Very high rate of misdiagnosis of celiac disease in clinical practice


Sociedad Argentina de Gastroenterología
Buenos Aires, Argentina
Very high rate of misdiagnosis of celiac disease in clinical practice

María Inés Pinto Sánchez, Edgardo Smecuol, Horacio Vázquez, Roberto Mazure, Eduardo Mauriño, Julio César Bai

Small Bowel Section, Department of Medicine; “Dr Carlos Bonorino Udaondo” Gastroenterology Hospital; Ciudad Autónoma de Buenos Aires, Argentina.


Summary

Objective. We evaluated the accuracy of the diagnosis of celiac disease (CD) performed in the community clinical setting compared with that of an academic experienced center. Materials. Original biopsy slides and reports used for diagnosis in the community setting and the CD serology were revised in 70 consecutive patients attending our institution for a second opinion. An expert team determined the final diagnosis unaware of the original consideration. Results. The poor quality of samples made histology assessment by the expert pathologist uncertain in 8.7% of slides with CD external diagnosis. We detected a divergent diagnosis between the two practice settings in 46.3% of available cases with a significant overdiagnosis of CD in the community (p<0.0001). Congruent serology results were demonstrated in 72.2% of cases. Conclusion. Our study detected a high rate of histopathological and serological misdiagnosis of CD in community practice which may have profound negative impact on patients.

Key words. Celiac disease, Antibodies, Serology, Histology, Diagnosis, Gastrointestinal pathology.

Elevada tasa de error diagnóstico de enfermedad celiaca en la práctica clínica

Resumen

Objetivo. Evaluamos la seguridad del diagnóstico de enfermedad celiaca (EC) realizado en la práctica clínica general comparándolo con una evaluación efectuada en un centro de referencia con experiencia académica. Material y métodos. Se evaluaron 70 pacientes consecutivos que asistieron a nuestra institución de nivel terciario en la búsqueda de una segunda opinión para confirmar o descartar EC. Los vidrios originales de biopsias duodenales y sus informes correspondientes fueron reevaluados por un patólogo experto. La serología específica para EC utilizada en la práctica clínica fue reiterada en nuestra institución. El diagnóstico final fue determinado por un grupo de expertos sobre la base de los resultados obtenidos en nuestra institución cegados al diagnóstico original. Resultados. La evaluación histológica por el patólogo experto no fue posible en un 8.7% de las muestras con diagnóstico de EC en la práctica comunitaria dada la pobre calidad de las muestras. La divergencia diagnóstica al comparar los dos escenarios de práctica clínica, la general y la "experta", se verificó en 46.3% de los casos disponibles con un significativo sobrediagnóstico de EC en la práctica general (p<0.0001). Se observaron resultados serológicos congruentes en 72.2% de los casos. Conclusión. Nuestro estudio detectó una alta tasa de errores diagnósticos histopatológicos y serológicos de EC en la práctica comunitaria que puede tener un profundo impacto negativo sobre los pacientes.

Palabras claves. Enfermedad celiaca, anticuerpos, serología, histología, diagnóstico, patología Gastrointestinal.

The diagnosis of celiac disease (CD) is based on the finding of a gluten-dependent characteristic enteropathy in the intestinal biopsy.1 Therefore, the adequate histological interpretation is essential for diagnosing CD.2 Celiac disease is a typical condition in which the appreciation of the finer points of the intestinal pathology may alter the perception of...
a biopsy specimen and result in a different diagnostic conclusion. The CD-related serology is widely used for suspicion and diagnosis of CD and a wide range of serological methods are available. The concomitance of a positive specific serology while the patient is consuming a gluten containing diet is the most commonly used surrogate marker of gluten dependency.

According to our review of the literature, there are anecdotal reports and very few studies assessing the inter-observer variability of the main tools used for diagnosing CD. From the histopathologic point of view, the degree of agreement in CD diagnosis has only been explored between pathologists of academic settings and there is a lack of investigations orientated to analyze the diagnostic performance of histological reports of intestinal biopsies according to the pathologist expertise. In terms of serology, variability of methods and lack of standardization are still major obstacles in practice to make reliable serological result. Furthermore, the performance of serological tools has only been assessed in referral centers and, therefore, the quality and accuracy of these tools in the community practice remains unknown.

In recent years, the medical community is faced with the challenge of a growing number of cases suspected of CD. There is a shortage of experienced clinicians, pathologists, and laboratory personnel who are knowledgeable about the diagnostic complexities in CD and pitfalls in diagnosing the disorder may have profound impact in patients and relatives. Therefore, the aim of this study was to evaluate the accuracy of CD diagnosis in the community clinical setting compared with an academic medical center.

**Methods**

Consecutive adult patients diagnosed at community clinics who consulted our tertiary institution for a second opinion were included in a retrospective study if original biopsy slides used for diagnosis and the corresponding reports were available as well as concomitant CD serology performed in both settings while patients were on a gluten containing diet. We assumed as original diagnosis that provided by the community histopathological report. An expert team blinded to original diagnosis made the final diagnosis based on clinical findings and follow-up, the experts’ assessment of histology, and serology test results obtained in our laboratory. We then compared the expert diagnosis and the original diagnosis made in community practice. For the expert analysis, the pathologist of the academic centre used the Marsh’s modified classification, considering as CD diagnosis a Marsh’s type IIIa or greater damage.

**Results**

Seventy cases fulfilled the inclusion criteria. In 6 cases (8.6%) the expert pathologist at our tertiary care center was not able to arrive at a diagnosis because of the poor quality of biopsy samples. Furthermore, the retrospective nature of the study determined that the expert team was not able to reach a definitive diagnosis in 10 (14.3%) additional patients. According to the original histopathological reports at the community clinic, 43 of the remaining 54 patients (79.6%) had been diagnosed for CD and 11 (20.4%) were ruled out for CD. In contrast, the experts at the academic center diagnosed only 22 patients (40.7%) for CD and determined that the other 32 (59.3%) patients did not have CD (Figure 1). Overall, 25 patients (46.3%) had a divergent diagnosis between the two practice settings (23 patients originally identified as CD and 2 diagnosed as non-CD).

**Figure 1.** Flow-chart of diagnosis in 54 patients as they were assessed at the community setting and at the specialized tertiary center. Full lines and dotted lines are indicating concordance in the diagnosis or divergent diagnosis, respectively.
CD) (kappa statistic: 0.16). Misdiagnosis in community practice for patients without CD as having the disorder based on histological assessment (53.5%) occurred more frequently than missed CD cases (18.2%) [OR: 25.5 (95% CI: 4.9-132.4),  \( p < 0.0001 \)]. The serology results of the expert and outside laboratories agreed in 72.2% of patients.

**Discussion**

A combination of clinical, laboratory and histopathological features may result in a diagnosis of CD, particularly if symptoms are resolved subsequently with a gluten-free diet. Although the diagnosis of CD may be often straightforward, sometimes several pitfalls in the interpretation of tests may result in misdiagnosis. An accurate histological assessment of intestinal biopsy samples is essential for correctly diagnosing CD. While a severe intestinal damage can be easy to identify by general pathologists, a finer appreciation for more subtle morphological changes may be difficult to the inexperienced eye. Poor quality of the endoscopically procured samples (small biopsies, inadequate orientation, and incorrect preparation and handling) contributes to the difficulties in the evaluation. Our present study aimed to explore the quality and appropriateness of CD diagnosis performed in community clinical practice compared with the evaluation performed in a tertiary referral academic center with expertise in CD where final diagnosis were based on congruent histological and serological findings and follow-up.

In the study, we found that the slides were considered insufficient for diagnosis by the expert pathologist in 8.6% of the samples having a definite diagnosis of CD by community pathologists. A similar observation has been recently reported by a multicenter European study. The study also reveals a strong divergence between settings that is evidenced by the very poor agreement in the histological characterization of CD. Our evaluation shows a great proportion of misdiagnosis in the community practice, particularly, a significant histological overdiagnosis of CD.

A positive serology result when the patient is consuming a gluten-containing diet is the most commonly used surrogate marker for gluten-dependent enteropathy. However, variability of these methods and a lack of standardization are still major obstacles in practice to routinely rely on serological tests for CD diagnosis. Our study revealed that although the concordance between settings was higher than the histological agreement, 28% of cases had discordant results.

Despite the study is clearly imbalanced in terms of tools used for supporting the diagnosis in both settings, the results clearly expose pitfalls in the diagnosis of CD that deserve to be recognized. Our findings evidenced that most histological diagnoses in the community were performed by general pathologists. Because that the nature of the interpretation of the wide spectrum of histological changes relies on subjective appreciations, standardization of the characteristic, but not patognomonic findings, has been attempted. Quantitative or semi-quantitative morphometric measurements were also developed in order to reduce subjectivity. However, dissemination of these notions has reached the academic medicine or highly complex institutions but less the general pathologist in the community practice whose daily menu includes biopsies from different parts of the human economy.

In conclusion, our study found a high rate of histological and serological misdiagnosis of CD in the community clinical setting. This was mainly due to a histological overdiagnosis of CD. Although the nature of consultations in our referral center suggests a potential overestimation of the true prevalence of the problem, pitfalls for diagnosing CD in the community practice may have profound negative impact on patients. Improving diagnosis skills can help avoid grief. The expertise of GI pathologists is critical and may result into a better and more effective diagnosis avoiding unnecessary strain on the patient and his family.

**Financial disclosure:** Nothing to declare.

**References**


