Combined goblet cell carcinoid and mucinous cystadenoma of the vermiform appendix

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INTRODUCTION
Goblet cell carcinoid (GCC) of the vermiform appendix is an uncommon neoplasm. It is characterized by dual endocrine and glandular differentiation. Whether goblet cell carcinoid represents a morphological variant of appendiceal classical carcinoid or a mucin-producing adenocarcinoma is a matter of conjecture. Rare cases of GCC combined with other benign and malignant epithelial appendiceal neoplasms have been reported; the relationship between GCC and these neoplasms is not clear. Herein, we report an unusual and rare case of combined GCC and mucinous cystadenoma (MCA) of the vermiform appendix and discuss the possible related histopathogenesis.

CASE REPORT
A 46-year-old woman presented with severe acute pain in the right iliac fossa and periumbilical region. Ultrasound and a computed tomography scan revealed a mucocele in the vermiform appendix, with a well defined lesion located at the mid zone of the appendix. The patient underwent right hemicolectomy, and her postoperative clinical course was uneventful. Gross examination of the surgical specimen showed an enlarged appendix, which was filled with thick mucinous material. A distinct lesion which involved the appendiceal wall, and measured 1.5 cm maximally, was identified in the mid-portion of the appendix. There was no evidence of perforation, extravasation of mucin into the periappendiceal tissue, or pseudomyxoma peritonei during surgery.

Histopathological examination showed combined GCC and MCA of the vermiform appendix (Figure 1A). The appendiceal lumen was dilated and lined by mucin-containing columnar epithelial cells (Figure 1B). There was no significant cytologic atypia, and no mitotic figures were identified. Papillary configurations of the lining epithelium, and mild epithelial pseudostratification were present. In addition, the appendiceal wall was infiltrated by glandular structures of various sizes which
were arranged in nests and tubules. These glandular structures comprised 2 distinct types of cells: (1) small to intermediate sized monotonous neuroendocrine cells with a small amount of finely granular eosinophilic cytoplasm, and mild cytonuclear atypia (Figure 1C); (2) mucin-filled intermediate sized cells (goblet cells), with peripherally located small, crescent-like hyperchromatic nuclei, and indistinct nucleoli (Figure 1D). Scattered infiltrating single goblet neoplastic cells were focally present. As previously described[1] the tumor nests appeared to arise from the basiglandular region of the intestinal crypts in close proximity to the MCA (Figure 1E). There was no lymphovascular invasion, although perineural and intraneural invasion was present. The tumor infiltrated the full thickness of the appendiceal wall and extended to the mesoappendix. Ten lymph nodes were histologically identified, of which all were negative for malignancy.

Immunohistochemically (Table 1), the tumor cells of the GCC were positive for chromogranin, synaptophysin, and serotonin, which are neuroendocrine markers. Diffuse staining for cytokeratin (CK) 20 (Figure 2), CK19, and CD99 was also present. The Ki67 proliferating index revealed nuclear staining in approximately 15% of the tumor cells. There was no staining for CK7.

**DISCUSSION**

GCC is an uncommon neoplasm of the vermiform appendix with uncertain histopathogenesis and biological behaviour. It is believed that GCC represents an amphicrine tumor, which originates from a single undifferentiated pluripotent intestinal stem cell with divergent neuroendocrine and mucinous differentiation[2], resulting in a composite biphasic neoplasm of 2 distinct populations of endoderm-derived cells. Whether this
makes GCC a variant of carcinoid tumor or a subtype of appendiceal adenocarcinoma which exhibits morphological and immunophenotypical features of neuroendocrine differentiation is still a subject of debate. Molecular studies have not elucidated the exact nature of GCC. There is a substantial overlap between GCC and classical carcinoid from a molecular standpoint\textsuperscript{[3,4]}. Morphological features such as minimal cytologic atypia, presence of non-goblet cells, tubuloacinar neuroendocrine elements, continuity with the basiglandular crypt cells of the mucosal membrane, and the lack of continuity and involvement with the luminal surface mucosa, favour the GCC being related to carcinoid tumor. However, compared to classical carcinoid, the positive immunostaining for CK20\textsuperscript{[5]}, the demonstration of IgA staining that is typical of intestinal crypt cells\textsuperscript{[6]}, the tendency for regional lymph node and distant metastasis, and tendency for recurrence and more aggressive clinical behaviour are common features for GCC. This suggests that GCC is histologically a form of “crypt cell carcinoma” or more accurately an “amphicrine carcinoma” rather than a variant of appendiceal carcinoid.

Rare cases of GCC coexisting with conventional appendiceal mucinous tumors were reported\textsuperscript{[1,7,8]}, of which 2 cases were MCA\textsuperscript{[1]}. Similar to our case, both patients were women, aged 54 and 64 years, who presented with clinical features of acute appendicitis and dull ache in the right iliac fossa. Histological examination revealed combined GCC and MCA. If GCC is a true subtype of carcinoid tumor, its coexistence with an appendiceal mucinous neoplasm would support the theory that GCC is derived from a single undifferentiated pluripotent intestinal stem cell with divergent dual neuroendocrine and mucinous differentiation (unitary stem cell hypothesis). The concomitant appendiceal mucinous neoplasm may be considered a coincidental occurrence and raises the possibility of a common etiological factor for both GCC and appendiceal epithelial neoplasms\textsuperscript{[9]}. If GCC is to be considered as an adenocarcinoma of crypt cell origin rather than a carcinoid, then the occurrence of combined GCC and appendiceal mucinous neoplasms may represent an example of adenoma-carcinoma sequence\textsuperscript{[6]}. The nature of GCC and its relation to other neuroendocrine and non-neuroendocrine epithelial tumors of the appendix needs further examination, and more cases of GCC with concomitant appendiceal epithelial neoplasms need to be recorded, which may help in explaining this rare association.

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