GOBLET CELL CARCINOID

Hanlin L. Wang, MD, PhD
University of California Los Angeles
hanlinwang@mednet.ucla.edu

Goblet cell carcinoid (GCC) is a unique type of mixed endocrine-exocrine neoplasm, almost exclusively seen in the appendix. Historically, it has been variably termed as adenocarcinoid, mucinous carcinoid, microglandular carcinoma, amphicrine neoplasm, mucin-producing neuroendocrine tumor or carcinoma, and crypt cell carcinoma. GCC is the preferred term in the current literature, but this remains debatable. Extraappendiceal GCC is exceedingly rare and has been reported to occur in the stomach, small bowel and colon [1]. This tumor was first described by Gagne and colleagues in 1969 and the name of GCC was coined by Subbuswamy and colleagues in 1974.

GCC is found in 0.3-0.9% of appendectomies and accounts for 35-58% of all appendiceal neoplasms [2, 3]. In the study by Pahlavan and Kanthan [4] who reviewed nearly 600 cases published in 57 articles from 1966 to 2004, the mean age of the patients was 59 years (ranging from 18 to 89 years), which was about 20 years older than that for classic carcinoid of the appendix. It affects males and females equally in most studies. The most common clinical presentation is acute appendicitis. In patients with disseminated disease, abdominal pain or a lower abdominal palpable mass may be the initial presentation.

Unlike classic carcinoid tumor, GCC rarely forms a well-defined mass lesion. Instead, it usually diffusely infiltrates the appendiceal wall circumferentially in a concentric manner. The hallmark of GCC is the presence of small tight clusters, nests or cords of tumor cells that exhibit a goblet cell or signet-ring cell morphology with a small compressed nucleus and conspicuous intracytoplasmic mucin. Most tumor clusters are solid and do not show luminal formation. Small extracellular mucin pools, which frequently contain clusters of tumor cells, are commonly seen. Nuclear atypia is typically minimal and mitoses are infrequent. Scattered Paneth cells may be present. Characteristically, the appendiceal mucosa does not show adenomatous or dysplastic changes. In fact, the mucosa is typically spared, except for the areas where tumor nests are connected with the base of crypts. Despite its infiltrative growth, desmoplastic reaction is not a feature of typical GCC. In contrast to classic carcinoids that typically show strong and diffuse immunoreactivity for neuroendocrine markers chromogranin and synaptophysin, GCC often shows only scattered positive cells.

The histogenesis of GCC remains to be elucidated. It is generally believed, however, that it derives from the pluripotent stem cells at the base of crypts that are capable of undergoing dual mucinous and neuroendocrine differentiation (unitary intestinal stem cell theory) [5]. Whether GCC should be considered as a variant of neuroendocrine tumor or a special type of adenocarcinoma has been a subject of debate. Indeed, studies have shown that GCC shares many features with classic carcinoid and adenocarcinoma of the appendix at the immunophenotypical and molecular levels (Table 1). Nevertheless, GCC is known to be frequently associated with adenocarcinoma, either signet-ring cell type or other poorly differentiated forms, which is

believed to represent a progression from preexisting GCC. In that case, a diagnostic term of mixed adenoneuroendocrine carcinoma as recommended by WHO Tumor Classification [6] or adenocarcinoma ex GCC by other investigators [7] is preferred.

Table 1. Immunophenotypical and molecular features of GCC in comparison with classic carcinoid and conventional adenocarcinoma [8-12]

Marker	GCC	Classic carcinoid	Adenocarcinoma
CEA	+	-	+
CK7	+/-	-	+/-
CK20	+	-	+
CDX2	+	+/-	+
CD56	+/-	+	-
Synaptophysin	+/-	+	-
Chromogranin	+/-	+	-
Beta-catenin (nuclear)	-	-	+
p53	-	-	+
Ki67	intermediate	low	high
MUC1	-	-	+
MUC2	+	-	+/-
KRAS mutation	-	-	+/-
BRAF mutation	-	-	+/-
MSI	-	-	+/-

GCC is thought to have a biologic behavior intermediate between classic carcinoid and conventional adenocarcinoma. At the time of diagnosis, over 50% of the cases may have already invaded through the serosa or into the mesoappendix. Trans-coelomic/peritoneal spread is the most common route of metastasis, which involves the peritoneal surface of the abdominal cavity and pelvis, as well as ovaries in female patients. Approximately 15-30% of cases may have metastasized to regional lymph nodes. Metastasis to solid organs such as the liver or lungs is uncommon. Five-year disease-specific survival varies from 58 to 81% depending on different studies [5, 13]. The 10-year survival rate is estimated to be 60% [14]. Peritoneal carcinomatosis is the most common cause of death.

Treatment options are primarily based on tumor stage [5]. Stage I tumors may be adequately treated with appendectomy alone. For higher stage tumors, right hemicolectomy is recommended with the aims of complete excision, adequate lymph node sampling and appropriate disease staging, but this approach has been controversial and is not universally endorsed [13, 15]. Prophylactic oophorectomy is also advocated by some authors, particularly for postmenopausal female patients, due to the high risk of ovarian metastasis. Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy may be an option for patients with peritoneal carcinomatosis [2]. Adjuvant chemotherapy with regimens similar to those for colorectal adenocarcinoma is also recommended for patients with disseminated or recurrent disease.

In addition to stage, tumor histology is another important determinant of patient survival. Interestingly, Ki67 proliferation index, which is a very useful prognostic parameter for classic carcinoid tumors, has been shown to have no prognostic value for GCC [13, 16, 17]. The 2 cm

size criterion used for classic carcinoid to help decide if the patient needs further right hemicolectomy after appendectomy may be difficult to apply to GCC because it rarely forms a mass lesion. Histologic assessment to identify tumor components that may signify a more aggressive behavior is thus imperative.

The distinction of mixed adenoneuroendocrine carcinoma from pure GCC was initially defined by Burke et al [18] as carcinomatous components accounting for >50% of the tumor volume. Carcinomatous growth patterns described in this early study included fused or cribriform glands, single file structures, infiltrating signet ring cells, or sheets of solid cells. This diagnosis (termed "mixed carcinoid-adenocarcinoma") was associated with a worse prognosis in comparison with GCC. A more recent study by Taggart et al [19] further stratified GCC and mixed GCC-adenocarcinoma into 3 groups: 1) GCC or GCC with <25% adenocarcinoma, 2) GCC with 25-50% adenocarcinoma, and 3) GCC with >50% adenocarcinoma. The overall survival was 83.8±34.6, 60.6±30.3, and 45.6±39.7 months for groups 1, 2, and 3, respectively. These studies highlight the importance of assessing the volume of adenocarcinoma in appendiceal GCC cases.

Table 2. Histopathologic classification of GCC by Tang et al [7]

Group	Morphologic criteria
A	Well defined goblet cells arranged in clusters or cohesive linear pattern Minimal cytologic atypia Minimal to no desmoplasia Minimal architectural distortion of the appendiceal wall Degenerative change with extracellular mucin is acceptable
B	Goblet cells or signet-ring cells arranged in irregular large clusters, but lack of confluent sheets of cells Discohesive single file or single cell infiltrating pattern Significant cytologic atypia Desmoplasia and associated destruction of the appendiceal wall
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

Tang et al [7] also subclassified GCC and mixed GCC-adenocarcinoma into 3 groups: A) typical GCC, B) adenocarcinoma ex GCC, signet-ring cell type, and C) adenocarcinoma ex GCC, poorly differentiated carcinoma type (Table 2). The 3-year and 5-year disease-specific survival rates were 100% and 100% for group A, 85% and 36% for group B, and 17% and 0% for group C. The mean survival time was close to 10 years for group A, but 43±6 months for group B, and 31±6 months for group C. When only the patients with metastasis (stage IV) were analyzed, the 3-year and 5-year survivals were still 100% for group A, with only one patient died after 119 months. The 3-year and 5-year survivals were 82% and 38% for group B. Group C patients had the worse outcome, comparable to those with stage-matched conventional adenocarcinoma of the appendix.

While the classification proposed by Tang et al has proven to be useful according to a few recent studies [13, 17, 20], there exist difficulties in distinguishing signet-ring cells from goblet cells in order to separate group B from group A [21]. Pathologists may even have difficulties to separate group B from group C [13]. In the study by Taggart et al [19], GCC patients with signet-ring cell adenocarcinoma had a worse prognosis when compared to patients with other poorly differentiated adenocarcinoma. These data are in contrast to those reported by Tang et al [7].

Table 3. Simplified 2-tier histologic grading system by Lee et al [22]

Feature	Description	Scoring
Cytologic atypia	At least one focus > 1 mm^2 in size* High N:C ratio with reduction in 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 one focus > 1 mm^2 in size Loss of distinct cell cluster architecture Cells tightly packed together with no or minimal intervening stroma***	0: Absent 1: Present
Total score		0-1: Low grade 2-3: High grade

*Four contiguous high power fields (x400) with a 0.55-mm field diameter are used to assess a 1 mm^2 area. At least one cytologically atypical tumor cell is required to be in each high power field.
**Desmoplasia of the submucosa or subserosal fat or serosal adhesions are insufficient.
***Spatially separate small foci of solid growth pattern, which aggregate to a total of 1 mm^2, are insufficient.

More recently, Lee et al [22] proposed a simplified 2-tier histologic grading system, which separated GCC cases into low grade and high grade categories (Table 3). Follow-up data showed good prognosis in patients with low grade histology with median and 10-year overall survivals of 51 months and 80.5%, respectively. These are in marked contrast to patients with high grade histology whose median and 10-year overall survivals were 16.5 months and 0%. Using this 2-tier system, nearly all (98%) of group A tumors (using the histologic criteria defined by Tang et al) were classified as low grade. All (100%) group C tumors were classified as high grade. Group B tumors were classified as either low grade (40%) or high grade (60%). An advantage of this simplified system is that it does not rely on a clear distinction between goblet cells and signet ring cells. However, histologic judgement of cytologic atypia can still be challenging to pathologists, and some degree of subjectivity appears unavoidable as authors admitted [22].

Interestingly, none of the above studies on mixed adenoneuroendocrine carcinoma or adenocarcinoma ex GCC has used WHO criteria requiring >30% for both components [6]. In a recent study on SEER data by Brathwaite et al [23] which used WHO criteria, appendiceal mixed adenoneuroendocrine carcinoma was demonstrated to be more aggressive than GCC. Specifically, the study included 249 appendiceal mixed adenoneuroendocrine carcinomas, 944 GCCs, 950 classic carcinoids, and 579 signet-ring cell carcinomas. The median overall survivals for these tumors were 6.5, 13.8, 39.4, and 2.1 years, respectively. More patients with mixed adenoneuroendocrine carcinoma had stage III or IV disease at the time of diagnosis (46%) than those with GCC (16%).

In summary, GCC is a unique clinicopathologic entity but is frequently associated with adenocarcinoma. Recent studies have shown that careful histologic assessment to identify and quantify adenocarcinoma is critically important in determining prognosis and thus in guiding the clinical management. From this perspective, the entire appendectomy specimen should be examined histologically when a GCC case is encountered.

References

1. Gui X, et al. Goblet cell carcinoids at extraappendiceal locations of gastrointestinal tract: an underrecognized diagnostic pitfall. J Surg Oncol 2011; 103:790-5.
2. Holt N, Grønbæk H. Goblet cell carcinoids of the appendix. ScientificWorldJournal. 2013; 2013:543696.
3. Rossi RE, et al. Goblet cell appendiceal tumors: management dilemmas and long-term outcomes. Surg Oncol. 2015; 24:47-53.
4. Pahlavan PS, Kanthan R. Goblet cell carcinoid of the appendix. World J Surg Oncol. 2005; 3:36.
5. Roy P, Chetty R. Goblet cell carcinoid tumors of the appendix: an overview. World J Gastrointest Oncol 2010; 2:251-8.
6. Bosman FT, et al. WHO Classification of Tumours of the Digestive System, 4th edition. IARC, Lyon, 2010.
7. Tang et al. Pathologic classification and clinical behavior of the spectrum of goblet cell carcinoid tumors of the appendix. Am J Surg Pathol 2008; 32:1429-43.
8. Shenoy S. Goblet cell carcinoids of the appendix: tumor biology, mutations and management strategies. World J Gastrointest Surg 2016; 8:660-9.
9. Dimmler A et al. EGFR, KRAS, BRAF-mutations and microsatellite instability are absent in goblet cell carcinoids of the appendix. Pathol Res Pract. 2014; 210:274-8.
10. Alsaad KO, et al. Cytokeratins 7 and 20 immunoexpression profile in goblet cell and classical carcinoids of appendix. Endocr Pathol. 2007; 18:16-22.
11. Jiang Y, et al. Clinicopathological features and immunoexpression profiles of goblet cell carcinoid and typical carcinoid of the appendix. Pathol Oncol Res. 2011; 17:127-32.
12. van Eeden S, et al. Goblet cell carcinoid of the appendix: a specific type of carcinoma. Histopathology. 2007; 51:763-73.
13. Lamarca A, et al. Appendiceal goblet cell carcinoids: management considerations from a reference peritoneal tumour service centre and ENETS centre of excellence. Neuroendocrinology 2016; 103:500-17.

14. McCusker ME, et al. Primary malignant neoplasms of the appendix: a population-based study from the surveillance, epidemiology and end-results program, 1973-1998. Cancer 2002; 94:3307-12.
15. Varisco B, et al. Adenocarcinoid of the appendix: is right hemicolectomy necessary? A meta-analysis of retrospective chart reviews. Am Surg 2004; 70:593-9.
16. Liu E, et al. The role of Ki-67 in predicting biological behavior of goblet cell carcinoid tumor in appendix. Am J Surg. 2011; 202:400-3.
17. Olsen IH, et al. Goblet cell carcinoids: characteristics of a Danish cohort of 83 patients. PLoS One. 2015; 10:e0117627.
18. Burke AP, et al. Goblet cell carcinoids and related tumors of the vermiform appendix. Am J Clin Pathol. 1990; 94:27-35.
19. Taggart MW, et al. Goblet cell carcinoid tumor, mixed goblet cell carcinoid-adenocarcinoma, and adenocarcinoma of the appendix: comparison of clinicopathologic features and prognosis. Arch Pathol Lab Med. 2015; 139:782-90.
20. Reid MD, et al. Adenocarcinoma ex-goblet cell carcinoid (appendiceal-type crypt cell adenocarcinoma) is a morphologically distinct entity with highly aggressive behavior and frequent association with peritoneal/intra-abdominal dissemination: an analysis of 77 cases. Mod Pathol. 2016; 29:1243-53.
21. Wang HL, Dhall D. Goblet or signet ring cells: that is the question. Adv Ant Pathol 2009; 16:247-54.
22. Lee LH, et al. Simplified 2-tier histologic grading system accurately predicts outcomes in goblet cell carcinoid of the appendix. Hum Pathol. 2015; 46:1881-9.
23. Brathwaite S, et al. Appendiceal mixed adenoneuroendocrine carcinoma: a population-based study of the Surveillance, Epidemiology, and End Results Registry. Front Oncol. 2016; 6:148.