



Inflammatory Bowel Disease: Anatomical and Histopathological Study

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Abstract: Worldwide, the frequency of chronic inflammatory bowel disease (CIBD), including ulcerative colitis (UC) and Crohn's disease (CD) increased rapidly through the last century making their histopathological diagnosis daily task for all pathologists. The accurate histopathological diagnosis of UC and CD requires an intimate correlations between the clinical, laboratory and endoscopic findings in conjunction to the suitable obtained biopsy material, as there are several diagnostic confusions between CIBD and non CIBD forms. The aim of this study was to focus and analyze certain practically selected histopathological features for the diagnosis of UC and CD including crypt architectural abnormalities, inflammation and an associated dysplasia or adenocarcinoma. This present study was performed on 100 specimens of tissue samples taken from small and large bowel including 3 ileocecal resections which were done for suspected an IBD. All the tissue samples received fixed in 10% neutral buffered formalin fixative solution, and paraffin-embedded tissue sections were prepared and examined microscopically for the histopathological features which distinguishing CIBD from non CIBD colitis. This study revealed 95 cases CIBD, among them 55 cases CD and 40 cases were UC, whereas the remaining 5 cases were non CIBD colitis. This study concluded that the diagnosis of IBD needs interdepartmental correlations to avoid under- or over-diagnosis. As well as the accurate discrimination of CIBD from non CIBD forms, differentiate UC from CD, and to identify any dysplastic lesions which is the backbone for therapeutic and prognostic strategies.

Keywords: IBD, UC, CD, Anatomical, and Histopathological

1. Introduction

The gastrointestinal tract (GIT) is responsible for digestion of food, absorption of nutrients, and elimination of wastes. Inflammation impairs the ability of gastrointestinal organs to function properly. The frequency of inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD) increased rapidly through the last century [1, 2]. However, tends to be at the uppermost limit in developed countries [3].

Ulcerative colitis (UC) and CD are CIBD of unknown cause. Clinically, both conditions usually begin gradually, but they can start abruptly and sometimes even present as fulminant disease. UC primarily affects the mucosa of the large bowel, while CD is a transmural disease that can affect the whole GIT [4, 5].

The histopathological diagnosis of CIBD is critically important in determining the choice of treatment, the

prognosis and the follow-up. The aim of the diagnosis is to; differentiate CIBD from other non CIBD colitis, differentiate UC from CD, and to identify any dysplastic lesions. In addition to the above, diagnosis of IBD is a complex procedure [6]. The microscopic picture of UC and CD is often composed of basic lesions that can also be observed in other diseases and only rarely appears to be pathognomonic [7].

The causes of IBD remain unknown. There is a genetic predisposition which increases the risk of IBD about tenfold in first degree relatives of someone with IBD and which may determine the pattern and severity of the conditions in any individual patient [8]. Numerous genes and genetic mutations connected to IBD have been identified. The first one discovered was a mutation in the NOD2/CARD15 gene, which was found to be associated with developing CD [9].

There is an established link between IBD and an increased risk of developing cancer, primarily in the colon. The risk of

colorectal cancer increases with the extent of disease, severity of inflammation, the age of onset and duration of the disease [10]. Dysplasia is the earliest histological derangements in the intestinal epithelium, and colorectal cancer in association with IBD is linked to inflammation-dysplasia-cancer sequence in the GIT, which is unique pathway and unrelated to the adenoma-cancer-sequence [11].

This study aimed to provide clinical, anatomical and histopathological data helping in accurate discrimination of CIBD from non CIBD forms and differentiate UC from CD.

2. Patients and Methods

The present study was performed on tissue sections specimens of 100 patients. Among them 3 cases were ileocecal resections, whereas majority of the received specimens were biopsies which obtained from the large and small bowel. These biopsies were obtained endoscopically in the surgical endoscopic unit in patients who were suspected clinically and radiographically to have IBD forms of colitis. The study was conducted in the Department of Pathology, Central Hospital, Arar City, Saudi Arabia, through the period from 2010 to September 2014. The Pathology Department

received surgical specimens came from 6 Central Hospitals in the Northern Region; KSA including more than 1000 beds. All the clinicoendoscopic data of the patients including age, gender, and clinical complaints were obtained from patient's medical records. All the surgical specimens were received fixed in 10% neutral buffered formalin solution, then processed and paraffin-embedded blocks were prepared, and were cut into 3 micron-thick tissue sections. These sections were stained by routine Hematoxylin and Eosin stains, and then examined microscopically. All the cases were assessed pathologically for IBD forms according to published mentioned criteria, yet certain selected histopathological features were chosen for diagnosis and evaluation. These features can be recognized by the surgical pathologists in the daily practice may be also combined together in many cases. These features represented by architectural abnormalities including crypt branching / shortening / decreased density, and mucosal-epithelial changes including intact mucosa, erosions, ulcerations, and inflammatory features which were including transmural inflammations, neutrophils in crypt epithelia (cryptitis), neutrophils in crypt lumina (crypt abscess), and epithelioid granulomas (Table 1) [7, 12, 13].

Table 1. Summarized selected histopathological features applied in the diagnosis of obtained specimens from all studied cases.

* Crypt architectural abnormalities (crypt distortion)	*Epithelial-mucosal changes	*Inflammatory features	*Associated dysplasia / carcinoma
1 Branching (irregular crypts with dilation)	Intact mucosa	Transmural inflammation	
2 Shortening (increasing distance between the bottom of crypts and the muscularis mucosae)	Erosions (small loss of surface epithelia with mild inflammation).	Cryptitis	
3 Decreased density (reduction in numbers of crypts).	Ulcerations (superficial or deep).	Crypt abscess	
4 Branching with decreased density	Mucin depletion (reduction in the numbers of goblet cells).	Granulomas (with giant cells, without giant cells).	
5		Locations of granulomas (superficial, deep, submucosa, serosal).	

The inflammatory features are defined as an increase of mononuclear inflammatory cells especially lymphoplasmacytic cells in the lamina propria, particularly when localized in its basal thirds, to distinguish CIBD from non CIBD and normal biopsies materials [14, 15]. In addition to the above, all the specimens were examined for any associated dysplasia, the earliest recognizable precursor for the development of colorectal cancer [11].

3. Results

In the normal cases the gastrointestinal tract (GIT) appeared as a hollow tube consisting of three layers: mucosa, submucosa, muscularis propria and loose areolar tissue covered by mesothelium where the tract borders on the body cavity (serosa). The examined normal mucosa is lined by flat epithelial surface composed of mucus secreting cells along

with goblet cells, parallel straight crypts; homogeneously sized, regular aligned and spaced, less than 10% of which are branching and whose bottom reaches the muscularis mucosae. The crypts within the mucosa are of uniform length, diameter and spacing. The crypts reach the muscularis mucosae in all areas of the colon except the rectum, where it is normal to have uniform mild shortening (Figure 1 & 2).

Clinico-endoscopic findings

All the clinicoendoscopic findings were summarized in Table (2 & 3). The study included 100 patients, 60 males and 40 females with ages ranged from 10 years to 60 years (Table 2). Endoscopically, hyperemia of the bowel mucosa found in 20% of the examined patients, whereas each of erosion, stricture, cobblestone appearance and pseudopolypoidal changes was seen in 10% of patients, and ulceration found in 15% of them (Figure 3) (Table 3).

Majority of the cases were found in children and adults

with more shift to the age groups which ranged from 21-30 years and more of these cases were seen in males (60%). Most of the patients were suffering from abdominal pain associated with diarrhea. In majority of cases diarrhea was associated with mucus and blood, whereas unexplained weight loss was detected in 15 patients.

In (Table 4) most of the received specimens were endoscopic biopsies which were obtained from the rectosigmoid colon and encompassed of 73% of the specimens. The ileal biopsy was taken from 10% of patients, whereas ileocecal resection was from 3%. Grossly all the received resections were formed of an areas of whitish mural indurations with hard whitish mesenteric reactions in conjunction with nodularity and hemorrhages (Figure 4 A&B).

Histopathological findings:

In concern to crypt architectural abnormalities, branching of the crypts was detected in the majority of cases and observed in 45% (Figure 5 A & B), whereas decreased density of the crypts seen in 25%. The inflammatory reactions considered one of the important parameters in the diagnosis of IBD. In this study each of cryptitis and crypt abscess was seen in 20% of biopsies (Figure 6), and granulomas were in 10% (Figure 7). In the same theme combined inflammatory reactions including mucosal superficial erosions (Figure 8), and transmural inflammations (Figure 9) were detected in 30% of cases. Regarding the precancerous associated dysplasia, it was seen in 6% of cases, one of them is of low grade type, whereas the other 5 are of high-grade type (Figure 8), while colon carcinoma was found in one case and it located in rectosigmoid region (Figure 10).

Table 2. Clinical features of all cases studied.

Sex		Age	# of case	Clinical manifestations	
Males	Females			Symptoms	# of cases
60	40	10-20	20	Abdominal pain	20
		21-30	50	Pain & diarrhea	30
		31-40	10	Bloody diarrhea	20
		41 – 50	15	Anemia	15
		51-60	5	Unexplained & weight loss	15
Total No. of cases		100		100	

Table 3. Endoscopic findings of all patients

Endoscopic manifestations	Number of cases
Hyperemic mucosa	20
Erosions	10
Ulcerations	15
Strictures	10
Cobblestone appearance	10
Mucosal granularity and friability	16
Discontinuous (skip) lesions	9
Pseudopolyps	10
Total No. of cases	100

Table 4. Anatomical locations and biopsy sites from all studied patients with IBD and normal subjects:

Site	Number of patients
Rectosigmoid biopsies	73
Ileal biopsies	10
Ileocecal resections specimens	3
Duodenal biopsies	6
Biopsies from duodenum, stomach and esophagus	3
Biopsy from ileum and colon	5
Total No. of cases	100

Table 5. Histopathological findings of all studied cases.

Crypt abnormalities	No. of cases	Mucosal-epithelial changes	No. of cases	Inflammation	No. of cases	Associations	No. of cases
Branching	45	Intact mucosa	25	Transmural	20	Dysplasia	6
Shortening	10	Erosions	50	Cryptitis	20	Cancer	1
↓ density	25	Ulcerations	10	Crypt abscess	20		
Branching with ↓ density	20	Mucin depletion	15	Granulomas	10		
				Combined	30		
Total No. of cases	100		100		100		

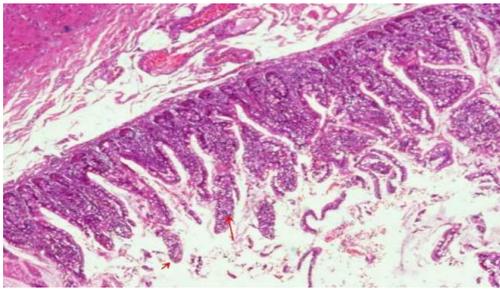


Figure 1. Section in normal small bowel mucosa revealing projecting villi (arrows) with secreting columnar lining and goblet cells (H&E, X40).

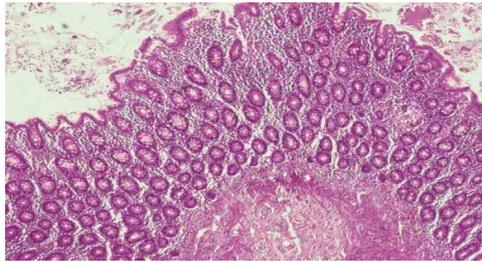


Figure 2. Cross section in normal colonic mucosa showing normal crypt architecture with intact surface epithelium, (H& E, X40).



Figure 3. Endoscopic features of examined colon in 22-years-old patient showing pseudopolyps (thick arrow) with an ulceration area (thin arrow).

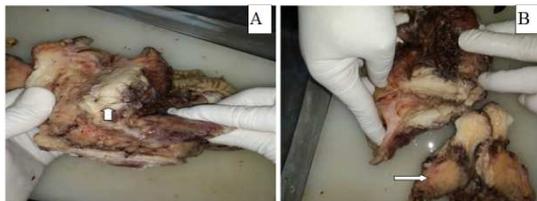


Figure 4 (A&B). A case of CD in 18 years male patient with ileocecal resection revealing whitish mural thickening with induration of the wall (A short arrow) and mesenteric nodularity with fat hemorrhages (B long arrow).

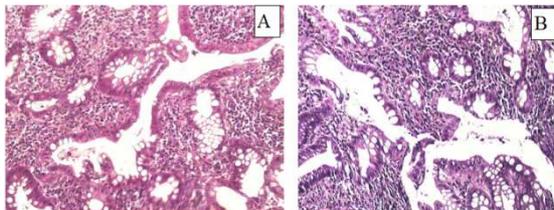


Figure 5 (A& B). Ulcerative colitis showing crypt abnormalities with branching, decreased density and increased lamina propria inflammatory cells (H& E, X100).

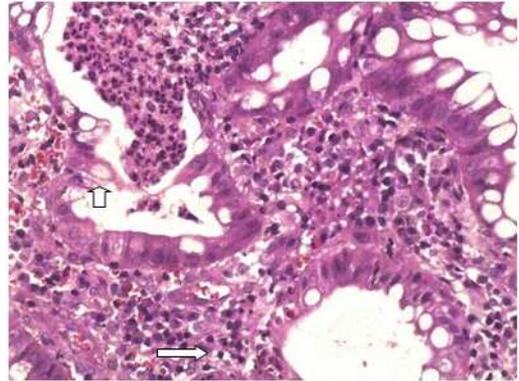


Figure 6. A case of UC revealing cryptitis (long arrow) and crypt abscess formation (short arrow) in conjunction with an increase of mononuclear inflammation (H&E, X100).

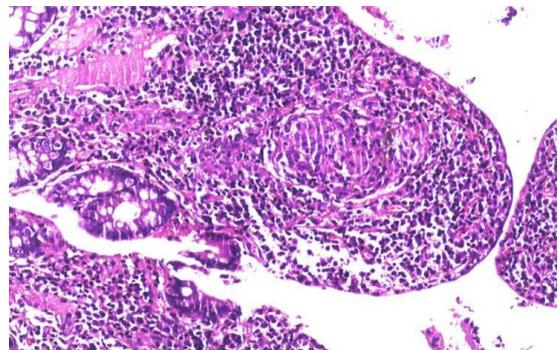


Figure 7. A case of CD from ileocecal resection specimen revealing non caseating-sarcoid granuloma in association with surface ulcerations and an increased mononuclear inflammation (H&E, X100).

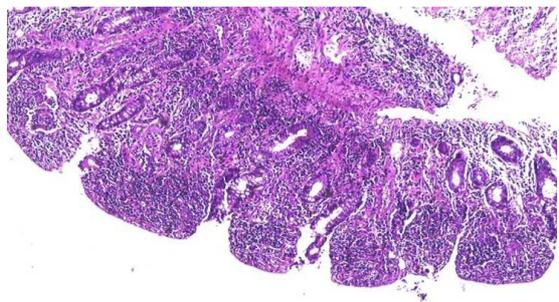


Figure 8. A case of CD affecting ileum showing combined severe transmural inflammation along with superficial and deep ulcerations (H& E, X100).

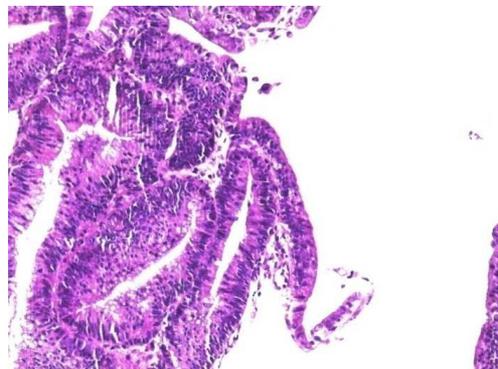


Figure 9. A case of UC showing an associated high grade dysplasia of the colonic epithelia (H&E, X200).

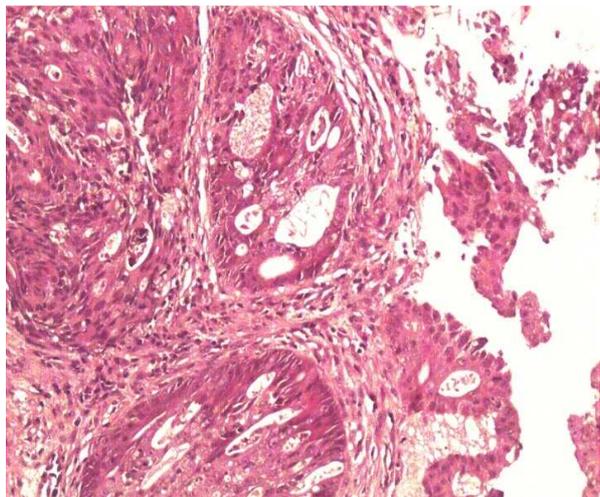


Figure 10. A case of colonic adenocarcinoma showing cribriform features with severe dysplasia in top of UC (H&E, X200).

4. Discussion

Colonoscopic biopsies are an essential step in the diagnostic work-up of patients with IBD. There are no single pathognomonic lesion has been identified to date for the most common forms of colitis, the diagnosis usually derives from a complex evaluation of multiple microscopic changes and their topographical distribution [16, 17]. Also, the diagnostic accuracy of IBD has been demonstrated to increase with the number of obtained biopsies. Therefore, it is mandatory to perform an extensive bioptic sampling, especially in the case of newly diagnosed IBD [18, 19].

In the present study the mucosal architecture abnormalities well apparent in the form of mucosal-epithelial surface changes in which loss of the typical flat profile, showing erosions or even a pseudovillous change. Another changes in the form of crypt distortion as irregular branching, and decrease in the density of crypts with increasing distance between the bottom of the crypts and the muscularis mucosae, these results in agreement with [5, 19].

The present study showed reduction in the number of goblet cells and/or in their mucus content either in the crypts or in the surface epithelium which were in agreement with [5, 19].

Regarding age groups majority of the cases seen among this study were under 30 years and were males. A study done by [20] reported that IBD is an important cause of GIT troubles in children and adolescents, and 10-20% of cases were diagnosed before the age of 18 years. In the same theme the epidemiology of inflammatory bowel diseases (IBD) has been well studied in adults, UC has an early onset; children could be at high risk of disease complications, surgery, and develop extra-intestinal manifestations [21].

Inflammation is considered one of the important distinguishing feature between IBD, normal subjects and non specific types of colitis and also can specify the duration of IBD. Inflammation was detected in 90% of cases, and with blind diagnosis and evaluation of IBD, it was seen in > 50%

of patients compared to normal biopsies [13, 22]. A study mentioned the best variables of predicting uncomplicated IBD are lamina propria lymphocytes (and eosinophils) with absence of lymphocytic infiltration of the epithelium [23]. In this study inflammatory reactions seen in almost all cases, among them each of transmural inflammation, cryptitis and crypt abscess formations found in 20%, whereas non sarcoid like epithelioid granulomas identified in 10% of cases. These findings are in near to results obtained by [5, 24]. The European consensus (2013) reported the features which are highly predictive of UC are including villous irregular architecture, crypt distortion as branching, inflammation and cryptitis [16]. In addition to the above, plasmacytosis particularly in the base of the crypts is still an important diagnostic feature of IBD from non-IBD colitis and is common in both UC (63%), as well as in CD (62%) [4, 13].

Transmural inflammation and granulomas are typical discriminating features for a diagnosis of CD as opposed to other conditions, particularly UC in both endoscopic biopsies and resection specimens [25]. In this study granulomas were observed in 10% and majority located in the submucosa, whereas in the resection cases were seen widely and extending to the mesentery. European consensus (2013) discussed the diagnostic features of CD included granulomas, crypt architectural abnormalities, in conjunction to inflammation [16]. An international workshop on the initial hisopathological diagnosis of colitis reported that 64% of cases were CD, and 74% were UC [18]. In addition to the above various histopathological features were mentioned to differentiate CIBD from non CIBD and also to discriminate UC from CD, among them a study used mentioned 16 features were significant, among them 3 discriminating features including an increase of lymphocytes, plasma cells in the lamina propria, branching of crypts, and cryptitis can diagnose UC in 89% of cases, whereas 3 others consider the best discriminating histopathological features of CD that were including mucosal surface aspect irregularities, epithelioid granuloma, and an excess of histiocytes (Seldenrijk 1991). Many reviewers were considering granuloma to be very specific, but not very sensitive feature for diagnosis of CD [18, 26]. Also, Bentley *et al.* 2002 [18] reported these histopathological features were better confirmed by multiple endoscopic biopsies rather than single rectal biopsy. This is consistent with the pathological nature of CD. In the same theme the presence of diffuse transmural inflammation in single biopsy or sequential colonic biopsies was found to discriminate CD from UC [27].

The used selected histopathological features in this study have been mentioned and reported in other authors with near similarities, as [28, 29] found crypt architectural irregularities, an increase of lymphocytes and plasma cells infiltrates, and cryptitis were diagnostic of IBD over non IBD colitis.

It is known that the most lethal long term complication of IBD is colorectal cancer (CRC), the risk of its development significantly increases in the patients of IBD. Patients with UC and CD bear an about 10- and 4-fold increased risk, respectively [1, 30, 31].

5. Conclusion

This study concluded that diagnosis of IBD needs interdepartmental correlations to avoid under- or over-diagnosis. As well as the accurate discrimination of CIBD from non CIBD forms is a backbone for therapeutic and prognostic strategies.

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