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Case report

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Adenocarcinoma of the appendix — case study

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The following study presents the case of a 58-year-old woman who was diagnosed, during the diagnosis of an ovarian tumor, with mucous metastatic adenocarcinoma of the appendix. Due to the severity of the disease and the low degree of differentiation of the cancer, the treatment of the patient required a continuous and intensive systemic treatment lasting three years. A significant role in the course of the disease was also played by surgical interventions, since the patient underwent 4 reoperations due to local recurrence. The history of the disease is an example of the problems in the therapy and diagnosis of atypical tumors resulting from non-specific symptoms and different evolution of the disease.

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Key words: adenocarcinoma of the appendix, palliative surgery, chemotherapy, molecular therapy, regorafenib, quality of life

Introduction

Colorectal cancer is the most common malignant tumor in Europe. It is almost always adenocarcinoma and is located in most cases in the rectum and sigmoid colon [1]. In contrast, primary adenocarcinoma of the appendix is a very rare tumor, representing less than 0.5% of all gastrointestinal cancers [2]. In literature, only about 250 cases have been described [3, 4]. The illnesses are most often diagnosed in patients between 40 and 80 years of age [5].

There are two types of adenocarcinoma of the appendix: mucinous adenocarcinoma and low-grade appendiceal mucinous neoplasm (LAMN) [1]. LAMN is characterised by the high degree of maturity of the cells, it grows slowly and spreads exclusively within the peritoneal cavity, creating an image of low-grade pseudomyxoma peritonei. On the other hand, mucinous adenocarcinoma invades the surrounding tissues and spreads through vessels [1, 2]. The most common location of metastases are the lymph nodes, peritoneal cavity and ovaries [6]. Ovarian metastases are diagnosed in 10% of patients and in the majority (70–80%) of them, they have spread to both ovaries [7, 8].

Lack of specific symptoms of the primary cancer of the appendix makes the initial preoperative diagnosis usually acute appendicitis, more rarely a gastrointestinal obstruction or ovarian tumor [2, 5]. A proper diagnosis of the cancer is only achieved on the basis of a histological examination of the removed appendix. The prognosis of patients with primary cancer of the appendix is very serious. 32% of patients have a chance of 5-year survival [6, 9].

Case report

Since December 2010, a 54-year-old patient was being diagnosed due to episodic pains in the mesogastrium, which spontaneously receded. In the district hospital, on the basis of a gynecological consultation, laboratory and image tests (USG and CT of the abdomen, which revealed no pathological changes), acute appendicitis and gynecological causes of the pain were excluded. A PET-CT examination was carried out, which noted an increased uptake of a marker in the right ovary plan.

In March 2011, the patient was qualified for surgery, with an initial diagnosis of a right ovarian tumor. In a histopathological examination, adenocarcinoma metastases were discovered. The range of operations was extended by performing hysterectomies and a right-sided hemicolectomy with appendages. Based on the histopathological

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examination of the procedute, mucinous adenocarcinoma of the appendix was diagnosed with a low degree of differentiation (*Adenocarcinoma mucinosum appendicis vermiformis* G3) infiltrating the greater omentum, the right ovary and a lymph node.

In April 2011, the patient was in good general condition (ECOG 0) and was admitted to the Department of Chemotherapy in the Clinic of Oncology in Poznan. In the physical examination, the patient complained about a slight abdominal pain in the right iliac fossa without the need for analgesics. The physical examination showed a scar after laparotomy without any evidence of recurrence and apart from that there were no abnormalities. The biochemical and morphotic parameters of blood were normal, with elevated tumor markers (CEA 5.1 ng/mL).

Due to the clinical advancement of pT4pN1M1, the patient was qualified for first-line palliative chemoimmunotherapy, following the FOLFIRI scheme with bevacizumab at a dose of 10 mg/kg. Anticipating long-term therapy for improved comfort of the patient, a vascular port was applied, providing permanent access to the veins. Up until October 2011, the patient received 12 courses every 14 days with good tolerance of the treatment being observed. The imaging control examinations (a CT of the chest, abdomen and pelvis) did not report any lesions suggesting a cancerous process and decreased levels of CEA (3.4 ng/ml) were noted.

In December 2011, the patient complained about a severe abdominal pain around the right iliac fossa radiating to the right groin. Because of the clinical features of the disease progression, invisible in the imaging examinations (the MRI of the pelvis showed no local recurrence), an exploratory laparotomy was decided. In January 2012, a local recurrence resection was carried out (removal of a distal ureteral section with an implantation of a proximal ureter section to the bladder, a resection of the right internal iliac artery and a segmental resection of the ileum with the Valtrac anastomosis). A PET-CT examination performed after the surgery showed no metabolic traits of recurrence or metastasis. From February to July 2012, the patient received 12 courses of palliative, post-surgery chemotherapy following the FOLFOX-4 scheme. The treatment was complicated by 3rd degree neutropenia (acc. CTCAE), requiring the use of G-CSF (filgrastim) in the secondary prevention.

In a PET-CT examination from August 2012 that evaluated the foregoing therapy, an outbreak of local recurrence was revealed in the pelvis. The CEA level at the time was 12.3 ng/mL. After an interdisciplinary consultation, the patient was qualified for a second reoperation during which a segmental resection of the sigmoid was done with an end-to-end anastomosis, and a segmental resection of the ileum with a side-to-side anastomosis.

In October 2012, a PET-CT, in which recurrences in the area of the post-seam ileum and an internal-right hip lymph node metastasis were detected, showed that surgery had proved ineffective. The possibility of molecularly targeted therapy was considered, but due to a (PCR test detected) mutation in exon 1 of the KRAS gene, the patient would not benefit from EGFR antagonists treatment (cetyksymab, pamitumumab). From November 2012 with third-line palliative chemotherapy, the patient received 4 courses of capecitabine (1250 mg/m^2, 2 times a day for 14 days) every 21 days without clinical and marker improvement.

Due to the exhaustion of available methods of treatment, a motion was filed to the National Health Fund to import a medicinal product — regorafenib from abroad. The drug in phase-III clinical studies showed better performance in terms of OS compared to placebo in patients who suffered the progression of the disease after applying all standard therapies. Despite clinical indications and the legitimacy of the application, there was no consent from the National Health Fund for the above-mentioned treatment with the product.

In March 2013, the patient was admitted to the Department of Chemotherapy in order to assess the current therapy of capecitabine. On admission, the patient reported the worsening of pain in the right hip radiating to the right groin, no stool for 5 days and constant fatigue. The overall health status of the patient was quite good (ECOG 1). A physical examination showed abnormalities: a palpable tumor in the right iliac fossa of about 5 cm in diameter. In laboratory tests, only small leukocytosis and 1st degree anemia (CTCAE) were found.

After surgical consultation, intestinal obstruction was excluded, and, as a result of intensive symptomatic and analgesia treatment, an overall improvement of the patient's state was achieved. An MRI of the pelvis revealed a pathological mass sized $70 \times 54 \times 85$ mm around the right iliac fossa, infiltrating the pelvic muscles, iliac vessels, and the bladder wall.

Due to significant clinical and marker progression (CEA 426 ng/mL), the patient was proposed treatment under clinical testing with regorafenib. She approved it and started an oral regorafenib treatment in the open clinical testing of phase III b (BAY 73-4506/15967) with a dose of 160 mg per day (1 × 4 tab. of 40 mg each for 21 days) every 28 days. After the first treatment cycle, the concentration of CEA decreased (319 ng/mL) and the improvement of the general condition of the patient was reached, including less pain and the normalisation of bowel habits. There were also no side effects of the treatment. On the basis of the MRI, the first evaluation of the efficacy of the treatment after 3 cycles demonstrated regression of the lesion size (45 mm in diameter, without evidence of infiltration of the bladder) and the decrease in the concentration of CEA to 286 ng/mL. Due to improved tolerance, partial radiological remission and decrease in tumor markers, it was decided to

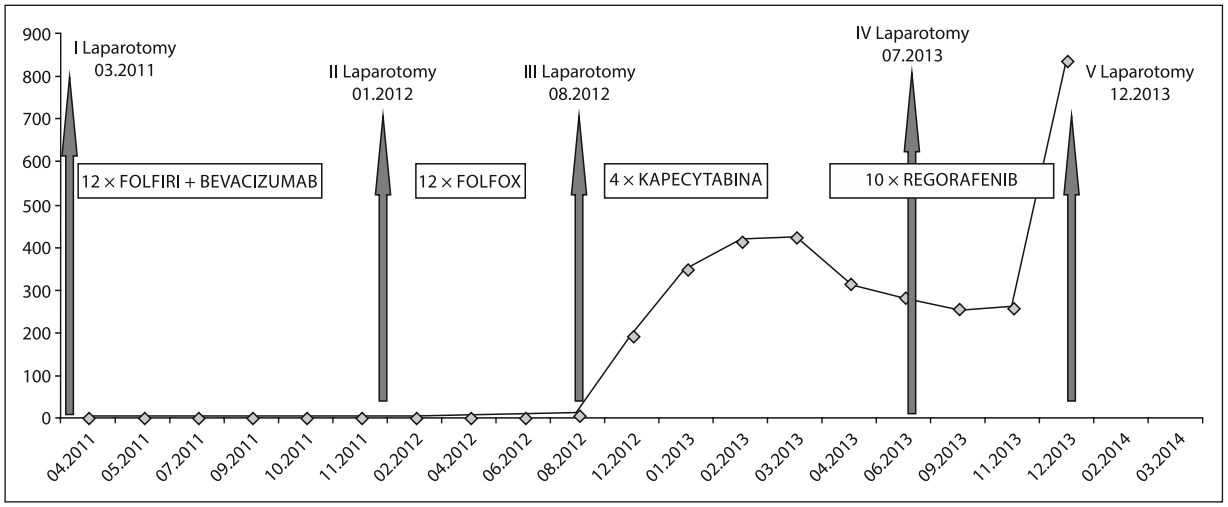

Figure. 1 CEA concentrations during the therapy [ng/mL]

continue the regorafenib therapy. In the 4-cycle due to 3rd degree anemia (according to CTCAE) and a lower urinary tract infection, the patient required a transfusion of 2 units of PRBC and antibiotic therapy.

Due to recurring symptoms of the urinary tract infection and the presence of fecal matter in general urine analysis, in July 2013 a PET-CT examination was performed, which confirmed the presence of a intestinovesicular fistula. The patient was qualified for surgery. A bypass anastomosis was performed within the jejunum and ileum.

After the 6th series of regorafenib immunotherapy, the patient began to lose weight steadily with good appetite, reaching the lowest weight during cycle 9 (3 deg. according to CTCAE), which was the reason for the reduction of the dose to 80 mg per day. Cycle 7 and 10 have been complicated by 3rd degree anemia (acc. CTCAE), requiring a transfusion of PRBC. A radiographic CT scan in November 2013 showed an increase in the size of the lesion in the right iliac fossa (81 × 64 mm), intestinovesicular fistula characteristics and a pressure onto the right internal obturator muscle.

In December 2013, the patient underwent another emergency reoperation due to an intestinal-vaginal fistula. A loop ileostomy was performed, achieving an improvement in the clinical condition of the patient.

Given the radiological and marker progression of the disease, as well as the weakening condition of the patient, emaciated by the intensive, multimedicine treatment which had lasted three years without interruption, it was decided to end the regorafenib immunotherapy after 10 cycles. For three months, the patient was under the care of a hospice, where, despite the best supportive care, the pain in her right lower abdomen intensified. There was also a partial paralysis of the right lower limb. In March 2014, 12 months after the start of regorafenib therapy, the patient died at home.

Summary

From the moment of the diagnosis of advanced adenocarcinoma of the appendix to the death of the patient, it was over 36 months; from the start of the regorafenib therapy, it was 12 months. Analysing the described case and the results of examination phase III CORRECT (in the group with regorafenib median OS — 6.4 months, and in the placebo group — 5.0 months (HR = 0.77, p = 0.0052), it can be certainly concluded that the patient received a clinical benefit from this treatment.

In clinical practice, this means that a monotherapy with this multikinase inhibitor can stabilise the disease for some time and consequently prolong the life of patients, who

Table I. Efficacy results obtained in the test CORRECT

Efficacy Parameter	Hazard ratio* (95% CI)	Value p (unilateral)	Median (95% CI) Stivarga plus BSC (n = 505)	Median (95% CI) Placebo plus BSC (n = 255)
Overall survival	0.774 (0.636, 0.942)	0.005178	6.4 months (5.9, 7.3)	5.0 months (4.4, 5.8)
Progression-free survival **	0.494 (0.419, 0.582)	< 0.000001	1.9 months (1.9, 2.1)	1.7 months (1.7, 1.7)

§Best Supportive Care
*The hazard ratio < 1 favors the Stivarga medicinal product
**Based on the investigator's assessment of the tumor response

are in good general condition and do not have any other treatment options. It is also worth noting that the patient tolerated the treatment well, and apart from losing weight, did not present any typical regorafenib side effects, such as hand-foot syndrome and hypertension. This would indicate that the side effects of the treatment may be due to the long prior chemotherapy and the progress of the disease.

Abbreviations:

CEA — carcinoembryonic antigen
CT— computed tomography
CTCAE — the evaluation scale of the toxicity of treatment (Common Terminology Criteria for Adverse Events)
ECOG — the scale of performance by the Eastern Cooperative Oncology Group
FOLFIRI — fluorouracil 400 mg/m^2 in a bolus and 600 mg/m^2 in a 48-hour infusion, calcium folinate 200 mg/m^2 in a 2-hour infusion, irinotecan 150 mg/m^2
FOLFOX-4 — oxaliplatin 85 mg/m^2 in a 2-hour infusion, fluorouracil 400 mg/m^2 in a bolus and 600 mg/m^2 in a 48-hour infusion, calcium folinate 200 mg/m^2 in a 2-hour infusion
G-CSF — granulocyte colony stimulating factor
OS — overall survival time
PFS — progression-free survival time
PRBC — the concentration of red blood cells
QoL — quality of life

Conflict of interest: none declared

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