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Case Report

# Goblet Cell Carcinoid (GCC) of the Appendix presenting as a Small Bowel Obstruction

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ABSTRACT

A 68 year old male presented to our Emergency Department with a one-day history of right sided abdominal pain, distention and vomiting on a background of no previous abdominal surgery. Abdominal CT demonstrated a high grade, closed loop small bowel obstruction involving the terminal segment of the ileum. Also of significance was a low-density appendiceal nodule. A subsequent laparoscopy revealed the tip of the appendix adherent to the mesosigmoid colon, forming a tight band and consequent mechanical bowel obstruction. Furthermore, the meso-appendix was embedded with crystal deposits and extruding mucin. The decision was made to convert to laparotomy and perform a caecectomy. Immunohistochemistry demonstrated reactivity to synaptophysin, chromogranin A and CD56, confirming the diagnosis of Goblet Cell Carcinoid. A staging CT after this initial surgery revealed no metastasis. After discussion at our oncology MDT, the patient went on to receive a completion right hemicolectomy which revealed no further malignancy on histology. The patient otherwise progressed well, and made a good post-operative recovery.



A 68-year-old male presented to our Emergency Department with acute right-sided abdominal pain, distention and vomiting in the setting of no previous abdominal surgery. Abdominal computed tomography (CT) demonstrated a high grade, closed loop small bowel obstruction involving the terminal ileum as well as a low-density, appendiceal nodule (Fig. 1).

A subsequent laparoscopy revealed the tip of the appendix adherent to the meso-sigmoid colon, forming a tight banded mechanical bowel obstruction. The decision was made to convert to laparotomy and perform a cecectomy. Immunohistochemistry demonstrated reactivity to synaptophysin, chromogranin A and CD56, confirming the diagnosis of goblet cell carcinoid (GCC) (Fig. 2).

A staging CT after this initial surgery revealed no metastasis. After discussion at our oncology multi-discpilinary team (MDT) meeting, the patient went on to receive a completion right hemicolectomy which revealed no further malignancy

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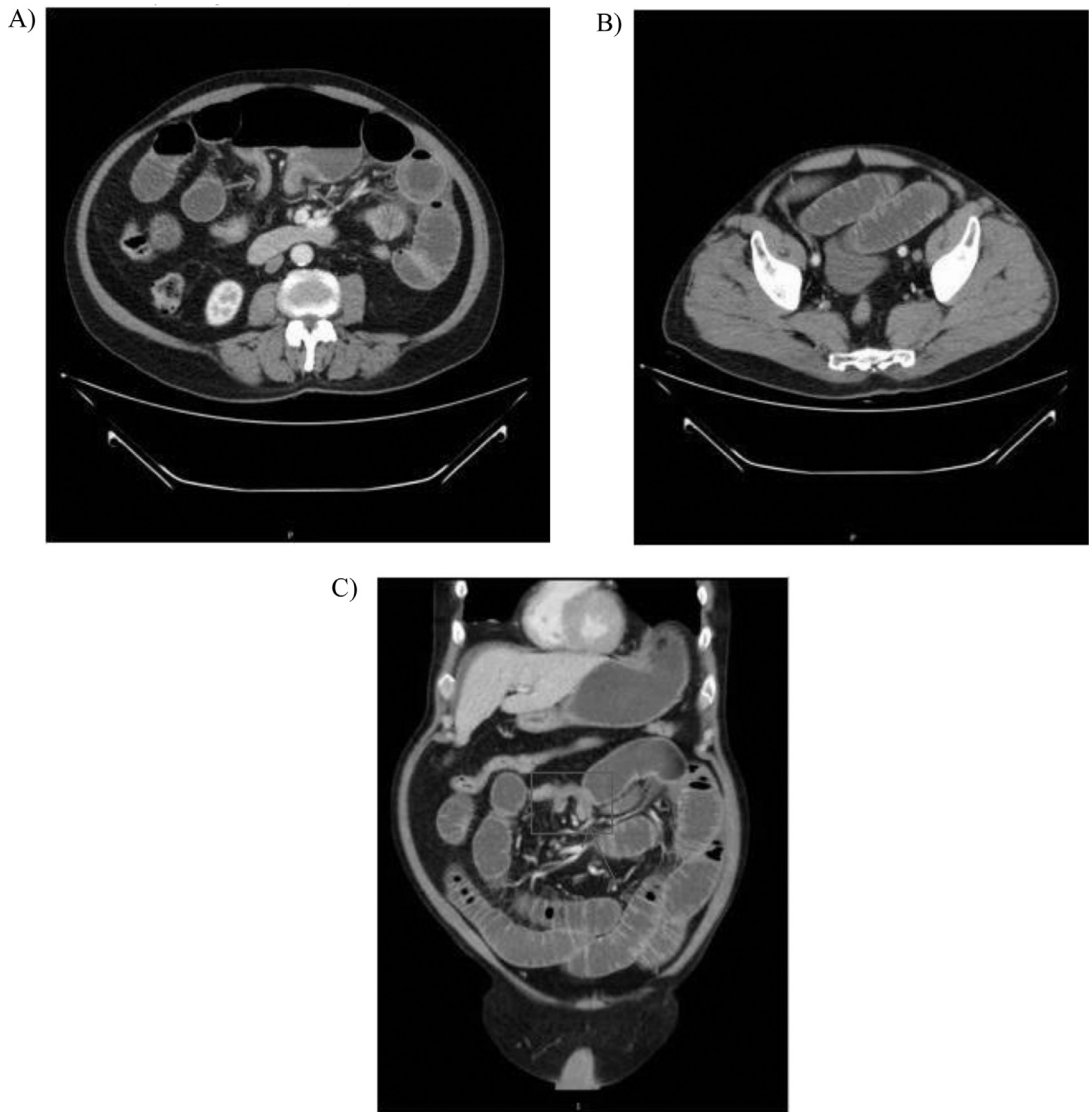


**Fig. 1 – (A, B, and C), A post IV contrast CT abdomen and pelvis demonstrating a high-grade mechanical small bowel obstruction involving the terminal segment of the ileum, with a configuration suggesting a closed loop obstruction. (A) An axial slice best demonstrating the 2 transition points lying side by side in one axial plane (demarcated by the green arrows). (B) An axial slice demonstrated the 8cm segment of terminal ileum, interposed between the transition points and is grossly dilated. (C) A coronal slice demonstrating an entirely collapsed bowel and mobile caecum displaced into the central abdomen. The red square box demonstrates the transition point with the grossly dilated small bowel proximally and the collapsed colon distally. The red arrow points to the appendix with a low-density nodule adjacent to it measuring 11 x 21 mm. There are no other discernible or specific features identified. The appendiceal nodule may potentially be characterized with MRI, however this was not available due to the acute surgical nature of this presentation.**

on histology. The patient otherwise progressed well, and made a good postoperative recovery.

## Typical presentation of goblet cell carcinoma

Compared with other carcinoid tumors which are usually asymptomatic, GCC often presents with clinical symptoms; the incidental diagnostic rate of such tumors only about 3%. The common clinical presentations in order of frequency are acute appendicitis (22.5%), asymptomatic (5.4%), nonlocalized abdominal pain (5.15%) and the presence of an appendiceal mass (3.09%) [1]. Pham et al also reported other symptoms including bowel obstruction, intussusception, gastrointestinal bleeding, and chronic intermittent lower abdominal pain [3]. It is rare for GCC to present as an infiltrative appendiceal lesion causing small bowel obstruction.

GCCs metastasize in 15%-30% of cases, particularly in higher age groups, compared to 2%-5% in appendiceal carcinoids. Spread usually occurs to the pelvic organs, abdominal

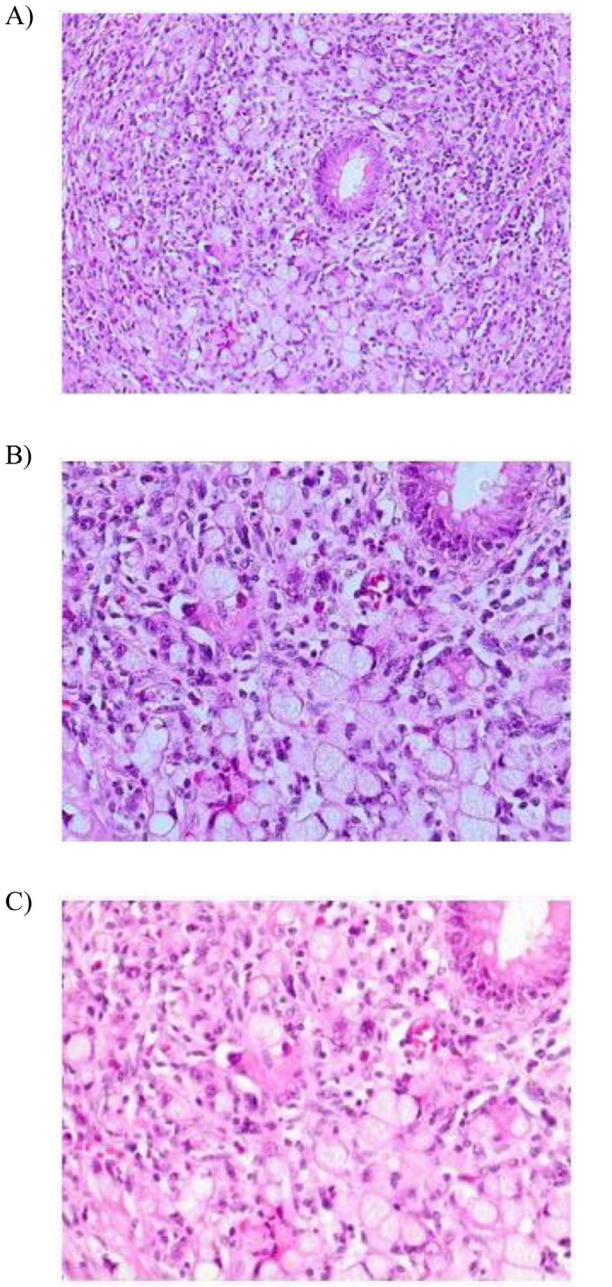


**Fig. 2 – (A, B, and C), The following are the histopathological slides with increasing magnification of the appendicectomy specimen described (100×, 200×, and 200× again). Reported are the features discussed in keeping with GCC:**
**• The tumor cells are composed of concentric proliferation of small nests of cells with abundant intracytoplasmic mucin and eccentric, compressed hyperchromatic nuclei, resembling goblet cells/signet ring cells.**
**• There are admixed bland tumor cells with patchy tubular formation, containing oval nuclei with stippled chromatin and granular cytoplasm.**
**• The lesion is focally positive for synaptophysin, chromogranin and CD56.**
**• The Ki-67 is 10%.**

cavity and associated peritoneum. Hematogenous metastasis to the liver or other distant organs is rare. The ovary is the most common site of metastasis and metastatic lesions sometimes show a histological picture of mucin-producing adenocarcinoma.

Until recently, there were no known discerning risk factors for GCC. A relatively new study by Jiang et al shows a possible connection between GCC and schistosomiasis, a potential risk factor [4]. It was suggested in this study that appendiceal schistosomiasis is associated with both increased proliferation and neuroendocrine differentiation of mucosal pluripotent crypt cells, and thereby may contribute to the development of GCC.

## Rarity and classification

GCC is a rare, low grade malignancy, occurring almost exclusively in the appendix. Carcinoid is revealed in 1 out of every 300 appendicectomies, and off those, 6% are pure GCC [1]. Hence, pure GCC is present in 0.02% of appendicectomies according to the literature.

A complicating issue that can be confusing when reviewing the literature is the classification of goblet cell tumors as neuroendocrine or carcinoma [2]. GCC has previously been described as mucinous producing carcinoid, adeno-carcinoid, intermediate type carcinoid and crypt cell carcinoma which are largely accurate descriptions. These alternate names, however, have been omitted from the current World Health Organization classification [2].

GCC is characteristically biphasic, derived from pluripotent intestinal stem cells that differentiate into both mucinous and neuroendocrine cells. Thus, it shares histologic features of both adenocarcinomas and carcinoid tumors respectively. The proportion of each can vary, and subclassification along this continuum has important associations with disease progression, prognosis and treatment.

The behavior of the tumor further complicates the tumor's classification as carcinoma versus carcinoid. Factors that demonstrate its carcinoid nature are the presence of neuroendocrine cells, neurosecretory granules, organoid growth pattern, lack of atypical cytology, lack of p53 mutations, and the usual absence of a mucosal, in situ precursor lesion [1]. Features more in keeping with adenocarcinoma, or at least an entity distinct from classic carcinoid, are the presence of intracellular mucin and its characteristic trans-coelomic spread with documented cases of metastases [1].

## Imaging

As mentioned, GCC presenting as a small bowel obstruction (SBO) is incredibly rare, and to our knowledge, only one previously reported case has been described [5]. In these rare settings, GCC may potentially be diagnosed on CT as the primary differential in an SBO secondary to an infiltrative appendiceal lesion.

The differential diagnosis for SBO with a concurrent appendiceal lesion radiologically include goblet cell carcinoid, classic carcinoid, lymphoma, and non-mucinous adenocarcinoma of the appendix [5]. This of course, is when adhesive SBO is unlikely, as with the current patient, with no previous history of abdominal surgery.

Classic carcinoid tumors of the appendix are not typically detected by direct imaging studies due to their small size and location. Lymphoma can demonstrate a markedly enlarged appendix with diffuse wall thickening, however tends to maintain the vermiform shape of the appendix. Finally, non-mucinous adenocarcinoma of the appendix can indeed manifest as an infiltrative appendiceal lesion with extra-appendiceal infiltration [6]. However, non-mucinous adenocarcinomas rarely occur in the appendix and tend not to form mucoceles as the name suggests. There may also be direct invasion of other organs which is less common with GCC.

In the rare circumstance of high grade SBO with an appendiceal nodule on CT, GCC could therefore be an important differential diagnosis.

## Histopathology

Evaluation of the morphologic features of GCC is crucial for both clinical management and prediction of outcome. GCC is immunohistochemically characterized by staining positive for synaptophysin, chromogranin A and CD56, all markers of neuroendocrine activity. Importantly, typical appendiceal carcinoids stain homogenously for these markers with GCCs tending to demonstrate a more scattered positivity. This is well in keeping with its known biphasic neuroendocrine and adenocarcinomatous nature.

This idea is complemented in a univariate analysis by Tang et al who identified an association between prognosis and the degree of positive staining [7]. Tang et al have described a subclassification that has proved useful for predicting clinical behavior and prognosis of GCC:

- Pure GCC (type A)
- Carcinoma ex GCC, signet ring type (type B)
- Carcinoma ex GCC, poorly differentiated type (type C)

In keeping with this classification, Tang group C specimens express the least positive neuro-endocrine activity, thus resembling poorly differentiated adenocarcinomas, and therefore associated with the least favorable prognosis.

There are other tumor markers which reflect the mucinous component of GCC. GCC shows the same CK7/CK20 immunoexpression as colorectal adenocarcinoma [8]. It is possible that the same tumor markers used to prognose colorectal adenocarcinoma can be used similarly in GCC. GCC is usually differentiated from other tumors by a raised CEA. However in our case, the patient had a raised Ca 19-9 and a normal CEA. The raised Ca19-9 could be associated with the adenocarcinomatous component of the tumor in keeping with the carcinomatous features on histopathology (Mucin pool, signet ring cells). Other documented cases of GCC with a raised Ca19-9 were in the setting of ovarian metastases.

The Ki-67 proliferation index is important to discuss, and is mandatory for grading the malignant potential of gastroenteropancreatic neuroendocrine tumors. The role of Ki-67 index in GCC remains controversial, with its significance found to be increasingly unremarkable [9]. In one study, the Ki-67 labelling index showed no correlation to mitotic activity, angiolymphatic or Perineural invasion. Patients with Tang Group C, however, had a median Ki-67 significantly higher than patients with Tang Group A and B. Despite this, Ki-67 was concluded to have no prognostic significance for goblet cell carcinoid tumors and should not be used solely to determine treatment and surgical approach [9]. Based on these results, the Tang grading is more indicative of the behavior of subtypes of GCCs than the Ki-67 index.

It would be useful to perform a larger, multicenter study to ascertain the true effectiveness of tumor markers and immuno-histochemical staining in GCC.

## Treatment

Even though GCC has a more aggressive phenotype than benign carcinoid tumors, the prognosis is generally good and surgery remains the treatment of choice. Right hemicolectomy is considered the standard surgical treatment of localized GCC and is recommended to take place within 3 months of the appendectomy [10]. However, there is still debate about management, especially whether appendectomy alone is an adequate treatment.

Byrn et al reviewed 16 cases of gastrointestinal goblet cell carcinoid and did not support right hemicolectomy for patients with non-metastatic goblet cell carcinoid of the appendix. Similarly Varisco et al emphasized that in patients with no concomitant cecal involvement and low-grade tumor histology; a simple appendectomy is sufficient [11]. It has been suggested that tumors confined to the appendiceal wall with a clear surgical margin and no carcinoma component can be treated by appendectomy alone.

Indications for Right hemicolectomy include [10]:

- Tumor recognized intraoperatively
- Appendiceal margin positive
- Involvement beyond muscularis propria
- Perforation
- Presence of carcinoma component

In some patients a more radical procedure is indicated. Peritoneal carcinomatosis from GCC is just as invasive as colorectal adenocarcinoma with peritoneal metastases. In such cases, complete or near-complete surgical removal, if possible, should be considered for cyto-reduction in combination with intraperitoneal chemotherapy. Some studies also suggest a prophylactic BSO in female patients, at the time of right hemi-colectomy due to the high propensity for ovarian metastases [10].

## Conclusion

We described the case of a small bowel obstruction secondary to a goblet cell carcinoid tumor of the appendix. This is indeed a rare entity and the importance of imaging, surgical exploration, histopathology discussion and completion surgery has been discussed.

## Declaration of Competing Interest

The first author is currently not a surgeon in training.

All authors are in agreement with the content of the manuscript.

There a no potential conflicts of interest.

Informed consent has been attained from the patient.

This manuscript has not been published previously and not under consideration elsewhere.

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