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CASE REPORT

Primary Uterine Primitive Neuroectodermal Tumor

Yen-Chang Chen[1], Yung-Hsiang Hsu[1], Yu-Chi Wei[2], Tang-Yuan Chu[2], Dah-Ching Ding[2]

Departments of [1]Pathology and [2]Obstetrics and Gynecology, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Tzu Chi University, Hualien, Taiwan, Republic of China

Primitive neuroectodermal tumors (PNETs) are rare malignant tumors and extremely rare in uterine corpus. We report a case of primary uterine PNET in Taiwan. A 68-year-old woman presented with vaginal bleeding and abdominal fullness for 2 weeks. Computed tomography revealed one 8.0 cm uterine corpus tumor with carcinomatosis peritonei and ascites. The cancer antigen 125 level was high (280.7 IU/ml). Pathology of endometrial biopsy diagnosed PNET according to the characteristic of small blue round cells with Homer-Wright rosettes and Friend leukemia integration 1 transcription factor (FLI-1) positive. She received dose-dense chemotherapy with paclitaxel and carboplatin, but the response was poor and the PENT metastasized to liver. PNETs belong to small blue round cell tumor group that is difficult to be diagnosed on histopathology. The immunohistochemistry for CD99 and FLI-1 provides high sensitivity and specificity for diagnosis, respectively. No optimal treatment is established due to rarity. The prognosis is poor, usually <3 years survival.

Key words: Primitive neuroectodermal tumor, small blue round cell tumor, Homer-Wright rosettes, CD99, Friend leukemia integration 1 transcription factor protein

INTRODUCTION

Primitive neuroectodermal tumors (PNETs, also called extraskeletal Ewing sarcomas [ESs]) are rare malignant tumors derived from neuroectoderm, belonging to the group of small blue round cell tumor (SBRCT).[1-3] The body sites in which PNETs commonly grow include the central nervous system, soft tissues, and bones. PNETs originated in the female genital tract are extremely rare, commonly in the ovary,[1] and unusually rare in the vulva, vagina, cervix, and uterine body.[3]

To our best knowledge, the related studies were mostly reported in the Western population. Yeh *et al*.[4] had reported the first case of primary uterine PNET in Taiwan. We present the second instance of this rare entity with a novel conception of the immunohistochemical study.

CASE REPORT

A 68-year-old woman (gravida 6 para 5, abortion 1) has a history of diabetes mellitus, hypertension, and peptic ulcer under medical control. She presented with vaginal bleeding for 2 weeks, accompanied with abdominal fullness and decreased appetite. On physical examination, she had oval-shaped abdomen with shifting dullness indicating ascites manifestation; she had diffuse tenderness and rebounding pain. Per-vaginal examination showed bleeding on the cervical os, and an endometrial biopsy was done. Ultrasonography depicted thickening endometrium with a mass lesion, and endometrial cancer was impressed. Abdomen to pelvis computed tomography (CT) revealed one 8.0 cm × 6.0 cm × 5.2 cm heterogeneous uterine corpus tumor with punctuate calcification and extending into the cervix [Figure 1]. It also showed carcinomatosis peritonei and massive ascites. Abdominal paracentesis with 1000 ml of ascites was performed and sent to cytology examination. Laboratory examination showed elevated carbohydrate antigen 125 (CA125) level, 280.7 IU/ml, and normal CA19-9 and carcinoembryonic antigen (CEA) level. Sequential pathology of endometrial biopsy displayed that the tumor was composed of monotonous small round primitive cells with

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Corresponding Author: Dr. Dah-Ching Ding, Department of Obstetrics and Gynecology, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, 707, Section 3, Chung-Yang Road, Hualien 970, Taiwan. Tel: 03-8561825-13381; Fax: 03-8577161. E-mail: dah1003@yahoo.com.tw

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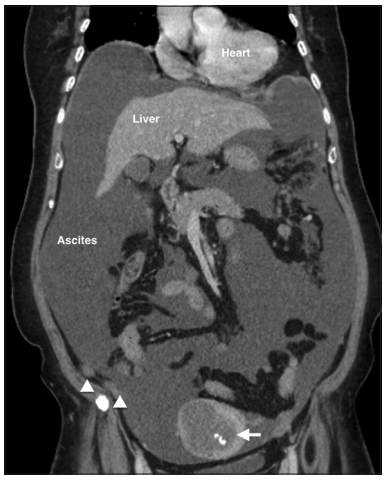

Figure 1: Abdomen to pelvis computed tomography showing coronal section of abdominal to pelvic cavity. One 8.0 cm × 6.0 cm × 5.2 cm heterogeneous uterine corpus tumor with punctuating calcification (arrow), carcinomatosis peritonei (arrowhead), and massive ascites (gray color)

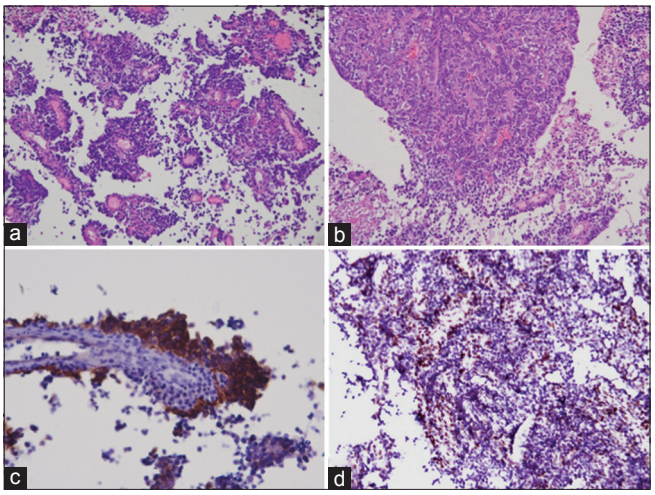

Figure 2: Pathology of cervical biopsy showing primitive neuroectodermal tumor composed of (a) monotonous small round primitive cells with papillary and sheet patterns (H and E, ×100) and (b) Homer-Wright rosettes. In rosettes, differentiated tumor cells surround the neuropil (H and E, ×400). Immunohistochemical study of primitive neuroectodermal tumor showing (c) CD99 (brown color, DAB ×200) and (d) Friend leukemia integration 1 transcription factor positive (brown color, DAB ×200)

high nuclear-to-cytoplasmic ratio in papillary, nest, and sheet patterns [Figure 2a] with Homer-Wright rosettes [Figure 2b]. Immunohistochemical study showed diffuse positivity for vimentin, CD99 [Figure 2c], and Friend leukemia integration 1 transcription factor (FLI-1) [Figure 2d] and focal positivity for cytokeratin with both membranous and dot-like staining pattern. A PNET was diagnosed. She did not want to receive surgery due to complicated medical diseases. Therefore, the patient received dose-dense chemotherapy with paclitaxel (80 mg/m^2 body surface area [BSA], Formoxol, Yungshin Pharm Ind. Co. Ltd, Taichung, Taiwan, ROC) and carboplatin (area under curve = 6, Paraplatin, Bristol-Myers Squibb S. R. L., Latina, Italy) for up to nine courses. Follow-up CA125 level declined to normal range 5 months after the beginning of chemotherapy. After nine courses of chemotherapy, the patient complained progressive abdominal fullness with dyspnea. Relapsed ascites was impressed, and abdominal paracentesis was performed again for symptom relief. Then, salvage chemotherapy with lipo-dox (40 mg/m^2 BSA, Taiwan Tong-Yang BioPharm, Taipei, Taiwan) for one course was performed. However, follow-up CT scan of the abdomen revealed compression fracture on the first lumbar vertebral body and new one metastatic nodular lesion on the fifth segment of liver, in addition to a stationary state of the uterine tumor and carcinomatosis peritonei. The CA125 level elevated again, measuring 371.5 IU/ml. After discussion with the patient on poor response to chemotherapy, she received palliative care now.

DISCUSSION

The uterine PNET mainly occurred in postmenopausal women (68%) or adolescent girls (21%), with relatively rare cases (11%) in women of reproductive age. Abnormal vaginal bleeding occurred most often in patients with endometrial cancer. The clinical symptom of PNET was also mostly abnormal vaginal bleeding (95%), but less uterine enlargement (53%), and seldom abdominal pain (11%). In contrast to early detectable endometrial cancer, about 42% of PNET cases were diagnosed at the advanced stages (above stage III), highlighting the aggressive behavior of PNET. Moreover, only about 20% of PENT cases were initially diagnosed of PNET, indicating the difficulty with several differential diagnoses of SBRCT.[3] We should consider this difficulty in diagnosis of PENT.

The group of SBRCT consists of numerous morphologically similar tumors including ES, rhabdomyosarcoma (RMS), neuroblastoma, small-cell osteosarcoma, lymphoblastic lymphoma (LBL),[5] poorly differentiated synovial sarcomas (PDSS), desmoplastic round cell tumor (DRCT), mesenchymal chondrosarcoma (MCS), and blastemal predominant Wilms' tumor (WT).[6] These tumors make the diagnosis difficult because they may be histopathologically indistinguishable, particularly when poorly differentiated or in a small specimen of biopsy. Immunohistochemistry, therefore, is a valuable diagnostic method for SBRCT.[6]

The characteristic histopathology of PNET is composed of small blue round cells with particular Homer Wright rosettes formation. The PNETs often express vimentin, CD99, neuron-specific enolase (NSE), neurofilaments, S-100, CD56, chromogranin, and synaptophysin, while glial fibrillary acidic protein and cytokeratin are less frequently positive.[2,3,7]

Elbashier *et al*.[7] analyzed 43 cases diagnosed of ES/PNET on the various body sites and summarized that vimentin expressed in 96.5% cases, CD99 in 93%, NSE in 78.3%, and cytokeratin in 40%. In previous practice, the CD99 was the most reliable and commonly used marker for the diagnosis of PNETs.[8] Our case also showed CD99 positive. However, CD99 may be expressed in over 90% cases of LBL, over 75% of PDSS, approximately 50% of MCS, 20%–25% of primitive RMS, the blastemal component of some cases of WT, and rare cases of small cell osteosarcoma and DRCT.[6] Thus, a new marker for diagnosing PNET is needed.

Currently, the immunohistochemistry for FLI-1 protein expression becomes a useful diagnostic method because of the high specificity of this marker.[6] Folpe *et al*. studied 132 cases diagnostic of SBRCTs including ES/PNETs and mimics. They showed FLI-1 protein expressed in 29 of 41 cases (71%) of ES/PNET compared with only 8 of 91 cases (9%) of non-ES/PNET. Among the non-ES/PNET cases who were positive for FLI-1, seven were LBL (diffuse strong positive) and one was DRCT (focal positive, 5%). FLI-1 did not express in any other mimics. The detection of FLI-1 for the diagnosis of ES/PNET showed 71% sensitivity and 91% specificity.[6] Now, the FLI-1 protein is an excellent diagnostic marker for the diagnosis of PNET, especially in the setting of small biopsies and in laboratories that cannot perform the gold standard cytogenetic and molecular genetic tests for identification of the PNET-associated translocations and fusion genes. The present case was diagnosed of PNET based on the characteristic histopathology of small blue round cells with rosettes formation and diffused positive FLI-1 staining.

The optimal treatment methods have not yet been established because of the rarity of this tumor. So far, the treatment for PNETs comprises multi-modal therapies including different combinations of surgery, radiation, and chemotherapy with variant agents such as vincristine, cyclophosphamide, cisplatin, doxorubicin, actinomycin-D, carboplatin, and etoposide (more recently ifosfamide and etoposide).[1,3] We used Taxol and carboplatin instead of those regimens. Further studies regarding suitable chemotherapy regimens are necessary.

Even though multi-modal treatments, most patients manifested rapid multiple dissemination of disease[3] or high relapse rate.[1] Subclinical metastasis should be assumed due to the aggressive behavior although the overt metastatic disease was found in fewer than 25% of patients at the time of diagnosis.[9]

The prognosis of PNET is poor with low survival, usually <3 years, in spite of active treatment, especially if high grade.[2,10] Two other factors related to prognosis. Younger patients have a better prognosis with 75% survival rate for at least 2 years compared with 32% in the postmenopausal group.[11] The cytokeratin-expressing tumors may have a more aggressive behavior.[12] Our patient is in the postmenopausal group; thus, she may have the worse prognosis than young patients.

Xiao *et al*. retrospectively analyzed primary PNETs in the female genital tract and reported that the CA125 level is mostly (73%) elevated before treatment and declined to normal range when the disease is controlled, while the level increased again as tumor progression,[13] as in our case. Therefore, CA125 could serve as an important marker for follow-up of PNET.

CONCLUSION

We presented a rare case of primary uterine PNET with peritoneal seeding and liver metastasis. Although the patient had received chemotherapy, peritoneal carcinomatosis and liver metastasis developed. The prognosis is poor.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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