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Extended Abstract

Adenocarcinoma Ex Goblet Cell Carcinoid (GCC) of the Appendix: Report of Five Cases and Pitfalls in Diagnosis of GCC

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Introduction:

Neoplasm of the appendix is relatively rare, with only 0.9-1.4% of all appendectomy specimens found to have it [1,2]. The GCC was first described in 1974 as a separate entity [3], and counts for less than 5% of all primary appendix neoplasms, with an average age of 58.8 [4]. Adenocarcinoma ex goblet cell carcinoid is an uncommon entity characterized by both neuroendocrine differentiation and adenocarcinoma of the colon. Its histogenesis and pathogenesis still remain controversial [5-9], although it has been suggested that GCC cells are from lysozyme-producing cells in small intestinal crypts [10]. Initially, GCC was believed to be a low-grade malignancy [3], however, later studies suggested higher malignant potentials of the GCC compared to the classic appendix carcinoids [11]. In this study, we reported five new cases with symptoms of or mimicking appendicitis, and radiology imaging findings suggestive of appendicitis or an appendiceal abscess. We reviewed the literature and discussed the importance of meticulous sampling and the pitfalls of misdiagnosis due to the presence of diverticulitis in some of these patients.

Case Reports:

Case 1 A 60- year-old male presented to the Emergency Department for an abdominal pain and was found to have perforated appendicitis with an abscess on the CT scan of the abdomen. The interventional radiology (IR) drain revealed purulent fluid, and the patient was treated with a two-week course of Ciprofloxacin and Flagyl, and was later discharged. Two months later, the patient was presented with a persistent loculated right lower quadrant (RLQ) fluid, and the drain study showed the fluid density concerning for appendiceal mucocele instead of the previously thought abscess. One month later, the patient was presented with a localized, sharp RLQ pain and a dark red fluid draining from his RLQ drain, as well as associated symptoms of hot flashes and dizziness. The CT scan of the abdomen and pelvis was suggestive of appendiceal mucinous neoplasm, so the patient was admitted for further treatments. Past medical history was significant for gastroesophageal reflux disease (GERD), gout, chronic back pain, depression, and tinea versicolor of the chest. Surgical history was significant for inguinal hernia repair, and family history was significant for breast cancer in the patient's mother and sister. Physical examination

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revealed serous drainage from the RLQ drain and the abdomen was soft and non-distended, with no tenderness to palpation. On admission, the patient weighed 173 lbs (78.5 kg), and his height was 5'7" (1.7 m) with a body mass index (BMI) of 27.1 kg/m2. Initial laboratory studies revealed unremarkable results for complete blood count (CBC), basic metabolic panel (BMP), carcinoembryonic antigen (CEA) (0.9 ng/ml), carbohydrate antigen CA19-9 (6 U/ml), and cancer antigen CA125 (10.6 U/ml). The CT of the abdomen and pelvis revealed abnormal tubular fluid collection in the RLQ measuring 3.7 × 3.8 × 7.0 cm (Figure 1A). The CT-guided drainage aspirated 25 ml of mucus fluid from the RLQ. On further workup, the cytopathology of this fluid revealed mucin and chronic inflammation, and showed no evidence of malignancy. Cultures showed negative growth for anaerobes, fungus, and acid-fast organisms, except positive growth for Streptococcus angiosus after 48 hours.

The patient underwent laparoscopic appendectomy and the specimen was obtained for histopathological examination. Grossly, the appendix had an increased wall thickness ranging from 0.5 cm to 1.5 cm with a pink-tan mucosal surface and prominent mucosal folds. The appendiceal lumen was filled with mucin and purulent fluid. Multiple inflammatory/pseudopolyps were identified on the surface of the mucosa ranging from 0.3 × 0.3 × 0.3 cm to 0.5 × 0.5 × 0.4 cm. Multiple diverticula were also identified, grossly extending into the muscularis layer (Figure 1B). Hematoxylin and Eosin (H&E) stains revealed multiple diverticula and fistula formations (Figure 1C), and tumor cells composed of goblet cell carcinoids and signet-ring cell carcinoma (Figures 1D, 2A-2B) infiltrating the appendiceal wall, predominantly located at the base (orifice) of the appendix which focally involved the proximal resection margin. Immunohistochemical stains were performed with adequate controls. The tumor cells were focally positive for synaptophysin (Figure 2C) and chromogranin (Figure 2D, left), diffusely positive for CK20, CDX2 (Figure 2D, right) and CEA, and negative for CK7. The Ki-67/MIB-1 stain highlighted scattered tumor nuclei of the goblet cell carcinoids with more prominent staining in the singlet signet ring cells. The tumor was diagnosed as adenocarcinoma ex goblet cell carcinoids, signet ring cell type (T3NxMx). However, no tumor was identified in the areas of diverticulitis or previously perforated site. The patient was later discharged after an uneventful one-day hospital course. The pathology report was then discussed with the patient and he was re-admitted after 15 days from the initial discharge date, for the right hemicolectomy. Rare signet ring tumor cells were present at the prior appendectomy site. The patient has been recovering well from the surgery, and has started on systemic therapy as we report this case.

Case 2:

A 34 year-old male presented with concerning symptoms for appendiceal abscess. Ultrasound (US) showed a large mass surrounding his appendix consistent with abscess. US and CT-guided biopsy was negative for inflammatory or neoplastic process. 14 days later, the repeated CT imaging revealed an enlargement of the mass that was suggestive of a neoplastic process. Subsequently, the patient underwent an exploratory laparotomy which revealed an appendiceal

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tumor with metastatic disease. The ileocecectomy specimen showed a 7.4 cm tumor. The H&E stain revealed poorly differentiated adenocarcinoma ex goblet cell carcinoid (T4bN2M1). Lymphovascular invasion and perineural invasion were present, and 14 of 18 lymph nodes were involved by the metastatic tumor. The tumor cells were focally positive for synaptophysin and chromogranin. Intraperitoneal metastasis beyond the RLQ including pseudomyxoma peritonei was present. The patient had a positive response to the chemotherapy with FOLFOX, 5-FU, and Avastin, and showed a 40% reduction in tumor sizes. The patient is currently considering hyperthermic intraperitoneal chemotherapy (HIPEC) treatment as we report this case.

Case 3

A 46 year-old male presented with symptoms of RLQ abdominal pain secondary to peritonitis from a perforated appendix. The histopathological examination of the appendectomy specimen revealed a 1.4 cm Grade 1, well-differentiated goblet cell carcinoid (T2N0Mx). No lymphovascular invasion was present. Subsequently, the patient was informed of his appendectomy specimen pathology report and underwent right hemicolectomy. The right hemicolectomy revealed a 1.2 cm Grade 1, well-differentiated neuroendocrine tumor of the small intestine. Lymphovascular invasion and perineural invasion were present. The patient was then placed under active surveillance with no evidence of recurrence for the past three years.

Discussion:

Here, we report five new cases with adenocarinoma ex goblet cell carcinoid. All five patients in our report were initially presented with symptoms of or mimicking appendicitis, with two patients having a perforated appendix, and two patients having diverticulitis. The initial presentation symptoms were RLQ pain, peritonitis from a perforated appendix, and hematochezia. Four of the five patients were male, while one was female with a tumor metastasis to her left ovary four years after her right hemicolectomy. GCC has a wide range of clinical presentations, therefore, it is important to always consider GCC in patients presenting with abdominal symptoms. Payam S Pahlavan and Rani Kathan reported that the most common clinical presentations for GCC of the appendix are in the order of frequency as follows: acute appendicitis (22.5%), asymptomatic (5.4%), non-localized abdominal pain (5.15%), and abdominal mass (3.09%) [12]. In female patients, GCC may be presented as Krukenberg tumors, while in half of the female patients it is initially presented as an ovarian mass [13-15]. Although GCC is almost exclusive to the appendix, the extra-appendiceal GCC is exceedingly rare [16]. The only potential risk factor for GCC that has been suggested to date is schitosomiasis [17]. Two of our patients had focally localized tumors. Combining that with the presence of diverticulitis in some of these patients, it may mislead the diagnosis. Therefore, a thorough gross examination of the appendectomy specimen and careful sampling are imperative to the diagnosis of GCC because of the lack of the discrete mass. The “tang classification” of GCC patients are

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divided into three groups (A, B, and C) and have shown to be a significant prognostic factor [5,18,19]. Typical GCC (Group A) was defined as well-defined goblet cells arranged in clusters or in a cohesive linear pattern, with minimal cytologic atypia and architectural distortion of the appendiceal wall, and minimal to no desmoplasia [5]. Adenocarcinoma ex GCC, signet ring cell type (Group B) was defined as goblet cells or signet ring cells arranged in irregular large clusters, with the lack of confluent sheets of cells in a discohesive single file or single cell infiltrating pattern with significant cytologic atypia, and desmoplasia and associated destruction of the appendiceal wall [5]. Adenocarcinoma ex GCC, poorly differentiated carcinoma type (Group C) was defined with the least focal evidence of goblet cell morphology and a component (>1 low power field or 1 mm2) that is not otherwise distinguishable from a poorly differentiated adenocarcinoma. It may appear as either gland forming, confluent sheets of signet ring cells, or undifferentiated carcinoma [5]. The 5- year survival rate was 100% in the typical GCC group (Group A), 36% in Adenocarcinoma ex GCC, signet ring cell type group (Group B), and 0% in Adenocarcinoma ex GCC, poorly differentiated adenocarcinoma type (Group C). In this study, the five cases include one in Group A, one in Group B, and three in Group C. An alternative histologic grading system, the simplified two-tier histologic grading system, was proposed, and has also shown good predictive values for the GCC outcome [19]. This histologic scoring system was created whereby one point was given for the presence of each of cytologic atypia, peritumoral stormal desmoplasia, and solid growth pattern (score ranges from 0 to 3). A histologic score of 0-1/3 was defined as low grade, and 2-3/3 was defined as high grade. This two-tier grading system demonstrated that the overall 10-year survival rate in the low-grade histology group was 80.5%, and 0% in the highgrade histology group. However, the role of Ki-67 as a prognostic marker has been controversial [5,18,20-23]. The Ki-67 proliferative index has shown close association with the Tang histologic classification. The Ki-67 staining was relatively low in Group A (11%) and B (18%) tumors, and Group C (80%) tumors demonstrated a high proliferative rate [5]. However, more recent study has shown no correlation between the Ki-67 and the behavior of the GCC tumors [23]. The treatment of GCC still lacks a unanimous consensus. However, it is acknowledged that the complete removal of the GCC in the appendix is imperative, even though the benefit of hemicolectomy in patients with GCC is not clear [24-26]. In addition, the possible bilateral oophorectomy in the female patients is also suggested due to the high incidences of GCC metastasis to the ovaries [13,27].

Conclusion:

We describe five new cases with adenocarcinoma ex goblet cell carcinoid, who were presented with symptoms of or mimicking acute appendicitis. The GCC has a wide range of clinical presentations, and more importantly, has no discrete mass except a focally thickened appendiceal wall, and cytopathology examination may reveal no evidence of malignancy. Furthermore, there is a significant overall survival rate difference in patients with the lower grade/stage GCC and higher grade/stage GCC. Therefore, it is important to keep in mind the pitfalls in diagnosis of GCC by careful sampling.

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