**Goblet Cell Carcinoid Tumors of the Appendix**

Goblet cell carcinoid tumors (GCCT) are uncommon neoplasms that predominantly occur in the vermiform appendix. They tend to occur in middle-aged adults with a near equal sex distribution. Most Goblet cell carcinoid tumors are discovered in appendices removed for acute appendicitis and for other reasons. Goblet cell carcinoid tumors demonstrate features of both classic carcinoid tumor and adenocarcinoma. Similar to classic carcinoid tumors, GCCT may involve the deep mucosa, but are not associated with dysplasia of the surface epithelium. The GCCT cells grow as nests, cords, and clusters in collagenous stroma. They contain abundant cytoplasmic mucin and display mild cytological atypia with a relatively low proliferation index, as measured by Ki-67 stain. Immunohistochemical stains for neuroendocrine markers, such as chromogranin and synaptophysin, demonstrate patchy positive staining of tumor cells.

Goblet cell carcinoid tumors also show several histological features that are not typical of classic appendiceal carcinoid tumors. Specifically, they tend to grow in a circumferential fashion and do not form a discrete nodule or mass. As a result, they are rarely suspected prior to histological examination of the appendix. They can occur in any region of the appendix, typically resulting in ill-defined mural thickening, and show frequent neurotropism. While immunostain for neuroendocrine markers are more pronounced in the classic carcinoid, proliferative index is higher in GCCT. The tumor cells also express CK20 (100%), CK7 (70%) and CEA, whereas classic carcinoid tumors are uniformly negative for these markers. Unlike colonic adenocarcinoma, they do not harbor K-RAS mutations.

Most importantly, goblet cell carcinoid tumors are more aggressive than classic carcinoid tumors of the appendix. Most GCCT invade deeply into the wall and penetrate the serosa, and a substantial number of cases are associated with regional lymph node metastases as well as peritoneal and/or ovarian deposits. Tumors that spread beyond the appendix often contain overtly carcinomatous elements. Up to 50% of the female patients show ovarian metastases. The clinical outcome of GCCT appears to be dictated by the tumor grade and stage, similar to carcinomas of other organs. Overall, the clinical outcome of GCCT is intermediate between carcinoids and adenocarcinomas of the appendix.

Based on a retrospective study of 63 goblet cell tumors of the appendix with mean follow-up time of 49 months, L.H. Tang et al. classified goblet cell carcinoid tumors as typical GCCT (group A) and adenocarcinoma ex GCCT. The adenocarcinoma ex GCCT group was further divided into signet ring cell type (group B) and poorly differentiated adenocarcinoma type (group C). Overall, more than half of these cases contained tumor signet ring cells, or poorly differentiated component. The authors found that even well-differentiated goblet cell carcinoid tumors showed aggressive features, in that 93% of them invade the wall beyond the muscularis propria, 19% cases showed lymph node metastases, and 33% disseminated to the peritoneum, or distant sites. Groups A and B have normal membranous stain of beta-catenin and e-cadherin, and proliferative index of 11% and 16%, respectively. They exhibited normal intestinal type mucin glycoprotein profile (i.e. negative MUC1 expression and preserved MUC2 immunoreactivity). On the follow-up, the stage IV-matched 5-year survival was 100% and 38%, respectively. Group C (11%) is composed of poorly differentiated adenocarcinoma with or without signet ring cell features or with morphologic features of a high-grade neuroendocrine carcinoma or undifferentiated carcinoma. This group demonstrated abnormal p53 and b-catenin immunoreactivity and a proliferative index of 80%. MUC2 expression is lost and MUC1 is overexpressed. The stage IV-matched 5-year survival of Group C was 0%.
Currently, there is no established classification of the goblet carcinoid tumors. Confusion also arises from the classification of the goblet carcinoid tumors as neuroendocrine by the most recent staging guidelines of both the WHO and AJCC. Yet, the AJCC staging criteria for goblet cell neoplasms do exist. The issue is further complicated by the existence of combined classical carcinoid and goblet cell carcinoid tumors of the appendix. The two components are found to be either intimately admixed or separated but closely apposed. Pelvic soft tissue and ovarian metastases appears to consist predominantly of a signet ring cell carcinoma with a minor component of goblet cells (an adenocarcinoma ex-GCCT).

The appendectomy specimen harboring goblet cell carcinoid tumor, regardless of its grade, should be submitted entirely for histological evaluation. The pathological assessment and reporting similar to that for adenocarcinoma should be performed. Surgical management with right hemicolectomy is recommended after appendectomy for most cases with goblet carcinoid tumor. All the patients with clinical stage I or IIA disease had a favorable outcome after appropriate surgery with or without chemotherapy.

**Summary of Goblet Cell Carcinoid Tumors of Appendix**

- Most are incidental finding.
- Features of both carcinoid and adenocarcinoma.
- Deep diffuse, infiltrative growth.
- Goblet cells, signet-ring cells.
- CK20(+), CEA(+), more Ki67(+).
- Weak Synaptophysin(+) & chromogranin(+).
- More aggressive than classic carcinoid.
- Assess, stage and report as for adenocarcinoma.
- Hemicolectomy for most cases.

**Reference / Suggested Readings**

