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Evaluation of dysplasias associated with inflammatory bowel disease

PhD Thesis

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LIST OF PAPERS THAT SERVED AS THE BASIS OF THE PHD THESIS

I. Szintia Almási*****, **Zsófia Balajthy***, Bence Baráth, Zsófia Krisztina Török, Panna Szaszák, Tamás Lantos, Bence Kővári, Anita Sejben: Examination of non-conventional dysplasias adjacent to colorectal adenocarcinoma in patients with IBD. Pathol Oncol Res. 2025; 3:30:1611978. doi: 10.3389/pore.2024.1611978

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III. **Zsófia Balajthy**, Szintia Almási, Tamás Lantos, Levente Kuthi, Georgios Deftereos, Won-Tak Choi, Anita Sejben: Whole-exome sequencing analysis of inflammatory bowel disease-associated serrated dysplasia. Pathol Oncol Res. 2025; 26:5704. doi: 10.3390/ijms26125704

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OTHER PUBLICATIONS

IV. Roland Fejes, Kitti Szonja Gyorgyev, Csaba Góg, László Krenács, Tamás Zombori, Zsófia Eszter Széll, **Zsófia Balajthy**, Tamás Pancsa and Zsolt Simonka: World J Surg Oncol. 2024; 22:299. doi: 10.1186/s12957-024-03563-7

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V. Roland Fejes*****, **Zsófia Balajthy***, Csaba Góg, Ágota Vajda, Fanni Hegedűs, Zsolt Simonka, Szabolcs Ábrahám: Colonic endometriosis: from subtotal bowel obstruction to malignant transformation - a case series and literature review. World J Surg Oncol. 2025; 23:230. doi: 10.1186/s12957-025-03888-x

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1. INTRODUCTION

Inflammatory bowel disease (IBD) incorporates ulcerative colitis (UC), Crohn's disease (CD), and indeterminate colitis. Due to the cumulative inflammatory burden, IBD predisposes patients to develop dysplasias earlier with a twofold increase than in the non-IBD population. However, effective anti-inflammatory treatment, surveillance colonoscopies, and advances in endoscopic resection have led to a decreasing risk of dysplasia or colorectal carcinoma (CRC) in the last few decades. Besides conventional dysplasia and CRC, IBD patients may also develop non-conventional dysplasia (NCD), that have been recently introduced, including hypermucinous and goblet cell-deficient (GCD), dysplasia with increased Paneth cell differentiation (DPD), crypt cell dysplasia (CCD), traditional serrated adenoma (TSA)-like, sessile serrated lesion (SSL)-like, and serrated dysplasia, not otherwise specified (NOS). Even though NCDs histologically usually reflect low-grade morphology, they have been associated with poorer prognosis; furthermore, some subtypes have been associated with flat or even invisible endoscopic morphology, necessitating more extensive sampling. These lesions have been observed more commonly at the same site as CRCs; therefore, they may represent potential precursor lesions. Based on our current knowledge, NCD may be present in approximately one-fourth to half of patients with IBD-associated colorectal adenocarcinomas. Given the limited information about these lesions, their clinical and histological identification remains difficult.

2. AIMS

1. To re-evaluate a cohort of IBD-associated adenocarcinoma cases, retrospectively identify associated NCDs and validate recent North American findings in a Central-Eastern European population.

2. To identify of IBD-associated NCDs within a consecutive single-center study, as well as to evaluate clinicopathological parameters influencing the prognosis of NCDs.

3. To further characterize serrated lesions and investigate their molecular features via whole-exome sequencing (WES).

3. MATERIALS AND METHODS

3.1. Ethical approval

Our investigations were approved by the Medical Research Council (BM/28834-1/2024) and the Regional and Institutional Human Biomedical Research Ethics Committee of the Szent-Györgyi Clinical Centre of the University of Szeged (4988 and 5670).

3.2. Examination of NCDs adjacent to colorectal adenocarcinoma in patients with IBD

A series of 28 randomly chosen cases of known IBD-associated colorectal adenocarcinomas, diagnosed between 2010 and 2022, at the Department of Pathology, University of Szeged was included. In all cases, the patient's gender, age both at the diagnosis of IBD and neoplasia, type and localisation of IBD, type of specimen, as well as the histological type, grade, localisation, and stage of cancer were obtained retrospectively. Furthermore, all the patients' prior gastrointestinal histology reports have been reviewed, and the mean histologic activity of IBD in a 5-year interval before the neoplastic sample was registered. The patients' index cases yielding the adenocarcinoma diagnosis were independently re-evaluated by 2 gastrointestinal pathologists, focusing on identifying conventional dysplasias and NCDs as candidate precursor lesions adjacent to the adenocarcinoma. If present, NCD was subclassified following current morphologic criteria.

3.3. Evaluation of dysplasias associated with IBD – a single-center, retrospective, 5-year experience

All IBD patients diagnosed at the Department of Pathology, University of Szeged, between 2011 and 2015 were identified based on ICD codes, and neoplastic samples from these patients were subsequently reviewed retrospectively. During database construction, clinicopathological characteristics including the age, sex, type, duration, and localization of IBD were collected. In cases of invasive tumors, additional data, including histological type, date of tumor diagnosis, grade, macroscopic morphology, localization, TNM stage, and the presence of vascular or lymphatic invasion. A diagnosis of NCD was established only when the observed lesion was present in at least 50% of the sample. If multiple types of NCDs were observed within a single slide, a dominant pattern was selected based on the extent and size of the lesions.

3.4. WES analysis of IBD-associated serrated dysplasia

We retrospectively reviewed data from 2396 patients treated for UC (n = 1400), CD (n = 970), and indeterminate colitis (n = 26) at the Department of Pathology, University of Szeged between 2011 and 2023. All serrated dysplastic lesions were re-evaluated and subtyped by 2 gastrointestinal pathologists based on the published morphologic criteria. For each patient, relevant clinicopathologic information was also collected from medical charts and pathology reports. This included age, gender, IBD characteristics (such as subtype, extent, and duration), presence of primary sclerosing cholangitis (PSC), and features of dysplasia. Additionally, data on any concurrent or subsequent dysplasia and CRC were collected. Where archival tissue blocks were available, WES was performed. After sectioning and deparaffinization, DNA was extracted using proteinase K digestion and magnetic bead purification. DNA quantity was measured with the Quant-iT dsDNA HS assay. Library preparation was carried out using the Twist Library Preparation EF Kit and Exome 2.0 Panel (Twist Bioscience), following the manufacturer's instructions, and library quality and fragment size distribution were verified by capillary electrophoresis. Sequencing was performed on the Illumina NovaSeq 6000 platform. Variants were annotated with the OncoKB and ClinVar databases and were manually reviewed for read quality. Only pathogenic or likely pathogenic variants, as well as frameshift, nonsense, splice-site, or transcription start site–altering variants in cancer-associated genes, were retained for interpretation.

3.5. Statictical analysis

Statistical analyses were carried out by the R statistical software (v4.1.1). The Mann Whitney test was used to compare two groups of independent samples (from non-normally distributed data). The association between categorical variables was examined by Fisher's exact test (with Bonferroni-Holm correction) and chi-square test. All statistical tests were two sided, and p-values of less than 0.05 were considered statistically significant.

4. RESULTS

4.1. Examination of NCDs adjacent to colorectal adenocarcinoma in patients with IBD

The mean age at carcinoma diagnosis was 47 years in the exclusively conventional and 50 years in the NCD group. The male-to-female ratio was 22:6, 10:1, and 6:2 in the IBD-associated adenocarcinoma, the exclusively conventional and NCD groups, respectively. In all groups, the majority of patients suffered from UC. The mean duration of IBD was 16 years. Previous histological samples and reports were not available in 8 cases. Active disease was defined in 12 patients with UC, and 5 CD patients. In the exclusively conventional dysplasia group (n = 11), UC was present in 8 patients, whereas in the exclusively NCD group (n = 8) it occurred in 7 patients. In the mixed-dysplasia group (n = 9), UC was identified in 5 patients. In UC, adenocarcinomas arose within previously inflamed colonic segments, occurring in the left colon in 55% and the right colon in 45% of cases. By contrast, patients with CD showed predominantly left-sided tumors (87.5%), with only a single right-sided case (12.5%).

Adjacent to the previously reported adenocarcinomas, exclusively conventional dysplasia was detected in 11, while exclusively NCD in 8 patients. Dysplasia comprised of a combination of conventional and at least one subtype of NCD was observed in 9 patients. Altogether, 25 NCD foci were identified, including hypermucinous (n = 9) (Figure 1A), GCD (n=6) (Figure 1B), serrated dysplasia, NOS (n=6) (Figure 1C), and TSA-like dysplasia (n = 4) (Figure 1D) subtypes.

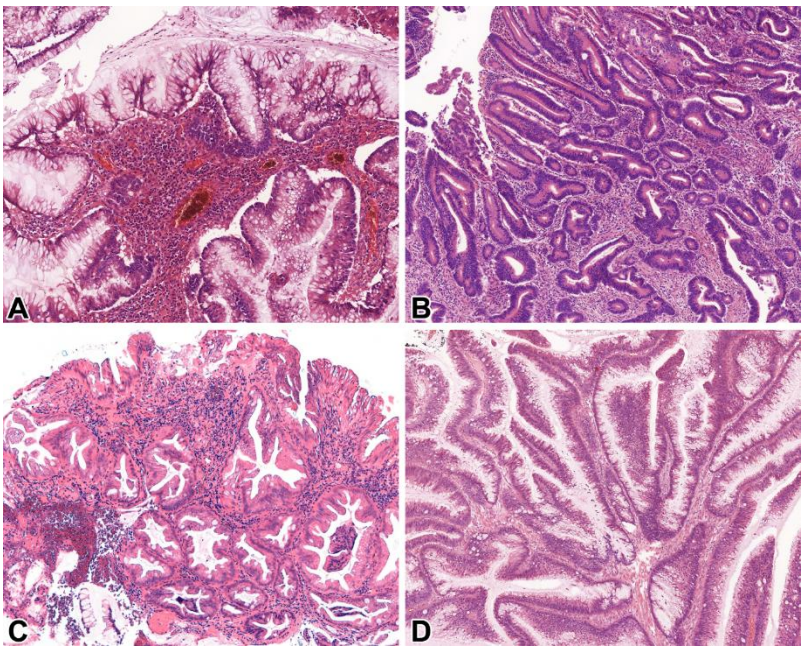

Figure 1 Microscopic features of IBD-associated NCDs of the examined population. (A): Hypermucinous dysplasia (10x, HE), (B): GCD (10x, HE), (C): Serrated dysplasia, NOS (10x, HE), (D): TSA-like dysplasia (20x, HE).

The cooccurrence of multiple NCD subtypes within the same case was common (n = 9/17; 53% of all cases with NCD) in resection specimens. The following combinations were observed: hypermucinous and serrated dysplasia, NOS (n = 4), hypermucinous and GCD (n = 2), hypermucinous, GCD, and TSA-like (n = 1), GCD and serrated dysplasia, NOS (n = 1), GCD and TSA-like (n = 1). Half of the 8 cases with only biopsy samples available showed exclusively conventional, while the other half demonstrated exclusively NCD. None of the included cases in our cohort had a concurrent or prior histologically proven endoscopically non-visible dysplasia in other bowel segments. Regarding the IBD-associated adenocarcinomas, they were histologically characterised as conventional (n = 8) and medullary (n = 3) in the exclusively conventional, and conventional (n = 4) and mucinous (n = 4) in the exclusively NCD cases. All mixed cases were associated with conventional adenocarcinomas (n = 9). A significant association was found between NCD and adenocarcinoma subtypes ($p = 0.014$), and the proportion of NCD was significantly different within mucinous and medullary subtypes ($p = 0.041$). Most examined adenocarcinomas were low-grade (grade 2) in all groups (64% in the exclusively conventional dysplasia, 63% in the exclusively NCD, and 56% in the mixed group). Regarding stage, most cases were diagnosed as pT3 in the exclusively conventional dysplasia (n = 7) and the mixed group (n = 7), while the adenocarcinomas with exclusively NCD proved to be mostly T4 (n = 4). Right colon localisation was observed in 5 adenocarcinomas associated with conventional and 5 adenocarcinomas associated with NCD, while the left colon was affected in 6 cases with adjacent conventional and 3 cases with adjacent NCD. In the cases associated with mixed dysplasia, left colon localisation was observed in 5, and right colon localisation was seen in 4 patients. No significant association was found between NCD and the grade ($p = 0.093$), stage ($p= 0.131$), and localisation ($p = 0.253$) of associated adenocarcinomas.

4.2. Evaluation of dysplasias associated with IBD – a single-center, retrospective, 5-year experience

In our examined 5-year period, a total of 921 IBD patients were included, and 57 possessed dysplasia or carcinoma samples. The mean age of the patients was 63.7 years (median: 65; range: 33–94). A male predominance was observed (n = 34; 59.6%), and most patients were treated for UC (n = 41; 71.9%). In half of the cases, IBD affected the left colon (n = 29; 50.9%), while pancolitis was reported in 17 cases (29.8%). The average duration of IBD prior to the diagnosis of neoplasia was 15 years (median: 14, range: 1–37).

Altogether 47 patients were identified with conventional dysplasias. The average age of patients was 65.2 years (median: 66, range: 33–94), and male predominance was observed with a male-to-female ratio proved to be 31:16. Patients were mostly diagnosed with UC (n = 33; 70.2%), with left colon localization (n = 22; 46.8%), followed by pancolitis (n = 15; 31.9%). The average IBD duration until dysplasia diagnosis was 14.8 years (median: 14; range: 1–37). The dysplastic lesions were mainly identified in the left colon (n = 31; 65.9%). The average microscopic size of dysplasia was 0.66 cm (median: 0.5; range: 0.2–2.5), with mostly polypoid endoscopic morphology (n = 34; 72.3%). The dominant histological pattern proved to be tubular adenoma in the majority of cases (n = 38; 80.8%), and tubulovillous adenoma was solely found in 9 cases (19.1%). Villous adenoma was not identified. Forty cases (85.1%) were defined as low-grade. . A significant association was found between conventional dysplasias and dysplasia localization ($p = 0.004$), size ($p = 0.012$), endoscopic appearance ($p = 0.006$), grade ($p = 0.011$), macroscopic appearance of colorectal carcinoma ($p = 0.009$), and pT stage ($p = 0.01$).

Of the 47 patients with conventional dysplasia, 12 patients (25.5%) were diagnosed with colorectal adenocarcinoma during follow-up, that were mainly localized to the left colon (n = 8; 66.7%), with average size of 4 cm (median: 3.75; range: 1–8.4), and infiltrative morphology (n = 7; 58.3%). The majority were identified as low-grade (n = 10; 83.3%). In half of the cases (n = 6), multiple CRCs developed. Histologically, 7 cases (58.3%) were characterized as conventional adenocarcinoma, followed by mucinous (n = 3; 25%), signet ring cell (n = 1; 8.3%), and GCD (n = 1; 8.3%) patterns. Altogether 8 cases (66.7%) were found in T3 or T4 stage. Lymphovascular invasion and distant metastases were both identified in 3-3 cases (25%), respectively. Microsatellite instability was identified in a single case (n = 1; 8.3%).

Among the 57 IBD patients with neoplastic samples, NCD was observed in 20 cases (35.1%). The mean age of these patients was 64.8 years (median: 66, range: 46–83), with a male-to-female ratio of 12:8. Most patients with NCD were diagnosed with UC (n = 14; 70%), and the IBD was predominantly localized to the left colon (n = 11; 55%). The average time from IBD diagnosis to the detection of dysplasia was also 15 years (median: 15, range: 4–28). Most dysplastic lesions were localized to the left colon (n = 17; 85%), with average size of 0.59 cm (median: 0.45; range: 0.2–2.5), and mostly flat endoscopic morphology (n = 12; 60%). The predominance of them were histologically evaluated as low-grade (n = 15; 75%). Serrated dysplasia, NOS proved to be the most frequently observed subtype of NCD (n = 6; 30%), followed by hypermucinous (n = 4; 20%) GCD (n = 4; 20%) SSL-like (n = 2; 10%), and TSA-like dysplasia (n = 1; 5%). A significant association was observed between the development of NCD and co-occurrence ($p < 0.001$), localization ($p = 0.001$), size ($p = 0.002$), macroscopic

appearance ($p = 0.01$), grade ($p = 0.005$), histological subtype ($p = 0.003$), pT stage ($p = 0.003$), pM stage ($p = 0.047$) of colorectal carcinoma and microsatellite status ($p < 0.001$).

Out of the 20 patients with NCD, 60% developed colorectal adenocarcinoma during follow-up. Altogether, 75% of tumors were located in the left colon. The detected adenocarcinomas were predominantly classified as low-grade (91.7%). Histologically, 66.7% of these cancers were conventional adenocarcinomas, followed by mucinous (16.7%), GCD (8.3%), and signet ring cell carcinomas (8.3%). The median tumor size was 3.5 cm (range: 0.2 – 7.5). Macroscopic evaluation most commonly demonstrated a polypoid morphology (58.3%), followed by sessile (25%) and flat lesions (16.7%). Tumors were identified as T1 (16.7%), T2 (35%), T3 (33.3%), and T4 (25%), respectively. Nodal involvement was observed only in N1 and N2 stages (8.3% and 16.7%). Distant metastases were detected in 33.3% of patients. Immunohistochemical analysis of microsatellite status was performed in 14 cases. Microsatellite instability (MSI) was identified in 1 case (8.3%), while 7 cases (58.3%) reflected mismatch repair proficiency. In the remaining 4 cases, no immunohistochemical was performed.

4.3. WES analysis of IBD-associated serrated dysplasia

The mean age at the time of the serrated dysplasia diagnosis was 56 years (range: 35–71). Serrated dysplasia occurred predominantly in men (73%). 91% of patients were diagnosed with UC, and 9% had CD. Pancolitis was observed in 64% of patients, whereas the remaining 36% had left-sided colitis. The mean duration of IBD at the time of serrated dysplasia diagnosis was 26 years (range: 5–59). No patient had a concurrent history of PSC. Of the 13 serrated dysplastic lesions, 38% exhibited characteristics of SSL-like dysplasia, 8% showed features of TSA-like dysplasia, 46% were classified as serrated dysplasia, NOS, and 8% displayed mixed features of SSL-like and TSA-like dysplasias. 69% of lesions were found in the left colon, including SSL-like dysplasia (60%) and serrated dysplasia, NOS (83%). 85% of lesions had a polypoid endoscopic appearance, while the remaining. The mean size of the lesions was less than 1 cm, except for the serrated dysplasia, NOS (mean: 1 cm, range: 0.3–2.5). The SSL-like dysplasia predominantly showed low-grade dysplasia (4/5; 80%), whereas half of the serrated dysplasia, NOS cases (3/6; 50%) displayed high-grade dysplasia. Among the 5 patients with either SSL-like dysplasia or serrated dysplasia, NOS, 1 (20%) also presented with conventional dysplasia. However, NCD was more frequently associated with the serrated dysplasia, NOS (3/5; 60%) than with the SSL-like dysplasia (1/5; 20%). During the follow-up, 5 (45%) of the 11 patients developed CRC, including 3 patients with the serrated dysplasia, NOS, 1 with the SSL-like

dysplasia, and 1 with the TSA-like dysplasia. The median progression-free survival was 22 months (range: 1–64) in the SSL-like dysplasia group and 15.8 months (range: 1–51) in the serrated dysplasia, NOS group, and proved to be 1 month in the patient diagnosed with TSA-like dysplasia and 36 months in the mixed SSL-like/TSA-like dysplasia patient.

WES was performed on 8 serrated dysplastic lesions from 7 patients. For the remaining 5 lesions, either paraffin blocks were unavailable or the samples were unsuitable for WES. The SSL-like dysplasia in patient #5 harbored a likely pathogenic variant in *MLH1*, along with a high number of pathogenic and likely pathogenic variants, most of which were small frameshift insertions or deletions, which is suggestive of a MSI. Among these, a *KRAS* p.G12C mutation and 2 mutations in *PTEN* were identified. Consistent with the *MLH1* mutation in patient #5, the immunohistochemistry for MLH1 and PMS2 showed a loss of staining, confirming MSI. Also, the SSL-like dysplasia in patient #3 showed an inactivating variant in *POLE*; however, this lesion did not exhibit a high number of mutations, suggesting that this variant is likely a passenger mutation rather than a driver mutation. Furthermore, the SSL-like dysplasia in patient #1 demonstrated a *BRAF* p.V600E mutation, whereas a class 3 *BRA*F mutation (p.G469A) was identified in the serrated dysplasia, NOS in patient #8. Both the SSL-like dysplasia (patients #1, #3, and #5) and serrated dysplasia, NOS (patients #4 and #8) showed likely pathogenic variants in *KMT2C* or *EXT1*. However, mutations in *TP53* or *POLG* were found only in the serrated dysplasia, NOS (patients #8 and #11, respectively). In line with the *TP53* mutation in patient #8, immunohistochemistry for p53 showed overexpression. Patient #6, who had both SSL-like dysplasia and mixed SSL-like/TSA-like dysplasia, exhibited a pathogenic mutation in *MUTYH* (p.R217H), along with mutations in *MADD*. Table 1 summarizes all pathogenic and likely pathogenic mutations in our cohort.

Patient #	**Subtype**	**Pathogenic mutations**	**Likely pathogenic mutations**
1	SSL-like dysplasia	*BRAF, ATR*	*KMT2C*
3	SSL-like dysplasia	*EXT1*	*POLE, CDKN1B*
4	Serrated dysplasia, NOS	-	*KMT2C, MAX, CDC6*
5	SSL-like dysplasia	*KRAS, PTEN, TSC1*	*MLH1, DICER1, HIF1A, ASXL1, ZNF292, EXT1, ACVR2A, KMT2C, MGA, SETD1B, TGFBR2*
6 (lesion #1)	SSL-like dysplasia	*MUTYH, MADD*	*SERPINB4*
6 (lesion #2)	Mixed SSL-like/TSA-like dysplasia	*MUTYH, MADD*	-
8	Serrated dysplasia, NOS	-	*TP53, BRAF, MPL, EXT1*
11	Serrated dysplasia, NOS	*POLG*	-

Table 1 Molecular features of serrated dysplasia.

5. DISCUSSION

5.1. Examination of NCDs adjacent to colorectal adenocarcinoma in patients with IBD

The classification of IBD-associated dysplasias has changed over the past years. The most recent and comprehensive classification includes 7 NCD subtypes. Based on our current knowledge, IBD-associated NCD may harbour aneuploidy, DNA abnormalities, and *p53* mutation more frequently than conventional counterparts. Regarding their development, high inflammatory activity has been proven to be an independent risk factor. Gastric metaplasia has been suspected as a candidate precursor lesion to some hypermucinous dysplasia. Furthermore, NCD in general is more commonly associated with UC and PSC. Moreover, CCD and GCD frequently present as flat or invisible lesions endoscopically, and most endoscopically undetected lesions were categorised as non-conventional. A correlation between NCD subtypes and special histologic types of invasive adenocarcinoma was also proposed. GCD and hypermucinous subtypes have been identified as candidate precursor lesions of low-grade tubuloglandular and mucinous adenocarcinomas, respectively. The presence of NCD has been associated with more frequent and earlier recurrence of intraepithelial neoplasia, larger lesion size, and high-grade adenocarcinomas. Overall, their molecular background, possibly flat or invisible morphology, and the high probability of relapse and high-grade features of associated adenocarcinomas all suggest an overall worse prognosis compared to conventional dysplasia. In most studies, the evaluation of NCD has been mainly determined by one or two expert gastrointestinal pathologists; therefore, the reproducibility of the new classification is uncertain.

This pilot study represents the first Hungarian analysis of IBD-associated colorectal adenocarcinomas with a focus on adjacent NCD. We retrospectively identified NCD in 60% of randomly selected cases and confirmed several clinicopathologic tendencies described in North American cohorts, including the frequent association of NCD with UC and its occurrence adjacent to carcinoma. Hypermucinous dysplasia emerged as the most common subtype in our cohort, while CCD and DPD were not observed, which may reflect population-specific patterns or the limited sample size. Although the distribution of several clinicopathological parameters aligned with international data, others could not be validated, likely due to the small cohort size and pilot design. Notably, mucinous adenocarcinomas occurred exclusively in association with NCD, supporting a possible inflammation–hypermucinous dysplasia–mucinous carcinoma sequence proposed in recent literature.

A key limitation of this study is its retrospective nature and non-consecutive case selection, which may have led to underrepresentation of flat or endoscopically non-visible lesions. Moreover, clinical management data were not available for correlation with histological

findings. Nonetheless, our results reinforce that NCD is a relevant and potentially under-recognized dysplasia subtype in IBD-associated neoplasia. Greater awareness among pathologists, along with individualized surveillance strategies and targeted biopsy protocols, may improve detection and risk assessment moving forward.

5.2. Evaluation of dysplasias associated with IBD – a single-center, retrospective, 5-year experience

NCDs are increasingly regarded as markers of poorer prognosis, given their association with aneuploidy, high-grade dysplasia, and high-risk carcinomas. Their frequent flat morphology further complicates endoscopic detection, making clinical and histological recognition challenging. In our cohort, both conventional dysplasia and NCD were commonly linked to left-sided UC, and each was associated with progression to CRC. Notably, NCDs often corresponded to advanced-stage tumors despite subtle endoscopic appearance, supporting the concept that these lesions represent heterogeneous pathways of neoplastic progression distinct from the classical inflammation–dysplasia–carcinoma sequence.

These observations underline the need for heightened diagnostic awareness and more targeted surveillance when NCD is identified. Differences in subtype distribution compared to other populations may reflect biological variation or previous under-recognition. Importantly, NCDs in our cohort were predominantly associated with microsatellite stable CRCs and more advanced stages, emphasizing their clinical relevance. As conventional dysplasia has been extensively studied for decades, the comparatively recent recognition of NCDs explains the limited data and diagnostic uncertainty. Our study represents the first systematic evaluation of these lesions in a Central European population. Given their diagnostic complexity and prognostic implications, NCDs warrant careful histopathological assessment, complete lesion removal when feasible, and closer endoscopic follow-up.

5.3. WES analysis of IBD-associated serrated dysplasia

The clinicopathologic characteristics of SSL-like dysplasia in IBD appear to differ from those of sporadic SSLs, suggesting that these lesions may represent a distinct IBD-associated pathway. In our cohort, SSL-like dysplasia tended to occur in younger patients and more often in the left colon, which contrasts with the right-sided and female-predominant distribution described in sporadic cases. Beyond the expected *BRAF* mutations, additional alterations, including *POLE*, *KMT2C*, and *EXT1*, were identified. The presence of *POLE* mutations is

particularly noteworthy, as these are rare in CRC and typically associated with unique molecular signatures and younger age at onset, raising the possibility that a subset of SSL-like dysplasias may act as precursors to *POLE*-mutant carcinomas. This supports the concept that SSL-like dysplasia in IBD does not simply mimic the sporadic serrated pathway but may follow alternative, inflammation-related routes of tumorigenesis. In contrast, serrated dysplasia, NOS demonstrated more aggressive biological behavior. This subtype was more frequently associated with high-grade dysplasia and occurred more often alongside NCD, a group already known to have higher malignant potential. Molecular alterations frequently involved *TP53*, and in some cases co-occurred with *BRAF* mutations in microsatellite-stable backgrounds - a profile linked to particularly aggressive CRC behavior. Although the role of *POLG* mutations remains uncertain, prior experimental findings suggest that inflammatory microenvironments may influence mitochondrial function and tumor progression, consistent with the broader concept of inflammation-driven serrated neoplasia in IBD. Collectively, these observations indicate that serrated dysplasia subtypes in IBD are molecularly and clinically heterogeneous, and should not be managed as a single entity. SSL-like dysplasia may represent an alternative serrated pathway with distinct precursor potential, whereas serrated dysplasia, NOS appears to carry greater immediate malignant risk. Recognition of these patterns in routine practice is essential, and complete excision with close surveillance may be warranted, particularly for lesions within the NOS category.

6. CONCLUSIONS

1. This first Hungarian pilot study investigated IBD-associated colorectal adenocarcinomas to assess the presence of NCD and compare findings with North American data. NCD was identified adjacent to 60% of cases, with hypermucinous dysplasia being the most common subtype. Mucinous adenocarcinomas were exclusively associated with NCD, and medullary types only with conventional dysplasia, suggesting distinct pathogenetic pathways. The results support a possible inflammation–foveolar metaplasia–hypermucinous dysplasia–mucinous adenocarcinoma sequence in IBD. Overall, this study extends international findings to a Central-Eastern European population and highlights the diagnostic and clinical significance of recognizing NCD in IBD-associated neoplasia.

2. This retrospective study from the University of Szeged examined neoplastic specimens from IBD patients to identify NCDs and evaluate their clinicopathological relevance. NCDs were most often associated with UC and found predominantly in the left colon, with serrated dysplasia, NOS and hypermucinous types being the most common. Their presence was linked to the development of CRC, and more advanced tumor stage. Unlike North American studies, certain NCD subtypes such as CCD and DPD were absent, indicating possible regional differences. Overall, this study highlights the importance of recognizing NCDs in IBD-related neoplasia and supports more vigilant endoscopic surveillance and complete lesion removal for affected patients.

3. This study highlights important advances in understanding serrated dysplastic lesions in IBD. The findings show that SSL-like dysplasia in IBD displays distinctive clinicopathologic and molecular profiles compared with its sporadic counterpart, including unique mutations not previously reported in serrated lesions. Notably, the discovery of *POLE*, *KMT2C*, and *EXT1* mutations suggests that these lesions may represent a novel molecular pathway and potential precursors to specific CRC subtypes. Serrated dysplasia, NOS demonstrated distinct molecular alterations, such as *TP53* and *POLG* mutations, and appeared to carry a higher malignant potential. Overall, these achievements refine the molecular classification of IBD-associated serrated dysplasia and underscore the importance of complete excision.

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