ACUTE ABDOMEN MASQUERADING A RARE FORM OF APPENDICULAR NEOPLASIA

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CASE REPORT

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Abstract

Appendix neoplasia is an uncommon and in many cases aggressive form of malignancy. Goblet cell carcinoma is found incidentally after appendectomies for acute appendicitis and it is frequent in an advanced stage. There are a lot of controversy regarding the proper management of a patient diagnosed with goblet cell carcinoma. We present the case of a 48-years old male patient with an aggressive form of appendiceal goblet cell carcinoma found after appendectomy, with a favorable outcome after completion with right hemicolectomy and adjuvant chemotherapy. Further trials and studies should bring more light to the proper guidelines for treatment of this particular neoplasia.

Keywords: acute appendicitis, appendiceal neoplasia, goblet cell carcinoma

Introduction

Appendiceal cancer is one of the rarest forms of neoplasia in the digestive tract, affecting 1,2 cases per 1 million people per year [1]. There is a wide variety of appendix malignant tumors that can be classified as:

- Neuroendocrine/Carcinoid tumor
- Epithelial Carcinoma:
  - Goblet cell – associated Carcinoma
  - Low-grade Mucinous Neoplasm
  - High-grade Mucinous Neoplasm
  - Adenocarcinoma (well-differentiated, moderately differentiated, poorly differentiated, signet ring cell adenocarcinoma) [2].

The goblet cell appendiceal adenocarcinoma has an incidence of 0, 05 cases per 100000 population per year reported in the United States alone [3]. This particular sub-type of appendix cancer has features of both neuroendocrine tumors and adenocarcinoma. More than 60% of the cases of malignant appendiceal tumors are found incidentally after emergency appendectomies for acute appendicitis [4]. There are no differences regarding the occurrence between male and female patients. The mean age of the patients diagnosed with goblet cell carcinoma is 52 years [5]. It is often diagnosed in an advanced stage due to the particular cell proliferation pattern and the lack of signs or symptoms until the appearance of clinical features of acute appendicitis [2], [6].

The intraoperative macroscopic aspect of the tumoral appendix is not always suggestive for a certain diagnosis. This occurs because of the submucosal cell proliferation pattern which prevents/delays the development of a tumoral mass, but induces and maintains the inflammatory process that cause the acute symptoms [7]. An accurate

diagnosis can only be made by proper histological examination and immunohistochemical characterization.

According to the American Joint Committee on Cancer (AJCC) the staging of goblet cell appendix adenocarcinoma is similar to other digestive tract adenocarcinomas [8].

The staging and grading of the tumor at diagnosis are the main predictor factors for prognosis. There are studies that have shown that the five year overall survival rate for stage I is 100%, for stage II is 76%, for stage III is 22% and only 14% for stage IV [9]. A more recent study shows a five year survival rate of 85,7%, 84,5%, 55,8% and 10% for stages I, II, III and respectively IV. In the same study, the five year overall survival associated with the grade of the tumor were 80,1% for grade I, 79,1% for grade II and 53,3% for grade III [10]. In another study, the histological grading, with no correlations with the stage of the tumor, shows the following results for median overall survival: 204 months for low-grade goblet cell carcinoma, 86 months for intermediate-grade and 29 months for high-grade goblet cell carcinoma [11].

Being a rare form of neoplasia and because of the histological and immunohistochemical characteristics, the goblet cell carcinoma brings controversy in the literature regarding both the classification and the appropriate management of this aggressive pathology.

The goblet cell adenocarcinoma is an aggressive type of cancer that is frequently diagnosed in advanced stages. The peritoneum is one of the most common site of metastatic spread, followed by the ovaries and liver [12]. Taking into account all these aspects, making a decision regarding the proper management of goblet cell adenocarcinoma remains a challenge. There are several approaches that have been reported: appendectomy alone, appendectomy + right hemicolectomy, appendectomy + cytoreductive surgery (CRS) and hyperthermic intra-peritoneal chemotherapy (HIPEC), appendectomy + CRS + HIPEC + right hemicolectomy, each method used in selected patients. Due to the lack of randomized trials and prospective studies, none of them represents the gold standard in the treatment of goblet cell appendicular adenocarcinoma [7].

Case presentation

We present a case of a 48 years-old male patient who came to the emergency department with nausea, several episodes of vomiting and pain in the right lower quadrant of the abdomen, symptoms that started 2 days prior his presentation and got progressively worse. Regarding the medical history, the patient had an inferior ST-elevation myocardial infarction (STEMI) Killip I in 2014 and hypertension. The patient was under anti-hypertensive medication and monotherapy with antiplatelet agent (Aspirin 75 mg). There were no relevant pathologies in his family medical history.

Physical examination revealed an obese male, BMI=34,29 kg/m2, with blood pressure of 128/78 mmHg, pulse 91 beats/minute, with normal body temperature and SpO2 of 99%. The abdomen was obese, painful spontaneously and on palpation in the inferior quadrant, with maximum intensity in the right iliac fossa, tenderness and guarding to palpation.

The blood tests were showing leukocytosis (white blood cells = 16,8 m/mm3) with neutrophilia (neutrophils = 88%) and no other significant changes.

The patient underwent abdominal ultrasonography, which showed only hepatic steatosis, and abdominal X-ray, which revealed a few air-fluid levels in the medial 1/3 of the abdomen. An abdominal computed tomography revealed evidence of acute appendicitis with distended appendix (13 mm at the base), densification of the adjacent mesenteric adipose tissue and a thickened wall of the last ileal loop.

Due to the clinical and paraclinical investigations, the patient was taken to the operating room for appendectomy. Intraoperatively, we ascertain a medium amount of purulent fluid, inflammatory block formed by the last ileal loop, urinary bladder and the cecum. The appendix was perforated with a gangrenous aspect and a classical anterograde appendectomy was performed. No other changes of the visible intraperitoneal organs were identified on the macroscopic examination. The postoperative evolution was favorable, with the remission of the symptoms.

The pathologic analysis of specimen revealed in the first instance moderately differentiated adenocarcinoma. The patient was referred to the oncology department for further evaluation. The immunohistochemical investigations came positive for CK7, CK20, CDX2, SSTR2, SSTR5, MSH2, MSH6, PMS2, MLH1 and Ki67 in 20-25% of the tumoral cells, which gave the final diagnosis of goblet cell appendicular adenocarcinoma.

The case was referred to a multidisciplinary team consisting of pathologists, oncologist, oncological surgeon and radiologist. The patient underwent a colonoscopy, which did not discover any significant changes. A chest, abdomen and pelvic CT scan was performed and there were no notable changes, except of two celiac lymph nodes of less than a centimeter in diameter.

The patient returned for the completion of the surgical treatment. Intraoperative we ascertain an intense adhesion process, tumor recurrence in the right iliac fossa that includes the cecum and the last ileal loop and the peritoneum with a macroscopic appearance of carcinomatosis. Biopsies were taken and the extemporaneous results revealed metastasis of mucinous adenocarcinoma. Right hemicolectomy with ileo-transvers anastomosis was performed. After the surgery, the patient started the adjuvant chemotherapy with folinic acid, fluorouracil and oxaliplatin (FOLFOX-6). No metastatic lesions were found on the thoracic, abdominal and pelvic CT scan revealed after 3 and 6 months.

Discussions

Goblet cell carcinoma (GCC) was classified as a carcinoid/neuroendocrine tumor for a long period because of the neuroendocrine component. Nowadays is considered a distinct form of neoplasia having mixed constituents, with features from both adenocarcinomas and neuroendocrine tumors. In addition, the goblet cell carcinoma is clinically more aggressive than a neuroendocrine tumor. The fact that goblet cell carcinoma is a separate entity because of its distinctive characteristics is one of the few statements that many authors agree upon [13], [14].

Tang et al proposed a classification based on the morphological features of the primary tumor. They divided the patients into three categories: group A (typical GCC), group B (adenocarcinomas ex GCC, signet ring cells) and group C (adenocarcinoma ex GCC, poorly differentiated carcinoma). This classification can guide the diagnosis and can be used for the prediction of prognosis in addition to the molecular investigation [15]. Another classification for GCC is the one proposed by the AJCC in 2010:

- Stage I - T1N0M0
- Stage II - T2/T3N0M0
- Stage III - any TN1M0
- Stage IV - any T any N M1 [16]

The immunohistochemistry investigation has an important role in the prediction of prognosis. There are high levels of carcinoembryonic antigen – CEA, cytokeratin 7 and 20 – CK7 and CK20 [17], and lower expression of the neuroendocrine markers such as chromogranin and synaptophysin. The proliferation index, Ki-67, is another factor of controversy. Tang et al. associated high levels of Ki-67 with worse prognosis [15], but other studies suggested that

there is no impact on the patient outcome in association with this marker [7], [18].

GCC is often found incidentally, after appendectomies for acute appendicitis in up to 70% of the cases [14]. Most of goblet cell tumors are localized in the appendix, but it can be also found in advanced stages with metastatic disease at presentation in up to 20% of the cases [19]. The peritoneum and the ovaries are the most common place of dissemination [20].

Goblet cell carcinoma of the appendix is a one of the rarest forms of cancer of the digestive tract. Due to its rarity, the therapeutic management is challenging with controversy regarding the optimal algorithm for treatment.

Many studies have shown that the hemicolectomy increase the survival rate comparing it with the appendectomy alone for patients in stage I to III [21]. There are studies that concluded that hemicolectomies conferred better survival rates for T3 and T4 tumors and no difference were seen for T1 and T2 regardless of the procedures performed (appendectomy alone vs. hemicolectomy) [22], [10]. The guidelines of the European Neuroendocrine Tumor Society (ENETS) suggests that the proper management is to complete de hemicolectomy within three months after the appendectomy, although there is not enough data at the moment [5].

The adjuvant chemotherapy was studied in several studies. One study revealed that there is improved overall survival in stage III patients that underwent adjuvant chemotherapy, but not for those with stage II [23]. There are also studies that have shown an improved overall survival for stages I – III [10].

The metastatic disease has a poor prognosis. Studies have shown that the overall survival rates for stage IV is 19 months [24] and the 5-year overall survival between 18% and 18,9% [10].

One of the most common places for dissemination is the peritoneum. The management of peritoneal carcinomatosis with cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy (HIPEC) has shown promising results in many cases. Sluiter et al. concluded that the overall survival increases from 17 month (patient treated without HIPEC) to 39 month (cytoreductive surgery + HIPEC) [25]. Similar data were reported by Berger et al. – an increase in the overall survival from 7,9 months (systemic chemotherapy) versus 24,6 months (cytoreductive surgery + HIPEC) [26]. The 5-year overall survival was reported to be up to 67% using the HIPEC method [27]. This procedure was studied also in loco-regional disease. The prospective study shows incredible results with 100% survival at the 3,5 years follow-up, but with a small number of patients enrolled [28].

Conclusions

Goblet cell carcinoma is one of the rarest neoplasia of the appendix, with poor prognosis and many controversies regarding the proper approach of the treatment. Particular importance must be given to interdisciplinary collaboration and forming multidisciplinary teams. Future prospective studies and randomized trials are needed to better understand the complexity of this pathology and to create standardized guidelines.

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