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A case report

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An extremely rare finding of goblet cell carcinoid of the appendix. A case report

Goblet cell carcinoid or carcinoma (GCC) refers to an extremely rare appendiceal tumor usually diagnosed on post-operative histology as an incidental finding. Primary cancers of the vermiform appendix are quite rare, representing less than 1% of all gastrointestinal malignancies. GCCs are considered as a distinct entity of appendiceal tumors, consisting of both epithelial (glandular) and neuroendocrine elements containing goblet cells. This entity tends to be more aggressive than typical carcinoid tumors as it often presents with metastatic disease. Therefore, an early recognition and an appropriate grading is essential. The 5-year overall survival is 14-22% in stage III-IV disease. As a matter of fact, GCC warrants more aggressive surgical and medical (chemotherapy) treatments than typical carcinoid tumors. We, hereby, report a case of a 67-year old male presenting with an acute abdominal obstruction and a severe tenderness predominant in his right lower quadrant, together with an endoscopic and radiological suspect of left colonic malignancy and acute appendicitis. Left hemicolectomy and appendicectomy were performed and pathological specimens revealed a low-grade adenocarcinoma of the descending colon and a high-grade appendiceal goblet cell carcinoid. Subsequent right hemicolectomy was performed according to the current guidelines. GCCs are more aggressive compared with conventional appendiceal tumors but less aggressive compared with adenocarcinomas and they often present with serosal and mesoappendiceal involvement. The lack of a standardized classification system for GCC and the discrepancies in specific reliable markers are responsible for an insufficient prognostic and predictive value at diagnosis.

KEY WORDS: *Appendiceal neoplasms, Carcinoid tumor, Colectomy, Goblet cells, Immunochemistry*

Introduction

Goblet cell carcinoid was first described in 1969 by Gagne et al. and later named by Subbuswamy et al. [1,2] as a rare primary tumor of the vermiform appendix characterized by mixed neuroendocrine differentiation and intestinal-type goblet cell morphology, whose exact biological behavior is uncertain. GCC represents 14-19% of primary appendix cancers [3,4] with an estimated incidence of 0.5 cases for every million individuals per year. It is a distinct entity consisting of both epithelial (glandular) and neuroendocrine elements containing goblet cells, more commonly diagnosed among Caucasians with a mean age at diagnosis of 58 and no known difference in incidence between sexes [3,5-7]. Currently, there are no known or established risk factors capable of increasing the incidence of GCC. Ki-67, an excellent marker to determine the growth fraction of a given cell population, is a widely used marker for NET grading and staging [8,9], showing a positive correlation with known prognostic factors, such as tumor size and metastatic status and has been extensively investigated in pancreatic and gastrointestinal NETs [10,11]. Giving the fact that NETs include a heterogeneous group of tumors, the interpre-

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TABLE I - *Histopathological (Tang) classification of goblet cell carcinomas proposed by Tang et al.*

Tang class	Designation	Characteristics
A	Typical GCC	Well defined goblet cells (clusters or linear) with minimal atypia, minimal or no desmoplasia, minimal distortion of appendiceal wall.
B	Adenocarcinoma ex-GCC, signet cell type	Goblet or signet ring-type cells in large, irregular clusters;single file or single cell infiltrative pattern;significant atypia;desmoplasia evident with destruction of appendiceal wall.
C	Adenocarcinoma ex-GCC, poorly differentiated carcinoma type	Minimum of focal evidence of goblet cell morphology. A component indistinguishable from poorly differentiated adenocarcinoma (e.g. gland-forming, confluent sheets of signet ring cells).

GCC, goblet cell carcinoma.

tation of the Ki-67 index for GCC is unreliable without an appropriately researched cut-off value, which is currently set between 20% and 30% for digestive tract NETs [12,13]. Nevertheless, surgery should be based on tumor size, invasiveness and careful evaluation of the morphological characteristics of GCC in addition to the Ki-67 index. An important morphological characteristic in GCC, reflecting prognosis and survival, is the adenocarcinoma component, which may be classified into signet ring-cell and non-signet ring-cell types [14,15]. The 2010 World Health Organization (WHO) tumor classification [16] considered GCCs as a subgroup of mixed adenoneuroendocrine carcinomas (MANECs). The tumor-node-metastasis (TNM) classification of malignant tumors by the Union for International Cancer Control, the American Joint Committee on Cancer and the European Neuroendocrine Tumor Society (ENETS), consider GCCs to be adenocarcinomas [6,17]. However, their complexity is so distinct that they were not included in the 2016 ENETS consensus guidelines for Neuroendocrine Neoplasms of the Appendix. Another diagnostic classification for GCC was proposed by Tang et al [12], based on the TNM classification for appendiceal adenocarcinomas and has been proven useful for predicting clinical behavior and prognosis. In Tang classification, tumors are subclassified into group A (typical GCC), group B (adenocarcinoma ex-GCC) and group C (adenocarcinoma ex-GCC; poorly differentiated) (Table I). Upon diagnosis, right hemicolectomy is recommended by the North American Neuroendocrine Tumor Society (NANETS) consensus guidelines as the mainstay of the treatment when the tumor is classified as intermediate or high-grade, it invades the base of the vermiform appendix, it sizes >2 cm and/or there is evidence of mesoappendiceal or lymphovascular infiltration with lymph node involvement [18]. Postoperatively, adjuvant chemotherapy reflects regimens similar to the ones used for colonic adenocarcinoma. We herein discuss through our single experience the clinical and histomorphological features of goblet cell carcinoid of the appendix.

Case Report

A 67-year-old male, with a merely past medical history of bilateral inguinal hernioplasty, presented with a 30-day history of mild right iliac fossa abdominal pain

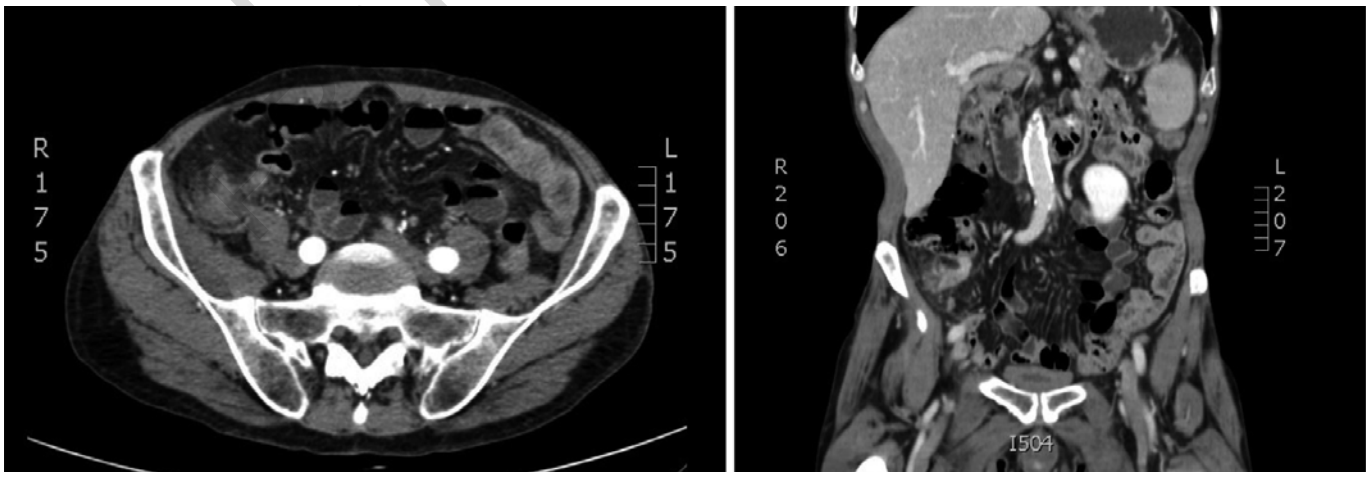

Fig. 1: Abdominal CT showed the appendix dilated with marked mural thickening and mild fat stranding, surrounded by a dishomogeneous fluid collection compatible with acute appendicitis.

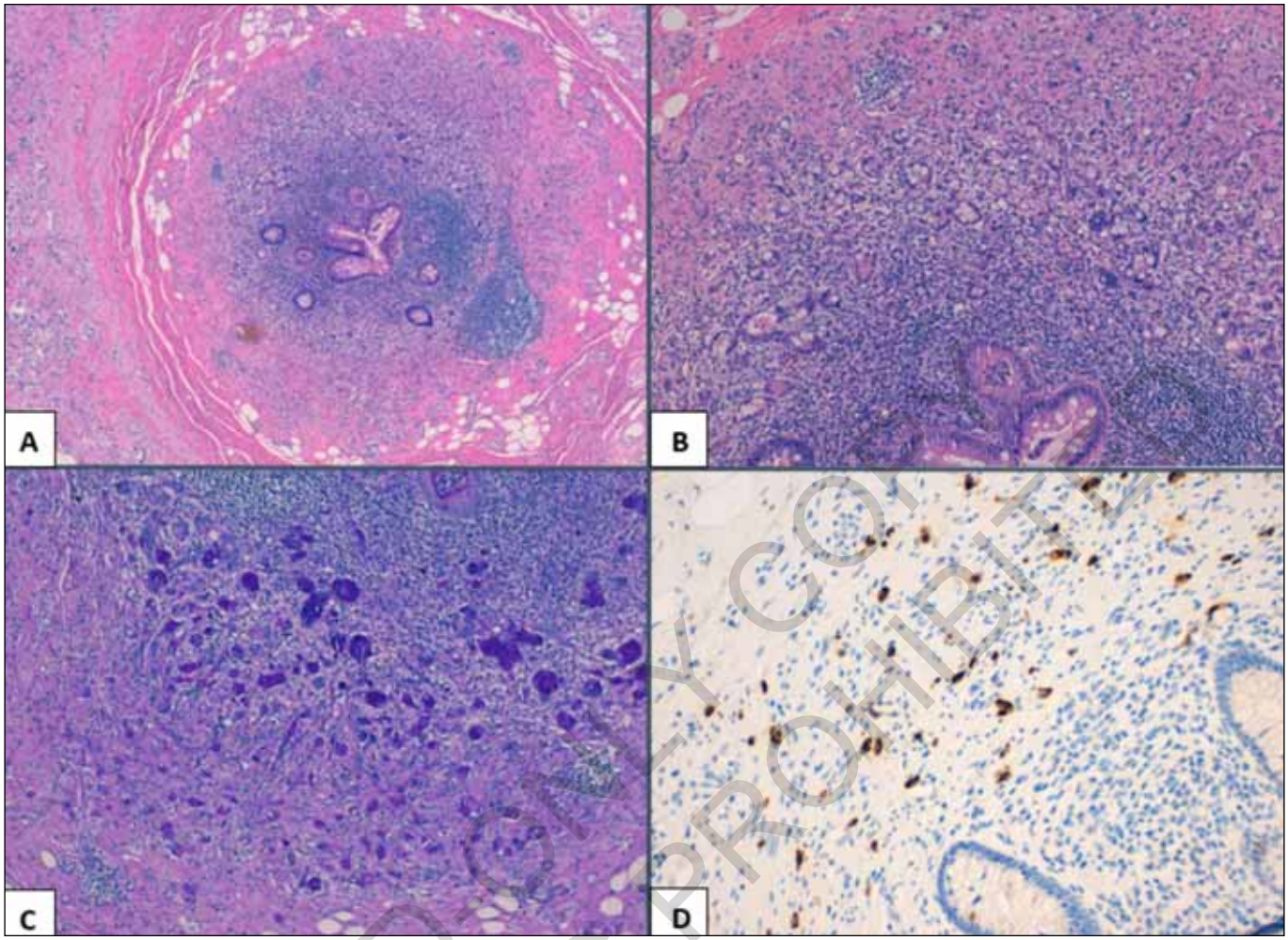

Fig. 2: Histopathological examination highlighting goblet cell carcinoma characterized by cohesive clusters of tumor cells with goblet-like mucinous cells resembling intestinal crypts, diffusely involving the appendix with subserosal invasion. A) H&E stain 4x. B) H&E stain 10x. C) the cells showing cytoplasmic periodic acid-Schiff positivity, PAS stain 10x. D) immunohistochemical staining of the appendiceal tissue revealing frequent positive expression of chromogranin A, 20x.

together with constipation and body weight loss. Two days before admission he underwent colonoscopy which revealed a severe partial stricture of the descending colon suspected for malignancy. On physical examination, vitals were stable, body temperature within normal limit, his abdomen showed tenderness to deep palpation in his right lower quadrant, with no rebound and Rovsing's sign was negative. Laboratory tests revealed mild neutrophilia and lymphocytopenia, hemoglobin 12.6 g/dL (reference range [13-17]), RCP 10.8 mg/dL (reference range 0.0-0.5), while tumor markers turned out within normal range. Abdominal contrast-enhanced computed tomography showed a parietal contrast-enhanced bowel loop surrounded by a dishomogeneous fluid collection in the right iliac fossa compatible with acute appendicitis and an ill-defined tortuous and partially contracted descending colon, without evidence of solid masses, significant lymphadenopathy or distant metastatic disease (Fig. 1). He was started on antibiotics and his symptoms rapidly improved. Patient was discharged waiting for virtual colonoscopy (VC) to be performed. VC later confirmed a partial stricture of the descending colon approximately 30 cm from the anal verge and elective surgery was scheduled. Ten days later, the patient was admitted with acute intestinal obstruction and severe constipation. A new endoscopy allowed colonic lesion detection and tattooing; surgery was scheduled for the following day. On laparotomy, vermiform appendix appeared to be mildly inflamed and dilated, tightly adhered to the small intestine through multiple bridles and adherences as a result of a likely chronic inflammation disease; macroscopically there was no evidence of involvement of the ascending colon. Therefore, uneventful appendectomy and left hemicolectomy were performed. Post-operative course was unremarkable and the patient was discharged eight days later. Histopathological

examination of the left colon revealed low-grade adenocarcinoma pT3 pN0, according to the current TNM classification, while appendix showed the presence of mucin-containing goblet-shaped epithelial cells arranged in small round or oval clusters diffusely involving the organ, with subserosal invasion (pT3NX staging), associated to mucin lakes within the periappendiceal fat tissue (Fig. 2). According to the current guidelines, elective right hemicolectomy was performed two months later [12,14,19,20]. Pathological specimen revealed glandular mucosal hyperplasia of the ascending colon together with submucosal fibrosis and signs of subserosal and omental chronic inflammation; moreover, all fifteen lymph nodes resected were found free of cancer. Both early outpatient follow-up and one-year outcome demonstrated excellent recovery and no signs of disease recurrence were detected within 2 years.

Discussion

Primary tumors of the vermiform appendix represent less than 1% of all gastrointestinal malignancies. They are characterized by significant morphological diversity and are further classified into adenocarcinoma, carcinoids (neuroendocrine tumors; NETs), mucinous tumors, signet ring cell tumors and goblet cell carcinoids (GCCs); GCC reaches 14-19% of the overall cases of primary appendix cancers [3,4]. In 50-60% of cases GCC frequently presents with acute abdominal pain and clinical findings of appendicitis [21,22], often diagnosed incidentally during appendectomy or ileocecal resection and confirmed on histopathological specimens.

Therefore, routine histopathological investigation due to unexpected and unusual findings, even in cases where the vermiform appendix appears macroscopically normal, is highly recommended [23]. Other clinical presentations include abdominal mass, in case of advanced diseases, and gastrointestinal bleeding. Unlike traditional carcinoid which presents with focal, apical tumors, GCC may involve, as in our experience, the entire length of the vermiform appendix. Given the more aggressive behavior of higher grade GCCs and the related post-operative management, it is important to identify malignancies correctly as GCC and categorize them appropriately according to Tang classification. GCC cells derive from pluripotent stem cells of intestinal APUD origin with eventual neuroendocrine and mucinous differentiation, whose microscopic hallmark are small rosettes with crescentic nuclei distended with mucin [2]. However, no association has been made with mismatch repair dysfunctionality and neuroendocrine tumors [24]. Molecular pathogenesis of GCC has not been understood yet and the only allelic loss found is of chromosomes 11q, 16q and 18q [25]. Prognosis is very good if diagnosed at stages I or II, while significantly worsens in stages III or IV where, respectively, it has been described a 22% and 14% five-year survival [20]. Once a goblet cell carcinoid has become frankly malignant, most authors advocate using the term "carcinoma (or adenocarcinoma) ex-goblet cell carcinoid" to avoid any potential confusion with conventional carcinoid tumor. There are several different classifications used for GCC, including the 2010 World Health Organization (WHO) classification for appendix tumors, the 2010 AJCC (TNM classifications) staging and the recently proposed Tang et al. classification specific for GCC of the appendix [19]. The AJCC stages tumors as stage I (T1, N0, M0), stage II (T2/T3, N0, M0), stage III (any T, N1, M0), and stage IV (any T, any N, M1) [26], while the Tang classification uses histologic features of the tumor at the primary site such as arrangements of goblet cells, degree of atypia and desmoplasia and includes typical GCC (group A), adenocarcinoma ex-GCC, signet ring cell (group B) and adenocarcinoma ex-GCC, poorly differentiated (group C). As demonstrated by Tang et al, tumors classified moving from group A to C represent progressively more aggressive phenotypes and worse prognosis with all patients in group C presenting with metastatic disease [12]. The mainstay of treatment for non-metastatic disease is surgical resection. Since many GCCs are found incidentally after appendectomy, the need for further complete oncologic resection (that is right hemicolectomy) is a debated question. Due to high risk of metastases and improvement in prognosis, both the North American and European Neuroendocrine Tumor Societies recommend right hemicolectomy as standard first-line treatment for GCC even after appendectomy [6,18,19].

However, several published analyses evaluating the extent of surgical resection in GCCs have suggested there is no benefit to perform right hemicolectomy in patients with low-grade and/or limited disease burden [27,28]. Therefore, Tang et al. demonstrated that histology rather than the size of the tumor should be used as a determining factor in order to decide the extent of oncologic resection (appendectomy versus right hemicolectomy) in higher grade tumors (groups B and C) which benefit from more extensive resection. Based on those data, it is reasonable to consider appendectomy alone in patients with tumor <2 cm and localized to the appendix with negative surgical margins, patients with typical GCC group A histology, and patients with pT1 or pT2 tumors. For all other patients, which include those with tumors >2 cm, locally advanced stage, positive margins, histology with signet ring group B or group C, or pT3 or pT4 tumors, it is recommended to perform a right hemicolectomy [12,18-20,29]. Furthermore, patients with stages II (Tang B and C) and III GCC should be offered adjuvant chemotherapy.

P. Izzo et al, giving the most often incidental finding of the neoplasm and the surgical treatment required in case malignancy is diagnosed, suggested performing intraoperative histological examination when the appendix might be suspect [30]. Metastasis in GCC are between 8

and 50% [31] and most commonly they have been described via lymphatics and intraperitoneal invasions, especially affecting ovaries in women. When peritoneal carcinosis is identified, cytoreduction in combination with intraperitoneal chemotherapy may be considered [32,33].

In the present case, our patient had been experiencing for a long time worsening abdominal pain in his right lower quadrant, whose symptoms were overlapped by an acute abdominal obstruction due to a distinct malignancy of the descending colon. Clinical and radiological suspects for an inflammation of the vermiform appendix were confirmed intraoperatively and pathology confirmed the rare nature of goblet cell carcinoid, which was found to involve the entire appendiceal organ. According to the current guidelines, pT3Nx goblet cell appendiceal carcinoid required further complete oncologic resection through right hemicolectomy. Due to the fact that GCCs are most commonly diagnosed incidentally following routine appendectomy, there is a lack of standardized classification system and a variety of discrepancies regarding specific reliable markers, such as Ki-67. The aim of our report is to emphasize the lack of such standardized classification system and reliable markers in order to achieve an appropriate prognosis and treatment and ensure optimal clinical management and outcome predictions.

Conclusions

Goblet cell carcinoid is an extremely rare and distinct entity of appendiceal tumor, characterized by both epithelial and neuroendocrine elements, containing goblet cells, which tends to be more aggressive than typical carcinoid tumors, often presenting with a metastatic involvement and a low 5-year survival in stages III and IV of the disease. It is essential that patients, presenting with tumors > 2 cm, pT3 or pT4, higher grade histology with signet ring (Tang grades B and C), locally advanced or with positive surgical margins on appendectomy, undergo right hemicolectomy. Moreover, consensus recommendation indicates adjuvant chemotherapy for stages II and III of the disease. Lack of a standardized classification and reliable markers may lead both to misdiagnosis and to suboptimal treatment and surgical approaches [34]. Clinical manifestations include a wide variety of occurrences ranging from an asymptomatic patient, till an advanced disease with metastatic features. As confirmed in our experience as well, it most frequently presents with symptoms of acute appendicitis. Therefore, when offering non-operative management of acute appendicitis, incidental malignancy must be kept in mind. Histopathology is essential to reach the diagnosis and to enhance knowledge concerning its biological behavior. Increased awareness of the disease will encourage the index of suspicion and possibly lead to an evidence-based treatment management.

Riassunto

Il carcinoide a cellule goblet rappresenta un'entità patologica estremamente rara nell'ambito dei tumori appendicolari, caratterizzata sia da elementi epiteliali, sia neuroendocrini, contenente cellule goblet e con la tendenza ad un'aggressività maggiore rispetto al tipico carcinoide, poiché spesso si presenta già alla diagnosi con coinvolgimento metastatico e una ridotta aspettativa di vita negli stadi più avanzati di malattia. È pertanto mandatorio che pazienti con carcinoidi a cellule goblet di dimensioni superiori a 2 cm, pT3 o pT4, con istologia caratteristica, patologia in stadio avanzato o con positività dei margini di resezione post appendicectomia, vengano sottoposti ad emicolectomia destra di completamento. E' altresì fortemente raccomandato l'impiego di terapia adiuvante negli stadi III e IV di malattia. La mancanza di una classificazione standardizzata e di marcatori affidabili comporta un insufficiente valore prognostico e predittivo al momento della diagnosi, generando frequentemente un ritardo sia nella diagnosi stessa che nei successivi trattamenti medici e chirurgici. Nella nostra esperienza riportiamo il caso di un paziente di 67 anni di sesso maschile presentatosi con un quadro di addome acuto occlusivo, associato ad un severo dolore addominale spiccatamente a carico del quadrante inferiore destro dell'addome. Il sospetto sia endoscopico sia radiologico era di neoplasia colica sinistra associata ad appendicite acuta. Il paziente è stato sottoposto ad emicolectomia sinistra ed appendicectomia; i campioni istologici hanno messo in evidenza un adenocarcinoma di basso grado del colon discendente ed un carcinoide a cellule goblet di alto grado dell'appendice. Alla luce di tale reperto il paziente veniva successivamente sottoposto ad emicolectomia destra e risulta in buone condizioni di salute ad un follow-up di 2 anni. Pertanto, qualora nella pratica clinica si optasse per un trattamento conservativo dell'appendicite acuta, l'evenienza che possa trattarsi di una neoplasia incidentale va tenuta in alta considerazione. L'analisi istopatologica è essenziale per raggiungere la diagnosi e meglio comprendere il comportamento biologico della neoplasia. Una miglior consapevolezza della patologia deve incoraggiare il tasso di sospetto e possibilmente guidare verso un trattamento sempre più fondato sulle evidenze.

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