

Coeliac disease diagnosis: has histopathology become redundant?

Muhammed Mubarak, Javed I Kazi

Department of Histopathology, Sindh Institute of Urology and Transplantation, Karachi, Pakistan.

Coeliac disease (CD), also known as Coeliac sprue, nontropical sprue, gluten-induced enteropathy, or gluten-sensitive enteropathy (GSE) is a chronic, systemic, autoimmune disorder predominantly affecting the small intestine, and caused by the hypersensitivity to certain ingredients in wheat (gluten), rye (secalins), and barley (hordeins), in genetically susceptible individuals.¹⁻⁴ Classically it affects infants and young children soon after weaning to wheat based diet, but the disease can afflict individuals of any age.⁵⁻⁷ Indeed, the disease is now being diagnosed more frequently in adults and elderly.^{8,9} The later forms of the disease are known as latent, late-onset, or subclinical GSE. An accurate diagnosis of these forms is also crucial, as continued ingestion of gluten in these individuals also predisposes them to the same type of long-term complications as the classic childhood-onset CD.³

The prevalence of the disease varies widely in different parts of the world; initially, it was thought to be a rare disease, and to affect predominantly the Caucasians.¹ However, more recent studies employing new highly sensitive and specific serologic assays have shown it to be a fairly common disease worldwide, although with marked regional and racial differences.¹⁰⁻¹⁴ This variability is most probably due to the differences in the diagnostic protocols used and the level of public health awareness, and partly to true differences in the incidence of the disease. The disease was initially presumed to be less common in Asian and African populations, but recent reports show rising trend of diagnosis.^{10,11} Recent surveys from the west show its prevalence to vary from 1 in 100 to 1 in 300 individuals.¹⁻⁴ There is no population based data on the incidence or prevalence of the disease in Pakistan.¹² However, single center based studies show that the disease is not uncommon in the paediatric population from this country presenting with chronic diarrhoea or failure to thrive.^{13,14} There is also very little information in the literature on the prevalence of the disease in adults from this country.¹⁵ However, these few reported cases, in all probability, represent only the tip of the iceberg; the main body has not been explored as yet in Pakistan.

The clinical presentation varies considerably from full-blown malabsorption syndrome seen in the classic childhood-onset disease to subtle and atypical symptomatology, especially in the late-onset forms of the disease. The clinical profile of cases detected because of

positive serological tests seems to be quite different compared to historical cases detected based on severe malabsorption and histopathology only (total villous atrophy).¹ The cases detected by positive serology often exhibit non-specific histopathological changes that are common in other conditions as well. Moreover, contrary to the previously held belief, symptomatology in this group does not seem to be related to the degree or length of the involved segment of the small intestine either.^{1,7} With this degree of non-specificity, the histopathology clearly fails to meet the gold standard criteria for the diagnosis of GSE. This, however, does not mean that histopathology has become a redundant test in the diagnosis of GSE; it still remains an important component in the diagnosis of GSE but its traditional role as the gold standard test has been questioned.¹

Thus, the diagnosis of CD has always been a challenge for the clinicians. There is no single specific or sensitive enough test to detect all cases of CD. Therefore, its diagnosis requires a combined clinicopathological approach including proximal small intestinal mucosal biopsy, serologic tests, and the effects of a gluten free diet (GFD) on the symptoms.¹⁻⁵ During the early era, the most prominent characteristic of the disease was the histopathological change on proximal small intestinal biopsy and the biopsy became the gold standard for diagnosis.³⁻⁵ However, as a result of marked changes in the mode of presentation and diagnosis of GSE during the past two decades, the role of duodenal biopsy as the gold standard has come under criticism.¹ With the increasing sensitivity, specificity, and the sophistication of serological and genetic tests, the spectrum and the problems of the histopathological evaluation of the small intestinal biopsies have expanded markedly. The widespread use of these tests has resulted in the detection of a very high frequency of "borderline" cases; potential CD (positive Coeliac serology with a normal small intestinal architecture) or sero-negative disease (typical Coeliac histology and response to the GFD with negative serology).¹

It is worth reiterating the fact that the mucosal histopathologic features on proximal small intestinal biopsy are very variable, ranging from mild abnormalities, including intraepithelial lymphocytosis (IELosis) with intact villi, to completely flat mucosa.^{1,3,7,16-21} The latter lesion was typical of the classic childhood form of CD and represented the advanced stage of the disease.¹⁻³ As a matter of fact, it

nowadays represents only the tip of the iceberg. It is timely to acknowledge the fact that for the majority of GSE cases, the histopathology is nonspecific and hence the histopathologist is only a member of the multidisciplinary team and not the one who could make the definite diagnosis of CD in isolation solely based on histopathology.¹ The sensitivity and specificity of the newer serological tests are far superior to histopathology. At this time, clinicians need to give more importance to the clinical symptoms; the presence of antibodies and histopathology should be interpreted cautiously based on these features, as both of these tests exhibit false-negative and false-positive results. Since patients with minimal histologic lesion of IELosis often present with normal serologic findings, biopsy diagnosis becomes more important for identifying such individuals. However, there is marked inter- and intra-observer variation in the histopathological evaluation of small bowel biopsy specimens. The number, size, and site of the biopsy samples, and correct orientation are all important factors that may confound the diagnosis of the disease. An adequate number of biopsy samples should be taken because CD is patchy and not all biopsy samples will be properly oriented for the interpretation of the crypt to villous ratio. A badly oriented biopsy, as shown by crypts cut tangentially, will falsely decrease the crypt to villous ratio. Deeper sectioning of such cases may reveal the true architectural picture. Negative serological tests or poor response to GFD should prompt review of the biopsy to ensure that the original interpretation was correct. The role of the experienced histopathologist in the interpretation of the biopsies is no less important. According to Green and Jabri, a major pitfall in the diagnosis of CD is in the pathological interpretation of the small intestinal biopsies.⁴ Considerable research is focused nowadays to provide new means to overcome the methodological issues and the subjectivity of interpretation related to the histopathological evaluation, but the problem is far from being completely solved.^{6,16-21} The classification of mucosal pathological lesions in GSE has also been a subject of controversy among the pathologists and needs to be revised according to the current understanding of the disease. Recently, Ensari has proposed an updated version of the time-honored Marsh classification, which is much simpler, and user-friendly from a pathologist's point of view.⁶ However, it needs to be validated in prospective studies in different centers of the world before it can get widespread acceptability.

Some investigators argue that it is the time to change the original dogma of biopsy as gold standard for the diagnosis of CD. According to them, nowadays, in the light of the current knowledge and complex clinical presentation, the true gold standard is not the biopsy but the "final diagnosis of CD made by the clinician."¹ The clinician is the only one who has complete knowledge of the patient profile,

institutes the tests and their timing, and therefore is the only one who can reasonably interpret the profile of available information (clinical, serological, histological and genetic). He/she is the one who can coordinate the essential multidisciplinary team of geneticists, histopathologists, and immunologists in making an accurate diagnosis. The role of the histopathologist is not dwarfed by the above approach but rather is always an essential element for the accurate CD diagnosis. This is especially true nowadays with a significant increase in borderline cases, which in some recent series represent 10-20% of the CD diagnoses. In these situations, an accurate assessment of the morphology of a properly procured and prepared duodenal biopsy is crucial for the final diagnosis of CD.^{1,4,6}

In conclusion, the diagnosis of CD is still as challenging as it was a few decades ago. With the increasing use of serology and genetic testing, the clinical and morphologic spectrum of CD is increasing and posing new diagnostic challenges. This has, at the same time, also led to a better equipment of the clinician with a range of diagnostic tests at his/her disposal to sort out the borderline cases. The role of histology is not diminished with the availability of these newer tools for the diagnosis of CD. However, in the light of new information, there is a need to revisit the historical dogma of the biopsy as the gold standard test for the diagnosis of CD.

References

- Volta U, Villanacci V. Coeliac disease: diagnostic criteria in progress. *Clin Mol Immunol* 2011; 8: 96-102.
- Di Sabatino A, Corazza GR. Coeliac disease. *Lancet* 2009; 373: 1480-93.
- Antonioni DA. Coeliac disease: a progress report. *Mod Pathol* 2003; 16: 342-6.
- Green PH, Jabri B. Coeliac Disease. *Lancet* 2003; 362: 383-91.
- Dickson BC, Streutker CJ, Chetty R. Coeliac disease: an update for pathologists. *J Clin Pathol* 2006; 59: 1008-16.
- Corazza GR, Villanacci V. Coeliac disease. *J Clin Pathol* 2005; 58: 573-4.
- Ensari A. Gluten-sensitive enteropathy (Coeliac disease): controversies in diagnosis and classification. *Arch Pathol Lab Med* 2010; 134: 826-36.
- Vilppula A, Kaukinen K, Luostarinen L, Kerkelä I, Patrikainen H, Valve R, et al. Increasing prevalence and high incidence of Coeliac disease in elderly people : a population-based study. *BMC Gastroenterol* 2009; 9: 49.
- Vivas S, Ruiz de Morales JM, Fernandez M, Hernando M, Herrero B, Casqueiro J, et al. Age-related clinical, serological, and histopathological features of Coeliac disease. *Am J Gastroenterol* 2008; 103: 2360-5.
- Cataldo F, Montalto G. Coeliac disease in the developing countries: A new and challenging public health problem. *World J Gastroenterol* 2007; 13: 2153-9.
- Gupta R, Reddy DN, Makharia GK, Sood A, Ramakrishna BS, Yaccha SK, et al. Indian task force for Coeliac disease: current status. *World J Gastroenterol* 2009; 15: 6028-33.
- Rashid M, Khan AG. Coeliac disease in Pakistan: challenges and opportunities. *J Ayub Med Coll Abbottabad* 2009; 21: 1-2.
- Aziz S, Muzaffar R, Zafar MN, Mehnaz A, Mubarak M, Abbas Z, et al. Coeliac disease in Pakistani children with persistent diarrhea. *J Pediatr Gastroenterol Nutr* 2005; 41: 494.
- Aziz S, Muzaffar R, Zafar MN, Mehnaz A, Mubarak M, Abbas Z, et al. Coeliac disease in children with persistent diarrhea and failure to thrive. *J Coll Physic Surg Pak* 2007; 17: 554-7.
- Memon MS, Solangi S, Shaikh FH, Ghori MA, Ansari MK, Dawoodpoto AW. Clinical, serological, and histological features of Coeliac disease in

- the adult population: a tertiary care hospital experience. *Med Channel* 2010; 16: 223-6.
16. Corazza GR, Bonvicini F, Frazzoni M, Gatto M, Gasbarrini G. Observer variation in assessment of jejunal biopsy specimens. A comparison between subjective criteria and morphometric measurement. *Gastroenterol* 1982; 83: 1217-22.
 17. Shidrawi RG, Przemioslo R, Davies DR, Tighe MR, Ciclitira PJ. Pitfalls in diagnosing Coeliac disease. *J Clin Pathol* 1994; 47: 693-4.
 18. Gasbarrini G, Malandrino N, Giorgio V, Fundaro C, Cammarota G, Merra G, et al. Coeliac disease: what's new about it? *Dig Dis* 2008; 26: 121-7.
 19. Hill PG, Holmes GK. Coeliac disease: a biopsy is not always necessary for diagnosis. *Aliment Pharmacol Ther* 2008; 27: 572-7.
 20. Anderson RP. Coeliac disease: current approach and future prospects. *Intern Med J* 2008; 38: 790-9.
 21. Murdock AM, Johnston SD. Diagnostic criteria for coeliac disease: time for change? *Eur J Gastroenterol Hepatol* 2005; 17: 41-3.
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