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Non-Conventional Dysplasia is Frequently Associated with Low-Grade Tubuloglandular and Mucinous Adenocarcinomas in Inflammatory Bowel Disease

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ABSTRACT

Aims: There is limited information regarding the clinicopathologic features of low-grade tubuloglandular (LGTGA) and mucinous (MAC) adenocarcinomas occurring in inflammatory bowel disease (IBD), especially in regards to their precursor lesions.

Methods and Results: Forty-six IBD colectomy specimens with LGTGA (n = 17) or MAC (n = 29) with adjacent precursor lesions were analyzed. As controls, 12 IBD colectomy specimens with well- to moderately-differentiated adenocarcinoma that lacked any mucinous, signet ring cell, low-grade tubuloglandular, or serrated features were also analyzed. Compared with MACs and controls, LGTGAs more often had a flat/invisible macroscopic appearance (LGTGAs: 88%, MACs: 34%, controls: 25%, $p < 0.001$). MACs were more likely to have high-grade differentiation (MACs: 31%, LGTGAs: 0%, controls: 0%, $p = 0.002$) and a higher pathologic stage (pT3 and pT4 MACs: 76%, LGTGAs: 35%, controls: 33%, $p = 0.007$) than LGTGAs and controls. LGTGAs (70%) and MACs (53%) were more frequently associated with non-conventional dysplasia than controls (0%) ($p < 0.001$). Crypt cell (40%) and hypermucinous (34%) dysplasias were the most common non-conventional subtypes associated with LGTGAs and MACs, respectively. Synchronous dysplasia often demonstrated non-conventional features in the LGTGA (33%) and MAC (47%) groups (vs. 0% for the control group, $p = 0.074$). Synchronous cancer frequently showed similar histologic features as the main tumor (LGTGA group: 60%, MAC group: 38%, control group: 100%).

Conclusions: Crypt cell and hypermucinous dysplasias are the most common precursor lesions associated with LGTGAs and MACs, respectively, and may serve as a marker of increased risk for these cancer subtypes.

Keywords – Colorectal cancer; dysplasia; inflammatory bowel disease; low-grade tubuloglandular adenocarcinoma; mucinous adenocarcinoma; non-conventional

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INTRODUCTION

Patients with inflammatory bowel disease (IBD) are at increased risk of developing dysplasia and/or colorectal cancer (CRC). [1, 2] Mucinous adenocarcinoma (MAC), which is defined as CRC with large pools of extracellular mucin representing > 50% of the tumor [3], occurs in a relatively high proportion of IBD patients (17-37%). [4-6] Levi *et al*. also described a unique subtype of IBD-associated CRC as low-grade tubuloglandular adenocarcinoma (LGTGA), a very well-differentiated adenocarcinoma with little to no desmoplasia. [7] LGTGAs account for ~11% of IBD-associated CRCs, with a significant proportion (57%) demonstrating mixed LGTGA and conventional adenocarcinoma morphology. Despite these distinct features, there is limited information regarding the clinicopathologic features of LGTGAs and MACs occurring in IBD, especially concerning their precursor lesions.

In this regard, our group and others recently characterized seven different types of non-conventional dysplasia that are morphologically distinct from conventional dysplasia. [8-19] They include (1) crypt cell dysplasia; (2) hypermucinous dysplasia; (3) goblet cell deficient dysplasia; (4) dysplasia with increased Paneth cell differentiation (DPD); (5) sessile serrated lesion (SSL)-like dysplasia; (6) traditional serrated adenoma (TSA)-like dysplasia; and (7) serrated dysplasia, not otherwise specified (NOS). These lesions are frequently found in the same colonic segment as conventional dysplasia, and often adjacent to a CRC. [8] In particular, crypt cell, hypermucinous, and goblet cell deficient dysplasias appear to represent high-risk subtypes for advanced neoplasia (high-grade dysplasia [HGD] or CRC), as they are more likely than conventional dysplasia to show molecular alterations characteristics of advanced neoplasia (e.g.,

aneuploidy and *KRAS* mutations) and to be associated with advanced neoplasia (40-93%) on follow-up, and the majority of them (42-100%) occur as flat/invisible lesions. [9-12, 15, 16, 20] Primary sclerosing cholangitis (PSC) is also commonly diagnosed in these patients, especially those with crypt cell dysplasia (13-40%). [9-12] Interestingly, in some of these earlier studies, we noted that crypt cell and hypermucinous dysplasias, which share some morphologic similarity with LGTGA and MAC, respectively, were often associated with these CRC subtypes, raising the possibility that they may represent the predominant precursor lesions for LGTGAs and MACs, respectively. [9-11] Therefore, this study aimed to further characterize LGTGAs and MACs, especially their precursor lesions, by analyzing IBD colectomy specimens with LGTGA or MAC.

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MATERIALS AND METHODS

Data Collection – A total of 46 IBD colectomy specimens with LGTGA (n = 17) or MAC (n = 29) with adjacent precursor lesions were collected by searching the pathology database at 8 different institutions using the term "tubuloglandular" or "mucinous adenocarcinoma" diagnosed in IBD patients between 2000 and 2022. The searches revealed 347 CRCs, of which 17 (5%) were diagnosed as LGTGA and 29 (8%) as MAC in the colectomy specimens. LGTGA was defined as a very well-differentiated adenocarcinoma characterized by relatively uniform, small- to medium-sized glands with round or tubular profiles, low-grade nuclear features, and limited or absent desmoplasia (Figures 1 and 2).[7] In heterogeneous tumors, the LGTGA component had to represent at least 50% of the tumor to be included in the study. MAC was defined as CRC having abundant extracellular mucin pools comprising at least 50% of the tumor (Figures 3 and 4).[3] A control group of 12 IBD colectomy cases with well- to moderately-differentiated adenocarcinoma that lacked any mucinous, signet ring cell, low-grade tubuloglandular, or serrated features while retaining some goblet cells were also analyzed. The control cases were selected by reviewing all IBD-associated CRCs identified between 2000 and 2022 at the University of California San Francisco (UCSF). The histologic subtype of dysplasia was recorded as either conventional or non-conventional dysplasia based on criteria described in our previous publications.[8-14, 17-19] If dysplasia showed features of one or more non-conventional subtypes (individual or combined components not exceeding 50% of the lesion) as well as conventional dysplasia, it was classified as a mixed type. The participating gastrointestinal (GI)

pathologists reviewed their own cases but submitted representative images to one GI pathologist (WTC) for central review.

For each case, pertinent clinicopathologic features were collected by reviewing electronic medical records, pathology reports, and glass slides. Dysplasia was defined as occurring adjacent to a CRC if it was detected on the same glass slide as the cancer. In all other instances, it was classified as synchronous dysplasia. Both CRC and dysplasia were categorized as flat/invisible only when there was no discrete lesion in the colectomy specimens. All lesions were found in segments of colon with histologic evidence of chronic and/or active colitis. The Institutional Review Board for human subjects research at UCSF approved the study (IRB # 16-21034).

Statistical Analysis – Categorical variables were described in terms of total number and percentage, while continuous variables were summarized with mean and range. Statistical analysis was carried out using the Pearson's chi-square or Fisher exact tests, as appropriate. For each analysis, a p value < 0.05 was considered to be statistically significant.

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RESULTS

Characteristics of IBD Patients with LGTGA or MAC – The demographic and clinical features of our cohort is summarized in Table 1. The study group with LGTGA or MAC included 46 patients, including 17 with LGTGA and 29 with MAC. There were 29 (63%) men and 17 (37%) women with a mean age of 53 years (range: 28-84). At the time of colectomy, most patients had longstanding IBD (mean duration: 18 years, range: 2-48) and pancolitis (n = 36; 78%). Thirty-one (67%) patients had ulcerative colitis (UC), 13 (28%) had Crohn's disease (CD), and 2 (4%) had indeterminate colitis. Eight (17%) patients had PSC. The study group did not significantly differ from the control group with respect to age, gender, ethnicity, IBD phenotype (subtype, duration, and extent), presence of PSC, and outcomes ($p > 0.05$). Seven (12%) patients, including 2 (12%) LGTGA, 4 (14%) MAC, and 1 (8%) control patients, died of the disease within a mean follow-up time of 65 months (range: 1-211).

Characteristics of LGTGAs and MACs – The clinicopathologic features of LGTGAs and MACs are detailed in Table 2. LGTGAs (88%) more often had a flat/invisible macroscopic appearance than MACs (34%) and controls (25%) ($p < 0.001$). Of the 17 LGTGA cases, 12 (71%) patients underwent a colectomy because of a new diagnosis of dysplasia or CRC on random biopsies (n = 5; 29%) or targeted biopsies of subtle flat mucosal abnormalities without discrete lesions (e.g., "erythema," "edema," or "granularity") (n = 7; 41%). Two (12%) patients had a polypoid lesion or mass diagnosed as dysplasia or CRC prior to colectomy. The remaining

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3 (18%) patients had medically refractory disease. In the colectomy specimens, 14 (82%) LGTGAs were identified by targeted sampling of subtle flat mucosal abnormalities (n = 12; 71%) or polypoid lesion/mass (n = 2; 12%). LGTGA was detected in 3 (18%) patients by random sampling. Compared with LGTGAs and controls, MACs were more likely to have high-grade differentiation (MACs: 31%, LGTGAs: 0%, controls: 0%, p = 0.002) and a higher pathologic stage (pT3 and pT4 MACs: 76%, LGTGAs: 35%, controls: 33%, p = 0.007). MACs (mean: 4.6 cm) were also significantly larger than LGTGAs (mean: 1.7 cm) and controls (mean: 2.5 cm) (p < 0.001). Although there was a trend toward increased frequency of lymphovascular invasion, perineural invasion, lymph node metastasis, and/or distant metastasis in the LGTGA and MAC groups compared with the control group, no statistically significant difference was noted (p > 0.05). All three subtypes of CRC showed a predilection for the left colon (48-67%). Synchronous CRC (defined as additional, smaller CRC(s) diagnosed in the same colectomy specimen) was not uncommon in these patients (LGTGA group: 29%, MAC group: 21%, control group: 25%, p = 0.798) and often demonstrated similar histologic features as the main tumor (LGTGA group: 60%; MAC group: 38%; control group: 100%).

Characteristics of Dysplasia Associated with LGTGAs or MACs – Fifty-two dysplastic lesions, including 20 from 17 LGTGA patients and 32 from 29 MAC patients, were detected adjacent to the main CRCs (Table 3). They were predominantly found in the left colon (44-67%). Notably, non-conventional dysplasia was more frequently associated with LGTGAs (70%) and MACs (53%) than controls (0%) (p < 0.001). Crypt cell dysplasia (40%) was the most common non-conventional subtype associated with LGTGAs (p = 0.001), followed by goblet cell deficient dysplasia (15%), hypermucinous dysplasia (10%), and TSA-like dysplasia (5%) (Figures 1 and 2). By contrast, hypermucinous dysplasia (34%) was the most common

non-conventional subtype associated with MACs ($p = 0.048$), followed by goblet cell deficient dysplasia (6%) (Figure 3). LGTGA-associated dysplastic lesions (40%) more often demonstrated a flat architectural profile than those of MACs (3%) and controls (0%) ($p < 0.001$). The rate of HGD was significantly lower in the LGTGA (65%) and MAC (50%) groups than in the control group (92%) ($p = 0.021$).

Synchronous dysplasia (defined as developing away from a CRC) was common, including 9 lesions in 7 (41%) LGTGA patients, 15 lesions in 10 (34%) MAC patients, and 6 lesions in 5 (42%) control patients ($p = 0.863$). The LGTGA group (89%) was more likely to have macroscopically flat/invisible synchronous dysplasia than the MAC (53%) and control (33%) groups ($p = 0.034$). Although synchronous dysplasia more often demonstrated conventional features (53-100%), non-conventional subtypes were also found in the LGTGA (33%) and MAC (47%) groups. Most synchronous dysplastic lesions were low-grade (83-89%) with either tubular or tubulovillous architecture (93-100%). Although synchronous dysplasia found in the LGTGA (56%) and MAC (60%) groups showed a predilection for the left colon, it was more evenly distributed in the control group (33% each for the right, transverse, and left colon) ($p = 0.535$). There was no significant difference in the size of synchronous dysplasia among the three groups ($p = 0.596$).

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DISCUSSION

LGTGA is a morphologic subtype unique to CRCs arising in IBD, but there is limited information regarding its precursor lesions. In this regard, we note that non-conventional dysplasia (70%) was more commonly detected adjacent to LGTGAs than conventional dysplasia (15%) ($p < 0.001$), with crypt cell dysplasia (40%) being the most common subtype (Table 3). Interestingly, Levi *et al*. reported that LGTGAs often showed striking similarities to the overlying low-grade or "indefinite" dysplastic crypts, and that one case arose directly from crypts that failed to reach the histologic threshold for low-grade dysplasia (likely describing crypt cell dysplasia), presumably due to the lack of surface involvement. [7] Despite having mild nuclear atypia, there is increasing evidence that crypt cell dysplasia may be a high-risk marker for advanced neoplasia. [9-12] In support of this, we previously demonstrated that all 14 crypt cell dysplastic lesions from 7 IBD patients had a flat/invisible endoscopic appearance and demonstrated aneuploidy, and that 6 (86%) patients subsequently developed advanced neoplasia. [9, 10] These results were further corroborated by our multi-institutional study demonstrating that 43 (96%) of 45 crypt cell dysplastic lesions were endoscopically invisible (n = 40) or flat (n = 3), and that 26 (72%) of 36 low-grade lesions with follow-up data were associated with subsequent detection of HGD (n = 21; 58%) or CRC (n = 5; 14%). [11] Notably, in that study, 2 (40%) of the 5 CRCs were LGTGAs [11], consistent with the current finding that crypt cell dysplasia is the predominant precursor lesion for LGTGAs. In addition, we recently reported that crypt cell dysplasia is the most common non-conventional subtype found in IBD patients with PSC,

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accounting for 30% of all dysplastic lesions (vs. 4% in those with IBD alone, $p < 0.001$). [12] This is also in agreement with our current result that nearly a third (29%) of LGTGA patients had a history of PSC (Table 1).

In addition to characterizing the precursor lesions of LGTGAs, our study contributes additional 17 cases to the published literature on the clinicopathologic features of LGTGAs. Similar to the prior results [7], LGTGA patients were relatively young (mean: 52 years) and had long-standing, extensive UC (mean duration: 19 years) (Table 1). The majority of LGTGAs were macroscopically flat/invisible (88%) and showed a predilection for the left colon (53%) (Table 2). LGTGAs were of diverse stages ranging from pT1 to pT3, but the lack of serosal invasion (pT4) is likely due to the fact that we included only LGTGAs with at least 50% of the tumor demonstrating LGTGA. Indeed, Levi *et al.* reported that LGTGAs with well-defined superficial regions of LGTGA progressing to conventional adenocarcinoma in deeper regions were significantly more advanced than LGTGAs that maintained low-grade histology throughout. [7]

Similar to LGTGAs, there was a strong association between MAC and non-conventional dysplasia (53% vs. 28% for conventional dysplasia, $p < 0.001$) (Table 3). However, hypermucinous dysplasia (34%) was the predominant precursor lesion detected adjacent to MACs (Figures 3B and 3C). This is consistent with the previous results suggesting that hypermucinous dysplasia may be another high-risk marker for advanced neoplasia. In support of this, Andersen *et al.* demonstrated that hypermucinous dysplasia, even without cytologic atypia, is associated with a higher rate of *KRAS* mutations (61%) than conventional LGD (4%, $p < 0.001$) or HGD (29%, $p > 0.05$). [15] Similarly, we reported a higher rate of aneuploidy in low-grade hypermucinous dysplasia (80%) than in low-grade conventional dysplasia (8%) or

sporadic adenomas (9%) ($p < 0.001$). [10] In a multi-institutional study, we also demonstrated that 19 (49%) of 39 low-grade hypermucinous dysplastic lesions with follow-up data were correlated with subsequent detection of HGD (n = 9; 23%) or CRC (n = 10; 26%). [11] Notably, in that study, 5 (50%) of the 10 CRCs were MACs [11], consistent with the current finding that hypermucinous dysplasia is the predominant precursor lesion for MACs.

A possible higher malignant potential of hypermucinous dysplasia is further supported by our current result that MACs were more likely to have high-grade differentiation and a higher pathologic stage compared with LGTGAs and controls (Table 2). In fact, MACs (mean: 4.6 cm) were substantially larger than LGTGAs (mean: 1.7 cm) and controls (mean: 2.5 cm) ($p < 0.001$). It is noteworthy that 38% of MACs were found in the right colon, which could be related to a higher percentage of CD patients (38%) included in the MAC cohort (Table 1). In support of this, some prior studies suggested a predominance of CRCs in the right colon in CD patients [21, 22], which demonstrated a higher rate of mucinous histology compared with UC-associated CRCs (35% vs. 13%, respectively, $p = 0.040$). [4] Nonetheless, MACs shared some similarities with LGTGAs. For instance, MACs affected relatively young patients (mean: 53 years) with a long duration of extensive IBD (mean: 18 years) (Table 1).

In conclusion, LGTGA and MAC have distinct clinicopathologic features. Although not uncommonly associated with conventional dysplasia or another non-conventional subtype, crypt cell and hypermucinous dysplasias were the most common precursor lesions associated with LGTGAs and MACs, respectively. This further supports that crypt cell and hypermucinous dysplasias may be high-risk markers for advanced neoplasia and could potentially serve as a marker of increased risk for LGTGA and MAC, respectively. Therefore, it is important for pathologists to recognize these non-conventional subtypes, and to recommend their complete

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removal and/or a careful follow-up to ensure that there is no unsampled advanced neoplasia in these patients.

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FIGURE LEGENDS

Figure 1. Low-grade tubuloglandular adenocarcinoma (LGTGA) with its associated dysplastic lesion. (**A, B**) A very well-differentiated LGTGA with circular and tubular profiles infiltrates into the submucosa. There is little to no desmoplasia. (**C, D**) Adjacent crypt cell dysplasia shows slightly elongated nuclei with mild nuclear enlargement, crowding, and hyperchromasia limited to the crypt base without surface involvement. High-power view (**D**) demonstrates increased mitoses. There is no significant architectural atypia or active inflammation.

Figure 2. Other non-conventional dysplastic subtypes associated with low-grade tubuloglandular adenocarcinoma (LGTGA). (**A, B**) A well-differentiated LGTGA (**A**) is associated with goblet cell deficient dysplasia characterized by a complete or near-complete absence of goblet cells, leading to intensely eosinophilic cytoplasm (**B**). (**C, D**) Another case of LGTGA invades into the submucosa (**C**) and is associated with hypermucinous dysplasia characterized by tall, prominent mucinous cells (**D**).

Figure 3. Mucinous adenocarcinoma (MAC) with its associated dysplastic lesions. (**A**) MAC with abundant extracellular mucin pools invades into the muscularis propria. (**B, C**) The overlying and adjacent mucosa shows hypermucinous dysplasia with tall, prominent mucinous cells. (**D**) Goblet cell deficient dysplasia is also identified adjacent to this tumor.

Figure 4. Other non-conventional dysplastic subtypes associated with mucinous adenocarcinoma (MAC). (**A**) Dysplasia with increased Paneth cell differentiation (DPD) is detected adjacent to a MAC (inset). DPD is morphologically similar to conventional dysplasia or sporadic adenomas but is defined by increased Paneth cell differentiation involving at least two contiguous dysplastic crypts in two different foci. (**B-D**) Another case of MAC (**B**) is associated with traditional serrated adenoma (TSA)-like dysplasia characterized by ectopic crypts and columnar cells with mild cytologic atypia and eosinophilic cytoplasm (**C**) as well as serrated dysplasia, not otherwise specified that lacks features of either sessile serrated lesion-like dysplasia or TSA-like dysplasia (**D**).

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