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Hypermucinous Dysplasia in Inflammatory Bowel Disease (IBD): Morphology, Molecular Features, and Its Place in the IBD-Associated Neoplastic Spectrum

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ABSTRACT

Long-standing inflammatory bowel disease (IBD) increases the risk of dysplasia and colorectal cancer (CRC), particularly in patients with extensive disease or coexisting primary sclerosing cholangitis (PSC). Several non-conventional dysplasia subtypes have been identified. Hypermucinous dysplasia was first formally proposed in 2020, and it arises predominantly in patients with long-standing ulcerative colitis, frequently in extensive disease and concomitant PSC. Histologically, hypermucinous dysplasia is characterized by a tubulovillous or villous architecture lined by tall, prominent, mucin-rich epithelial cells comprising more than 50% of the lesion, with minimal-to-mild cytologic atypia. Although often classified as low-grade dysplasia according to previously established criteria, hypermucinous dysplasia is disproportionately associated with advanced neoplasia, including high-grade dysplasia and CRC, and frequently coexists with both conventional and other non-conventional dysplasias. Molecular alterations commonly include aneuploidy and occasional *TP53* mutation. Emerging evidence suggests that non-dysplastic, mucin-rich epithelial proliferation, such as hypermucinous mucosa and foveolar metaplasia, may represent putative precursor lesions within a broader metaplasia–dysplasia sequence. This review provides the first comprehensive synthesis focusing exclusively on hypermucinous dysplasia, highlighting the consistency in histopathologic definitions, proposed precursor lesions, clinicopathological associations, molecular features, and diagnostic reproducibility. Increased awareness of hypermucinous dysplasia is essential for accurate diagnosis, risk stratification, high-risk IBD population screening, and optimal management of patients with IBD.

1 | Introduction

Long-standing inflammatory bowel disease (IBD), mainly encompassing ulcerative colitis (UC) and Crohn's disease (CD), causes a chronic inflamed niche, altered microbial compositions, and immunological changes that lead to a predisposition to early dysplasia and an overall twofold increase in the risk of developing neoplasia and colorectal cancer (CRC) when compared to the general population [1–3]. The risk of CRC is even higher in patients with IBD and primary sclerosing cholangitis (PSC), manifesting clinically with an earlier IBD onset (at approximately 23 years of age), milder but more extensive colitis that spares the rectum (about 75%), and backwash ileitis [4]. Patients with IBD are at a high risk of developing both conventional and non-conventional dysplasia due to chronic inflammation, and the risk of developing CRC increases with disease duration and anatomical extent [5].

The pathogenesis of IBD encapsulates dysbiosis, genetic predisposition, and immune dysregulation. Although the mucosal

epithelium forms a barrier that prevents the free mixing of luminal antigens with immune cells of the lamina propria, the gastrointestinal (GI) tract has often been described to be in a state of "low-grade inflammation" [6]. Dysregulation of mucosal immunity includes T helper 1 (Th-1) cytokines, including tumor necrosis factor (TNF), interleukin (IL)-12, and interferon (IFN)-γ, as well as Th-17 cytokines such as IL-17 and IL-23 being elevated in CD, while IL-4 and IL-13, alongside IL-17 and IL-23, show elevation in areas of active disease in UC. The balance between these proinflammatory cytokines and anti-inflammatory cytokines (e.g., IL-10) is lost in IBD, and TNF is chronically elevated [7]. Owing to chronic inflammation, as the first step in the metaplasia–dysplasia–cancer sequence, gastric foveolar metaplasia may present, which has been described as an adaptive mechanism and is considered to serve as the substrate for most non-conventional dysplasia prior to *TP53* mutation. This has also been demonstrated via MUC5AC and p53 immunohistochemistry—aberrant p53 staining pattern has been shown to be more frequent in non-conventional dysplasia that lacks MUC5AC expression, while MUC5AC expression shows a wild-type p53 pattern, indicating that foveolar metaplasia precedes *TP53* mutation. Via immunohistochemistry, a strong association between MUC5AC expression and partial loss of CDX2 has been found [8]. Loss of special AT-rich sequence-binding protein 2 (SATB2) has also been reported in IBD-associated dysplasia and CRC, but not in sporadic cases, further supporting foveolar metaplasia as a precursor lesion in the IBD-associated tumorigenesis pathway [9]. An earlier occurrence of *TP53* mutation in IBD-associated CRC has also been documented, in contrast to sporadic cases in which *KRAS* mutations typically arise earlier, followed by *TP53* alterations [10].

IBD-related dysplasia was first classified based on the Riddell grading system, which categorized it into low-grade (LGD) and high-grade dysplasia (HGD), respectively, according to the cytological and/or architectural atypia [11]. Before the establishment of the Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients: International Consensus Recommendations (SCENIC) guidelines, clinical management of dysplasia in IBD relied heavily on the concept of dysplasia-associated lesion or mass (DALM) [12]. Under this framework, visible DALMs were generally considered to carry a high risk of developing synchronous or metachronous carcinoma, and colectomy was frequently recommended. Similarly, the detection of "invisible" dysplasia—identified on random surveillance biopsies without a corresponding endoscopically visible lesion—was often managed surgically because of concerns regarding sampling limitations and a potential presence of undetected advanced neoplasia. Recently, these lesions are managed according to the SCENIC guidelines based on their endoscopic appearance (i.e., visible or invisible) . Precisely, polypoid or visible lesions may be treated by endoscopic resection; however, colectomy is recommended for multifocal flat or invisible LGD detected on screening biopsies due to its stronger association with advanced neoplasia (HGD or CRC) [13–15].

Recently, several morphological patterns of non-conventional dysplasia have been described, including hypermucinous dysplasia, goblet cell-deficient dysplasia (GCD), dysplasia with increased Paneth cell differentiation (DPD), crypt cell dysplasia (CCD), sessile serrated lesion (SSL)-like dysplasia, traditional serrated adenoma (TSA)-like dysplasia, and serrated dysplasia not otherwise specified (NOS) [13, 15, 16]. Despite their low-grade appearance, non-conventional dysplasia is more frequently associated with advanced neoplasms, aneuploidy, and *KRAS* mutation [2, 16].

At present, there is insufficient evidence regarding IBD-associated hypermucinous dysplasia, including its genetic background, potential precursor lesions, association with CRC and other subtypes of IBD-associated non-conventional dysplasias, and patient prognosis. Given that hypermucinous dysplasia was formally defined in 2020, a comprehensive synthesis of the available literature is not yet available. Therefore, we systematically collected, synthesized, and critically evaluated the currently available evidence on hypermucinous dysplasia, including its precursor lesions, histopathological features, clinicopathological characteristics, and potential association with CRC, to provide a coherent overview and identify gaps for future research.

2 | Precursor Lesions of Hypermucinous Dysplasia

In 1999, Andersen et al. first introduced the term hypermucinous mucosa, and reported an association between hypermucinous mucosa and *K-ras* mutation in 61% of the cases with long-standing UC [17]; however, its definition was not well delineated. One described a villous surface architecture with an increased number of goblet cells in the absence of nuclear atypia, while another variant was characterized by abundant goblet cells, a flat surface architecture, and similarly lacked nuclear atypia [18]. Although the architectural features appear comparable to those included in current definitions, it should be emphasized that contemporary diagnostic criteria require the presence of at least mild nuclear atypia. Pierce [19] used similar definitions and described hypermucinous mucosa as a precursor to dysplasia, classifying it alongside hyperplastic-like mucosal change, serrated epithelial change (SEC), flat serrated change, goblet cell-rich mucosa, and epithelial hyperplasia, thereby suggesting a metaplastic origin for these lesions. This is similar to Kamarádová et al.'s study [5] which defined villous hypermucinous change as a putative preneoplastic lesion (PPL; including SEC/dysplasia, NOS, sessile serrated adenoma, and TSA), in which histologically, the formation of predominantly sessile, slender villous mucosal projections composing of enterocytes containing abundant intracellular mucin within variably sized vacuoles is visible, resulting in a frothy and markedly pale appearance. The nuclei were described as small, round, often vesicular, and basally located, lacking prominent mitotic activity. All five examined cases in this study were associated with CRC; three were identified to be adjacent to the tumor, while two exhibited features resembling gastric mucosa [5]. A further study of these authors used the same definition for villous hypermucinous change and mentioned combined, partially serrated areas as well; villous hypermucinous change was associated with aberrant MLH1 loss (1 of 6), and with strong p53 expression via immunohistochemistry (1 of 6), O^6-methylaguanine DNA methyltransferase (MGMT) loss (4 of 6), and *KRAS* mutation (2 of 6) [18].

In Kővári et al.'s multi-institutional series of 64 IBD patients, hypermucinous dysplasia and related non-dysplastic mucinous proliferative lesions (NDMPLs), which were defined as mucinous proliferative lesions not fulfilling all criteria of hypermucinous dysplasia, demonstrated heterogeneous mucinous differentiation, including intestinal, foveolar, and mixed phenotypes. Hypermucinous dysplasia often coexisted with conventional or other non-conventional dysplasia and, in about half the cases, with adenocarcinoma. Notably, foveolar hypermucinous dysplasia was frequently associated with adjacent non-dysplastic mucinous lesions and foveolar metaplasia, highlighting a potential spectrum from metaplasia to dysplasia [20]. Based on these results, it can be hypothesized that foveolar metaplasia may be a precursor lesion to hypermucinous dysplasia. Furthermore, these results underscore the morphological diversity of IBD-associated hypermucinous lesions and emphasize the importance of recognizing foveolar differentiation to improve detection and assess biological significance.

In summary, non-dysplastic, mucin-rich epithelial lesions, such as hypermucinous mucosa and foveolar metaplasia, have been reported in association with hypermucinous dysplasia and may represent PPLs. These lesions share architectural and molecular features with dysplasia, including *KRAS* mutations and p53 or MLH1 abnormalities, supporting their potential roles in a preneoplastic spectrum.

3 | Histopathological Definition of Hypermucinous Dysplasia

Hypermucinous dysplasia was first proposed by Choi et al. in 2020, which serves as the current reference for hypermucinous dysplasia, including a tubulovillous or villous structure with tall, prominent cells representing over 50% of the lesion, displaying mucinous differentiation and minimal-to-mild atypia with decreasing tendency towards the surface of the villi. Across all datasets, the definitions are consistent with the original one. A recurring feature is the gradient of atypia, with nuclear abnormalities more pronounced in the lower crypts and diminishing towards the villous surface, often attributed to prominent mucinous differentiation. Several descriptions emphasize gastric foveolar-like morphology and abundant cytoplasmic mucin, while surface epithelium typically shows minimal atypia. Overall, these features align well with hypermucinous dysplasia.

There are no major qualitative differences among the descriptions of hypermucinous dysplasia; the variation is mainly in level of detail and terminology. Some studies explicitly note hyperchromasia and nuclear elongation, while others emphasize mucin quantity or gastric foveolar resemblance, and a few entries lack data. Importantly, all available descriptions converge on the same core morphologic pattern, suggesting strong inter-study consistency rather than biologically distinct subgroups. The representative morphological characteristics of hypermucinous dysplasia are presented in Figure 1, and its previously reported definitions are summarized in Table 1 [1–4, 13–16, 21–27].

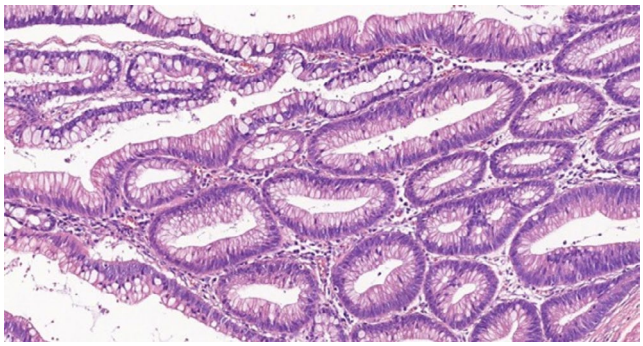

FIGURE 1 | Histological features of hypermucinous dysplasia characterized by tubulovillous structures with tall, prominent cells reflecting mucinous differentiation of both foveolar and intestinal types (HE stain, ×20).

From a differential diagnostic perspective, hypermucinous dysplasia has to be differentiated from other mucin-rich lesions, including foveolar metaplasia, villous hypermucinous change/hypermucinous mucosa, and mucinous adenocarcinoma. Foveolar metaplasia is usually limited to surface epithelial alterations without evident neoplastic stratification. Villous hypermucinous change may show abundant mucin, but generally lacks significant cytologic atypia or structural disorganization. In contrast, mucinous adenocarcinoma exhibits marked nuclear atypia, complex glandular architecture, and depth of invasion into the lamina propria or deeper layers. Therefore, assessment of cytologic atypia, structural disorganization, and evident invasion are essential to distinguish IBD-associated hypermucinous dysplasia from reactive or metaplastic mucinous changes and overt malignancy, ensuring accurate pathological diagnosis and guiding clinical management [5].

4 | Clinicopathological Characteristics

Currently, 15 studies have reported hypermucinous dysplasia, including 12 original articles [1–4, 13–16, 21, 22, 25, 26], 2 case reports [23, 27], and one review article [24] which incorporates a summary of hypermucinous, GCD, CCD, TSA-like dysplasia, SSL-like dysplasia, DPD, and SEC. Hypermucinous dysplasia is predominantly observed in individuals of Caucasian ethnicity (94%–100%) [2, 13, 15, 23]; however, it should be emphasized that the existing literatures on IBD-associated neoplasms have largely investigated the cohorts of Caucasian ethnicity, and therefore it remains uncertain whether broad or generalizable conclusions can be reliably drawn from these data. The ratio of male to female was 1.7, showing a significant male predominance [2, 13, 15, 22, 23, 27]. The mean age of the patients at the time of hypermucinous dysplasia diagnosis was approximately 60 years (range 20–83 years) [2, 13, 15, 23, 27]. Bahceci et al. compared the clinicopathological and morphological characteristics of IBD-associated dysplasia between pediatric/adolescent and adult patient cohorts. They found that hypermucinous dysplasia, together with other high-risk non-conventional dysplasia subtypes, was significantly more frequent in the pediatric/adolescent group than in adults (9% [5 of 56] vs. 2% [7 of 315], $p = 0.009$). However, this study did not provide further clinicopathological characterization of

TABLE 1 | Histological definitions of hypermucinous dysplasia.

First author (year of publication)	Type of article	Definition of hypermucinous dysplasia
Choi (2020) [14]	Original article	Tubulovillous/villous architecture with mild nuclear atypia and prominent mucinous differentiation (> 50% of the lesion). The degree of atypia seems to decrease towards the surface of the villi.
Lee (2021) [13]	Original article	Tubulovillous/villous lesion with prominent mucinous cells with minimal to mild nuclear enlargement and hyperchromasia representing over 50% of the lesion.
Zhang (2022) [4]	Original article	Tall, prominent, mucinous cells representing > 50% of the lesion with nuclear atypia, typically more prominent in the lower portion of crypts.
Choi (2022) [15]	Original article	Tall, prominent mucinous cells; cytological atypia is typically more prominent in the lower portion of crypts, and the degree of atypia tends to decrease towards the surface epithelium due to prominent mucinous differentiation.
Nguyen (2022) [21]	Original article	Tubulovillous/villous architecture lined by tall, prominent mucinous cells > 50% of the lesion. The degree of atypia is more prominent in the lower portion of crypts and diminishes towards the surface epithelium.
Akarca (2023) [22]	Original article	Tall, prominent mucinous cells.
Almási (2023) [23]	Case report	Tubulovillous/villous architecture with a large amount of cytoplasmic mucin in > 50% of the lesion, minimal atypia towards the tip of the lesion but more pronounced in the basal regions.
Alipour (2024) [24]	Review article	Villous or tubulovillous architecture, the villi are lined by tall, mucinous columnar epithelial cells with gastric foveolar-like morphology, minimal atypia towards the tip of the lesion. For a mixed lesion, at least 50% of the lesion must have hypermucinous morphology.
Bahceci (2024) [25]	Original article	Tall, prominent mucinous cells with mild cytologic atypia.
Xiao (2024) [16]	Original article	NA
Almási (2025) [1]	Original article	NA, according to Choi et al.'s study [14]
Bahceci (2025) [26]	Original article	Tall, prominent mucinous cells that resemble gastric foveolar cells. Cytologic atypia is typically more pronounced in the lower part of the crypts and tends to diminish towards the surface epithelium.
Balajthy (2025) [2]	Original article	NA
Lang-Schwarz (2025) [3]	Original article	Tall mucinous cells with mildly elongated, hyperchromatic nuclei in > 50% of the lesion.
Lu (2025) [27]	Case report	Tubulovillous architecture with tall, prominent mucinous cells with mildly elongated and hyperchromatic nuclei.

Abbreviation: NA, not applicable.

hypermucinous dysplasia specifically in comparison with other non-conventional dysplasia subtypes [26].

Hypermucinous dysplasia has been reported to be primarily in association with UC [2, 13, 15, 21, 23, 27]. Among the reported cases, the mean duration of IBD was 20 years (range 3–49 years). Pancolitis was reported in 47 cases, whereas left-sided colonic involvement was observed in 5 cases. None of the studies reported right-sided colonic predominance [2, 15, 23]. In addition, LGD was identified in 58 cases, while HGD was observed in 10 cases [2, 13, 15, 23, 27]. And multifocality was present in 7 lesions [1, 15]. Hypermucinous dysplasia was localized to the right colon in 12 cases, transverse colon in 11, left colon in 43, and sigmoid colon in 2 cases; 12 lesions were found in the same segment as CRC without further specifications [2, 13–15, 23, 27]. Based on available data, the mean size of the lesion ranged from 0.5 cm to 2.5 cm (range 0.2–20 cm) [2, 13, 15, 27]. The endoscopic appearance was most frequently polypoid (42 of 68), followed by invisible lesions (15 of 68), while flat lesions were the least common (11 of 68) [2, 13, 15, 23, 27]. Association with PSC was found in up to 82.1% (23 of 28) of all cases [4]. At present, follow-up data regarding this entity remain extremely limited. To date, such information has been reported only in the case study by Almási et al., and no additional follow-up data are currently available. Consequently, long-term clinical behavior and prognosis of this condition remain insufficiently characterized [23].

TABLE 2 | Clinicopathological characteristics of hypermucinous dysplasia.

First author (year of publication)	Type of article	Sample size (*n*)	Caucasian ethnicity (*n*, %)	Male: female ratio	Age at hypermucinous dysplasia diagnosis, years (mean with range)	Type of IBD	IBD duration, years (mean or median with range)	Extent of IBD	Grade of dysplasia (*n*)	Multifocality of hypermucinous dysplasia	Location of hypermucinous dysplasia (*n*)
Choi (2020) [14]	Original article	15	NA	NA	NA	NA	NA	NA	NA	NA	12 in the same segment as CRC, no further specified
Lee (2021) [13]	Original article	7	7 (100)	4:3	49 (32–65)	6 UC	23 (7–43)	NA	5 LGD, 2 HGD	NA	4 left-sided colon, 1 transverse, 2 right-sided colon
Zhang (2022) [4]	Original article	28	NA	NA	NA	NA	NA	NA	NA	NA	NA
Choi (2022) [15]	Original article	47 (55 foci)	44 (94)	30:17	50 (20–77)	27 UC, 16 CD, 4 indeterminate colitis	21 (3–49)	42 pancolitis, 5 left colon	47 LGD, 8 HGD	7	10 right-sided colon, 35 left-sided colon, 10 transverse colon
Nguyen (2022) [21]	Original article	11	NA	NA	NA	UC	NA	NA	NA	NA	NA
Akarca (2023) [22]	Original article	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Almási (2023) [23]	Case report	1	1 (100)	Female	62	UC	14	Pancolitis	LGD	No	Sigmoid colon
Alipour (2024) [24]	Review	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Bahceci (2024) [25]	Original article	12	NA	NA	NA	NA	NA	NA	NA	NA	NA
Xiao (2024) [16]	Original article	3	NA	NA	NA	NA	NA	NA	NA	NA	NA
Almási (2025) [1]	Original article	9 foci	NA	NA	NA	NA	NA	NA	NA	Present, no further specified	NA
Bahceci (2025) [26]	Original article	5 foci	NA	NA	NA	NA	NA	NA	NA	NA	NA
Balajthy (2025) [2]	Original article	4	4 (100)	3:1	65 (median 66 [48–83])	4 UC	15.9 (median 15 [9–28])	4 pancolitis	4 LGD	NA	4 left-sided colon
Lang-Schwarz (2025) [3]	Original article	30	NA	NA	NA	NA	NA	NA	NA	NA	NA

(Continues)

TABLE 2 | (Continued)

First author (year of publication)	Type of article	Sample size (*n*)	Caucasian ethnicity (*n*, %)	Male: female ratio	Age at hypermucinous dysplasia diagnosis, years (mean with range)	Type of IBD	IBD duration, years (mean or median with range)	Extent of IBD	Grade of dysplasia (*n*)	Multifocality of hypermucinous dysplasia	Location of hypermucinous dysplasia (*n*)
Lu (2025) [27]	Case report	1	NA	M	73	UC	NA	NA	LGD	0	Sigmoid colon
Choi (2020) [14]	NA	NA		NA	8	NA	5	NA	NA	NA	NA
Lee (2021) [13]	2.1 (0.7–5)	6 polypoid, 1 flat/invisible		2	NA	NA	4, including HGD	NA	NA	80% aneuploidy	NA
Zhang (2022) [4]	NA	NA		23	NA	NA	NA	NA	NA	NA	NA
Choi (2022) [15]	2.5 (0.2–20)	32 polypoid, 8 flat, 15 invisible		10	15 LGD, 9, HGD	NA	10	NA	4 p53 null/ mutant	NA	NA
Nguyen (2022) [21]	NA	NA		NA	NA	NA	NA	NA	NA	NA	NA
Akarca (2023) [22]	NA	NA		NA	NA	NA	LGTGA: 2 (10); MAC: 11 (34)	11 (34)	NA	NA	NA
Almási (2023) [23]	NA	Polypoid		No	No	1 (GCD)	Yes	No	NA	NA	60
Alipour (2024) [24]	NA	NA		NA	NA	NA	NA	NA	NA	NA	NA
Bahceci (2024) [25]	NA	NA		NA	NA	NA	NA	NA	12 associated with SEC	NA	NA
Xiao (2024) [16]	NA	NA		NA	NA	NA	2 GCDAC, 1 serrated	NA	NA	NA	NA
Almási (2025) [1]	NA	NA		NA	NA	7 (serrated dysplasia, NOS, GCD, TSA-like)	NA	NA	NA	NA	NA
Bahceci (2025) [26]	NA	NA		NA	NA	NA	NA	NA	NA	NA	NA
Balajthy (2025) [2]	NA Mean: 0.55, median: 0.4 (0.5–1.6)	2 polypoid, 2 flat		NA	3	2	2	NA	NA	NA	NA
Lang-Schwarz (2025) [3]	NA	NA		NA	NA	NA	9 CRC or HGIN	NA	18 no IBD	NA	NA
Lu (2025) [27]	0.5	Polypoid		NA	NA	NA	NA	NA	NA	NA	NA

Abbreviations: CD, Crohn's disease; CRC, colorectal cancer; GCD, goblet cell-deficient dysplasia; GCDAC, goblet cell-deficient adenocarcinoma; HGD, high-grade dysplasia; HGIN, high-grade intraepithelial neoplasia; IBD, inflammatory bowel disease; LGD, low-grade dysplasia; LGTGA, low-grade tubuloglandular adenocarcinoma; MAC, mucinous adenocarcinoma; NA, not applicable; NOS, not otherwise specified; SEC, serrated epithelial change; TSA-like, traditional serrated adenoma-like dysplasia; UC, ulcerative colitis.

5 | Association Between Hypermucinous Dysplasia and Conventional and Non-Conventional Dysplasia and CRC

Hypermucinous dysplasia was found to be associated with conventional dysplasia in 35 lesions [2, 14, 15], while non-conventional dysplasia was recorded adjacent to hypermucinous dysplasia in 10 cases, including GCD ($n = 3$), serrated dysplasia, NOS ($n = 4$), TSA-like dysplasia ($n = 1$), and not specified in 2 cases [1, 2, 23]. CRC was reported in 18 cases with hypermucinous dysplasia [2, 14, 15, 23]. In addition, 13 cases were found to be related to CRC or HGD/high-grade intraepithelial neoplasia (HGIN), without further specifying the exact number of cases in each category [3, 13]. Furthermore, its association with low-grade tubuloglandular adenocarcinoma (LGTGA), goblet cell-deficient adenocarcinoma (GCDAC), and serrated adenocarcinoma was seen in 2 cases, 2 cases, and one case, respectively [16, 22], while related mucinous adenocarcinoma was only described by one study in 11 cases, which accounted for 34% of the patient population [22].

6 | Discussion

Hypermucinous dysplasia is a recently defined, non-conventional form of IBD-associated colorectal dysplasia which was formally characterized in 2020 [14]. Based on previous studies, it arises in long-standing IBD—predominantly UC—and typically affects patients with extensive, long-duration disease, often with concomitant PSC [5]. Hypermucinous dysplasia appears to be on a biological spectrum with non-dysplastic mucin-rich epithelial proliferation, such as hypermucinous mucosa and foveolar metaplasia, which may represent PPLs [5, 17–19]. Hypermucinous dysplasia is characterized by a tubulovillous or villous architecture lined by tall, prominent, mucin-rich epithelial cells comprising over 50% of the lesion, with minimal-to-mild cytologic atypia. A characteristic feature is the gradient of atypia, which is more pronounced in the lower crypts and diminishes towards the surface, often accompanied by gastric foveolar-like differentiation. Despite variations in terminology across the studies, there is strong inter-study consistency in this core morphologic pattern [1–4, 13–16, 21–27]. Molecular alterations include aneuploidy and *TP53* mutation [13, 15]. Although it is often regarded as LGD based on morphological criteria, hypermucinous dysplasia is disproportionately associated with advanced neoplasia, including HGD and CRC, and frequently coexists with conventional and other non-conventional dysplasias [1–3, 13–16, 22, 23]. Lesions are most often polypoid, but may be flat or endoscopically invisible, complicating detection and management [1–4, 13–16, 21–27].

The diagnosis of non-conventional dysplasias in IBD can be challenging; however, pathologists with GI expertise are generally able to classify these lesions accurately, as demonstrated in the study of Bahceci et al. [28], including seven GI pathologists who independently evaluated 38 cases. Although this article mainly focused on the reproducibility of SEC, the diagnostic categories included hyperplastic polyp, SSL, TSA, hypermucinous dysplasia, and no serrated change or dysplasia. The pathologists first evaluated each case under the assumption of an endoscopically normal mucosa and made a diagnosis. Subsequently, they reassessed the same cases, this time considering them as nodular or polypoid lesions, and again rendered a diagnosis. The authors demonstrated that although the diagnostic rate varied depending on the definition applied (i.e., endoscopically invisible, superficial hyperplastic polyp-like mucosal changes without dysplasia vs. nodular or polypoid lesions with disorganized crypt architecture, goblet cell-rich epithelium, and full-thickness serration), the total number of potential SEC mimics remained consistent across definitions. Regarding hypermucinous dysplasia, substantial interobserver agreement was observed ($\kappa = 0.79$). To the best of our knowledge, this is the first study in any way investigating the reproducibility of IBD-associated dysplasias, including hypermucinous dysplasia [28].

Current evidence on hypermucinous dysplasia is limited by small cohorts, retrospective study design, and incomplete molecular characterization. The quality of the studies is heterogeneous, comprising retrospective studies, small-scale case reports, and multicenter studies. A formal stratified assessment of study quality or evidence level was not performed. Consequently, the strength of the evidence varies. In particular, conclusions derived from small case reports may have limited the generalizability of the results and should be interpreted with caution. In contrast, multicenter studies generally provide a higher level of evidence due to larger sample sizes and broader population representations. Therefore, our review should be considered in light of the variability in study design and evidence levels. Future studies incorporating standardized quality assessment tools and higher level evidence are needed to further validate these findings. As presented in Table 2, in several of the included studies, variables such as IBD disease duration and lesion size were reported only as ranges. Moreover, some of the referenced articles did not provide the required information in a usable form, indicating that the relevant data were not reported and therefore could not be extracted. Long-term outcome and optimal management strategies remain undefined, underscoring the need for further clinicopathological and molecular studies. The importance of our review lies in the fact that it is the first comprehensive review to focus solely on hypermucinous dysplasia, which is a recently described and possibly underdiagnosed entity [2, 16, 24].

Future research should focus on several key areas to advance understanding and clinical management of this condition. Multicenter prospective cohort studies are needed to clarify potential prodromal lesions and better define the natural history of hypermucinous dysplasia. In addition, further investigation into molecular markers may facilitate earlier and more accurate diagnosis. Furthermore, the establishment of standardized diagnostic criteria and management guidelines would help improve consistency in clinical practice and patient outcomes.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data underlying this article are available in PubMed. For individual articles included in the review, see the list of references.

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