Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

Diagnostic Dilemma of Inflammatory Bowel Disease: Study from a Tertiary Hospital in South India

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Abstract

Introduction: Diagnosis of inflammatory bowel disease (IBD) and other inflammatory conditions of the colon cannot be established when only one or few features are present as they share many pathological features. Hence, this study is undertaken to develop reproducible criteria which are valid in the diagnosis of IBD and to differentiate it further from ulcerative colitis (UC) and Crohn's disease (CD).

Purpose: The purpose of the study was (1) to study the histopathological patterns of the colonic biopsy specimen, (2) to develop the reproducible criteria which aid in the diagnosis of UC and CD, and (3) to evaluate the extent of interobserver variability over the final diagnosis.

Materials and Methods: Endoscopic punch biopsy procedure was done for 35 cases with suspected IBD which were sent to the Histopathology Department of Bengaluru Medical College. Tissue bits were fixed in 10% formalin and processed by the conventional method and embedded in paraffin blocks. Sections from these blocks were stained with hematoxylin and eosin according to standard procedures. After initial histomorphological reporting was done, the 35 slides were reported again by two pathologists. Cases with proven malignancy were excluded from the study.

Results: UC was diagnosed in 19 cases (53%) of 35 cases followed by indefinite for IBD in nine cases (25%). CD was seen in five cases (14%) followed by tuberculosis in two cases (5%). One case had evidence of dysplasia along with features of UC. The agreement between pathologists for the final diagnosis is 68.5%. Based on *P* value, the significant features which are most useful in the diagnosis of UC are: For activity – (1) cryptitis, (2) neutrophilic infiltration in lamina propria, and (3) crypt abscess; for chronicity – (1) crypt distortion, (2) crypt branching, (3) Mucin depletion, (4) crypt atrophy, and (5) crypt dilation.

Conclusion: UC was found to be more commonly reported among the IBD cases. Considerable disagreement can be seen between experienced pathologists reporting the same slides. Therefore, salient histological features based on better reproducibility along with adequate clinical and endoscopy findings can aid in distinguishing between UC and CD.

Key words: Agreement, Histopathology of ulcerative colitis and Crohn's disease, Inflammatory bowel disease, Reproducible criteria

INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory bowel diseases (IBD) of unknown cause. "Indefinite for inflammatory bowel disease (IBD)" is applied as a temporary classification to cases where a definite diagnosis cannot be made because of the absence of diagnostic features of CD and UC.[1]

The two diseases have similar histopathological features and the discriminating characteristics are often subtle and ill-defined.[2-6] Observer variation assessment may identify diagnostic problem areas and may have great therapeutic consequences in clinical practice.[7-10]

The diagnosis of IBD is established by a combination of medical history, clinical evaluation, laboratory data, which includes negative stool examinations for infectious

Access this article online

www.ijss-sn.com

Month of Submission : 04-2020
Month of Peer Review : 05-2020
Month of Acceptance : 05-2020
Month of Publishing : 06-2020

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agents, and typical endoscopic, histologic, and radiological findings.[11] Other non-infectious causes of diarrhea should be ruled out before a diagnosis is made.[12]

Colonoscopy with biopsies is the most accurate assessment method for the determination of disease extent and activity.[13,14] Pathologists should be aware of the frequency of various features in different settings and should also bear in mind the reproducibility of each feature.

There are rising incidence and prevalence of IBD in India topping the Southeast Asian (SEA) countries.[15] This topic is receiving emerging attention, as medical therapies, surgical approaches, and leading prognostic outcomes require more and more disease-specific strategies in IBD patients.[16]

Table 1: Disease-specific gender distribution

Sex	Impression				Total
	Crohn's	Indefinite for IBD	Tuberculosis	UC	
F					
Count	4	5	2	6	17
% within sex	23.5	29.4	11.8	35.3	100.0
M					
Count	1	8	0	9	18
% within sex	5.6	44.4	0.0	50.0	100.0

IBD: Inflammatory bowel disease, UC: Ulcerative colitis

MATERIALS AND METHODS

After obtaining approval and clearance from the institutional ethical committee, suspected cases of IBD were included in the study. Cases with proven malignancy were excluded from the study. A four-quadrant punch biopsy was obtained from the endoscopic procedure. The grossing of endoscopic biopsies sent to the histopathology department was done conventionally. Tissue bits so obtained were fixed in 10% formalin and processed by the conventional method and embedded in paraffin blocks. Sections from these blocks were stained with hematoxylin and eosin (H and E) according to standard procedures. A systematic histological assessment was made. The H and E stained slides were assessed for the histomorphological features. After initial reporting was done, the 35 slides were reported again by two pathologists.

Table 2: Incidence of individual features in regard to histopathology diagnosis

Features	CD (%)	Indefinite for IBD (%)	TB (%)	UC (%)	*P*-value	Kappa value	Percentage agreement
Cryptitis	2 (10)	4 (20)	0 (0)	14 (70)	0.002*	0.533	77
Neutrophilic infiltration	2 (9.5)	5 (23.8)	0 (0.0)	14 (66.7)	0.013*	0.419	68
Epithelioid granuloma	5 (62.5)	0 (0)	2 (25)	1 (12.5)	0.008*	0.410	83
Langhans giant cell	0 (0)	0 (0)	2 (100)	0 (0)	0.002*	0.000	94
Neutrophils in lamina	3 (10)	11 (36.7)	1 (3.3)	15 (50)	0.070 (NS)	0.236	66
Crypt distortion	2 (14.3)	1 (7.1)	0 (0.0)	11 (78.6)	0.001*	0.578	80
Crypt abscess	3 (20)	0 (0.0)	0 (0.0)	12 (80)	0.005*	0.452	75
Loss of crypt architecture	2 (20)	0 (0.0)	0 (0.0)	8 (80)	0.016*	0.404	77
Ulceration	4 (14.8)	9 (33.3)	1 (3.7)	13 (8.1)	0.091 (NS)	0.269	70
Mucin depletion	1 (7.1)	2 (14.3)	0 (0.0)	11 (78.6)	0.006*	0.416	75
Lymphoid follicles in LP	1 (11.1)	3 (33.3)	0 (0.0)	5 (55.6)	0.067 (NS)	0.267	63
Mucosal inflammation	4 (14.8)	10 (37)	2 (7.4)	11 (40.7)	0.001*	0.576	86
Eosinophils	2 (8.3)	11 (45.8)	1 (4.2)	10 (41.7)	0.008*	0.442	77
Crypt abscess disruption	2 (22.2)	0 (0.0)	0 (0.0)	7 (77.8)	0.439 (NS)	−0.129	60
Submucosal lymphoid aggregate	1 (25)	1 (25)	0 (0.0)	2 (50)	0.064 (NS)	0.305	82
Crypt branching	1 (7.7)	0 (0.0)	0 (0.0)	12 (92.3)	0.009*	0.440	83
Paneth cell metaplasia	0 (0.0)	0 (0.0)	0 (0.0)	6 (100)	0.025*	0.545	77
Diffuse inflammation	4 (14.3)	9 (32.1)	2 (7.1)	13 (46.4)	0.159 (NS)	0.237	73
Plasma cells	5 (15.6)	10 (31.2)	2 (6.2)	15 (46.9)	0.324 (NS)	0.160	83
Villous configuration	0 (0.0)	0 (0.0)	0 (0.0)	3 (100)	0.324(NS)	0.160	83
Crypt atrophy	1 (10)	1 (10)	0 (0.0)	8 (80)	0.002*	0.524	80
Inflammatory polyp	1 (10)	0 (0.0)	0 (0.0)	9 (90)	0.002*	0.203	74
Submucosal fibrosis	3 (37.5)	0 (0.0)	0 (0.0)	5 (62.5)	0.049*	0.273	80
Crypt dilatation	2 (25)	0 (0.0)	0 (0.0)	6 (75)	0.674 (NS)	0.070	63
Thickened muscularis	3 (12)	9 (36)	0 (0.0)	13 (52)	0.005*	0.452	75
Regenerative change	1 (20)	1 (20)	0 (0.0)	3 (60)	0.049*	0.267	69
Crypt hyperplasia	2 (66.7)	0 (00.0)	0 (0.0)	1 (33.3)	0.000*	0.637	94
Edema lamina propria	4 (16)	8 (32)	1 (4)	12 (48)	0.319 (NS)	0.165	63
Ectatic blood vessels	2 (13.3)	9 (60.0)	2 (13.3)	2 (13.3)	0.002*	0.496	74
Neuronal hyperplasia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-		93
Submucosal edema	1 (20)	0 (0.0)	0 (0.0)	4 (80)	0.007*	0.440	89

*P<0.05 – significant (Fischer's exact test). NS: Not significant. IBD: Inflammatory bowel disease, UC: Ulcerative colitis, CD: Crohn's disease

Statistical Analysis

The patient's details were recorded in a standardized format. Results were analyzed in the form of tables, graphs, and pie-charts. Histological parameters were evaluated. Values are expressed as $P < 0.05$ is considered statistically significant. SPSS 18.0 software is used for statistical analysis. Kappa values were calculated for interobserver variation.

RESULTS

The patients were in the age range of 7–65 years with a mean age of 40.1 years and standard deviation of 14.5. The peak incidence of IBD cases was found in the age group between 41 and 50 years, accounting to 31% of the cases followed by the age group of 31–40 years which constituted 20% of the cases.

There was a slight male preponderance in the cases of IBD which constituted 51.4% of all cases with females accounting to 48.6% of all IBD. The male to female sex ratio being 1.05:1. The mean age group of involvement among male patients was 44 years, whereas females it was 35.7.

UC was diagnosed in 19 cases (53%) of 35 cases followed by indefinite for IBD in nine cases (25%). CD was seen in five cases (14%) followed by tuberculosis in two cases (5%). One case had evidence of dysplasia along with features of UC.

Based on the *P*-value, the significant features which are most useful in diagnosis of UC are:

- For activity – (1) cryptitis, (2) neutrophilic infiltration in lamina propria, and (3) crypt abscess
- For chronicity – (1) crypt distortion, (2) crypt branching, (3) Mucin depletion, (4) crypt atrophy, and (5) crypt dilation.

The agreement between pathologists for the final diagnosis is 68.5% [Tables 1-4].

In our study, the strongest features based on the agreement were:

UC	CD
Cryptitis	Epithelioid granuloma
Neutrophilic infiltration in lamina propria	Thickened muscularis mucosa
Crypt distortion	Crypt hyperplasia
Crypt abscess	Basal plasmacytosis
Loss of crypt architecture	Neutrophilic infiltration in lamina propria
Mucin depletion	Mucosal inflammation
Crypt branching	Submucosal edema
Crypt atrophy	Eosinophils

UC: Ulcerative colitis, CD: Crohn's disease

DISCUSSION

Diagnosis of IBD based solely on histological features is challenging as no feature is absolute for diagnosis of IBD or type of IBD. Diagnostic accuracy is optimized if several features rather than a single feature are assessed along with the distribution of the disease with clinical and endoscopic picture. A stepwise approach is advisable so as not to miss any feature that might be contributing to the diagnosis.[17] Timing of biopsy is also important criteria where the cases are divided as – (a) early untreated IBD (<4 weeks), (b) established untreated IBD, and (c) long-standing IBD.[17]

In tropical countries like ours, differentiation of TB from CD is a difficult diagnostic dilemma as there has been a rise in the number of cases of CD.[18]

There has been a paucity of accurate epidemiologic data due to the diagnostic overlap of the IBD entities with conditions such as infectious colitis. Overall, both the incidence and prevalence of CD and UC are increasing with time. This can be attributed to a number of factors, including improved sanitation, diet, and medication exposures, increased IBD awareness among patients and clinicians, use of improved endoscopic and radiologic diagnostic modalities, and widened health-care access.[15]

The most common feature among these studies was crypt abscess followed by neutrophilic infiltration in lamina propria. However, these can be seen present in infectious etiology as well as in indefinite for IBD. Other features in our study such as cryptitis, mucin depletion, crypt branching, and crypt atrophy have been seen to strengthen the diagnosis of UC.

In the present study, features which showed poor agreement between the two observers were crypt abscess disruption, basal cell plasmacytosis, villous configuration, edema of lamina propria, and crypt dilatation. Features which are rarely observed usually have low kappa values. For example, crypt dilatation was present in 22% of the observations leading to a kappa of 0.07. Epithelioid granulomas were also observed in 22% cases, but the associated kappa value was considerably higher at 0.41, indicating that when seen, there was much closer agreement on their presence. By contrast, common features such as lymphoid aggregates may have poorer agreements.

Interobserver variability remains a major problem: In a study by Charles Bernstein, the range of agreement over the final diagnosis was only 65–76%. The greatest disagreement was seen in diagnosing CD, and it was most frequently diagnosed as UC. Even some normal cases were reported as CD or UC.[19] This study highlights that

Table 3: Frequency of detection of the reproducible features

Features	*P*-value A Theodossi *et al.*	*P*-value Le Berre	*P*-value Seldenrijk	*P*-value Ahmed	*P*-value current study
Cryptitis	<0.001	<0.0001	0.0000	<0.0001	0.002*
Neutrophilic infiltration	<0.001	<0.01	0.0000	<0.0001	0.013*
Epithelioid granuloma	<0.001	<0.01	0.0416	NS	0.008*
Langhans giant cell	<0.001	-	-	NS	0.002*
Neutrophils in lamina	<0.001	<0.0001	-	<0.0001	0.070 (NS)
Crypt distortion	<0.001	<0.0001	-	<0.0001	0.001*
Crypt abscess	<0.001	<0.0001	1.0000	<0.001	0.005*
Loss of crypt architecture	<0.001	<0.0001	0.0000	<0.0001	0.016*
Ulceration	<0.001	<0.05	0.0022	<0.001	0.091 (NS)
Mucin depletion	<0.001	<0.0001	-	<0.0001	0.006*
Lymphoid follicle in LP	<0.001	-	-	<0.0001	0.067 (NS)
Mucosal inflammation	<0.001	<0.05	-	NS	0.001*
Eosinophils	<0.001	-	-	<0.0001	0.008*
Crypt abscess disruption	<0.001	-	0.0111	<0.05	0.439 (NS)
Submucosal lymphoid aggregate	<0.001	-	-	NS	0.064 (NS)
Crypt branching	<0.001	-	0.0000	NS	0.009*
Paneth cell metaplasia	<0.001	-	-	NS	0.025*
Diffuse inflammation	<0.001	<0.05	0.0547	NS	0.159 (NS)
Plasma cells	<0.001	-	0.0000	NS	0.324 (NS)
Villous configuration	<0.001	-	0.0004	<0.01	0.324 (NS)
Crypt atrophy	<0.001	<0.01	-	<0.001	0.002*
Inflammatory polyp	<0.05	-	-	<0.05	0.002*
Submucosal fibrosis	<0.11	-	-	NS	0.049*
Crypt dilation	<0.001	-	0.1134	<0.001	0.674 (NS)
Thickened muscularis	<0.001	-	-	<0.0001	0.005*
Regenerative change	0.01	-	-	<0.05	0.049*
Crypt hyperplasia		-	-	NS	0.000*
Edema lamina propria	<0.001	-	-	NS	0.319 (NS)
Ectatic blood vessels	<0.001	<0.05	-	NS	0.002*
Neuronal hyperplasia	0.27	-	-	NS	-
Submucosal edema	0.19	-	-	NS	0.007*

personal interpretations play a major role even after criteria are set for experts. In our study, the agreement between the observers was around 70%, with disagreement found predominantly in distinguishing UC from indefinite for IBD due to overlapping features.

Hence, the clinician and pathologist must maintain an open dialog when it comes to reaching conclusions regarding the final diagnosis. The acceptable criterion for reliability of a particular microscopic feature was that it had been shown, in more than one valid study, to have a minimum value of 0.4 or a percentage observer agreement of at least 80%. For diagnosis of UC, crypt architectural distortion decreased crypt density, a villous mucosal surface, and transmucosal inflammation emerged as the most reliable. For a diagnosis of CD, the most reliable parameters were granulomas, discontinuous crypt distortion, and discontinuous mucosal inflammation. To diagnose infectious colitis, only normal crypt architecture and superficial mucosal inflammation satisfied the criteria.

Therefore, according to multiple studies, features which distinguish IBD from infective colitis with high reliability are basal plasmacytosis, crypt architecture abnormality such as crypt distortion, branching, and atrophy though some interobserver variability is encountered. The irregular or villous mucosal surface can also be taken as a high reliable diagnostic feature.[20-22]

Fairly reliable features are granuloma for CD, basal lymphoid aggregates, but it can be difficult to distinguish it from normal lymphoid aggregates. However, due to less sample size and limited observers, kappa value is lower and hence the features vary in the diagnosis of CD. Features such as lamina propria chronic inflammation and hypercellularity are considered to be less reliable as it has low reproducibility. Paneth cell metaplasia seen distal to splenic flexure has some interobserver variation and importance may be restricted to long-standing disease.[17,23,24]

These features were in accordance with the present study where the interobserver agreement determined by kappa value was 0.4 signifying fair agreement. Features helpful in identifying activity (active inflammation) of UC are crypt abscess and neutrophilic infiltration in lamina propria and cryptitis. For identifying chronicity, the features are crypt

Table 4: Comparative study of kappa value agreement

Features	Kappa value Theodossi *et al.*	Kappa value present study
Cryptitis	0.47	0.533
Neutrophilic infiltration	0.41	0.419
Epithelioid granuloma	0.41	0.410
Langhans giant cell	0.40	0.000
Neutrophils in lamina	0.40	0.236
Crypt distortion	0.38	0.578
Crypt abscess	0.37	0.452
Loss of crypt architecture	0.36	0.404
Ulceration	0.36	0.269
Mucin depletion	0.34	0.416
Lymphoid follicle in LP	0.33	0.267
Mucosal inflammation	0.33	0.576
Eosinophils	0.32	0.442
Crypt abscess disruption	0.31	-0.129
Submucosal lymphoid aggregate	0.31	0.305
Crypt branching	0.30	0.440
Paneth cell metaplasia	0.29	0.420
Diffuse inflammation	0.29	0.237
Plasma cells	0.27	0.160
Villous configuration	0.26	0.160
Crypt atrophy	0.24	0.524
Inflammatory polyp	0.22	0.203
Submucosal fibrosis	0.20	0.273
Crypt dilation	0.23	0.070
Thickened muscularis	0.17	0.452
Regenerative change	0.17	0.267
Crypt hyperplasia	0.15	0.637
Edema lamina propria	0.15	0.165
Ectatic blood vessels	0.10	0.496
Neuronal hyperplasia	0.14	0.000
Submucosal edema	0.10	0.440

distortion, loss of crypt architecture, crypt branching, crypt atrophy, and mucin depletion.

CONCLUSION

UC was found to be more commonly reported among the IBD cases. To reduce the interobserver variability, salient histological features based on better reproducibility can aid in distinguishing between UC and CD. Limitations faced in our study were inadequate samples which were sent unlabeled or from single numbers of observers and incomplete endoscopic findings.

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How to cite this article: Rath I, Ahmed S, Biligi DS. Diagnostic Dilemma of Inflammatory Bowel Disease: Study from a Tertiary Hospital in South India. Int J Sci Stud 2020;8(3):29-33.

Source of Support: Nil, **Conflicts of Interest:** None declared.