

## Colonic Goblet Cell Carcinoid: Rarity of a Rarity! A Case Report and Review of Literature

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### Abbreviations:

GCC - Goblet cell carcinoids;  
NET - neuro-endocrine tumour;  
IBD - inflammatory bowel disease;  
EGD - esophagogastroduodenoscopy;

### Rezumat

*Carcinoid cu celule colonice goblet: o raritate! O prezentare de caz și o revizuire a literaturii*

Carcinoizii cu celule goblet (GCC) sunt tumori neuroendocrine extrem de rare și sunt caracterizate prin combinația lor unică de două tipuri de celule canceroase - neuroendocrine (carcinoide) și epiteliale (adenocarcinom). În ciuda faptului că GCC este considerată tumoră neuro-endocrină (NET), nu prezintă sindromul carcinoid ilicit. GCC apare de obicei în anexă și reprezintă mai puțin de 14% din toate tumorile apendiceale. GCC extra-apendiceal primar a fost raportat la stomac, duoden, intestinul subțire, colon și rect. Lucrarea prezintă un caz rar de GCC a colonului ascendent la un bărbat de 57 de ani.

**Cuvinte cheie:** carcinoid cu celule goblet, tumori neuroendocrine, glandă apocrină, celule care prezintă antigen

### Abstract

Goblet cell carcinoids (GCC) are extremely rare neuroendocrine tumours, and characterised by their unique combination of two types of cancer cells – neuroendocrine (carcinoid) and epithelial (adeno-carcinoma). In spite of the fact that GCC is regarded as Neuro-Endocrine Tumour (NET), it does not illicit carcinoid

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syndrome. GCC usually arises in the appendix and accounting for less than 14% of all appendiceal tumours. Primary extra-appendiceal GCC have been reported as stomach, duodenum, small intestine, colon and rectum. The paper presents a rare case of GCC of the ascending colon in a 57-year-old male.

**Key words:** goblet cell carcinoid, neuroendocrine tumours, apocrine gland, antigen-presenting cells

## Introduction

Goblet cell carcinoid (GCC) is a unique and rare tumour almost exclusively involving appendix with some exceptional locations elsewhere (1). GCC has been a topic of debate since it was first described by Gagne et al in 1969 due to its peculiar histology and biological variability. Consequently, this tumour has been adorned with various different names over the years however, currently all other names except for GCC have been excluded from World Health Organisation (WHO) classification (2). GCC is a hybrid mix of tumour constituting of both epithelial (adenocarcinoma) and neuroendocrine (carcinoid) components containing goblet cells. Current grading systems identify these tumours on the basis of a goblet cell carcinoid tumour containing features of adenocarcinoma, which is a distinguishing factor of this tumour from other gastrointestinal tract adenocarcinomas (3). Although it is commonly diagnosed incidentally following an appendectomy or an ileocecal resection (4), due diligence should be applied to recognise and appropriately perform grading of these tumours due to their aggressive nature and metastatic potential (5). Prognosis is good if diagnosed in earlier stages with simple appendectomy requiring for stage I, disease-specific 5-year survivals for stages I, II, III, and IV were 100%, 76%, 22%, and 14%, respectively with overall mean survival was  $47 \pm 3$  months (6).

Appendiceal GCC is predominant in Caucasian population with mean age at diagnosis of 58, there is no variation in incidence between men and women (7). Development of GCC has not been associated with any

particular risk factors (8). Another thing of note is despite its histological resemblance, this tumour does not illicit carcinoid syndrome.

Literature review using Pub Med search engine was performed using search term "Goblet Cell Carcinoid", majority of the articles published as of date described appendiceal GCC. Our study gives a detailed account of an extremely rare case of colonic GCC encountered in a 57-year-old male.

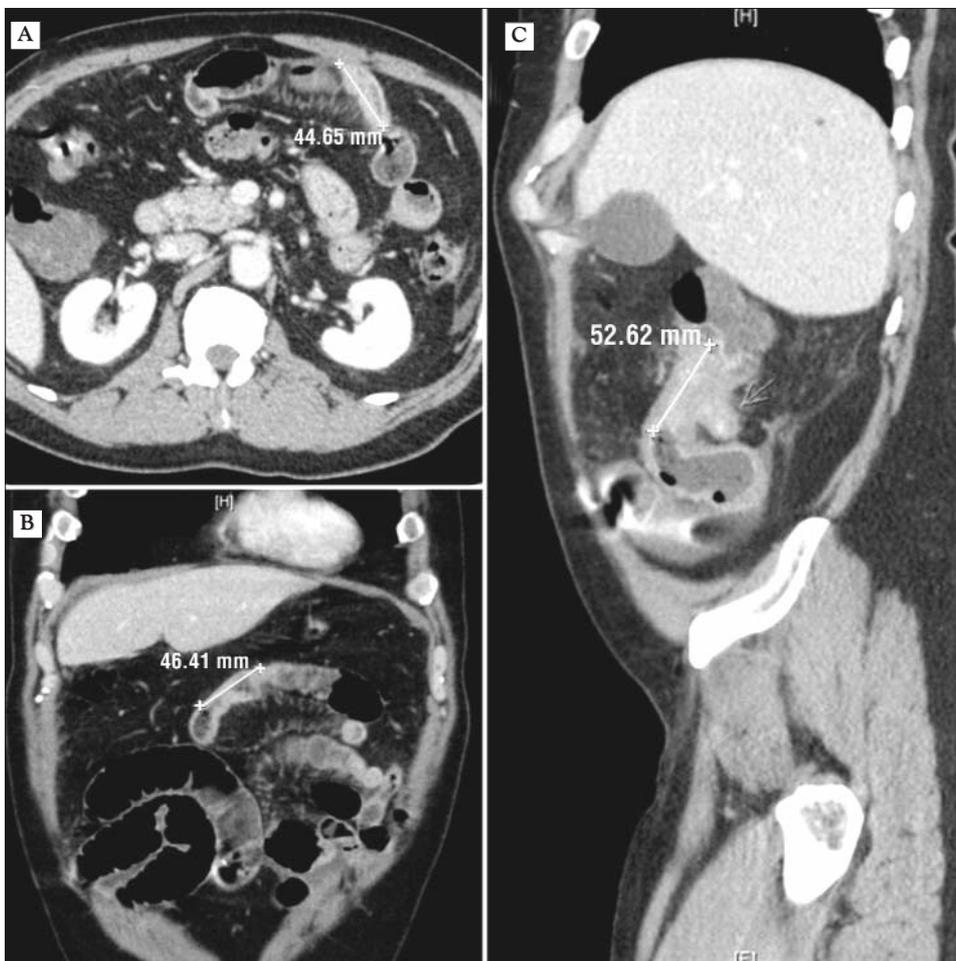
## Case Report

We present a case of goblet cell carcinoid in a 57-year-old man that initially presented to the hospital with one episode of emesis and a 6-week history of persistent lower abdominal cramping and pain. His past medical history includes 30 pack-year smoking history, 7 g weekly cannabis use, left hip arthroplasty and right knee meniscal repair. The patient has no family history of gastrointestinal malignancy, polyps or inflammatory bowel disease. He sought medical attention as he was unable to relieve his symptoms with over-the-counter analgesics including acetaminophen and ibuprofen. An outpatient ultrasound ordered by his family physician was suggestive of intussusception in his right abdomen, and he was advised to seek urgent medical attention. He presented to the emergency department where a CT scan demonstrated moderate-to-severe cecal wall thickening at the ileocecal valve with mucosal hyperenhancement extending to the terminal ileum, suggestive of inflammatory or infectious aetiologies, in particular inflammatory bowel disease (IBD). Several focal areas of mucosal hyper-enhancement and luminal narrowing were seen on CT

(Fig. 1). However, due to the mass-like appearance of the abnormality, the differential also included a cecal neoplasm. Furthermore, there were multiple hyperenhancing mesenteric lymph nodes adjacent to the terminal ileum, and a prominent hyperenhancing linear structure adjacent to the posterior wall of the cecum measuring up to 1.1 cm in calibre that was suggestive of either inflammatory appendix, in particular Crohn's appendicitis, or an adjacent inflammatory lymph node (Fig. 1C). There was also luminal narrowing noted in keeping with low to moderate grade partial small bowel obstruction. Upon evaluation in the emergency department, the

patient was discharged for urgent outpatient colonoscopy.

The following week, the patient received an esophagogastroduodenoscopy (EGD) and colonoscopy, which demonstrated obstruction in proximal ascending colon with circumferential firm thickening and reduced lumen diameter to approximately 5 mm. At that time, patient reported worsening abdominal pain and distention, inability to tolerate solid oral intake, as well as his stool being more loose and stringy, and was therefore admitted for bowel obstruction. Shortly thereafter, he underwent right hemicolectomy, initially laparoscopically for the obstructing mass,



**Figure 1.** Abdominal CT images of mucosal hyperenhancement and luminal narrowing of the small bowel. **(A)** Axial plane. **(B)** Coronal plane. **(C)** Sagittal plane showing a linear hyperenhancing structure suspicious for appendicitis or inflamed lymph node, marked by green arrowhead. A green line is used to highlight the length of the hyper-enhanced small bowel lesions in millimetres (mm).

which was converted to open for en-bloc resection of the right hemi-colon with anterior Gerota's fascia, as the mass was found to be invading the retroperitoneum.

Upon gross examination, the tumour was 4.7 x 3.9 x 4.5 cm, firm, pale-tan circumferential mass with ill-defined borders, located in the ascending colon adjacent to and involving the ileocecal valve. The tumour had clear resection margins, but grossly appeared to penetrate through the serosal surface, combining with surrounding adipose tissue. The appendix was not grossly identified in the hemicolectomy specimen.

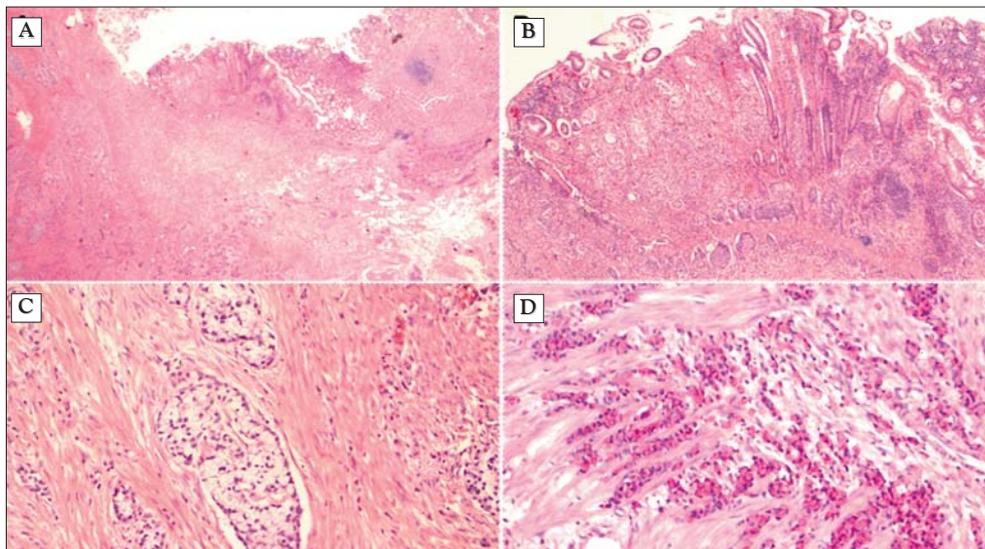
Microscopically, the tumour is seen infiltrating normal colonic glands as nests and small clusters of cells with small bland monomorphic nuclei with eosinophilic cytoplasm and abundant cytoplasmic mucin with signet cell morphology resembling goblet cells (*Fig. 2*). Serosal involvement, as well as lympho-vascular and perineural invasion was confirmed microscopically. Moreover, 17 out of 19 lymph nodes examined were involved. Immunohistochemically, the tumour cells

positively reacted with neuroendocrine markers CD56 and synaptophysin (*Fig. 3*). Moreover, epithelial marker CAM 5.2 was also positive, as well as CK7, CK20, CDX2 (*Fig. 3*). The tumour also showed 30% of the cells cycling with Ki-67. Subsequently, the diagnosis of grade 3, poorly differentiated goblet cell carcinoid, pT4a N2b, was made (*Table 1*).

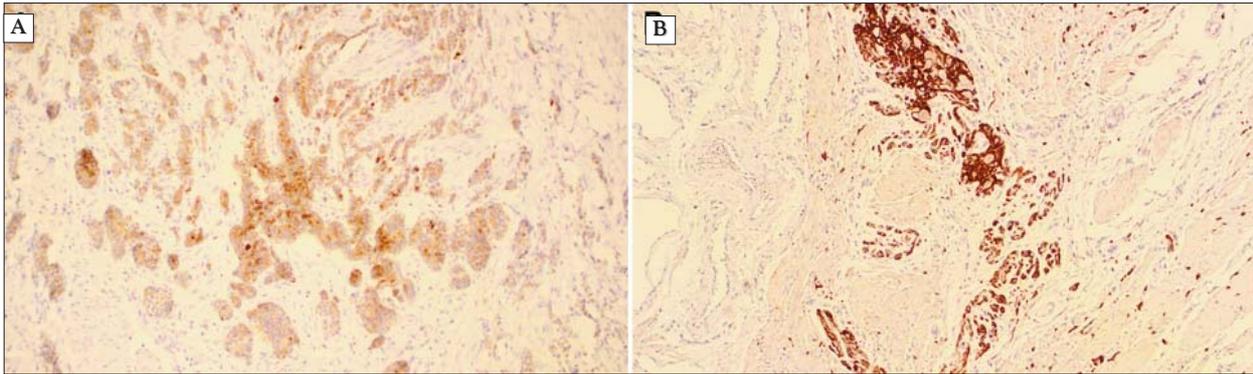
## Discussion

The gastro-intestinal epithelium is composed from various differentiated cell types, each type carries out unique and specialized functions.

Among these types, there is enterocytes, which are responsible for nutrient and water absorption, entero-endocrine cells that secrete hormones, the Paneth cells that release antimicrobial factors, the chemosensory tuft cells which play a key role in defense against helminths, M cells which are responsible for presentation of luminal antigens to the immune system and goblet cells that secrete mucins.



**Figure 2.** Representative morphological images of goblet cell carcinoid. **(A)** Tumour arising from mucosa and infiltrating through the muscularispropria, H&E staining, x12.5 magnification. **(B)** Tumour arising from mucosa and infiltrating through submucosa, H&E staining, x40 magnification. **(C)** Tumour cells showing dark monotonous cells and cells with signet cell (goblet) morphology infiltrating the muscularispropria, H&E, x200 magnification. **(D)** Signet cells showing cytoplasmic mucin highlighted by PASD (Periodic Acid-Schiff with Diastase staining, x200 magnification).



**Figure 3.** Representative images of immunohistochemistry of goblet cell carcinoid. **(A)** Tumour cells positive for epithelial marker CAM5.2, x100 magnification. **(B)** Tumour cells positive for neuroendocrine marker CD56, x100 magnification.

Generally speaking, the majority of cell types located in the colon are also found in the small intestine; these include the enterocytes

(also referred to as colonocytes in colon), entero-endocrine cells, goblet cells, and tuft cells (9).

The term goblet refers to the cell's goblet-like shape. The apical portion is shaped like a cup, the abundant mucus laden granules causing distention of the apical portion; its basal portion lacks these granules and is shaped like a stem (*Fig. 4*).

Goblet cells are typically found in the respiratory tract, reproductive system, gastrointestinal tracts and conjunctiva, usually are surrounded by other columnar epithelial cells (10,11).

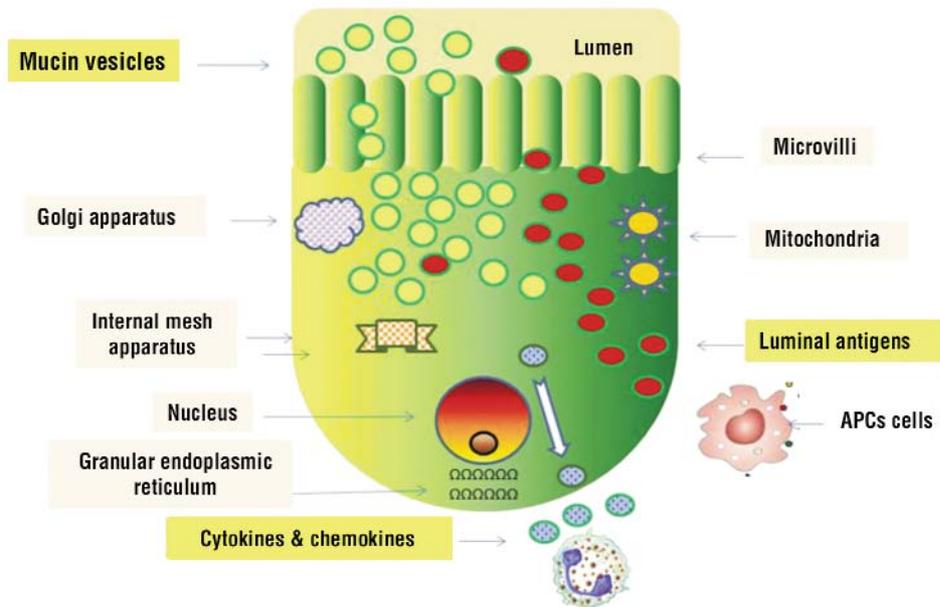
It has been well-documented how mucin, (high-molecular-weight glycoprotein produced by the goblet cells), is an integral component of both mucosal homeostasis and defence from infection. The mucin itself is functioning as a dynamic protective barrier to protect the intestinal mucosa, where mucus layer separates the underlying intestinal epithelium from luminal microbes. Mucins are the first molecules that interact with the invading pathogens and thus, can limit microbes binding to other glycoproteins and neutralize the pathogen (12).

Goblet cell is an exocrine glandular cell, uses mainly the merocrine (eccrine) pathway of secretion, secreting vesicles into a duct lumen by exocytosis (*Fig. 4*). However, some of them may use apocrine way of secretion by budding-off their secretions, where the apical portion of the secretory cell of the gland

**Table 1.** Clinico-pathological characteristics of the presented case

Age	57
Gender	Male
Presenting symptoms	Abdominal pain, vomiting
Carcinoid syndrome	No
Site	Ascending colon
Gross appearance	37 mm, firm mass with ill-defined borders
Serosal involvement	Yes
Microscopic features	
Morphology	Nests and small clusters of mucin cells mucin with signet cell morphology resembling goblet cells
Cytoplasm	Eosinophilic with abundant mucin
Nuclei	Small bland monomorphic
Lympho-vascular invasion	Present
Perineural invasion	Present
Staining	
Mucicarmine/PAS*	Positive
IHC	
Synaptophysin	Positive
Cam5.2	Positive
Cytokeratin-7	Positive
Cytokeratin-20	Positive
CDX-2	Positive
CD56	Positive
Ki-67	30%
Lymph nodes	Involved , 17 out of 19

\*PAS: Periodic acid-Schiff



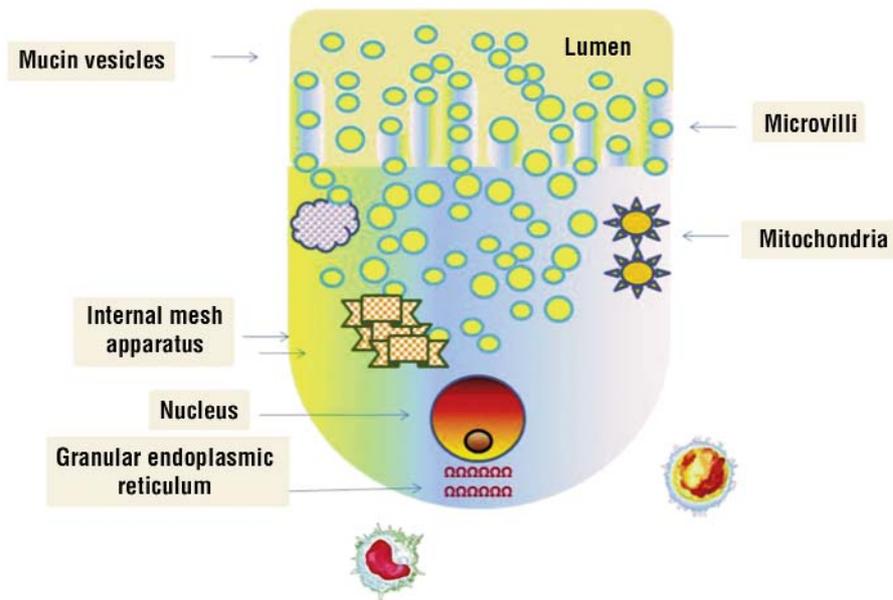
**Figure 4.** Function of Goblet cell, mucin production through merocrine pathway, goblet cell-associated antigen passages (GAP) to the antigen-presenting cells (APCs) cells and chemokines & cytokines production.

\*Adapted from Knoop et al, 2018 (11).

pinches off and enters the duct system lumen (Fig. 5).

McDole et al from Washington University in

2012 first demonstrated that small intestinal goblet cells are capable by endocytosis to pass antigens from the gut lumen through goblet



**Figure 5.** Apocrine secretory pathway, the apical portion of the secretory cell of the gland pinches off and enters the duct system lumen containing the mucin.

\*Adapted from Knoop et al, 2018 (11).

cell-associated antigen passages (GAP) to the dendritic lamina propria (LP) antigen-presenting cells (APCs) cells located deep to the basement membrane (*Fig. 4*), this results in inducing adaptive immune responses against the pathogens (13). Also the goblet cells secrete anti-microbial proteins, chemokines, and cytokines which play role in innate immunity beyond barrier maintenance function of the mucin (11).

Goblet cell carcinoid (GCC) is a rare tumour, was first described by Gagne in 1969 (14,15), in addition World Health Organization accepted the term “mucinous carcinoid” as a name for this condition (16).

GCC usually occurs in 5th -6th decade of life with median age at diagnosis of 58.9 years and no significant gender disparity(17,18),it is characterized by mixed phenotype of dual neuroendocrine and glandular differentiation. The majority of primary malignant appendiceal tumours are carcinoid, followed by mucinous adenocarcinoma, GCC remains as uncommon primary tumour of the appendix, and infrequent to occur elsewhere (19,20). GCC has an estimated incidence of 1 per 2 million individuals, usually arises in the appendix and accounting for less than 14% of all appendiceal tumours (16,18).

Goblet cell carcinoid has been regarded as a distinctive entity, not related to classic carcinoid tumours. A few cases of combined classic carcinoid and goblet cell carcinoid (GCC) tumour have been reported (morphologic variant believed to represent dual parallel differentiation although collision tumour (separate, independent primaries) must also be considered as a possibility (19).

There are rare cases of ostensibly primary extra-appendiceal GCC have been reported as stomach, duodenum, ampulla of Vater (21), jejunum, ileum, cecum, splenic flexure (22,23), ascending colon (24) and rectum (22,25,26, 27,28).

Goblet cell carcinoid of the colon (GCCC) is rare, its clinical behaviour ranges from aggressive to relatively indolent disease. Treatment is based on tumour site, extent of the disease, histological tumour grade and individual

patient characteristics (29).

The colorectal neuro-endocrine tumour (NET) including GCCC does not present with any specific symptoms, however may present with abdominal pain, large mass, constipation, intestinal obstruction, tenesmus, haematochezia or anal pain, however as other goblet cell carcinomas, GCCCs tumour does not illicit carcinoid syndrome. These tumours can be detected incidentally during routine investigations such as colonoscopy (17,30,31,32).

Ulcerative colitis patients are at increased risk of mucosal dysplasia and colorectal malignancy development, NET has been reported to be diagnosed with a patients with a long history of ulcerative colitis, however this finding is extremely rare and only 14 cases have been documented between 1980 to 2015 (31).

GCC is also reported to be associated with Neurofibromatosis Type 1 as well as ovarian mucinous cystadenocarcinoma, it has been diagnosed concurrently with conventional colonic adenocarcinoma (24,27,33).

Histologically, the bulk of the tumour is in the lamina propria or submucosal layer, there are two types of tumour cells; a relatively small to intermediate cells, with eosinophilic finely vacuolar or granular eosinophilic cytoplasm, vesicular round nuclei, prominent nucleoli, and mild cytologic atypia, reminiscent of typical carcinoids. The second type is the signet-ring-like (goblet) cell filled with abundant cytoplasmic mucin and crescentic nuclei. Neoplastic cells formed small nests in a solid, cord-like, or glandular pattern separated by stroma or large pools of mucin (1,27,28).

This condition should be differentiated from signet cell carcinoma, which a rare colonic neoplasm and characterized by cells with abundant intracytoplasmic mucin and peripherally placed nuclei, however it is negative with neuroendocrine immunohistochemistry markers. When signet ring cell adenocarcinoma is encountered in a colonic lesion, a colon primary is supported if the neoplastic cells have a cytokeratin 7 (-)/cytokeratin 20 (+) staining pattern, (34,35,36).

Immunohistochemistry has a role in diag-

nosis of GCC, Cytokeratin 7 (CK7) is a basic type II keratin of simple non-keratinizing epithelia protein, which shows strong expression in different epithelial tissues as breast, upper gastrointestinal tract, endometrium, urinary bladder, pancreas, biliary tract, and lungs (37,38), it shows positivity in the carcinoids and up to 70% of the GCC cases (39,40).

Cytokeratin-20 (CK20) is a sensitive marker for Merkel cell carcinoma (Positive in 90–100% of cases), it also shows expression in some cases of extra-pulmonary small cell lung carcinoma (40). In GCC, up to 100% of cases exhibits positivity to CK20 (39).

CAM 5.2 is an immune-stain used to detect Cytokeratin 8(CK8) and Cytokeratin. It is positive in breast, lung, ovary and urothelium tissues. The neuro-endocrine cells are positive for Cam 5.2 stains (41,42).

DCX2 is a homeobox gene that encodes a nuclear transcription factor critical for intestinal embryonic development; relatively specific for intestinal epithelium. It shows positive staining in carcinoid tumours (43).

Synaptophysin (Trans-membrane Channel Protein) is a common specific but not sensitive endocrine marker, it is used in carcinoid tumour, Merkel cell carcinoma (MCC) and small cell carcinoma (3,32,40,44,45).

CD56 (Homophilic binding glycoprotein with role in cell–cell adhesion) is a common endocrine marker, it is a sensitive marker for MCC as well as for NK-cell lymphoma, however it lacks specificity (40). Neuroendocrine carcinomas are positive for CD56 (5,46,47).

About 11.6% of GCCs patients presented with a distant metastatic disease at the time of diagnosis, other than the regional lymph nodes ovaries being the most common metastatic site, followed by peritoneal carcinomatosis (7).

The appendicular GCCs are more aggressive compared with conventional appendiceal tumours but less aggressive compared with adenocarcinomas, and they often present with serosal and meso-appendiceal involvement (2).

Whereas surgical resection of GCC remains the mainstay of resectable disease, chemotherapy options offered are 5-fluorouracil (5-FU) and leucovorin (LV) (28). Cytoreductive

surgery (CRS) and intraperitoneal chemotherapy have been employed for the peritoneal disease (29,32).

## Conclusion

The colon is unusual site of goblet cell carcinoma, a very rare case of ascending colon goblet cell carcinoma has been described. For proper management pathway, colonic GCC should be differentiated from metastasis of appendiceal GC. Another differential diagnosis is signet ring cell carcinoma, which usually forms luminal space and is negative for immunohistochemistry markers. More research is needed to achieve better understanding of the biologic characteristics and implement optimal treatment strategies for this rare neoplasm.

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## Author's Contributions

All authors contributed equally to the manuscript.

## Conflict of Interest

The authors declare no conflicts of interests.

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