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Goblet Cell Adenocarcinoma of the Appendix: Case Report and Short Review

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Abstract

Goblet cell adenocarcinoma (GCA) is a rare malignant neoplasm of the vermiform appendix. The disease incidence peaks at 6th and 7th decades of life, with Caucasians having the highest prevalence compared to other races. Affected patients usually present with features of acute appendicitis; however, some cases may present with metastasis, and aggressive clinical behavior. The tumor cells originate from undifferentiated stem cells, and they exhibit variable expression of both neuroendocrine, and colonic-type adenocarcinoma immunohistochemical markers. GCA is prognostically categorized, based on the tumor architecture, and predominant cells that constitute the lesion. The tumor stage depends on the depth of tumor invasion rather than the size of the tumor, and it is the most important prognostic factor. Surgery with or without chemotherapy is the mainstay of treatment.

Introduction

Goblet cell carcinoid tumor (GCC), also called mucinous carcinoid tumor, among other names, is a specific but rare neoplasm occurring in the appendix.**[**1**]** It was first described by Gagne et al. in 1969.**[**2**]** Although classified as a neuroendocrine tumor. Yet, controversy abounds whether to consider GCC as a variant of typical carcinoid or a mucin-producing adenocarcinoma.**[**3**]** The variation in clinical features, and the histological profile, caused conflicting views among pathologists, oncologists, and surgeons.**[**4**]** Due to organoid pattern of growth, morphological characteristics, lack of p53 mutation, and absence of precursor lesion, some authors consider the disease a form of carcinoid tumor.**[**5-7**]** Whereas, the presence of intracellular mucin and trans coelomic pattern of tumor spread with consequent metastasis compelled some researchers to categorize the tumor as adenocarcinoma for classification purposes.**[**8,9**]** In 2019, the WHO renamed GCC to goblet cell adenocarcinoma (GCA) of the appendix as it was found to have abundant mucin-producing cells and little neuro-endocrine components.**[**10**]**

Epidemiology

This extremely rare unique neoplasm of the appendix occurs in 0.3-0.79% of appendicectomies. It accounts for 35-58% of all appendiceal tumors, **[**11,12**]**, and less than 14% of all malignant tumors of

the appendix.[9] The age-adjusted incidence of GCA is 2.0/100,000 in men, and 2.4/100,000 in women.[9]

It usually occurs between the second to the ninth decade of life, and the incidence peaks in individuals aged 50-69 years.[9] The prevalence of the disease is higher in Caucasians than in any other race.[9]

Clinical features

Majority of patients present with symptoms of acute appendicitis. GCA causes diffuse thickening across the whole length of the appendix or involves only the base resulting in luminal occlusion. [13,14] In advanced cases, patients may present with abdominal mass and weight loss in addition to abdominal pain.[9]

Gross examination findings

GCA usually appears as a poorly defined firm, nodular thickening of the vermiform appendix and rarely presents as a well-defined appendiceal mass. Most GCA are > 2cm in dimension, with an average size of 2.4cm.[15] The gross tumor size is difficult to assess because of the diffuse pattern of invasion in this tumor. Usually, the disease is situated in the tip of the appendix but may affect the base of the appendix. Mostly the tumor circumferentially involved the appendiceal wall, with the propensity of longitudinal extension. Hence, the whole appendix needs to be examined grossly for accurate analysis of the lesion.[15]

Histopathology

Subbuswamy and colleagues first described this tumor as having cells with mucin-filled cytoplasm and eccentric nuclei, architecturally forming nests and rosettes with no apparent lumen, as depicted in figures 1 & 2. Most tumor mass is situated in the sub-mucosa or the lamina propria, surrounding the basal-glandular crypts (figure 1).[16] Tumor is composed of small to intermediate-sized cells with granular, finely vacuolar eosinophilic cytoplasm, vesicular nuclei, prominent nucleoli, and mild cytologic atypia. Paneth cells and occasional large goblet cells within the mucin pool may be seen.[16] Morphologically, GCA is sub-divided into low-grade and high-grade lesions.[17] The former have tubules or mucin small pool of mucin containing goblet cells forming ring-like appearance and surrounded dense collagenous stroma. Whereas the latter is more common, it microscopically lacks tubule formation and nested appearance. It is morphologically similar to conventional adenocarcinoma

but with signet ring cells or mucinous differentiation.[17] GCA cells usually pick Sevier-Munger stain and are therefore argyrophilic and may occasionally be argentaffin-positive (stain with Masson-Fontana). All mucin-containing cells stain positive with PAS, PAS with diastase, and Alcian blue.[18] Mitotic activity is usually rare but may reach up to 4/10 high power fields in metastatic and high-grade lesions.[19] Infiltration of the peri-appendiceal fat, as well as perineural and vascular invasion, are commonly seen. Microscopic features of acute appendicitis can be seen in some instances.[19]

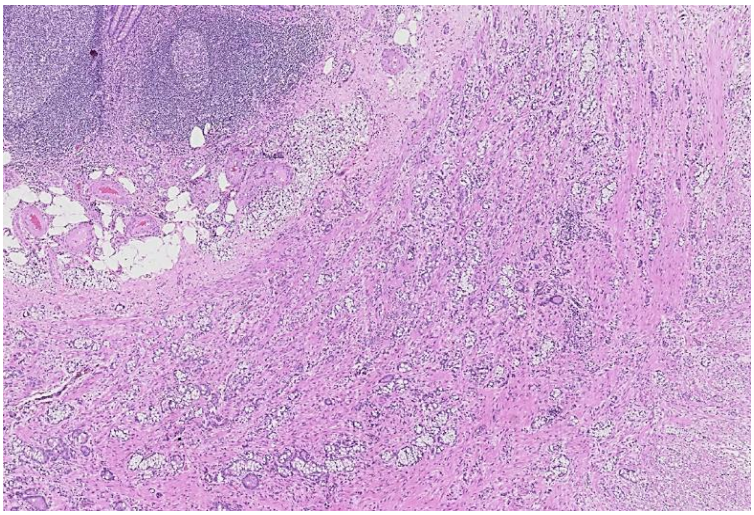

Figure 1: Goblet cell adenocarcinoma (Low Power)

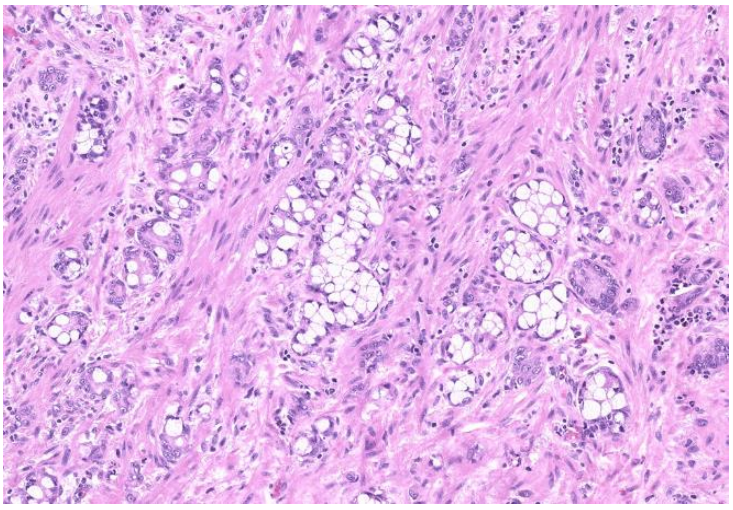

Figure 2: Goblet cell adenocarcinoma (High Power)

Immunohistochemical staining pattern

All GCA cases show positive immunostaining for synaptophysin (either focally or diffusely) (Figure.3). CDX2 immunostain is diffusely positive in all cases of GCA, which supports the hypothesis that these tumors are derived from the colorectal-type epithelium; in contrast, serotonin is only positive in some cases.**[**20**]** GCAs exhibit strong positivity to CEA (Figure 4), CAM 5.2, and CD19, and their expression do not correlate with prognosis, unlike gastrointestinal/pulmonary neuroendocrine tumors. The tumor shows a variable expression of CD20 (Figure 5), CD7, and CD 99.4 chromogranin (figure 6), and other neuroendocrine markers (seen in about half of cases), and the usual pattern of staining in positive cases is focal and patchy. 4 Groups A and B GCAs express MUC2, akin to the normal gastrointestinal mucosa, whereas group C lesions overexpress MUC1 and exhibit loss of MUC2 expression.**[**15**]**

This tumor is negative for S100, Leu7(CD57), and NCAM(CD56), unlike the carcinoid tumors.**[**21**]** There is a variable expression of proliferation markers like Ki-67 and PCNA.(11;15) Immunohistochemical analysis of microsatellite showed an intact nuclear expression for MLH1, MSH2, MSH6, and PMS2 in all cases, proving the absence of microsatellite instability in GCA.**[**20**]** The pathogenesis of CGA occurs through a p53 independent process, evidenced by the absence of p53 and p16 immunostains in the majority of cases. In addition, overexpression of cyclin D1 and p21 points to cell cycle abnormality in some cases.**[**11**]** Furthermore, GCAs demonstrate strong membrane staining for both E-cadherin and β-catenin. **[**22**]**

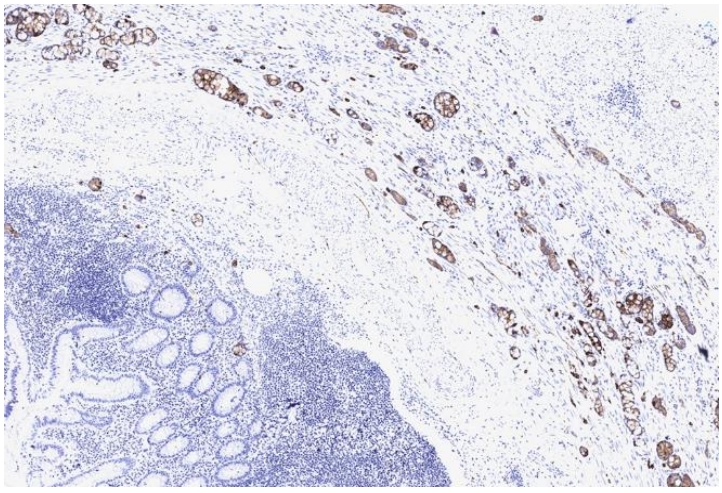

Figure 3: Immunohistochemical stain for Synaptophysin

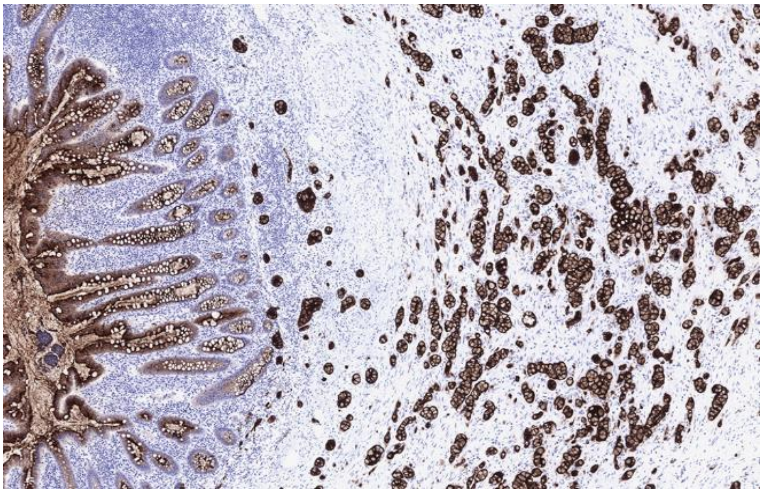

Figure 4: Immunohistochemical stains for CEA

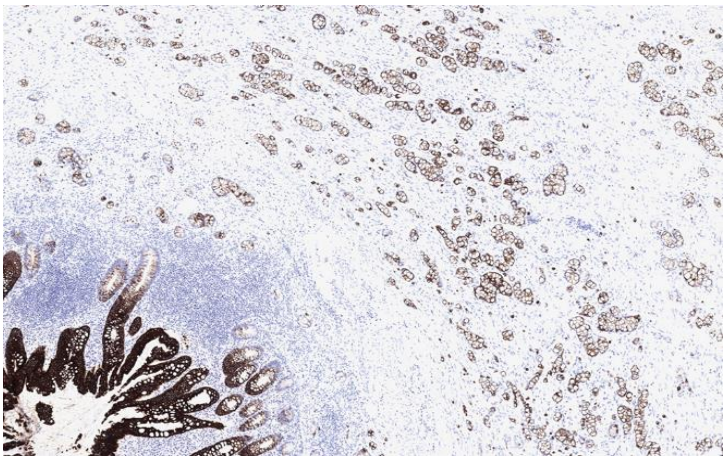

Figure 5: Immunohistochemical stain for CK20

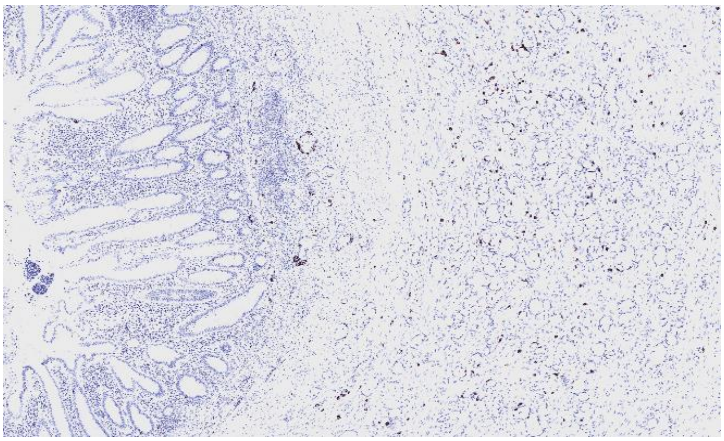

Figure 6: Immunohistochemical stain for Chromogranin

Origin

GCAs are derived from undifferentiated pluripotent stem cells, unlike carcinoids derived from endocrine cells from the mucosal stroma.[23] The tumor cells have two separate granules, predominantly acid mucinous; specific immunohistochemical stains can identify that.[18]

Molecular characterization

Jesinghaus et al. reported that 4/11 of GCA cases showed singular mutations involving T53, non V600E BRAF, TGFBR2, and ERBB2 genes. However, no mutation involving major colorectal cancer-associated genes like APC, KRAS, NRAS, PTEN, PIK3CA, or SMAD4 was noted without copy number variations.[20] Other studies showed the most prevalent mutated genes in GCAs to be TP53 (24.0%), ARID1A (14.4%), SMAD4 (9.4%), and KRAS (7.5%). Whereas pathway-specific changes were noted in the cell cycle, MAPK, TGFβ, and epigenetics signaling pathways.[24]

Some authors reported a loss of chromosomes 11q,16q, and 18q allele, among certain cases, which is similar to the ileal carcinoids.[25] Increase molecular expression of CgA, MTA1, NAPIL1, and MAGE-D2, together with decreased expression of NALP1, are noted in GCA, compared to non-diseased mucosa, and similar to carcinoid of the small intestines.[26]

Classification (Tumor grading and staging)

Tang et al. classified GCA into group A (Typical GCA) and adenocarcinoma ex-GCA, which is further sub-divided into group B (Signet ring cell type) and group C (Poorly differentiated adenocarcinoma type). The classification is based on microscopic findings at the primary site of the neoplasm.15 This classification correlates with pathologic grading of GCA, with group A as the most differentiated, having cytologically bland epithelial cells. Group B is considered moderately differentiated. It is characterized by partial or near-total loss of goblet cell clusters, cytologic atypia, and the presence of irregular signet ring cell clusters. In contrast, group C tumors are labeled poorly differentiated due to high-grade, least differentiated morphology. The tumor outcome depends on its grade, with grade A having the best prognosis and group C having the poorest survival.[15] Based on CAP, GCA is graded into Gx (cannot be assessed), grade 1 (well-differentiated), grade 2 (moderately differentiated), grade 3 (poorly differentiated), and grade 4 (undifferentiated). The WHO grading is similar to the above grading, and signet ring GCA and high-grade GCA are considered grade 3 and 4, respectively.[27]

GCC is staged per the criteria for appendiceal adenocarcinoma, based on American Joint Committee on Cancer (AJCC) due to its close biologic behavior to adenocarcinomas of the appendix. The stage depends on the depth of tumor invasion rather than the size of the tumor, and it is the most important prognostic factor.28 CAP staged this tumor using the pTNM system, where PT is the primary tumor, PN is regional lymph node involvement, and PM is distant metastasis. Similarly, the WHO staging utilized the TNM system where T, N, and M stand for the primary tumor, regional lymph node, and distant metastasis.[27] The two systems share significant resemblance and can accurately be used to prognosticate cases.

Treatment and Prognosis

The treatment approach of GCC is similar to intestinal adenocarcinoma, with surgery as the mainstay of therapy.[15] Patients with localized stage I disease may be treated with appendectomy alone, whereas higher stage tumors are treated with right hemicolectomy or debulking surgery.[15] Depending on the stage, 5-fluorouracil-based chemotherapy may also be indicated.[29]

Tang et al. reported a total disease-specific survival of 77% for all tumor subtypes. Patients with stage I or IIA cancer have a good prognosis following surgery with or without chemotherapy. The overall outcome of disseminated GCA depends on the histologic subgroup. The 5-year survival for GCA is 100%, 38%, and 0% for groups A, B, and C, respectively.[15]

Conclusion

GCA is considered a unique neoplasm of the appendix with distinctive clinical features and morphologic profiles. Diligent evaluation of the histologic features, and appropriate pathologic classification, are essential for treatment and prediction of prognosis.

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