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CASE REPORT

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Goblet cell adenocarcinoma of the ascending colon: An underrecognized diagnostic pitfall

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Abstract

Goblet cell adenocarcinomas (GCA) are infrequent neoplasms of the digestive system that exhibit both mucinous and neuroendocrine differentiation. They predominate in the appendix and rarely involve the colon. Herein, the authors report a case of GCA involving the ascending colon in a 60-year-old woman who presented with severe anemia.

KEYWORDS

anemia, cancer, colon, extra appendiceal goblet cell carcinoid, goblet cell adenocarcinoma, immunohistochemistry, pathology

1 | INTRODUCTION

Also called adenocarcinoid, mucinous carcinoid, crypt cell carcinoma, goblet cell carcinoid, and goblet cell carcinoma, goblet cell adenocarcinoma (GCA) is a clinicopathologically distinctive and aggressive hybrid epithelial-neuroendocrine tumor that usually arises in the appendix.[1] This entity is included in the fifth WHO classification of appendiceal tumors, but it is not included in other organ classifications.[2] A few cases of extra-appendiceal GCA have been reported in the literature. In this paper, we report a case of GCA involving the ascending colon with no detectable appendiceal tumor. Our aim was to raise awareness of this uncommon entity and to highlight the difficulty in accurately establishing its diagnosis.

2 | CLINICAL HISTORY

A 60-year-old previously healthy woman presented with abdominal pain and weight loss of 30 kg during the past 6 months. On admission, the patient was pale with altered general health. Physical examination revealed a palpable mass of the right iliac fossa. Laboratory tests showed hypochromic microcytic anemia (with hemoglobin = 4.4 g/dl, mean corpuscular volume = 65 fl, mean corpuscular hemoglobin = 19.3 pg and hematocrit = 15%). An abdominal computed tomography scan revealed an irregularly shaped mass at the right colon with circumferential thickening of the colonic wall (Figure 1A). The patient underwent a right hemicolectomy after being transfused. Grossly, there was a tumor located in the ascending colon and invading the ileocecal valve. It measured 13.5 × 8 cm and was firm, pale-tan, nodular, circumferential with ill-defined borders, (Figure 1B,C). The tumor had clear resection margins, and there were no associated polyps in the adjacent colonic mucosa. The appendix was macroscopically unremarkable and was entirely sectioned and submitted for histological examination. Microscopically, the colonic tumor demonstrated proliferating neoplastic cells exhibiting both mucinous and neuroendocrine differentiation (Figure 2A–C). The tumor arose from the mucosa of the colon and invaded the subserosa (Figure 2A). There was no evidence of dysplasia in the adjacent colonic epithelium. The tumor proliferation consisted of nests, cords,

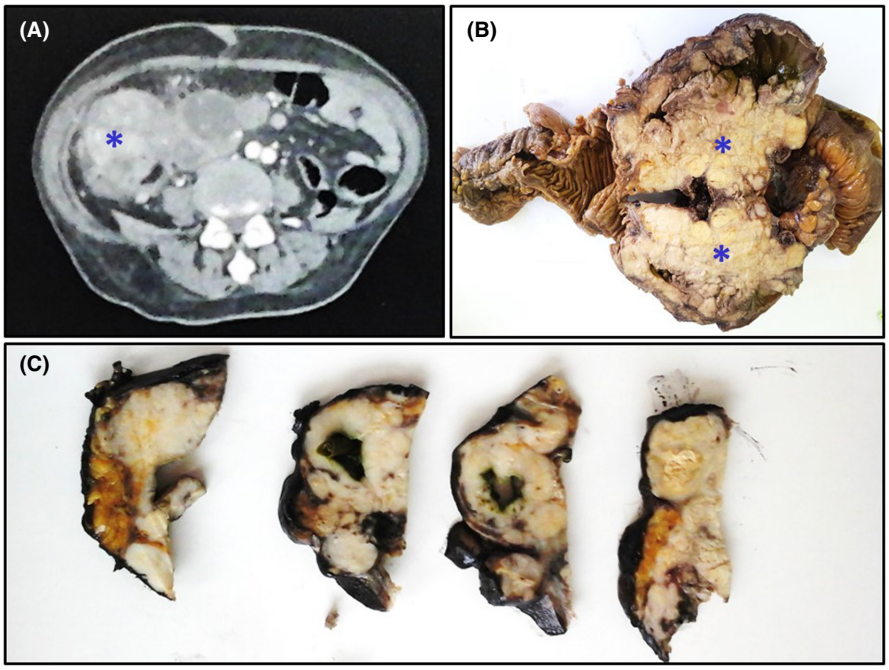

FIGURE 1 (A) Computed tomography scan revealed an irregularly shaped mass at the right colon with circumferential thickening of the colonic wall (Blue asterisk). (B) Gross findings of the right hemicolectomy specimen showing a large mass in the ascending colon measuring 13 × 8 cm and invading the ileocecal valve (Blue asterisk). (C) On cut section, the tumor was nodular, white and yellowish in color. It invaded the colonic wall and extended to the subserosa.

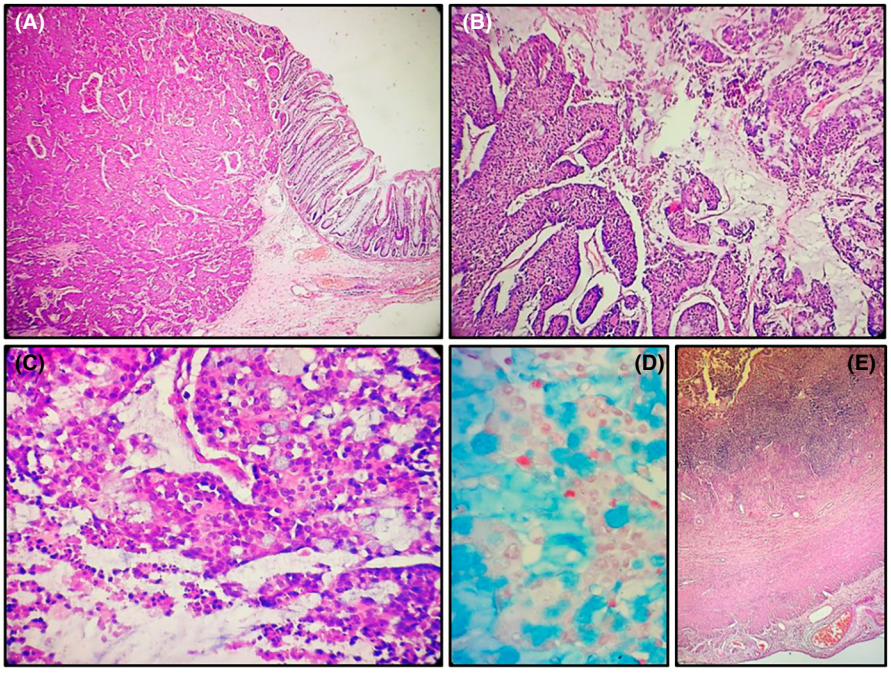

FIGURE 2 (A) Microscopic examination of the colonic mass showing a tumor proliferation arising from the mucosa of the colon and infiltrating the submucosa. It is arranged in lobules of neuroendocrine cells admixed with a population of signet ring-like cells that resemble intestinal goblet cells (Hematoxylin and eosin, magnification ×40). (B) Lobules of neuroendocrine cells arranged in organoid patterns admixed with a population of signet ring-like cells that resemble intestinal goblet cells. Extracellular mucin was present and abundant. (Hematoxylin and eosin, magnification ×200). (C) Admixed populations of mature goblet cell-looking and mucin-laden cells and granulated monotonous neuroendocrine cells that are arranged in distinctive infiltrative and organoid patterns. Extracellular mucin was present and abundant. (Hematoxylin and eosin, magnification ×400). (D) Alcian blue special stain highlighting extracellular mucin and goblet cells which exhibit voluminous bubbly cytoplasm containing basophilic mucin. (Alcian Blue, magnification ×400). (E) Histological examination of the appendix was unremarkable. (Hematoxylin and eosin, magnification ×100).

tubules, and lobules of neuroendocrine cells arranged in organoid patterns (Figure 2A,B) admixed with a population of signet ring-like cells that resemble intestinal goblet cells arranged in small rounded nests or cords. The neuroendocrine cells had indistinct cell borders, eosinophilic granular cytoplasm, and basally located, moderately

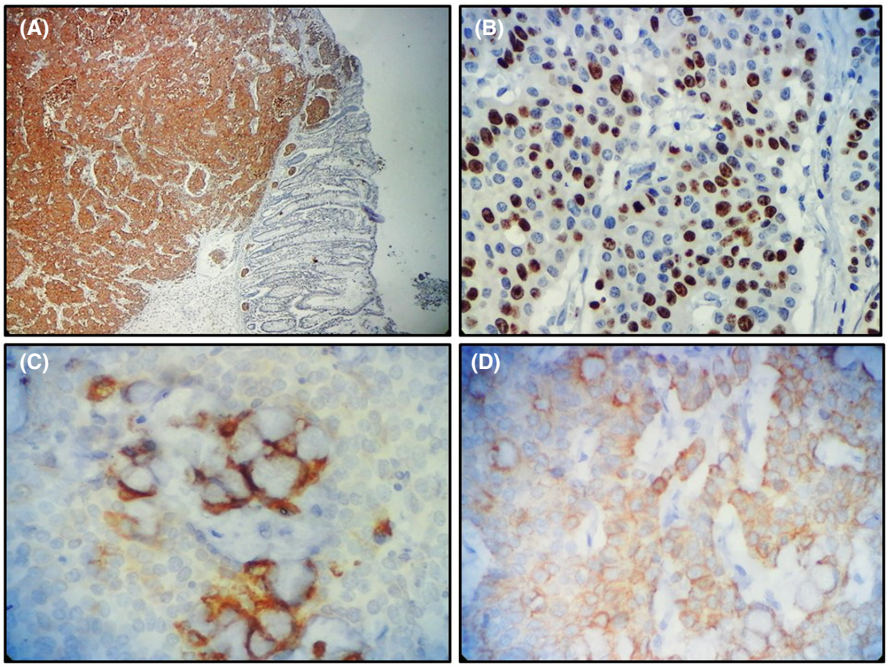

FIGURE 3 (A) Immunohistochemistry demonstrating strong and diffuse staining of the tumor cells with synaptophysin (Immunohistochemistry, magnification ×400). (B) Ki67 staining showed a highly proliferative pattern of 80% (Immunohistochemistry, magnification ×400). (C) Immunohistochemistry demonstrating strong staining of goblet cells with MUC2 (Immunohistochemistry, magnification ×400). (D) Immunohistochemistry demonstrating strong and diffuse staining of the tumor cells with cytokeratin 20 (Immunohistochemistry, magnification ×400).

atypical nuclei with fine granular chromatin (Figure 2C). The goblet cells had irregular hyperchromatic nuclei and bubbly cytoplasm that contained basophilic mucin (Figure 2C). Extracellular mucin was present and was abundant. Alcian blue special stain highlights extracellular mucin and goblet cells (Figure 2D). The mitotic index was high (>20/20 high power fields), with lympho-vascular and perineural invasion. Fourteen out of 29 lymph nodes were metastatic. Histologic examination of the appendix (Figure 2E) was unremarkable and did not disclose any tumor proliferation. Immunohistochemically, the neuroendocrine cell component positively reacted with synaptophysin and chromogranin A (Figure 3A). Ki67 staining showed a highly proliferative pattern of 80% (Figure 3B). The goblet cell component was immunoreactive for MUC2 (Figure 3C), CEA, CDX2, and CK20 (Figure 3D). Based on the histopathological and immunohistochemical findings, the diagnosis primary high-grade GCA of the ascending colon was established. On postoperative day two, the patient died due to septic shock.

3 | DISCUSSION

Initially described by Gagne et al. in 1969, GCA has been a topic of debate due to its peculiar histology and biological variability. This tumor has been adorned with various different names over the years. The term goblet cell carcinoid coined by Subbuswamy et al. in 1974 has been widely used for decades.[3] With a better understanding of the entity, this name is now thought to be less ideal in reflecting its biological nature. In the fifth edition of the WHO classification of tumors of the digestive system, goblet cell carcinoid/carcinoma has been renamed GCA. According to the fifth edition of the WHO classification of tumors of the digestive system, GCA is defined as an amphicrine tumor composed of goblet-like mucinous cells, as well as variable numbers of endocrine cells and Paneth-like cells, typically arranged as tubules resembling intestinal crypts.[4] This entity is included in the fifth WHO classification of appendiceal tumors, but it is not included in other organ classifications.[4] GCAs represent approximately 14% of all appendiceal tumors. They usually occur in the fifth to sixth decade of life with a median age at diagnosis of 58.9 years and no significant gender disparity.[1] Owing to their varying nomenclature, classification systems, and rarity, the incidence of GCA has been difficult to establish. According to some authors, their estimated incidence is of 1 per 2 million individuals.[2] GCA has been reported to be associated with ulcerative colitis, neurofibromatosis type 1, and ovarian mucinous cystadenocarcinoma. It has also been diagnosed concurrently with conventional colonic adenocarcinoma.[5–7] In one study, genetic profiling of GCA revealed mutations in genes in the WNT signaling pathway (USP9X, NOTCH1, CTNNA1, CTNNB1, and TRRAP).[4,8] Other studies have shown mutations in chromatin remodeling genes, including ARID1A, ARID2, KDM6A, and KMT2D (MLL2). Mutations in genes typical of colorectal adenocarcinoma (KRAS, APC, and SMAD4) are rare in GCA.[4,8] A few cases of primary extra-appendiceal GCA involving the small bowel, the colorectum, and the stomach have been reported in the literature.[1,9,10] The diagnosis of primary

TABLE 1 Clinicopathologic data of eight cases of goblet cell adenocarcinomas of the colon reported in the literature.[1,2,7,11–13]

Case [Ref.]	Age/Sex	Presentation	Tumor size	Appendiceal status	Follow-up
1 [10]	32/M	Colon, splenic flexure, causing colon obstruction	Constricting lesion, 7 cm, transmural invasion into serosa	No examination described	N/A
2 [1]	80/M	Cecum and terminal ileum (bowel obstruction)	Mass, with diffuse bowel thickening, invasion from serosa to submucosa	Appendiceal primary found 2 years later after reviewing appendectomy slides 5 years ago for acute appendicitis	Died 2 years later, massive peritoneal seedings found on autopsy
4 [12]	41/F	Sigmoid colon Abdominal pain Weight loss	8 cm	No examination described	No recurrence No metastasis
5 [7]	79/M	Multiple polypoid masses, ascending colon	Three separate, large, polypoid masses in the ascending colon that measured 1.7 cm (mass 1), 3.4 cm (mass 2), and 1.5 cm (mass 3)	Appendix unremarkable	No recurrence No metastasis 17 months
6 [13]	N/A	Cecum	N/A	N/A	N/A
7 [13]	N/A	Cecum	N/A	N/A	N/A
8 [2]	57/M	Ascending colon abdominal, emesis cramping and pain	4.7 × 3.9 × 4.5 cm	The appendix was not grossly identified in the hemicolectomy specimen	N/A
Our case	60/F	Ascending colon Weight loss, anemia, abdominal pain	13.5 × 8 cm, invasion of the subserosa	Appendix unremarkable	Died due to septic shock

Abbreviation: N/A, not available.

extra-appendiceal GCA should only be determined after the definitive exclusion of appendiceal origin. In this manuscript, we performed a literature review using the PubMed search engine using the search terms "Goblet Cell Carcinoid," "adenocarcinoid," and "goblet cell adenocarcinoma." To the best of our knowledge, only eight cases of GCA of the colon have been reported in the literature (Table 1).[1,2,7,11–13] Among these cases, an appendiceal origin was excluded in only one case.[7]

Patients with GCA of the colon may present with several symptoms including abdominal pain, weight loss, altered general health, emesis, anemia, or bowel obstruction.[1,2,7,11–13]

Our patient presented with abdominal pain, weight loss and had severe hypochromic microcytic anemia. The incidence of anemia has been reported to be high in patients with cancer of the right colon, of a large size and in advanced clinical stage. Anemia in colorectal cancer patients originates not only from occult or visible bleeding from the tumor itself, but also from a systemic inflammatory response. In colorectal cancer patients, anemia, even mild degree, was shown to be a risk factor for postoperative complications and longer hospital stay.[14,15] Severe anemia can increase tumor aggressiveness and blood transfusion may induce immunosuppression and promote cancer recurrence.[14,15] Histologically, GCA consists of intimately admixed populations of mature goblet cell-looking and mucin-laden cells and granulated neuroendocrine cells that are arranged in distinctive infiltrative and organoid patterns and may include glandular elements.[1] Several histologic classification/grading systems of GCA have been proposed. According to the fifth WHO classification of appendiceal tumors, GCA are classified into low-grade GCA and high-grade GCA. The differential diagnoses of GCA include signet-ring cell adenocarcinoma, mixed adenoneuroendocrine carcinoma, and mucinous adenocarcinoma. Due to their rarity and the prior lack of international consensus regarding nomenclature, the optimal management of GCA is challenging. These tumors are staged according to the Union for International Cancer Control system for adenocarcinomas rather than with neuroendocrine tumors, because of their more-aggressive course.[4] Whereas surgical resection of GCA

remains the mainstay of resectable disease, chemotherapy options offered are 5-fluorouracil and leucovorin.[2,13,16] According to one study, chemotherapy may play an important role in this disease, both in the adjuvant setting and in the metastatic setting.[13] Cytoreductive surgery and intraperitoneal chemotherapy have been employed for the peritoneal disease.[17] Extra-appendiceal GCA usually exhibit aggressive behavior and present in advanced stages.[1,10] Prognosis depends on stage and tumor grade. The most common sites of metastasis are the peritoneum, omentum, abdominal wall, and ovaries. GCAs exhibit positive staining for neuroendocrine markers like a traditional well-differentiated neuroendocrine tumor, but are recognized to behave more aggressively like conventional adenocarcinomas.

In summary, extra-appendiceal GCA are uncommon and their treatment protocol is not well-established. The diagnosis of primary colonic GCA should only be established after the definitive exclusion of an appendiceal origin. Therefore, a thorough histopathological examination of the appendix is mandatory to classify the tumor as a primary extra-appendiceal GCA. Careful evaluation of the morphological features of these tumors is crucial for accurate diagnosis and clinical management. Furthermore, pathologists should always specify the pathological status of the appendix in the histopathological report. Our case highlights the difficulty in accurately diagnosing GCA in the absence of histological evidence. Further accumulation of extra-appendiceal GCA could help establish an accurate diagnosis earlier. Early discovery of these tumors may allow better treatment strategies and better prognosis. To improve patient outcomes, a better understanding of GCA among clinicians is required. More research is needed to achieve a better understanding of the biological characteristics and implement optimal treatment strategies for this rare neoplasm. In the future, it would be useful to conduct prospective and adequate randomized trials of this tumor to assure adequate therapy promptly.

AUTHOR CONTRIBUTIONS

Faten Limaiem: Conceptualization; formal analysis; methodology; resources; supervision; writing – original draft; writing – review and editing. **Sahir Omrani:** Formal analysis; resources; writing – review and editing. **Mohamed Hajri:** Resources; supervision; validation; visualization; writing – review and editing.

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None.

CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

All procedures performed were in accordance with the ethical standards. The examination was made in accordance with the approved principles.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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