Introduction. Gestational trophoblastic diseases (GTD) are a spectrum of tumors with a various of biological behavior and potential for metastases. It consists of hydatiform mole, invasive mole, choriocarcinoma and placental site trophoblastic tumor. Choriocarcinoma presents a very aggressive tumor with high malignant potential. Case report. We presented the two cases of choriocarcinoma with brain metastases. The first one was manifested by neurological deterioration as the first sign of metastasis, while the second patient had firstly metrorrhagia and in the further course neurological disturbances that suggested the presence of brain tumor. In both cases we applied a combined treatment of surgery, chemotherapy and radiation therapy. Both patients survived with high quality of life. Conclusion. A successful outcome of brain metastases of choriocarcinoma was obtained by the use of a combined treatment of surgery, chemotherapy and radiation therapy. In cases of young women with brain metastases, gynecological malignancy should be always considered.

Key words: choriocarcinoma; neoplasm metastasis; brain neoplasms; diagnosis; drug therapy; radiotherapy; neurosurgical procedures; treatment outcome.
to a higher number of chemotherapeutical cures with no fertility sparing. This emphasizes the necessity of complete body screening, including computed tomography (CT) of the brain when the diagnosis of choriocarcinoma is made.

**Case report**

**Case 1**

A 19-year-old female patient was admitted to the Institute of Neurosurgery, Clinical Center of Serbia, as an emergency due to spontaneous right parietal intracerebral hematoma whose presence was verified by computerized CT of the brain (Figure 1).

A week before admission the patient had a headache associated with vision impairment. On the admission day, the patient suddenly lost consciousness. Neurological examination revealed uncommunicative patient with circular pupil responding to light, as well as dextral paresis of the lower level. Her medical history recorded one vaginal birth. After 3 days of admission, her condition was abruptly aggravated with respiratory arrest, and appropriate cardiopulmonary resuscitation (CPR) measures were applied. Control brain CT showed the enlargement of hematoma mass and cerebral edema, due to which the patient immediately operated on and hematoma evacuated. Control brain CT revealed hypodense changes in the remaining hematoma, i.e. tumor or malformations of cerebral blood vessels, requiring digital subtraction angiography which ruled out the presence of vascular malformation as the cause of hemorrhage. Eight days later, the patient was reoperated, and the right paraventricular tumor of about 2 cm in size removed (Figure 2). After operation, the patient was aware with the passing dexter hemiparesis and psychoorganic syndrome of the mid degree.

Given that preliminary histopathological examination aroused suspicion about the choriocarcinoma, CT of the chest, abdomen and small pelvis was carried out immediately, which demonstrated multiple circular soft-tissue changes scattered in both lungs. Other findings were regular. Subsequently, blood tests for alpha-fetoprotein and beta hCG were carried out, revealing the serum beta hCG concentration over 225000.0 IU/L (less than 5 is normal), and alpha-fetoprotein of 0.5 µg/L (13.4 µg/L is normal). Immunohistochemical examination of the tumor confirmed the choriocarcinoma.

The Medical Board decided to introduce 20 cGy radiation therapy. The patient tolerated radiotherapy well, with no antiedematous therapy, and consciously but slightly slow from psychic aspect. After completed radiotherapy, the patient was transported to the Clinic of Gynecology and Obstetrics because of metastatic pulmonary changes, further diagnostics and treatment of choriocarcinoma. Upon Trophoblastic Diseases Board consideration, it was concluded that the patient had brain choriocarcinoma and metastases to lungs without any evidence of underlying uterine disease. Considering that it was the patient with FIGO stage IV, WHO 17, with beta hCG value of 470,235 IU/L, it was decided to employ chemotherapy (etoposide, methotrexate, actinomycin D, cyclophosphamide and Oncovin – EMACO). Until a complete remission (41 days), the patient was administered two therapies according to this protocol. The patient was discharged recovered with preserved fertility. Neurological status on discharge and two months later was completely normal.

**Case 2**

A 35-year-old female patient was admitted to the Clinic of Gynecology and Obstetrics, Clinical Center of Serbia, in December 2010 due to previous histopathologically verified uterine choriocarcinoma upon exploration curettage which had been performed for abundant uterine bleeding. Her personal anamnesis reads that she had two deliveries by Cesarian section in 2002 and 2008. Between two births, the pa-

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tient had one complete molar pregnancy (complete hydatid mole) which, because of being refractory, was treated by methotrexate. On admission, ultrasonography verified the isthmic-cervical uterine tumor and magnetic resonance imaging (MRI) of the abdomen and small pelvis corroborated the presence of $96 \times 77 \times 66$ mm tumor with bilateral parailiac and inguinal lymphadenopathy. The chest X-ray was normal. The patient was staged by Trophoblastic Diseases Board as WHO 9, FIGO I, and urgent hysterectomy with bilateral ovarian conservation was indicated. Immediately prior to surgery, beta hCG was 188,871 IU/L. In post-operative course, the patient received one course of chemotherapy by EMACO Protocol. Control MRI of the abdomen and chest detected metastatic changes to lungs, on what account the patient was restaged by the Board as FIGO 3, WHO 10, and accordingly, two courses of EMACO chemotherapy were added; this new administration resulted in 90-day remission of the disease and complete normalization of beta subunits. The patient was rehospitalized in May 2010 due to vertigo and occasional vision field incidents, what aroused the suspicion to metastatic changes in the brain. Neurological status revealed discrete dexter hemiparesis. Endocranial CT verified the presence of the right parietooccipital tumor (Figure 3).

Repeated rise of beta hCG was 2,284 IU/L and the patient received IV, V and VI course of chemotherapy, and neurosurgical examination (MRI, liquor puncture) found congenital cavernous angioma. Chemotherapy resulted in regression of brain tumor and normalization of beta subunits. The patient was discharged recovered in July 2010, and advised by the neurosurgeon to have her control done in 3 months. At the beginning of October, the patient manifested again the same symptoms as in earlier hospitalization. Based on endocranial CT scanning and symptoms (vertigo, dizziness and crural hemiparesis to the left), the neurosurgeon decided to operate on her. In addition, the increase of blood beta hCG level was increased again. Upon tumor extirpation, the patient was again transferred to the Clinic of Obstetrics and Gynecology to receive VII and VIII course of EMACO chemotherapy. A histopathological finding indicated the metastatic brain choriocarcinoma which was hemorrhagically and necrotically modified. According to the decision made by Neurosurgery Board, palliative 20 cGy radiotherapy was applied. After radiation therapy, the patient went well, but her fertility was not preserved. Neurological status on discharge was normal.

**Discussion**

The risk of choriocarcinoma is rare before the age of 20 years, and it is significantly increased in individuals over 40 years. Both presented cases are beyond typical etiology of choriocarcinoma.

GTDs are most frequent in Asian countries with the annual incidence of 1/2000 of all pregnancies (births and miscarriages). Recent literature has described only 150 choriocarcinomas metastasized to the lungs and brain. In diagnosis of choriocarcinoma, metastatic changes are detected in about 30% of patients. Due to hematogenic spread of trophoblastic tissue, the metastases are manifested very early, and their symptoms are usually related to bleeding from metastatic focus. Staging of patients based on WHO and FIGO criteria allows for rapid orientation and prompt treatment. The WHO criteria suggest that any patient with WHO score over 8 is considered at high risk and the initiation of treatment is suggested as soon as possible without additional therapy such as surgery or radiation therapy. Both presented cases had high WHO score (17 and 9, respectively).

Treatment of choriocarcinoma consists of polychemotherapy. Initiation of EMACO radiotherapy is the first treatment choice. Surgical treatment is used in cases of local, chemoresistant metastatic focus and recurring disease. Nevertheless, some studies show that surgical treatment of metastatic changes shortens the time of cure.

Application of radiotherapy in cases of metastatic brain choriocarcinoma is controversial. Certain authors suggest 30 to 40 Gy radiotherapy along with chemotherapy. Study on 78 subjects affected by choriocarcinoma with brain metastases demonstrated survival of 50% in patients treated both by chemo- and radiotherapy vs 24% survival rate in those treated with chemotherapy only.

Our experience in both cases show that the synergism of chemotherapy, surgical evacuation of tumorous changes, and, finally, radiotherapy is a pathway to preservation of reproductive ability and healing of patients.

**Conclusion**

Treatment of GTD with metastatic changes in the brain is a great challenge. Nevertheless, the incidence of cure is high. The first treatment choice is chemotherapy and surgery, and in cases where it is required, radiotherapy, as well. Given high metastatic potential, choriocarcinoma should be considered in cases of intracranial hemorrhage with the unusual location in reproductive women. Histopathological findings and measurements of beta hCG are necessary for making the diagnosis of choriocarcinoma.

REFERENCES


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