Synchronous placental site trophoblastic tumor and choriocarcinoma

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ABSTRACT

Introduction: Gestational trophoblastic neoplasia (GTN) comprises a series of malignancies characterized by abnormal proliferation of fetal trophoblastic tissue. GTN lesions refer to a class of malignant lesions that have distinct histopathologic features, including invasive hydatidiform moles, choriocarcinomas, placental site trophoblastic tumors (PSTT), and epithelioid trophoblastic tumor (ETT). Most often, they occur coexist separately, but there are also cases of mixed GTN with a combination of histologic PSTT, ETT, or choriocarcinoma. PSTT is a rare form of gestational trophoblastic disease (GTD). The percent incidence of this disease is 0.23% of total GTD and 1-2% of total GTN. The incidence rate of choriocarcinoma is also limited. Data collection on the incidence of mixed GTN has been more challenging due to the rarity of this disease. Case Description: We report a case of a 26-year-old female patient with choriocarcinoma and PSTT. The patient's beta-human chorionic gonadotropin (β-hCG) levels remained elevated despite treatment with single-agent chemotherapeutic regimen. She underwent a series of chemotherapy treatments and two surgeries were required. The histological examination of the uterine tumor revealed a choriocarcinoma whilst the hysterectomy thereafter showed a PSTT. After the hysterectomy the β-hCG level continued to rise. Due to chemotherapy resistance, EMACO (etoposide, methotrexate, actinomycin-D, cyclophosphamide, vincristine) was changed to EP-EMA (Etoposide, cisplatin, etoposide, methotrexate, actinomycin-D). After two administrations of EP-EMA, β-hCG levels normalized. Conclusion: This is a rare case of mixed GTN of choriocarcinoma and PSTT. Mixed GTN should be considered when chemotherapy is not effective in the treatment of GTN. These cases need to be reported to improve the diagnosis and management of patients. Keywords: Gestational trophoblastic neoplasia, choriocarcinoma, placental site trophoblastic tumor.

INTRODUCTION

Placental site trophoblastic tumor (PSTT) is still associated with gestational trophoblastic disease (GTD) and is a rare disease. To date, no more than 300 cases of PSTT have been reported to date.¹ In the United Kingdom, the incidence is 0.23% of all GTD and 1-2% of gestational trophoblastic neoplasia (GTN).² The disease is unpredictable and has a clinical spectrum ranging from benign to metastatic. A malignant condition is present in up to 10-15% of cases.³ Metastasis usually occurs slowly. PSTT produces low levels of β-hCG (beta - human chorionic gonadotropin) compared to other GTN.⁴ Choriocarcinoma is the most aggressive histological type of GTN, and is characterized by early vascular invasion and extensive metastasis. The clinical presentation of choriocarcinoma depends on the extent of the disease and the location of metastasis. Hematogenous metastasis occurs in choriocarcinoma.⁵ Although both PSTT and choriocarcinoma arise from abnormal trophoblastic proliferation, choriocarcinoma is completely different from PSTT in terms of diagnosis and treatment. Some patients may present with have mixed GTN consisting of PSTT and choriocarcinoma. Suspected mixed GTN can be clarified by dilation and curettage before treatment. Alternatively, patients initially diagnosed with choriocarcinoma may undergo surgery due to chemoresistance after chemotherapy. Postoperative pathologic findings have then revealed a coexisting intermediate trophoblastic tumor, which may elucidate the underlying chemotherapy resistance.⁶ However, due to its rarity and lack of available data, mixed GTN has been discussed mainly in case reports, making diagnosis and management difficult. CASE DESCRIPTION

A 28-year-old woman presented with complaints of vaginal bleeding after a spontaneous abortion two months earlier. The β-hCG level had increased from 15,000 IU/L to 129,301 IU/L for two months, and a transvaginal ultrasound examination revealed a 2 cm mass in the uterus. Considering the elevated β-hCG levels after abortion and the mass on transvaginal ultrasound, we determined that this patient had GTN. Instead of proceeding with a chest, abdomen, and pelvis examination CT (computed tomography), we performed only a chest X-ray, which revealed no abnormalities. Single-agent chemotherapy with methotrexate was administered every two weeks (Figure 1).

The β-hCG levels initially fell to 6,825 IU/L by the fourth methotrexate administration. However, it was revealed...
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despite the combination chemotherapy (EMACO), there had been a renewed increase in β-hCG levels and there were lung nodules with suspected metastases. After the patient and her family were well informed, it was decided to perform a hysterectomy. In the uterine specimen, there was a white-tan nodule with a diameter of 2 cm in the fundal region. Histopathological examination revealed that it was PSTT. The nodular mass was infiltrated into the myometrium. There was an infiltrative growth pattern, consisting of aggregates or sheets of large, predominantly mononuclear cells composed of intermediate trophoblastic cells from the implantation site (Figure 3). Serial β-hCG result after hysterectomy still showed an increase, from 567 IU/L to 1211 IU/L. Second-line chemotherapy with EP-EMA (etoposide, cisplatin, etoposide, methotrexate, actinomycin-D) was administered. After two administrations of EP-EMA, β-hCG levels normalized. We also re-examined the chest x-ray to determine whether nodules or lung metastases were still present, but the results were normal. Subsequently, 3 courses of EP-EMA consolidation chemotherapy were administered. After undetectable β-hCG levels were achieved, further β-hCG levels are determined monthly during a year of surveillance. In our hospital, there were no differences in surveillance guidelines between choriocarcinoma, PSTT, post molar GTN, or their combinations.

DISCUSSION

PSTT typically affects women who are quite young (under 40 years). The most common symptom is abnormal vaginal bleeding. Although the clinical condition of the patient was similar to those mentioned above, the very high β-hCG level distinguished this case from PSTT cases in general. Previous literature mentioned that β-hCG levels were low at initial diagnosis (below 1000 IU/L in 72.8% of patients). This makes it somewhat difficult to distinguish PSTT from early stage choriocarcinoma/GTN or quiescent GTD. One of the FIGO criteria for the diagnosis of post molar GTN is an increase in β-hCG in 3 consecutive weekly measurements, for at
least 2 weeks or more. This is often the basis for establishing a GTN diagnosis and immediately administering chemotherapy without first performing histopathological examination.

The patient did not respond to the administration of methotrexate chemotherapy alone, so this was followed up with excision of the mass in the uterus (preservation of fertility). We decided to remove the mass first rather than change chemotherapy because the mass in the uterus grew steadily over four months, from 2 cm to 8 cm. We suspect that this mass is the cause of the β-hCG levels not dropping because they continuously produce β-hCG. However, β-hCG levels increased again and lung metastases occurred. There was a difference in histopathology results between the first surgery and the second surgery.

Cases have been reported in which mixed GTN (a combination of choriocarcinoma, PSTT, or ETT) may occur. Although PSTT generally have low β-hCG levels, they can also reach over 100,000 IU/L when mixed GTN are present, such as in the presence of choriocarcinoma tissue. In addition, the difficulty in diagnosing PSTT may also be caused by tumors that are synchronous with hydatidiform moles or when PSTT is not detected during curettage examination.

The pathogenesis of mixed GTN is unknown. According to Mao et al., choriocarcinoma is the most primitive trophoblastic tumor, with varying amounts of cytotrophoblast, syncytiotrophoblast, and intermediate trophoblast. PSTT, on the other hand, is more differentiated. At the implantation site, a neoplastic cytotrophoblast differentiates into intermediate trophoblastic cells. This patient has another choriocarcinoma after chemotherapy, which coexists with the postoperative PSTT. According to Shih and Kurman, multiple chemotherapies may have destroyed the most sensitive choriocarcinoma tumor cells, while the remaining cells differentiated into intermediate trophoblastic cells that were resistant to chemotherapy. Given the rarity of mixed GTN, it is difficult to draw conclusions about the prognosis of patients with mixed GTN because there are so few published cases.

Detection of mixed GTN may depend on the thoroughness of the diagnostic process and can occur in both early and late stages of progression. This is different from other cancers such as ovarian cancer, which are more commonly diagnosed at an advanced stage. Generally, tumors confined to the uterus have a good prognosis if treated only surgically. However, if metastases have occurred, surgical therapy alone is not sufficient. In PSTT, hysterectomy is the most commonly performed surgical procedure compared to excision of the lesion (86.7%).

Chemotherapy such as methotrexate and actinomycin for PSTT is not very sensitive for choriocarcinomas, but combination chemotherapy such as EMACO or EP-EMA has been reported to give good results. Consequently, in mixed GTN (PSTT and choriocarcinoma), excision of the tumor alone or hysterectomy is insufficient and requires concomitant chemotherapy (EMACO or EP-EMA).

Mixed GTN with lung metastases can be treated with satisfactory results by hysterectomy followed by chemotherapy. This is the same as for lung metastases in non-mixed GTN where the satisfactory cure rate can reach 100%. In this case, as the patient was resistant to the administration of EMACO, the patient was administered EP-EMA after hysterectomy until the β-hCG level was normal.

The patient faces a dilemma and a difficult situation, especially if she decides to undergo hysterectomy. The patient still considers herself young and needs to preserve her fertility. However, after being counselled and educated, especially after there was a re-increase in β-hCG levels, the disease did not respond to combination chemotherapy, and there was an increased risk of metastases that could potentially be life-threatening, the patient agreed to a hysterectomy. A multidisciplinary approach is needed, and the patient must present at tumor board meetings at multiple institutions. Options for fertility preservation or cryopreservation need to be discussed.

Treatment of metastatic cases is based on only a small number of patients and there are no generally accepted therapeutic guidelines. Hysterectomy appears to be the most effective treatment and the gold standard in all cases where the disease is confined to the uterus. In cases where metastases have occurred, chemotherapy may be successful, although some cases may be fatal despite therapy. This case report may be an important addition to the literature as it is a presentation of mixed
GTN that occurs in current gynecological practice. New studies and research are still underway to clarify precisely the etiopathogenesis of mixed GTN, especially the combination of choriocarcinoma and PSTT.

CONCLUSION
The co-occurrence of choriocarcinoma and PSTT is rare, and it can be difficult to correctly diagnose such patients at initial presentation. Histologic evaluation and consideration of the co-existing PSTT component should be performed in patients with refractory, chemo-resistant choriocarcinoma. On the contrary, PSTT patients with high β-hCG levels should be suspected of having coexisting choriocarcinoma. Pathologists should carefully review specimens to ensure that they do not miss the possibility of co-existing choriocarcinoma. The best treatment for choriocarcinoma coexisting with PSTT is surgery combined with chemotherapy. These rare cases need to be reported to improve diagnosis and management of patients.

CONFLICT OF INTEREST
The author declares no conflict of interest.

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