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Perforated Goblet Cell Carcinoid Tumors of the Appendix: Navigating the Management Conundrum

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Appendix is the most common site of occurrence for a goblet cell carcinoid tumor. A diagnosis of an appendiceal goblet cell carcinoid is made in retrospect the majority of the time. These tumors are best treated with a right hemicolectomy and adjuvant therapies tailored according to the presence or absence of residual disease. Presentation as a perforated appendix is seen in 16% of these tumors. The natural history and the ideal management strategy in such a scenario are not well described. In those with peritoneal spread cytoreductive surgery with HIPEC (hyperthermic intraperitoneal chemotherapy) offers the best disease-free and progression-free survival. Close follow-up with cross-sectional imaging helps in identifying recurrences at the earliest. Multimodality management involving patient participation in every aspect of care accomplishes high-value care in the treatment of these tumors.

Key words: Goblet cell carcinoid – Hyperthermic intra-peritoneal chemotherapy – Surveillance epidemiology and end results – Chromogranin

Neoplasms of the appendix constitute 0.4% of gastrointestinal cancers.[1] Appendiceal goblet cell carcinoids (GCC) are rare tumors with an incidence of 0.01–0.05 per 100,000 per year and constitute less than 15 % of all the malignant tumors of the appendix.[2,3] A population-based study of the SEER (Surveillance, Epidemiology, and End Results) database of 25 years demonstrates that goblet cell carcinoids of the appendix are uncommon and follow mucinous adenocarcinoma, colonic adenocarcinoma, and malignant carcinoid tumors in incidence.[3] Appendix is the most common site of occurrence for a goblet cell carcinoid; however, extra-appendiceal locations like ileum, rectum, and colon, are also described.[4,5] Presentation as a perforated tumor is rare and poses challenging management decisions. Sparse literature exists to describe the ideal strategy in such a situation. We intend to

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review the current evidence and describe the principles of management of a perforated goblet cell carcinoid tumor of the appendix.

Material and Methods

A comprehensive literature search was performed using PubMed, OvidSP, Cochrane, and Embase search engines. NLM Medical Text Indexer (MTI) was used to find MeSH terms. "Goblet cell carcinoid," "GCC," "neuroendocrine tumor," "NET," "carcinoid," "adenocarcinoid," and "appendiceal neoplasms" search terms were used. In addition a free text search was also performed. A meta-analysis was not intended due to the expected heterogeneity of the data. All the papers were thoroughly analyzed for the quality and content. Major societal guidelines (European Neuroendocrine Tumor Society or ENETS and North American Neuroendocrine Tumor Society or NANETS) were also reviewed. A descriptive analysis of the search results was performed and is cited in the review.

Results and Discussion

Histogenesis

These tumors were first described in 1969 by Gagne *et al*,[6] whereas the term "goblet cell" carcinoid was introduced by Subbuswamy *et al* in 1974,[7] because the predominant cell type was thought to be similar to the goblet cell of the intestinal tract. These tumors are synonymously known as adenocarcinoids, mucinous carcinoids, amphicrine (endo-exocrine) neoplasia, or microglandular carcinomas.[8–10] The normal lining epithelium of appendix is composed of colonic type mucin-secreting cells, neuroendocrine cells of the crypts, and Paneth cells. Epithelial tumors of the appendix essentially resemble conventional colonic adenocarcinomas. In contrast, typical carcinoid tumors of the appendix exhibit an exclusive neuroendocrine phenotype with the capacity for amine and peptide hormone production. In contrast, goblet cell carcinoid (GCC) tumors of the appendix have a mixed phenotype, with partial neuroendocrine differentiation and intestinal type goblet cell morphology and are grouped under the category of adenocarcinoids.[11]

Perforated GCC of appendix

How is it different?

Although the principles of management for a nonperforated GCC tumor of appendix are fairly standard, appendiceal perforation with an underlying tumor should be viewed from a different perspective. In a collective review of 625 cases of appendiceal carcinoid tumors, perforation complicated the picture in 16 % (n = 100) of the patients. At a mean follow-up of 50 months the 5-year survival rates are 100% with no peritoneal metastases described at follow-up.[12] For classical carcinoids, there seems to be no influence of perforation on outcome.[12] Does the same philosophy hold true for GCC tumors? Can we extrapolate the data from carcinoid tumor to GCC and treat them the same? There is no consensus on the management in such a clinical scenario. The issues that are of major concern are the extent of tumor spillage from perforation, seeding of the peritoneum with tumor deposits, surveillance protocol to detect any synchronous or metachronous lesions at the earliest, best imaging modalities to be used at follow-up, and role of adjuvant therapies be it chemotherapy, radiotherapy, or radiopharmaceutical ablation. The rarity of these tumors and the lack of precise understanding of the natural history of these perforated tumors preclude affirmative answers to the above questions.

Natural history of perforated GCC appendix

A literature review of perforated goblet cell carcinoids involving high quality data revealed a total of 6 case series involving 78 patients with GCC. A perforation of the appendix was noted in 18 (20%) of these patients.[12] At a median follow-up of 5 years (24–62 months) peritoneal recurrences are noted in 14% –30 % (1/7 to 1/3) patients. Similar rates of recurrence are noted in a series of 48 patients from UK treated over 17 years. The recurrence rate is 21% at a median follow-up of 28 months.[13] The pattern of recurrence tends to involve lymph nodes in the mesocolon and the peritoneum. In females, deposits on the ovary and pelvic peritoneum are not uncommon. However, distant metastasis to liver lung, bone, and brain are rare. So what is evident from data is that perforation in a goblet cell appendiceal tumor has a greater metastatic potential to the peritoneum than classical carcinoids. GCC closely mimic adenocarcinoma in biologic behavior. Whether a cause-and-effect relation exists between perforation and tumor spillage is not proven as recurrences are noted even in nonperforated cases with same duration of follow-up.[12] In the best interests of long-term survival of the patient it seems prudent to consider the risk as real carefully

balancing the risk versus benefit of all the treatment modalities.

Management principles

Once the patient has recovered from the index operation for a perforated appendicitis, and the biopsy is a GCC of the appendix, a comprehensive care program should be implemented. The patient should be involved in the selection of management decisions at every further aspect of care. A multidisciplinary meeting in a tumor board with inputs from medical oncology, surgery, radiology, radiation oncology, nuclear medicine, and pathology, considering the patient's functional status and the available resources, provides the best long-term care for these patients (Fig. 1). GCC lack classical neuroendocrine differentiation and hence serum cgA is of limited use in diagnosing and monitoring of GCC tumors after resection.[14,15] Epithelial cell markers (CEA, CA-19-9, and CA-125) have been shown to be elevated in GCC in up to 80% of patients. The ENETS recommends to use CEA, CA-19-9, and CA-125 at presentation and during follow-up.[16] The most useful of staging work-up, however, is cross-sectional imaging. Multi-detector computed tomography and magnetic resonance imaging (MRI) are more sensitive than any other imaging modality and should be performed in all patients.[15,17] Because GCC carry a higher risk of distant metastases, ENETS recommends a chest CT in addition to a CT of abdomen and pelvis or alternatively MRI of the abdomen and pelvis together with somatostatin receptor scintigraphy.[18] GCC tumors lack avid expression of somatostatin receptors. Hence somatostatin receptor scintigraphy (SRS) alone or Gallium DOTANOC-PET scans without a fusion cross sectional imaging are of limited use.[19] FDGPET likewise has a limited role. Only high grade GCC tumors (Ki-67 $>$ 3/10 HPF) appear to be FDG-PET avid and it's routine use in every GCC is of limited value.[20]

In the absence of regional (peritoneal) and disseminated (liver, lung, or bone) disease a right hemicolectomy is performed in all patients be it perforated or nonperforated (see aforementioned) irrespective of size and location of perforation. Considering the proclivity for metachronous ovarian and pelvic spread prophylactic bilateral salpingoopherectomy is recommended in females by certain groups.[10] However, such an approach is not universally accepted and careful consideration should be given to the patient's age, menopausal status, and planned pregnancies.[21] If there is no residual disease in the colectomy specimen, no adjuvant therapy is warranted and the patients should be enrolled in a dedicated multidisciplinary surveillance protocol (see the following material). Adjuvant therapy as a routine in all perforated appendices with GCC to prevent peritoneal or distant metastasis is not proven; however, it is recommended by some expert groups.[22] On the other hand, if there is residual disease in the colectomy specimen or metastasis in the lymph nodes, adjuvant FOLFOX, like in colorectal cancer, is recommended.[13,18] Peritoneal carcinomatosis from GCC are addressed in a similar fashion to epithelial tumors of colon and ovary. Cytoreductive surgery (CRS) followed by HIPEC (hyperthermic intraperitoneal chemotherapy) appears to provide the best long-term survival in these patients.[10,23] Mahteme *et al* reported a series of 22 patients with GCC of the appendix treated with CRS + HIPEC. The overall median survival was 18.5 (range: 3.2–95.1) months, with 2- and 5-year survival rates of 39% and 25%, respectively.[23] Additionally, McConnell *et al* reported on 45 GCC patients treated with CRS + HIPEC and described a 3-year progression-free survival (PFS) of 42.7% and overall survival of 68.1% for GCC.[24] In patients with nonresectable peritoneal disease or systemic disease, 5-fluorouracil (5-FU) based chemotherapeutic regimens [FOLFOX or FOLFIRI]offer PFS of up to 12 months.[10,14,25,26,27] As the tumors lack expression of somatostatin receptors, targeted peptide receptor therapy using 90Y-DOTATOC and 177Lu – DOTATATE is less effective and should be considered investigational at this point of time.[28] In case of liver-only metastasis from GCC tumors, it seems prudent to apply the principles of colorectal liver metastasis as the biology of the tumors that metastasize to liver closely resemble adenocarcinoma[2] though robust evidence is lacking.

Surveillance

Considering the invasive nature of these tumors, general recommendations for colorectal cancer surveillance are followed.[21] Every patient with a perforated GCC appendix having a curative resection should have a follow-up that includes clinical exam, and biochemical and cross-sectional imaging every 3–6 months for the first 5 years and then yearly for a lifetime.[13,18] These recommendations are guidelines[18] based; large-scale studies proving the

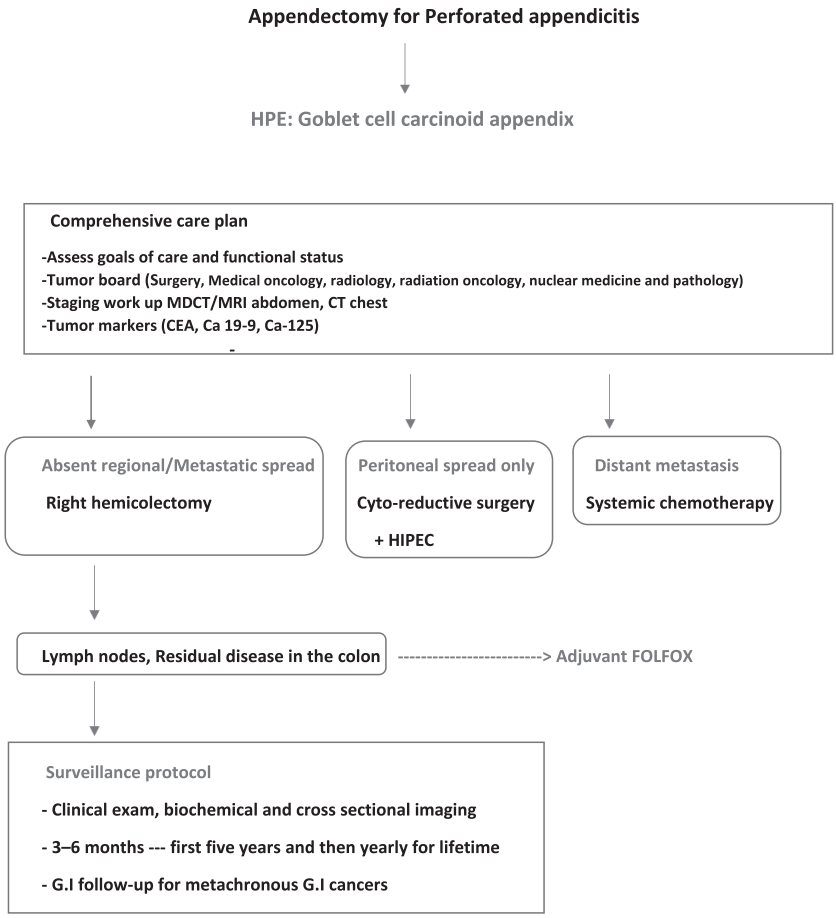

Fig. 1 Algorithmic approach to the management of perforated Goblet cell tumor of the appendix.

efficacy of such a protocol are lacking. Furthermore gastrointestinal (GI) tumors are highly co-incident (40%–50%) in these patients and hence GI follow-up is also recommended.[30]

Prognosis

In a summative multi-institutional review of 7 case series involving 78 patients with GCC tumors, perforation was noted in 18 patients .The overall survival of patients with perforated appendix is 75% at a median follow-up of 37 months.[12] Extension of the tumor beyond the appendix to the ovaries or the abdominal cavity greatly worsens the prognosis with a mean survival of 7 to 9 months.[31,32] Widespread intraabdominal dissemination can be fatal even in a short time[33] and is considered the most common cause of death in these patients. Tumor size, higher grade, mixed histology (signet ring type) aside from peritoneal dissemination are considered some of the worse prognostic features.[10,23]

Conclusion

GCC are rare mixed epithelial-endocrine tumors with biologic behavior and prognosis intermediate between carcinoid and adenocarcinoma. Presentation as a perforated appendicitis is uncommon and the natural history of such tumors is not well known. At a minimum these tumors are treated with a right hemicolectomy and adjuvant therapies tailored according to the presence or absence of residual disease. In those with a peritoneal spread cytoreductive surgery with HIPEC offers the best disease- and progression-free survival. After curative surgery, close follow-up is essential to detect disease recurrence at the earliest. Multimodality management involving patient participation in every aspect of care accomplishes high value care in the treatment of these tumors.

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