FLAT MUCOSAL DYSPLASIA IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE: EXPERIENCE IN A TERTIARY CARE REFERRAL HOSPITAL

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ABSTRACT

Context: Inflammation associated CRC (colorectal carcinoma) develop along an inflammation-dysplasia-carcinoma sequence, with varying progression rates from Low Grade Dysplasia (LGD) or Indefinite for Dysplasia (IND) to High Grade Dysplasia (HGD)

Aims: Assessment of the frequency of progression of Inflammatory Bowel Disease (IBD) to LGD and IND including the assessment of factors associated with the risk of progression.

Settings and Design: This retrospective analytical study conducted between January 2011 to 2015.

Methods And Material: All patients diagnosed with IBD between 2011 to 2015 were reviewed, including Ulcerative Colitis (UC), Crohns Disease (CD), Indeterminate colitis (IC) and Idiopathic colitis. Medical charts, endoscopy, histopathology, and surgery reports were collected.

Results: Out of 393 patients diagnosed with IBD, 29 patients developed LGD and 12 showed IND. No association was observed between the subtype of IBD with progression. The mean duration of disease and multifocality correlated with the presence of LGD or IND. The presence of extensive colitis conferred a higher risk of developing LGD over IND.

Conclusions: The features favoring the development of LGD or IND include the mean duration of disease at the time of diagnosis, multifocality and the presence of extensive colitis. The use of adjunct biomarkers like p53 may aid in evaluating progression.

KEYWORDS : Inflammatory Bowel Disease, Colorectal Carcinoma, LGD, IND, HGD.

INTRODUCTION:

Patients with longstanding IBD like UC or CD are at increased risk of developing CRC.^[1-3] Inflammation associated CRC is supposedly developing along an inflammation-dysplasia-carcinoma sequence.^[4] Dysplasia is classified microscopically as LGD, HGD, or IND.^[5] HGD is associated with a high risk of synchronous or metachronous carcinoma.^[6] It is therefore generally considered an unambiguous indication for colectomy. Management and therapeutic decision regarding flat LGD and IND, however, is not straightforward. Progression rates of flat LGD to HGD or CRC varied greatly in previous studies, ranging from no progression to 5-year progression rates of more than 50%.^[7-10]

These diverging results may be due to the selections of study populations and design, endoscopy-related matters or due to variations in site of biopsies. Dysplasia in the indefinite and low-grade categories in particular is associated with a poor interobserver agreement amongst pathologists also.^[11,12] Moreover, data on the natural course of IND are lacking. We studied the frequency of progression of IBD to LGD and IND. Furthermore, we have tried to assess some of the factors associated with the risk of progression.

MATERIAL AND METHODS

Study Population

All patients diagnosed with IBD from between January 2011 until January 2015 were first isolated. Spectrum of inflammatory lesions included colitis, UC, IC, idiopathic colitis, and CD. A biopsy was defined as "flat" when the histopathological diagnosis of LGD or IND was made in a mucosal biopsy that was taken from endoscopically normal mucosa, as documented in the colonoscopy report. Only patients diagnosed with flat LGD or IND for the first time were identified during the follow up period.

Patients with LGD or IND in raised or otherwise suspected mucosa, those who were previously diagnosed with HGD or CRC or synchronously at the time of flat LGD/IND diagnosis, patients with a previous or concomitant subtotal or total colectomy, patients without any endoscopic or surgical follow-up, and patients with incomplete or missing medical charts were excluded.

Data Collection

In UC patients or patients with IC, proctitis was considered as disease limited to the rectum, left-sided colitis considered as disease proximal to the rectum but distal to the splenic flexure, and extensive colitis considered as disease proximal to the splenic flexure.

In CD patients, disease extent was considered as ileal if disease was located in the ileum, colonic if disease was located in the colon, and ileocolonic if disease was located in both the ileum and colon.

Dysplasia was defined as "unifocal" if only one specimen container contained dysplasia and "multifocal" if two or more specimen containers contained dysplasia.

Duration of follow-up was measured in months and defined as the time from beginning of the study to first flat LGD/IND diagnosis or to one of the following endpoints: 1) end of follow-up (1st of September 2017); 2) death; 3) subtotal or total colectomy; or 4) lost-to-follow-up. When dysplasia was found during follow-up, location, grade, and mucosal appearance were documented.

Pathology Review

Histology slides from patients with flat LGD or IND were retrieved from departmental slide archive by three expert GI pathologists and reviewed by one of these three pathologists in a blinded fashion. Slides were reviewed according to the criteria and definitions as articulated by Riddell et al.^[5] When one pathologist doubted the degree of dysplasia or when disagreement occurred between the original and the revised diagnosis, slides were discussed and reassessed by all three pathologists in a meeting in order to obtain a consensus diagnosis.

Statistical Analysis

The unpaired t test was performed for comparisons of continuous data between multiple groups. The Fischer's exact test was used for analysis of categorical variables. P-value <0.05 was considered as significant. Statistical software (GRAPHPAD PRISM 6) was used for analysis.

Ethical Considerations

This study was carried out with the approval of and in accordance with the institutional ethical guidelines.

RESULTS:

Our search yielded 393 IBD patients including UC, CD and IC. Review of medical charts, endoscopy, histopathology, and surgery reports resulted in exclusion of 352 patients, leaving 29 IBD patients developing flat LGD and 12 IBD patients developing IND during follow up. The reasons of exclusion are shown in the flowchart [Figure 1].

Amongst 393 patients 19 patients progressed to HGD (5%), 3 of whom developed CRC subsequently. Of these one patient was operated on after the detection of HGD and CRC was found in the surgical specimen. In one patient, CRC was found during colonoscopy performed 4 months after the detection of HGD. In the third patient HGD and CRC were detected synchronously. In 181 patients with no endoscopic or histological evidence of progression, low grade or advanced neoplasia was found in the follow up period of 30 months. In 16 patients no progression of HGD to CRC was found during the follow up period of 30 months.

Figure-1 : Distribution And Progression Of IBD Cases

Progression of IBD to LGD or IND is shown in Table 1. Diagnosis of flat LGD was made in 19 UC patients (67.85%), in 8 CD patients (88.8%), and in 2 IC patients (50.0%). Similarly IND was diagnosed in 9 UC patients (32.1%), 1CD patient (11.1%) and 2 IC patients (50.00%). There is no statistically significant correlation found between subtype of IBD and progression to LGD and IND (p= 0.718, 0.239 and 0.567 for UC, CD and IC respectively).

Table 1: Progression Of IBD To LGD Or IND

DISEASE	LGD	IND
UC (28)	19	9
CD(9)	8	1
IC(4)	2	2
TOTAL(41)	29	12

Table 2: Clinical Characteristics Of These Patients

CLINICAL FEATURES		LGD	IND
SEX	MALE	20 (69%)	6(50%)
	FEMALE	9 (31%)	6(50%)
MEDIAN AGE AT DIAGNOSIS (YRS RANGE)		26.5 (7-45)	28 (15-52)
MEDIAN AGE AT FIRST DIAGNOSIS OF DYSPLASIA (YRS RANGE)		49 (32-70)	49 (29-63)
MEAN DURATION OF IBD AT INITIAL DYSPLASIA (YRS RANGE)		18.5 (9-34)	18 (4-29)

Clinical characteristics of these patients are shown in Table 2. Male

female ratio in LGD cases was approximately 2:1 and in IND cases was 1:1. Mean age at diagnosis of LGD cases was 28.14±11.11 and the same for IND cases was 28.75±11.31. Mean age at diagnosis of dysplasia in LGD cases was 50.31±10.26 and the same for IND cases was 45±10.39. There was no statistically significant difference in mean age at diagnosis of IBD with presence of LGD or IND (p= 0.8744) and mean age at the diagnosis of flat dysplasia with presence of LGD or IND (p = 0.1410). Mean duration of disease at the initial diagnosis of dysplasia in LGD cases was 21.48 ± 7.53 years and in cases of IND it was 15.42± 7.18 years. A statistically significant correlation was observed between presence of LGD or IND with the mean duration of disease at the initial diagnosis of dysplasia (p = 0.0225).

Table 3: Distribution Of Focality And Location Amongst LGD And IND Patients

		LGD	IND
FOCALITY	UNIFOCAAL	15	11
	MULTIFOCAAL	14	1
LOCATION OF DYSPLASIA	RECTUM	4	7
	SIGMOID COLON	3	4
	DESCENDING COLON	3	0
	TRANSVERSE COLON	3	0
	ASCENDING COLON	2	0
	COECUM	1	0
	MULTIFOCAAL	12	1
EXTENT OF UC	PROCTITIS	0	2
	LEFT SIDED COLITIS	4	6
	EXTENSIVE COLITIS	15	1
EXTENT OF CD	COLONIC<50%	1	0
	COLONIC>50%	3	0

Distribution of focality and location amongst LGD and IND patients are shown in Table 3. In more than half of the patients, flat LGD was found to be unifocal (total 15 cases), predominantly located in the rectum. Fourteen patients had multifocal flat LGD, which was located distally to the splenic flexure in 7 patients (54%). Most of UC and IC cases were extensive colitis and most of the CD cases were colonic lesions with >50% involvement. Patients were followed for a median duration of 16.27 months (range 6–29 months). But the presence of LGD was more in cases of multifocal dysplasia in comparison to unifocal dysplasia and the difference is statistically significant ($p=0.029$).

In most of the patients, flat IND was found to be unifocal (total 11 cases), predominantly located in the rectum. Single patient had multifocal flat IND, which was located distally to the splenic flexure. Most of UC cases were left sided colitis and all IC cases were extensive colitis. Single CD case was colonic lesions with >50% involvement. Patients were followed for a median duration of 16.28 months (range 6–25 months).

Presence of IND in rectal location is statistically more significant compared to presence of LGD in non-rectal colonic location ($p=0.0066$). Extensive colitis cases developed LGD in higher rate than IND and this difference is also statistically significant ($p=0.0133$).

Table 4: Medical And Surgical History In LGD And IND Cases

		LGD	IND
MEDICAL	TWO-DRUG	16(55%)	3(33.33%)
	THREE-DRUG	13(45%)	9(66.67%)
SURGICAL	TWO-DRUG	11(78.57%)	0(0%)
	THREE-DRUG	3(21.43%)	0(0%)

Medical and surgical history in LGD and IND cases are shown in Table 4. More than half of LGD cases were having therapy with two categories of drugs; anti-inflammatory like 5 aminosalicylates (either sulfasalazine or mesalamine) and corticosteroids before the development of dysplasia. Amongst them 16 patients (55%) developed dysplasia in the follow up period. Less than half of LGD cases were having therapy with three categories of drugs like anti-inflammatory like 5 aminosalicylates (either sulfasalazine or mesalamine), corticosteroids and immunosuppressants (like cyclosporine) before the development of dysplasia. Amongst them 13 patients (45%) developed dysplasia in the follow up period. Incidence of development of dysplasia was not different significantly between the patients receiving two-drug or three-drug regime.

Only 3 IND cases (33.33%) were having therapy with two categories of drugs like anti-inflammatory like 5 aminosalicylates (either sulfasalazine or mesalamine) and corticosteroids before the development of dysplasia. Nine IND cases (66.7%) were having therapy with three categories of drugs like anti-inflammatory like 5 aminosalicylates (either sulfasalazine or mesalamine), corticosteroids and immunosuppressants (like cyclosporine) before the development of dysplasia.

DISCUSSION

This study demonstrates that a diagnosis of LGD in patients with IBD largely depends on the interpretation of the consulting pathologist [Figure 2].

Furthermore, the study demonstrates that thorough histological examination can detect LGD and IND even in colonoscopically normal mucosa.

Previous studies showed that flat LGD and IND patients progressed to advanced neoplasia 37% cases with flat LGD^[13] This was much higher than the 5-year progression rate of 5% in IND patients.^[13] This low risk of progression of IND is in line with several other, previously published studies.^[14,15]

In other previous studies, conflicting data with respect to the clinical course of flat LGD have been reported ranging from no increased progression to 5-year progression rates of more than 50%.^[10] In Ullman et al study, the 5-year progression rate to flat LGD was higher than that in our series. Whether differences in mesalazine prescription or other risk factors might have played a role in this respect is a matter of speculation. Another high progression rate was reported by Connell et al.^[8] In contrast, in the study of Befrits et al.,^[7] in 60 patients with flat

LGD only 2 progressed to advanced neoplasia (HGD).

Figure- 2: Upper left: Cryptitis in UC in H&E (×400) Upper right: Crypt abscess in UC in H&E (×400) Middle left: Mucosal fat entrapment in CD in H&E (×100) Middle right: Mononuclear inflammation of lamina propria in CD and IND in H&E (×400) Lower left: Acute inflammatory exudate in UC in H&E (×100) Lower right: Crypt abscess in UC in H&E (×100)

Figure-3: Upper left: IND in IBD in H&E (×100) Upper right: IND in IBD in H&E (×400) Lower left: LGD in IBD H&E (×100) Lower right: LGD in IBD H&E (×400)

Pekow et al^[16] found a higher incidence rate for advanced neoplasia in patients with IND confirmed by two expert pathologists compared to patients with flat LGD. However, that study had the limitation of low patient numbers in both groups, which may have influenced the results. Both Connell et al and Ullman et al reported progression rates for only UC patients. We have studied both UC, CD and IC patients. As the inflammation-dysplasia carcinoma sequence is thought to be the pathogenetic denominator in all subgroups, we feel that inclusion of UC and CD patients is justified and that this does not explain the lower progression rates in our study.

We have identified clinical or pathological factors that are associated with the risk of progression to LGD and IND. Although multifocal dysplasia seemed to be a predictor of progression it is associated more with LGD than IND and the difference is statistically significant. Study by Fiona D.M. van Schaik et al also got the similar findings.^[13]

Mesalazine treatment has been suggested to exert chemoprotective effects in longstanding colitis patients, although this is solely based on data from retrospective studies.^[17-19] We were not, however, able to assess the contribution of drug-related parameters in the current analysis. There is no statistically significant difference in patients with LGD receiving two-drug and three-drug regime.

The mean number of biopsies per colonoscopy was rather low in our study (13 for LGD and 10 for IND). This is lower than mean number of biopsies than guidelines generally advise.^[20,21] This might have resulted in an underestimation of the presence of multifocal LGD or synchronous flat HGD due to sampling errors. However, since most cases of advanced neoplasia can easily be identified by endoscopic abnormality, the effect of this phenomenon on our results is probably small.

Another problematic area is the large discrepancy and poor interobserver agreement for dysplasia, which is a well-known phenomenon in literature.^[11,12] In a study by Lim et al,^[22] LGD slides from 40 patients were reviewed by five specialist GI pathologists. A consensus diagnosis, defined as agreement between at least three of five pathologists, was reached in 15 of 40 cases (38%) only.

The real challenge remains the management of patients with flat LGD. No consistent policy exists for the treatment of flat LGD; either more frequent follow up and intensification of the surveillance program or a proctocolectomy is recommended.^[6,10,23] The differences in progression rates of flat LGD leave room for doubt regarding the progression rates reported in previous studies without performing a methodical histopathological review of the slides. Every histological slide with (a suspicion of) dysplasia should be reviewed by a panel of expert GI pathologists. In clinical practice this may cause a logistic problem. Therefore, every slide should be reviewed by at least one expert GI pathologist. The fact that not all flat LGD patients develop advanced neoplasia stresses the importance of identifying other factors that reliably identify patients at an increased risk of CRC.

CONCLUSION

In conclusion, this study indicates that patients with different types of IBD developing confirmed diagnosis of flat LGD or IND, there is no significant correlation between the subtype of IBD and the development of flat dysplasia. IND develops following lesser duration of IBD than LGD. Multifocality is more commonly seen in cases of LGD than in cases of IND. IND develops more commonly in rectum and LGD in non-rectal location. Extensive colitis patients develops LGD more frequently rather than IND.

LIMITATIONS

Although histopathological review by GI pathologists increases the detection rate of dysplasia, its use in daily practice might be hampered by logistics and costs and time constraints. Unfortunately, we were not able to identify other clinical parameters reliably predicting the development of advanced neoplasia in these patients. Evaluation of the use of potentially interesting biomarkers, such as p53, might provide valuable additional tools in this respect.

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