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ORIGINAL ARTICLE

Histopathological Spectrum and Clinical Correlation of Gastrointestinal Mucosal Biopsies in Patients with Chronic Diarrhea. A Cross-Sectional Study

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ABSTRACT

Background: Chronic diarrhea, defined as diarrhea lasting four weeks or more, is a common clinical problem with a wide range of etiologies. Its causes may include infectious, inflammatory, autoimmune, and neoplastic conditions. While clinical assessment and laboratory investigations provide useful insights, histopathological evaluation of gastrointestinal mucosal biopsies remains the gold standard for accurate diagnosis and management.

Objective: To determine the histopathological spectrum of gastrointestinal mucosal biopsies in patients with chronic diarrhea and to correlate these findings with clinical features.

Methods: This cross-sectional study was conducted in the Department of Pathology in collaboration with the Department of Gastroenterology, Khyber Teaching Hospital, Peshawar, Pakistan, from January 2022 to July 2023. A total of 100 patients with diarrhea persisting for more than four weeks were included. Endoscopic biopsies were obtained and processed using hematoxylin and eosin staining. Special stains were employed when required. Clinical features were recorded, and correlation with histopathological findings was analyzed using SPSS version 25.

Results: The mean age of patients was 39.2 ± 13.1 years, with a male predominance (55%). The most common presenting symptom was watery diarrhea (62%), followed by weight loss (48%) and abdominal pain (40%). Histopathology revealed inflammatory bowel disease in 28% of cases, chronic nonspecific colitis in 22%, infectious colitis in 15%, celiac disease in 12%, microscopic colitis in 8%, and neoplastic lesions in 7%. Significant clinicopathological correlations were observed, particularly in cases of IBD (p=0.01) and celiac disease (p=0.02).

Conclusion: Histopathological examination of gastrointestinal mucosal biopsies provides invaluable diagnostic information in patients with chronic diarrhea. Routine biopsy is recommended in all such patients to differentiate overlapping conditions, ensure accurate diagnosis, and guide effective treatment strategies.

Keywords: Chronic diarrhea, gastrointestinal mucosa, histopathology, inflammatory bowel disease, celiac disease, colitis.

INTRODUCTION

Chronic diarrhea, defined as the passage of loose or watery stools persisting for more than four weeks, is a frequent clinical problem encountered worldwide and constitutes a major cause of morbidity, particularly in low- and middle-income countries[1]. The differential diagnosis of chronic diarrhea is broad, encompassing infectious, inflammatory, autoimmune, neoplastic, and functional disorders of the gastrointestinal tract. Due to this wide spectrum, establishing a precise etiology is often challenging, yet it is critical for guiding appropriate therapeutic strategies and improving patient outcomes[2].

In the evaluation of chronic diarrhea, clinical history and stool analysis provide initial clues but are frequently insufficient to reach a definitive diagnosis. Radiological and serological investigations offer supportive information but lack specificity in many cases[3]. Endoscopic examination of the gastrointestinal tract combined with histopathological assessment of mucosal biopsies remains the gold standard for diagnosis. Histology provides valuable insights by identifying structural and cellular changes such as villous atrophy in celiac disease, crypt distortion and granulomas in inflammatory bowel disease, intraepithelial lymphocytosis in microscopic colitis, or dysplasia and neoplasia in malignant conditions. Such findings are crucial not only for diagnosis but also for differentiating between conditions with overlapping clinical presentations[4,5].

The global epidemiology of chronic diarrheal diseases is evolving. In developed countries, immune-mediated and inflammatory conditions such as celiac disease, microscopic colitis, and inflammatory bowel disease predominate. In contrast, in developing countries like Pakistan, infectious causes still contribute significantly due to high burdens of enteric pathogens, inadequate sanitation, and limited access to healthcare. However, with increasing urbanization, dietary changes, and greater awareness, chronic inflammatory disorders are being recognized more frequently in South Asian populations. This shift underscores the importance of updated region-specific studies to highlight the current histopathological spectrum[6-9].

Several studies conducted internationally have highlighted the diagnostic yield of gastrointestinal mucosal biopsies in chronic diarrhea, demonstrating a high prevalence of conditions such as inflammatory bowel disease, celiac disease, and microscopic colitis[10]. Yet, there remains a paucity of literature from Pakistan that comprehensively evaluates histopathological patterns in patients presenting with chronic diarrhea and correlates them with clinical features. This gap is significant, as regional differences in genetic predisposition, environmental exposures, and infectious disease prevalence may influence disease patterns[7,11].

The present study was therefore undertaken to assess the histopathological spectrum of gastrointestinal mucosal biopsies in patients presenting with chronic diarrhea and to correlate these findings with clinical features. By doing so, we aim to contribute to a more precise understanding of the local disease burden and to reinforce the importance of biopsy-based diagnosis in the effective management of chronic diarrheal disorders[12].

MATERIALS AND METHODS

Study Design and Setting: This study was designed as a cross-sectional observational analysis and was conducted in the Department of Pathology in collaboration with the Department of Gastroenterology at Khyber Teaching Hospital (KTH), Peshawar, Pakistan. The study duration extended over an eighteen-month period, from January 2022 to July 2023, allowing sufficient time for

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the recruitment of participants, collection of data, and detailed histopathological evaluation of gastrointestinal mucosal biopsies.

Sample Size: A total of one hundred patients were included in the study. These patients were selected using a non-probability purposive sampling technique based on their clinical presentation and fulfillment of the eligibility criteria. The chosen sample size was considered adequate to evaluate the histopathological spectrum and to establish meaningful clinicopathological correlations in cases of chronic diarrhea.

Inclusion and Exclusion Criteria: Patients of both genders, aged between fifteen and seventy years, who presented with diarrhea persisting for four weeks or more were considered eligible for inclusion. Only those patients who underwent endoscopic examination with mucosal biopsy were enrolled. Exclusion criteria were strictly applied, and patients with acute diarrheal illness of less than four weeks duration, those with previously diagnosed gastrointestinal malignancies under treatment, and individuals with incomplete clinical or histological data were excluded. Patients who refused consent were also not considered for participation.

Data Collection Procedure: After obtaining informed consent, demographic and clinical details of each participant were recorded, including age, sex, type and duration of diarrhea, and associated symptoms such as abdominal pain, fever, and weight loss. Relevant past medical history and the presence of comorbidities were also noted. Laboratory investigations were carried out where indicated, including complete blood count, erythrocyte sedimentation rate, C-reactive protein, stool culture, and serological testing such as anti-tissue transglutaminase antibodies in suspected cases of celiac disease.

All patients underwent endoscopic evaluation. Upper gastrointestinal endoscopy was performed in cases of suspected malabsorption and duodenal pathology, while colonoscopy and sigmoidoscopy were carried out in patients presenting with colitis-like symptoms. Multiple mucosal biopsies were taken both from areas of grossly abnormal mucosa and, when clinically justified, from apparently normal mucosa.

Histopathological Examination: Biopsy specimens were fixed immediately in ten percent neutral buffered formalin and subsequently processed in the pathology laboratory. Paraffin-embedded tissue sections were prepared and stained with hematoxylin and eosin for routine histological evaluation. In selected cases where additional diagnostic clarity was required, special stains were employed. Periodic acid–Schiff stain was used for the identification of fungal organisms and basement membrane alterations, Ziehl–Neelsen stain was applied for the detection of acid-fast bacilli, and Giemsa stain was utilized in cases where parasitic infestations or Helicobacter pylori infection were suspected. Histopathological diagnosis was made based on internationally recognized criteria, with each biopsy carefully examined for inflammatory, infectious, autoimmune, or neoplastic features.

Data Analysis: All data were compiled and analyzed using the Statistical Package for the Social Sciences (SPSS) version 25. Quantitative variables such as age were expressed as mean and standard deviation, while categorical variables such as gender, type of diarrhea, and histopathological diagnoses were presented as frequencies and percentages. Statistical associations between clinical presentation and histopathological findings were determined using the Chi-square test. A p-value of less than 0.05 was taken as statistically significant.

Ethical Considerations: The study was conducted in accordance with the ethical standards of medical research. Approval was obtained from the Ethical Review Committee of Khyber Teaching Hospital, Peshawar, before initiation of the study. Written informed consent was taken from each participant, and complete confidentiality of patient data was maintained throughout the research process.

RESULTS

Demographic Characteristics: A total of one hundred patients who met the inclusion criteria were enrolled in the study. The mean age of the patients was 39.2 ± 13.1 years, ranging from 16 to 68 years. The age distribution revealed that the majority of patients belonged to the 21–40-year age group (42%), followed by the 41–60-year age group (36%), while 15% of patients were older than 60 years. The male-to-female ratio was approximately 1.2:1, with 55 males (55%) and 45 females (45%). These findings suggest that chronic diarrhea was slightly more prevalent among males in our studied population (Table 1).

Table 1: Age and Gender Distribution of Patients (n=100)

Age Group (years)	Male (n=55)	Female (n=45)	Total (%)
15–20	7	5	12 (12%)
21–40	25	17	42 (42%)
41–60	18	18	36 (36%)
>60	5	5	10 (10%)
Total	55 (55%)	45 (45%)	100 (100%)

Table 1 demonstrates that the majority of patients belonged to the 21–40 years age group, with a slight male predominance.

Clinical Features: The clinical presentation of the patients varied, although diarrhea of more than four weeks was the primary inclusion criterion. The most common type of diarrhea was watery diarrhea, reported in 62 patients (62%), followed by bloody diarrhea in 18 patients (18%), mucoid diarrhea in 10 patients (10%), and mixed patterns in the remaining cases. Weight loss was observed in 48 patients (48%), abdominal pain in 40 patients (40%), and fever in 20 patients (20%). Rectal bleeding was documented in 12 cases (12%). These features illustrate the heterogeneity of chronic diarrhea presentations in the studied population (Table 2).

Table 2: Clinical Features of Patients with Chronic Diarrhea (n=100)

Clinical Feature	Frequency (n)	Percentage (%)
Watery diarrhea	62	62%
Bloody diarrhea	18	18%
Mucoid diarrhea	10	10%
Mixed type	10	10%
Weight loss	48	48%
Abdominal pain	40	40%
Fever	20	20%
Rectal bleeding	12	12%

Table 2 highlights watery diarrhea as the predominant symptom, with weight loss and abdominal pain being the most frequent associated features.

Histopathological Spectrum: Histopathological analysis of gastrointestinal mucosal biopsies revealed a wide variety of pathological changes. Inflammatory bowel disease (IBD) was the most common diagnosis, identified in 28 cases (28%). This group included both ulcerative colitis and Crohn's disease, with histological features such as crypt distortion, basal plasmacytosis, and granulomatous inflammation in selected cases.

The second most frequent diagnosis was chronic nonspecific colitis, seen in 22 cases (22%), where biopsy showed nonspecific inflammatory changes without specific features of IBD, infection, or autoimmune pathology. Infectious colitis was diagnosed in 15 cases (15%), confirmed by the presence of neutrophilic infiltration, ulceration, and in some cases, organisms highlighted by special stains. Celiac disease was reported in 12 cases (12%), characterized by villous atrophy, crypt hyperplasia, and intraepithelial lymphocytosis.

Microscopic colitis accounted for 8 cases (8%), divided into collagenous and lymphocytic subtypes. Neoplastic lesions were found in 7 patients (7%), including adenocarcinomas and one case of primary gastrointestinal lymphoma. Other less frequent but noteworthy findings included eosinophilic colitis and ischemic colitis in a small number of cases (Table 3).

Table 3: Histopathological Spectrum of Gastrointestinal Mucosal Biopsies (n=100)

Histopathological Diagnosis	Frequency (n)	Percentage (%)
Inflammatory bowel disease (IBD)	28	28%
Chronic nonspecific colitis	22	22%
Infectious colitis	15	15%
Celiac disease	12	12%
Microscopic colitis	8	8%
Neoplasia (Adenocarcinoma, Lymphoma)	7	7%
Other (eosinophilic, ischemic)	8	8%

Table 3 demonstrates that IBD was the most common histopathological finding, followed by chronic nonspecific colitis and infectious colitis.

Clinicopathological Correlation: A significant association was observed between clinical features and histopathological diagnoses. Patients with bloody diarrhea and abdominal pain were more frequently diagnosed with inflammatory bowel disease, and this association was statistically significant (p=0.01). Celiac disease was strongly correlated with weight loss, malabsorption features, and anemia (p=0.02). Infectious colitis was more commonly found among younger patients presenting with fever and acute-onset symptoms. Neoplastic lesions were strongly associated with rectal bleeding and advanced age.

DISCUSSION

The present study highlights the critical role of histopathological examination of gastrointestinal mucosal biopsies in determining the etiology of chronic diarrhea. Our findings demonstrated that inflammatory bowel disease (IBD) constituted the most frequent diagnosis, followed by chronic nonspecific colitis, infectious colitis, celiac disease, microscopic colitis, and neoplasia[13]. These results emphasize the heterogeneous nature of chronic diarrhea and underline the necessity of integrating histological analysis with clinical assessment for accurate diagnosis[12-14].

The predominance of IBD in our study (28%) aligns with reports from both regional and global literature. A systematic review by Ng et al. documented a rising global incidence of IBD, particularly in newly industrialized countries, including those in South Asia, where urbanization and dietary changes are hypothesized to play a role[17]. The presence of crypt distortion, basal plasmacytosis, and granulomatous inflammation in our biopsies reinforced the accuracy of IBD diagnoses, and the significant correlation with clinical features such as bloody diarrhea and abdominal pain further validated these findings[15-18].

Chronic nonspecific colitis was the second most common category in our study, accounting for 22% of cases. Similar observations have been made in other South Asian studies, where nonspecific inflammatory changes without defining features are frequently reported[19]. This category likely represents a diagnostic gray zone that may overlap with early or resolving infectious colitis, functional disorders, or mild forms of IBD. The high proportion in our cohort may reflect environmental and dietary influences, as well as the limitations of routine histopathological assessment without adjunctive molecular tools[20].

Infectious colitis accounted for 15% of cases, consistent with the epidemiological profile of Pakistan, where enteric infections remain a significant public health concern due to sanitation challenges and waterborne pathogens. Histological findings of neutrophilic infiltration and mucosal ulceration were commonly observed, and in certain cases, organisms were confirmed using Ziehl–Neelsen and PAS stains. This finding mirrors earlier work from regional hospitals where bacterial and parasitic causes continue to contribute substantially to chronic diarrhea[20,21].

Celiac disease was identified in 12% of patients, which is noteworthy considering that the disorder was once considered rare in South Asia. Our results align with more recent studies indicating that celiac disease is increasingly recognized in Pakistani populations, likely due to improved awareness and the availability of serological testing. The strong correlation of weight loss, malabsorption, and anemia with histological findings of villous atrophy and crypt hyperplasia reaffirms the diagnostic utility of mucosal biopsies in suspected cases[17-22].

Microscopic colitis, detected in 8% of cases, represents an often overlooked but important cause of chronic watery diarrhea. International studies, particularly from Western populations, report higher frequencies, ranging between 10–15%. The relatively lower prevalence in our cohort could be due to underdiagnosis, as microscopic colitis requires targeted biopsies and awareness among clinicians to suspect it even in macroscopically normal mucosa[14,17,23].

Neoplastic lesions were found in 7% of patients, including adenocarcinomas and lymphoma. Although less frequent compared to inflammatory and infectious conditions, their identification is of paramount importance due to significant therapeutic and prognostic implications. The association of neoplastic lesions with advanced age and rectal bleeding in our study is consistent with established literature[24].

Our findings reaffirm that clinicopathological correlation is essential in the evaluation of chronic diarrhea. Clinical features such as watery versus bloody diarrhea, weight loss, and systemic symptoms provided important diagnostic clues, but histopathology was indispensable in differentiating overlapping conditions. This synergy between clinical assessment and biopsy interpretation allows for tailored treatment strategies and avoidance of misdiagnosis[25].

Limitations of this study should be acknowledged. It was a single-center study with a sample size of 100, which may not fully reflect the diversity of the regional population. Additionally, advanced diagnostic modalities such as immunohistochemistry and molecular testing were not routinely available, potentially leading to under-recognition of certain pathologies. Despite these limitations, the study provides valuable insights into the histopathological spectrum of chronic diarrhea in a tertiary care setting in Pakistan[20,25].

CONCLUSION

Histopathological evaluation of gastrointestinal mucosal biopsies is an indispensable diagnostic tool in patients with chronic diarrhea. In this study conducted at Khyber Teaching Hospital, Peshawar, inflammatory bowel disease emerged as the most common cause, followed by chronic nonspecific colitis, infectious colitis, celiac disease, microscopic colitis, and neoplastic lesions. Significant clinicopathological correlations were observed, particularly in IBD and celiac disease, underscoring the combined role of clinical evaluation and histology in reaching accurate diagnoses.

The findings highlight the diverse etiologies of chronic diarrhea in the local population and reinforce the need for routine biopsy in all patients presenting with persistent symptoms. Early and accurate histological diagnosis not only guides appropriate therapy but also prevents complications associated with delayed or incorrect treatment. Future multi-center studies with larger cohorts and advanced diagnostic modalities are recommended to further delineate the disease burden and improve patient outcomes in Pakistan.

Declarations

Authors' Contributions: SK, MZ, and MAM conceived and designed the study. AJA and SS were involved in data collection and patient recruitment. IUH performed statistical analysis and contributed to interpretation of results. All authors contributed to drafting, revising, and final approval of the manuscript.

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