

Histologic findings in biopsies/resection specimens from the small intestine with special emphasis on celiac disease: experience from a developing country in South Asia^{☆,☆☆}

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Abstract

Biopsies from the small intestine especially the duodenum are now being performed much more frequently than in the past. The most frequent reason for performing duodenal biopsies is to evaluate for malabsorption. In the last few years, increased awareness has resulted in more biopsies sent for evaluation of malabsorption, especially celiac disease (CD). In the duodenum, features of malabsorption (increased intraepithelial lymphocytes, villous shortening, and atrophy) were the most common histologic finding seen in 63.4% of cases. Serum tTG levels were available for correlation in 52.8% of cases. In patients with confirmed CD, 53.4% were MARSH IIIb, and 29.5% were MARSH IIIc. The most common specific condition diagnosed in the ileum was tuberculosis (35.6%), and 80.8% with ileal tuberculosis were women. Our findings, although preliminary, indicate that CD is not so rare in Pakistan. These are the first findings from Pakistan on this subject, and larger studies are required to determine the true frequency and impact of CD in Pakistan. © 2012 Elsevier Inc. All rights reserved.

Keywords: Small intestine; Celiac Disease; Malabsorption; Tuberculosis

1. Background

Small bowel biopsies are commonly received in the Section of Histopathology, Aga Khan University Hospital, Karachi. Occasionally, resection specimens are also received. We are the biggest center for histopathology in Pakistan, a country of 170 million people, and we receive cases from the whole country. Although we recommend that 4 to 6 biopsies should be taken, in practice, we mostly receive 2 to 3. Duodenal biopsies are the most common, followed by terminal ileal biopsies. Jejunal biopsies are

received occasionally. Biopsies from the distal duodenum are very important in the evaluation of patients with suspected malabsorption [1], although terminal ileal biopsies are being increasingly performed especially in patients having lower intestinal symptoms [2]. The most important reason for performing duodenal biopsies is for the evaluation of malabsorption. Other common reasons for which duodenal and ileal biopsies are performed include infections, especially giardiasis and tuberculosis, and neoplastic lesions. In the last few years, increasing awareness among both gastroenterologists and histopathologists in this country has resulted in increasing number of biopsies being sent for evaluation of a specific type of malabsorption, that is, celiac disease (CD) or gluten-sensitive enteropathy.

Celiac disease (or gluten-sensitive enteropathy) is an autoimmune disorder that is triggered by gluten and related prolamins (present in wheat, barley, rye, oat, etc) in genetically susceptible individuals (strong association with HLA DQ2 and, to a lesser extent, with HLA DQ8 alleles) and manifests in its classical (or typical) form as abdominal discomfort, chronic diarrhea, weight loss, and steatorrhea [3–5]. It is now clear that CD is much more

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common worldwide than what was previously thought and, in addition, that it may be diagnosed at any age including late adulthood instead of being a disease confined to children [4,5].

It was also widely believed that CD almost exclusively affects people of European origin, but now, the availability of new, simple, very sensitive, and highly specific serologic tests (antigliadin, antiendomysium, and antitransglutaminase antibodies) has made it very evident that CD is the most common food intolerance in the world affecting not only Europeans and people of European ancestry (North and South Americans and Australians) but also populations where, until a few years ago, it was considered extremely rare, such as in the Middle East, North Africa, South Asia, and other [6,7].

Celiac disease was believed to be extremely rare in Pakistan, and there are no studies or statistics about its prevalence in Pakistani population. However, with greater awareness among gastroenterologists and the availability of serologic tests (especially antitissue transglutaminase or anti tTG), realization is slowly dawning that CD may not be so rare in Pakistan.

Because wheat is the major staple diet in Pakistan, there is every reason to suspect that CD may be much more common in our population than what is conventionally believed.

The objective of this study was to document the histologic findings in small intestinal biopsies seen in our practice to determine the frequency of various pathologic conditions with special emphasis on malabsorption especially CD on which no previous data in our population were available.

2. Discussion

In a review of 500 small intestinal biopsies and surgical specimens carried out in the Section of Histopathology, Aga Khan University Hospital, 404 (80.8%) were from the duodenum (excluding the ampullary/periampullary region). Biopsies from the terminal ileum, ampullary/periampullary region, and jejunum comprised 73 (14.6%), 18 (3.6%), and 5 (1.0%) cases, respectively. Of a total of 500 specimens, 473 (94.6%) were endoscopic biopsies, whereas 27(5.4%) were surgical/resection specimens.

In the duodenal biopsies, features of malabsorption (increased intraepithelial lymphocytes, villous shortening, blunting, or atrophy) were the most common histologic findings seen in 256 (63.4%) of 404 cases. The second largest group of duodenal biopsies comprised those biopsies that were unremarkable or showed only mild nonspecific inflammation. These comprised 110 (27.2%) of 404 cases (Table 1). In a few cases showing increased intraepithelial lymphocytes, villous blunting, and other (10/256, or 3.9%), these histologic features were due to conditions such as giardiasis, tuberculosis, lymphoma, gastrointestinal stromal tumor (GIST), neuroendocrine neoplasm, and other. However, in the large majority of cases (246/256, or 96.1%),

Table 1

Breakup of histologic findings in the biopsies/surgical specimens from the duodenum (n = 404)

Specimen no.	Histologic findings	No.	%
01	Malabsorption	256	63.4
02	Adenocarcinoma	9	2.2
03	Giardiasis	9	2.2
04	Neuroendocrine neoplasms	6	1.5
05	GIST	5	1.2
06	Lymphoma	3	0.7
07	Tuberculosis	3	0.7
08	Lymphangiectasia	2	0.5
09	Brunner gland hyperplasia	1	0.2
10	Unremarkable or mild nonspecific inflammation	110	27.2

these histologic features were associated with more specific causes of malabsorption, especially CD. Of these 246 cases, serum tTG levels were available for correlation in 130 cases (52.8%). We diagnosed these cases as CD. In an additional 46 (18.7%) of 246 cases, clinical impression was that of CD, and the patient's history/requisition slip mentioned that serum tTG levels were raised. However, these levels were not provided for correlation. It needs to be reiterated that we receive cases from the whole country including very remote areas and that it is often very difficult to communicate with the clinicians. We diagnosed such cases as compatible with the clinical diagnosis of CD and added a comment that the histologic findings should be correlated with serum tTG levels. In 4 cases (1.6%), a clinical history of vitamin B₁₂ and folic acid deficiencies was provided. In these cases, we raised the possibility that tropical sprue should be excluded, adding a comment that vitamin B₁₂ and folic acid deficiencies can also be the result of malabsorption from any cause rather than being the primary cause itself. In the remaining 66 (26.8%) of 246 with histologic appearances of malabsorption, no clinical history was provided. In these cases, the histologic diagnosis simply mentioned the histologic findings, and we added a note recommending clinical and serologic correlations to confirm/rule out specific causes of malabsorption. Thus, our current protocol in biopsies with histologic features of malabsorption is to give a confirmed diagnosis of CD when raised serum tTG levels are known to us and to give a diagnosis of "compatible with the clinical diagnosis of CD" when clinical details on the requisition slip mention that serum tTG levels are raised but the exact levels are not provided for correlation. In these cases, we also add a comment that histologic findings should be correlated with serum tTG levels. In the cases where biopsies show histologic appearances of malabsorption but no clinical history is provided, we simply report that histologic findings are consistent with malabsorption and append a note that clinical (including serologic) workup be carried out to confirm/rule out specific causes of malabsorption such as CD. In this study, of the 176 cases with confirmed CD (raised serum tTG levels available for correlation) or findings compatible with clinical diagnosis of CD (serum tTG levels raised according to clinical

Table 2

Breakup of cases with raised serum tTG levels and histologic features of malabsorption according to MARSH grade (n = 176)

Specimen no.	MARSH grade	No.	%
01	I	18	10.2
02	III a	12	6.8
03	III b	94	53.4
04	III c	52	29.5

information but not provided for correlation), no significant difference was found in sex distribution. There were 90 women (51.1%) and 86 men (48.9%). The age range and mean age at diagnosis in both sexes combined were 3 to 75 years and 32.3 years, respectively. The age range and mean age at diagnosis in women alone were 13 to 55 years and 29.5 years, respectively. The age range and mean age at diagnosis in men alone were 3 to 75 years and 36.3 years, respectively. Of the 176 patients, 35 (19.9%) were younger than 15 years.

No significant variation was noted in distribution of patients in different areas of the country. The genetic significance of this, if any, is not known at present, but environmentally, it may be a reflection of the fact that wheat is the staple diet of the entire population of Pakistan irrespective of the geographic regions.

In these 176 cases, we also graded the histologic findings according to the MARSH grade [8]. It is our protocol that we do MARSH grading in all cases where tTG levels are available or if clinical history mentions that serum tTG levels are raised, even if the levels are not provided to us. The breakup of these cases according to MARSH grade is shown in Table 2.

Of the 18 cases of MARSH grade I, only 2 cases were associated with significantly raised serum tTG levels. The remaining 16 cases showed only mildly increased serum tTG levels. It is believed that MARSH I cases represent latent CD, and only a small percentage of such cases progress to fully developed CD [9–11]. No significant statistical correlation was found in our study between the severity of the histologic findings and the rise in serum tTG levels for MARSH types IIIa, b, and c.

Of 176 patients, 35 (19.9%) were younger than 15 years. The breakup of these 35 children according to MARSH grade is given in Table 3. The breakup of the 141 patients older than 15 years according to MARSH grade is given in Table 4.

Table 3

Breakup of patients younger than 15 years with histologic features of malabsorption according to MARSH grade (n = 35)

Specimen no.	MARSH grade	No.	%
01	I	3	8.6
02	III a	2	5.7
03	III b	17	48.6
04	III c	13	37.1

Table 4

Breakup of patients older than 15 years with histologic features of malabsorption according to MARSH grade (n = 141)

Specimen no.	MARSH grade	No.	%
01	I	8	5.7
02	III a	13	9.2
03	III b	80	56.7
04	III c	40	28.4

Clinical signs and symptoms were available in only a small percentage of cases. Anemia was present in 21 cases, chronic diarrhea in 17, and weight loss in 14, and vomiting was seen in 3 cases.

Our findings, although preliminary and involving a relatively small number of patients, indicate that CD is not so rare in Pakistan, a South Asian country, as was previously believed, a fact that is compatible with findings of other investigators such as Accomando and Cataldo [7]. Our findings are also compatible with the observation of Cataldo and Montalto [6], who argued that CD is common in developing countries where wheat is the major staple diet whether in South Asia, Middle East, Africa, or South America.

In our study, most cases were diagnosed in adulthood (mean age at diagnosis, 32.3 years). As indicated by other investigators [12], most adults with CD, especially in areas where wheat is the major staple diet, may initially have a subclinical form of the disease and not exhibit classical symptoms of CD such as diarrhea and weight loss. They may initially present only with subtle manifestations such as an isolated iron deficiency anemia. The diagnosis may thus be delayed. It is very important in our setting to investigate unexplained gastrointestinal symptoms in adults by conducting serologic tests for CD. It is critical to increase awareness about CD among general physicians. In a developing country such as Pakistan, the situation is further complicated by the fact that a large number of children, especially girls, and women in the reproductive age group have nutritional or blood loss iron deficiency anemia and may not be investigated for CD at all.

We need to conduct much larger studies to assess the true incidence and prevalence of CD in our population. In a country, such as Pakistan, where there is no awareness about CD among the general public and where commercial gluten-free products are not available, a major challenge will be to maintain patients with CD on a permanent gluten-free diet. Gluten-free products will not become available in Pakistan until large studies can demonstrate that CD is reasonably common. Thus, CD can be a widespread health problem in developing countries [6] because of lack of awareness and unavailability of gluten-free products.

The second biggest group of diagnosis made in duodenal biopsies was unremarkable or mild nonspecific inflammation (Table 1). Because gastrointestinal tract infections are extremely common in a developing country such as Pakistan because of poor hygienic conditions, we tend to give a diagnosis of mild nonspecific duodenitis if we see even few

lymphocytes or plasma cells in the lamina propria. However, it is surprising that specific infections such as giardiasis or tuberculosis were not more frequent. As shown in [Table 1](#), the frequency of giardiasis in our series was only 2.2% of all duodenal biopsies, whereas that of tuberculosis was even lower, that is, only 0.7%. The frequency of tuberculosis was, however, much higher in the ileum, comprising 35.6% of all ileal biopsies ([Table 2](#)).

Giardiasis is a common infection especially in developing countries where hygienic conditions are poor and water supplies are often contaminated by fecal matter [13]. The low frequency of giardiasis in our series needs to be further investigated by conducting much larger studies to assess its true incidence and prevalence in our population. Our cases were almost equally distributed between men and women; age range was 15 to 50 years, with a mean age of 27 years. However, our numbers were too few to give a clear idea about sex and age distribution.

Surprisingly, at least in this series, the number of duodenal adenocarcinomas other than those of the ampullary region was greater than that of neuroendocrine neoplasms, GISTs, or lymphomas ([Table 1](#)). According to and 19.2% of small intestinal carcinomas are found in duodenum, jejunum and ileum respectively [14]. However, a much larger series of cases will be required to give the true picture regarding the relative frequencies of these conditions in the duodenum. Of the 9 cases of adenocarcinomas, 7 (77.8%) were women; age range was 46 to 72 years, with a mean age of 58.1 years.

Diseases of the ileum encompassed a wide variety of conditions. However, the most common specific condition diagnosed in the ileum was tuberculosis. This was followed by mild nonspecific inflammation ([Table 5](#)). Ileal tuberculosis was much more common in women. Of 26 cases, 21 (80.8%) were women. The age range was between 7 and 45 years with a mean age of 20.7 years. The much greater frequency of ileal tuberculosis in young women reflects the “inferior” status of women in this country. Especially in the lower socioeconomic groups, girls are often anemic and

malnourished and much more prone to develop diseases that thrive under conditions of poverty, poor hygiene, malnourishment, and other. Tuberculosis of the small bowel is still quite frequent in developing countries [15].

In the ileal biopsies, adenocarcinoma was more frequent than lymphoma or neuroendocrine neoplasms ([Table 5](#)). There was no case of ileal GIST in our series. Inflammatory myofibroblastic tumor/inflammatory fibroid polyp, was, however, relatively common ([Table 2](#)). Inflammatory fibroid polyps mainly occur in the small intestine and stomach [16].

Of the 17 adenocarcinomas diagnosed in the duodenum and ileum, there were 4 resection specimens. All 4 were advanced lesions with pathologic stage pT3pN2.

Ileal perforations were seen in 14 (19.2%) of 73 cases. Of these 14 cases, perforation was due to tuberculosis in 4 cases (28.5%) and due to typhoid fever and lymphoma in 1 case (7.1%) each. In the remaining 8 cases, no specific cause could be found.

Of the 18 cases from the ampullary/periampullary region, 16 (88.9%) were adenocarcinomas, whereas 2 (11.1%) were inflammatory. Of the 16 patients with adenocarcinoma, 13 (81.2%) were men. The age range was 45 to 65 years, and the mean age at diagnosis was 54.3 years. There were 3 resection specimens (Whipple procedure); all were T2 and N1. Studies show that more than 80% of ampullary epithelial neoplasms are adenocarcinomas [17]. We are currently working on a large series of ampullary/periampullary carcinomas that will, it is to be hoped, give us a truer picture about these tumors in our population.

Of the 5 cases from the jejunum, 3 (60%) showed nonspecific inflammation; 1, tuberculosis; and 1, adenocarcinoma.

We hope that this series of 500 biopsies/resection specimens from the small intestine received in the biggest center for histopathology in Pakistan will provide an overview about the frequency of various pathologies in the small intestine that we encounter in our practice. We also hope that this study will lead to much larger studies to assess the true frequency and impact of CD in Pakistan.

3. Summary

Our findings, although preliminary and involving a relatively small number of patients, indicate that CD is not so rare in Pakistan, a South Asian country, as was previously believed, a fact that is compatible with findings of other investigators. Our findings are also compatible with the observation of others who argued that CD is common in developing countries where wheat is the major staple diet whether in South Asia, Middle East, Africa, or South America. In most of our patients, the disease was diagnosed in adulthood.

As indicated by other investigators, most adults with CD, especially in areas where wheat is the major staple diet, may initially have a subclinical form of the disease and not exhibit classical symptoms of CD such as diarrhea and weight loss

Table 5
Breakup of histologic findings in the biopsies/surgical specimens from the terminal ileum (n = 73)

Specimen no.	Histologic findings	No.	%
01	Tuberculosis	26	35.6
02	Adenocarcinoma	8	10.9
03	Lymphoma	5	6.8
04	Inflammatory myofibroblastic tumor/inflammatory fibroid polyp	4	5.5
05	Neuroendocrine neoplasms	3	4.1
06	Meckel diverticulum	3	4.1
07	Crohn disease	2	2.7
08	Typhoid fever	2	2.7
09	Tubular adenoma	1	1.4
10	Unremarkable or mild nonspecific inflammation	19	26

and may only present with subtle manifestations such as an isolated iron deficiency anemia, which may delay referral to a gastroenterologist and therefore delay the diagnosis. It is very important in our setting to investigate unexplained gastrointestinal symptoms in adults by conducting serologic tests for CD. For this to occur, it is critical to increase awareness about CD among general physicians. In a developing country such as Pakistan, the situation is further complicated by the fact that a large number of children, especially girls, and women in the reproductive age group have nutritional or blood loss iron deficiency anemia and may not be investigated for CD at all.

We need to conduct much larger studies to assess the true incidence and prevalence of CD in our population. In a country, such as Pakistan, where commercial gluten-free products are not available, a major challenge, if the disease is indeed found to be more common than what is presently believed, will be to maintain patients with CD on a permanent gluten-free diet. Gluten-free products will not become available in Pakistan until there are published data to show that CD is reasonably common in this country. Thus, CD can be a widespread health problem in developing countries because of lack of awareness and unavailability of gluten-free products.

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