Goblet-cell carcinoid (WHO GEP/NET tumors – group IV) of the appendix

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Goblet-cell carcinoid (GCC) is a rare and slow-growing tumour commonly affecting the appendix. It shares pathological and clinical features of both adenocarcinoma and neuroendocrine tumour (NET), being significantly more malignant than onther types of neuroendocrine tumours but less than adenocarcinoma. Because of the relatively long, non-symptomatic growth of GCC it is usually diagnosed in its metastatic form. According to the 2010 WHO classification of GEP/NET tumours GCC belongs to group 4 – mixed adenoneuroendocrine carcinoma (MANEC).

In the paper we present the case of a 45-year old woman. This allows us to review the diagnosis, pathology and management of GCC. The patient had been admitted to the Institute of Oncology in Warsaw with a 6-month history of a palpable tumour in the left illiac fossa. She underwent ovariectomy and simple appendectomy. The pathology report confirmed GCC of the appendix infiltrating the right colon and metastatising to the ovaries, uterus and omentum. The patient died after 46 months of treatment. Basing upon the case history we postulate the necessity for an individual approach in the diagnosis and treatment of GCC.

Key words: Goblet cell carcinoid, appendix, Krukenberg tumor.

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Introduction

The term "Goblet cell carcinoma" (GCC) was introduced in 1974 in order to characterise tumours of the appendix other than carcinoids and adenocarcinomas [1]. It is an incredibly rare malignancy (up to date approx. 600 cases have been reported worldwide) reported to bear the clinical features of both adenocarcinoma and neuroendocrine tumour (NET) [2–4]. It consists of cells differentiated into endocrine and egzocrine [2, 3, 5, 6]. According to data GCC has a higher potential of malignancy than a typical endocrine tumour and lower than adenocarcinoma [7, 8]. Goblet cell carcinoma is usually detected equally in both sexes in the 5th decade of life. In some 90% of cases the primary site is located in the appendix [2, 9] and symptoms may imitate those of appendicitis. Clinical symptoms appear late and therefore the malignancy is usually diagnosed at the stage of dissemination – as in the presented case. Its morphological and clinical dissimilarity calls for the necessity to individualise both the diagnostic process and treatment.

Case report

A 45-year old woman had been admitted to the Department of Gynecology of the Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology in order to diagnose and treat a tumour located near the left ovary. The first symptoms included irregular menorrhagia-like bleeding, which she had been observing for the previous five months. During that period the patient had been administered hormonal therapy (Marvelon) with good results. Twenty years earlier she had undergone electroconization of the uterine cervix. Further history was insubstantial, while family history involved the death of her father due to hepatic cancer.

Results of routine investigations (mammography, chest X-ray, laboratory blood analyses) were normal. Ultrasound examination of the abdomen revealed the present of a homgeno-cystic tumour (5.5 × 4.8 cm) (Fig. 1) in the lower left abdomen. No other abnormalities were observed. The patient was referred for laparotomy. Intraoperatively a tumour of the left ovary (4 × 5 × 6 cm) was removed. During intraoperative pathological examination this was diagnosed as a metastasis of adenocarcinoma. Except for a thickening of the wall of the appendix no other intraabdominal pathology was observed. In view of this appendectomy was performed and a part of the

greater omentum was removed for further examination. Pathological examination provided the diagnosis of goblet cell carcionoid in its disseminated stage, infiltrating the surgical margin, a metastases to the ovary and the greater omentum. The diagnosis was confirmed immunohistochemically (chromogranin and mucicarmine – Fig. 2–4).

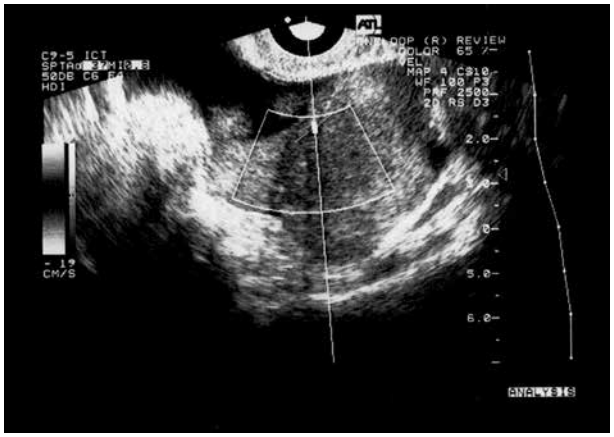

Fig. 1. Ultrasound examination of the tumour of the left ovary

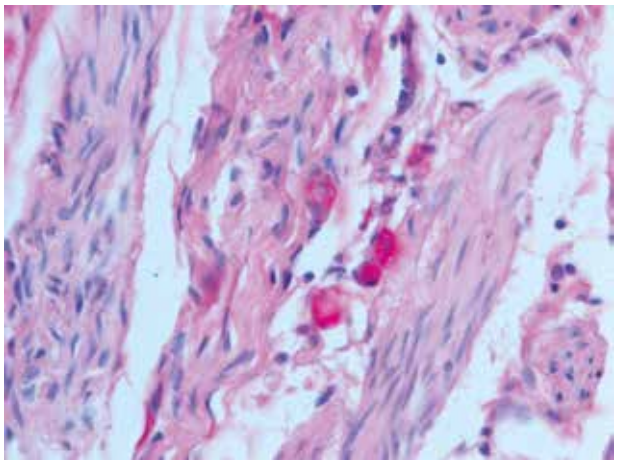

Fig. 2. Goblet cell carcinoid of the appendix, staining for mucykamin

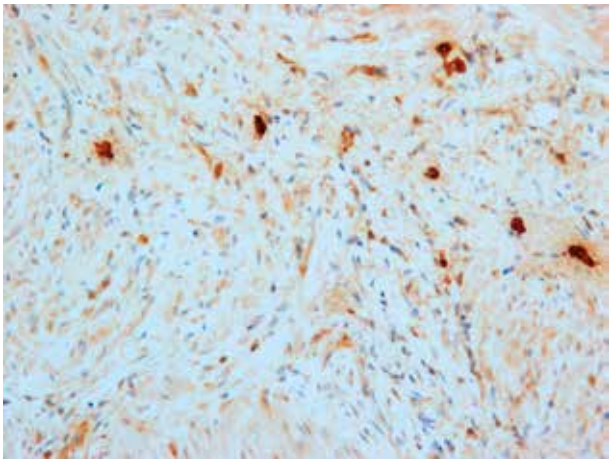

Fig. 3. Goblet cell carcinoid of the appendix, staining for chromogranin

Due to the presence of cancerous infiltration within the surgical margin after appendectomy and a high probability (approx. 50%) of the presence of metastases in the right ovary the patient was qualified to undergo right hemicolectomy with excirpation of the uterus, right ovariectomy and omentectomy. This procedure was performed 2 months later at the Upper Digestive Tract Cancers and was macroscopically radical. Postoperative pathological examination revealed GCC infiltrations of the cecum, the body of the uterus, the right ovary and the omentum. The surgical margins of the colon were unaffected and no metastases were found within the dissected lymph nodes. The patient was discharged from hospital 15 days after surgery and due to the lack of standards regarding adjuvant treatment she remained in follow-up.

After 8 months she reported occasional pain in the lower abdomen, followed by nausea and flatulence. Clininical investigations revealed a non-resectable homogenous mass in the lower abdomen 3.5 × 3 × 9 cm in size infiltrating the iliac vessels (Fig. 5). Gynecological examination revealed infiltration of the vagina and GCC was confirmed in tissue specimens.

Due to the lack of indications (no haemorrhage) radiotherapists refrained from palliative radiotherapy of the apex of the vagina, suggesting that the symptoms were caused by inhibited bowel movement. The patient was qualified for palliative chemotherapy acc. to the Cisplatin, Adriamycin, 5-Fluorouracil protocol. After 9 months of treatment the diseased progressed further. Control abdominal ultrasound revealed right-sided hydronephrosis due to infiltartion of the right urether. In order to control the symptoms right-sided nephrostomy was performed and chemotherapy was maintained. Three years after the initial surgery the patient developed symptoms of subileus. She underwent surgical treatment at Department of Upper Digestive Tract Cancers due to massive intraabdominal dissemination no resective procedure was performed and the patient was referred for palliative treatment. She eventually died 46 months after the diagnosis (which was made in the phase of malignant dissemination).

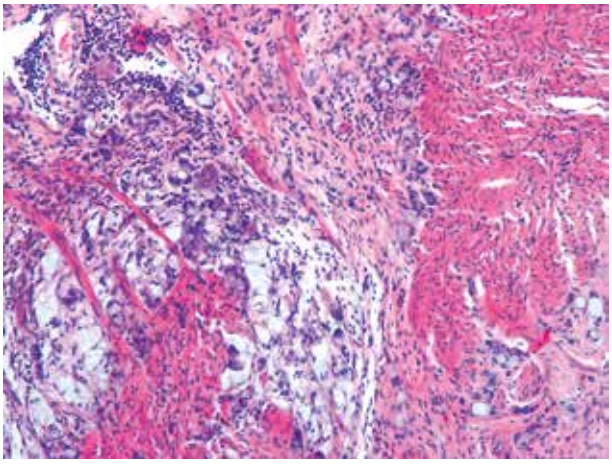

Fig. 4. Goblet cell carcinoid of the appendix – *Muscularis mucosae* infiltration

Discussion

Neuroendocrine tumours

Aqccording to the WHO goblet-cell carcinoma is a neuroendocrine tumour of the alimentary tract belonging to the Gastro-Entero-Pancreatic NeuroEndocrine Tumours – GEP/NET) [5]. These tumours account for some 65% of all neuroendocrine tumours and some 2% of tumours of the alimentary tract [11]. The term "carcinoid" has been introduced in 1907 by Oberndorfer for tumours which resembled adenoid carcinoma but had a less malignant course. The WHO classification of GEP/NET tumours developed by the WHO in the year 2000 and modified in 2010 allows for tumour localisation, the lack or presence of clinical symptoms, pathological features, histological and immunochemical characteristics and a unified system which divides these tumours into four groups:

- Group 1: G1 neuroendocrine tumours (NET G1):
  – tumours with low proliferative activity; mitotic index < 2/10 HPF and Ki-67 < 3%.
- Group 2: G2 neuroendocrine tumours (NET G2):
  – tumours with medial proliferative activity: mitotic index = 2–20/10 HPF and Ki-67 3–20%.
- Group 3: G3 low-differentiated neuroendocrine carcinoma (large cell or small cell type NEC):
  – tumours with high proliferative activity: mitotic index > 20/10HPF and Ki-67 > 20%.
- Group 4: mixed adenoneuroendocrine carcinoma, (MANEC) which we had diagnosed in the presented case.

Due to their clinical and morphologic characteristics GEP/NET are nonhomogenous. They may be divided into nonexcreting (silent) and excreting. The latter are symptomatic due local increases in hormone activity. GEP/NET originate from the diffuse endocrine system (DES) and are dispersed throughout the body, including the alimentary tract. They show expression of neuroendocrine markers, such as synaptophysin and chromogranin A (CgA) and, depending on the type of specialised cell, different peptide hormons and biogenic amines. The release of these substances into the systemic blood stream causes unique syndromes associated with the type of endocrine tumour [15]. GEP/NET are usually highly differentiated (88%), develop slowly and have little or no hormonal activity and therefore are recognised at a late stage. Many NETs bear somatostatin receptors and therefore they may be diagnosed using receptor scintigraphy and treated with somatostatin analogues or with receptor-directed radiotherapy or chemotherapy [16–18]. Beside imaging methods (USG, CT, MRI) other diagnostic techniques include markers, such as neurospecific enolase, synaptophysin and CgA (which is especially helpful in the diagnosis of micrometastases and tumours with an ambivalent phenotype) [19, 20].

Goblet cell carcinoid

Goblet cell carcinoid is an extremely rare malignancy with only some 600 hundred cases reported throughout the world. Its cells present both egzo- and endogenic activity [2–4]. According to some authors CGG originates from a pluripotential stem cell, which would explain its heterogenous structure [2, 21]. Here the significant role of the p53 gene has been suggested [21–23]. Some papers prove, that a certain part in the development of this tumours may involve the deletion of 11q, 16q or 18q chromosomes [24].

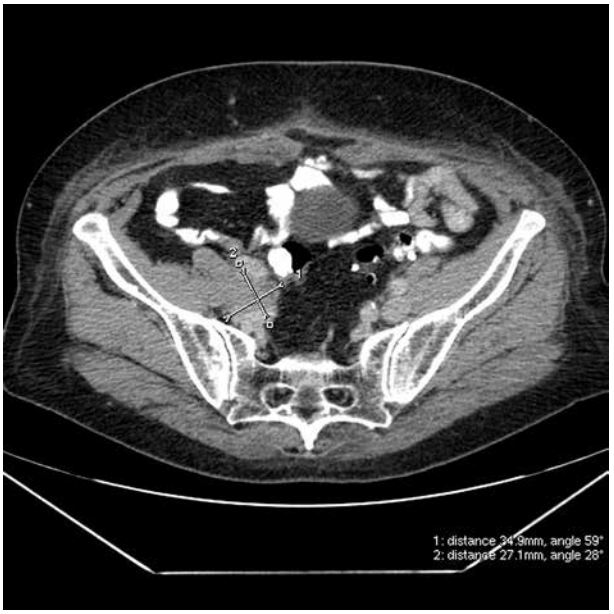

Fig. 5. Pelvic recurrence of GCC

A distinct morphological feature of GCC and other GEP/NET is their intramural spread beneath the mucosa without necrosis and tissue destruction, while significant differences include the lack of mucosa involvement and larger size, as compared to classic GEP/NET. Usually GCC is located at the apex of the eppendix and infiltrates its wall circularly, without developing a solid tumour mass [2, 5, 7, 14]. Such a growth pattern provides a significant diagnostic issue, because the spread of the tumour remains asymptomatic for a long time [2, 14].

Goblet cell carcinoid is usually recognised between the fifth and the sixth decade of life and shows no predominance in either sex, whilst classic neuroendocrine tumours are usually found in women between the age of 30 and 40 [2, 5, 6, 25]. Goblet cell carcinoid metastasizes in 15–30% of patients, while carcinoid only in some 2–5%. Goblet cell carcinoid spreads mainly along lymphatic vessels, veins and intraabdominaly. Goblet cell carcinoid metastases are usually localized in the peritoneum and, in women, in the ovaries (as has been illustrated in the presented case). They may also appear in the ribs, the spinal, lymph nodes and the liver. Very often on initial diagnosis the malignancy has already afected sites beyond the appendix, infiltrating its mesenteriumin 20% of cases and local lymph nodes in 8% of cases [2, 3, 5, 7, 14, 25]. Goblet cell carcinoid is rarely diagnosed preoperatively – it is usually an accidental finding in patients undergoing laparotomy due to symptoms of acute appendicitis (22.5%). The symptoms include non-specific abdominal pain (5.15%), palpable tumour mass within the lower right abdomen (3.09%), gastrointestinal bleeding and Krukenberg tumour within the ovaries in women [2, 3, 5, 7, 13, 25].

The diagnosis of GCC is based entirely on postoperative pathology findings, therefore intraoperative assessment of features possible associated with GCC are highly important. These including a distinct thickening of the wall of the appendix and a retention of mucus within it. When in doubt representative specimens must be harvested for pathological examination. Intraoperative pathologic assessment of frozen tissue may aid the diagnosis of malignancy, but in order to provide a final diagnosis immunohistochemical staining must be performed. Abdominal X-ray may reveal expanded small intestine in case of mechanical ileus, while CT examination may show the thickened, cancerous wall of the appedix. Indium scintigraphy is widely used to localize matestases. Blood analysis may show a slight increase in the level of inflammatory markers, which are usualyy a symptom of the acute phase of appendicitis [2, 3, 7, 14, 25]. In case of a typical localisation of GCC standard therapy includes simple appendectomy which may be extended by right hemicolectomy in the following cases:

- the presence of differentiated cells,
- the diagnosis of GCC,
- features of angio- or neuroinvasion,
- high mitotic activity,
- positive surgical margin,
- infiltration of the base of the appendix with infiltration of the cecal wall or the appendicital mesenterium (as in the case which we report),
- nodal metastases,
- the presence of a tumour; arger than 1 cm acc. to the guidelines of the Polish Neuroendocrine Tumour Network.

In women with Krukenberg tumours when the initial focus of the tumour cannot be identified the recommended procedure is appendectomy with bilateral ovariectomy and, in some cases, total hysterectomy [2, 5, 7, 25]. If there is at least a chance of total or subtotal resection of the tumour mass cytoreductive surgery should be performed and intraperitoneal chemotherapy should be considered. If hepatic metastases are present then, apart from resection, additional treatment, such as embolization or chemoembolization of hepatic arteries may be beneficial [26]. Following surgery in unclear cases systemic chemotherapy may be a possible approach because intraperitoneal dissemination may sometimes be followed by nodular spread. In case of the presence of metastases the efficacy of chemotherapy has not been proven, but some authors report very good results achieved (including total remission) with this method, specifically using 5-Fu and leucovorine [2, 6, 27]. The treatment of Krukenberg tumours originating from GCC should always include combined treatment (surgery and chemotherapy) [2, 7].

Effective palliative treatment, especially aimed at alleviating or stopping symptoms of carcinoid syndrome, may be based on the administration of somatostatin analogues. Octreotid alleviates symptoms and limits the number of episoded in 50–80% of patients, but it is rarely associated with tumour regression and provides stabilisation of the disease ion some 40-80% of patients. Similar results may be achieved with isotope techniques – 131I-MIBG, 125I-NIBG or indium-marked somatostatin analogues [28]. In the case of our patient the symptoms of disease progression were dominanted by the effects of intraperitoneal dissemination (subileus, urether infiltration) and therefore there were no indications for somatostatin administration.

Goblet cell carcinoid-associated survival remains between survivals reported for adenocarcinoma and for neuroendocrine tumours (allowing for patient age and stage of the malignant process – from 5 months to 20 years). When GCC coexists with other malignancies, such as bladder cancer, prostate cancer, ovarian cancer, gastric cancer and breast cancer the prognosis is significantly worse, as is the case in patients with angioinvasion [2, 7, 25]. In women in whom GCC has metastatised to the ovaries mean survival is 7–9 months. In the case of our patient with primarily disseminated GCC of the appendix the 8 month survival from surgical radicalisation to disease progression and an overall survival of 46 months from diagnosis appears to support the need for an individualised approach in GCC patients.

The authors declare no conflict of interest.

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