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Original Research Article

Histopathological spectrum of infectious diseases in endoscopic mucosal biopsies of the gastrointestinal tract: A one-year study at a tertiary care hospital in Kerala

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ABSTRACT

Background: Gastrointestinal infections, caused due to various viruses, bacteria, fungi, and parasites, are a major global health concern, causing significant morbidity and mortality.
Aims & Objectives: The present study was undertaken to study the histopathological spectrum of infectious diseases of the gastrointestinal tract detected from endoscopic mucosal biopsies at our tertiary care hospital, as well as review the available, relevant clinical details.
Materials and Methods: This retrospective study included biopsies over a period of 1 year (January 2022 to December 2022) in the Department of Pathology, VPS Lakeshore Hospital, Ernakulam, Kerala, India.
Results: A total of 90 cases of infections of the GIT were included in the study, out of which 76 cases were bacterial, 10 cases were viral and 4 were due to other parasites.
Conclusions: While dealing with infections of the GIT, a thorough knowledge of the microscopic findings and supportive ancillary tests, alongwith clinical findings, aid in confirming the diagnosis and providing options for appropriate patient management.

1. Introduction

Gastrointestinal (GI) infections are a leading cause of morbidity and mortality worldwide, second only to upper respiratory tract infections.[1] The global mortality rates were estimated to be about 3 million per year in 1992, which dropped to about 1.5 million by 2005.[2,3] A wide variety of viruses, bacteria, fungi, and parasites have been discovered to have putative roles in the pathogenesis.

The majority of gastrointestinal infections, particularly gastroenteritis with diarrhea, are diagnosed on clinical grounds without the help of stool examination, microbiological cultures, serologies or biopsy.[1] Biopsies may be undertaken in specific circumstances., e.g., to provide a specific diagnosis (e.g., CMV infection), or to identify a broad group of organisms (e.g., yeast forms in tissues or identification of acid-fast organisms), or to identify a tissue reaction associated with a limited number of organisms, thereby narrowing the differential diagnosis (e.g., granulomatous inflammation or suppurative inflammation). A variety of tests are available to assist in the diagnosis of GI infections; e.g, stool microscopy for ova and parasites, culture, stool antigen assays (e.g., for detection of toxins) , serology and PCR (e.g., for detection of mycobacteria).[1]

The most common change seen in enteric infections in admitted patients is typical acute self-limited colitis, characterized histologically by lack of architectural distortion and basal plasmacytosis, and by the presence of mucosal hyperemia, edema, and if severe, by acute inflammation, with neutrophilic infiltration of crypts (cryptitis and crypt abscesses).[4–7] In addition, certain specific histologic patterns may be associated with certain specific infections; for example, pseudomembranous

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enterocolitis is typically linked to C. difficile infection; and granulomas may be observed in tuberculosis and fungal infections. In some instances, the cause of the enteric infection can be diagnosed because the offending organism (e.g., Giardia, Entamoeba) or its characteristic cytopathic changes (e.g., in the case of CMV infection) can be identified in tissue sections. A variety of histochemical stains are useful in highlighting various organisms, e.g., periodic acid–Schiff (PAS), Giemsa, mucicarmine, and acidfast stains.

So, the pathologist must be aware of the various histopathological features of the common as well as uncommon organisms, and should also be able to distinguish these from non-infectious inflammatory conditions that mimic infection. Additionally, the pathologist should be provided with the relevant clinically significant data and the necessary additional studies (special stains, immunohistochemistry [IHC] or molecular tests (e.g., PCR), for a correct diagnosis to be rendered. With a robust knowledge in this field, the pathologist's findings and inputs can contribute immensely towards patient care.

While there have been a few review articles about gastrointestinal infections in general,[2–4] there is a scarcity of studies based on actual cases, covering the range of gastrointestinal infections that are encountered in a hospital. The main objective of our research was to study the whole gamut of infectious diseases of the gastrointestinal tract detected from endoscopic mucosal biopsies at our tertiary care centre; including the incidence and the histomorphological spectrum of GI infections, as well as the relevant clinical features pertaining to these cases.

2. Materials & Methods

2.1. Study design

Ours was a retrospective observational descriptive-type study. The collected data comprised of all endoscopic mucosal biopsies over a one-year period, from 1^{st} January 2022 to 31^{st} December 2022 obtained at the department of Pathology at VPS Lakeshore Hospital, Ernakulam, Kerala.

2.2. Selection criteria

1. Both upper gastrointestinal (i.e., from the esophagus and stomach) as well as lower gastrointestinal (i.e., from the small intestine and the large intestine upto the anal canal) endoscopic mucosal biopsies were included. Out of these biopsies, those cases which were reported as showing an organism and/or other histological evidence of infective etiology, were selected for further study. The slides and clinical details of these cases were reviewed.
2. Only mucosal biopsies were included in our study; surgical resection specimens were excluded. Additionally, there were patients in whom non-specific self-limiting infectious colitis was suspected based on the histological and clinical findings; but as no specific organism was detected, these were excluded from our primary study sample.

2.3. Sample size

1. 90 cases (During the study period, endoscopic mucosal biopsies from various sites of the alimentary tract, had been obtained from 2946 patients. Out of these, 90 cases were reported as showing an organism and/or other histological evidence of infection: these 90 cases constituted our study sample.)

2.4. Data collection and analysis

1. Hematoxylin and eosin slides of these 90 cases were reviewed. The details of clinical history of each of these patients were collected from medical case records. All data thus collected was entered in Microsoft Excel to prepare a master chart and was subjected to statistical analysis using SPSS software.
2. For all cases, variables such as age and gender were analysed; and other details of clinical history were recorded, including symptoms, pertinent predisposing factors, drug history and endoscopic/ colonoscopic findings.
3. Apart from these, certain specific parameters were analysed for certain specific infections:

   (a) For Helicobacter pylori-associated gastritis, the parameters that were graded included: the intensity of the gastritis, including the mononuclear infiltrate (none / mild /moderate /severe), the inflammatory activity ie., neutrophilic infiltration (none/ mild/ moderate/ severe), H pylori density (mild/ moderate/ severe), glandular atrophy (none/ mild/ moderate/ severe) and metaplasia (none/ mild/ moderate/ severe).

   (b) For the cases of tuberculosis, the presence of granulomas, caseating necrosis, giant cells and ulcers was also noted.

   (c) Linear variables (such as age) were presented as mean, whereas nominal variables (such as gender) and categorical variables (such as grading of mild/moderate/severe gastritis) were summarized using percentage and proportions.

   (d) All the results were presented in appropriate tables and figures.

3. Results

Out of the 90 cases in our study sample, 71 patients were male (78.89%) and 19 were female (21.11%). The age of the patients ranged from 24 to 75, with a mean age of 50.27.

The main findings of the spectrum of infectious organisms included in our study, are summarized in Table 1.

Table 1: Histopathological spectrum of infectious diseases in endoscopic mucosal biopsies of the gastrointestinal tract at our tertiary care hospital

Infectious Organism	Number of cases	Anatomical site(s) involved (Number of cases in which biopsies obtained from that particular site showed the organism)
Bacterial		
H pylori	61	Pyloric antrum (59), Corpus of stomach (2)
Tuberculosis	8	Ileum (3), Colon (4), Rectum(1)
Clostridium (Pseudomembranous colitis)	7	Colon(6), Rectum(1)
Viral		
CMV alone	8	Esophagus(4), Gastroesophageal junction (1), Stomach (1), Colon (2)
Co-infection (CMV & HSV)	1	Esophagus (1)
HSV (with candida)	1	Esophagus(1)
Parasites		
Cryptosporidium	1	Colon(1)
Schistosomiasis	2	Colorectal biopsies(2)
Giardiasis	1	Duodenum(1)
Total	90	

Among these 90 cases, the largest number obtained was that of Helicobacter pylori infection. In 61 cases, all of which were gastric mucosal biopsies, the bacilli were seen in Hematoxylin and Eosin-stained slides, and were better highlighted by Modified Giemsa stain. The findings from the histopathological reports of these cases, are summarized in Table 2.

Table 2: Histopathological findings in the cases of H pylori-induced gastritis (61 cases)

Variables graded	None	Mild	Moderate	Severe
Gastritis (including the mononuclear infiltrate)		13	42	6
Activity (Neutrophilic infiltrate)	4	30	25	2
H Pylori density		47	8	6
Glandular atrophy	54	5	2	
Metaplasia	51	7	3	

Other bacterial infections included 8 cases of tuberculosis and 7 cases showing histological evidence of infection with Clostridium species. Table 3 highlights the salient histopathological findings of the cases of tuberculosis in our study.

Table 3: Histopathological findings in the cases of Tuberculosis (8 cases)

Histopathological finding	Percentage of cases (Out of the 8 cases of tuberculosis)
Granulomas	100% (90% cases showed confluent granulomas)
Caseating necrosis	71.4%
Giant cells	88.9%
Ulcers	88.9%

Apart from these, the detected viral organisms comprised of 8 cases of cytomegalovirus infection, 1 case of co-infection of cytomegalovirus and herpes simplex virus, and another case of herpetic infection in which Candidal spores were also seen. Other rare parasites detected in the intestine included 2 cases of schistosomiasis, 1 case of giardiasis and 1 case of infection by Cryptosporidium species.

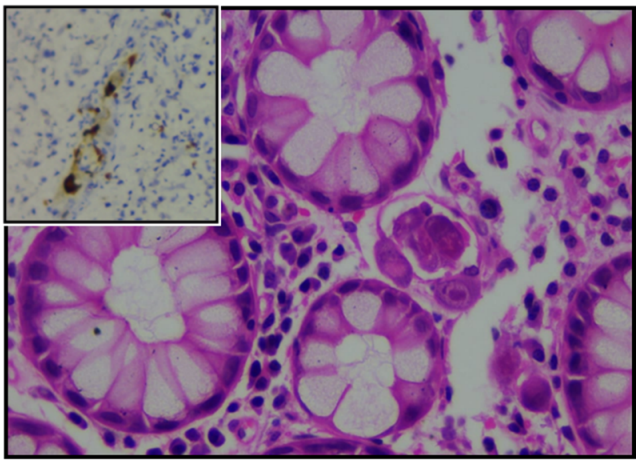

Figure 1: A case of CMV colitis, with nucleomegaly and amphophilic inclusions within the endothelial and stromal cells. (H & E, 40x) Inset shows the inclusions highlighted by IHC

4. Discussion

In our study, along with the histopathological findings of the GI infectious organisms, we have attempted to document the accessible clinical details, gross and endoscopic findings, other laboratory data, and the outcomes of pertinent ancillary tests.

Helicobacter pylori (H pylori) gastritis is a common treatable form of gastritis caused by gram-negative rods. Histopathology shows a superficial mononuclear (lymphoplasmacytic) infiltrate with prominent lymphoid follicles and mucosal neutrophils. Slender curved bacilli are typically seen in the mucin coat of lining epithelial cells.[8] In our study, 61 cases showed H pylori-induced gastritis. The result of the grading of variables (Table 2) were similar to a study by Selvi et al.[9]

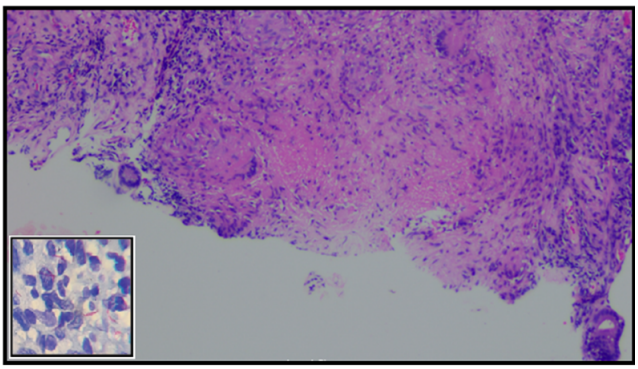

Figure 2: Tuberculosis, Rectal biopsy: Showing confluent granulomas with foci of caseation and multinucleate giant cells. (H&E, 10x) Inset shows the acid fast bacilli in Ziehl- Neelson stain

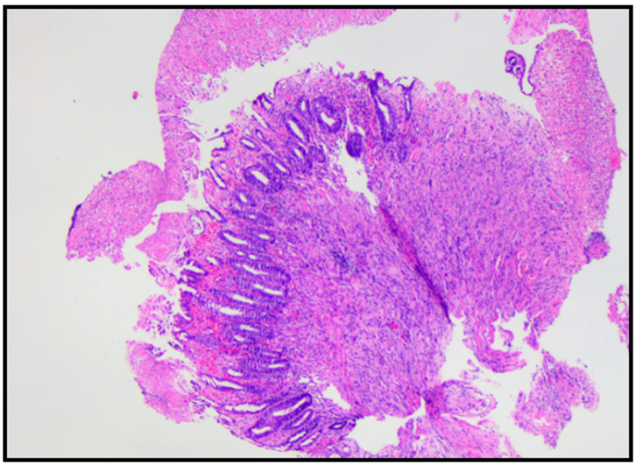

Figure 3: Pseudomembranous colitis (H&E, 4x), with the eruptive, lamellated pseudomembrane

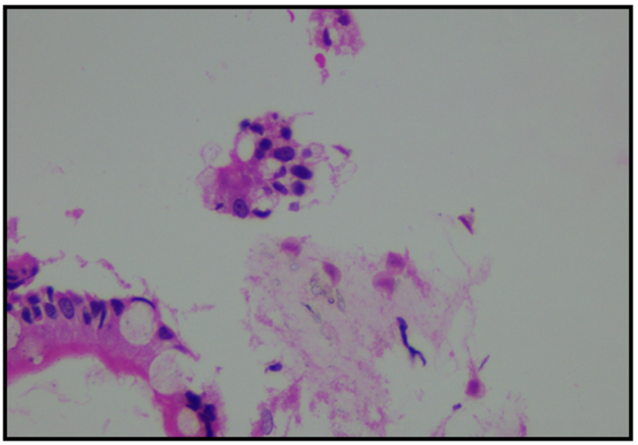

Figure 4: Giardiasis, Duodenal biopsy: Showing the pear-shaped trophozoites towards the luminal surface in a scattered distribution. (H&E, 40x)

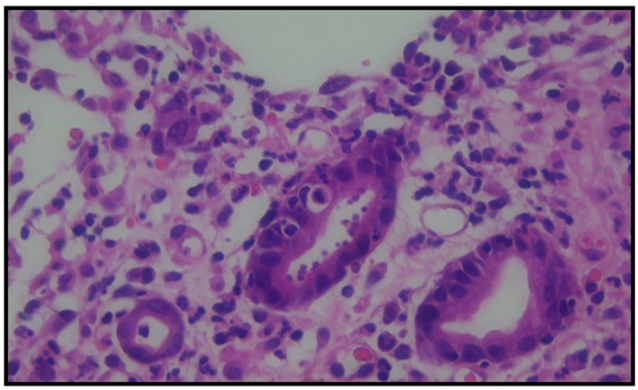

Figure 5: Cryptosporidial organisms seen as basophilic "blue beads" bulging from the apical surface of epithelial cells, along the luminal border. (H&E, 40x)

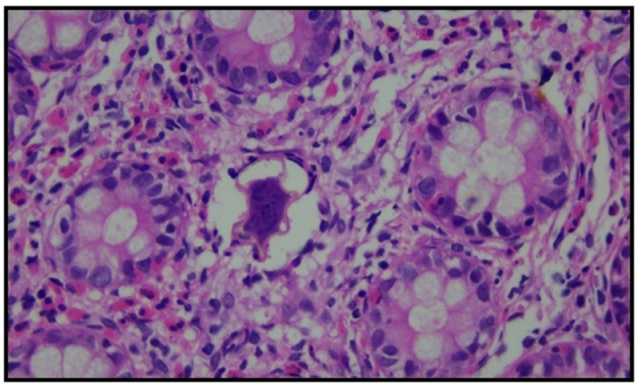

Figure 6: Schistosomiasis: Degenerated parasitic eggs seen within a crypt (H&E, 40x)

In the esophagus, HSV infects the squamous epithelial cells, which show nuclear inclusions, nuclear molding and multinucleation; whereas CMV infects mesenchymal (endothelial and stromal) and columnar cells, causing cytomegaly, nucleomegaly, with cytoplasmic and nuclear inclusions.[8] In the intestine too, CMV inclusions are preferentially found in endothelial cells, stromal cells, and macrophages, and rarely, in glandular epithelial cells. (Figure 1). Immunocompromised individuals are more susceptible to CMV and herpes infections. Out of the 10 cases of viral infection in our study, 7 patients were immunosuppressed: 3 cases of IBD, 1 case of multiple myeloma on chemotherapy, 2 cases post renal transplant and 1 case of pemphigus on immunosuppressants. The histopathological findings included cytomegaly, nucleomegaly, multinucleation, with inclusions, that were highlighted by IHC. (Figure 1)

Tuberculosis commonly affects the terminal ileum and colon; which may be grossly evident in the form of transverse or circumferential ulcers, with or without serosal tubercles. Microscopically, granulomas of varying sizes

and shapes are found, with multinucleate giant cells, foci of confluence and central caseation with nuclear debris. The diagnosis is confirmed by demonstration of acid-fast organisms with Ziehl-Neelson stain or PCR-based assays. The bacteria (Mycobacterium tuberculosis) appear as slender rod-shaped organisms with slightly beaded appearance.[1] Our study included 8 cases (all involving the intestine), in which a histopatholgical diagnosis of "consistent with tuberculosis" was rendered, based on the finding of multiple medium to large-sized confluent granulomas and/or foci of caseous necrosis (Figure 2). In Table 3, the histopathological findings of our study are listed. Out of these 8 cases, the details of colonoscopic findings were available for 4 cases, all of which showed circumferential narrowing and ulcers. By ZN staining, Acid fast bacilli were demonstrated in 3 cases, and PCR confirmation was done in 2 other cases. Apart from these 8 cases, there were 18 other cases for which, based on the finding of occasional large-sized granulomas, a histopathological diagnosis or comment was rendered as "suggestive of tuberculosis", in the absence of more defining features. These were not included in our primary study sample of 90 cases. Compared to our study, similar studies on gastrointestinal tuberculosis by Bandi et al reported granulomas, caseating necrosis and giant cells in 97.3%, 79.26% and 95.56% cases respectively; and a study by Cheng et al. reported granulomas, caseating necrosis and ulcers in 70.6%, 24.7% and 65.9% cases repectively.[10,11]

Infection by Clostridium difficile is suspected in patients with a recent history of intake of antibiotics, presenting with watery diarrhea, often accompanied by abdominal distension and leukocytosis.[12] Endoscopically, the lesions are cream-colored shiny plaques, that are resistant to being rubbed off. Histologically, the typical pseudomembrane begins as a focal volcano-like exudate of neutrophils and mucin from a small breach in the intercrypt luminal epithelium. As the lesion develops, it takes on a more laminated appearance, with fibrin, RBCs and inflammatory cells.[1] Our study included 7 cases in which the diagnosis of "consistent with / suggestive of Pseudomembranous colitis" was rendered based on the finding, in histopathological sections, of necrosis of the superficial epithelium with thick eruptive exudates forming pseudomembranes (Figure 3). Among these, there were 2 cases of IBD, one case of extensive pelvic endometriosis, and one case of synchronous endometrial adenocarcinoma and rectal adenocarcinoma; these 4 cases had a definite documented history of recent hospitalization and/or antibiotic intake, which coincided with the onset of the diarrheal episodes.

Patients affected by giardiasis (Giardia lamblia infection), frequently present with explosive watery diarrhea, often with an unremarkable endoscopic picture. Small intestinal biopsies often show no inflammatory reaction; one has to carefully hunt for the organisms. Giardia trophozoites are found in the luminal surface, in a scattered distribution, called a "falling leaves" pattern. These morphologically resemble pears that are cut lengthwise and contain two ovoid nuclei.[13,14] The patient in our study, presented with dyspepsia for two months. Duodenal biopsy showed the organisms in the luminal surface (Figure 4), and an eosinophil-rich inflammation in the lamina propria.

Cryptosporidial species are typically seen as basophilic "blue beads", 2- to5 μm in size, bulging out at the apex of epithelial cells along the luminal border.[15] The patient in our study had previously undergone Low Anterior Resection, and was diagnosed as attenuated Familial adenomatous polyposis (FAP). During followup surveillance, colonscopic biopsies showed multiple tubular adenomas, one of which showed the Cryptosporidial organisms within the crypt lumen (Figure 5).

Chronic infection in schistosomiasis causes the formation of inflammatory polyps, called bilharziomas.[16] Histology shows mucosal ulcers with associated granulomatous inflammation and an eosinophilic infiltrate. In H&E-stained sections, the calcified eggs are typically dark blue, and the slender and elongated worms are occasionally seen in veins in the submucosa of the bowel. As lesions progress, there is increased fibrosis, as well as an increase in macrophages and multinucleated giant cells.[8,17] Out of the 2 cases that we studied, one patient presented with recurrent abdominal discomfort; colonoscopy showed multiple aphthae in the descending colon. Biopsy from the caecum and descending colon revealed scattered crypts showing degenerated eggs, surrounded by concentric fibrosis, and occasional medium-sized granulomas. The other patient had a history of anal discomfort for three years. Colonoscopy revealed a polyp in the rectum, which microscopically, showed ulceration with severe active colitis, alongwith the parasitic eggs (Figure 6). This patient was a resident of Africa, a region known to be endemic for the disease.

In addition to these 90 cases, the diagnosis in 37 other cases stated, "A possibility of infectious colitis may be considered." These likely represented cases of acute self-limiting colitis; however, as no particular pathogen was found, these were not included in our primary study sample.

Since the incidence of infections can be influenced by various factors such as topography and climatic changes, our single-hospital-based study may not be entirely representative of all the cases throughout the state of Kerala. Also, it being a retrospective study, details of ancillary tests and other clinical details of all patients were not available due to many patients being lost on followup. Hence, in the future, similar studies should be done involving multiple tertiary care centres, more patients and a longer time period, while ensuring follow-up.

5. Conclusion

The main purpose of our research was to investigate the whole range of histopathological characteristics linked to the different infectious agents that impact the gastrointestinal system. In the common agents like H pylori, we have graded the injury using various parameters; in tuberculosis, we have reviewed the common histological findings. In other uncommon infections, such as schistosomiasis, cryptosporidiosis, and giardiasis, we have documented the main histological findings, and attempted to correlate with the important clinical and colonoscopic findings. In most of these cases, where definite histopathological evidence of infection was reported, a clear-cut treatment protocol could be implemented, and contributed to better patient outcome. Thus, whatever the etiology, a thorough knowledge of the microscopic findings and supportive ancillary tests, in conjunction with clinical findings, aid in confirming the diagnosis and providing options for appropriate patient management.

6. Abbreviations

GI: Gastrointestinal; **IBD**: Inflammatory bowel disease; **CMV**: Cytomegalovirus; **HSV**: Herpes simplex virus; ***H.pylori:*** *Helicobacterpylori*; ***C. difficile*****:** *Clostridium difficile*; **ZN:** Ziehl-neelson; **FAP**: Familial adenomatous polyposis.

7. Source of Funding

None.

8. Conflict of Interest

None.

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