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Original contribution

Appendiceal goblet cell carcinoid: common errors in staging and clinical interpretation with a proposal for an improved terminology☆

Kwun Wah Wen MD, PhD[a], Gillian Hale MD, MPH[a], Nafis Shafizadeh MD[b], Mojgan Hosseini MD[c], Anne Huang MD, MPH[d], Sanjay Kakar MD[a,*]

[a]*Department of Pathology, University of California, San Francisco, San Francisco, CA 91343, United States*
[b]*Kaiser Permanente, Woodland Hills, CA 91367, United States*
[c]*University of California, San Diego, San Diego, CA 92093, United States*
[d]*Vista Pathology, Medford, OR 97504, United States*

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Summary Goblet cell carcinoid (GCC) is staged and treated as adenocarcinoma (AC) and not as neuroendocrine tumor (NET) or neuroendocrine carcinoma. The term *carcinoid* may lead to incorrect interpretation as NET. The aim of the study was to explore pitfalls in staging and clinical interpretation of GCC and mixed GCC-AC, and propose strategies to avoid common errors. Diagnostic terminology, staging, and clinical interpretation were evaluated in 58 cases (27 GCCs, 31 mixed GCC-ACs). Opinions were collected from 23 pathologists using a survey. Clinical notes were reviewed to assess the interpretation of pathology diagnoses by oncologists. NET staging was incorrectly used for 25% of GCCs and 5% of mixed GCC-ACs. In the survey, 43% of pathologists incorrectly indicated that NET staging is applicable to GCCs, and 43% incorrectly responded that Ki-67 proliferation index is necessary for GCC grading. Two cases each of GCC and mixed GCC-AC were incorrectly interpreted as neuroendocrine neoplasms by oncologists, and platinum-based therapy was considered for 2 GCC-AC cases because of the mistaken impression of neuroendocrine carcinoma created by use of the World Health Organization 2010 term *mixed adenoneuroendocrine carcinoma*. The term *carcinoid* in GCC and use of *mixed adenoneuroendocrine carcinoma* for mixed GCC-AC lead to errors in staging and treatment. We propose that *goblet cell carcinoid* should be changed to *goblet cell carcinoma*, whereas GCC with AC should be referred to as *mixed GCC-AC* with a comment about the proportion of each component and the histologic subtype of AC. This terminology will facilitate appropriate staging and clinical management, and avoid errors in interpretation.

1. Introduction

Goblet cell carcinoid (GCC) is a malignant primary epithelial tumor of the appendix composed of tumor cells that resemble goblet cells and often shows positive staining with neuroendocrine markers like synaptophysin and chromogranin [1]. The term *goblet cell carcinoid* was introduced by

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* Corresponding author at: Department of Anatomic Pathology, GI-Hepatobiliary Pathology, University of California, San Francisco, 505 Parnassus Ave, San Francisco, CA 94143, USA.
E-mail address: sanjay.kakar@ucsf.edu (S. Kakar).

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Subbuswamy et al in 1974 to reflect intestinal-type goblet cell morphology and expression of neuroendocrine markers [2-6]. Other terms that have been used to describe GCC include *crypt cell carcinoma* [7,8], *microglandular carcinoma, adenocarcinoid* [7,9-11], and *mucinous carcinoid tumor* [10,12].

The inclusion of the term *carcinoid* in GCC leads to potential confusion with neuroendocrine tumor (NET) [13]. GCCs harbor the potential for lymph node and peritoneal metastases [14-19], and are staged as adenocarcinomas (ACs) as per the American Joint Committee on Cancer (AJCC) recommendations [20]. Like ACs, the T category for GCC is based on depth of invasion, whereas the T category of appendiceal NETs is based on tumor size [20,21]. The grading of NETs is based on mitoses and Ki-67 proliferation index. Although these parameters may be of prognostic relevance in GCC, the grading scheme used for NET is not applicable to GCC. The surgical approach and management of NETs and GCCs are also different. The consensus guidelines by the North American Neuroendocrine Tumor Society and European Neuroendocrine Tumor Society recommend right hemicolectomy after initial appendectomy for GCC, regardless of the depth of invasion, given the high metastatic risk and poor prognosis with metastatic disease [22,23]. Adjuvant chemotherapy regimen with 5-fluorouracil, leucovorin and oxaliplatin-4 is recommended for cases with nodal or peritoneal involvement [24]. On the other hand, surgical resection is indicated in well-differentiated NET only in the presence of high-risk features [1], whereas platinum-based therapy used in poorly differentiated neuroendocrine carcinoma is not applicable to GCC.

GCC can be accompanied by an additional component that resembles an AC, which can be conventional, mucinous, or signet ring cell type. These tumors have been designated by a number of different terms. The 2010 World Health Organization (WHO) classification [25] uses the term *mixed adenoneuroendocrine carcinoma* (MANEC) [26] for these cases, which is potentially misleading because these cases do not have a component of high-grade neuroendocrine carcinoma [1]. Tang et al [27] have proposed dividing these tumors based on a 3-tier scheme. The first category is pure GCC, and the other 2 comprise GCC with an AC component. In this scheme, the tumor is referred to as *adenocarcinoma ex goblet cell carcinoid, signet ring cell type* when the AC component is a signet ring cell carcinoma and as *adenocarcinoma ex goblet cell carcinoid, poorly differentiated type* when the AC component is a poorly differentiated carcinoma [27]. Other proposed schemes include stratification of GCC into low grade and high grade, the latter referring to cases of GCC with an additional AC component [28]. Both the 3-tier and 2-tier schemes have been shown to predict survival [27,28].

The genetic features of GCC have not been widely studied. *KRAS* mutations are absent or rare [4,29,30]. The data on p53 status are variable, ranging from negative by immunohistochemistry [4,29] on one hand and presence of *TP53* mutation in one-fourth of the cases on the other [30]. Poorly differentiated AC component of mixed GCC-AC can be positive for p53 by immunohistochemistry [27]. Other mutations seen in gastrointestinal ACs like *DPC* and *CTNNB1* mutations have not been observed [4,29]. Allelic loss of chromosomes 11q, 16q, and 18q have been reported [29].

This study explores the pitfalls of GCC terminology that can lead to errors in staging, grading, and clinical interpretation, and proposes a new terminology to avoid common errors and appropriately report the findings to surgeons and oncologists for appropriate management.

2. Materials and methods

The study comprises 58 cases of appendiceal GCC and mixed GCC-AC from the University of California, San Francisco Medical Center (retrospective search of surgical pathology database from January 1995 to June 2015); University of California, San Diego; Kaiser Permanente at Woodland Hills; and Vista Pathology at Medford. The study was approved by the institutional review board. The terminology for diagnoses, staging protocol, clinical interpretation, and management were obtained from pathology reports for 27 GCCs and 31 mixed GCC-ACs. The hematoxylin-eosin–stained slides were independently reviewed by 2 pathologists to confirm the diagnoses. A 4-question survey (Fig. 1) was sent to more than 50 pathologists, including subspecialty-trained gastrointestinal pathologists and general pathologists who routinely signed out gastrointestinal pathology.

3. Results

3.1. GCC: terminology and staging

For GCC, the term *goblet cell carcinoid* was used in 25 of 27 (93%) cases (Table 1). More than 1 term was used in the final diagnosis in 12 cases. The other terms included *adenocarcinoid* (n = 4, 15%) and *mixed adenoneuroendocrine carcinoma* (MANEC) (n = 2, 7%). Staging information was provided in the pathology report in 8 of 27 (30%) GCC cases. Of these, 6 (75%) were staged using the protocol for AC, whereas the NET protocol was used in 2 (25%) cases.

3.2. GCC-AC: terminology and staging

For the 31 cases of mixed GCC-AC, the term *adenocarcinoma ex goblet cell carcinoid* (AC ex GCC) was used in 16 (52%) cases, followed by *mixed goblet cell carcinoid–adenocarcinoma* (GCC-AC) in 11 (35%) cases, *mixed adenoneuroendocrine carcinoma* (MANEC) in 7 (23%) cases, and *signet ring/goblet cell adenocarcinoma* in 1 (3%) case (Table 2). The AC component in the mixed GCC-AC was signet ring carcinoma (n = 13), poorly differentiated AC (n = 7), well/moderately differentiated AC (n = 8), and mucinous carcinoma (n = 3). Mixed histologic types were observed in 7