Case Report

Goblet Cell Adenocarcinoma of the Appendix: A Case Report and Literature Review

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Goblet cell adenocarcinomas (GCC) are rare, aggressive types of appendiceal tumors. Having features of both adenocarcinomas and neuroendocrine tumors, GCCs usually need pathological diagnosis obtained by surgical intervention. Considering that these tumors have worse prognosis than typical neuroendocrine tumors, more aggressive surgical and medical (chemotherapy) interventions may be recommended.

We report a case of a 68-year-old woman who experienced vomiting with abdominal pain for one day. Abdominal computed tomography revealed distended small bowel loops and wall thickening over the ileocecal region suspected of ileocolic intussusception with obstruction. The patient underwent exploratory laparotomy for right hemicolectomy. Pathological diagnosis was GCC stage III with pericolic lymph node invasion. No distant metastasis was noted. Adjuvant chemotherapy underwent smoothly.

Although having features of neuroendocrine tumors, GCC should be staged and treated like adenocarcinomas. It is recommended that patients who have tumors > 2 cm, pT3 or pT4 (locally advanced), or with positive surgical margins on appendectomy undergo a right hemicolectomy. Adjuvant chemotherapy regimen based on 5-fluorouracil is recommended for cases with nodal involvement.

[*J Soc Colon Rectal Surgeon* (*Taiwan*) *2020;31:286-292*]

Key Words
Goblet cell adenocarcinoma;
Appendiceal tumor;
Neuroendocrine tumor

Primary cancers of the appendix are relatively rare, representing less than 1% of all gastrointestinal malignancies with an annual incidence of approximately 1.2 cases per 100,000 people in the USA.[1] Goblet cell adenocarcinomas (GCC) of the appendix are rare neoplasms with mixed adenocarcinomas and neuroendocrine differentiation.[2] Carcinoid tumors represent more than 50% of appendix neoplasms that demonstrate no specific clinical presentation and present as acute appendicitis. They are usually diagnosed incidentally after appendectomy.[3]

Although GCCs are morphologically like neuroendocrine tumors (NETs), these rare neoplasms from the appendix are staged according to the system for

Received: June 1, 2020. Accepted: July 27, 2020.
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adenocarcinomas (The American Joint Committee on Cancer (AJCC), 8th edition).[4] The 5-year disease specific survival rate of appendiceal NETs is greater than 90%, whereas in GCC, this rate ranges from 58% to 81%.[1] Considering the different clinical behaviors of GCC, treatment plans for these tumors remain unclear for decades.

There are limited data to guide adjuvant treatment and most appropriate chemotherapy regimen. Through this case report, we provide a brief introduction on GCC staging guidelines and surgical management and review the literature for proper treatment suggestions.

Case Report

We present a case of a 68-year-old Asian woman with medical history of hypertension under medication control. Medications at the time of diagnosis included amlodipine and valsartan. A family history of colon cancer (uncle) was noted. Our patient denied history of alcohol, tobacco, or drug abuse and had no history of occupational or chemical exposure. According to the patient, intermittent cramping abdominal pain for 1 month was noted, accompanied by small-caliber and loose stool. Because of abdominal pain exacerbation with vomiting several times, patient was brought to the emergent department. At presentation, clinical examination showed that the patient was afebrile and mildly hypertensive with blood pressure of 143/76 mmHg, heart rate of 75 beats per minute, and respiratory rate of 20 breaths per minute. She had normal cardiac rate and rhythm, and abnormal breathing sounds on respiratory examination were not observed. Her abdomen had hypoactive bowel sounds on auscultation, which was soft and non-tender with distension. A neurologic examination demonstrated normal neurologic function without sensory deficits and normal muscle strength.

Abdominal computed tomography revealed minimal wall thickening at the ileocecal valve with small bowel dilatation suspected of tumor obstruction or intussusception. Multiple hypodense lesions in the liver, suspected of hepatic cysts, were observed. Small-sized lymph nodes were noted along the ileocecal ligament (Fig. 1). Because intussusception or hepatic flexure tumor obstruction was suspected, right hemicolectomy was arranged in September 2019 after preoperative evaluation. During surgical procedure, a firm appendiceal tumor, approximately 3 cm, with cecal wall invasion was noted as the major cause of ileocolic intussusception and obstruction. Pericolic

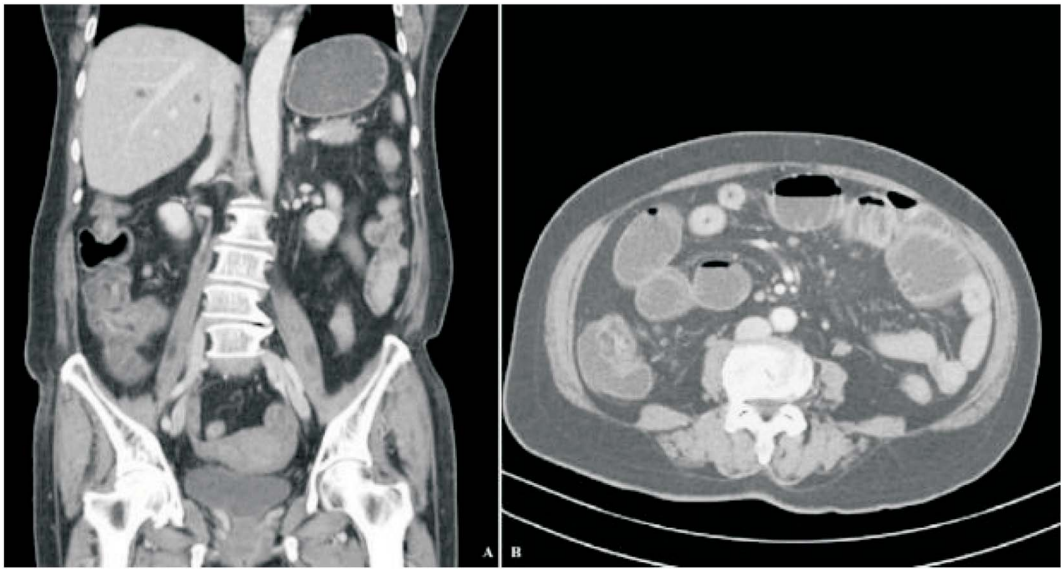

Fig. 1. Minimal wall thickening at the ileocecal valve with small bowel dilatation suspected of tumor obstruction or intussusception. Multiple hypodense lesions in the liver suggestive of hepatic cysts. Small-sized lymph nodes were noted along the ileocecal ligament.

lymph node sampling was performed. Patient tolerated the whole surgical intervention well. Specimens from right hemicolectomy were sent for expert consultation.

According to preoperative evaluation, complete blood count (CBC) revealed the following: white blood cell count, 6.3 × 10^3/uL (reference range, 4.5-11); hemoglobin, 12.8 g/dL (reference range, 12-16); mean corpuscular volume, 89.9 fL (reference range, 80-96); and platelet count, 253 K/mm^3 (reference range, 150-350). Based on preoperative basic chemistry test, the patient's sodium, potassium, blood urea nitrogen, and creatinine levels were within the normal ranges.

Based on pathological review, a circumferentially infiltrating tumor in the appendix, measuring 3 × 1 × 1 cm with serosa retraction, and both perineural and lymphovascular invasions were noted. Four of the 13 lymph nodes were considered high-grade metastatic carcinoma. Circumferential margin was uninvolved by invasive carcinomas, and the depth of invasion was noted with visceral peritoneum perforation. Tumor cells were immunoreactive to cdx-2 and CK20, whereas these cells were negative for CK7. Focal neuroendocrine differentiation was demonstrated by synaptophysin. Ki-67 proliferation index was 85% at the hot spot area. Signet ring cell presented with mucinous component < 25% and thus was classified as adenocarcinoma ex-goblet cell carcinoid, Tang group B. The final pathological staging of the patient's tumor was pT4aN2M0, stage IIIB according to the recommendations of the AJCC (8th edition) (Fig. 2).

Postoperatively, we discussed adjuvant chemotherapy with the patient. 5-fluorouracil (5-FU)-based chemotherapy was first considered based on several previous studies. Patient agreed for further chemotherapy; thus, 5-FU/leucovorin/oxaliplatin (FOLFOX) regimen was started 1 month after surgery. Currently, patient underwent ten courses of FOLFOX smoothly

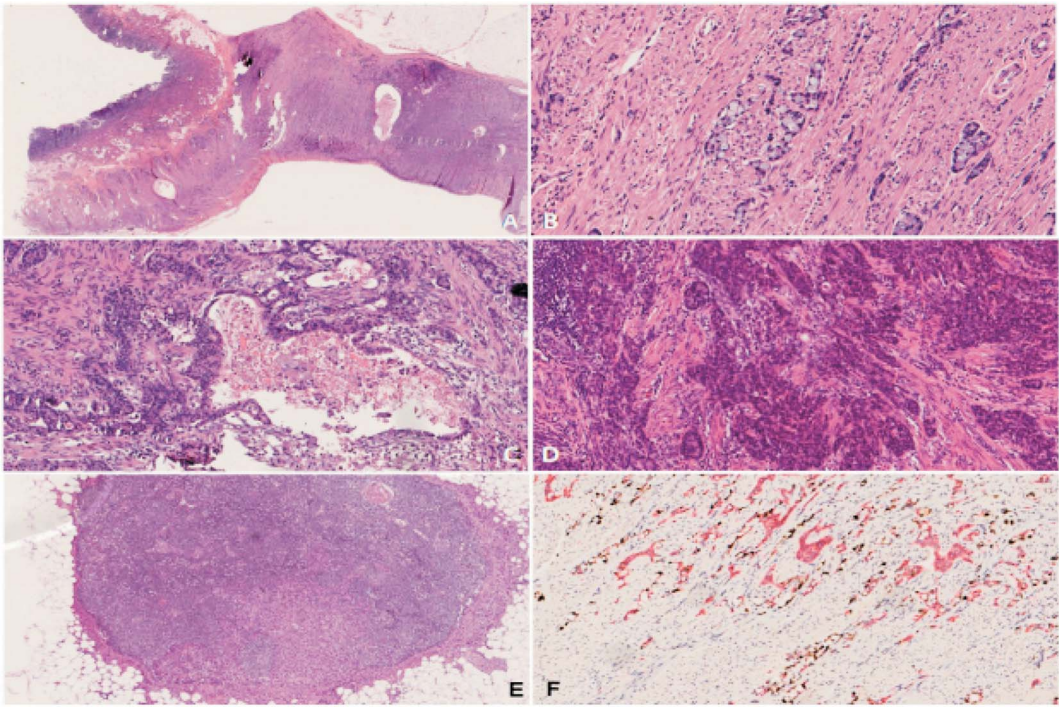

Fig. 2. (A) Whole view of the specimens shows tumor cells infiltrating through the submucosa to the serosal surface (T4a, 1X). (B) Low-grade pattern in goblet cell adenocarcinoma, and high-power view of tumor clusters shows that they comprise goblet-like mucinous cells. (300×). High-grade histological pattern in goblet cell adenocarcinoma, (C) jagged glands lined by cuboidal cells with high-grade cytologic features resembling conventional adenocarcinoma and, (D) sheet-like growth pattern, (E) high-grade metastatic tumor cells in the regional lymph node, (F) tumor cells are positive for synaptophysin (red) in focal areas, and the Ki-67 (brown) index is higher in non-synaptophysin-positive areas.

with tolerable side effects.

Discussion

We presented the case of a 68-year-old Asian woman without cancer history who was diagnosed with primary stage III GCC, Tang group B. She underwent right hemicolectomy followed by adjuvant chemotherapy with FOLFOX. Usually, metastatic rates at first diagnosis were 33%, 88%, and 100% for Tang groups A, B, and C, respectively. The most common clinical presentation was abdominal pain and a palpable mass (50%), followed by symptoms related to acute appendicitis (44%), incidental diagnosis (3%), and other nonspecific findings (3%).[5] The patient presented with intermittent abdominal pain due to intussusception. Fortunately, no distant metastasis was noted at diagnosis.

GCCs are unique and distinctive tumor types that are mostly observed in the appendix. They are found in 0.3% to 0.9% of appendectomies, where they comprise 35~58% of all appendiceal neoplasms and less than 14% of all malignant neoplasms of the appendix.[6] GCC was under a great debate for a long time, and the term "carcinoid" once led to incorrect interpretation as NET considering that GCCs are morphologically similar with NET, which has a better prognosis and often shows positive staining with neuroendocrine markers such as synaptophysin and chromogranin.[1] Correct diagnosis depends mainly on pathological interpretation. Immunohistochemical distinction between the GCC and NET manifest as the stronger expression of CEA, CDX-2, CAM5.2 and cytokeratin (CK) in the former relative to the latter.[7] The expression of Math1 (transcription factor) and HD5 (human defensin 5 for the detection of Paneth cell differentiation) was similar in goblet cell adenocarcinomas and colonic adenocarcinoma but absent in classical carcinoids.[7] At the time of diagnosis, over 50% of patients show tumor invasion through the serosa or into the mesoappendix. Approximately 15% to 30% of patients have regional lymph node metastasis.[6,8] The peritoneum is the most common site of metastasis, assumed through trans-coelomic spread, and is also the most common site of tumor relapse in reported series.[9] The ovary is a common metastatic site in women. Metastasis to the solid organs, such as the liver, bone, and brain, is rare.[10]

GCCs are staged as adenocarcinomas according to the AJCC recommendations. Similar with adenocarcinomas, the T category for GCC is based on the depth of invasion.[8] Based on a pathological view, Tang et al. divided these tumors based on a three-tier scheme. The first category is pure GCC (group A), and the other two comprise GCC with an adenocarcinoma component referred to as "adenocarcinoma ex-goblet cell carcinoid, signet ring cell type" (group B) and "adenocarcinoma ex-goblet cell carcinoid, poorly differentiated type" (group C).[5]

Our patient was diagnosed with T4a, N1, M0, stage IIIB based on the AJCC tumor-node-metastasis staging classification system. A circumferentially infiltrating tumor in the appendix contained signet ring cell, which presented with mucinous component < 25%. Thus, it was classified as adenocarcinoma ex-goblet cell carcinoid, Tang group B.

Considering the rarity of GCC, there is no standard guideline for treatment decisions. Common consensus for nonmetastatic GCC's treatment was surgical resection. However, determining whether appendectomy is superior to right hemicolectomy as a therapeutic regimen was under a great debate for a long time. Because GCCs can be correctly diagnosed by pathological examination, ensuring a free surgical margin is significantly important. The European Neuroendocrine Tumor Society collected an expert opinion to establish tentative guidelines for the most appropriate treatment strategy for GCC. Right hemicolectomy was recommended after initial appendectomy due to GCC's poor prognosis and high metastatic rates. However, some researchers believe that appendectomy alone was suitable for GCC < 1 cm and localized tumors, without serosal, mesoappendiceal, or cecal invasion and with low proliferative index considering that the morbidity rate of right hemicolectomy may be as high as 40% in the elderly.[11] A review article from the *World Journal of Gastrointestinal Oncology* suggested that appendectomy could be suitable for stage I GCC, and further right hemicolectomy

might be performed in higher GCC stage, with lymph node metastasis or cecal involvement. Further oophorectomy may be suggested, specifically for postmenopausal women, to reduce metastatic rate.[12]

Considering that only a few cases of GCCs are reported, evidenced-based guidelines regarding the effectiveness of systemic chemotherapy do not exist. A case series from Clift et al. suggested that chemotherapy should be applied in patients with stage II GCC, specifically Tang group B/C, and higher stages.[9] Considering the histological and clinical resemblance of GCCs to colorectal adenocarcinomas, choices for adjuvant chemotherapies are similar. FOLFOX and FOLFIRI are recommended as standard chemotherapies.[13] For GCCs with peritoneal carcinomatosis, cytoreductive surgery/hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) can be considered as a main treatment option if cytoreductive surgery is feasible.[14] A prospective cohort study comprising 48 GCC patients collected from 2009 to 2016 showed that the median survival was 3.2 years [95% confidence interval (CI) 2.3-4.1] for 27 patients with peritoneal spread and eligible for CRS+HIPEC.[15] In contrast, the median survival was 1.3 years (95% CI 0.6-2.0) for 7 patients with too-extensive intraperitoneal disease treated with palliative chemotherapy.[15] In the per-protocol analysis of 13 patients with evidence of carcinomatosis who underwent complete CRS+HIPEC, the 3- and 5-year survival rates were 76 and 57%, respectively.[15] However, 21 patients with peritoneal spread not treatable with CRS+HIPEC, the 3-year survival rate was 20%.[15] This study believed that CRS+HIPEC was associated with a favorable outcome in GCC patient at high-risk of developing peritoneal spread.[15] Long-term survival can be achieved in GCC patient with peritoneal spread treated with CRS+HIPEC.[15]

Based on a literature review, our patient was diagnosed with stage IIIB, Tang group B. Hence, adjuvant chemotherapy was arranged after the patient underwent right hemicolectomy. The selected chemotherapy regimen for this patient was FOLFOX. The patient was able to tolerate chemotherapy well with acceptable side effects. Further follow-up arrangement was scheduled for our patient.

Prognosis and survival rate are based on staging. A study from Brigham and Women's Hospital in Boston that analyzed 2552 patients with GCCs of the appendix showed that the 5-year survival rates for stage I, II, III, and IV diseases were 91.1%, 90.5%, 57.0%, and 18.9% (95% confidence interval, 9.3%-31.0%), respectively.[16] Another study that reviewed a database comprising 63 patients collected from 1993 to 2005 in Memorial Sloan Kettering Cancer Center (New York) revealed that the survival rates of patients belonging in groups A, B, and C were 96%, 73%, and 14%, respectively, after a minimum of 8 months and maximum of 191 months of follow-up. Both the 3-year and 5-year disease-specific survival rates of group A tumors were 100%, and these rates were 85% and 36% in group B and 17% and 0% in group C, respectively.[5]

Conclusion

GCCs are rare diseases with high metastatic rate at first diagnosis and are more aggressive than typical carcinoid tumors. Simple appendectomy was suitable for GCC < 1 cm and localized tumor without serosal, mesoappendiceal, and cecal invasion. Right hemicolectomy may be performed in higher stages of GCC or in GCCs with lymph node metastasis. Although consensus regarding the most appropriate treatment for GCC is insufficient, chemotherapies based on 5-FU are recommended for stage II GCCs, specifically Tang group B/C, or GCCs in higher stages.

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病例報告

闌尾之杯狀細胞腺癌 – 個案報告以及文獻回顧

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杯狀細胞癌是一個少見且極具侵略性的一種源自闌尾的腫瘤。因為同時具有腺癌和神經內分泌腫瘤兩者的特色，杯狀細胞癌必須透過手術才能確診。因為比典型的神經細胞瘤預後較差，比較侵犯性的手術以及化療方式是必須的。

我們在此分享一個 68 歲女性個案腹痛加上嘔吐一天。腹部電腦斷層顯示小腸擴張以及迴腸結腸交界處腸壁變厚，疑似迴腸結腸套疊合併阻塞。病人接受了剖腹探查並進行右半結腸切除手術。病理報告顯示為杯狀細胞癌第三期合併結腸旁淋巴侵犯。沒有發現遠端轉移。輔助的化學治療順利進行中。

雖然擁有內分泌細胞瘤的特色，但是杯狀細胞癌需要以腺癌的方式來做為分期與治療標準。建議在腫瘤大於 2 公分、病理 T3 或 T4、局部侵犯或者是闌尾切除術後手術邊緣不乾淨者，需進行右半結腸切除手術。淋巴侵犯者建議術後輔助化療以 5-氟尿嘧啶為主。

關鍵詞 杯狀細胞癌、闌尾腫瘤、神經內分泌腫瘤。