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CASE REPORT

Placental Site Trophoblastic Tumor

Clinical and Pathological Report of Two Cases

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Placental site trophoblastic tumor (PSTT) is the rarest disease of the gestational trophoblast. Our two cases will be interesting not only because of the rarity of the disease, but because both were recognized before operation. Since the tumor cells are lined up tightly side by side, this disease must be distinguished primarily from tumors of epithelial origin. The authors highlight that the diagnosis should rely on intense hPL-positivity as well as the ultrastructural image of the tumor. In histologically equivocal cases, the determination of hPL, hCG, and MIB-1 immunologic markers can be recommended as routinely performed morphological examinations. Serum hCG monitoring is recommended to follow the evolution of the tumor. (Pathology Oncology Research Vol 6, No 4, 292–294, 2000)

Keywords: placental trophoblastic tumor, choriocarcinoma, immunohistology, intermediate trophoblast

Introduction

Placental site trophoblastic tumor (PSTT) is the rarest disease of the gestational trophoblast. While Marchand in 1895 used the term of „atypical choriocarcinoma", today's terminology comes from Kurman who described this pathology in 1976 as a "pseudotumor", and regarded it as an exaggerated reaction of the placental bed.[7,9] As became clear later on, the underlying pathology is a proliferation of the intermediate trophoblast cells. It is not always possible to recognize this disorder in tissue sample (curettage), because of the difficulty of differentiating it from choriocarcinoma, from benign nodule or pathological reaction of the placental bed.[8] The behavior of the tumor is variable. The majority of the (approximately) 80 cases published in the English literature so far had good prognosis but rapidly metastasizing, fatal cases have also been reported.[1,8,13] Some cases have been associated with nephrosis syndrome, which stopped after hysterectomy.[2] Our cases will be interesting not only because of the rarity of the disease, but because both have been recognized before operation. No cases have been found in the Hungarian literature.

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Case reports

Case 1

The 28-year old woman (P: 2, ab: 1) had a normal gestational period and gave birth to a healthy newborn by cesarean section (1996). Three months after delivery, she was readmitted because of bleeding to the county hospital, Miskolc. A tissue sample was taken and the histological examination proved PSTT. The patient was transferred to the Department of Obstetrics and Gynecology, Faculty of Health Sciences, Semmelweis University, where a second biopsy confirmed the first diagnosis. Because of continuous bleeding the patient underwent an abdominal hysterectomy. An isolated tumor was found in the uterus and chemotherapy was not administered. The patient is well and has had no symptoms for 4 years with regular follow-up.

Case 2

This 30-year old woman (P: 1, ab: 2) was admitted for suspected missed abortion (1995). A diagnosis of PSTT was established upon histological examination after

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removal of the mass from the uterus with D & C. This was followed by hysterectomy, with the adnexa preserved. In the uterus a tumorous mass was found that extended to about half of the myometrium. The patient had no symptoms in the postoperative period and after the final histological results she received multiagent chemotherapy. She has had no symptoms for 5 years.

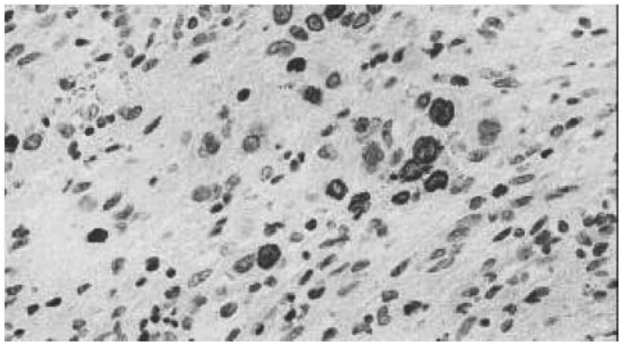

Figure 1. *Case No 1. MIB-1 expression in the nucleus of the atypical trophoblastic (250x).*

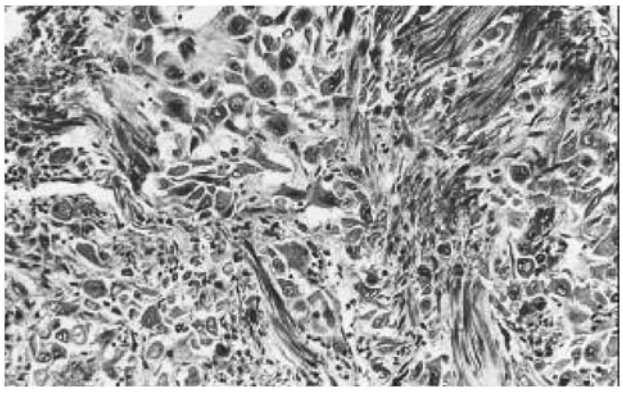

Figure 2. *Case No 2. Infiltration of the atypical intermediate trophoblastic cells between the smooth muscle cells of the uterine wall. (HE, 160x).*

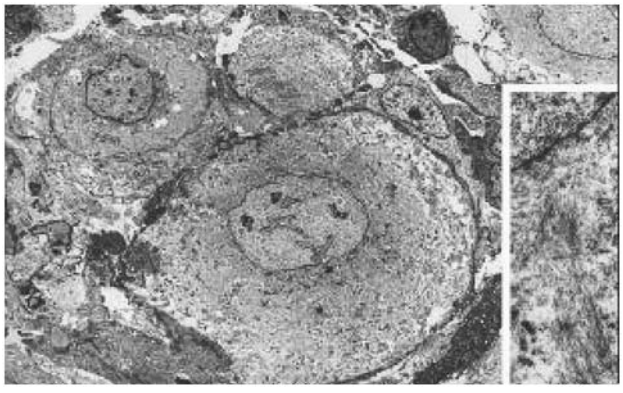

Figure 3. *Case No 1. Electronmicroscopy of PSTT. Neoplastic trophoblastic cells with large cytoplasm are sorrounded by smooth muscle cells. Insert: Small bundles of perinuclear filaments (3000x, insert: 21000).*

Morphological observations

The removed samples in both cases showed proliferation of monomorphic, intermediate trophoblast cells, with a large amout of cytoplasm. Nuclei were round, and sometimes segmented or polynucleated forms could be seen. Within the nuclei, adhesion of the chromatin to the nuclear membrane was observed. Dividing cells were rarely seen, but the proliferating activity of the tumor cells was remarkable in both cases (MIB-1) (***Figure 1***). Syncytiotrophoblasts were not found. It has been observed in the tumors of the removed uteri that the trophoblast cells infiltrated into the uterine wall pushing forward among the smooth muscle fibers, but the invasion reached only to the upper third of the myometrium (***Figure 2***).

Several immunohistochemical reactions were performed for both cases. In addition to the above mentioned proliferation marker, the tumor cells were strongly positive for an epithelial marker (keratin), as well as hPL-positivity. The hCG-reaction was also positive, but less intensely than was hPL. Smooth muscle actin staining of the tumor cells was negative.

An ultrastructural investigation was also performed for case 1. Under the electron microscope, the tumor cells proved to be a combination of the cytotrophoblasts characterized by a poor cytoplasm, and the synticyotrophoblasts, which are rich in organelles. The cells were arranged tightly side by side, with a minimal intercellular space. Abundant endoplasmic reticule membranes and intermediate filament fibers were seen in the cytoplasm, sometimes concentrated around the nucleus (***Figure 3***).

Discussion

The WHO classification distinguishes 4 classes of gestational trophoblast diseases. The first class is the hydatiform mole and it is further divided into two subclasses: complete and a partial mole. The second class is the invasive mola, while the third one is reserved for the choriocarcinoma. The most rarely occurring placental site trophoblastic tumor (PSTT) belongs to the fourth group. The first three pathologies are characterized by the pathological proliferation of both existing types of trophoblasts, although not to the same extent. In PSTT, only intermediate trophoblasts are involved. These cells constitute a transitional form between cytotrophoblasts and synticyotrophoblasts. Their physiological role is to form the placental bed, which is why they are also called extravillous trophoblasts.[6] Intermediate trophoblasts may have a pathological role in three kinds of anomalies, two forms of them are benign disorders. The nodule of the placental bed is an isolated one usually of microscopic size, that consists of intermediate trophoblasts. This residue may cause menorrhagia after delivery or abortion, and may cicatrize. The other benign anom-

aly is the so-called exaggerated placental site reaction.[6] By its size and its morphology, it may be similar to PSTT, can be the cause of bleeding disorders, but can be treated with endometrial ablation. On the other hand, PSTT is a real tumor of the intermediate trophoblast cells.

The first symptoms of the disease are usually seen after delivery or abortion. The dominating signs of the clinical picture are vaginal bleeding and enlargement of the uterus.[2,3] These symptoms were characteristic of our cases as well. The serum-hCG was elevated, but not so high as in other gestational trophoblast diseases. The explanation of this moderated elevation of hCG is that these cells produce primarily hPL and less hCG. This is why it may be difficult at times to establish the diagnosis preoperatively. Our cases were not an exception in this aspect: serum-hCG was 25 mIU/mL for case # 1, and 50 mIU/mL for case # 2.

The morphological diagnosis is not without problems either. In a case published by Orell, the biopsy sample was examined by 24 pathologists whose opinion divided, 12 favoring benign and 12 malignancy.[10] Since the tumor cells are lined up tightly side by side, this disease must be distinguished primarily from tumors of epithelial origin.

The authors highlighted that from an immunohistological perspective, the trophoblast presents epithelial characteristics, which is not very helpful for diagnosis. The diagnosis should therefore rely on intense hPL-positivity as well as the ultrastructural image of the tumor. Another differential diagnostic question is the distinction of Placental Site Trophoblastic Tumor from epithelioid smooth muscle tumors. In immunohistochemical tests with alpha smooth muscle actin, smooth muscle tumors do stain while PSTT does not, as shown in our cases. High mitotic activity is not characteristic of PSTT, and therefore the benign disorders of the intermediate trophoblast have to be also taken into account in the differential diagnosis. Nevertheless, the proliferative activity is always higher than in the benign trophoblastic anomalies. Other authors also mention this observation.[2,5] Shih and Kurman developed a new test in which the intermediate trophoblasts express a specific marker, which is the melanoma cell adhesion molecule (Mel-CAM) and which can be displayed by immunohistochemical methods. This molecule can be found in intermediate trophoblasts, whether under normal or pathological circumstances. Cytotrophoblasts and syncytiotrophoblasts do not present this marker and do not react. It seems therefore highly probable that Mel-CAM is a specific and sensitive marker of differentiation for intermediate trophoblasts.[12]

Thus, in histologically equivocal cases, the determination of hPL, hCG, and MIB-1 immunologic markers can be actually recommended as routinely performed morphological examinations.

There is an ambiguity judgment in the literature about DNA flow cytometry in PSTT.[3,5,11] In a PSTT case described by Remadi with pulmonary metastasis, tetraploid DNA-content was found. Diploid content was reported in each of the three case published by Fukunaga.[3,11]

The therapy of the tumor is primarily surgical treatment. Hysterectomy seems to be sufficient in most of the cases. Although PSTT does not react as positively to chemotherapy as does choricarcinoma, chemotherapy is still used as an adjuvant. In the three above-mentioned diploid cases of Fukunaga for example, 2 had no tumor following combined treatment, while the third patient developed extensive metastases in spite of the same therapy and died.[3]. Serum hCG monitoring is recommended for the control of the evolution of the tumor[2,13] As for prognosis, literature on PSTT may be controversial in several points but all agree that it is not possible to define any reliable clinical or morphological marker to predict the biological behavior of these tumors.[2,3,10,13]

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