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Goblet Cell Carcinoid (GCC) Tumors of the Appendix: Report of Two Cases and a Short Review of the Literature

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Abstract: The authors report 2 cases of a rare neoplasm of the appendix, which was discovered incidentally upon surgical treatment of acute appendicitis. After the specimens were pathologically reviewed, the results revealed a case of Goblet Cell Carcinoid (GCC) of the appendix. Most patients presented with signs and symptoms of acute appendicitis, Two common immunohistochemical markers associated with this tumor are Synaptophysin and Chromogranin. The pathogenesis and malignant potential of this tumor are not well defined. Goblet cell carcinoid is more aggressive than classic carcinoid.

Key words: GCC, tumors of the appendix, case report, pathology

INTRODUCTION

The most common malignant tumor of the appendix, found in 32-57% of appendiceal neoplasms, is the carcinoid tumor. Incidentally, it is most commonly found during an appendectomy, with a prevalence of 0.3-0.9% (Goede *et al*., 2003). Classic appendiceal carcinoids show a slight but consistently higher incidence among female patients, with the mean age for their diagnosis at 35.9 years (Tampanakis *et al*., 2006). Certain criteria have been suggested to determine if additional surgery is indicated in cases of carcinoid tumor of the appendix. These criteria include a tumor greater than 2 cm, location at the base of the appendix and invasion of the tumor into the serosa or extension into the mesoappendix (Safioleas *et al*., 2005).

Goblet Cell Carcinoid (GCC) of the appendix is considered a rare tumor comprising approximately 6% of appendiceal carcinoids (Tuompanakis *et al*., 2006). The typical presentation in the majority of cases is acute appendicitis. Alternatively named Goblet cell type adenocarcinoid, crypt cell carcinoma, microglandular carcinoma or mucinous carcinoid, goblet cell appendiceal carcinoid is histological and behaviorally distinct from both carcinoid and adenocarcinoma of the appendix (Varisco *et al*., 2004). The mean age for diagnosing goblet cell appendiceal carcinoid is 58.8 years, with equal representation in both sexes (Aizawa *et al*., 2003). GCC of the appendix has propensity for ovarian metastasis (Edmonds *et al*., 1984; Butler *et al*., 1994; Heisterberg *et al*., 1982; Hood *et al*., 1986) and carcinomatosis (Bak *et al*., 1988). Although this tumor is found in almost any area of the gastrointestinal tract, the appendix is the most common location. The following 2 cases report of this rare neoplasm of the appendix.

Case report no. 1: This case presents a 33-year-old female with generalized abdominal pain that had commenced the previous evening. Pain was 10/10, with no nausea, vomiting or diarrhea noted. Past medical, surgical and social history was non-contributory. The patient was afebrile at the time of admission and physical examination revealed moderate tenderness to palpation of the right and left lower quadrants of the abdomen. Blood analysis revealed leukocytosis of 12×10^3 mm^{-3} with 84.7% neutrophils. The remaining labs were within normal limits. CT scan of the abdomen and pelvis revealed a blind ending tubular structure arising off cecum, 1 cm in length with enhancing walls, consistent with acute appendicitis.

The patient underwent a Laparoscopic Appendectomy the following day. The pathology revealed a diagnosis of GCC of the appendix. The tumor showed full thickness invasion of the wall, perineural invasion (Fig. 1) and lymphatic channel involvement. The tumor cells were positive for CK7, CK20, Chromogranin (Fig. 2) and Synaptophysin, which favored the diagnosis. Postoperatively, the patient recovered promptly and was discharged the following day.

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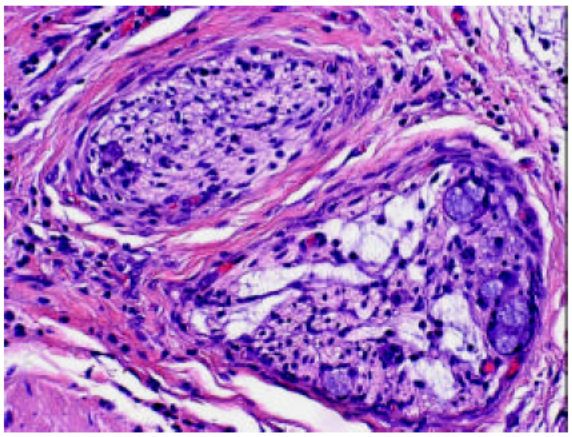

Fig. 1: (Case #1) Perineural invasion by tumor cells

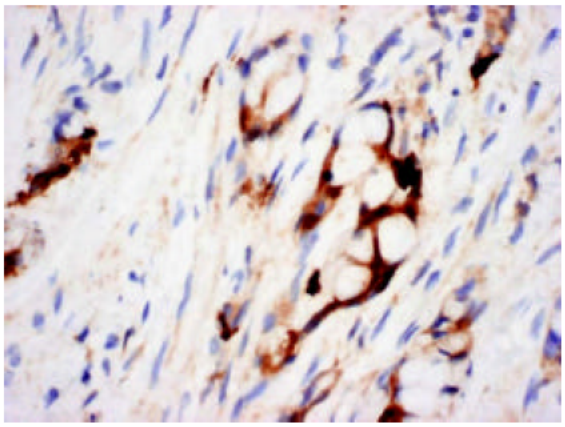

Fig. 2: (Case #1) Immunohistochemically stained tumor cells with Chromogranin

Case report no. 2: This case presents a 78-year-old female with right-sided abdominal pain for one day. Pain was 5/10, mainly located in the right lower quadrant. The patient admitted to experiencing constipation for one week and denied any nausea, vomiting, or diarrhea. Medical history included uterine cancer with a hysterectomy performed in 2005, as well as amaurosis bilaterally. Social history was non-contributory. Patient was afebrile upon admission. On physical examination, tenderness to palpation was located in the right lower quadrant. The patient had normal bowel sounds and no abdominal pulsatile masses and the remainder of the physical exam was unremarkable. Upon blood analysis, leukocytosis was noted at 15.4×10^{3} mm^{-3}. The remainder of the labs was unremarkable. The CT scan of the abdomen/pelvis revealed a 13mm dilated tubular structure with fat stranding and a few subcentimeter reactive lymph nodes within the region consistent with acute appendicitis.

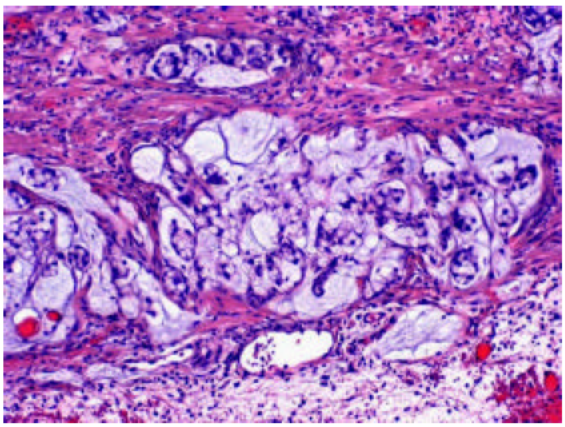

Fig. 3: (Case #2) Tumor composed of cells with abundant intracytoplasmic mucin arranged in small clusters and rosettes

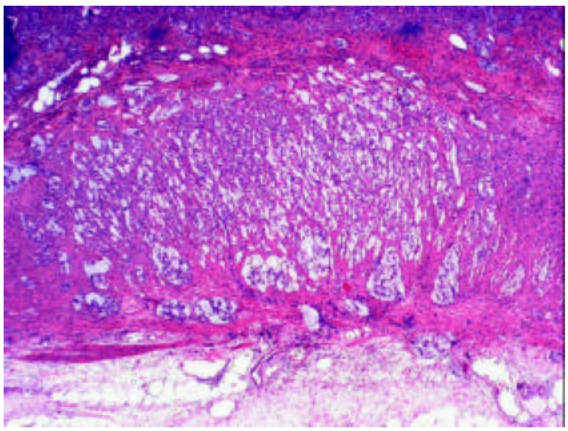

Fig. 4: (Case #2) Tumor diffusely infiltrating the appendiceal wall extending into the periappendiceal adipose tissue

The patient underwent a Laparoscopic Appendectomy that same day. The tip of the appendix was adherent in the retroperitoneum with inflammatory changes. The pathology revealed a GCC, composed of abundant intracytoplasmic mucin arranged in small clusters and rosettes (Fig. 3). The appendiceal wall was diffusely infiltrated and extended into the periappendiceal adipose tissue (Fig. 4). The tumor involved the middle-distal portion of the appendix and stained positive for CD56, CK20 and synaptophysin. The tumor was negative for CK7 and chromogranin. Postoperatively, the patient had a prompt recovery and was discharged the following day.

DISCUSSION

In 1969, Gagne first described the GCC tumor pathologically (Gagne *et al*., 1969). Subbuswamy and

Warkel then expounded on the behavior and histopathology of this rare entity (Subbuswamy *et al*., 1974; Wakel *et al*., 1978). The pathogenesis of these tumors is not clear. Some studies suggest a link to the occurrence of p53 mutations and especially to G:C to A:T transitions (Ramnani *et al*., 1999). Other studies concluded that an allelic loss of chromosomes 11q, 16q and 18q is common with this rare neoplasm (Stancu *et al*., 2003).

In the 2 cases detailed above, the initial presentation was that of acute appendicitis. Upon appendectomy and pathological evaluation of the specimens, the tumors involved the mid-distal portions of the appendix and contained mucin producing tumor cells. Both tumors stained positive for synaptophysin and CK20, while only one stained positive for chromogranin and CK7.

The results of a recent retrospective study of 15 patients diagnosed histologically with goblet cell appendiceal carcinoid from 1996-2005, by Toumpanakis *et al*., are as follows. Presentation of symptoms included acute appendicitis (46.7%), bowel obstruction (33.3%), chronic vague abdominal pain (13.3%) and chronic diarrhea (6.7%) (Toumpanakis *et al*., 2006). Tumor location included the base of the appendix (60%), invading the cecum (13.3%), in the tip of the appendix (26.7%), unidentifiable due to mass involvement of surrounding structures (13.3%) and Krukenberg pattern of spread (6.7%) (Toumpanakis *et al*., 2006). All 15 tumors were mucin-filled GCC cells identified via morphology and neuroendocrine immunostaining to detect the scattered endocrine cells (Toumpanakis *et al*., 2006). Tumor size ranged from 0.4-2.5 cm with three cases of metastasis at the time of diagnosis (Toumpanakis *et al*., 2006). Immunohistochemistry showed 73.3% of the tumors were chromogranin positive, 86.7% were synaptophysin positive and 46.7% were positive for neuron-specific enolase (Toumpanakis *et al*., 2006).

The malignant potential of GCCs has been most accurately characterized as intermediate between classic carcinoid and adenocarcinoma (McCusker *et al*., 2002). In a study by Byrn *et al*. (2006) it was concluded that the behavior of GCC tumors is malignant and that pathologic invasion is not predictive of residual disease in the subsequent surgical specimens, such as right hemicolectomy (Byrn *et al*., 2006). Therefore, the choice of performing right hemicolectomy based solely on pathological results cannot be recommended and must be determined based on the individual patient (Byrn *et al*., 2006). Certain criteria have been suggested to determine if additional surgery is necessary in cases of carcinoid tumor of the appendix. These criteria include size greater than 2 cm, location of the tumor at the base of the appendix and invasion of the tumor into the serosa or extension into the mesoappendix (Safioleas *et al*., 2005). In the two cases presented, both patients are awaiting to undergo a right colectomy in the near future.

CONCLUSION

The goblet cell carcinoid is a rare neoplasm of the appendix. Most patients present with signs and symptoms of acute appendicitis, most commonly located at the base of the appendix. Synaptophysin and chromogranin are common immunohistochemical markers associated with this tumor. The pathogenesis and malignant potential of this tumor are not well defined. In addition, pathological diagnosis alone is not adequate for the basis of performing a right colectomy.

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