CASE REPORT

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Fatal outcome in the patient with the suspected ectopic pregnancy and diagnosed epithelioid trophoblastic tumor

Fatalan ishod sumnjive ektopične trudnoće kod bolesnice sa konačnom dijagnozom epiteloidnog trofoblastnog tumora

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Abstract

Introduction. Epithelioid trophoblastic tumor (ETT) is an extremely rare form and unusual type of trophoblastic tumor. In 1998 ETT became an independent entity because it possesses specific histological and immunohistochemical features which make it different from placental site tumor and choriocarcinoma. ETT origins from intermediate trophoblast and it can overlap with the squamous cell carcinoma as per differential diagnosis. The relevant literature data suggest that surgical treatment is a treatment of choice for ETT considering that its response to chemotherapy is considerably poor. **Case report.** A 35-years-old patient G3 P2 came to an examination due to the low pelvic pain and absence of menstrual cycle. She reported that menstrual cycles were irregular during the past year. During the bimanual pelvic examination, a painful tumefaction being approximately 8 cm was palpated in the pouch of Douglas. The patient was operated on as being suspected for ectopic pregnancy when it was noticed that the aforementioned tumefaction was located retroperitoneally immediately against rectosigmoid part of the colon. After the histopathological analysis of the sample, in order to make the final diagnosis, the immunohistochemical test was performed and it found that this ETT. Due to an inadequate response to administered chemotherapy, both resection of rectosigmoid colon with appurtenant tumor and left hepatectomy with salpingectomy on both sides were performed considering a possibility of gestational trophoblastic neoplasia (GTN) after ectopic pregnancy. Because of dehiscence of colorectal anastomosis, relaparotomy with colostomy bag fitting was performed. The patient died on the day 40 after surgical treatment due to hepatic insufficiency. **Conclusion.** In order to make as much adequate treatment method of ETT as possible, it is necessary to organize a team work with multidisciplinary approach. Surgical resection of the tumor is a primary method for treating ETT.

Key words:
diagnosis; histological techniques; postoperative complications; pregnancy, ectopic; surgical procedures, operative; treatment outcome; trophoblastic neoplasms.

Apstrakt

Uvod. Epiteloidni trofoblastni tumor (ETT) je ekstremno retka forma trofoblastnog tumora. Kao poseban entitet definisan je 1998. godine zahvaljujući specifičnim histološkim i imunohistohemijskim karakteristikama koje su ga činile različitim od tumora placentnog ležišta i horiokarcinoma. ETT potiče od intermedijarnog trofoblasta i može se diferencijalno dijagnostički preklapati sa skvamoznim karcinomom. Podaci iz literature sugerišu da je tretman izbora hirurška resekcija tumora s obzirom na njegovu relativnu rezistentnost na hemioterapiju. **Prikaz bolesnika.** Trideset i pet godina stara pacijentkinja G3 P2 javila se na pregled zbog bolova u maloj karlici i izostanka menstruacije. Bimanuelnim ginekološkim pregledom palpirala se bolno osetljiva tumefakcija promera oko 8 centimetara u Douglasovom prostoru. Pacijentkinja je operisana pod sumnjom da se radi o ektopičnoj trudnoći. U toku operacije uočeno je da se tumefakcija nalazi retroperitonealno neposredno uz rektosigmoidni deo kolona. Nakon biopsije i patohistološke analize uzorka bila je neophodna imunohistohemijska analiza nakon čega je konstatovano da se radi o ETT. S obzirom na neadekvatan odgovor na primenjenu hemioterapiju učinjena je resekcija rektosigmoidnog kolona sa pripadajućim

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tumorom kao i leva hepatektomija uz obostranu salpingektomiju uzimajući u obzir mogućnost primarne lokalizacije gestacijske trofoblastne neoplazije (GTN) nakon ektopične trudnoće. U postoperativnom toku došlo je do dehiscencije kolorektalne anastomoze te je učinjena relaparatomija sa kolostomom. Pacijentkinja je umrla četrdeset dana nakon operacije zbog hepatične insuficijencije. **Zaključak.** U cilju najbolje odluke o metodi lečenja ETT neophodan je timski rad sa multidisciplinarnim pristupom. Primarni metod lečenja ETT je hirurška resekcija.

Ključne reči:
dijagnoza; histološke tehnike; postoperativne komplikacije; trudnoća, ektopična; hirurgija, operativne procedure; lečenje, ishod; neoplazme, trofoblastne.

Introduction

Gestational trophoblastic neoplasia (GTN) implies an invasive mole, choriocarcinoma, placental site tumor and epithelioid trophoblastic tumor (ETT). ETT is an extremely rare form and unusual type of trophoblastic tumor. A term ETT was proposed in 1994 for the first time when it was thought that this kind of tumor occurred as a consequence of administering chemotherapy in the patients with choriocarcinoma, i.e., that chemotherapy influenced the tumor growth by mechanism of drug induced cell changes. In 1998 study by Shih and Kurman [1], it was shown that ETT became an independent entity because it has for some specific histological and immunohistochemical features which make it different from placental site tumor and choriocarcinoma [1–3]. ETT origins from intermediate trophoblast and it can overlap with squamous cell carcinoma as per differential diagnosis considering its common localization in the lower uterine segment or cervix when some cases of ETT were noted in oviducts and *ligamenta lata* [4, 5]. The relevant literature data suggest that a surgical treatment is a treatment of choice for ETT considering that its response to chemotherapy is considerably poor. The ETT affects patients with previous pregnancies during their reproductive period of life. The time between pregnancy and clinical presentation of the disease is from one to eighteen years. Mostly, ETT occurs after term pregnancies. The value of beta-human chronic gonodotropin (β-hCG) at a time when diagnosis is made is increased, but unlike choriocarcinoma, it generally does not exceed about 2.500 mLU/mL [5, 6]. Shih and Kurman [1] reported a rate of metastasis being 25% and a rate of mortality being 10% in ETT. To our knowledge, 94 cases of ETT has been described so far in the literature.

Case report

A 35-years-old patient, G3 P2, was sent by a gynecologist to our institution due to the low pelvic pain and absence of menstrual cycle. For anamnesis, she reported that menstrual cycles were irregular during the past year. During the bimanual pelvic examination, a painful tumefaction being approximately 8 cm was palpated in the pouch of Douglas. An ultrasound view clearly differentiated uterus and both ovaries while the left ovary was located immediately against the aforementioned tumefaction which appeared like hematic mass within the pouch of Douglas. Blood test results were within normal ranges including complete blood count, biochemical parameters and tumor markers (Ca - 125, Ca 19-9, HE-4 and Roma index), except for the increased value of β-hCG which was 198.70 mIU/mL (normal less then 5 mIU/mL). In view of the aforementioned symptomatology which was presented as the low pelvic pain and absence of menstrual cycle as well as an inadequate increase in β-hCG which was 220.01 mIU/mL after 48 h, it was decided to operate the patient in order to explore adnexa. The patient was operated on (on 24 August 2016) as being suspected for ectopic pregnancy when it was noticed that the aforementioned tumefaction was located retroperitoneally immediately against rectosigmoid part of the colon. A surgeon was invited for consultations, a sample was taken for biopsy (*ex tempore* – malignant) and he proposed that further treatment was to be made after obtaining the final histopathological finding and after additional diagnostic procedures. After the pathohistological analysis of the sample, in order to make the final diagnosis, the immunohistochemical test was performed and it was found that this was GTN, i.e., ETT with a suggestion that due to possibility of immunoprofile overlapping, it was necessary to exclude existing of squamous cell carcinoma within anal and genital area. The immunophenotype characteristics of the tumor were the following: panCK+, CK7 focally+, CK18+; CK20-, HPL focally +CEA+/-, p63-/+, p16+, inhibin focally +, beta hCG focally +, OCT3/4-, TTF-, KI67+. Both colposcopic finding and Pap test result were regular. The exploratory curretage exluded presence of GTN within the uterus. The lungs and head were X-rayed, the pelvic and abdominal area were examined with multislice computed tomography (MSCT), and colposcopy was performed. MSCT confirmed both the existance of aforementioned tumefaction in the pelvic area without being clearly differentiated from the surrounding structures and metastatic changes in both liver lobes where the most part of left lobe was changed by metastasis and the size of this change was about 10 cm (Figure 1).

Colonoscopy found polyps in rectosigmoid junction and a sample was taken for a biopsy. X-ray pictures of the head and lungs were regular. After the diagnostic procedures was finished, the International Federation of Gynecology and Obstetrics (FIGO) scores was 11 and the patient was in a high risk group, so multiagent chemotherapy was indicated. Two cycles of cytostatic therapy (methotrexate + cyclophosphamide) were administered to the patient in accordance with a protocol for poor prognosis GTN. The therapy was administered as per the following mode: metotrexate dose of 1 mg/kg, as intramuscular injections on day one, day three, day five and day seven plus folic acid in a dose of 25 to 30 mg on day two, day four, day six and day eight.

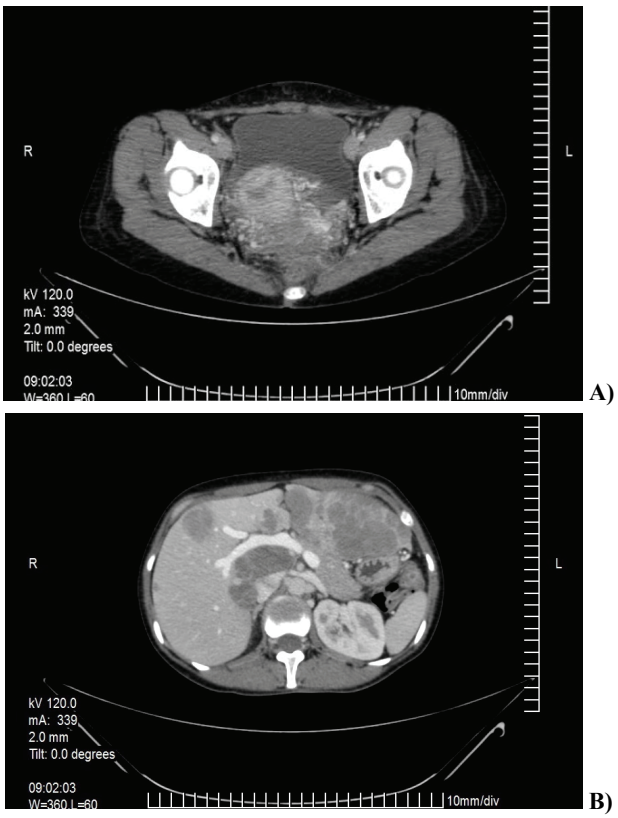

Fig. 1 – A) Tumefaction in pelvic area without clear differentiation from the surrounding structures; B) Metastatic changes in both liver lobes where the most part of left lobe was changed.

Cyclophoshamide dose of 300 mg was administered intravenously. On day seven, after administered chemotherapy, the patient received blood due to severe anemia. Dynamics in the changes of β-hCG values during the treatment did not present any significant deviations from the initial value (at admission 198.70 mIU/mL, at discharge 323.44 mIU/mL). Ultrasonography viewed the tumor mass which dimensions did not change in comparison to the finding prior surgical intervention (Figure 2).

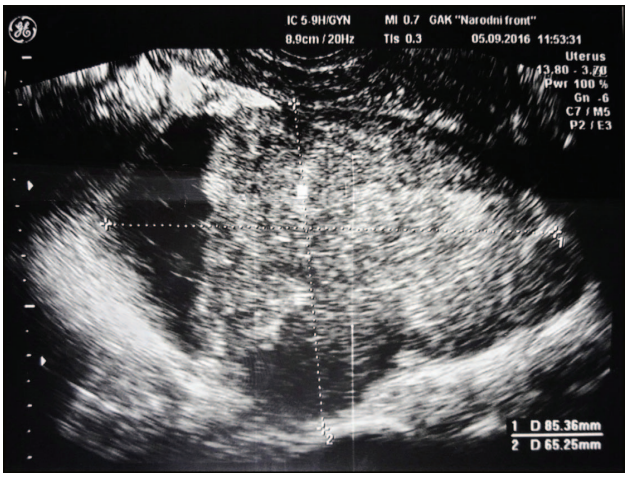

Fig. 2 – Ultrasound image of pelvic mass after chemotherapy revealed left ovary located immediately against the tumefaction (the same as the initial finding).

Because of inadequate response to administered chemotherpy, it was decided that patient was to be subjected to corresponding surgical treatment and in accordance with the localization of the tumor, she was transferred to the Surgery Department of University Medical Centar Bežanijska kosa where both resection of rectosigmoid colon with appurtenant tumor (Figure 3), and left hepatectomy (Figure 4), were performed on October 1, 2016. Figure 5 shows a part of rectosigmoid colon with the tumor and termino-terminal (TT) anastomosis after resection of the tumor.

During this operation, salpingectomy on both sides was performed considering possible primary localization in tubes, i.e., a possibility of GTN after ectopic pregnancy. The right liver lobe was also changed with several minor, individual secondary deposites (Figure 6).

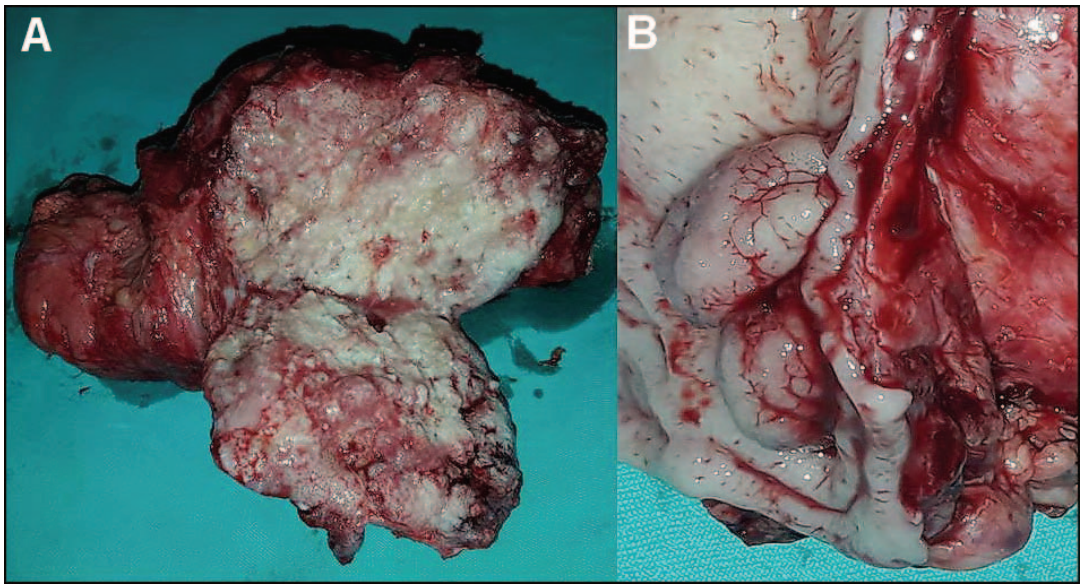

Fig. 3 – A) Macroscopic view of the tumor; B) Polyp which belongs to the resected part of the colon.

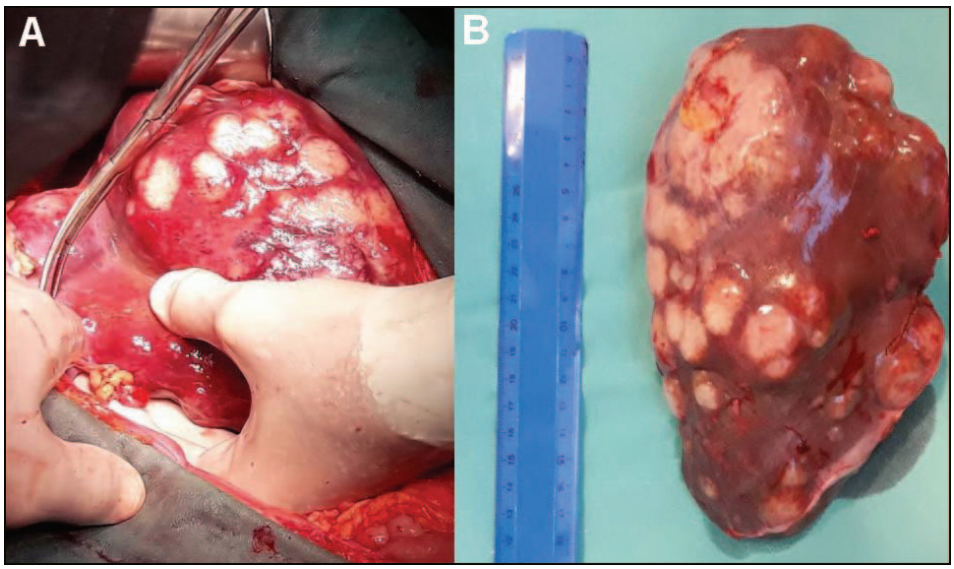

**Fig 4 – A) The left liver lobe changed by metastasis;
B) The sample after the left hepatectomy.**

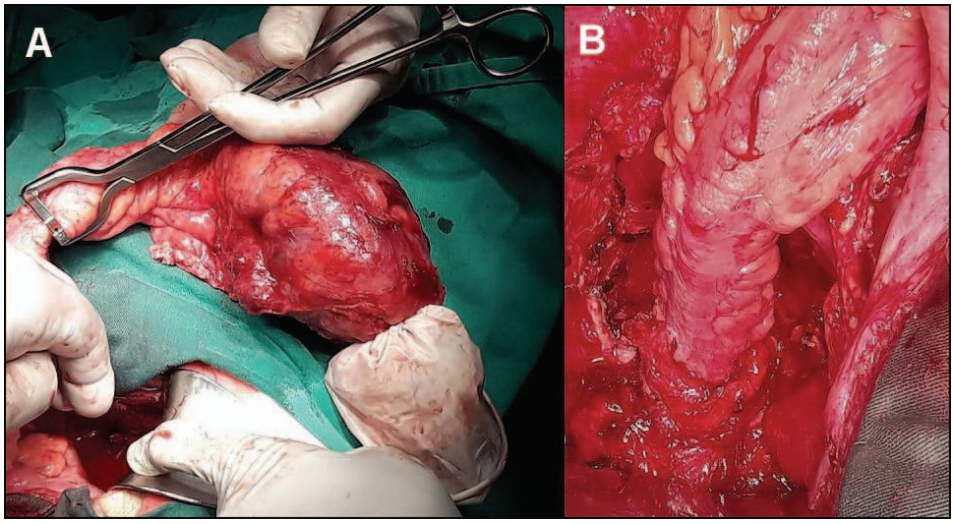

**Fig. 5 – A) A part of rectosigmoid colon with the tumor;
B) Termino-terminal anastamosis after resection of the tumor.**

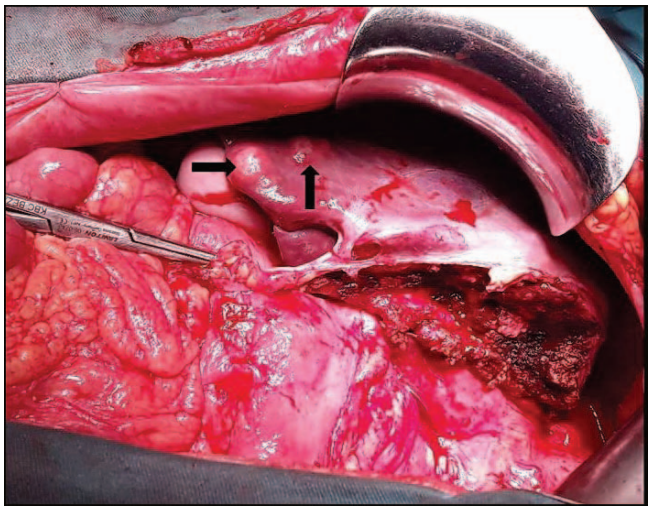

**Fig. 6 – Metastatic changes on the right liver lobe
indicated with black arrows.**

On day 16 after the operation, dehiscence of colorectal anastomosis occured and relaparatomy with colostomy bag fitting was performed. The follow-up values of β-hCG after the surgery did not change significantly and these were 460.80 mIU/mL. Due to the disease expansion, and removal of the left liver lobe presence of due to many secondary deposits, as well as some metastatic changes in the right liver lobe, the patient died on day 40 afer the surgical treatment due to hepatic insufficiency.

Discussion

ETT is a very rare form of trophoblastic tumor which is most often followed by previous term pregnancy, spontaneous miscarriage, ectopic pregnancy and hydatidiform mole, but it is also recorded in nulliparous women. Although it most often occurs at the age group from 15 to 48 years (average 36.1 years), it is also described in the patients in the postmenopausal period [1, 4, 5]. The most common symptoms for this disease are abnormal vaginal bleeding and irregular menstrual cycles [1]. Regarding the usage of ultrasonography in making a diagnosis, there are no specific guidelines which would be used as a basis for suspecting this type of the tumor [7, 8]. Uterus is the most common primary location of ETT (40%) as well as endocervix (31%). The extrauterine location of ETT is rare, and it is often very hard to determine a primary origin of the tumor [6, 9]. ETT most often spreads into the lungs, but also into some other tissues such as brain, liver, pelvic lymph nodes [10]. In our case, this was a very rare retroperitoneal tumor location without the proved primary origin. The fractional exploration curettage excluded presence of the tumor in the uterus and the histopathological finding after salpingectomy of both sides did not confirm possible primary tubular localization. After presurgery chemotherapy had been administered, there was no any improvement, i.e., β-hCG kept its values and the tumor size did not change. Considering resistance of the tumor to the administered treatment, both resection of rectosigmoid colon with the tumor and the resection of the left liver lobe which was completely changed with the tumor, were decided to be done. It was planned to continue with the cytostatic therapy after surgical treatment and the tumor mass reduction. In general, the patients should have one, or two cycles after lowering the β-hCG values to the normal values. Radiotherapy is also possible, while resection of metastasis is recommended for all cases when feasible [11].

Conclusion

The ETT is a rare disease which do not have established treatment protocols. In order to make as much adequate decision on a treatment method as possible, it is necessary to organize a team work with multidisciplinary approach. Despite the fact that the application of diagnostics could have been faster and more precise and that the applied treatment, primarily surgical, was awaited for some time, we believe that this would not have any influence on the treatment outcome considering the fact that it was the late stage of the disease. A surgical resection of the tumor is a primary method for treating ETT. There is neither any standard nor effective chemotherapy protocol due to very small number of cases. Therapy mode varies greatly, and chemotherapy can be administered before and after surgical treatment.

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