

REVIEW ARTICLE

Goblet cell carcinoid of the appendix. Review of the literature a propos of a rare case of endometrial metastases

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Summary

Background: Carcinoid tumors are rare tumors most commonly found in the gastrointestinal tract. They represent the most common malignancies of the appendix. As a distinct entity from both adenocarcinomas and carcinoids, Goblet cell carcinoid (GCC) was initially described in the literature in 1969.

The GCC is almost exclusive to the appendix, but rarely can be found in rectum, ileum and colon. More than 50% of the patients at the time of diagnosis already have advanced-stage disease. The most common metastatic sites are the peritoneal surfaces of the pelvis and abdominal cavity, and ovaries in women. Surgery is the main form of treatment in patients with GCC.

Case presentation: A 49-year-old woman was treated at the Institute of Oncology and Radiology of Serbia with histopathological findings of GCC. In a 8-year period the patient was treated with initial appendectomy and three more operations because of locoregional disease progression. The last operation was performed in March 2016 because of endometrial metastases. Since then the patient is on regular follow up without disease progression.

Conclusion: GCC is a very rare entity. Multidisciplinary approach is necessary for adequate patient treatment.

Key words: Goblet cell carcinoid, surgery

History of GCC

As a distinct entity from both adenocarcinomas and carcinoids, GCC was initially described in the literature in 1969 [1], while the term GCC was first introduced by Subbuswamy et al. in 1974 [2]. Since then, in many different papers different names were proposed, such as adenocarcinoid, mucinous carcinoid, mucin-producing neuroendocrine tumor, crypt cell carcinoma, microglandular carcinoma, intermediate cell car-

cinoid, amphicrine neoplasia and composite tumor; but there still has not been any consensus about classification and nomenclature of GCC [1,3-6].

Today, the WHO recognizes only two names for this malignancy, "Goblet cell carcinoid" and "mucinous carcinoid", and classifies it into a group of epithelial appendiceal tumors, different than both carcinoids and adenocarcinoma [7,8].

Epidemiology

Carcinoid tumors are rare tumors most commonly found in the gastrointestinal tract (67.5%) and in the bronchopulmonary system (25.3%) [9]. They represent the most common malignancies of the appendix (85%). However, GCC which is a mixed tumor with partly neuroendocrine differentiation and partly goblet cell type morphology is confirmed in only 5% of appendiceal tumors [10-12]. Usually, it is accidentally found in 0.3-0.9% of all surgically-removed appendices [13,14]. The GCC is almost exclusive to the appendix, but rarely can be found in the rectum, ileum and colon [15,16]. Although some studies showed increased frequency among women compared to males [17,18], the largest population-based study from the National Cancer Institute's "Surveillance, Epidemiology and End-Results (SEER)" database, 1973-1998, found equal distribution among genders [19]. The majority of patients are in their fifties and sixties [11,18], but this condition has been diagnosed in patients aged 18 to 89 [19]. Furthermore, some cases have been described in children [20]. It is usually seen in Caucasians compared with other races [18,19].

Clinical presentation

Appendiceal carcinoids can be asymptomatic, but up to 60% of the patients present with acute appendicitis due to luminal obstruction when after the appendectomy GCC is incidentally diagnosed [18,21,22]. Some patients can experience recurrent episodes of abdominal pain due to partial obstruction of the appendiceal lumen by a tumor, lower abdominal palpable mass, intestinal obstruction or gastrointestinal bleeding with symptoms of anemia [17,23].

More than 50% of the patients at the time of diagnosis already have stage III or IV disease. The most common metastatic sites are the peritoneal surfaces of the pelvis and abdominal cavity, and ovaries in women (83%), all affected by spreading the tumor through serosa or invading the mesoappendix. Metastasis in ribs, vertebrae, lymph nodes and prostate are rare but have been reported [7,17,19,24,25]. Interestingly, most studies showed that disease presented in stage IV is found more often in female patients [18,26,27].

Diagnosis

The diagnosis of GCC is made by pathological

examination. Appendiceal carcinoids are usually divided into three histological patterns:

- A. Group A - the typical argentaffin-enterochromaffin (EC)-cell carcinoid.
- B. Group B - the nonargentaffin L-cell carcinoid.
- C. Group C - poorly differentiated GCC.

GCC is clearly distinguished from other forms of appendiceal carcinoids. It is biologically more aggressive and very often serosal and mesoappendiceal involvements are present [28,29].

There are still no standard markers pathognomonic for GCC, although standard investigations upon diagnosis include estimation of plasma chromogranin A concentration, which is positive in neuroendocrine tumors, but usually negative in GCC and 24-hour urinary levels of 5-hydroxyindolacetic acid [30,31]. CK20 is positive in 100% of GCC cells and CK7 in 70.5% [32]. Different studies showed that most cells in GCC will show positivity for argyrophil and negativity for argentaffin, and also some of the neuroendocrine markers can be positive including synaptophysin, somatostatin, serotonin, neuron specific enolase and pancreatic polypeptide [17].

Treatment

Surgery is the main kind of treatment in patients with GCC. It is still unclear if the simple appendectomy is sufficient in stage I disease, but it is known that right hemicolectomy is a method of choice in higher stages [17,18,24,33]. Prophylactic removal of the ovaries in women due to high risk of metastases to the ovaries is something that should be discussed with a patient, with regards to patient's age, menopausal status and planned pregnancies [17,30]. In case where peritoneal carcinomatosis is confirmed, the use of intraperitoneal hyperthermic chemotherapy (HIPEC) should be taken into consideration [27,34,35].

Patients with stage IV disease at the time of presentation usually undergo debulking surgery followed by chemotherapy based on 5-fluorouracil [36].

Follow up

After surgery, blood tests including CEA, CA-125, and CA-19-9 tumor markers, as well as radiological imaging are recommended as a part of a regular follow up. Standard practice includes ¹¹¹In-labelled octreotide scintigraphy for the diagnosis and staging of metastatic disease, computed

tomography (CT) scanning or magnetic resonance imaging (MRI) to rule out metastasis in lymph nodes, while use of PET-CT is still controversial [36].

Survival and prognosis

Apart from well-established prognostic factors, such as size and location of the tumor and whether or not the cancer has metastasized, there are some markers which might have prognostic value in GCC like mitotic activity, invasion and cell atypia [10]. Patients with GCC have a prognosis intermediate between carcinoid and adenocarcinoma of the appendix. The literature data about survival is very limited; some studies report mean overall survival of 47 months, while 5-year-survival is 76% [7,18,30].

Case presentation

The case presented herein is the first case of GCC reported at the Institute of Oncology and Radiology of Serbia, where we perform approximately 60-80 appendectomies per year.

In May 2008, a 49-year-old woman was admitted to our hospital with intense right lower abdominal pain that lasted for two days. She was afebrile, with nausea but without vomiting and diarrhea, and did not report any weight loss. On physical examination there was rebound tenderness in the right iliac fossa. All blood tests were normal, except a white cell count of $11 \times 10^9/L$ and C-reactive protein of 140 mg/L. Family history for inflammatory bowel disease was negative.

After the initial assessment, she underwent appendectomy with complete resection of left ovary and partial resection of the right ovary. Histopathology revealed low grade Goblet cell carcinoid and mucinous adenocarcinoma.

Due to the pathological findings, additional surgery was performed one month later: right hemicolectomy with dissection of paraaortic lymph nodes and right adnexectomy. At the same act, hyperthermic intraperitoneal chemotherapy (HIPEC) with mitomycin was carried out. The patient was discharged and put on regular follow up and was feeling fine, without any signs of relapse.

In April and June 2011 she underwent two smaller surgical interventions for removal of benign tumors at the anterior abdominal wall and on the back, when histopathology confirmed desmoid fibromatosis and epidermoid cyst, respectively.

In April 2013, due to signs of bowel obstruction, the patient underwent an urgent resection of the terminal small bowel, alongside with resection of the transverse colon. Histopathology showed intestinal adhesions, granuloma corporis, alienitextus fibroadiposis, sinus histiocytosis and hyperplasia follicularis.

In early 2016, the patient noticed blood-stained vaginal discharge, so curettage of the uterus was performed and histopathological study of the material obtained showed poorly differentiated adenocarcinoma with intracellular and extracellular mucin production and tumor infiltrates of the deep layers of endometrium. Additional special stainings were PAS+, AB-/+, and the immunohistochemistry results were CK20+/-, CA125+/-, estrogen-, progesterone-, CDX2+, MUC5+, CA19.9+, EMA+, chromogranin+/-, synaptophysin-, NSE+, CEA+, E-cadherin+/-, Ki67 15%. Morphologically and by immunohistochemistry the diagnosis of mixed tumor was made, with dominantly mucinous adenocarcinoma type in combination with multiple foci of neuroendocrine tumor / Goblet cell carcinoid.

A subsequently performed multidetector computed tomography of the abdomen and pelvis detected enlarged uterus with irregular cavity and unequal wall thickening, with numerous calcifications, small fibroids and cystic-shape secondary deposits on its surface measuring 34x20 mm in size. Fluid between small bowel and uterus was also seen. Chest X-ray did not reveal any abnormalities, as well as blood analysis. Soon after all the imaging and blood/serum examinations were completed, hysterectomy with left salpingectomy were performed in March 2016. Histopathology confirmed that the cervix, uterine isthmus, body of the uterus, tubes and fibroadipose tissue were all infiltrated by GCC. Tumor immune phenotype was CDX-2+, EMA+, CK20+, CK7-, CD56 focal, Chromogranin +/-, Synaptophysin-, CEA+.

Since then, the patient has been on regular follow up and with no further signs of disease recurrence. Last check up was in January 2018 with no evidence of disease.

Discussion

GCC is usually diagnosed after simple appendectomy; therefore a histopathological report is necessary in all of the patients. A patient with diagnosed GCC after appendectomy should be instructed to an institution where all additional diagnostic procedures could be performed together

with evaluation of pathological report and radicalization of surgery.

Surgical treatment is the main treatment modality. The extent of surgical procedure could range from simple appendectomy to multivisceral resections combined with HIPEC, so adequate surgical skills and doctrine are required [37].

In GCC with ovarian metastasis, in addition to ovariectomy, HIPEC certainly has its place due to minimizing further intraperitoneal spreading [38,39].

Conclusion

GCC is a rare entity. A multidisciplinary approach is necessary and pathological report and adequate surgery are the keys for either cure or achievement of longer overall survival.

Conflict of interests

The authors declare no conflict of interests.

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