Refractory metastatic choriocarcinoma treated surgically with polychemotherapy - case report

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Summary

The authors present the course of treatment of refractory metastatic choriocarcinoma in a 49-year-old woman was treated surgically by hsterectomy and resection of suprarenal gland metastases. During the treatment the patient received 15 courses of polychemotherapy with different protocols. After five years of treatment and seven years of follow-up there is no evidence of recurency of the disease.

Key words: Choriocarcinoma; Metastasis; Suprarenal gland; Polychemotherapy.

Introduction

Gestational trophoblastic diseases include disorders of placental development, hydatidiform mole, neoplasms of the trophoblast, choriocarcinoma and placental site trophoblastic tumor [3]. Optimal treatment is based on correct diagnostic procedures, estimation of risk score and adequate therapy [2].

Case Report

The patient 49 years old, from Belgrade, was hospitalized at the Institute of Obstetrics and Gynecology and of the Clinical Center of Serbia in September 1996 in very serious condition with hematemesis and melena because of suspected choriocarcinoma.

The patient had a history of two vaginal deliveries and five abortions, the last in November 1995. Her last menstrual period was in April 1996. The first symptom of disease was abnormal vaginal bleeding after five months of amenorrhoea. Due to enlargement of the uterus and suspicion of an ectopic pregnancy, curettage was performed in November 1995. The first four menstrual cycles following curettage were regular. From the beginning of June 1996 symptoms including dizziness and hematemesis had started. Chest X-ray scan disclosed metastatic tumor masses. Thyroid gland hyperfunction was also present. In August 1996 she was hospitalized because of excessive vaginal bleeding mixed with sponge-like tissue particles. After gynecological examination and one blood transfusion she was transfered to our Institute with the diagnosis of choriocarcinoma.

On admission to hospital the patient was conscious, diaphoretic and pale, with signs of abdominal defence. Gynecological examination showed normal findings of external genitalia and vaginal walls. The cevix was about 2 cm long, firm, smooth, mobile and painless, with livid changes in length of 1 cm in diameter near the external os. Uterine size was slightly enlarged, corresponding to a pregnancy of two months, with normal consistency and mobility. The adnexa was normal on the left side but painful on the right side. The Douglas pouch was painless and free of tumor. Ultrasound scan showed an enlarged uterus with an arteriovenus fistula, 123 x 29 mm in diameter. The endometrium was thick with hyperechogenic shadows on the posterior uterine wall. A cyst of 37 mm in diameter was present in the left ovary, while the right ovary appeared normal. Ultrasound also disclosed enlargment of the right liver lobe with milliary metastatic deposits of different sizes. Chest X-ray showed numerous bilateral pulmonal nodular shadows of different sizes. The beta-hCG titers were 18,000 IU/l.

Considering a possible gestational trophoblastic neoplasia it was decided to apply polychemotherapy (MAC protocol) with lowered doses of cytostatics due to the poor condition of the patient who had severe anemia. After correction of the anemia with five units of blood, the patient received the first cycle of chemotherapy according to the MAC protocol in September 1996. During and after this cycle she received an additional 14 units of blood. Side-effects of chemotherapy included inflammation of the bucal mucosa, dysphagia, nausea and vomiting, subfebrile body temperature and relative thrombocytosis due to reactive sideropenic anemia.

The second cycle of chemotherapy following the MAC protocol started in October 1996. During that cycle the patient received three units of blood. Side-effects of chemotherapy included skin petechiae and glossitis with dysphagia.

The patient was operated on after the second cycle of chemotherapy in November 1996. Operative findings included interintestinal adhesions of the small intestine as well as adhesions on the posterior uterine wall and right side parametria as a result of tumor spread through the uterine wall involving the intestinal serosa. Tumor also infiltrated the pouch of Douglas, right uterine wall, right parametria along the major blood vessels and right side of the infundibulopelvic ligament causing thickening and lividity. The uterus was the size of a female fist, soft, livid and vulnerable on manipulation. The left ovary was small, the left side the fallopian tube was livid and fixed to the peritoneum of the Douglas pouch. Total hysterectomy with bilateral salpingo-oohporectomy was performed as well as intestinal adhesiolysis and identification of the right side of the urether and drainage of the Douglas pouch. The postoperative course was regular with administration of broad-spectrum antibiotics, anticoagulants and one unit of blood transfusion.

Histopathology was as follows: Macroscopic examination showed an irregularly shaped uterus 50 x 50 x 40 mm in diameter, with a cone-shaped cervix of 25 x 28 mm and one adnexa

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of 90 g in weight. The uterine surface was brownish and rough. The myometrium was 25 mm thick with few intramural, firm, infiltrating, yellowish nodes 11 to 17 mm in diameter. The uterine cavity was partially filled with a soft, finger-shaped formation 15 x 5 mm in size. The endometrium was yellowish, smooth and shiny. The adjacent fallopian tube was 30 x 5 mm in size, and the cervix was without any significant macroscopic changes. The ovary (the largest part) was 15 x 25 x 10 mm in size, brownish and semi-firm. In the remaining material, the right side of the adnexa, along with a few parts of blood clot-like tissue, weighed 2 g. In this mass the right fallopian tube was present and was 5 x 70 mm in size. Another ovary, 25 x 30 x 15 mm in diameter, had a brownish, smooth, cystic defect at the core which was 20 mm in diameter. Microscopic analysis of the myometrium revealed several eosinophilic foci of necrosis containing few isolated trophoblast cells with hyperchromatic nuclei; a typical appearance of choriocarcinoma.

After surgical treatment, the patient received a third cycle of polychemotherapy according to the MAC protocol. The level of beta-hCG after this cycle lowered from 58.8 IU/l to only 10.4 IU/l, but the following control showed a value of 3,784 IU/l. The fourth cycle of chemotherapy was started in January 1997, according to the VBP regimen (vinblastin, cisplatin, bleomycin). Side-effects in this cycle included nausea and vomiting, abdominal pain and anemia, which were corrected with one unit of blood. After this cycle, values of beta-hCG lowered, and the patient received another two cycles of chemotherapy according to the VBP protocol (in February and March 1997).

Consecutive chest X-ray scans and abdominal ultrasound scans showed complete regression of all pulmonary and liver deposits after the fifth cycle of chemotherapy. The patient was discharged in April 1997 when the beta-hCG level was of normal value (4.5 IU/l), and followed monthly for beta-hCG determination the next 15 months. Since beta-hCG levels had not exceeded 5 IU/l, the patient was then followed-up once in three months starting from August 1998. In November 1998 beta-hCG levels suddenly rose to 500 IU/l remaining at that level in the following weeks. Due to evident onset of recurrent disease, the patient was admitted to our Institute in January 1999 and received another four cycles of polychemotherapy (EMA-CO, POMB, 5-fluorouracil) which lowered β-hCG levels to 30 IU/l. An ectopic focus was disclosed in the right side of the suprarenal gland by magnetic resonance imaging (MRI) in June 1999.

Starting in July 1999 the patient received another four cycles of chemotherapy according to the ICE regimen (iphosphamide, carboplatin, etoposide). During that period beta-hCG values were never below 100 IU/l, and suddenly rose immediately after the last cycle of polychemotherapy. Unfortunately, a control MRI scan of the right side of the suprarenal gland performed in December 1999 showed no changes in size of the metastatic focus.

In December 1999 the patient was reoperated. Due to infiltrative spread of the tumor in the glandular tissue as well as in the right hemidiaphragm and adjacent structures, only partial resection of the tumor was carried out. Histology showed tumor on the right side of the suprarenal gland, fragmentated in two pieces each 2 cm in diameter, red to yellow color, partially firm, weighing 25 g and 15 g. Microscopically, it consisted of polymorphic, polygonal cells with abundant cytoplasm and vesicular nuclei and partially of cells with a high mitotic index with significant necrosis. Tumor infiltrated the blood vessels and surrounding adipose tissue, and was diagnosed as *carcinoma glandula suprarenalis*. After reoperation, levels of beta-hCG lowered to 347 IU/l.

Immunohistochemistry of both tumors, of the suprarenal gland and uterine tumor extirpated in 1996, performed at the Institute for Application of Nuclear Energy - INEP, Zemun, however, showed that the suprarenal node was a metastasis of the same beta-hCG producing neoplasm (Figure 1). During two months, the period needed for this diagnostic procedure, the beta-hCG level rose again up to 31,800 IU/l. In the meantime, the patient was hospitalized again due to pulmonary symptoms and pleural effusion containing malignant cells. Pleural puncture was performed three times. Another three cycles of chemotherapy, this time following the ICE protocol, were started in February 2000 until April 2000. Values of beta-hCG were controlled weekly, and were falling gradually. Blood panel, liver enzymes and coagulation factors were also controlled on a daily basis. Because of severe anemia the patient received four units of blood during the last cycle, after which beta-hCG titers were 205 IU/l.

From the beginning of the disease, the patient received overall 15 cycles of chemotherapy, following different protocols. After the last hospitalization, she was followed weekly by assessing beta-hCG titers. Regular follow-up has continued monthly, bimonthly, and at six-month intervals until today. The patient is still in remission of disease.

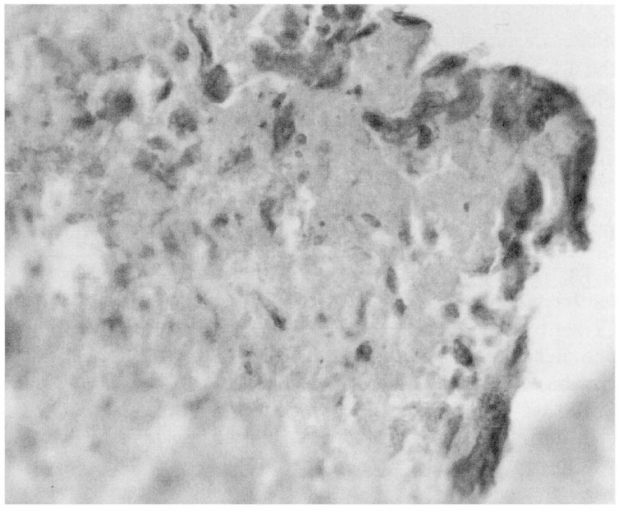

Figure 1. — Immunohistochemical staining for beta-hCG in metastatic tumor of the suprarenal gland.

Discussion and Conclusion

The incidence of choriocarcinoma is 1 in 40,000 pregnancies. The risk is significant in pregnant women older than 45, and slightly less in the 40-45-year age group. Our patient was 49 years old at the onset of the disease.

Clinical presentation varies from case to case. The most common symptoms of choriocarcinoma are vaginal bleeding or discharge, somtimes along with abdominal pain and palpable pelvic masses. The first symptom in the described case was vaginal bleeding after amenorrhea and because of the patient's age diagnosis was posed after ten months, in the advanced stage of the disease.

Due to a cross-reaction between the alpha-hCG subunit and TSH, thyroid hyperfunction is common. Our patient also had this symptom.

In one-third of the cases, symptoms related to metastases are the first indication that choriocarcinoma is present. Because of the slow development of the disease, as well as its aggressive nature, metastases are present at the moment of diagnosis in 60% of cases. The most common metastatic sites are the lungs, central nervous system and liver. In about 10% of cases the suprarenal gland is involved.

Choriocarcinoma is often diagnosed with increased beta-hCG levels in connection with metastatic lesions in other organs disclosed by radiography. MRI, which located the metastasis of choriocaracinoma in our patient, showed infiltration with trophoblastic tumor as diffuse enlargement of the uterus, focal tumor masses, loss of local anatomic structures and pathlogical vascularization [6].

No correlation was found between X-ray findings and beta-hCG levels, nor with specific histological type of trophoblastic tumor.

Prognosis for patients with trophoblastic diseases refractory to chemotherapy is generally very poor [4]. Few publications deal with treatment of refractory trophoblastic diseases. Only three papers elaborate application of the ICE regimen for treatment of refractory trophoblastic diseases with CNS metastases.

New chemotherapeutic protocols containing etoposide, cisplatin and iphosphamide, along with resection of foci resistent to chemotherapy, are effective in most cases [5]. New technologies and application of colony stimulating factors are reducing the interval between courses of chemotherapy and drug dosage, and along with autologous bone marrow transplantation have a major role in the future treatment of patients exibiting drug resistance [7]. The goal in the treatment of trophoblastic diseases refractory to conventional chemotherapy today is finding new efficient protocols [1].

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