Case report
Prikaz bolesnice

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Pregnancy complicated by small cell neuroendocrine carcinoma of the cervix: a case presentation

Sitnostanični neuroendokrini rak vrata maternice u trudnoći – prikaz bolesnice

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Summary

Small cell neuroendocrine carcinoma of the cervix (SCNCC) is considered to be an extremely rare, highly invasive and aggressive subtype of squamous cell carcinoma. It is particulary rare during pregnancy. Here we report a case in which a 32-year-old patient who was admitted to our Department at 27 completed weeks of gestation with intermittent vaginal spotting and a large amount of malodorous vaginal discharge. Gynecological examination revealed a 2 cm exophytic polypoid tumor coming out of the cervix. On rectal examination there was no clinically evident parametrial invasion. Biopsy of the cervix was performed and the diagnosis of small cell neuroendocrine carcinoma was established. We reviewed and discussed the features, diagnosis, treatment and prognosis of SCNCC diagnosed during pregnancy.

Key words: pregnancy, small cell neuroendocrine carcinoma, cervix

Sažetak

Sitnostanični neuroendokrini rak cerviksa je iznimno rijedak, visoko invazivan i agresivan podtip pločastog raka cerviksa. Poglavito je rijedak tijekom trudnoće. U ovom radu prikazujemo slučaj 32-godišnje bolesnice koja je zaprimljena u našu kliniku s navršenih 27 tjedana trudnoće, s oskudnim vaginalnim krvarenjem, te obilnim iscjetkom neugodnog mirisa. Pregledom u spekulima smo pronašli polipoidnu tvorbu veličine 2 cm koja je prominirala iz cerviksa. Rektalnim pregledom nismo pronašli zahvaćenost parametrija. Učinjena je biopsija polipoidne tvorbe i postavljena dijagnoza sitnostaničnog neuroendokrinog raka cerviksa. U prikazu slučaja raspravljamo o značajkama, dijagnozi, liječenju i prognozi ovoga raka dijagnosticiranog tijekom trudnoće

Ključne riječi: trudnoća, sitnostanični neuroendokrini karcinom, cerviks

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Introduction

The incidence of cancer diagnosis during pregnancy is estimated to be 1 in every 1,000 pregnant women. It is expected to increase in the coming years, likely because of the growing age of childbearing, associated with amplified risk of developing age-dependent malignancies.[1-4] The most

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common solid malignancies during pregnancy are breast, gynecological and gastrointestinal cancer, and melanomas. Cervical cancer is the third most common cancer during pregnancy after breast cancer and lymphoma.[1,2,5] Small cell neuroendocrine carcinoma of the cervix (SCNCC) is very rare and a high-grade malignant tumor.[6,7] It comprises 1–3% of cervical carcinomas and is the most common of four neuroendocrine tumors, according to the College of American Pathologists and the National Cancer Institute.[8] This uncommon histological subtype of cervical cancer is associated with poor survival and its occurrence during pregnancy is particularly rare.[9] So far only 18 cases of SCNCC have been reported in pregnancy.[7] Early diagnosis and staging are of the importance for treatment and prognosis of patients with such cancer.[1] We are presenting the case of the patient who was diagnosed with SCNCC during advanced pregnancy.

Case report

A 32-year-old woman, gravida 3, para 2, was referred to our department in November 2022, at 27 completed weeks of gestation with intermittent vaginal spotting and a large amount of malodorous vaginal discharge. Gynecological examination revealed a 2 cm exophyticpolypoid tumor coming out of the cervix, without clinically evident parametrial invasion. She had no family history of malignancy. Previously the patient had laparoscopic removal of ovarian cyst and no history of other medical conditions. Last PAP smear was performed in March 2022, (eight months earlier) and it did not show any abnormality. Cervix biopsy was performed and fragmented pieces of tumor measuring 1×0.7 cm in total were submitted for pathohistological analysis. Microscopically, the tumor was composed of sheets of highly atypical cells with hyperchromatic nuclei, scarce to moderately abundant cytoplasm, with occasional rosette-like formation and signet-ring cells. Mitotic activity was brisk. Apoptotic bodies were numerous. Immunohistochemically, the tumor was positive for cytokeratin 7 (CK7), p16-INK, synaptophysin (Syn) and chromogranin A (CHGA) (Figure 1). The following immunohistochemical markers were negative: cytokeratin 5/6 (CK5/6), p40, p63 and CD45 LCA. More than 85% of tumor cells were Ki-67 positive (Figure 1). Based on the histological appearance and immunohistochemical stains the diagnosis of small cell neuroendocrine carcinoma of the cervix (SCNCC) was established. MRI of the abdomen and pelvis did not show any nodal metastases. CT scan of the brain and lungs did not show any distant metastases. Termination of pregnancy was offered to the patient but she refused it. After careful multidisciplinary team approach, we started neoadjuvant chemotherapy (NACT) with 3 cycles of cisplatin (CDDP; 50 mg/m^2) and etoposide (VP-16; 100 mg/m^2) every three weeks. There was no associated maternal toxicity and fetal development was good. The patient was clinically followed every two weeks with obstetrical examinations. Fetal control was regularly performed on weekly basis with FHR monitoring, ultrasound and Doppler examination. After three cycles of NACT, we performed control MRI and CT in order to see the presence of nodal and distant metastases. There were no nodal and distant metastases. Reduction in tumor size was noticed (32×20×24 mm compared to 17×9×6 mm) (Figure 2). The patient was on iron supplementation and we weekly checked CBC in order to avoid anaemia of pregnancy.

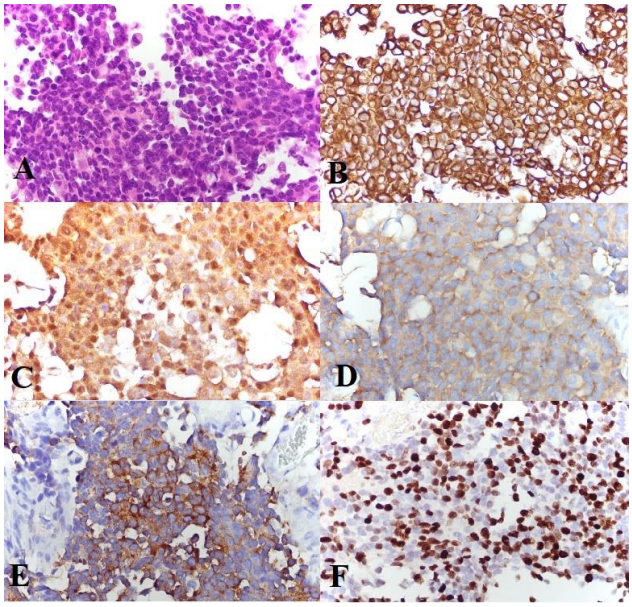

Figure 1 A) Pathohistologic examination showed a tumor composed of sheets of highly atypical cells with scant to imperceptible cytoplasm, ovoid to slightly spindle hyperchromatic nuclei. Mitosis and apoptotic bodies are numerous (HE, original magnification ×400). Tumor shows diffuse cytokeratin 7 (B), p-16 INK (C), synaptophysin (D) and chromogranin (E) positivity (original magnification ×400). Proliferation index was high and determined using anti-body Ki-67 (F) (original magnification ×400).

Slika 1. A) Patohistološki pregled pokazuje tumor sastavljen od nakupina visoko atipičnih stanica s oskudnom citoplazmom, te ovoidnim, do blago vretenastim jezgrama. Mitoze i apopptoska tjelešca su brojna. Imunohstokemijski stanice su pozitivne na citokeratin 7 (B), p-16 INK (C), sinaptofizin (D) i kromogranin (E). Proliferacijski indeks je određen uporabom protutijela na Ki-67.

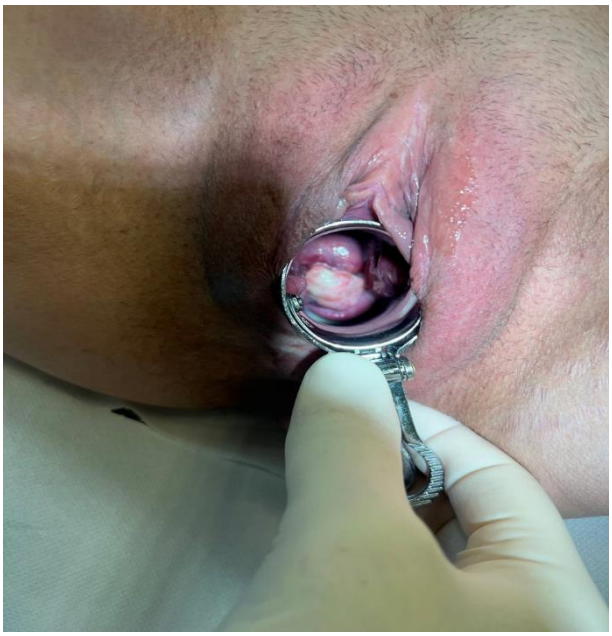

Figure 2 Macroscopic appearance of small cell neuroendocrine carcinoma of the cervix after three cycles of neoadjuvant chemotherapy.
Slika 2. Makroskopski prikaz sitnostaničnog neuroendokrinog karcinoma cerviksa nakon tri ciklusa neoadjuvantne kemoterapije.

Two weeks after completed three courses of NACT, at 37[5/7] completed week, we performed cesarean section and delivered a female newborn 2840 gr /47 cm. APGAR score was 10 in 1 and 5 min. In the same act, the patient underwent radical hysterectomy type Piver 2 with bilateral salpingo-oophorectomy and pelvic lymphadenectomy (Figure 3 and 4). Blood loss during procedure was less than 500 ml. During the postoperative period, the patient received LMWH and early postoperative recovery was normal. There was no need for transfusion during puerperium. With these pre, intra and postoperative measures we respected the key goals of patient blood management PBM: (a) to identify, evaluate, and manage anemia; (b) reduce iatrogenic blood loss; (c) optimize hemostasis; and (d) establish decision thresholds for transfusion. She was dismissed from hospital on the fourth postoperative day. Breastfeeding was discouraged because she had to complete chemotherapy after delivery. In that case, and when time elapsed from the previous chemotherapy cycle did not reach at least three weeks breastfeeding was discouraged.[1,10] On pathological examination dimension of uterus were 24.5×12.5×4cm with left (11×3cm) and right (10×3cm) parametria. The length of the vaginal fornix was 1.5 cm. Final patohistological examination revealed a cervical tumor size 4×2.5cm with no parametrial and LVSI involvement, and according to FIGO it is classified 1B2. There was minimally invasion of stroma (<1mm). Histopathologically type was neuroendocruine carcinoma of the cervix, gradus 3.

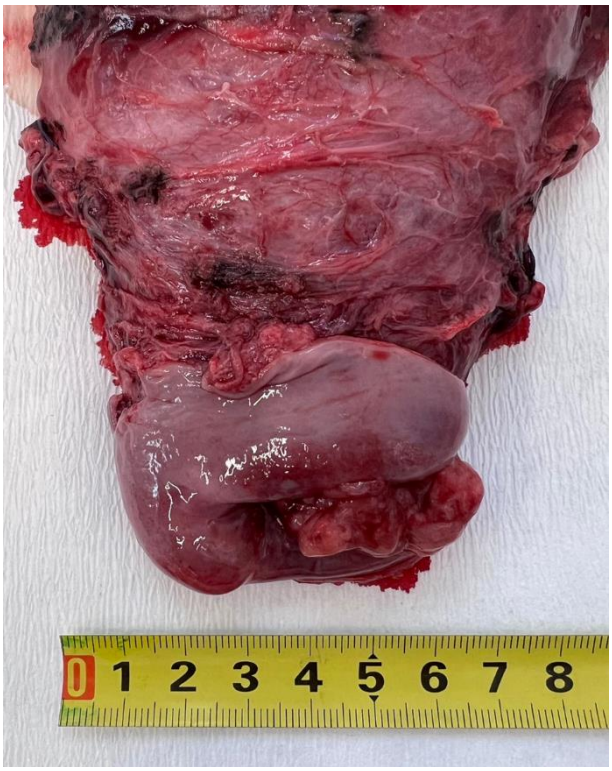

Figure 3 Specimen after radical hysterectomy.
Slika 3. Preparat nakon radikalne histerektomije

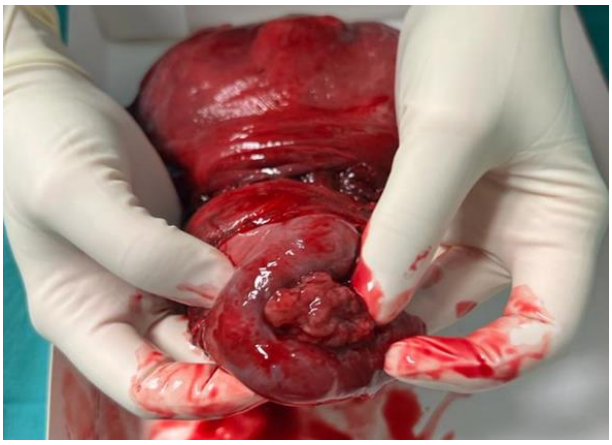

Figure 4 Specimen after radical hysterectomy.
Slika 4. Preparat nakon radikalne histerektomije

Discussion

In this article we present a case of small cell neuroendocrine carcinoma of the cervix (SCNCC) diagnosed and treated during advanced pregnancy. This pathological type of cervical carcinoma is considered to be an extremely rare, highly invasive

and aggressive subtype of squamous cell carcinoma. Outside of pregnancy, the behaviour of this malignancy is different from squamous cell carcinomas because it has a high propensity for metastases, nodal and distant. Typical sites of metastasis are the lung, liver and bones.[7,11,12] Histopathologically, the tumors are recognized by their microscopic closeness to pulmonary small cell carcinomas (oat cell or intermediate types). The phenotypic and pathological features of small cell cervical carcinoma (SCCC) and small cell lung cancer (SCLC) are very similar.[6] In fact, small cell neuroendocrine carcinoma represents an extrapulmonary variant of small cell lung cancer. Most of these tumors express one or more markers of neuroendocrine activeness and discerment.[7,12,13] On immunohistochemistry, these tumors have been found to be immunoreactive for cytokeratin, epithelial membrane antigen, carcino-embryonic antigen (CEA), neuron-specific enolase (NSE), Leu 7, synaptophysin (SYN), chromogranin (CHG) and a variety of other peptide amine hormones. Electron microscopy may demonstrate dense core granules in most of the cases.[7,12,13] SYN and CD56 are the most sensitive markers. However, in some cases of SCNCC expression of neuroendocrine markers may be negative.[12]

The presence of high-risk HPV DNA has been revealed in the majority of small cell and large cell neuroendocrine carcinoma of the cervix (NECC), similary to squamous cell cervical carcinoma.[12] Various researchers have confirmed the presence of Human Papilloma Virus type 18 DNA or messenger RNA in almost two thirds of these cases. They are more often seen in tumors in which a neuroendocrine differentiation has been shown.[12] In a metaanalysis, Castle et al. analyzed HPV infection data in 403 cases of small cell and 45 cases of large cell NECC. They found that 85 and 88% of cases were HPV positive, respectively. The predominant subtypes were HPV18 and HPV16.[14] It was previously mentioned that PAP smear was performed eight months before the final diagnosis and it has not shown any abnormalities. Also, it is confusing that in medical documentation, from the beginning of the pregnancy, there was no data about polypoid mass extruding from the cervical canal. This can be explained with rapid growth of these tumors. Sometimes in the beginning, small cell neuroendocrine carcinomas of the cervix may be misdiagnosed as cervical myomas or rapidlyd growing polyps in the cervix.[7,9] The incidence of abnormal cervical cytology, during pregnancy, is similar to that in nonpregnant women.There is an overall higher rate of false-positive results. This can be explained by stromal decidualization which leads to large nuclei that may be wrongly interpreted as dysplastic cells, particularly during the second half of pregnancy.[15–17] Reports on natural history of CIN 2/3 in pregnant women are conflicting.[16] Origoni et al. reported an extremely rare progression rate to invasive cervical cancer of 0.4%.[16] By contrast, in another study a progression rate of 13.3% was observed which is 33 times higher compared to Origoni. In this study, there was also progression to microinvasive cancer occurring in four of 30 women.[15,17,18] Spontaneous regression postpartum is reported to occur in 16.7–69.3% of pregnant women with CIN 2/3.[17] Some of the possible and plausibile explanation is that over expression of sex hormones during pregnancy can modify the local immune system and facilitate cervical carcinogenesis by inducing squamous metaplasia in the transformation zone.[15]

Management of cervical cancer during pregnancy needs a multidisciplinary approach that must consider the benefit–risk ratio for the mother and fetus. It also includes some ethical and moral issues which are beyond the scope of this article. The cornerstone of cervical cancer management in advanced pregnancy is neoadjuvant chemotherapy followed by surgery.

The management of cervical carcinoma during pregnancy mainly depends on the size, type and stage of cancer, duration of pregnancy, and histological subtype.[13,19] There is paucity of data in literature on treatment schemes for NECC. Due to the features of cervical SCNCC during pregnancy being low morbidity, highly malignant, powerful invasiveness, and poor prognosis, and lack of prospective clinical trials because of the rarity of these malignancies there is no established standard treatment for SCNCC in pregnancy.[13] So far only, 18 cases of SCNCC have been reported in pregnancy.[7] Multimodality treatment with radical surgery and adjuvant or neoadjuvant chemotherapy with etoposide and cisplatin is the mainstay of treatment for early stage disease while combined radiochemotherapy and chemotherapy are appropriate for women with locally advanced or recurrent NECC. For SCNCC, different multimodality approaches have been used, mainly derived from the therapy of cervical cancer in general as well as from neuroedocrine tumors of the lung in particular.[12] A large number of chemotherapy regimens have been described in the treatment of patients with NECC but cisplatin/carboplatin and etoposide alone or in combination with other substances have been described in more than two thirds of the published studies. So far The Society of Gynecologic Oncology (SGO), Gynecologic Cancer Inter Group (GCIG) and The European Society for Medical Oncology ESMO published documents on

the management of women with NECC and SCNCC.[15,20–22] The Society of Gynecologic Oncology (SGO) published a clinical document on the management of women with NECC.[12,20] The Gynecologic Cancer Inter Group (GCIG), in 2014 published a consensus review on the treatment of small cell carcinoma of the cervix (SCCC).[21] Both of them recommend radical surgery for early stage disease, either primarily or after neoadjuvant chemotherapy. For patients with an advanced stage disease, the GCIG recommends chemoradiation or systemic chemotherapy consisting of etoposide and cisplatin.[21] The European Society for Medical Oncology (ESMO) clinical practice guidelines recommend the use of platinum-based chemotherapy with or without paclitaxel for the second trimester.[22] This therapy is extrapolated from therapy for small cell carcinoma of the lungs. The use of platinum-based chemotherapy during pregnancy is described in the literature, and its efficacy, combined with good maternal and neonatal tolerance at birth and during the follow-up period (median: 17 months), make their use reasonable.[22,23] Regarding recent recommendations, carboplatin is now preferred over cisplatin due to the risk of dose-dependent ototoxicity in children after cisplatin exposure during pregnancy and the better maternal toxicity profile of carboplatin.[22–25]. The possibility of transplacental transfer of the drug, impact on fetal growth and risk of teratogenicity is of particular importance for obstetricians. In order to understand this possibility we must be aware of the significant physiological pharmacokinetic/dinamic variations observed in pregnant women that may have an impact on the transplacental transfer of anticancer agents.[1,23] Generally, molecules that are not ionized at physiological pH and weakly bound to plasma proteins, which are highly lipophilica and low-molecular-weight are likely to cross the placental barrier more easily.[1,10] Most anticancer agents fulfill these criteria and can therefore theoretically cross the placenta and reach the fetal circulation. So far we know that extent of placental transfer of different chemotherapeutic agents varies considerably.[1,10] In the study of placental transport of chemotherapeutic drugs commonly used in pregnant baboon models results showed that the average concentration of carboplatin in baboon fetal plasma was 57.5% of the maternal body.[26] There are suggestions that there is the possibility of a platinum placental filtration mechanism because the platinum concentrations in the fetal cord blood and amniotic fluid were 23%-65% and 11%-24% of maternal blood, respectively.[26,27] Anticancer drugs can act on the growing fetus, directly or indirectly through the placenta.[26] Mechanisms by which chemotherapeutics could induce teratogenic effects are incompletely understood. Recent study found that chemotherapy was associated with an increased risk of major congenital malformations only in the first 12 weeks of pregnancy.[28] The rate of malformations following exposure to CDDP in the first trimester was 20%; however, in the second or third trimester of pregnancy, that percentage decreased to 1%. The most frequent minor and major malformations were blepharophimosis, microcephaly and hydrocephalus and the incidence of IUGR was 13%. For VP16, the rate was 3% of major malformations following administration in the second and third trimesters and 24% fetal growth restriction have been reported. The most frequent major malformation associated with VP16 was cerebral atrophy and ventriculomegaly.[3,23,29]

In cases of SCNCC, a cesarean section must be performed to avoid dissemination in the episiotomy or vaginal injury site, and a corporeal incision is advised to avoid abdominal dissemination.[1,2,26] Moreover, there are reports of cases of vertical tumor transmission during vaginal delivery from mothers with cervical cancer to their children.[26]

In conclusion, SCNCC is extremelly rare and its characteristics during pregnancy are high malignancy, invasiveness and mortality. It is interrelated with highrisk HPV16 and HPV18. Careful examination of the cervix per speculam during pregnancy is mandatory in order to avoid misdiagnosis of cervical myomas or rapidly growing polyps in the cervix. There is no established standard treatment for SCNCC in pregnancy because of the rarity of this malignancy duringe pregnancy and consequently the lack of prospective studies. Current recomendation for SCNCC treatment in advanced pregnancy is neoadjuvant chemotherapy followed by radical surgery. The optimal choise for neoadjuvant chemotherapy is cisplatin/carboplatin and etoposide alone. The reccomended mode of delivery is a cesarean section with corporeal incision in order to avoid dissemination in the abdomen, episiotomy or vaginal injury site. In order to find more effective therapy for SCNCC during advanced pregnancy, we need more prospective studies.

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