Goblet cell carcinoid of the appendix: Two case reports and a review of the literature

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Abstract. Goblet cell carcinoid or carcinoma (GCC) is a rare tumor found incidentally during routine management of acute appendicitis. GCCs are more aggressive compared with conventional appendiceal tumors but less aggressive compared with adenocarcinomas, and they often present with serosal and mesoappendiceal involvement. We herein report two cases of acute appendicitis in a 45-year-old female and a 60-year-old male with varied clinical symptoms. Pathological examination of the appendix revealed the presence of adenocarcinoma with goblet cells and a Ki-67 index of 25% (grade 3) and 15% (grade 2), respectively. Subsequent right hemicolectomy was performed according to the current guidelines. No signs of disease recurrence or metastasis were detected during regular follow-up. However, the lack of a standardized classification system for GCC and the discrepancies in specific reliable markers renders their prognostic and predictive value in GCC at diagnosis insufficient. The present study also aimed to address current concerns regarding the diagnosis, treatment and prognosis of GCC, as well as the need to review and update current guidelines. To conclude, proper clinical management and the prediction of outcome for patients with GCC varies according to the classifications or staging criteria used by the clinicians; hence, a review of the current guidelines should be considered.

Introduction

Appendiceal carcinomas occur in adults with a mean age at onset of 55-65 years for primary tumors and 38 years for malignant tumors (1,2). First described by Gagne *et al* (2,4) in 1969, goblet cell carcinoids (GCCs) exhibit mixed neuroendocrine differentiation and intestinal-type goblet cell morphology; for this reason, they are described as an entity separate from carcinoids and mucinous adenocarcinomas. The incidence of GCC is ~1.2 cases for every million individuals per year among Caucasian women and it is less common among children (2-5). Metastasis has been documented in 8-20% of the cases, with 5-year survival rates ranging from 55 to 80% (6,7).

The diagnosis of GCC is confirmed by pathological examination based on consensus guidelines. Currently, a variety of different classification systems for the nomenclature, grading and staging of neuroendocrine tumors (NETs) are available in an attempt to segregate groups by prognostic value, management and survival (8-13). The 2010 World Health Organization (WHO) tumor classification (8) considered GCCs as a subgroup of mixed adenoneuroendocrine carcinomas (MANECs). The tumor-node-metastasis (TNM) classification of malignant tumors by the Union for International Cancer Control, the American Joint Committee on Cancer and the European Neuroendocrine Tumor Society (ENETS), consider GCCs to be adenocarcinomas (5,9). However, their complexity is such that GCCs were not included in the 2016 ENETS consensus guidelines for Neuroendocrine Neoplasms of the Appendix. Another diagnostic classification for GCC was proposed by Tang *et al* (10), based on the TNM classification for appendiceal adenocarcinomas, and has been proven useful for predicting clinical behavior and prognosis. In the Tang classification, tumors are subclassified into group A (typical GCC), group B (adenocarcinoma ex-GCC) and group C (adenocarcinoma ex-GCC; poorly differentiated). Additionally, several pathological markers and clinical findings are used to determine prognosis and the course of action for NETs, including origin, stage, grade, tumor size (<2 or >2 cm), histological differentiation (well- or poorly differentiated), invasion of muscularis propria, histopathological examination (hematoxylin and eosin, chromogranin A, synaptophysin and CD56), assessment of mitotic index (mitoses per high-power field), Ki-67 index (<2, >2 and >30%), biological behavior (benign, low-grade and high-grade), lymphovascular invasion and metastasis (10,14). In parallel, a general classification has been established for midgut, hindgut and foregut NETs based on Ki-67 index, including grades 1 (≤2%), 2 (3-20%) and 3 (>20%), as described by Rindi *et al* (15). In addition, in a recent study by Yozu *et al* (12), a new grading system was proposed, based

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Table I. Comparison of clinicopathological characteristics of GCC between the two cases.

Clinical characteristics	Case 1	Case 2
Age, years	45	60
Carcinoid syndrome	No	No
Primary symptoms	Abdominal tenderness in the right lower quadrant	Abdominal pain, fever, nausea and decreased appetite
Gross appearance	<2 cm, well-defined mass	<2 cm, ill-defined mass
Microscopic appearance		
Morphology	Clusters of goblet cells or signet ring cells	Cords of goblet cells
Atypia	Minimal	Minimal
Mitoses	Absent	Present
Vascular and perineural invasion	Absent	Absent
Infiltrative margins	Absent	Absent
Staining		
Mucicarmine/PAS	Positive in goblet cells	Positive in goblet cells
IHC		
MNF-116	Positive	Positive
Chromogranin A	Positive	Positive
Synaptophysin	Positive	Positive
Cytokeratin-20	Positive	Positive
CDX-2	Positive	Positive
CD56	Positive	Positive
CEA	Positive	Positive
WT-1	Negative	Negative
Cytokeratin-7	Negative	Negative
Ki-67	25%	15%

GCC, goblet cell carcinoid; PAS, periodic acid-Schiff; IHC, immunohostochemistry; CEA, carcinoembryonic antigen; WT-1, Wilms' tumor-1.

on the classification of GCCs as adenocarcinomas, similar to colorectal adenocarcinoma. This complex grading system represents a challenge for the pathologist in routine practice.

Upon diagnosis, surgical management by right hemicolectomy is recommended as the standard surgical approach by the North American Neuroendocrine Tumor Society (NANETS) consensus guidelines if the tumor invasion is at the base of the appendix, for tumors sized >2 cm, and/or if there is evidence of mesoappendiceal or lymphovascular infiltration with lymph node involvement and for intermediate or high-grade tumors (13). Postoperatively, adjuvant chemotherapy includes regimens with or without debulking followed by chemotherapy similar to that for the treatment of adenocarcinoma of the colon (7,10,13). We herein report the cases of two GCC patients with varied clinical presentation who underwent right hemicolectomy, and provide a literature review of similar clinical cases.

Case report

Case 1. A 45-year-old female patient presented to the emergency department of Barzilai Medical Hospital with lower abdominal pain and nausea that started 1 day prior to admission. The findings on physical examination and blood tests were unremarkable, except for abdominal tenderness in the right lower quadrant. There were no associated comorbidities. Abdominal contrast-enhanced computed tomography confirmed the diagnosis of acute appendicitis and an appendectomy was performed. Additionally, the patient had previously undergone hysterectomy due to leiomyoma. Macroscopically, the appendix appeared inflamed and dilated; on palpation, a solid, moderately hard, elastic mass with an estimated size of 1.5x0.5 cm was identified. Histopathological examination of the appendix revealed a well-preserved appendiceal epithelium, with no evidence of neoplastic changes. However, circumferential involvement of the appendiceal wall by a poorly differentiated adenocarcinoma with longitudinal extension along the length of the appendix was observed. The main morphological characteristics included i) the presence of mucin-containing goblet-shaped epithelial cells arranged in small round or oval clusters; ii) disorganized arrangement of the tumor cells, with predominant signet ring cells with focal moderate/severe cellular atypia and irregular hyperchromatic nuclei; iii) cells exhibiting a single-cell infiltrating pattern with areas of confluent growth and iv) desmoplastic response within the appendiceal submucosal wall, and muscle bundles of the muscularis propria divided by tumor cell clusters (Fig. 1). The tumor cells were positive for MNF-116, chromogranin A, synaptophysin, cytokeratin-20, CDX-2, CD56, carcinoembryonic antigen (CEA) (signet ring cell and goblet cell type); however, they were negative for Wilms' tumor-1

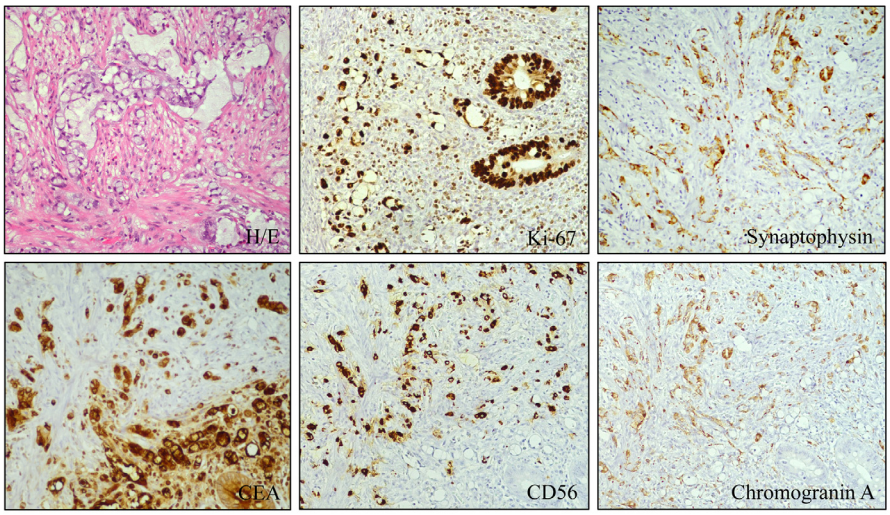

Figure 1. Adenocarcinoma ex-GCC, poorly differentiated adenocarcinoma type (group C) in case 1. Gland-forming carcinoma and poorly differentiated adenocarcinoma components are indistinguishable. Immunohistochemical staining of the appendiceal tissue revealed frequent positive expression of Ki-67, synaptophysin, CEA, CD56 and chromogranin A. Magnification, x100. GCC, goblet cell carcinoid; H/E, hematoxylin and eosin. CEA, carcinoembryonic antigen.

Table II. Characteristics and outcomes of GCC patients.

Author	All patients	Median age (range), years	Sex	Ki-67	R/H (%)	(Refs.)
Clift *et al*	21	55 (32-77)	9 M, 12 F	<2%: 3/18 3-20%: 6/18 <20%: 9/18	15/21 (71)	(6)
Tsang *et al*	86	54 (25-91)	42 M, 44 F	<2%: 1/86 3-20%: 12/86 <20%: 6/86 Unknown: 67/86	51/67 (76)	(16)
Madsen *et al*	48	52 (32-75)	18 M, 30 F	N/A	16/21 (76)	(17)
Nonaka *et al*	105	54 (25-79)	54 M, 51 F	N/A	45/105 (43)	(18)
Yu *et al*	15	52 (36-74)	9 M, 6 F	31.9±6.3%[a]	N/A	(19)
Lamarca *et al*	74	56 (26-83)	34 M, 40 F	N/A	42/74 (57)	(21)

[a]Ki-67 index is presented as the mean ± standard error. M, male; F, female; R/H, right hemicolectomy; GCC, goblet cell carcinoid.

(WT-1) and cytokeratin-7. Ki-67 was positive in ~25% of the tumor cells (grade 3). Signet ring cells were positive for mucicarmine, a natural gastrointestinal tumor type mucin, and PAS. The tumor invaded through the muscularis propria into the subserosa (Table I). Elective right hemicolectomy and bilateral oophorectomy were performed, according to the current guidelines (13), followed by adjuvant chemotherapy with capecitabine and oxaliplatin (XeLox) for eight cycles. Macroscopic examination revealed no changes in the large intestine, with preserved rugal folds and ileocecal valve. The analysis of 24 regional lymph nodes revealed no metastatic changes. Since then, the patient has been on regular follow-up and no signs of disease recurrence have been detected within 2 years.

Case 2. A 60-year-old male patient presented to the emergency department with abdominal pain, fever, nausea and decreased appetite over the previous 2 days. The patient displayed no signs of acute abdomen suggestive of acute appendicitis. There were no associated comorbidities. Abdominal ultrasound revealed appendiceal inflammation, with a transverse appendiceal diameter of 8 cm. The patient was operated for acute appendicitis. Macroscopically, the specimen was intact, with neoplastic proliferation in the distal portion of the appendix (1x1.2 cm). Additionally, a superimposed perforated diverticular structure with exudate over the serosal surface was identified. The microscopic appearance indicated a tumor cell nest pattern composed of large goblet cells mimicking lumen-devoid crypts. Additionally, cords of single enlarged cuboidal-shaped goblet cells with macronucleoli and some mitotic figures were observed, which were absent in Case 1. The specimen exhibited no lymphovascular space invasion. The immunohistochemical profile of the tumor was identical to that in Case 1. Ki-67 staining was positive in ~15% of the tumor cells (Grade 2). Signet cells were mucicarmine- and PAS-positive (Table I). Elective right hemicolectomy was performed (13). Macroscopic examination revealed no macroscopic changes in the large intestine, and regional analysis of 21 lymph nodes revealed no metastatic changes. The patient declined adjuvant chemotherapy. Over a clinical follow-up period of 10 years, no tumor recurrence has been observed, and the 5-HIAA levels have remained normal.

Discussion

Appendiceal carcinomas are found incidentally during surgery in cases of acute appendicitis, representing 1% of appendectomies (2). Appendiceal cancer presents with significant morphological diversity and is further classified into carcinoid (NET), mucinous cystadenocarcinoma, adenocarcinoma, GCC and signet ring cell tumors (2,3). Due to the fact that GCCs are discovered incidentally during routine appendectomy, there is a lack of a standardized classification system and discrepancies regarding specific reliable markers, such as Ki-67; this may lead to misdiagnosis and suboptimal treatment and surgical approaches (i.e., hemicolectomy or multivisceral resection). A literature review of GCCs revealed a constant steady increase in the number of GCC cases over the past decade, evidenced by an increase in case series reports, possibly due to improved detection methods and clinicians' awareness (Table II). The aim of the present case report was to emphasize the lack of a standardized classification system and reliable markers for adequate prognosis, management and/or treatment.

For clinicians, it is a challenging task to develop an evidence-based treatment plan. In addition, there remains the question of whether a right hemicolectomy should have been performed in Case 2. Although surgery in this case is recommended by both NANETS and ENETS (5,13), the extent of surgical resection with appendectomy versus right hemicolectomy is debated. Recent evidence suggests limited or no benefit of right hemicolectomy, primarily in patients with low-grade and/or limited disease burden (20). In another study, Lamarca *et al* (21) assessed the effects of right hemicolectomy on disease-free survival. The results suggested a higher risk of relapse in patients who underwent right hemicolectomy vs. those receiving appendectomy alone. Despite these results, the authors concluded that appendectomy alone is only justifiable in patients with Tang class A, stage I/II tumours that are unable to undergo surgery due to comorbidities. A meta-analysis by Varisco *et al* (22) including 100 patients with GCC also failed to identify a significant benefit of hemicolectomy relative to appendectomy.

The marker Ki-67, used to measure cell proliferation, is a widely used marker for NET grading and staging (23,24). Additionally, Ki-67 has exhibited a positive correlation with known prognostic factors (tumor size and metastatic status) and has been extensively investigated in pancreatic and gastrointestinal NETs (25,26); however, no studies have yet provided sufficient evidence for GCCs. Currently, prognosis based on the pathological gradient is mostly dependent on the Ki-67 proliferative index, despite its dynamic change over time (21). A recent study by Liu *et al* (27) examined the role of Ki-67 as a prognostic factor for GCC. That study, which included 12 patients with GCC, revealed no prognostic significance for GCC. The fact that NETs comprise a heterogeneous group of tumors renders the interpretation of the Ki-67 index for GCC unreliable without an adequate researched cut-off value, which is currently set between 20 and 30% for digestive tract NETs (10,14). In the present case report, Case 1 had a Ki-67 index of 25%, whereas Case 2 had a Ki-67 index of 15%. Both patients underwent right hemicolectomy based on the guidelines; however, surgical intervention should be based on tumor size, invasiveness and careful evaluation of the morphological characteristics of GCC in addition to the Ki-67 index. An important morphological characteristic in GCC reflecting prognosis and survival is the adenocarcinoma component, which may be classified into signet ring-cell and non-signet ring-cell types (28,29). Based on the results reported by Taggart *et al* (28), the amount of the carcinomatous component should be included in the diagnosis of GCC, since it is associated with the clinical characteristics and stage. Consequently, a consensus guideline assessing the value of the new staging classification is of paramount importance, since there is a 40% risk of morbidity with right hemicolectomy in elderly patients with respiratory and cardiovascular complications (cardiac arrest, pneumonia, pulmonary embolism) (7). Finally, an update of the current 2008 guidelines (7) should consider the following recommendations on the section for GCC of the appendix: i) Tumor marker use (MNF-116, chromogranin A, synaptophysin, keratin-20, CDX-2, CD56, CEA and Ki-67) along with the current staging system (7,20); ii) addition of a Ki-67 cut-off point of >25% in cases treated with right hemicolectomy; and iii) in the early stages, when the tumor is confined to the mucosa and defined as carcinoma *in situ*, appendectomy alone is adequate, regardless of the Ki-67 value (Tang class A, stage I/II tumors). However, in more advanced stages, when submucosa involvement and possibly lymphatic spread have occurred, prognosis should be revised along with other markers (i.e., Ki-67) to determine whether right hemicolectomy should be performed. To conclude, the overall survival for patients with GCCs varies according to the different references, classifications or staging criteria used. Hence, there is a need for standardization of the classification system to ensure optimal clinical management and outcome predictions.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

NA and TH were involved in diagnosis, treatment and data acquisition. EGC was involved in analysis and interpretation of the data and drafting of the manuscript. AL performed the pathological examination of the specimens. MS was involved in diagnosis and critical revision of the manuscript. AD, EGC and MS contributed to the critical revision and final approval of the manuscript. All authors have read and approved the final version of this manuscript for publication.

Ethics approval and consent to participate

Institutional Ethics Board approval was obtained and both patients signed an informed consent form. The analysis of the data was conducted according to the principles outlined in the Declaration of Helsinki.

Patient consent for publication

Written consent was obtained from the patients regarding surgical treatment, pathological examination and publication, including associated images.

Competing interests

All authors declare that they have no competing interests.

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