

Management of Goblet Cell Carcinoid

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Background and Objectives: Goblet cell carcinoid, a rare tumor of intermediate malignant potential, is known to account for a significant minority of appendiceal neoplasms. Sixteen new cases of gastrointestinal goblet cell carcinoid were reviewed to describe their presentation, treatment, and outcome.

Methods: A review of 16 cases from a single institution.

Results: Sixteen patients were diagnosed with goblet cell carcinoid between 1995 and 2005. Presenting diagnoses included appendicitis (n = 8), abdominal or liver mass (n = 5), uterine fibroids (n = 1), ovarian mass (n = 1), and Crohn's Disease exacerbation (n = 1). Mean follow-up was 12 months with a mortality of 19% (n = 3). Patients were divided into two groups: those where the diagnosis was an incidental finding at operation (Group 1) and those where the presentation was of an abdominal mass or metastatic disease (Group 2). Nine of ten patients in Group 1 initially received appendectomies. Group 2 included patients presenting with Krukenberg type lesions (n = 2) and abdominal masses (n = 4).

Conclusions: Goblet cell carcinoid is a rare malignant tumor largely affecting the appendix. In patients presenting with appendicitis, our series does not support the recommendation of right hemicolectomy based on pathologic diagnosis alone and surgical intervention must be customized to the individual patient.

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INTRODUCTION

The pathologic characteristics of goblet cell carcinoid tumors, also known as adenocarcinoid, were first described by Gagne in 1969 [1]. Over the following decade, Subbuswamy and Warkel further elucidated the histopathology and clinical behavior of this unusual tumor [2,3]. Although the tumor is found in almost any area of the gastrointestinal tract, these early reports illustrated that the appendix is the most common location. Goblet cell carcinoid is now known to account for 13.8% of appendiceal neoplasms [4]. Many early descriptions considered the tumor to be largely benign, like classic carcinoid tumors, where simple appendectomy was a sufficient oncologic resection. More contemporary literature, however, has found goblet cell carcinoid tumors to be more malignant with some authors recommending formal right hemicolectomy based on pathologic identification alone [5–7]. While these most recent studies conclude that right hemicolectomy is indicated for goblet cell carcinoid tumors of the

appendix, less than 50% of patients actually are treated accordingly [4].

In our study, we review 16 new cases of gastrointestinal goblet cell carcinoid and describe their presentation, treatment, and outcome. A secondary goal was to assess the usefulness of serum Chromogranin A, which has been proposed as the best neuroendocrine serum tumor marker, in the management of goblet cell carcinoid patients [8,9].

MATERIALS AND METHODS

After approval by the Mount Sinai School of Medicine Institutional Review Board, a retrospective review of 16 patients with goblet cell carcinoid of the

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gastrointestinal tract was performed. The hospital and outpatient records were investigated for information on patient age, sex, clinical presentation, operative details, disease status at last follow-up, and serum Chromogranin A level. A senior pathologist reviewed all histologic diagnoses, and pathology reports were examined for information on extent of disease at presentation and evidence of residual disease upon re-operation.

RESULTS

Sixteen patients were diagnosed with goblet cell carcinoid between 1995 and 2005. Common presenting diagnoses included appendicitis ($n=8$), abdominal or liver mass ($n=5$), uterine fibroids ($n=1$), ovarian mass ($n=1$), and Crohn's Disease exacerbation ($n=1$). Mean follow-up was 12 months with a mortality of 19% ($n=3$). Mean survival in the mortality patients was 16 months. The 16 cases were divided into two groups: Group 1 where the diagnosis was an incidental finding after operation for another indication and Group 2 where the presentation was of an abdominal mass or metastatic disease.

Goblet cell carcinoid was diagnosed incidentally after appendectomy or ileocolic resection in 63% (10/16) of patients (Group 1). These cases are summarized in Table I. The mean age in this group was 46.9 years with a male-to-female ratio of 1. The clinical outcomes for these patients are summarized in Figure 1. The patient who ultimately expired from her disease (Group 1-patient 3) presented with metastases 2 years following her initial operation, at which time, a hemicolectomy was undertaken. The Chromogranin A levels, when drawn, are listed. Only two cases revealed a level greater than the normal value of 18 U/L. No female patients ($n=0/5$) had documented ovarian metastases.

Goblet cell carcinoid was diagnosed in 37% (6/16) of patients after presenting with an abdominal or pelvic mass consistent with that of a malignant process (Group 2). All patients underwent surgical resection for their disease. These cases are summarized in Table II. The mean age of this group is 53.7 years with a male-to-female ratio of 1:2. Two patients presented with large ovarian masses, Krukenberg type lesions, where the appendix was found to be the source of goblet cell carcinoid. One additional patient with a large abdominal mass also had ovarian involvement ($n=3/4$ female patients). Two cases were that of an abdominal mass localized to the cecum, but not specifically attributed to the appendix. Lastly, Group 2-patient 3 carried a tentative diagnosis of carcinoid into laparotomy from a CT guided biopsy. The final pathology revealed goblet cell carcinoid changes and significant abdominal spread. Chromogranin A levels in this group were available for five of six

patients. Two cases had normal levels and three were elevated.

Table III illustrates the duration of symptoms for each subgroup as reported by the patient. Fifty percent (4/8) of patients presenting with goblet cell carcinoid as an incidental finding presented without delay while 60% (3/5) of patients presenting with abdominal mass or metastases presented after 3 months of symptoms.

DISCUSSION

While Gagne is credited with the first histopathologic description of a goblet cell carcinoid tumor, Subbuswamy was the first to comprehensively elucidate the histopathologic characteristics [1,2]. Subbuswamy also reviewed the clinical course of the 12 patients, and while noting the possibility of metastatic spread, concluded that this was a tumor of low malignant potential and that hemicolectomy was only warranted if the appendiceal margins were positive [2]. Warkel, a few years later, published the largest and most comprehensive series of 39 patients, divided into two subgroups-tubular and goblet cell [3]. He reported that the malignant potential of these tumors was greater than that of a classic carcinoid but stopped short of recommending hemicolectomy for all goblet cell carcinoid tumors of the appendix [3]. Instead, he opted for a surgical approach guided by cellular atypia, mitotic figure frequency, and invasion beyond the appendix in the pathologic specimen. Since these early reports, the histogenesis of this rare tumor has also been the main topic of debate in the literature [10–13]. The prevailing theory of histogenesis, as summarized by Kanthan [14], is that these tumors consist of divergent neuroendocrine and mucinous components arising from a single pluripotent cell.

While much interest has been generated regarding the histopathology and histogenesis of goblet cell carcinoid, what remains insufficiently addressed are the implications that this diagnosis has on surgical treatment. Many studies recommend right hemicolectomy based solely on pathologic diagnosis of goblet cell carcinoid [6,15,16]. Others support Warkel recommendations that more formal oncologic resections be based on pathologic evidence of invasion or spread [17–20]. These studies share the view that significant spread of these tumors either at diagnosis or postoperatively warrants a more radical surgical resection. They also cite the lack of prognostic value of size and inconsistencies between primary pathology of invasion and recurrence. Like Warkel early work, a recent report recommended hemicolectomy based on size, mitotic figures, and depth of invasion [21].

The malignant potential of goblet cell carcinoids is clearly not that of a classic carcinoid and is most

TABLE I. Characteristics of Patients Presenting With Tumors as Incidental Findings (Group 1)

Patient no.	Age	Sex	Pathologic characteristics	Re-operation*	Residual disease in follow-up specimen	Chromogranin A serum level	Status at last follow-up**
1	40	F	Terminal ileum/cecum with some active ileitis/ chronic inflammation, appendix with 0.5 cm goblet cell CA, extension into muscularis propria, moderate nuclear pleomorphism, rare mitotic figures. 0/7 lymph nodes positive for tumor	NA-original procedure was ileocolic resection	NA	Not known	No follow-up
2	44	M	2.5 cm goblet cell extending into the subserosa with perineural invasion	Right hemicolectomy (14 days)	Yes-goblet cell in stump, pericolic adipose tissue, 0/16 nodes positive for tumor	Normal	Clinically free of disease with negative octreotide scan (2 months)
3		F	Goblet cell at tip of appendix, invades mesenteric fat, margins clear	TAHBSO, partial cystectomy, right hemicolectomy (2 years)	Yes-goblet cell carcinoïd metastatic to ovaries, pelvic nodes, small bowel, 2/11 colectomy nodes positive for tumor	6.5	Deceased due to disease (2.75 years)
4	80	M	Goblet cell adenocarcinoid	No	NA	13.9	Free of disease clinically and by octreotide scan (5 months)
5	43	M	Appendiceal goblet cell adenocarcinoid, involves wall of appendix and periappendiceal adipose tissue. Perineural invasion with negative surgical margins	Right hemicolectomy (2 months)	Invasion into peri-intestinal tissue with infiltrates consistent with residual tumor; negative margins, 4 mitosis/10 hpf, 1/7 nodes positive for tumor	Elevated	Mass adjacent to liver with hydronephrosis (2 years)
6	51	F	Goblet cell adenocarcinoma involving 6 cm length of appendix, transmural invasion, 1 mit/10 hpf	Right hemicolectomy (6 weeks)	No residual tumor, resection margins negative, 0/5 nodes positive for tumor	Normal	Clinically free of disease (7 months)
7	53	M	Transmural infiltration of appendix wall involving more than 50% of appendix. Base free of tumor. Minute foci of goblet cell in peri-appendiceal fat	Right hemicolectomy (6 weeks)	No residual tumor at stump, 0/11 nodes positive for tumor	Not known	Clinically free of disease (6 months)
8	61	M	Goblet cell carcinoïd, tumor extends microscopically through appendix wall into adjacent soft tissue, perineural invasion identified. Margins negative	Ileocolic resection (2 weeks)	Negative for tumor, no residual tumor in appendix stump, 0/9 nodes positive for tumor	Not known	No follow-up

9	31	F	Adenocarcinoid with transmural invasion into mesoappendix and perineural invasion, microacinar/acinar pattern. No tumor in proximal margin or visceral peritoneum	Ileocolic resection (3 weeks)	No residual adenocarcinoid, colonic mucosa normal, 0/13 nodes positive for tumor	Not known	No follow-up
10	58	F	Not known-appendectomy performed for appendiceal mass	Small bowel resection and right nephrostomy tube (5 years)	Metastatic goblet cell carcinoid	26.6	No follow-up

*Time after initial procedure.

**Follow-up interval from original procedure.

accurately characterized as intermediate between classic carcinoid and adenocarcinoma [4]. Although published series are limited by the scarcity of cases and incomplete follow-up, a clear case for surgical intervention beyond simple appendectomy is gaining support. Despite this, the SEER publication from 2002 finds that only 42% of appendiceal goblet cell carcinoid patients receive right hemicolectomy for their disease [4].

Our results confirm two conclusions from the literature. First, the behavior of goblet cell carcinoid tumors is malignant. Six of sixteen patients presented with metastatic disease (Group 2) and three of ten patients presenting with presumed appendicitis progressed to widely metastatic disease 2–5 years postoperatively (Group 1). Secondly, pathologic invasion is not predictive of residual disease in the subsequent surgical specimens. In five patients with invasion through the appendiceal wall who later underwent right hemicolectomy, only one patient was found to have residual disease in the hemicolectomy specimen. One additional patient had residual disease in the hemicolectomy specimen, but this patient’s original specimen had invasion only to the subserosa. Although follow-up was limited, one out of seven patients were known to have recurrent disease after hemicolectomy.

Chromogranin A levels are believed to be a reliable indicator of typical and atypical carcinoid tumors presence or progression [8,9]. In our series, only two of the five patients who presented with metastatic disease had elevated serum Chromogranin A levels, limiting our ability to make any definitive conclusions.

Three patients presented with metastatic goblet cell carcinoid involving the ovary. No patients with goblet cell carcinoid as an incidental finding (Group 1) had documented ovarian metastases (n = 0/5). Although this is largely a topic of Krukenberg case reports, Butler et al. [5] addressed this specifically when recommending bilateral oophorectomy for patients with goblet cell carcinoid of the appendix [22,23]. Our series supports the conclusion that goblet cell carcinoid of the appendix is prone to ovarian metastases; however, spread to the ovaries was not isolated in our patients. Further follow-up of our patients may illustrate isolated spread to the ovaries, but our current data does not allow conclusions to be drawn on the therapeutic benefit of oophorectomy.

While case follow-up was the major limitation of our study, one measure of the usefulness of hemicolectomy in our appendiceal tumor patients could be the presence of disease in the hemicolectomy specimen. This is based on the observation that spread of this tumor is known to occur locally and not remotely. With this in mind, our current data does not unequivocally support the therapeutic benefit of hemicolectomy. To assess the value of hemicolectomy, an increase in case numbers or, more

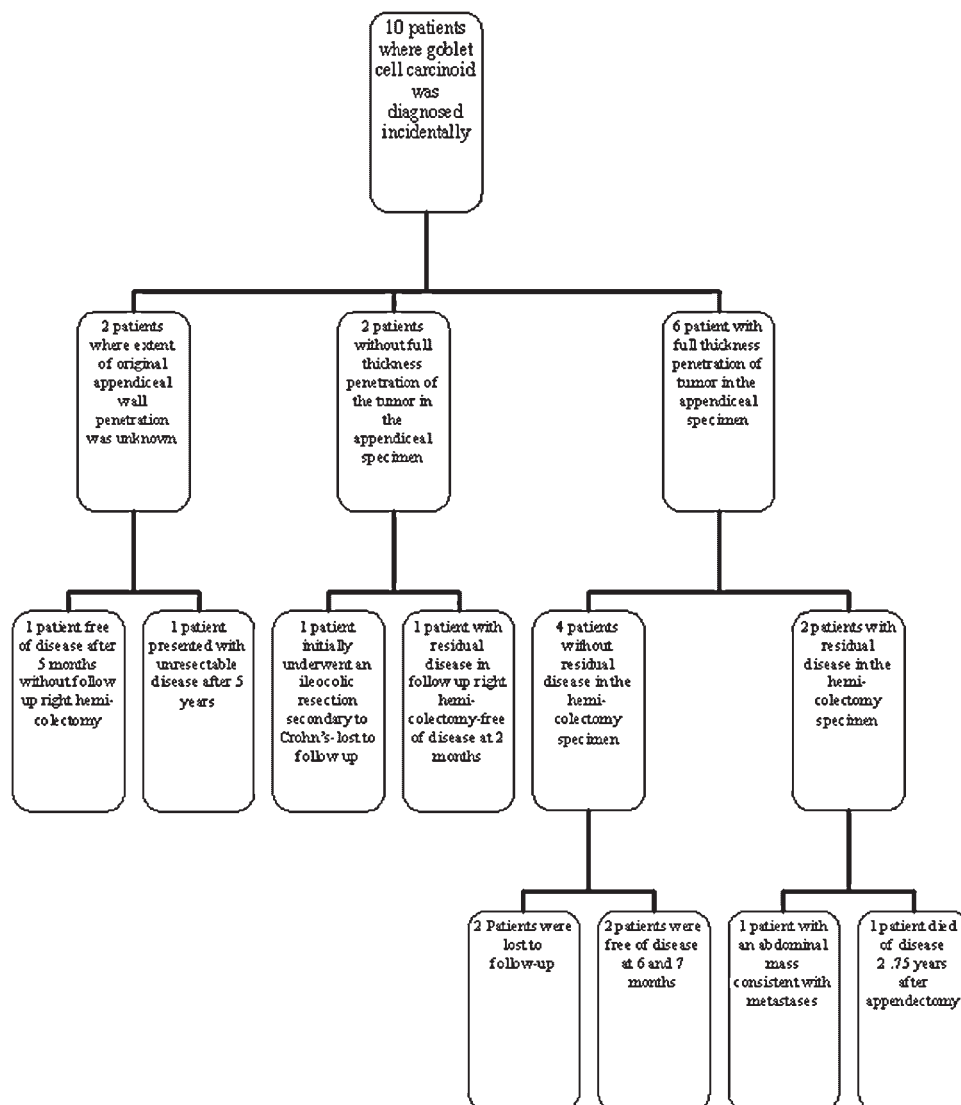


Fig. 1. The outcomes for the patients presenting with goblet cell carcinoid as an incidental finding at appendectomy with full thickness penetration of tumor.

importantly, longer-term follow-up would be needed [24]. However, as in the literature, a significant number of our cases were metastatic at presentation (6 out of 16). This limits the probability of a study with a significant number of patients and long-term follow-up illustrating the usefulness of hemicolectomy.

A more interesting question may be what makes some goblet cell carcinoid patients present with metastatic disease. In particular, is there a measurable clinical or genetic factor that predisposes patients to more aggressive disease? In our study, Group 2 was older, included more female patients, and had a longer duration of symptoms (See Table III). However, the small number of patients makes any clear differentiation between the groups difficult. In a recent publication, 16 goblet cell carcinoid

tumors were screened for eight different cancer-related genetic alterations [25]. While there was no relationship to known oncogenes, a relationship to allelic loss of chromosomes 11q, 16q, 18q was shown. Other studies have shown some consistent cellular p53 defects in goblet cell carcinoid tumors, but were not conclusive [26,27]. Despite these inconclusive studies, it is possible that the best next direction for the study of goblet cell carcinoid tumors is further genetic investigation, especially considering the limitations of clinical study.

CONCLUSIONS

Goblet cell carcinoid tumors occur largely in the appendix and often present with diffuse metastatic

TABLE II. Characteristics of Patients Presenting With Metastatic Disease (Group 2)

Patient no.	Age	Sex	Presenting diagnosis	Involved organs	Pathologic characteristics	Chromogranin A	Status and last follow-up
1	56	F	Uterine fibroids	Ovary, uterus, appendix	Mucinous adenocarcinoid type arising from appendix. Krukenberg type	123.5	Alive 2 years out
2	68	F	Ovarian cancer	Bilateral ovaries, omentum, appendix, cecum, peritoneum	Goblet cell carcinoid. Krukenberg type	11.9 → 56 over 9 months	Alive 9 months out
3	72	M	Carcinoid metastatic to liver-unknown primary	Liver, small bowel, tumor encases SMA	Typical carcinoid with focus of goblet cell carcinoid, mild pleomorphism, 1 mit/10 hpf	73.8	Alive 4 months out
4	35	F	Abdominal mass	Bilateral ovaries, uterus, sigmoid, cecum, anterior abdominal wall, peritoneum, ascites	Metastatic adenocarcinoid extending from ovaries to uterus, small bowel serosa	14.8	Deceased—greater than 5 months out
5	47	F	Cecal mass	Cecum, ileocecal valve	2 cm goblet cell carcinoid, invasion of ileocecal valve, muscularis propria, vascular and perineural spaces, serosa free of tumor and cecal/colonic stumps free as well	Not known	Died in MVA, octreotide scan negative 5 months out, clinically without disease 11 months out
6	44	M	Abdominal mass	Cecum	Right colon with goblet cell carcinoid and cacinomatosis. Tumor invades cyst wall. Pools of mucin along serosa. Cyst measures 15 × 14 × 8 cm. Poorly differentiated	11.9	No follow-up

TABLE III. Reported Duration of Symptoms for Patients Presenting With a Tumor as an Incidental Finding (Group 1) and Patients Presenting With Metastases (Group 2)

Subgroup	Duration unknown	No delay	Duration of 1–2 months	Duration 2 months	Duration \geq 3 months
Group 1	2	4	3	1	0
Group 2	1	1	1	0	3

spread. For patients who do not have metastatic disease at initial diagnosis, the most likely presentation is that of an incidental finding at appendectomy for appendicitis. The therapeutic advantage of right hemicolectomy in these patients remains unproven in the literature and is inconsistently followed. Oophorectomy is even less well established. Based on our series, conclusions cannot be drawn on the therapeutic benefit of right hemicolectomy or oophorectomy for patients with non-metastatic goblet cell carcinoid of the appendix. Considering the inherent risks of these procedures, a recommendation of right hemicolectomy cannot be made based on pathologic diagnosis alone and surgical intervention must be customized to the individual patient. Furthermore, our patients did not show the presence or absence of tumor invasion to be predictive of metastatic disease clinically or in the follow-up resection specimen. Conclusions cannot be drawn on the utility of Chromogranin A as a serum marker for disease from our study. Lastly, because of what appeared to be two different presentation subgroups, one metastatic and one more indolent, a route of further investigation into these tumors may be on genetic differences between groups and not the clinical factors predicting metastases.

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