

Adenocarcinoma Ex Goblet Cell Carcinoid in a Renal Transplant Patient: A Case Report and Review of the Literature

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Abstract. *Adenocarcinoma ex goblet cell carcinoid is a rare neoplasm of appendiceal origin that contains features of both carcinoid tumor and adenocarcinoma. We report on a case of a 45-year-old woman, post-renal transplant who presented with ovarian metastases from this tumor. This appears to be the first report of an adenocarcinoma ex goblet cell carcinoid in a renal transplant recipient.*

Adenocarcinoma ex goblet cell carcinoid is a rare neoplasm of appendiceal origin that contains features of both carcinoid tumor and adenocarcinoma. The case of a 45-year-old woman post-renal transplant who presented with ovarian metastases from this tumor is reported. Although no primary tumor in the appendix was evident at the time of laparotomy, subsequent staining for Homeobox protein CDX-2, a protein that in humans is encoded by the *CDX2* gene (*CDX2*) and the pathology of the tumor were suggestive of an occult primary appendiceal tumor. There are two previous reports in the literature of appendiceal tumors in renal transplant recipients, both combined carcinoid and mucinous cystadenoma. This appears to be the first report of an adenocarcinoma ex goblet cell carcinoid in a renal transplant recipient.

Case Report

A 45-year-old woman presented for medical attention with abdominal bloating and pain. She had a history of living related renal transplant from her sister two years previously for fibrillary glomerulonephritis, and was taking

mycophenolate and tacrolimus for immunosuppression. A pelvic MRI revealed bilateral ovarian masses, 11.8×11.6×11.3 cm on the right and 6×3.5 cm on the left. Tumor markers were notable for normal serotonin, chromogranin and cancer antigen 125 (CA-125). She had a carcinoembryonic antigen (CEA) level of 16.8 ng/ml (normal range: 0-3 ng/ml). The patient underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy. At the time of the surgery, a small amount of ascites and military studding of the small bowel omentum was seen. There were no abnormalities in the appendix. One day postoperatively, CEA had declined to 4.3 ng/ml, and one month after surgery to 1.8 ng/ml.

Pathology from both ovaries revealed a metastatic signet ring adenocarcinoma with extensive neuroendocrine differentiation, characteristic of adenocarcinoma ex goblet cell carcinoma. The tumor had features of adenocarcinoma, including signet-ring cells and pools of mucin, and some areas of tumor had histological features of neuroendocrine tumor. However, all areas, including the signet-ring cells, stained strongly positively for synaptophysin. The tumor cells were focally-positive for chromogranin and there was strong positivity for cytokeratin-0 (CK20) and focal positivity for cytokeratin-7 (CK7). The tumor stained strongly positively for CDX2 and negative for paired box gene-8 (PAX-8), suggesting that the ovarian mass was a metastasis from a primary tumor of gastrointestinal origin. The mitotic activity in the tumor was high, with >20 mitoses per high-powered field. Subsequently, a colonoscopy was carried out and no abnormalities were seen. The patient was then started on capecitabine and oxaliplatin.

Subsequent (PET-CT) scans have shown postoperative changes in the surgical bed, but otherwise no evidence of disease up to six months after surgery.

Discussion

Carcinoid tumors are the most common neoplasm of the appendix, with appendiceal carcinoids found in 1 out of every 300 appendectomies. Goblet cell carcinoid (GCC) is a

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Table I. Clinical features in cases of appendiceal goblet cell carcinoids in transplant patients.

Age/ Gender	Transplanted organ	Years post- transplant	Immunosuppressive medications	Tumor pathology	Tumor extent	Treatment	Outcome	Reference
44/F	Deceased donor renal transplant	20	Cyclosporine Azathioprine Prednisone Mycophenolate	Goblet cell carcinoid mixed with mucinous cystadenoma	Appendix and right ovary	TH/O Cyclosporine switched to sirolimus Re-resection	Local recurrence at 1 month NED, time unknown	20
42/M	Deceased donor renal transplant	14	Unknown	Goblet cell carcinoid mixed with mucinous cystadenoma	0.8 cm tumor in the appendix	No further treatment	Unknown	20
45/F	Living related renal transplant	2	Mycophenolate Tacrolimus	Goblet cell carcinoid mixed with adenocarcinoma, signet ring type	Bilateral ovaries, right fallopian tube	TH/BSO Capecitabine/ oxaliplatin	NED at 6 months	Present case

TH/O, Total hysterectomy, ovariectomy; TH/BSO, total hysterectomy, bilateral salpingo-oophorectomy; NED: no evidence of disease.

rare subtype that comprises 6% of carcinoids (1) and fewer than 5% of primary appendiceal tumors overall (2). GCC is characterized by neoplastic cells with features of both neuroendocrine and mucinous cells (3). In a SEER-based population study, the incidence of GCC was equal in men and women (4). The age at presentation for GCC was intermediate between that for classical carcinoid and for adenocarcinoma of the appendix; the average age at presentation for carcinoid was 38 years, for GCC 52 years, and for adenocarcinoma 60 years (4). The biological behavior and prognosis of GCC is worse than that of carcinoids; while appendiceal carcinoids metastasize in 2-5% of cases, GCCs have a rate of metastasis of 15-30% (2, 4). These differential features between appendiceal carcinoids and GCCs support the concept that GCC is a tumor type that is biologically distinct from classical carcinoids (5).

Patients with GCC most commonly present with either an acute appendicitis, or abdominal symptoms such as pain and bloating with a palpable abdominal mass (Table I). GCC often presents at an advanced stage with transmural invasion of the appendiceal wall on pathology; studies have estimated that 65-97% of tumors are T3 or T4 at the time of diagnosis (4, 6). The most frequent metastatic sites include local extension into the right colon or ileum, and peritoneal or omental spread. Women can present with Krukenberg tumor, and among women the ovary is the most common site of metastasis site (6, 7). In our case, no abnormalities in the appendix were noted at the time of surgery. This is not unusual, however, as in a review of 30 cases of Krukenberg tumor of appendiceal origin, 16 were due to GCC of the appendix, and four out of the 16 required a second laparotomy to identify the primary site in the appendix (8).

Because GCC's are typically infiltrative and do not present as well-defined macroscopically evident masses or discrete tumors, they can be clinically occult at the time of laparotomy for the ovarian lesions (9-11).

Immunohistochemistry in GCC frequently demonstrates the presence of the neuroendocrine markers synaptophysin and chromogranin (5). Serum chromogranin-A levels are also often elevated. In our patient, all cells, including the signet-ring cells, stained with synaptophysin, indicating that the tumor was not likely to be a collision tumor consisting of adenocarcinoma and neuroendocrine tumor originating from two separate primaries. GCC also stains positively for CK20, CK7 (less commonly than CK20), and neuron-specific enolase (5). Although our patient had no signs or symptoms of a primary tumor in the gastrointestinal tract, lack of PAX-8- and CDX2-positive staining suggested that the tumor originated from a gastrointestinal, rather than an ovarian, site.

A retrospective study of 63 cases of appendiceal GCC sub-classified the tumors by histology into three types: A:) Typical GCC; B:) adenocarcinoma EX GCC, signet-ring type; C) Adenocarcinoma exGCC, poorly-differentiated type (6) The histological subtype of GCC as defined by this group was found to be predictive of survival at advanced stage, with a 5-year survival in stage IV disease of 100%, 38%, and 0%, respectively. However it has been noted that the distinction between types B and C is not always clear, and can be difficult to accomplish prospectively (12). In our case, signet ring features were suggestive of type B disease, however the patient had a high mitotic index in the tumor (>20 mitoses per hpf), which in this series was more common among type C tumors, although not used as a

criterion for classification as a type C tumor (12). The authors of this retrospective study also found p53 staining to be more common in type C than in type B tumors, and in future this could be evaluated as a way to distinguish between the two prospectively.

Due to the rarity of adenocarcinoma ex GCC, the management of this tumor is extrapolated from case series of metastatic GCCs. In a series of four patients with diffuse peritoneal involvement from GCC, debulking surgery alone resulted in a median survival of seven (range 5-24) months (13). In a series of 22 patients with peritoneal disease and mucinous ascites from GCC of the appendix, a comparatively longer median overall survival of 18.5 (range 3.2-95.1) months was seen with debulking surgery and intraperitoneal chemotherapy (14). The patients in this series that did not receive intraperitoneal chemotherapy (n=2) had a shorter survival of 4.1 and 6 months. The extent of intraperitoneal disease preoperatively (measured by the peritoneal cancer index) was negatively-correlated with survival, while the degree of cytoreduction achieved (measured by the completeness of cytoreduction score), was positively-correlated with survival.

Case series of ovarian and peritoneal metastasis from GCC have also described the use of adjuvant chemotherapy with 5-fluorouracil (5-FU) and leucovorin, with minimal effect (15, 16). In another case, cisplatin-based chemotherapy given both intraperitoneally and *i.v.* resulted in survival for 24 months after surgery (8). One case report of adjuvant oxaliplatin, 5-FU and leucovorin (FOLFOX4) in a woman with diffuse peritoneal and lymph node metastases reported a complete remission of the cancer for up to three years after diagnosis (17). The rarity of this tumor makes prospective studies using FOLFOX in appendiceal GCC unlikely, however the more aggressive adenocarcinomatous component likely drives the prognosis in this tumor and FOLFOX has been used more for appendiceal carcinomas with some success in the adjuvant setting (18).

One unique aspect of this case is that the patient's cancer arose two years after renal transplant. It has been well-documented that the incidence of malignancy is increased in the post-transplant setting, and this has been ascribed to the effects of chronic immunosuppression. Although the most common types of cancers in the post-transplant setting are squamous cell carcinomas and lymphoproliferative disorders, it is increasingly recognized that the incidence of other types of cancers is also slightly higher (19).

No prior cases of adenocarcinoma ex goblet cell carcinoid appear to have been published, although two cases of mixed tumors consisting of mucinous cystadenoma and goblet cell carcinoid have been published in the same report (20). In one of these cases the patient presented with ovarian metastasis and had radical surgery with no recurrence, although the period of follow-up after surgery

was not reported. In the second case, the tumor was suspected at the time of second renal transplant when the appendix appeared enlarged, and appendectomy was performed, revealing mucinous cystadenoma and GCC. It is unclear in our case whether an occult appendiceal GCC predated the patient's transplant and evolved into adenocarcinoma after immunosuppression was started, or whether this was a tumor that arose *de novo* in the setting of immunosuppressive therapy. With the increasing rate of solid-organ transplantation, we expect that more rare tumors will be diagnosed in post-transplant patients. It remains to be seen whether immunosuppression contributes to the risk of transformation of more benign entities such as typical GCC to more aggressive histologies such as signet ring or poorly differentiated GCC.

Conclusion

This case of adenocarcinoma Ex goblet cell carcinoid in a woman two years after a renal transplant, had features suggestive of aggressive disease such as the presence of signet ring cells and a high mitotic index. The absence of an obvious primary tumor in the appendix is not unusual in this case and points to the importance of considering the appendix as a potential site for a primary tumor at the time of oophorectomy for Krukenberg tumor of unknown origin.

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