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Goblet cells carcinoid with mucinous adenocarcinoma of the vermiform appendix: a step towards the unitary intestinal stem cell theory?

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Abstract. – Associations of various histotypes in appendiceal neoplasms may help elucidate the histogenesis of such uncommon tumors. We present the fourth published case of Goblet Cell Carcinoid (GCC) associated with mucinous adenocarcinoma of the appendix. This association has been described only for GCC and not for classic appendix carcinoids which are thought to originate from neuroendocrine-committed cells. The GCC-mucinous association adds more towards the theory of a pluripotent intestinal stem cell with amphicrine possibilities of differentiation.

Key Words:
Goblet cell carcinoid, Mucinous adenocarcinoma, Appendix.

Introduction

Appendiceal tumors are important neoplasms which can be encountered in both district general hospitals and tertiary referral centres. They are frequently discovered incidentally on appendicectomy specimens (0.1-0.8%)[1], but can also present with acute appendicitis caused by luminal obstruction from the tumor mass, or with more severe symptoms due to local widespread dissemination (pseudomyxoma peritonei in cases of mucinous types or peritoneal carcinomatosis for adenocarcinomas)[2-4]. Historically five histotypes have been described[3]: mucinous adenocarcinomas represent the most common type of appendiceal tumors (37%), followed by colonic-type adenocarcinomas (25%), carcinoids (20%), goblet cell carcinoids (GCC – 14%), and signet ring cell carcinomas (4%)[5]. Carcinoids are associated with the best prognosis and signet ring cell carcinomas with the worst[5].

Among all appendiceal tumors mucinous adenocarcinomas and GCC are those that pose numerous controversial issues currently under debate. Uncertainties about their malignant behaviour are reflected in the number of classifications available and in the use of terms such as "uncertain malignant potential" or "low malignant potential" to describe histologic grading between the classic progression adenoma-carcinoma[4,6,7]. "Low-grade" mucinous neoplasms can spread to the peritoneum and the ovaries without local invasion of the appendix[4]. Therefore, pseudomyxoma peritonei is associated with mucinous neoplasms of low malignant potential despite it represents a disseminated disease[4]. The clinical significance of localised pseudomyxoma peritonei (i.e. during ruptured mucinous neoplasms) is also uncertain, although many of the local recurrences are determined by malignant cells in the periappendiceal mucin pool[4,8].

Differently from mucinous adenocarcinomas, globet cell carcinoids are amphicrine tumors of the appendix. Amphicrine tumors are neoplasms that contain cells with both exocrine and endocrine features[9] and, therefore, not easily classifiable. These rare neoplasms can be found in numerous organs of the respiratory and gastrointestinal tract, glands (thyroid, breast, prostate) and epithelia (ear, skin, cervix, vulva)[9]. In the case of appendiceal tumors, goblet cells contain both histological and immunohystochemical features of colonic adenocarcinomas (CK 20 positivity, IGA staining) and classic carcinoids (minimal atypia, rare mitotic figures), suggesting a common origin from an undifferentiated pluripotent intestinal stem cell with divergent differentiation[10,11]. This cell type is not present in the appendiceal mucosa and is thought to be generated from an epithelial metaplasia[12].

The debate about the histologic origins of appendiceal tumors is one of the most fascinating controversies. In the present article we present a rare case of appendiceal neoplasm in which both

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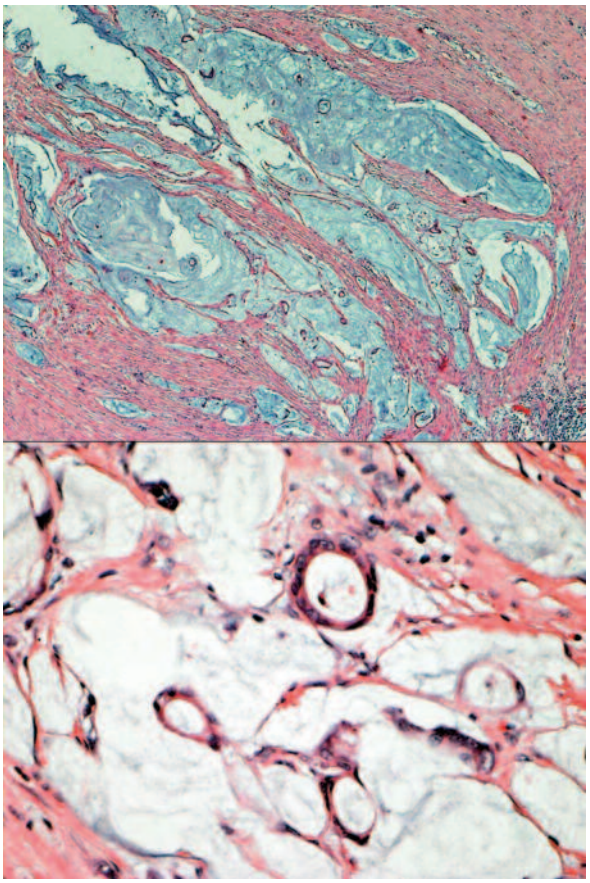

Figure 1. *Upper panel*: adenocarcinoma with abundant extracellular mucin and floating glandular elements (10x). *Lower quadrant*: abundant extracellular mucin and floating glandular elements (40x).

GCC and mucinous adenocarcinoma coexisted in the same specimen. The significance of this report adds towards the unifying theory of a single totipotent intestinal stem cell that could originate most appendiceal neoplasms.

Case Report

A 62-year-old female patient presented to the Emergency Department with a 48-hour history of right iliac fossa pain. Symptoms were previously managed by the family doctor as urinary tract infection with oral antibiotics without improvement. The past medical history included hypertension, previous laparoscopic cholecystectomy and hysterectomy. On admission she was febrile and tachycardic with tenderness to palpation over McBurney's point. Routine blood analysis revealed raised inflammatory markers (White Cell Count – WCC 15.2 and C-Reactive Protein – CRP 147). A working diagnosis of appendicitis was assigned and immediate treatment with IV antibiotics was commenced. The following morning a Computed Tomography scan of the abdomen demonstrated a mixed density mass (7x6 cm) in the right iliac fossa extending in the pelvis with surrounding inflammatory changes. Differential diagnosis at this stage included appendicular mass, inflammatory bowel disease or malignancy. General clinical conditions and blood analysis improved progressively. Therefore, the decision was to continue the conservative management and request a colonoscopy as an outpatient. The patient was discharged home 6 days after the admission and the outpatient colonoscopy showed only evidence of diverticulosis in the sigmoid and descending colon.

Three months later the patient presented again to the Emergency Department complaining of lower abdominal pain, occasional rectal bleeding and raised inflammatory markers (WCC 12.2, CRP 28). A provisional diagnosis of acute diverticulitis was made and intravenous antibiotic treatment commenced. The mass in the right iliac fossa was again noted and a repeat CT scan showed inflammatory changes associated with the cecal pole. However, compared to the previous study the inflammatory appearances were less severe. Repeated blood tests the following day showed continued derangement of the inflammatory markers (WCC 10, CRP 112) and, therefore, the patient was offered a surgical approach. Intraoperative findings consisted of an ileocaecal mass wrapped in the omentum and tightly adherent to the right lateral pelvic wall and the right ovary. En-bloc resection was performed and the specimen sent for analysis. Recovery was characterised by a postoperative ileus that spontaneously resolved with conservative treatment, and a wound infection treated with regular change of dressings. The histology diagnosed a mixed GCC and mucinous adenocarcinoma of appendicular origin (Figures 1 and 2), with one node positive out of 13 examined (staging pT3 pN1 Dukes C1). The patient underwent adjuvant chemotherapy with Oxaliplatin and Capecitabine and at present does not show any signs of local or systemic recurrence.

Discussion

Amphicrine tumors are interesting variants of the more common exocrine or endocrine counterparts.

Histological features, and quite often their clinical behaviour, lie between these two extremes. A morphological classification divides them into those with separation of the two components at a cellular level (cells contain either exocrine or endocrine granules) but intermixed in the tumor mass; those where the two components are separated at a cellular level and in the mass (juxtaposed – collision tumors)[13]; those in which the two components are intermixed within the cell, further subdivided if exocrine granules are in separated cytoplasmic areas from endocrine or are mixed with them[14].

GCC are peculiar amphicrine tumors that almost exclusively present in the appendix[15]. Their cells contain both endocrine and exocrine features and their histogenesis is still under debate. GCC could be a variant of the neuroendocrine carcinoid with exocrine differentiation or a subtype of adenocarcinoma with neuroendocrine differentiation[15]. A more unifying theory sees the GCC origin from a "single undifferentiated pluripotent intestinal epithelial crypt base progenitor stem cell with divergent neuroendocrine and mucinous glandular differentiation" (unitary intestinal stem cell theory)[12,15]. This theory is confirmed by the presence in rare case reports of the association between GCC and mucinous neoplasms[10,13,16], never found in classical carcinoids. For this reason classic carcinoids would originate from dedicated neuroendocrine stem cells that lack the possibility of an exocrine phenotype while GCC would originate from an earlier precursor that can still produce exocrine features[15]. Typical GCCs have also been described in association with signet ring or poorly differentiated carcinomas of the appendix which would suggest, similarly for the association with mucinous neoplasm, a common origin from an early histogenetic precursor (unitary intestinal stem cell theory)[12,15].

In our case the coexistence of GCC with mucinous adenocarcinoma adds to the current literature of cases described with such association. The importance of our case report is that it is, to the best of our knowledge, the fourth reported case towards the unitary intestinal stem cell theory.

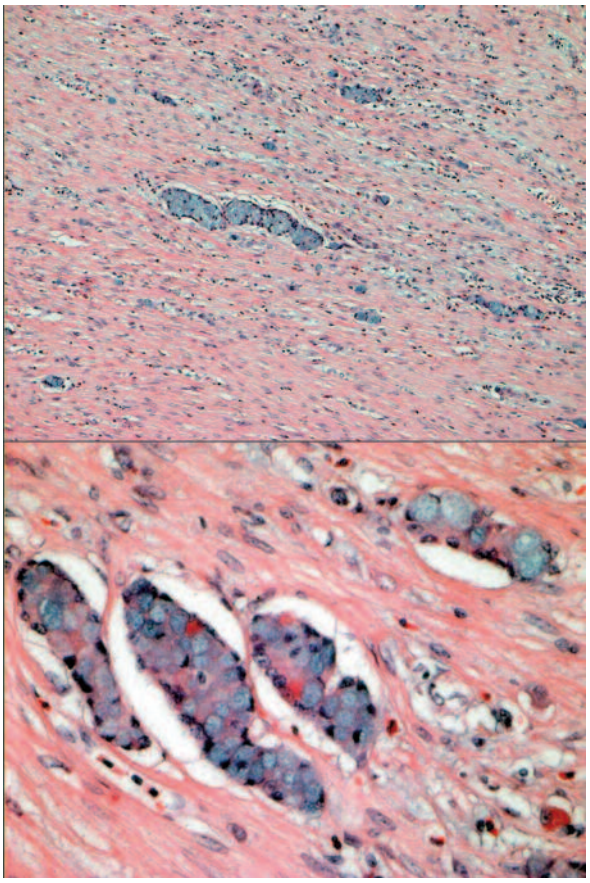

Figure 2. *Upper panel*: goblet cell carcinoid characterised by nests of goblet cells (10x). *Lower panel*: goblet cell clusters with occasional Paneth cells (40x).

Conclusions

The debate about the origin of appendiceal neoplasms is far from being solved and every day new pieces of information are gathered by case reports and small series due to the rarity of these diseases. Different from classic carcinoids and colonic-type adenocarcinomas, for which the originating stem cells have already been found, GCC, mucinous adenocarcinomas and signet ring cell carcinomas have still not been offered such a possibility. However, the co-existence of GCC and mucinous neoplasms in the same specimen increase the likelihood of a common precursor that could differentiate towards both histotypes during the proliferative pathway. Although our report represents only a single patient, its importance lies in the fact that is the fourth reported in the literature of such association, therefore, adding more probabilities towards the unitary intestinal stem cell theory.

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