CASE REPORT

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Hypercalcemic type of small cell carcinoma of the ovary

Hiperkalcemični tip sitnoćelijskog karcinoma jajnika

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Abstract

Introduction. Extrapulmonary small cell carcinoma is a rare, prognostically bad tumor category. Primary, it can be localized in every organ, even in the ovary, where, due to its clinical specificities, it represents a challenge in diagnosis, as well as in therapy. Small cell ovarian carcinoma (SCOC) is biologically very aggressive malignant tumor of unknown histogenesis. We presented a rare case of SCOC with hypercalcemia of aggressive course and fatal outcome in a postmenopausal woman at International Federation of Gynecology and Obstetrics (FIGO) Ia stage. **Case report.** A 60-year-old woman, Caucasian, came to the doctor because of discomfort in the lower abdomen and pain of greater intensity in last few days. Ultrasound examination and CT scan of the abdomen confirmed the presence of large adnexal masses of cystic-solid appearance with the largest diameter of 13 cm, regular structure of the other gynecological organs, without verifying the existence of metastatic deposits. All the results of laboratory analysis gave normal values, except for calcium, which was elevated. Explorative laparotomy with complete hysterectomy, bilateral salpingo-oophorectomy, dissection of lymph nodes and omentectomy were conducted. Based on pathohistological analysis of the operative material, SCOC at FIGO Ia stage was diagnosed. No complications were observed in a postsurgery period and after 10 days the patient was discharged in a good condition and with normal calcemia. The treatment was continued with concurrent radiotherapy and chemotherapy. However, in spite of overall treatment, the disease progressed, and the patient died of disseminated metastatic disease, 26 months after the diagnosis. **Conclusion.** Small cell carcinoma localized in the ovary is generally a tumor category with bad prognosis depending on the stage of the disease.

Key words:
carcinoma, small cell; ovarian neoplasms; diagnosis; immunohistochemistry; neoplasm metastasis; treatment outcome.

Apstrakt

Uvod. Ekstrapulmonalni sitnoćelijski karcinom je retka, prognostički loša kategorija tumora. Primarno, može da se lokalizuje u skoro svim organima, pa i u jajniku, gde zbog svojih kliničkih specifičnosti, često predstavlja pravi dijagnostički i terapijski izazov. Sitnoćelijski karcinom jajnika (*small cell ovarian carcinoma* – SCOC) biološki je vrlo agresivan maligni tumor nepoznate histogeneze. U radu je prikazana bolesnica u post-menopauzi sa sitnoćelijskim karcinomom jajnika i hiperkalcemijom, agresivnog toka i fatalnog ishoda, u *International Federation of Gynecology and Obstetrics* – FIGO Ia stadijumu. **Prikaz bolesnika.** Žena stara 60 godina, javila se zbog tegoba u donjem abdomenu praćenih bolom jakog intenziteta. Ultrazvučnim pregledom i kompjuterizovanom tomografijom abdomena ustanovljeno je prisustvo velike adneksalne mase cističnog izgleda sa najvećim promerom od 13 cm, sa urednom strukturom drugih ginekoloških organa i bez prisustva metastatskih depozita. Svi rezultati laboratorijske analize bili su u granicama normalnih vrednosti izuzev povišenih nivoa kalcijuma u serumu. Izvršena je eksplorativna laparotomija sa kompletnom histerektomijom, bileteralnom salpingooforektomijom, disekcijom limfnih čvorova i omentektomijom. Na osnovu patohistološke analize operatvnog materijala postavljena je dijagnoza SCOC stadijuma Ia. U postoperativnom periodu nije bilo komplikacija i bolesnica je otpuštena deset dana posle operacije u dobrom stanju i normalizovanom kalcemijom. Lečenje je nastavljeno istovremenom radio- i hemioterapijom. Međutim, bez obzira na preduzete mere lečenja, bolest je progradirala i bolesnica je umrla zbog diseminovane metastatske bolesti 26 meseci posle postavljanja dijagnoze. **Zaključak.** Sitnoćelijski karcinom lokalizovan u jajniku najčešće je kategorija tumora sa lošom prognozom u zavisnosti od faze bolesti.

Ključne reči:
karcinom malih ćelija; jajnik, neoplazme; dijagnoza; imunohistohemija; neoplazme, metastaze; lečenje, ishod.

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Introduction

Extrapulmonary small cell carcinoma is rare, prognostically bad tumor category [1–3]. Primary, it can be present in almost every organ and very often it represents a real challenge in diagnosis and therapy. Small cell carcinoma localized in the ovary (SCOC) is very rare tumor of aggressive course with relatively fast and fatal outcome.

The first description of SCOC dates back to 1975, but seven years later, while describing some other cases Cannon et al. [4], and Dickersin et al. [5] defined SCOC as separate tumor category. World Health Organization (WHO) classification from 2003, puts SCOC into the group of different ovary tumors [6]. Works of Young et al. [7] and multicentric study of Harrison et al. [8] (with the precise description of diagnosis, treatment and course of the disease in 17 patients from Australia, Canada and Europe for the period of time between 1989 to 2004) give us the greatest amount of information about SCOC.

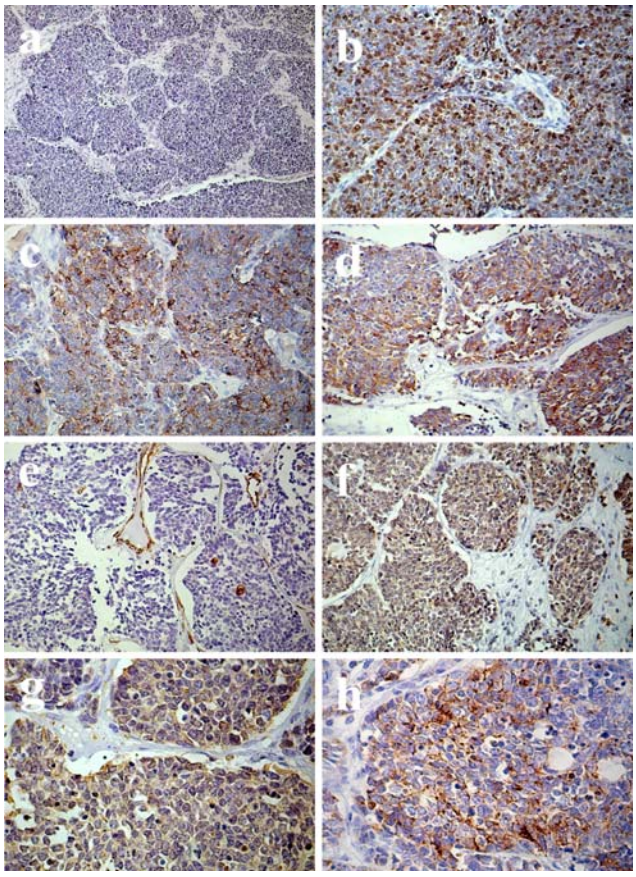

Fig. 1 – Histological features of ovarian small cell carcinoma: a) tumor islands formed by small cells with scant cytoplasm and hyperchromatic round to oval nuclei (HE, ×100); b) proliferative activity is very high; about 90% of nuclei show immunoreactivity for Ki-67 (×200); tumor cells are positive to: c) low molecular weight cytokeratin (CK LMW) (×200); d) Epithelial membrane antigen (EMA) (×200); e) vimentin positive staining in endothelial cells, while tumor cells are negative (×200); and positive for: f) sinaptophysin (Syn) (×200); g) neuron specific enolose (NSE) (×400) and h) chromogramin A (ChroA) (×400).

It most commonly arises in younger women between the age of 13 and 55. Single cases of SCOC in girls and postmenopausal women are described [9, 10]. Clinical presentation is deficient. Symptomatology and manifestation usually appear in the sense of discomfort or pain in the abdomen when the tumor reaches greater size, and with 2/3 of the patients paraneoplastic hypercalcemia also appears [7, 11].

SCOC prognosis is generally bad even tough aggressive regime of treatment is applied. The overall survival of patients at Ic *International Federation of Gynecology and Obstetrics* (FIGO) stage is a bit higher than 10% and for those in higher stages is only 6.5% [7].

Case report

A 60-year-old woman, Caucasian, gravida 4, para 2, menarche at 17 and menopause at 48, came to the doctor because of discomfort in the lower abdomen and pain of greater intensity in last few days. Apart from the echinococcal liver cyst operation five years ago, the patient did not mention any other significant gynecological or other health problems. The report of physical examination showed a soft abdomen with sensitivity to pain and fullness in the right lower quadrant, and bimanual gynecological examination showed the presence of large adnexal masses on the right. Ultrasound examination and CT scan of the abdomen confirmed the presence of large adnexal masses of cystic-solid appearance with the largest diameter of 13 cm, regular structure of the other gynecological organs, without verifying the existence of metastatic deposits. All the results of laboratory analysis gave normal values, except for calcium, which was elevated (2.69 mmol/L) (normal range 2.10–2.55 mmol/L). Medical council of gynecologists recommended operative treatment. Explorative laparotomy with complete hysterectomy, bilateral salpingo-oophorectomy, dissection of lymph nodes and omentectomy was conducted.

The operative material was submitted for pathohistological analysis. The omentum, lymph nodes, uterus with cervix, both uterine tubes and the left ovary were without significant micromorphological changes. The sample of the right ovary was of irregular spherical shape with the smooth, pale gray surface, with diameter of 13 × 11 cm, and the weight of 330 g. The cross section showed a whitish tumor mass, mostly solid with a small cystic part, with extensive areas of bleeding and necrosis. Microscopically, the tumor was formed of relatively uniform small cells which made diffuse field or forming solid nests, thick ribbons and follicle–like structures. Tumor cells were spherical or with slight spindle elongation, with scant of cytoplasm, oval nuclei with granular chromatin pattern and sporadically prominent nucleoli (Figure 1a). Mitoses were numerous; more than 20 mitotic figures could be seen in 10 fields of high power magnification (Figure 1b). Fields of extensive necrosis were present, as well as bleeding focuses, capsular infiltration without its bursting, with evident invasion of lymphatic vessels. Immunohistochemically (Figure 1c-h), tumor cells were vimentin negative, and positive to epithelial membrane antigen (EMA), low molecular weight cytokeratin (LMW CK) and to neuroendocrine differentiation markers:

neuron specific enolase (NSE), chromogranin A (Chro A) and synaptophysin (Syn). Thyroid transcripton factor-1 (TTF-1) negativity with external positive control (Figure 2a and 2b), excluded small cell carcinoma of the lung. Proliferative activity was very high; about 90% of nuclei showed immunoreactivity for Ki-67 (Figure 1b). Based on this pathohistological analysis, SCOC at FIGO Ia stage was diagnosed.

No complications were observed in a postsurgery period and after 10 days the patient was discharged in a good condition and with normal calcemia. The treatment was continued with concurrent radiotherapy and chemotherapy. However, in spite of overall treatment, the disease progressed, and the patient died of disseminated metastatic disease, 26 months after the diagnosis

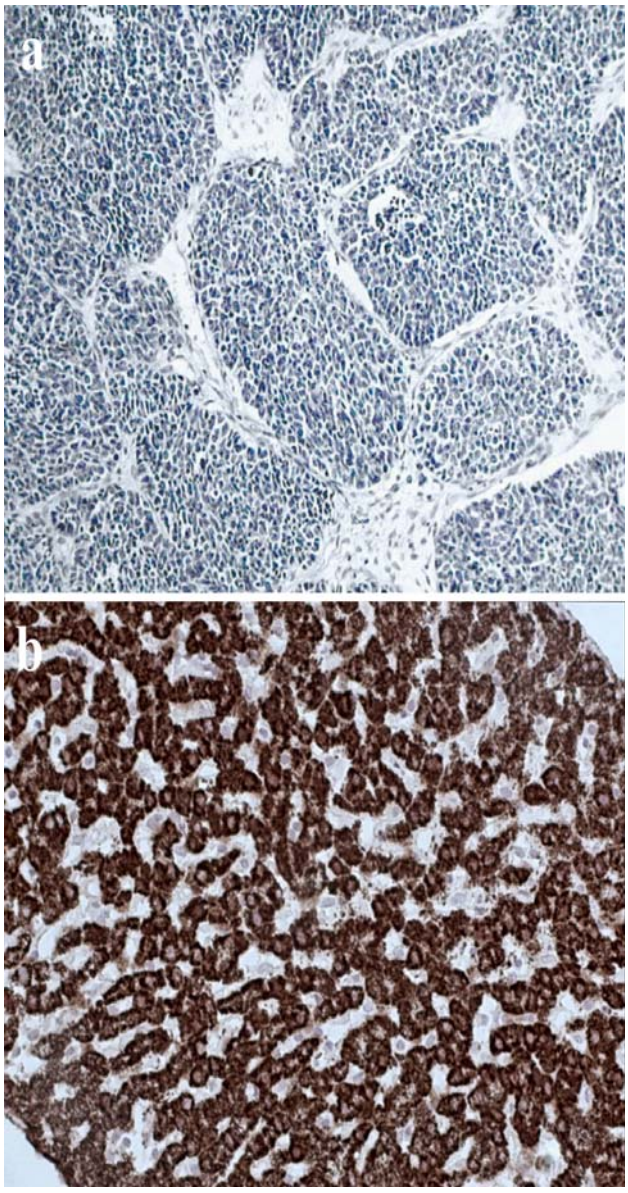

Fig. 2 – Immunoexpression of Thyroid Transcription Factor-1 (TTF-1): a) tumor cells are negative for TTF-1 (×200); b) positive control for TTF-1 (cytoplasmatic expression in the liver tissue, ×200).

Discussion

Primary extrapulmonary small cell carcinomas are very rare, making 2.5–4% of all small cell carcinomas [1–3]. They are of aggressive course with bad prognosis and usually recidivate shortly after the therapy [2]. They can be localized in various organs including the pleura, thymus, kidney, prostate, ovary, cervix, larynx, trachea, thyroid gland, lymph node, CNS, liver, skin, sinuses, salivary glands, peritoneum, stomach, esophagus, pancreas, gall bladder, colon, skin etc [2, 3].

In the series by Kim et al. [12, 13], the most common extrapulmonary localization was cervix while the another authors indicated that those are esophagus and thymus.

SCOC commonly arises between the age of 13 and 55, more often with younger women [7]. However, Pantier et al. [10] presented 11 cases of menopausal and postmenopausal women with histologically and immunohistochemically confirmed SCOC. It is considered that about two thirds of the patients have hypercalcemia at the moment of diagnosis, although symptomatology of hypercalcemia is rarely present [14]. Our presentation also referred to these rare cases of SCOC arising in postmenopausal women, with elevated level of calcium in the serum, and without clinical manifestation of hypercalcemia.

SCOC is unilateral, while bilaterality is usually present in patients with wide-spread metastatic disease and in this case tumor deposits on the other ovary are actually the result of metastasis [7]. There are also descriptions of bilateral SCOC which appear within a family [7, 15]. In the series by Young et al. [7] there was 1 pair of first-degree relatives (mother and daughter) and 1 pair of second-degree relatives (cousins).

The histogenesis of SCOC is unknown. Malignant cells do not originate from the surface epithelium of ovary, sex cords and stroma, as well as germinative and neuroendocrine cells [16]. Animal models used in the research of SCOC origin did not show the connection of SCOC with epithelial and germinative ovary tumors either [17].

Some authors believe that for the diagnosis the classical histological picture of small cell carcinoma on tissue sections stained with the standard Hematoxylin and Eosin (H&E) method is sufficient. However, since differential diagnostical dilemma is likely to appear, it is necessary to detect the immunophenotype and to prove a neuroendocrine differentiation in a special way. A certain immunophenotype helps in differentiation of SCOC from the other tumors of epithelial origin, lymphoma, melanoma, primary neuroectodermal tumors, tumors of germinative origin and the sex cords and stromal origine [18, 19]. In the presented case, neuroendocrine differentiation was imunohistohemically proved in combination with classical hystomorphological picture; tumor cells are Chro A, Syn and NSE positive. Immunohistochemically, small cell carcinomas generally show the sporadic positivity for LMW CK, and 30–75% is immunoreactive to EMA [20]. Although the positivity for vimentin is often present, this staining is considered to be nonspecific. In the original description of this tumor, 5 out of 7 cases showed positive staining to a parathyroid hormone–related protein (PTHrP) [21]. Differential diagnosis

excludes metastasis of the small cell lung carcinoma with negativity for TTF1 [22].

SCOC treatment is not clearly defined. The multiple model which includes surgery, chemo- and radiotherapy is recommended [2, 8, 10]. In unilateral cases the usual procedure is hycterectomy with bilateral salpingo-oophorectomy, while in younger women unilateral oophorectomy is an option. Chemotherapy and radiotherapy are applied concurrently or sequentially, and depending on the stage of disease they are applied preoperatively or adjuvantly. In the cases of complete therapeutic response prophylactic cranial irradiation is applied. The base of chemotherapy regime consists of cisplatin, etoposide, cyclophosphamide and doxorubicin in a variety of combinations. The overall response rate in the extensive disease, using cisplatin-based or cyclophosphamide/doxorubicin with vincristine or etoposide chemotherapy, is 70–90% [2, 3, 12]. However, despite the aggressive complex model of treatment more than 50% of women at Ia stage of the disease die within 2 years, while 33% of women have a 6-year interval without the disease [7]. Women with smaller tumors at Ia stage have better prognosis than those with tumor masses larger than 10 cm [7]. The presented patient belonged to this prognostically worse category. Although the disease was at Ia FIGO stage, with optimal treatment regime, the patient died 26 months after the SCOC diagnosis.

Conclusion

Small cell carcinoma localized in the ovary is generally a tumor category with bad prognosis depending on the stage of the disease.

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