific duodenitis, 2 cases (2%) were of giardiasis, while 14 biopsies (14%) were unremarkable with no significant pathology.

Conclusion: A significant number of cases clinically suspected of celiac disease may not be showing histological features consistent with celiac disease on duodenal biopsies. Due to the changing presentation of disease, as well as the recognition of a number of potential clinical and histopathological mimics, communication between pathologists and gastroenterologists is essential for appropriate interpretation of duodenal biopsy specimens.

Keywords: Celiac disease, Chronic non specific duodenitis, Duodenal biopsy.

INTRODUCTION

Celiac disease (CD) is an immune mediated enteropathy characterized by intolerance to gluten diet and occurs in genetically predisposed individuals[1]. It is a common autoimmune disorder affecting at least 1% population in many regions of the world[2,3]. The incidence of this disease is high in individuals with family history of CD or a personal history of autoimmune disease[4]. The clinical manifestations vary widely ranging from subclinical to severe malabsorption syndromes[5]. Diagnosis rate of CD is increasing due to increase in true prevalence of the disease[6] as well as improved awareness of its clinical presentation and better diagnostic facilities[7]. Initially, up to 1950, mainstay of diagnosis was based on features of malabsorption and clinical follow up. Later on, duodenal biopsy became the gold-standard for confirmation of diagnosis of CD, which stands till today[8]. The diagnosis of CD needs a high degree of clinical suspicion. There is no single test, which is diagnostic of celiac disease; rather the diagnosis is made in combination with clinical features, serological assays for relevant antibodies and histological findings in duodenal biopsy. After clinical suspicion, serology may be the first step and in patients with raised serum antib`odies relevant to CD, duodenal biopsies can be performed for confirmation of celiac disease[9]. Four guidelines have been published by different gastrointestinal

Correspondence: Dr Tariq Sarfraz, Head of Pathology Dept, Army Medical College Rawalpindi Pakistan
Email: tskhan_65@outlook.com
Received: 13 Sep 2017; revised received: 13 Oct 2017; accepted: 19 Oct 2017

organizations since 2012 for diagnosis CD. According to American College of Gastroenterology (ACG) guidelines issued in 2013, combination of both small intestinal biopsy and serologic tests including anti-tissue transglutaminase (tTG) antibodies and anti-deamidated gliadin peptide (DGP) antibodies are recommended for diagnosis of CD. Another guideline issued by European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) in 2012 suggested that, in pediatric patients having symptoms consistent with CD the diagnosis can be made without duodenal biopsy confirmation, if they have tTG antibody titer >10-fold of normal, a positive endomysial antibody (EMA) in a separate blood sample, and have the human leukocyte antigen (HLA) DQ2 or DQ8 haplotype[10]. The British Society of Gastroenterology (BSG) guidelines recommend that serologic tests, either tTG, EMA, or DGP should be done as the first step in diagnosis, followed by small intestinal biopsy as a definitive test to diagnose CD. This guideline suggests that serological testing alone cannot currently replace the duodenal biopsy for diagnosis of CD[11]. Recent guidelines from the World Gastroenterological Association (WGA) recommend that serologic testing including anti-tTG and/or anti-EMA, or anti-DGP are required for diagnosis of CD. According to these guidelines, duodenal biopsy is suggested but is not mandatory for diagnosis of CD, which is appropriate for countries with limited healthcare resources[12]. To summarize, 2 guidelines (ACG and BSG) recommend duodenal biopsy as a mandatory test in addition to the serological studies for diagnosis of CD, while 2 other guidelines (ESPGHAN and WGA) do not make duodenal biopsy mandatory for the diagnosis of CD and according to these, positive serological tests for relevant antibodies are enough for diagnosis of CD.

As the diagnosis of CD is quite challenging at times due to an overlap of clinical features, serological as says and histological features and there are many mimickers of the CD on duodenal biopsy, this study was carried out to find out the histological outcome of duodenal biopsies, which were done in patients who were clinically suspected of celiac disease and to see the final diagnosis in these patients, being consistent with CD or other wise. The aim was to see the compatibility between clinical presentation and histological diagnosis.

MATERIAL AND METHODS

This prospective descriptive study was carried out at Histopathology department of Army Medical College, Rawalpindi. The study extended over a period of 6 months with effect from 1 Jan 2017 to 30 Jun 2017. Duodenal biopsies received in histopathology department of Army Medical College, which were done in clinically suspected cases of CD were analyzed histologically to see the histological evidence of CD or otherwise. All the normal and histological features in these duodenal biopsies were noted in detail to make histological diagnosis.

Duodenal biopsies carried out in patients with clinical and / or serological suspicion of CD were included in the study. Duodenal biopsies having inadequate material were excluded from the study. The specimens were labeled and fixed in 10% formalin. Paraffin blocks were made and sectioned at 3-5 micrometer thickness. The sections were stained with haematoxylin and eosin (H&E). The slides were examined by consultant histopathologist and presence or absence of histological features consistent with CD, including, villous architecture, villous height: crypt length ratio, crypt hyperplasia, surface enterocytes, increased intraepithelial lymphocytes (IEL) and other histological findings like parasites, granuloma, dysplasia or evidence of malignancy were noted. Data was entered and analyzed by using SPSS version 17. As it was a non-interventional, observational descriptive study, so no statistical test was applicable for the study.

RESULTS

A total of 100 duodenal biopsies done in patients suspected for CD were analyzed histologically for the presence or otherwise of

histological features consistent with CD. They included 61 (61%) males and 39 (39%) females. The age range was between 1–51 years with a mean age of 10.58 years. Maximum number of cases numbering 55 (55%) were between 1–10 years, followed by 15 cases (15%) which were between 10–20 years. All 100 cases were suspected clinically and/or serologically for celiac disease in view of presence of the symptoms, including failure to thrive, pallor, weight loss, diarrhoea, malabsorption and serological assays of relevant antibodies for CD.

DISCUSSION

The diagnosis of CD has always been a challenge for the clinicians as well as for the histo pathologists. Diagnosis of CD is based on patient's clinical symptoms, CD-specific antibody levels, the presence of HLA-DQ2 and/or HLA-DQ8, and characteristic histological changes in the duodenal biopsy. Despite the existence of highly sensitive serological assays, small-bowel mucosal biopsy is still considered the gold standard and definitive method for diagnosis of CD[13]. The classical histological findings of CD include effaced/blunted/atrophic villi, which can be focal, subtotal or total. Other classical histological findings are crypt hyperplasia, decreased villous height, crypt length ratio, loss of surface enterocytes, which can be focal or complete and increased number of intra-epithelial lymphocytes (IELs). The number of IELs in CD is usually more than 40 lymphocytes/ 100 enterocytes and is one of the important histological features. In addition to these classical findings, additional histopathological findings, which can be seen in CD include, neutrophilic and eosinophilic infiltration, increased subepithelial collagen and associated lymphocytic gastritis[14].

Table: Histological outcome of duodenal biopsies in patients suspected of Celiac Disease.

S. No	Histological Diagnosis	Frequency	Percentage (%)
1.	Celiac disease	46	46.0
2.	Chronic Non Specific Duodenitis	38	38.0
3.	Unremarkable/Normal	14	14
4.	Giardiasis	02	2.0
5.	Total	100	100.0

In the clinical information provided with these duodenal biopsies, only 10 contained results of serological assays, revealing raised serum anti tTG levels. Rest of the duodenal biopsies were sent with clinical information including the clinical features but with no mention of serological status of the patients, which may either have not been done or done but not mentioned in clinical details.

Out of these 100 cases of clinically and / or serologically suspected CD, duodenal biopsies of 46 (46%) revealed histological features consistent with celiac disease. Out of 10 patients in which serological analysis were provided with the clinical information, indicating raised levels of tTG antibodies, 8 cases (80%) showed histological features consistent with celiac disease. Among the others, 38 cases (38%) revealed chronic non specific duodenitis, 2 cases (2.0%) showed giardiasis, while 14 biopsies (14%) were unremarkable, showing no significant pathology. A summary of results of duodenal biopsies is given in table.

In our study, though a significant number of cases (46%) revealed histological findings consistent with CD, however at the same time, a significant number of cases clinically suspected for CD showed no histological evidence of CD. In majority of cases with positive serological assays, histological features were consistent with CD. Chronic non specific duodenitis was one of the

major histological outcomes followed by CD which was seen in patients presenting with symptoms mimicking celiac disease. This finding was comparable to a study done in India, revealing chronic non specific duodenitis as the leading cause of malabsorption followed by celiac disease[15]. The reason may be that gastrointestinal infections are very common in developing countries of the subcontinent, producing clinical symptoms, mimicking those of CD. Another important finding was a significant number of normal biopsies, which raise the possibility of some pathology in other parts of gastrointestinal tract responsible for symptoms mimicking CD. In the western world, CD does account for at least 90% of enteropathy, however the histological features of CD are not very specific and are also associated with disorders like giardia infection, common variable immune deficiency, Crohn's disease, and Helicobacter pylori infection[16]. The histological finding of increased intraepithelial lymphocytes (IELs), is recognized as one of the important feature potentially consistent with CD, however, by itself, this finding lacks specificity. Increased IELs can be found in other disorders and medications that cause small intestinal inflammation. The recognized etiologies of lymphocytic infiltration of the intestinal epithelium in the absence of villous atrophy include non-steroidal anti-inflammatory drugs, proton pump inhibitors, small intestinal bacterial over growth, helicobacter pylori infection, inflammatory bowel disease, and eosinophilic gastroenteritis[17]. About 2.5% of proximal small intestinal mucosal biopsies display increased IELs in the absence of villous architectural change[18,19]. Determining the etiology of increased intraepithelial lymphocytosis at times can be challenging and relies on assessment of clinical, serological, and histopathological data[20]. In general, patients with increased IELs should have celiac serology tested, but if these are negative, CD can be confidently ruled out in most cases. So, increased number of IELs though one of the important histological feature on which the histological diagnosis of CD is based, should be interpreted cautiously, if it is not correlating with the results of serum antibodies specific to CD. In this situation, the above mentioned alternative pathologies causing increased IELs must be investigated.

CONCLUSION

A significant number of cases clinically suspected of celiac disease may not be showing histological features consistent with celiac disease on duodenal biopsies. Due to the changing presentation of disease, as well as the recognition of a number of potential clinical and histo-pathological mimics, communication between pathologists and gastroenterologists is essential for appropriate interpretation of duodenal biopsy specimens.

RECOMMENDATION

The cases suspected of celiac disease must be evaluated in correlation with clinical features, serological assays for relevant antibodies and histological findings on duodenal biopsies.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

REFERENCES

1. Ludvigsson JF, Leffler DA, Bai JC, Biagi F, Fasano A, Green PHR, et al. The Oslo definitions for coeliac disease and related terms. Gut 2013; 62(1): 43–52.
2. Rostom A, Murray JA, Kagnoff MF. American Gastro-enterological Association (AGA) Institute Technical Review on the diagnosis and management of Celiac Disease. Am J Gastroenterol 2006; 131(6): 1981–2002.
3. Green PH, Jabri B. Coeliac disease. Lancet 2003; 362(9381): 383–91.
4. Maglio M, Florian F, Vecchiet M, Auricchio R, Paparo F, Spadaro R, et al. Majority of children with type 1 diabetes produce and deposit anti-tissue trans glutaminase antibodies in the small intestine. Diabetes 2009; 58(7): 1578–84.
5. Jamma S, Rubio-Tapia A, Kelly CP, Murray J, Najarian R, Sheth S, et al. Celiac crisis is a rare but serious complication of celiac disease in adults. Clin Gastroenterol Hepatol 2010; 8(7): 587–90.
6. Rubio-Tapia A, Ludvigsson JF, Brantner TL, Murray JA, Everhart JE. The prevalence of celiac disease in the United States. Am J Gastroenterol 2012; 107(10): 1538–44.
7. Rubio A, Hill ID, Kelly CP, Calderwood AH, Murray JA. ACG clinical guidelines: Diagnosis and management of celiac disease. Am J Gastroenterol 2013; 108(5): 656–76.
8. Marsh MN. Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ('Celiac Sprue'). Am J Gastroenterol 1992; 102(1): 330–54.

9. Tatiana S, Gama ES, Tania W. Diagnosis of celiac disease in adults. Rev Assoc Med Bras 2010; 56(1): 122-6.
10. Husby S, Koletzko S, Korponay-Szabo IR, Mearin ML, Phillips A, Shamir R, et al. European society for pediatric gastroenterology, hepatology and nutrition guidelines for the diagnosis of coeliac disease. J Pediatr Gastroenterol Nutr 2012; 54(1): 136–60.
11. Ludvigsson JF, Bai JC, Biagi F, Card TR, Ciacci C, Ciclitira PJ, et al. A Diagnosis and management of adult coeliac disease: Guidelines from the British Society of Gastroenterology. Gut 2014; 63(8): 1210–28.
12. Bai J, Zeballos E, Fried M, Corraza G. World gastroenterology organisation practice guidelines: Celiac Disease; world gastroenterology organisation: Milwaukee, WI, USA, 2013; 48, 1–18.
13. Meini A, Pillan NM, Villanacci V, Monafo V, Ugazio AG, Plebani A. Prevalence and diagnosis of celiac disease in IgA-deficient children. Ann Allergy Asthma Immunol 1996; 77(4): 333–36.
14. Brown IS, Smith J, Rosty C. Gastrointestinal pathology in celiac disease: A case series of 150 consecutive newly diagnosed patients. Am J Clin Pathol 2012; 138(1): 42–9.
15. Kaur A, Jadeja P, Garg N, Rai SM, Mogra N. Evaluation of Small Intestinal Biopsies in Malabsorption Syndromes. Ann Lab Med 2016; 3 (suppl-5): A408-14.
16. Pallav K, Leffler DA, Tariq S, Kabbani T, Hansen J, Peer A, et al. Noncoeliac enteropathy: The differential diagnosis of villous atrophy in contemporary clinical practice. Aliment Pharmacol Ther 2012; 35(3): 380–90.
17. Hammer STG, Greenson JK. The clinical significance of duodenal lymphocytosis with normal villus architecture. Arch Pathol Lab Med 2013; 137: 1216–19.
18. Brown I, Mino-Kenudson M, Deshpande V, Lauwers GY. Intraepithelial lymphocytosis in architecturally preserved proximal small intestinal mucosa: An increasing diagnostic problem with a wide differential diagnosis. Arch Pathol Lab Med 2006; 130(7): 1020–25.
19. Kakar S, Nehra V, Murray J A, Dayharsh GA, Burgart LJ. Significance of intraepithelial lymphocytosis in small bowel biopsy samples with normal mucosal architecture. Am J Gastroenterol 2003; 98(9): 2027-33.
20. Zanini B, Caselani F, Magni A, Turini D, Ferraresi A, Lanzarotto F, et al. A Celiac disease with mild enteropathy is not mild disease. Clin Gastroenterol Hepatol 2013; 11(3): 253–58.