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Goblet cell carcinoid of the appendix – An interobserver variability study using two proposed classification systems

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ABSTRACT

Goblet cell carcinoid (GCC) is an uncommon tumor of the vermiform appendix. Due to a broad spectrum of morphological differentiation, subclassification and grading of GCCs remains an area of controversy. Two separate systems have proposed classifying GCC tumors into three (classical GCC; adenocarcinoma ex-GCC, signet ring cell type; adenocarcinoma ex-GCC, poorly differentiated carcinoma type) OR two subgroups (low and high grade GCC) based on morphological criteria. We independently compared the inter-observer variability associated with each classification system. Overall, both systems had moderate interobserver agreement, with the two-tiered system ($\kappa = 0.54$) performing slightly better than the three-tiered system ($\kappa = 0.42$). GI-specialist pathologists had substantial agreement for both two and three-tiered systems ($\kappa = 0.65$ vs. 0.65). Non-GI trained pathologists had lower overall agreement than GI trained pathologists, but their agreement was better using the two-tiered system ($\kappa = 0.44$) than the three-tiered system ($\kappa = 0.22$). A sub-analysis of 6 cases with a high rate of discordant classification revealed several challenges that exist in applying current criteria, including differentiating "goblet" vs. "signet ring" cell morphology, applying a 1 mm^2 criteria to multifocal non-contiguous glandular and single infiltrating cell architecture, differentiating fibro-inflammatory stroma from desmoplastic stroma, and solid architecture in cases with abundant extracellular mucin, and distinguishing "reactive" nuclear atypia from true "cytologic atypia". Despite these challenges, the study identified better agreement among GI pathologists than non-GI trained pathologists. While GI pathologist review may be helpful, further research on objective classification criteria remains an area of interest.

1. Introduction

Goblet cell carcinoid (GCC) is a rare tumor occurring almost exclusively in the vermiform appendix [1-3]. GCC constitutes about 5% of all primary appendiceal neoplasms [4]. The tumor has a mixed morphologic phenotype, as the neoplastic cells have properties of both intestinal goblet cells and neuroendocrine cells [5]. In general, the natural history of this disease is intermediate in aggressiveness, falling somewhere between appendiceal adenocarcinoma and neuroendocrine tumor [6,7]. Although many patients with GCC have a relatively indolent disease course, some present with widespread metastases to the peritoneal cavity and gynecologic tract [8,9]. GCC management recommendations are currently based on surgical and systemic therapy protocols for colorectal adenocarcinoma [10,11]. However, there are some areas of controversy in management where grading might be considered as part of a clinical decision tool, particularly in future therapeutic trials [12].

Due to the wide morphologic and prognostic spectrum of GCC, there have been recent proposals to classify GCCs using histopathologic features for risk-stratification following appendectomy. Two major classification systems have been proposed, and are briefly summarized in Table 1 [13,14]. The first, by Tang et al., classifies GCC tumors into 3 subgroups based on histomorphology: typical GCC (group A); adenocarcinoma ex GCC, signet ring cell type (group B); and adenocarcinoma ex GCC, poorly differentiated carcinoma type (group C) [13]. They demonstrated that this three-tiered classification correlates with disease specific survival. Despite detailed descriptions and illustration in the original manuscript, this classification system has received some criticism for subjective diagnostic criteria, such as "minimal" architectural distortion, "significant" cytological atypia and "large" clusters but lack of "confluent sheets" of cells [15]. The authors of a recent morphologic study of adenocarcinoma ex-GCC cases felt they could not reliably

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Table 1
Annotated GCC classification systems as outlined by each original article.

Lee et al. Features for Scoring [14]		
Cytologic atypia	At least 1 focus > 1 mm^2 in size High nuclear-to-cytoplasmic ratio with reduction or loss of intracytoplasmic mucin Nuclei are enlarged and hyperchromatic with irregular nuclear shape and contours	0: Absent 1: Present
Stromal desmoplasia	Dense fibrous connective tissue surrounding tumor cell clusters or individual tumor cells Replaces surrounding smooth muscle of the muscularis propria Results in distortion of the normal appendiceal architecture	0: Absent 1: Present
Solid growth pattern	At least 1 focus > 1 mm^2 in size Cells tightly packed together with no or minimal intervening stroma Total score out of 3	0: Absent 1: Present Low grade: 0–1 High grade: 2–3
Tang et al. Morphologic Criteria [13]		
Typical GCC (A)	Minimal cytologic atypia, minimal to no desmoplasia and minimal architectural distortion of the appendiceal wall	
Adenocarcinoma ex-GCC, signet ring cell type (B)	Discohesive single file or single cell infiltrating pattern, significant cytologic atypia Desmoplasia and associated destruction of the appendiceal wall	
Adenocarcinoma ex-GCC, poorly differentiated carcinoma type (C)	At least focal evidence of goblet cell morphology A component (> 1 low power field or 1 mm^2) not otherwise distinguishable from a poorly differentiated adenocarcinoma, which may appear as either (a) gland forming, (b) confluent sheets of signet ring cells, or c) undifferentiated carcinoma	

classify widely disseminated GCCs using the Tang classification [16].

The more recently proposed classification system, by Lee et al., classifies GGCs into 2 subgroups on the basis of histologic features: low grade (score of 0–1 out of 3) and high grade (score of 2–3 out of 3) [14]. The histologic features used in the two-tiered scoring system include cytologic atypia, stromal desmoplasia and the presence of solid growth pattern. Lee et al. contend that the two-tiered system has more objective criteria.

An inter-observer variability analysis was included in the original manuscript describing Tang's 3-tiered GCC classification system. Apart from this, there remains scant data on pathologist inter-observer variability associated with each of these two proposed classification systems. Moreover, no data exists on the variability associated with classification of GCCs by general (non-subspecialty) anatomic pathologists, who are often the first to diagnose GCC in appendectomies. The primary aim of this study was to independently compare the inter-observer variability associated with the two and three-tiered classification systems. A secondary objective was to identify histologic patterns that are associated with discordant classification by pathologists.

2. Materials and methods

2.1. Case selection

An electronic search identified 34 cases of GCC in the pathology archives at our institution from 1990 to 2015. A total of 20 cases were selected for the current review, including 8 external consultation cases referred in from the community and 12 internal surgical pathology cases. The 20 cases were selected mainly based on the quality of the slides available (typically local cases with minimal fading of the slides were chosen over cases with fading of the stain and consults with only a single archived slide). All pathologic material from each case was reviewed by a sub-specialty trained Gastrointestinal (GI) pathologist to confirm the GCC diagnosis. One slide, felt to represent the overall highest histologic grade, was selected from each case. Each slide was de-identified and assigned a study number.

2.2. Case assessment

Six pathologists (3 subspecialty GI pathologists and 3 general anatomical pathologists) volunteered to review a single slide from each case and classify the tumor using both the two and three tiered classification system. Each pathologist was provided with a summary of each grading system [13,14], including photomicrographs of salient features of each grading scheme (from the original articles) as well as a copy of the original manuscript describing each classification system. Each participant was blinded to the original reported diagnosis, demographics and case details. Cases were independently scored by each pathologist using both classification systems, blind to the opinions of the other five pathologists. Scores were entered into a database (Excel v16.0 Microsoft Corporation, Redmond, Washington) by a pathology resident who was not a case reviewer.

2.3. Statistical analysis

Data was analyzed using SPSS Statistics software (v23.0, IBM, Armonk, New York). Fleiss' kappa (κ), which assesses the reliability of agreement between a fixed number of raters who assign nominal-scale ratings to a number of items, was determined [17]. The average pairwise percent agreement (in which the agreements of all possible pairs are calculated) was determined for each scoring system. The κ scores were assessed as having slight (0.01–0.2), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80) or almost perfect (0.81–0.99) agreement between pathologists [18]. A sub-analysis was performed to determine the κ scores on the three diagnostic criteria described in the two-tiered classification system: cytologic atypia, stromal desmoplasia and presence of solid growth. The multiple parameters described in the three-tiered classification system precluded further sub analysis for inter-observer variability associated with each specific criterion.

2.4. Discordant case analysis

Six cases from the study with a high rate of discordance among pathologist reviewers were selected following completion of the independent scoring and data analysis. These six cases were reviewed by two GI-specialist pathologists to identify histologic patterns that might have contributed to high discordance.

3. Results

3.1. Interobserver variability

All 6 pathologists assessed each of the 20 GCC cases using both the two and three-tiered classification systems, as shown in Table 2. The overall κ for the three-tiered system was 0.42 (moderate agreement) versus 0.54 (moderate agreement) for the two-tiered system (Table 3).