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Review Article

Goblet Cell Adenocarcinoma of the Appendix: Diagnosis, Prognosis and Nomenclature

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Abstract

Goblet cell adenocarcinoma (GCA) is a new name for goblet cell carcinoid used by the fifth edition of the World Health Organization Classification of Tumors of the Digestive System published in 2019. This name change put an end to the years' name confusion and led to the simplification and standardization of the diagnostic criteria and grading system for this unique epithelial neoplasm almost exclusively occurring in the appendix. This is extremely important because accurate diagnosis and grading are essential to patient management and prognostication. Under this new name, GCA is recognized to have low-grade and high-grade components with variable proportions. As such, the presence of the low-grade components is required for the diagnosis, but the proportion of the high-grade components dictates the prognosis. With regard to the nomenclature, GCA does not seem to be an ideal name for this tumor because goblet cells are apparently not the cell origin nor the unique cell population of the tumor. While the histogenesis remains ambiguous, the name "crypt cell carcinoma" would appear more appropriate for this tumor, as it would at least emphasize the crypt-like architecture and cellular composition of the tumor nests.

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Introduction

Goblet cell adenocarcinoma (GCA) is almost exclusively seen in the appendix. True extra-appendiceal GCA is exceedingly rare and likely represents an extra-appendiceal presentation of an occult appendiceal primary.[1] This unique type of epithelial neoplasm of the appendix has been termed "goblet cell carcinoid" (GCC) since 1974, because of the close resemblance of the primary cell type to the normal intestinal goblet cells, the presence of considerable numbers of argentaffin cells and Paneth cells, the basiglandular position of the tumor, the well-differentiated appearance, and the relatively good prognosis following simple appendectomy.[2] In the fifth edition of the World Health Organization (WHO) Classification of Tumors of the Digestive System published in 2019,[3] the name of GCA was formally used and the use of GCC was not recommended. This name change clearly helped clarify the confusion created by the fourth edition of the WHO tumor classification where GCC was listed under the category of neuroendocrine neoplasms (NENs) but described in both chapters of "Adenocarcinoma of the appendix" and "Neuroendocrine neoplasms of the appendix" under the subtitle of mixed adenoneuroendocrine carcinoma (MANEC).[4,5] However, the fifth edition still defined GCA as "an amphicrine tumor composed of goblet-like mucinous cells, as well as variable numbers of endocrine cells and Paneth cell-like cells".[3] This definition does not seem entirely appropriate because the term "amphicrine" is supposed to be used to describe cells capable of both neuroendocrine and exocrine secretions.[6] By immunohistochemistry, "amphicrine" refers to the expression of both neuroendocrine and non-neuroendocrine markers in the same cell. However, this is clearly not the case for GCA because the primary cell type, the goblet-like mucinous cells, do not aberrantly express neuroendocrine markers. Furthermore, the numbers of neuroendocrine cells in GCA are typically scattered and vary from case to case and from area to area even in the same case. This feature is similar to what is seen in conventional adenocarcinomas of the gastrointestinal tract that frequently show neuroendocrine differentiation.[7] Since these adenocarcinomas with neuroendocrine differentiation are not considered "amphicrine", there does not appear to be any additional reason that GCA should. While it remains debatable whether amphicrine carcinoma should be regarded as a type of mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN), the current WHO Classification of Neuroendocrine Neoplasms considered it to be a specific entity distinctive from adenocarcinoma or NEN biologically and histologically.[6]

An advantage of the name change from GCC to GCA is the simplification and standardization of the diagnostic criteria and the grading system. Pathologists no longer need to struggle with the distinction between typical GCC and adenocarcinoma ex GCC, the distinction between goblet cells

Keywords: Goblet cell adenocarcinoma; Crypt cell carcinoma; Goblet cell carcinoid; Appendix.

Abbreviations: GCA, goblet cell adenocarcinoma; GCC, goblet cell carcinoid; MANEC, mixed adenoneuroendocrine carcinoma; MiNEN, mixed neuroendocrine-non-neuroendocrine neoplasm; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor; pT, primary tumor; WHO, World Health Organization; AJCC, the American Joint Committee on Cancer.

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Table 1. Low-grade and high-grade histologic patterns of goblet cell adenocarcinoma[11]

Low-grade histologic patterns	High-grade histologic patterns
Tubular growth with round to oval discrete tumor clusters comprising a mixture of goblet cells, cuboidal cells, and Paneth-like cells with or without lumens.	Single cells, including nonmucinous single cells and signet-ring-like cells, often admixed with abortive tubules.
Simple trabecular growth consistent with tubules sectioned longitudinally.	Single file growth or sheets of tumor cells often admixed with abortive tubules.
Limited tubule fusion or crowding.	Fusion of goblet cell clusters to form an anastomosing complex growth of goblet cell clusters or tubules.
Mucin pools with discrete tubules or clusters, including ectatic tubules.	Very large aggregates of goblet cells or drifts of goblet cells in extracellular mucin.
Tubular nonmucinous glands including oncocytic tubules.	Mucin-poor tumor cells in nests or clusters with high nucl ear-to-cytoplasmic ratio and jagged outlines.
	Glands lined by cuboidal or columnar cells with a high cytologic grade that resemble conventional adenocarcinoma.
	Glands floating in mucin lined by columnar cells with a high cytologic grade.

and signet-ring cells, and the distinction between signet-ring cell adenocarcinoma and poorly differentiated adenocarcinoma.[8–10] In this article, the newly proposed diagnostic criteria and grading schema, prognostic factors, and evolution of the nomenclature for GCA are reviewed.

Diagnosis and grading

The proposed diagnostic criteria and grading schema for GCA in the fifth edition of the WHO Classification of Tumors of the Digestive System[3] were essentially entirely based on a single study by Yozu *et al*. published in 2018.[11] In this study, the authors collected 126 cases that were diagnosed as GCC or adenocarcinoma ex GCC spanning over a period of 36 years from 1981 to 2017. On the basis of the histology and outcome, the authors were able to characterize an array of low-grade and high-grade histologic patterns seen in these tumors.

The low-grade patterns are felt to recapitulate the intestinal crypts (Table 1),[11] characterized by small tight round or oval tubules, clusters, nests or short cords of tumor cells composed predominantly of cohesive goblet-like mucinous cells with variable numbers of neuroendocrine cells and Paneth cells (Fig. 1a). There may or may not be luminal formation, and most of the time, the tumor clusters are solid and lack recognizable lumina. The cells in the tumor clusters exhibit a low nuclear-to-cytoplasmic ratio, mild nuclear atypia, and infrequent mitoses. Some tumor clusters may not contain recognizable goblet-like cells, which are still considered low-grade as long as they maintain a simple clustered or tubular architecture. A histologic hallmark of low-grade patterns is the circumferential infiltration of the appendiceal wall by tumor clusters in a concentric fashion without eliciting desmoplastic reaction (Fig. 1b).[10] Extracellular mucin is often present and can be abundant. Recognition of these low-grade features is important because the diagnosis of GCA requires the presence of at least a focal low-grade GCA component in the tumor. The neuroendocrine cells in the tumor can be demonstrated by immunohistochemistry using neuroendocrine markers, but the stains are not required for the diagnosis because GCA is no longer regarded as a special type of NEN or MiNEN.[3]

High-grade patterns are essentially conventional adenocarcinomatous components, which include any histologic

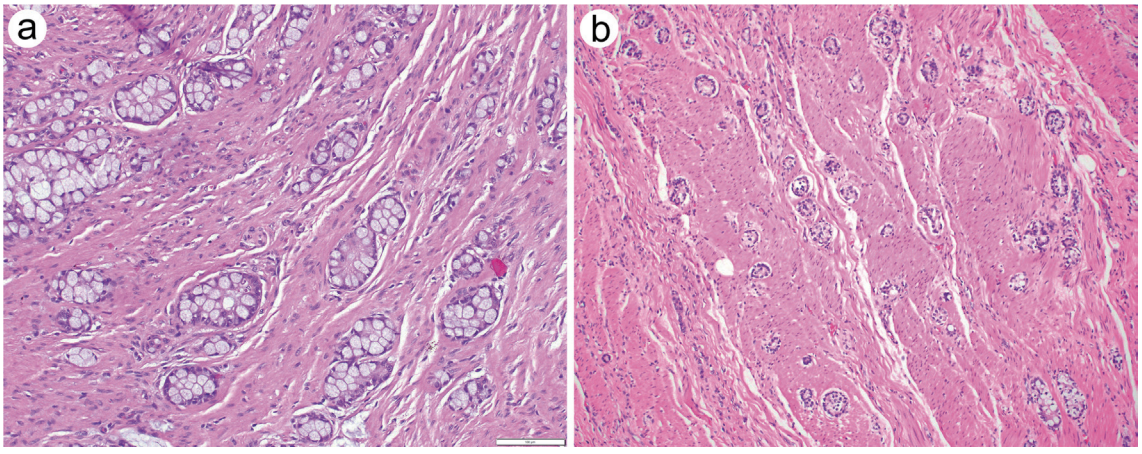

Fig. 1. Low-grade patterns of goblet cell adenocarcinoma showing tumor clusters or tubules composed mainly of cohesive goblet-like mucinous cells. Paneth cells and luminal formation are not prominent in this example (a, original magnification ×200). Tumor clusters infiltrate the appendiceal wall in a concentric fashion without destruction of the muscularis propria and desmoplastic reaction (b, original magnification ×100).

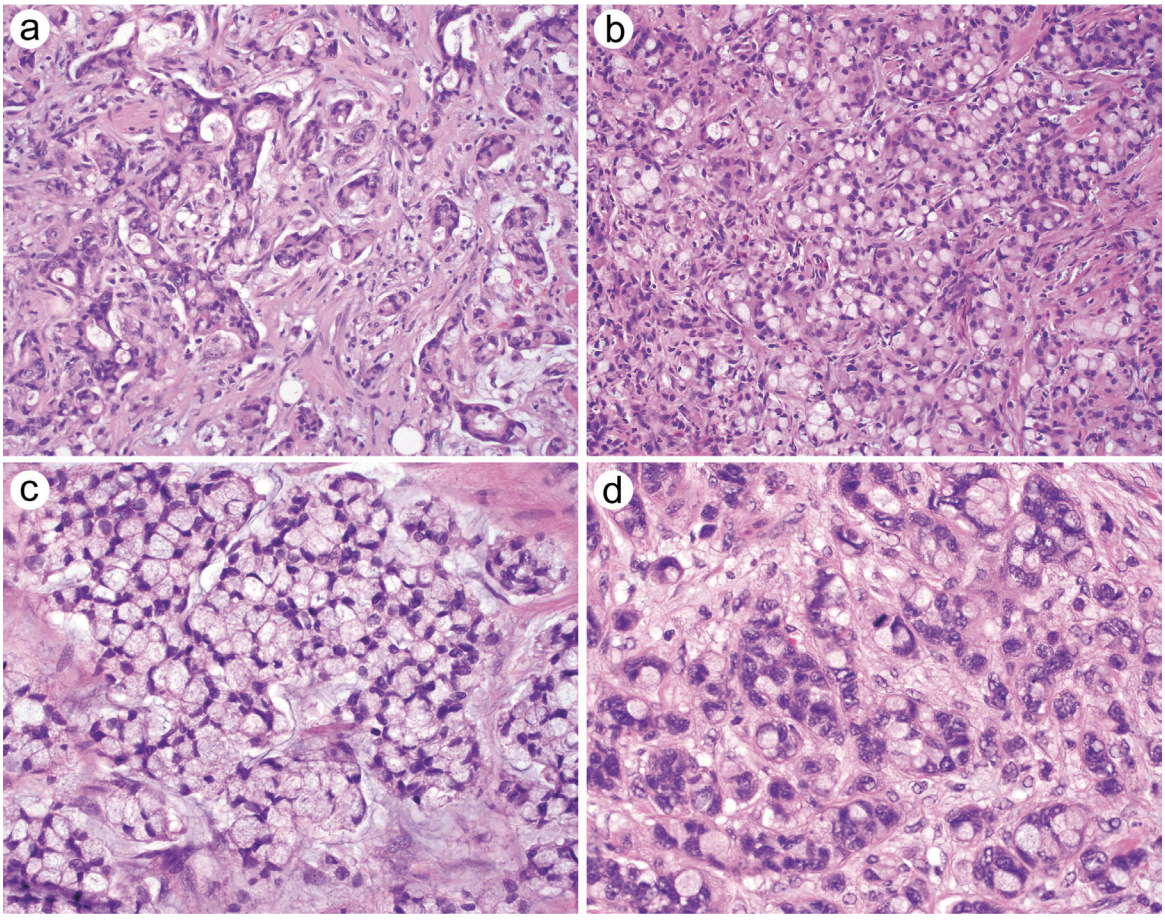

Fig. 2. High-grade patterns of goblet cell adenocarcinoma showing conventional adenocarcinomatous component in a desmoplastic stroma (a, original magnification ×200) and/or large irregular sheets of goblet-like or signet-ring-like cells (b, original magnification ×200). Nuclear atypia is typically prominent in high-grade patterns (c and d, original magnification ×400).

pattern that deviates from the simple clustered or tubular low-grade patterns (Table 1). In addition to conventional gland-forming and mucinous adenocarcinomas, high-grade patterns may include anastomosing or cribriforming architecture, large solid sheets or large irregular aggregates of goblet-like or signet-ring-like cells, poorly cohesive infiltrating mucinous (signet-ring) or nonmucinous cells, and single filing of nonmucinous cells (Fig. 2a–d). High-grade patterns typically exhibit obvious nuclear atypia and frequent mitoses. Atypical mitoses and tumor necrosis may be seen. High-grade patterns are commonly associated with destruction of the muscularis propria and stromal desmoplasia. Lymphovascular invasion is more frequently seen in high-grade tumors. The distinction of high-grade GCA patterns from conventional adenocarcinomas, such as signet-ring cell carcinoma, is based on the presence of a low-grade GCA component in the same tumor.

GCA is graded according to the proportion of the low-grade and high-grade components (Table 2).[3,11] This three-tiered schema somewhat mirrors the practice of grading conventional adenocarcinomas of the gastrointestinal tract based on the proportion of the tumor with gland formation.[11] To achieve accurate grading, the entire appendix should be submitted for histologic assessment. Examination of the entire appendix also helps achieve more accurate primary tumor (pT) staging and better margin evaluation, which further help determine if right hemicolectomy is necessary.[12] It should be noted that a GCA may exhibit several different high-grade patterns, which should be combined to constitute the total proportion for grading. Perineural invasion is common in both low-grade and high-grade components, which does not bear prognostic significance and is thus not useful for grading. The Ki67 proliferation index, a very useful biomarker for grading well-differentiated neuroendocrine tumors (NETs), has been shown to have no prognostic value for GCA, and is thus not required for GCA grading.[10]

Table 2. Grading schema for goblet cell adenocarcinoma[3,11]

Grade	Low-grade patterns (%)	High-grade patterns (%)
1 (low-grade)	>75	<25
2 (intermediate-grade)	50–75	25–50
3 (high-grade)	<50	>50

Prognosis

Besides tumor stage, tumor grade has been shown to be another important prognostic parameter for patients with GCA. This is not surprising because high-grade tumors usually present at more advanced stages at the time of surgical resection. In the study by Yozu *et al*.,[11] two of 47 (4%) grade 1 tumors were staged pT1, three (6%) were pT2, 37 (79%) were pT3, and five (11%) were pT4. None of grade 1 tumors had lymph node or distant metastasis. Therefore, all grade 1 tumors in this study were either stage I (5; 11%) or stage II (42; 89%) at the time of appendectomy or right hemicolectomy. In contrast, all 57 grade 3 tumors were staged either pT3 (24; 42%) or pT4 (33; 58%). No pT1 or pT2 grade 3 tumors were found in this group. Twenty-two (39%) grade 3 tumors had lymph node metastasis and 28 (49%) had distant metastasis. Therefore, 40 (70%) grade 3 tumors were either stage III (12; 21%) or stage IV (28; 49%). No stage I tumor was found in the grade 3 group. Multivariate analysis showed that the overall patient survival was significantly different among the three grades independent of tumor stage with a median overall survival of 204, 86, and 29 months for grade 1, 2, and 3 tumors, respectively. The five- and 10-year survival was 82% and 78%, 55% and 33%, and 22% and 4% for grade 1, 2 and 3 tumors, respectively.

Other studies have also demonstrated that it is the high-grade or conventional adenocarcinomatous component in GCA that dictates the prognosis. Back to 1990, Burke *et al*. recognized the presence of adenocarcinomatous growth patterns in GCC, which were characterized by fused or cribriform glands, single file structures, diffusely infiltrating signet-ring cells, or solid sheets of cells.[13] These cases were diagnosed as "mixed carcinoid-adenocarcinoma" by the authors, which required the carcinomatous growth patterns to comprise at least 50% of the tumor volume. The follow-up data showed a much worse prognosis in patients with "mixed carcinoid-adenocarcinoma" in comparison with pure GCC cases. Eight of 10 patients with a mean follow-up time of 16 months died of disease despite right hemicolectomies. Tumor cells were found to directly spread to adjacent structures and to metastasize to lymph nodes and distant organs. In contrast, none of the 22 patients with pure GCC died of disease nor showed metastasis with a mean follow-up time of 19 months irrespective of whether right hemicolectomy was performed or not.

Tang *et al*. analyzed the histopathologic features of 63 cases and were able to divide them into three groups: typical GCC (group A), adenocarcinoma ex GCC, signet-ring cell type (group B), and adenocarcinoma ex GCC, poorly differentiated carcinoma type (group C).[8] At the time of initial presentation, 10 of 30 patients (33%) in group A, 23 of 26 patients (88%) in group B, and all seven patients (100%) in group C had stage IV disease. The common sites of extra-appendiceal involvement included the right colon and ileum by direct extension, and the peritoneum and omentum by metastatic spread. In female patients, the ovary was the most common site of metastasis. With a follow-up time ranging from eight to 191 months, the overall disease-specific survival was 96%, 73%, and 14% for groups A, B, and C, respectively. The mean survival time was close to 10 years for group A, but only 43±6 months for group B, and 31±6 months for group C. Not surprisingly, group C had the worst outcome with three- and five-year survivals of 17% and 0%, respectively, similar to those of stage-matched conventional adenocarcinoma of the appendix. In contrast, the three- and five-year survivals were 100% for group A, in which only one patient died 119 months later following the initial presentation.

Using different classification criteria, Taggart *et al*. studied 74 GCC cases and divided them into three groups based on the proportion of coexisting adenocarcinoma: group 1, <25% adenocarcinoma, group 2, 25–50% adenocarcinoma, and group 3, >50% adenocarcinoma.[14] Significant differences in staging and survival were observed among the different groups. At the time of surgical resection, 20 of 23 patients (87%) in group 1, 18 of 27 patients (67%) in group 2, and seven of 24 patients (29%) in group 3 had stage II tumors. Only one (4%) patient in group 1 had stage IV disease in marked contrast to groups 2 and 3 where six (22%) and 16 (67%) patients had stage IV tumors, respectively. The overall patient survival was 83.8±34.6, 60.6±30.3, and 45.6±39.7 months for groups 1, 2, and 3, respectively. The staging and survival data for group 3 (>50% adenocarcinoma) were essentially similar to those of conventional poorly differentiated adenocarcinoma of the appendix without a GCC component.

Similarly, the tumor stage and the high-grade component were found to correlate with cancer-specific survival in the study by Nonaka *et al*.[15] In this study, the authors divided 105 GCA cases into three groups according to the proportion of high-grade components: ≤39%, 40–89%, and ≥90%. The high-grade components were defined by any signs of loss of organoid pattern and acquired irregularity and complexity in tumor nests as well as high-grade nuclear features. During a follow-up time ranging from four to 277 months (median: 56 months), 43 patients (41%) died of disease. All deceased patients were found to have progressive peritoneal disease. Three patients also had extraperitoneal metastasis to the liver, brain, and/or bone. The median cancer-specific survival for all patients was 67 months, but there was a significant difference among the three groups. The group with ≤39% high-grade components had the best survival, and the group with ≥90% high-grade components had the worst. The authors also analyzed their cases with the 25% and 50% cut-off points used by Taggart *et al*.,[14] and found that the >50% group had a poorer cancer-specific survival compared to the <25% and 25–50% groups, but the <25% and 25–50% groups did not differ in survival. These data further underscored the importance of quantifying the proportion of high-grade or adenocarcinomatous components in GCA cases.

Nomenclature and histogenesis

GCA was first described in French literature in 1969 by Gagné *et al*. as a type of appendiceal tumor with features intermediate between carcinoid and adenocarcinoma of the gastrointestinal tract.[16] It was formally named as GCC by Subbuswamy *et al*. in 1974,[2] and this name had since dominated the literature for the past 45 years till the WHO changed it to GCA in 2019.[3] While it is generally agreed that GCA carries an intermediate biologic behavior between classic NET and conventional adenocarcinoma, the cell origin of the tumor remains elusive. The lack of knowledge of histogenesis has led to the use of various terminologies in the literature and to the continuous debate on whether the tumor should be classified under carcinoma or NEN.[10,17] One may recall that when GCC was classified under the category of NEN in the fourth edition of the WHO tumor classification,[4] the seventh edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual actually staged it according to the criteria of adenocarcinoma because its behavior was believed to be closer to adenocarcinoma rather than carcinoid.[18] Even Subbuswamy *et al*. stated, when they coined the term GCC in 1974, that "the number of argentaffin cells observed was considerable, but no greater than is seen in some adenocarcinomas of the stomach and colon" and that "it might be

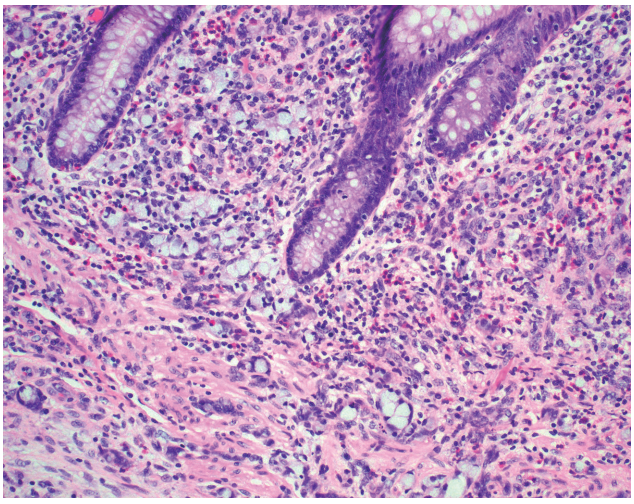

Fig. 3. Tumor clusters and single signet-ring-like cells are present around the base of crypts. No adenomatous change is seen in the appendiceal mucosa (original magnification ×400).

argued that this tumor is a type of very well-differentiated mucinous adenocarcinoma".[2]

With more recent studies, it has become clear that this tumor should be regarded as a type of adenocarcinoma.[8,11,15,19,20] The question is then if GCA is an appropriate name. Ideally, the name of a tumor should refer to its cell origin or histogenesis, that is, a tumor is best named according to the cell type from which it arises and of which it consists. A tumor may also be named according to its unique morphology, immunophenotype, molecular signature, or biologic behavior. While goblet cells are the predominant cell type in GCA, it is highly unlikely that goblet cells would be the cell origin that gives rise to the tumor. This is so because goblet cells themselves arise and differentiate from pluripotent stem cells,[21] and terminally differentiated cells are generally believed to have lost their potential to undergo further mitotic division. The presence of neuroendocrine and Paneth cells within the tumor nests as well as the exclusive appendiceal location also argue against the possibility of a goblet cell origin. Furthermore, goblet cells are not only seen in GCA, but are also commonly present in conventional adenocarcinomas, including those of the appendix and the gastrointestinal tract. From these points of view, GCA does not appear to be an ideal name for this tumor.

In addition to its nested or tubular architecture that circumferentially infiltrates the appendiceal wall in a concentric fashion, the focal connection of the tumor nests with the base of crypts in the absence of adenomatous or dysplastic change in the mucosa is another histologic feature unique to GCA (Fig. 3). This latter feature supports the current hypothesis that GCA is derived from the pluripotent intestinal stem cells at the base of crypts that are capable of undergoing divergent mucinous and neuroendocrine differentiation.[22–24] However, this unitary intestinal stem cell theory still does not explain why GCA almost never occurs in the small intestine and right colon that have more numerous crypts with cell constituents similar to or indistinguishable from those of the appendix.

As described above, a typical GCA nest contains three distinctive types of differentiated cells: goblet cells, neuroendocrine cells and Paneth cells, architecturally and cytologically recapitulating an intestinal crypt. Based on this observation as well as its basiglandular involvement of the mucosa, in 1978, Warkel *et al*. suggested the possibility that the crypts might be proliferating as a unit.[25] In 1981, Isaacson further believed that GCA was derived from lysozyme-producing cells normally present in small intestinal crypts and coined the term "crypt cell carcinoma".[26] This term has been advocated by several investigators,[15,20,27–30] but has never gained popularity probably because it specifically indicates a cell lineage that is in fact uncertain. Nevertheless, the name "crypt cell carcinoma" appears more appropriate than GCA at least at the conceptual level, as it emphasizes the crypt-like architecture and cellular composition of the tumor.

Conclusions

The name change from GCC to GCA allows pathologists to diagnose and grade this unique appendiceal tumor with a higher level of confidence and reproducibility. This is extremely important because accurate diagnosis and grading is essential to patient management and prognostication. The histogenesis of GCA remains elusive, and "crypt cell carcinoma" appears to be a more appropriate name than GCA for this tumor.

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Conflict of interest

Wang HL has been an editorial board member of the *Journal of Clinical and Translational Pathology* since May 2022. The author has no other conflict of interests to disclose.

Author contributions

Wang HL is the sole author of this article.

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