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STUDY OF PATTERNS OF DYSPLASIA IN INFLAMMATORY BOWEL DISEASES

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ABSTRACT

BACKGROUND: Inflammatory bowel disease (IBD) comprises of Ulcerative colitis, Crohn's disease and colitis of indeterminate type. Patients with long established IBD are at a greater risk for development of colorectal carcinoma (CRC). The best marker for cancer risk in IBD is dysplasia. IBD on biopsy can show low grade dysplasia (LGD) or high grade dysplasia (HGD) or histological features indefinite for dysplasia. **AIMS:** 1) Determination of the incidence of LGD, HGD and CRC in IBD patients. 2) Evaluation of presence of any correlation between duration of IBD and extent of intestinal involvement by IBD and between duration of IBD and multifocality of dysplasia. **MATERIALS AND METHOD:** 393 patients with clinical suspicion of IBD were enrolled in this study. During surveillance endoscopy number of biopsy samples taken from each case were 10-15. Histopathological examination of these biopsy samples was done. **RESULTS:** Out of 266 patients of IBD who turned up for surveillance endoscopy, the incidences of LGD, HGD, CRC and IBD indeterminate for dysplasia were found to be 10.90%, 4.51%, 4.51% and 2.63% respectively. On statistical analysis it was discovered that in both UC and CD the extent of intestinal involvement was directly proportional to the duration of the disease. In both UC and CD, longer disease durations were linked to more foci of dysplasia. **CONCLUSION:** In both UC and CD, longer disease durations is linked to the extent of intestinal involvement and number of foci of dysplasia while type of dysplasia (LGD/HGD) is not related to duration of IBD. In IBD with UC incidence of PSC is linked with the extent of intestinal involvement.

INTRODUCTION

Inflammatory bowel disease (IBD) comprises of Ulcerative colitis (UC), Crohn's disease (CD) and colitis of indeterminate type. Patients with long established IBD are at greater risk for development of colorectal carcinoma (CRC) [1]. The best marker for cancer risk in IBD is dysplasia and it is seen in intestine both adjacent to and away from IBD associated CRC [2]. IBD on biopsy can show low grade dysplasia (LGD) or high grade dysplasia (HGD) or histological features indefinite for dysplasia.

In our study the primary aim was to determine the incidence LGD, HGD and CRC in IBD patients. We evaluated if there is any correlation between duration of IBD and extent of intestinal involvement by IBD. We also looked for presence of any correlation between duration of IBD and multifocality of dysplasia.

MATERIALS AND METHODS

A prospective study was conducted from March 2016 to April 2019 in collaboration with the Departments of Gastroenterology of a tertiary care Institute. 393 patients with clinical suspicion of IBD were enrolled in this study. Detailed history was obtained and informed consent was taken. 25 out of 393 patients underwent concomitant colectomy as a protective measure. The diagnosis of IBD was ruled out in 6 out of 393 patients. Amongst 387 patients, 266 patients turned up for surveillance endoscopy. The remaining patients were excluded from statistical analysis. During surveillance endoscopy number of biopsy samples taken were10 to15. Histopathological examination of these biopsy samples was done. Incidences of LGD, HGD, CRC and IBD indefinite for dysplasia were evaluated. Percentage of cases of IBD that did not progress to LGD, HGD and CRC was calculated. This study is approved by the Research Advisory Committee (RAC) of IPGMER, Kolkata.

RESULTS

Out of 387 patients of IBD 266 patient turned up for surveillance endoscopy. Among 387 cases 86 are diagnosed as CD, 264 cases are diagnosed as UC and 37 cases are diagnosed as colitis of IND type.[Table 1] the incidences of LGD, HGD, CRC and IBD indeterminate for dysplasia are found to be 10.90%, 4.51%, 4.51% and 2.63% respectively.[Table 2] 181 out of 266 patients (68.04%) do not progress to dysplasia or CRC. The 25 patients who had undergone concomitant colectomy did not show recurrence of IBD.

TABLE 1: Incidence of Inflammatory bowel diseases

Type of IBD	Number of Cases (N-387)
Crohn's Disease	86
Ulcerative Colitis	264
Colitis of Indeterminate Type	37

TABLE 2: Incidence of dysplasia and malignancy

Type of Dysplasia/ CRC	Number of Cases (N-60)
Low Grade Dysplasia	29
High Grade Dysplasia	12
IBD indeterminate for dysplasia	12
CRC	07

High grade and low grade dysplasia are more common as unifocal (63.6%) lesion than as multifocal (36.4) lesion. [Table 3] Most of the dysplastic foci are located either in the rectum or the entire colon in cases of extensive involvement. [Table 4]

TABLE 3: Focality of lesion in High grade and Low grade dysplasia

Pattern of Dysplastic Foci	Number of Cases (N-41)
Unifocal Dysplastic Foci	26
Multifocal Dysplastic Foci	15

TABLE 4: Location of dysplastic foci in High grade and Low grade dysplasia

Location of Dysplastic Foci	Number of Cases (N-41)
Cecum	1
Ascending Colon	2
Transverse Colon	3
Descending Colon	3
Sigmoid Colon	6
Rectum	11
Extensive	15

Wilcoxon signed rank test is used to analyse the correlation between duration of CD and UC with the colonoscopic extent it is found that in both CD and UC. Calculated p value is 0.0039 for CD and < 0.0001 for UC, The extent of intestinal involvement is directly proportional to the duration of the disease. In both UC and CD, longer disease durations are linked to more foci of dysplasia. For CD the p value is 0.0039 and for UC it is < .0001 and both are statistically significant. Chances of developing PSC were seen to increase as the extent of intestinal involvement by UC increased (p value is 0.0034). No significant correlation was found between

duration of IBD and type of dysplasia (LGD/HGD) and between type of IBD (CD/UC) and type of dysplasia (LGD/IND).

DISCUSSION

IBD comprises of UC, CD and colitis of indeterminate type . UC can occur at any age, though it is rare between age of 5 years and 75 years. The highest incidence of UC is found in second and third decades of life. In UC male to female ratio is 1:1. CD occurs mostly between 15 to 30 years of age but it can be diagnosed at any age. The median age of diagnosis is approximately 30 years [3,4]. In CD, female-to-male ratio is 1.3:1 in adult patients [5]. In the paediatric population there are more males having CD disease than females [6].

IBD results from inappropriate mucosal immune activation. The genes associated with CD are NOD2, ATG16L1 and IRGM. Polymorphisms of HNFA and ECM1 are associated with UC.

The gross features in favour of CD over UC in colon are skip areas of involvement, rectal sparing and preferential localisation on right side. The distinguishing histopathological features of CD are fissuring ulcers, non- necrotising granulomas and transmural inflammation. On microscopy UC shows architectural distortion and mucosal inflammation [Figure 1]. Colitis of indeterminate type is found in 5- 10% of operative specimens. Its pathological features are ambiguous and exact distinction of CD from UC cannot be done.

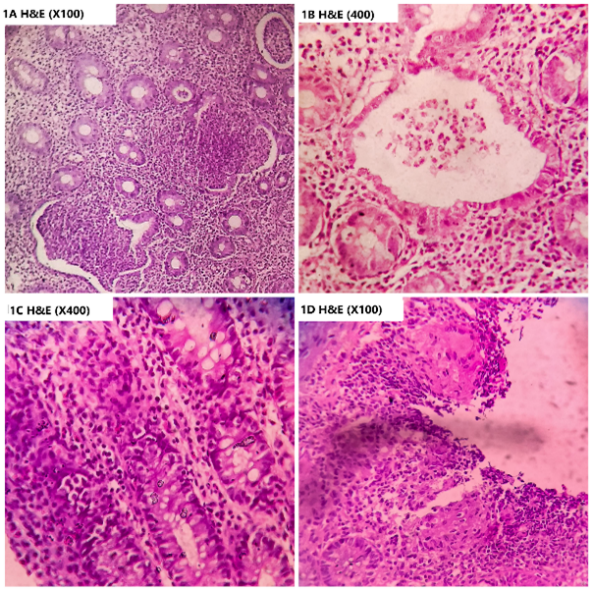

Figure 1:

1A: Ulcerative colitis, crypt abscesses
1B: Ulcerative colitis, crypt abscesses
1C: Cryptitis and monomuclear inflammation of lamina propria, Chron's disease
1D: Illformed granuloma in Chron's disease

CRC is the third most common cancer in men after lung cancer and prostate cancer and the second most common cancer in women after breast cancer [7]. CRC can be either sporadic (65-85%) or familial (10-30%). IBD is the cause for 1-2% of all CRCs in the general population. There is a greater risk of CRC development in patients with long established IBD. Patients with IBD have CRC at younger age as compared to patients with sporadic CRC (Mean age 40-50yrs versus 60yrs). IBD associated CRC is mostly flat and infiltrative. CRC in IBD patients is more aggressive and multifocal and it also presents at a more advanced stage compared to sporadic CRC [8]. Therefore prognosis of CRC developing in IBD is worse. One out of six IBD patients die because of the CRC [9].

Dysplasia is the best marker for cancer risk in IBD. CRC appears within foci of HGD in IBD patients. Dysplasia can be seen in colon both adjacent to and away from colitis associated carcinoma. Dysplastic epithelium shows loss of polarity, cellular stratification, cellular crowding, cells with high nuclear to cytoplasmic ratio, nuclear pleomorphism and irregular nuclear contour. Granular chromatin with multiple nucleoli and nearby cryptitis and crypt abscess favour reparative epithelium over dysplastic epithelium [Figure 2].

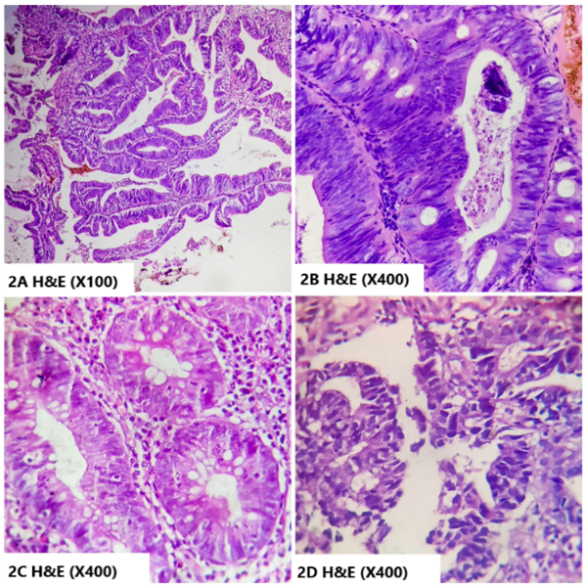

Figure 2:

2A: High grade dysplasia
2B: High grade dysplasia
2C: Low grade dysplasia
2D: Low grade dysplasia

IBD on biopsy can show LGD or HGD or histological features indefinite for dysplasia. HGD is associated with distortion of mucosal architecture and more marked dysplastic features than LGD. The term IBD indefinite for dysplasia is used when the histological features are unusual but are insufficient to form a diagnosis of dysplasia.

In our study more the duration of CD, greater was the extent of intestinal involvement and as the duration of CD increased, dysplasia became multifocal. Similarly, more the duration of UC, greater was the extent of intestinal involvement and as the duration of UC increased, dysplasia became multifocal. This implies that greater the extent of intestinal involvement by UC/CD more are the chances of dysplasia becoming multifocal. Though surveillance endoscopy with biopsy in IBD patients has significant limitations including sampling error yet with increased duration of IBD chances of detecting dysplasia increases because dysplasia becomes multifocal. Nevertheless, there was no significant correlation between duration of IBD and type of dysplasia. We also could not find any correlation between type of IBD (CD/UC) and type of dysplasia (LGD/IND). In a study involving 418 UC patients, Gupta et al. correlated the histology score of inflammation to cancer development and found that there is notable association between inflammatory score and advanced lesions (defined as either HGD or cancer) [10]. Although implementation of surveillance colonoscopy in IBD patients is supported and universally advocated, there is lack of evidence of reduction in CRC incidence and mortality as a result of the surveillance [11].

In patients with more than 40 years of IBD, the probability of developing CRC has been found in some studies to be as high as 60%, while others have shown that the risk of cancer in IBD

is similar to that of the general population [12,13]. In our study we found the incidence of CRC in IBD to be 2.63%.

PSC is an idiopathic chronic inflammatory disease of the intrahepatic and extra-hepatic bile ducts. It is strongly associated with IBD and 70–80% of patients with PSC have IBD. In patients with PSC and IBD, 85–90% have UC with the remaining ones suffer from CD [14]. PSC occurs in approximately 3% of patients of UC. The presence of PSC escalates the risk of CRC in UC but the evidence in CD is unclear. In our study we found that chance of developing PSC becomes more as the extent of intestinal involvement by UC increases.

PSC results in fibrosis and gradually cirrhosis and hepatic failure. Radiologically PSC exhibits beading, irregularity and strictures in the bile ducts. PSC is diagnosed on either MR cholangiopancreatography or endoscopic retrograde cholangiopancreatography. A liver biopsy can support the diagnosis of PSC but it is rarely diagnostic. The characteristic histopathological features of PSC on liver biopsy is the onion skin pattern. There is presence of concentric fibrosis around the small bile ducts and eventually obliteration of the ducts. The histopathological features can be variable ranging from chronic in ammatory cell infiltration in the portal tracts to cirrhosis.

PSC is independent of the underlying colitis. It mostly follows a progressive course many years after presence of stable disease. The incidence of pancolitis, rectal sparing and backwash ileitis is more in UC patients with PSC than UC patients without PSC. It is noteworthy that the presence of PSC diminishes the in ammation in UC so patients with UC and PSC have a more clinically quiescent colitis than UC patients without PSC [15-17]. Liver transplantation for PSC worsens the course of UC [18,19]. However, even if the colitis is less severe in UC patients with PSC, they is higher risk for colorectal dysplasia and cancer.

This differential diagnoses of IBD include infections and non-infectious causes. The most common organisms causing infectious colitis are Salmonella, Shigella, and Campylobacter. Non infectious causes include acute self-limited colitis, Behçet's disease diverticulitis, colitis associated with drugs and toxins, eosinophilic colitis, graft-versus-host disease, ischemic colitis et cetera.

CONCLUSION

In both UC and CD, longer disease durations are linked to the extent of intestinal involvement and number of foci of dysplasia while type of dysplasia (LGD/HGD) is not related to duration of IBD. In IBD with UC incidence of PSC is linked with the extent of intestinal involvement. Further studies with larger population need to be undertaken in this direction.

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Ethical Compliance with Human Study: This study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration; or, This study was conducted in compliance with all the applicable institutional ethical guidelines .

Data Availability: No additional data available.

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