

Postmenopausal choriocarcinoma: a case report

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Abstract

Postmenopausal uterine choriocarcinoma is very rare and benefits of curative chemotherapy. We present here the case of 62-year-old women with uterine bleeding. Emergency surgery revealed a uterine tumor and histopathology findings were consistent with choriocarcinoma. Immunohistochemistry tests confirmed β hCG and cytokeratin expression by malignant cells, thus establishing the positive diagnosis.

Keywords: uterine choriocarcinoma, uterine bleeding, immunohistochemistry, human chorionic gonadotropin.

Introduction

Choriocarcinoma is a highly malignant epithelial tumor originating in trophoblast. Usually present within a hydatyform mole, it primarily occurs during the fertile period and is extremely rare after menopause [1].

Choriocarcinoma is a biphasic proliferation of trophoblast and syncytiotrophoblast, with morphology similar to primitive trophoblast of the placental previllous stage; chorial villi are absent in this tumor type. Choriocarcinoma shows variable clinical signs and symptoms, the most frequent being abnormal uterine bleedings.

However, signs linked to metastases presence, often pulmonary, can sometimes be the first to suggest the diagnosis. Other secondary locations also include brain, liver, gastrointestinal or urinary tract, and haemorrhage is a frequent clinical sign [2].

Materials and methods

A 62-year-old woman presented with abundant postmenopausal vaginal bleeding requiring emergency surgical intervention.

Anamnesis reveals four at-term deliveries, climax at 52, and suspicion of untreated perimenopausal leiomyomatosis. She was admitted for surgery and underwent total interadnexial hysterectomy.

For both routine histopathological examination and immunohistochemistry, tissue specimens were fixed in 10% (v/v) phosphate-buffered formalin for up to 24 hours, then dehydrated using graded alcohols, cleared in xylene and embedded in paraffin wax.

Hematoxylin-eosin staining was performed on 4 μ m-thick sections after dewaxing in xylene and rehydration (chemicals and dyes from Merck KGaA, Darmstadt, Germany).

Immunohistochemistry (IHC) analysis was required in order to ascertain the choriocarcinoma diagnosis, due to the high cell pleomorphism seen.

Sections (4 μ m thick) were deparaffinized, rehydrated and kept in buffer solution. Heat-induced antigen retrieval in citrate buffer was used for β hCG immunostaining.

Briefly, slides were blocked with normal serum, incubated with the primary antibodies (used at final dilutions indicated below) for 1 hour at room temperature and then with biotinylated secondary antibodies.

Detection was based on the labeled streptavidin-biotin complex technique (LSAB kit, DAKO, Glostrup, Denmark), using 3,3'-diaminobenzidine (DAB) as chromogenic substrate.

Negative controls were prepared following the same procedure, but using antibody dilution buffer instead of primary antibodies.

Primary monoclonal antibodies used, their clones, final dilutions and producers were:

- mouse *anti- β hCG*, clone M94138, prediluted, Biogenex (San Ramon, CA, USA);
- mouse *anti-cytokeratin* (large spectrum), clone KL1, final dilution 1:200, Coulter Immunotech (Fullerton, CA, USA);
- mouse *anti-epithelial-membrane antigen* (EMA), clone E29, final dilution 1:200, DakoCytomation (Glostrup, Denmark);
- mouse *anti-vimentin* clone V9, final dilution 1:100, DakoCytomation (Glostrup, Denmark);
- *anti-smooth muscle α -actin*, clone 1A4, final dilution 1:2000, Sigma (St. Louis, MO, USA).

Results

Macroscopic examination of tissue samples removed during the surgery showed a 7 \times 7 \times 4 cm globular uterus. Cervix inspection revealed os enlargement and a transversal perforation.

Upon sectioning, a 4 \times 3 \times 3 cm polyp-like tumor was found inside the uterine cavity with uneven, cauliflower-like appearance.

In cross-section, the neoplasm had a fleshy consistency with diffuse necrotic/hemorrhagic sheets and was dark-red with small green spots.

The tumor pediculum was attached to the uterine fundus, nearby a 3-cm formation (of increased consistency, pale, encapsulated, whirl-looking upon sectioning). Intraoperative exploration found sclero-hyalinized 2 \times 2 \times 1 cm ovaries.

Microscopic examination helped establishing positive diagnosis based on the presence of highly pleomorphic malignant cells within the polyp-like tumor. Some cells were multinucleated showing enlarged, intricate nuclei with abundant atypical mitoses, granular, uneven chromatin and numerous nucleoli.

A different cell population was also present, polygonal with vesicular nuclei; cells formed distinct areas (sometimes alveolae-like structures) and invaded the superficial myometrium, where lympho-monocyte infiltrate and haemosiderin accumulation were also present (Figures 1 and 2).

Localized human beta chorionic gonadotropin immunopositivity demonstrated the presence of syncytiotrophoblast (Figure 3).

Malignant cells were immunoreactive with pancytokeratin antibodies (Figure 4) and, to a lesser extent, with antibodies against epithelial-membrane antigen.

Diffuse vimentin expression was also noted, although not associated with the malignant trophoblast cells (Figure 5). Antibodies against smooth muscle actin decorated mainly the vascular walls (Figure 6).

Discussions

Choriocarcinoma is a condition difficult to diagnose in women above reproductive age due to its very low incidence. The most frequent symptom in patients with uterine choriocarcinoma is abnormal vaginal bleeding, but medical assistance can also be sought for due to signs related to lung metastases [3].

Rare cases of extragenital primary choriocarcinoma are also reported (abdominal [4], urinary bladder [5], stomach [6], extraovarian [7], lung [8]).

Histopathological diagnosis is based on the absence of chorionic villi, although their presence does not always exclude the diagnostic.

Choriocarcinoma cell populations include malignant cytotrophoblast, intermediate trophoblast and syncytiotrophoblast.

Malignant cytotrophoblast and intermediary trophoblast are preferentially arranged in nest-like and field structures, separated by syncytiotrophoblast, creating a biphasic pattern.

Differential diagnosis issues are raised by atypic morphology (e.g. predominance of cytotrophoblast and intermediary trophoblast forming areas of monomorphic cohesive cells), that require IHC and serologic investigations.

High β -hCG serum levels and positive immunohistochemistry tests for β -hCG, hPL (human placental lactogen) and α -inhibin may be indicative of choriocarcinoma.

An early and correct diagnosis of trophoblastic disease is very important due to its susceptibility to chemotherapy. Choriocarcinoma is considered the most curable gynecological cancer, even in the presence of metastatic disease, with overall survival rates of 82-100% [9, 10].

Identification of high-risk and low-risk patients ensures appropriate chemotherapy regimens.

High-risk factors are, according to WHO, advanced maternal age, intervals longer than 4 months between last pregnancy and diagnosis, large tumor mass, serum β hCG levels higher than 40.000 mIU/ml and the presence of metastases (other than pulmonary or vaginal) [11].

However, the importance of the first two risk factors is difficult to evaluate in postmenopausal choriocarcinoma.

Conclusions

In conclusion, macroscopic and microscopic examination findings suggested a possible diagnosis of choriocarcinoma in a post-menopausal woman admitted for vaginal bleeding.

Immunohistochemistry tests excluded undifferentiated uterine carcinoma and metastatic carcinoma (digestive, urinary, mammary or pulmonary), since somatic tumors, although able to sometimes produce β hCG, do not show a biphasic growth pattern. Positive diagnosis of postmenopausal choriocarcinoma, a rare condition, was thus possible, excluding additional clinical evaluations.

Untreated choriocarcinoma can cause liver, lungs and brain metastases, (although vagina, kidneys, GI tract, and skin can also be involved), that are usually leading to therapy failures. Lymph nodes metastasis appears as tertiary lesion, after other organs had already been affected.

Death frequently occurs by haemorrhage and/or respiratory failure. Hemorrhage is mainly located within CNS and lungs, but can also be intraperitoneal or gastrointestinal.

Thus, awareness of choriocarcinoma as a cause of uterine bleedings after menopause, together with appropriate histopathology and immunohistochemistry examinations can lead to timely and accurate diagnosis. It probably is the first step towards curing this malignant disease, as very effective chemotherapy regimens are well-established.

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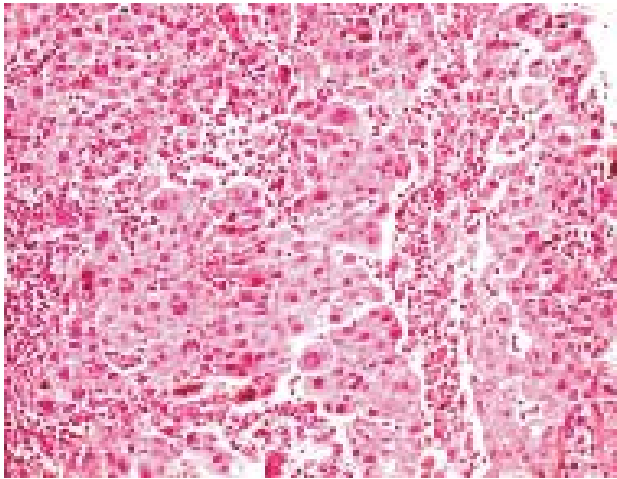


Figure 1 – Choriocarcinoma, HE stain, low-power microscopic view (×200). Areas of large malignant mononucleated trophoblastic cells are seen, with surrounding moderate lympho-monocyte infiltrate; some malignant syncytiotrophoblast cells are also present

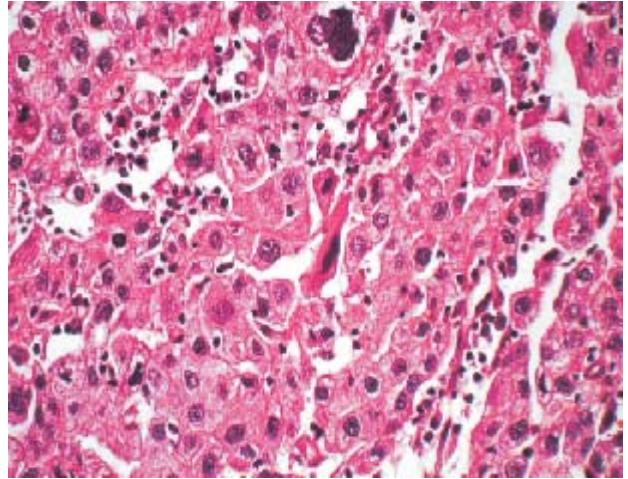


Figure 2 – High-power (×400) microscopic view of choriocarcinoma. Mixed multinucleated and mononucleated malignant trophoblastic cells are visible. Tumor cells have variable cytoplasm, ranging from pale-stained to intensely eosinophilic and nuclei of variable size and composition (HE stain)

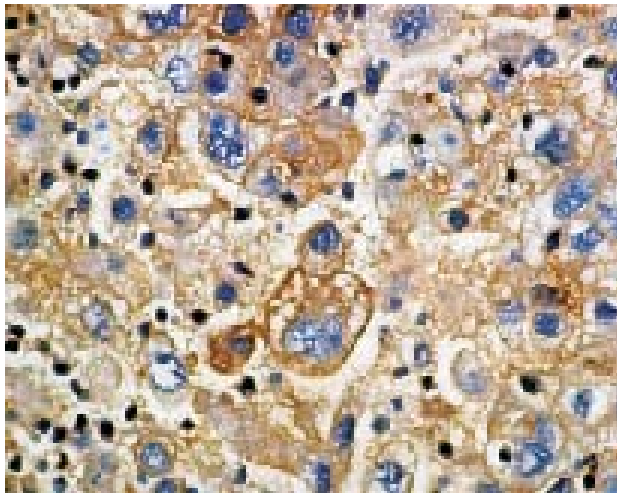


Figure 3 – Immunohistochemistry detection of β hCG. Malignant active trophoblast shows cytoplasmic β HCG immunoreactivity. Mayer's hematoxylin nuclear counterstaining, ×400

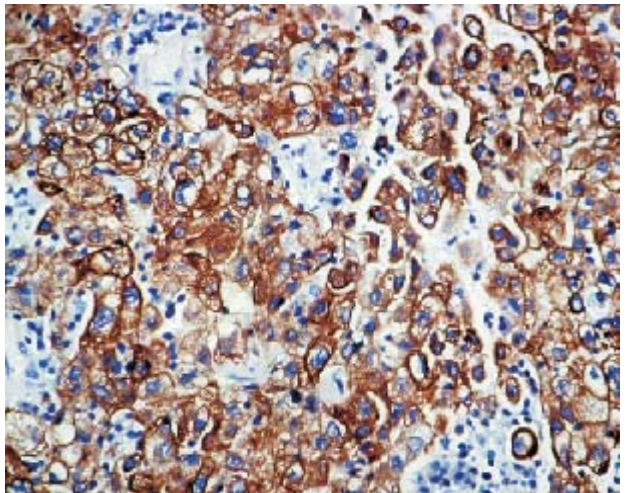


Figure 4 – Malignant trophoblastic cells are detected by KL-1 antibodies, with broad anti-keratin reactivity. Immunohistochemistry, Mayer's hematoxylin nuclear counterstaining, ×200

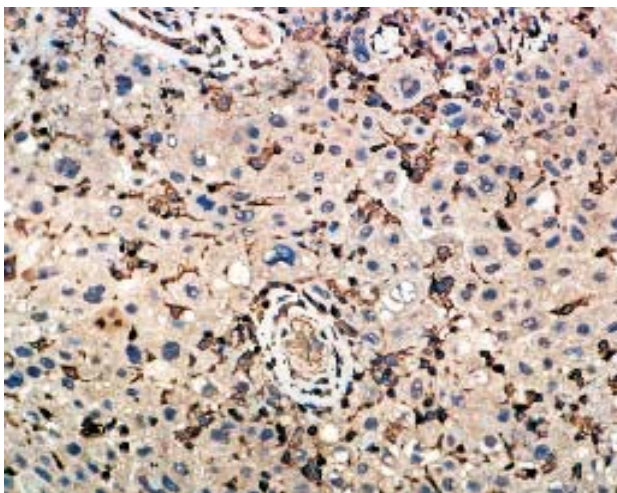


Figure 5 – Vimentin immunoreactivity is not associated with malignant trophoblastic cells. Immunohistochemistry, Mayer's hematoxylin nuclear counterstaining, ×200

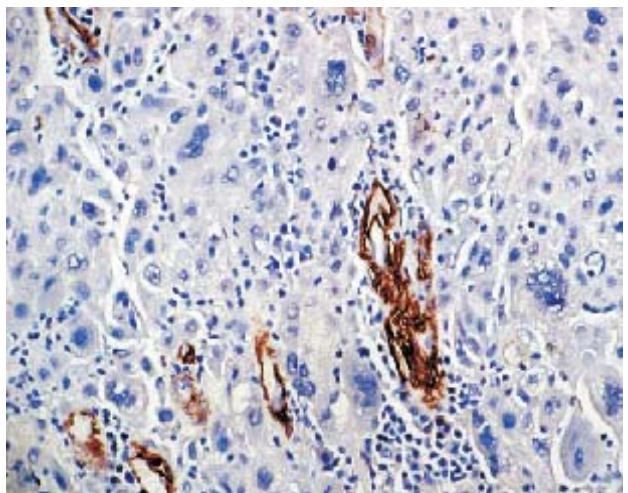


Figure 6 – Blood vessels within the tumor are immunopositive for smooth muscle actin. Immunohistochemistry, Mayer's hematoxylin nuclear counterstaining, ×200

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