Original Article
Coexisting epithelioid trophoblastic tumor and placental site trophoblastic tumor of the uterus following a term pregnancy: report of a case and review of literature

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Abstract: Gestational trophoblastic neoplasms are a group of fetal trophoblastic tumors including choriocarcinomas, epithelioid trophoblastic tumors (ETTs), and placental site trophoblastic tumors (PSTTs). Mixed gestational trophoblastic neoplasms are extremely rare. The existence of mixed gestational trophoblastic neoplasms that were composed of choriocarcinoma and/or PSTT and/or ETT was also reported. Herein, we present a case of uterine mixed gestational trophoblastic neoplasm which is ETT admixed with PSTT, and reviewed 9 cases of mixed gestational trophoblastic neoplasms reported in English literature available. The most common combination was a choriocarcinoma admixed with an ETT and/or PSTT. Mixed gestational trophoblastic neoplasms present in women of reproductive age and rare in postmenopausal. Abnormal vaginal bleeding is the most common presenting symptom, serum β-HCG levels are elevated, mostly below 2500 mIU/ml, the tumor was limited to uterus in 7 cases, the rest of 3 with pulmonary metastases at the time of diagnosis. Mixed gestational trophoblastic neoplasms have more similar clinical features with intermediate trophoblastic tumors (ITTs). Total hysterectomy with lymph node dissection is recommended treatment for mixed gestational trophoblastic neoplasms, and chemotherapy should be used in patients with metastatic disease and with nonmetastatic disease who have adverse prognostic factors.

Keywords: Epithelioid trophoblastic tumor, placental site trophoblastic tumor, gestational trophoblastic neoplasia

Introduction

Gestational trophoblastic neoplasms are a group of fetal trophoblastic tumors including choriocarcinomas, epithelioid trophoblastic tumors (ETTs), and placental site trophoblastic tumors (PSTTs) [1]. Mixed gestational trophoblastic neoplasms which are composed of choriocarcinomas and/or PSTTs and/or ETTs are extremely rare. The most common combination is a choriocarcinoma admixed with an ETT and/or PSTT. The reported mixed Gestational trophoblastic neoplasms were only 9 cases [2-8], of which mixed PSTT and ETT reported were only two cases. Herein, we present a case of uterine mixed PSTT and ETT following a term pregnancy.

Case report

A 34-year-old Chinese woman, presented with pelvic mass for eight months. She had normal menstruation except for menorrhagia once during this period. She had 2 normal pregnancies and deliveries. Her previous pregnancy was at term and uncomplicated 4 years ago.

Pelvic ultrasound revealed a 6×6×5 cm sized solid mass in the posterior portion of the uterus, suspicious for leiomyoma. Laparoscopic myomectomy was undergone, intraoperative findings included a yellow-tan and fine mass located at the posterior wall of the uterus and protruding to uterine cavity. Malignant tumor was diagnosed in operation by frozen section. Hysterectomy and bilateral salpingo-oophorectomy were performed.

Gross examination showed broken mass was focally hemorrhaged; the cut surface was yellow-tan and fine without necrosis. Microscopically, the tumor consisted of strips and cords of monomorphic intermediate trophoblastic
Figure 1. A. The tumor consisted of strips and cords of monomorphic intermediate trophoblastic cells with abundant eosinophilic cytoplasm. They were polygonal and pleomorphic, invaded the myometrium in cell cords, dissecting and separating the smooth muscle bundles. B. Immunohistochemistry showed a diffuse positive staining for hPL. C. Negative for p63. D. A focal nodular lesion consisting of relatively uniform epithelioid cells arranged in nests. These tumor cells had distinct cell borders, clear cytoplasm, and relatively uniform round nuclei with fine chromatin. Multinucleated cells were occasionally found. Dense eosinophilic hyaline-like material and necrotic debris surrounding or in the center of neoplastic cells nests. E. Immunohistochemistry showed moderate staining for P63. F. Focal positive or negative for hPL.
Table 1. Summary of 9 reported cases of mixed gestational trophoblastic neoplasms in the English literature

<table>
<thead>
<tr>
<th>Case</th>
<th>ages</th>
<th>Clinica presentation</th>
<th>HCG (mIU/ml)</th>
<th>Previous history/(interval)</th>
<th>Mixed GTN (proportion of component)</th>
<th>Treatment</th>
<th>Follow-up</th>
<th>Ref. No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>Vaginal bleeding</td>
<td>33328</td>
<td>Term pregnant/7 m</td>
<td>EtT+focal areas cc</td>
<td>Hysterectomy+Chemotherapy</td>
<td>A&amp;W 23 m</td>
<td>3</td>
</tr>
<tr>
<td>1</td>
<td>50</td>
<td>Vaginal spotting</td>
<td>192.2</td>
<td>Complete mole/3 y</td>
<td>1/3CC+2/3ETT</td>
<td>Hysterectomy+Chemotherapy</td>
<td>A&amp;W 18 m</td>
<td>4</td>
</tr>
<tr>
<td>1</td>
<td>32</td>
<td>Vaginal bleeding</td>
<td>945</td>
<td>Artificial abortion/1 y</td>
<td>EtT+focal cc</td>
<td>Hysterectomy+Chemotherapy</td>
<td>A&amp;W 48 m</td>
<td>5</td>
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<tr>
<td>1</td>
<td>15</td>
<td>Vaginal bleeding</td>
<td>NA</td>
<td>Complete mole/1 y</td>
<td>ETT+focal areas PSTT</td>
<td>Hysterectomy</td>
<td>A&amp;W 84 m</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>39</td>
<td>Vaginal bleeding</td>
<td>2304</td>
<td>Term pregnant/7 y</td>
<td>EtT+focal areas cc+ +focal areas pstt</td>
<td>Hysterectomy</td>
<td>A&amp;W 1 m</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>42</td>
<td>Lung mass</td>
<td>1300</td>
<td>Term pregnant/NA</td>
<td>Equivalent amount of CC+ETT</td>
<td>Lung resection+Chemotherapy</td>
<td>Lost to follow up</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>41</td>
<td>Menorrhagia</td>
<td>2,223</td>
<td>Term pregnant/NA</td>
<td>CC+ETT (not mentioned)</td>
<td>Hysterectomy</td>
<td>A&amp;W 60 m</td>
<td>6</td>
</tr>
<tr>
<td>1</td>
<td>60</td>
<td>Cough</td>
<td>381561</td>
<td>Term pregnant/38 y</td>
<td>Cc+focal areas itt</td>
<td>Hysterectomy+Chemotherapy</td>
<td>A&amp;W 60 m</td>
<td>7</td>
</tr>
<tr>
<td>1</td>
<td>41</td>
<td>Vaginal bleeding</td>
<td>1 (1 week after curettage)</td>
<td>Cesarean delivery/1 y</td>
<td>EtT+psst (not mentioned)</td>
<td>Hysterectomy</td>
<td>A&amp;W 30 m</td>
<td>8</td>
</tr>
</tbody>
</table>

NA, not available; A&W, alive and well; CC, choriocarcinoma.
findings were consistent with features of a PSTT. We also found a focal nodular lesion consisting of relatively uniform epithelioid cells arranged in nests. These tumor cells had distinct cell borders, clear cytoplasm, and relatively uniform round nuclei with fine chromatin. Multinucleated cells were occasionally found. Dense eosinophilic hyaline-like material and necrotic debris surrounding or in the center of neoplastic cells nests (Figure 1D). Immunohistochemistry showed strong staining for CK18, moderate staining for P63 (Figure 1E), focal positive or negative for MEL-CAM and hPL (Figure 1F). The Ki-67 proliferative index was about 20%. The morphologic and immunohistochemical features of these epithelioid cells were characteristic of an ETT.

The patient’s serum β-hCG level was 4552 mIU/mL at 8 days after operation, which was her first detection because gestational trophoblastic neoplasms wasn’t suspected until clear pathologic diagnosis was made postoperation. The serum hCG titer gradually fell after operation. The patient was lost follow-up after hospital discharge.

Discussion

ETTs and PSTTs are rare gestational trophoblastic neoplasms with differentiation toward choriocarcinoma-type intermediate trophoblasts (ITs) and implantation-site ITs respectively [9]. Although ETT was recognized as a distinct gestational trophoblastic neoplasm entity till 1998 by Shih and Kurman [2], the frequency of ETTs combined with other gestational trophoblastic neoplasms is not low. Reviewed all cases English literature published, we found 9 cases mixed gestational trophoblastic neoplasms, the clinicopathologic findings for each case are listed in Table 1. The majority of them had the component of choriocarcinoma, while only two cases mixed ETT and PSTT without choriocarcinoma component. All of 10 cases of mixed gestational trophoblastic neoplasms (including ours) had elevated serum β-HCG level except two mixed ETT and PSTT unaviable. 5 of 8 cases, the level of serum β-HCG were below 2500 mIU/ml, which was consistent with a pure ETT. The two cases had high level serum β-HCG which was 33328, 381561 mIU/ml respectively were all mixed choriocarcinoma and ITT. The striking common feature of these two cases was concomitant with lung metastasis. So we may speculate that high level serum β-HCG might be related to metastasis. The proportion of choriocarcinoma component in mixed gestational trophoblastic neoplasms should also be concerned as well. High level serum β-HCG in ETTs also hinted the presence of a large tumor volume and unusually high mitotic activity [9]. About 20% of patients with a PSTT or ETT had no elevated serum β-HCG, glypican 3 was recently suggested to be a potential serum tumor marker of gestational trophoblastic neoplasms [10].

Most of the reported mixed gestational trophoblastic neoplasms cases have occurred in women of reproductive age, ranging from 15 to 50-years of old (mean, 34.9 years). Only one mixed choriocarcinoma and ITT was reported to occur in a postmenopausal woman.6 cases mixed gestational trophoblastic neoplasms presenting symptom was abnormal vaginal bleeding, two mixed ETT and choriocarcinoma whose complaint was cough and lung mass for lung metastasis, and the other two mixed gestational trophoblastic neoplasms had history of menorrhagia. Mixed gestational trophoblastic neoplasms are associated with a previous gestational event, a prior normal pregnancy constitutes 70% of cases, hydatidiform mole 20%, spontaneous abortion 10%. The interval between the preceding gestation and the diagnosis of mixed gestational trophoblastic neoplasms has ranged from 7 months to 38 years. The three Mixed ETT and PSTT seemed to have no difference with the other 7 cases mixed gestational trophoblastic neoplasms in clinical features.

Surgery is the primary treatment modality for mixed gestational trophoblastic neoplasms, Hysterectomy with lymph node dissection is recommended. The two stages I mixed ETT and PSTT, with Hysterectomy alone, had favorable prognosis by follow-up 84 and 30 months respectively. Three cases mixed gestational trophoblastic neoplasms with lung metastasis underwent surgery along with multiagent chemotherapy also had favorable prognosis except one lost to follow-up. For pure ETT or PSTT, Chemotherapy should be used in patients with metastatic disease and in patients with non-metastatic disease who have adverse prophyl-
tic factors, such as interval from last known pregnancy to diagnosis >2 years, deep myometrial invasion, tumor necrosis, and mitotic count >6/10 high power fields [11]. Admixed with the component of ETT and/or PSTT, due to their chemoresistance and adequate outcome in cases treated with surgery alone and because of the rarity of ETT, data regarding the best chemotherapeutic regimen to treat advanced stage is limited [12].

We found that all ten mixed gestational trophoblastic neoplasms underwent a hysterectomy with or without postoperative chemotherapy had no evidence of tumor recurrence or metastasis except two lost to follow-up. Compared to the other 8 mixed GTNs and pure PSTT or ETT, The clinical behavior of the two mixed ETT and PSTT seems similar to them. But long-term follow-up is essential for patients with a mixed ETT and PSTT, because patients with a stage I pure ETT or PSTT occasionally have local recurrence or distant metastasis during the follow-up period [2, 13, 14].

The present mixed choriocarcinoma and/or PSTT and/or ETT were consistent with the proposed model of pathogenesis of gestational trophoblastic neoplasms [15]. In this model, trophoblastic stem cells, presumably cytotrophoblast, retain differentiation. After neoplastic transformation, specific differentiation programs determine the type of trophoblastic tumor that will develop. Variable amounts of neoplastic cytotrophoblast, syncytiotrophoblast, and intermediate trophoblast constitute choriocarcinoma. While in PSTTs and ETTs, neoplastic cytotrophoblast differentiates mainly into implantation site intermediate trophoblastic cells, chorionic-type intermediate trophoblastic cells respectively. According to this model, choriocarcinoma is the most primitive trophoblastic tumor whereas PSTT and ETT are more differentiated. This may explain, in part, why choriocarcinoma is sensitive to chemotherapy and PSTT and ETT are not. The relative proportions of ETT and coexisting choriocarcinoma or ETT are variable. From the 8 mixed gestational trophoblastic neoplasms with definite histology description, we found 5 cases with ETT predominant, choriocarcinoma and/or PSTT only focal, one case with equivalent amount of choriocarcinoma and ETT, one case with the choriocarcinoma predominant, ITT focal. PSTT was the predominant component in our case, while ETT was local, which had some difference with other mixed gestational trophoblastic neoplasms. What factor determine trophoblastic stem cells developing different proportion or component of the mixed gestational trophoblastic neoplasms, we don’t know. Maybe the constants of trophoblastic differentiation are multifactorial and depend on the tumor microenvironment [16].

It is essential to distinguish ITTs from choriocarcinoma, particularly for small curettage samples, to identify components of trophoblastic neoplasms: ETTs, PSTTs, choriocarcinomas, or their combinations. Therapeutic schema for gestational trophoblastic tumors is based on the differentiation of neoplastic trophoblasts. An immunohistochemical panel including cytokeratin 18, HLA-G, HSD3B1, β-HCG, hPL, MEL-CAM, p63, and Ki-67 can be of great help in establishing a correct diagnosis [15, 17].

Conclusion

Mixed gestational trophoblastic neoplasms have more similar clinical features with intermediate trophoblastic tumors (ITTs). Total hysterectomy with lymph node dissection is recommended treatment for mixed gestational trophoblastic neoplasms. Chemotherapy should be used in patients with metastatic disease and in patients with nonmetastatic disease who have adverse prognostic factors.

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Disclosure of conflict of interest

None.

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References

ETT and PSTT review of literature


