Case Analysis

Goblet Cell Carcinoid of the Appendix: Diagnosis, Management and Literature Review

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Key Words
Goblet cell carcinoid;
Adenocarcinoid;
Appendectomy;
Right hemicolectomy

Objective. Goblet cell carcinoid is a very rare neoplasm of the gastrointestinal tract. In the present study, we share the treatment experience related to goblet cell carcinoid of the appendix in our hospital and review recent advances reported in the literature.
Methods. In a chart and pathological review of cases treated at our hospital from 1983 to 2007, we selected cases with available appendectomy specimens or right hemicolectomy specimens with appendices. All appendectomy specimen slides were validated by final diagnosis and reviewed by a single pathologist.
Results. A total of 43,808 specimens were reviewed in this present study, of which. 39 cases were diagnosed as carcinoid tumor. Of these 39 cases, only 10 had a final diagnosis of goblet cell carcinoid of the appendix. The male-to-female ratio was 1:1. There was no reported peri-operative mortality. Two female patients had peritoneal dissemination and survived with stable disease after 20 months of follow-up.
Conclusions. The clinical behavior of goblet cell carcinoid was between the classical carcinoid and adenocarcinoma of the appendix. More aggressive treatment improved patient outcome.
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Goblet cell carcinoid (GCC) is a very rare gastrointestinal tract neoplasm that was first described by Subbuswamyet al.[1] in 1974. Other terms used to describe this condition include "adenocarcinoid,"[2] "crypt cell carcinoma,"[3] "mucinous carcinoid,"[4] and "microglandular carcinoid." The existence of a diverse nomenclature for GCC indicates that this tumor is not only rare, but its behavior remains unclear. The most common site of occurrence of this tumor is the appendix, although other sites such as the small bowel, stomach, duodenum, rectum, and mediastinum have also been reported. Because of the limited number of cases published on this tumor, the details of its pathology remain vague. Clinical observation has shown that its behavior is similar to that of invasive adenocarcinoma and classical carcinoid of the appendix. The optimal treatment strategy for this neoplasm is still controversial as it needs additional clinical information. Therefore, we have reviewed cases involving this neoplasm at our hospital and share our experience in the management of this tumor.

Materials and Methods

A total of 43,808 appendix specimens were col-

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lected from cases treated at our hospital from January 1983 January to December 2007. Of these, 39 cases were diagnosed as carcinoid tumors, which were further classified as follows: 28 were classical carcinoid of the appendix, 10 were GCC, and 1 was tubular carcinoid. The incidence of carcinoid of the appendix was approximately 0.089%. GCC accounted for approximately 25.6% of the appendical carcinoid tumors.

The data analyzed in the present study were collected from chart reviews. Patient information including age, sex, clinical presentation, operative methods, tumor characteristics and stage, adjuvant treatment, and outcome were analyzed.

Case Presentation

A total of 10 patients were diagnosed as GCC of the appendix. Information on patient age, clinical presentation, tumor characteristics, and operation methods are presented in Table 1. We present 3 typical cases and 2 untypical cases as follows:

Case No. 3

This is a 44-year-old male who arrived at the emergency room (ER) due to acute-onset right lower abdominal pain. Laboratory data and physical examination showed leukocytosis and focal peritonitis. Under the impression of acute appendicitis, he underwent appendectomy. Inflammatory change of the appendix with purulent fibrin coating was observed during surgery. No tumor mass was detected. The pathological reportindicated as GCC with acute appendicitis. The resection margin was negative.

Case No. 5

This is a 52-year-old male with right renal cell carcinoma with chest wall metastasis. He underwent right nephrectomy and chest wall irradiation. Intraoperative findings showed a cecal mass at the appendiceal base. He underwent right hemicolectomy to remove thececal mass, and the pathological report indicated GCC of the appendix with cecal invasion. The resection margin was free of any tumors.

Case No. 6

This is a 56-year-old male who was transferred from a local hospital due to appendiceal tumor with incomplete resection. He showed symptoms/signs of acute appendicitis and had underwent appendectomy at the local hospital. Unfortunately, the pathological

Table 1. Summary of cases of goblet cell carcinoid of the appendix

No.	Age/sex	Symptoms/signs	OP method	Size of primary tumor (cm)	Local invasion	Distant metastasis
1	26/F	Appendicitis	Appendectomy	N/A	No	No
2	26/F	Appendicitis	Appendectomythen R hemi	N/A	No	No
3	44/M	Appendicitis	Appendectomy	0.3 × 0.4 × 0.2	No	No
4	43/M	Appendicitis	Appendectomy	N/A	No	No
5	52/M	Intra-OP incidental finding	R hemi	3.5 × 3 × 2	Yes: to cecum	No
6	56/M	Appendicitis	Appendectomy then R hemi	N/A	Yes: to cecum	No
7	78/F	Mechanical bowel obstruction	R hemi	2 × 2 × 1.5	Yes: to cecum	No
8	85/M	Mechanical bowel obstruction	R hemi	1 × 0.8 × 0.8	No	No
9	63/F	Bilateral ovary mass	ATH + BSO + R hemi	2 × 2 × 1	Yes	Yes
10	42/F	Bilateral ovary mass	ATH + BSO + R hemi + LAR	6 × 1 × 1	Yes	Yes

N/A: Not accessible.
R hemi: Right hemicolectomy.
ATH: Abdominal total hysterectomy.
BSO: Bilateral salpingo-oophorectomy.
LAR: Low anterior resection.

report showed tumor invasion of appendiceal margin. He received subsequent right hemicolectomy for the residual tumor at our hospital for radical resection.

Case No. 7

This is a 78-year-old female who arrived at our ER with progressive abdominal distension and tenderness. Constipation without stool passage for 1 week and progression of abdominal girth was also observed. Laboratory data showed leukocytosis and CT of the abdomen showed a cecal mass causing bowel obstruction. The patient underwent right colectomy to remove the cecal mass. The pathological report indicated appendiceal GCC with cecal invasion and induced bowel obstruction.

Case No. 10

This is a 42-year-old female who consulted our GYN clinic due to a palpable lower abdominal mass that was initially noticed 3 months prior. The mass had enlarged over time and exhibited mild tenderness. She underwent laparotomy due to the impression of ovarian cancer with carcinomatosis after serial examination. The intra-operative findings were a cecal mass with pelvic seeding and rectal invasion. Bilateral ovary metastasis and uterus invasion were also observed. The patient underwent cytoreductive surgery, including right hemicolectomy, low anterior resection of the rectum, bilateral salpingo-oophorectomy, hysterectomy, and omentectomy to reduce the tumor burden and achieve R1 resection. The pathological report indicated appendiceal GCC with peritoneal seeding and ovary metastasis. After cytoreductive surgery, the patient received 12 courses of FOLFOX4 chemotherapy and remained stationary with disease after at 20 months follow-up. Table 1 presents the data on these 10 GCC patients.

Results

A total of 10 cases were diagnosed with GCC during this study period. The gender ratio of male to female was 1 to 1. The age at diagnosis ranged from 26 years old to 85 years old, with a median age of approximately 48 years old. In our series, 7 patients presented as acute abdominal condition, including 5 cases with acute appendicitis and 2 patients with mechanical bowel obstruction. The other cases included one who was detected incidentally during nephrectomy and 2 female patients who presented with lower abdominal mass.

Seven cases underwent extended resection, including a right hemicolectomy and intended excision of intra-peritoneal seeding. Only 3 cases underwent simple appendectomy. The 2 female patients who initially presented as peritoneal seeding and bilateral ovarian metastasis underwent cytoreductive surgery, followed by 5-fluorouracil (5-FU) based adjuvant chemotherapy. The patients remained stable with the diseases for a limited follow-up period (20 months). The other cases survived without recurrence after a median follow-up period of 50 months (range: 20 to 123 months).

No surgical mortality was reported in this patient series. One case that underwent right hemicolectomy for appendiceal goblet cell carcinoid suffered from anastomosis insufficiency and received secondary operation with diverting ileostomy.

Pathology

The cells of GCC predominantly showed submucosal growth and invasion from the muscular layer to the adventitia, with subsequent rupture into the peritoneal cavity. It typically invades the appendiceal wall in a concentric manner without producing a tumor mass.[5] The involvement of this tumor could result in appendiceal lumen stenosis that induces appendicitis, which is why most of these tumors initially presented as acute appendicitis.

Microscopic examination showed that, the tumor cells resemble signet ring cells and were arranged as small round nests (Fig. 1). These cells were also similar to normal intestinal goblet cells. Immunochemical staining showed that these tumors were positive for neuron-specific enoase (NSE), synaptophysin, chromogranin A, and carcinoma embryonic antigen (CEA),

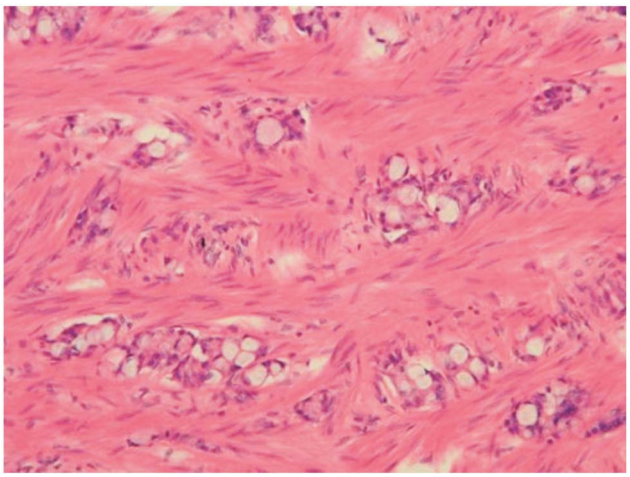

Fig. 1. Hematoxylin and eosinstaining with Microscopy 20*10 showing typical goblet cell-like tumor cells arranged as nests and surrounded by stroma.

which facilitates in our differentiation of this tumor from classical appendiceal adenocarcinoma. NSE occurs in a variety of normal and neoplastic neuroendocrine cells and predominates in the brain. NSE has been utilizedas a specific marker for neuroendocrine differentiation.

Synaptophysin is a glycoprotein that is localized to the neuroendocrine secretory granule membrane. It is a broad-spectrum neuroendocrine marker with higher sensitivity, but lower specificity.

Chromogranins (types A, B, and C) are a group of monomeric proteins that comprise the major portion of the soluble proteins of neuroendocrine cells. Chromogranin A shows a strong correlation with endocrine-type secretory granules in cell.

GCC generally shows strong CEA staining compared to classical carcinoid tumor, which is usually negative. Both GCC and classical carcinoid tumorshow positive staining for neuroendocrine markers such as NSE, chromogranins, and synaptophysin, whereas colorectal signet ring cell carcinoma or adenocarcinoma/carcinoid mixed the neoplasms are generally synaptophysin-negativeand chromogranin- negative.

To differentiate these three types of neoplasms, immunohistochemical staining was conducted to differentiate these tumors. Table 2 shows the differencesamong these tumors based on immunohistochemical staining features.[6]

Discussion

In 1969, Gagne et al. described 3 unusual tumors of the appendix[7] that showed common features such as: 1) association of nests of enterochromaffin cells with mucus- secreting glandular structures, 2) integrity of the appendiceal mucosa, and 3) an infiltrative pattern similar to that of carcinoid tumors but with a propensity to invade nerves.[8] In 1974, Klein reported three cases of mucinous carcinoid of the appendix.[4] However the first reported casesusing theterm GCC were those of Subbuswamy et al. in 1974. All names except GCC have been omitted from the current World Health Organization (WHO) classification.[9] GCC occurs most frequently in the appendix; however, is very rare. As reported by Rutledge et al.,[10] the most common appendiceal neoplasm is the carcinoid, which accounts for 85% of the cases, followed by mucinous neoplasms (8%) and adenocarcinoma (4%). Adenocarcinoids accounts for only 2% of all neoplasms involving the appendix. GCC has also been reported in the liver, pancreas, small bowel, colorectum, and mediastinum. The use of a diverse nomenclature for this tumor is indicative ofits lack of detailed characterization.

This tumor has several histological features thatoften result in difficulties in its differentiation from classical carcinoids. Similar to classical carcinoids, GCC shows submucosal growth with invasion through the whole layer of the appendix without mucosal involvement. The tumor is composed of small, round nests of cells that are separated by stroma (Fig. 1). The tumor cell has mucinous granules in its cytoplasm, resembling a signet-ring cell or normal intestinal goblet cell, from which theterm GCC was derived.

Based on this wide range of features, it is therefore not surprising that this tumor has several theories of origin. In the 1980s, several authors proposed that these tumors arose from a single neoplastic intestinal cell with divergent differentiation.[3,8] This single neoplastic intestinal cell had endocrine and exocrine properties. During the 1990s, the observation of the simultaneous presentation of GCC and cystadenoma[11] was an indication that this neoplasm might have occurred from a adenoma/adenocarcinoma sequence

Table 2. Immunohistochemistry of GCC, classical carcinoid and adenocarcinoma

	CK7	CK20	NSE	Chromograin A	Synaptophysin	CEA
Adenocarcinoma	-	+	-	-	-	+
Classical carcinoid	-	+	+	+	+	-
Goblet cell carcinoid	+	+	+	+	+	+

similar to that of colorectal adenocarcinoma. In recent years, with the advances in immunohistochemistry, several authors have reported that these cells were stained by neuron-specific enoase (NSE), synaptophysin, and chromogranins, which are neuroendocrine markersproperties.[12] Base on these findings, it has been accepted that this tumor cell arose from a single pluripotent stem cell that differentiated into a secretory stem celland later transformed into this unique neoplasm.

A large series review conducted by Variscoet al.[13] showed that this neoplasm occurs most frequently during middle age (about the 5th decade), with similar incidences in males and females. These earlier findings are similarto that of our series. At clinical presentation, seven of our patients had acute abdomen presentation similar to that of acute appendicitis (5/10) and mechanical bowel obstruction (2/10). Similar to other series[14] most of our cases initially presented as acute appendicitis. The other two female patients who presented with a pelvic mass were similar to the reported 2nd most frequent symptom of this neoplasm.

What is the most appropriate management strategy for this neoplasm? According to our literature review, the behavior of this tumor showed features of malignant appendiceal adenocarcinoma and classical carcinoid of the appendix. This behavior was also supported by the findings of a recent study[15] wherein most of these tumor cells were unlike colon adenocarcinoma cells, which were negative to MIB-1, p53, and bcl-2. These markers represent the malignant potential of a neoplasm. Thus, there are conflicts regarding radical resection, such as right hemicolectomy or local excision, similar to appendectomy, which was appropriate management scheme. These contentions have been discussed in several reports.[13]

Several major surgical textbooks show that extended resection of the appendix for mucinous-producing neoplasms or right hemicolectomy for appendicealadenocarcinoid are the main treatment options of GCC. However, Variscoet al.[13] reviewed reports published before 2004 and concluded that if the neoplasm was localized, local excision such as appendectomy was enough for the treatment of this neoplasm. This opinion is based on the observation that most of the tumor recurrence involved peritoneal dissemination without localized diseases. This phenomenon may be due to undiscovered peritoneal seeding, but not the initial incomplete resection of the primary tumor. In the present study, metastasis or recurrence was due to direct tumor spreading into the peritoneal cavity caused by breakage through the appendiceal adventitia. On the other hand, in female patients with localized disease, prophylactic bilateral oophorectomy was indicated due to the higher risk for ovarian metastasis.[16]

In 2005, Bucher et al.[17] proposed the following criteria for local excision of appendiceal GCC: 1. Tumor size of < 1 cm in diameter; 2. Tumor cell not extending across the appendix adventitia; 3. Tumor has < 2 mitosis in 10 high- power magnification fields; and 4. The surgical margin is free of tumor.

Unfortunately, approximately 20% of these neoplasms initially or subsequently develop peritoneal seeding or distant metastasis (similar to that of the ovary). With the recent advances in immunohistochemical staining, GCCs that stained positive to MIB-1 (Ki-67) showed a higher potential of metastasis to the peritoneum, ovary, and uterus.[18] Because MIB-1 is a marker of proliferation index, the phenomenon of higher mitotic index is also indicative of a higher malignancy potential and thus requires a more aggressive, radical surgical approach.

How should we manage the advanced diseases such as peritoneal seeding? Cytoreductive surgery with intra-peritoneal chemotherapy may be performed, similar to that in colorectal cancer. In a study

conducted bySugarbaker et al.,[19] patients who received cytoreductive surgery with intra-peritoneal chemotherapy were compared tothose who received systemic chemotherapy only. The median survival improved from 5 months to 19.5 months. The 2-year and 5-year survival rates were 39% and 25%, respectively. The report also concluded that the completeness of cytoreduction influenced patient survival. This was also observed in our series, in which the female patients who received intensive cytoreductive surgery survived with stable disease after 20 months of surgery.

Due to the limited experience in systemic chemotherapy for this disease, several regimens such as cisplatin- or fluorouracil-based chemotherapies[20] have been introduced to the treatment of advanced GCC. Unfortunately, no significant effects have been reported using these regimens. In the literature review, there was only 1 case report that described a complete remission of metastatic lesions after FOLFOX4 regimen.[21] One of our cases, Case No. 10, who suffered from peritoneal metastasis and underwent intensive cytoreductive surgery, had received 12 courses of FOLFOX4 chemotherapy after surgery. This adjuvant therapy had prolonged her survival to more than 30 months (stable with disease) compared to the literature-reported metastasis cases, which showed a median survival of approximately 5-8 months.

In our study, two female patients who developed peritoneal seeding and ovary metastasis underwent intensive cytoreductive surgery. This procedure included resection of the primary lesion, bilateral ovaries, and uterus, as well as peritoneal seeding. Despite the significant reduction in tumor mass index in these patients, all of them experienced tumor recurrence after adjuvant chemotherapy. Fortunately, these procedures and the adjuvant therapy improved their survival from < 8 months to > 24 months. These results show that intensive resection of the peritoneal tumor mass coupled with adjuvant chemotherapy improved treatment results.

Conclusions

GCC tumor is a very rare neoplasm involving the gastrointestinal tract and generally originates in theappendix. Our review of clinicalcases showed that the tumor shows similarities in behavior with that of classical carcinoid tumors and appendiceal adenocarcinomas. GCC undergoes less liver or lung metastasis, but shows a propensity for of direct peritoneal seeding or ovary metastasis in female patients. A recent study had described that this neoplasm is a specific type of carcinoma that should be differentiated from adenocarcinoma and aggressive surgical treatment. Based on our experience, intensive treatment strategy improves patient survival. To establish the effectiveness of systemic chemotherapy such as that involving FOLFOX4, additional casesre warranted.

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病例分析

闌尾部位的杯狀細胞類癌，診斷，處置與文獻回顧

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目的 闌尾部位的杯狀細胞類癌是一種非常少見的腫瘤，本篇目的在報告於本院處理此一腫瘤的經驗與分析最近文獻上的進展。

方法 利用病例回顧與病理組織回顧等方式，我們回溯從 1983 到 2007 年總共 24 年間所有的闌尾檢體或是右側大腸檢體含闌尾部分，所有檢索出來的檢體均由同一位病理科醫師進行再次檢驗。

結果 總共有 43803 件闌尾部檢體，其中有 39 件診斷為類癌，這 39 件中僅有 10 件最終診斷為杯狀細胞類癌。男女比例剛好為一比一。所有病人都沒有手術後死亡案例，有兩位婦女有腹腔內轉移，但接受積極治療後至少有 20 個月的存活。

結論 闌尾部杯狀細胞類癌的臨床表現是介於類癌與腺癌之間，然而積極的治療的確可以給病人更佳的存活機率。

關鍵詞 杯狀細胞類癌、腺類癌、闌尾部、闌尾切除、右側大腸切除。