Primary Vaginal Extraosseous Ewing Sarcoma/Primitive Neuroectodermal Tumor with Cranial Metastasis

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Extraosseous Ewing sarcoma is now regarded as a member of the Ewing sarcoma/primitive neuroectodermal tumor (PNET) family. It typically involves the soft tissues of the chest wall, pelvis, paravertebral region, abdominal wall, retroperitoneal region and extremities of children, adolescents and young adults, but it seldom occurs in the female genital tract. We report an extremely rare case of retrospective diagnosis of vaginal extraosseous Ewing sarcoma/PNET which metastasized to the right frontoparietal scalp, skull, and dura. Surgical resection, followed by adjuvant radiotherapy and chemotherapy resulted in a favourable clinical outcome. Both the vaginal and head tumors had similar light microscopic features supporting the diagnosis. [*J Chin Med Assoc* 2009;72(6):332–335]

Key Words: extraosseous Ewing sarcoma, metastasis, PNET, vagina

Introduction

Ewing sarcoma and primitive neuroectodermal tumor (PNET) represent a single group of bone and soft-tissue tumors in which typical undifferentiated Ewing sarcoma lies at one end of the spectrum and PNET with clear evidence of neural differentiation lies at the other.[1,2] Ewing sarcoma/PNET of the female genital tract is very unusual, but has been reported to involve the ovary, uterine corpus, uterine cervix, and vulva.[2–5] To our knowledge, only 4 cases of primary vaginal Ewing sarcoma/PNET have previously been reported in the English literature,[2–5] and all of them had no evidence of metastasis when reported. Here, we present a rare case of primary vaginal Ewing sarcoma/PNET with cranial metastasis.

Case Report

In November 2004, a 28-year-old woman, gravida 2, para 2, presented with a nearly 2-month history of a progressive bulging mass in the right frontoparietal region. Her medical history revealed that she had undergone partial resection of a nodular lesion located near the vaginal introitus close to the left side of the urethral orifice in October 2003. The pathology report stated an undifferentiated carcinoma based on the presence of cohesive sheets of hyperchromatic cells without specific differentiation such as gland formation, mucus secretion, or squamous differentiation. She had then been referred to our Obstetrics & Gynecology department for further management. At the Obstetrics & Gynecology outpatient department, abdominal computed tomography (CT) showed negative findings; physical examination revealed no palpable inguinal lymph node. Extensive surgical resection of the residual lesion, which was about 2 cm in size, was not recommended due to the patient's young age and the location of the tumor. Hence, curative radiotherapy with a total dosage of 7,000 cGy using appositional field method was applied to the vaginal tumor bed and administered from November 2003 to January 2004. A series of vaginal and cervical smears before this admission revealed no malignancy; also, the patient's regularly checked tumor markers, including CEA and

SCC-associated antigen, were within normal limits. She was regularly followed-up at our Obstetrics & Gynecology outpatient department. She was doing well until October 2004 when she found a protruding mass on her right frontoparietal skull. She was referred to our Neurosurgery outpatient department after a whole-body bone scan performed.

On this admission, the patient's general physical examination revealed a tender, fixed, and bulging tumor about 4 cm in size in the right frontoparietal region. Both cranial CT and brain magnetic resonance imaging (MRI) showed a well-enhanced soft-tissue mass at the right high frontoparietal region with epidural and scalp extension and mild compression of the adjacent brain parenchyma. Whole-body bone scan disclosed a hot ovid area over the right frontoparietal skull, indicative of a metastatic lesion.

The patient underwent a right frontoparietal craniectomy with total removal of the tumor, the invaded dura, skull and the invaded scalp, followed by duraplasty and cranioplasty. Histologically, the tumor was composed of sheets of uniform small round cells with scant amphophilic cytoplasm; the nuclei contained vesicular to stippled chromatin with inconspicuous nucleoli and indistinct cytoplasmic borders (Figure 1). There was prominent mitotic activity, necrosis and hemorrhage, but no rosettes, pseudorosettes or neurotubules were present. The cytoplasm was negative for periodic acid-Schiff stain (Figure 2A). The tumor was negative for pan cytokeratin (CK), CK 7, CK20, low-molecular-weight cytokeratin, high-molecular-weight cytokeratin, epithelial membrane antigen, desmin, smooth muscle actin, myogenine, MyoD1, chromogranin, WT-1 (Wilm's tumor protein), inhibin, and leukocyte common antigen. However, the tumor was focally positive for synaptophysin, CD56, and neuron-specific enolase,

and diffusely positive for vimentin and CD99 (MIC2) (Figure 2B). Ki-67 was present in 30% of tumor cells. The morphology of the tumor in the right frontoparietal region was similar to that of the vaginal tumor resected previously (Figure 3). Therefore, based on the results of histopathologic examination, metastatic Ewing sarcoma/PNET originating from the vagina was diagnosed.

The patient was discharged without any complications or neurologic deficits. Postoperative adjuvant cranial radiotherapy with total dosage of 6,000 cGy followed by 12 courses of systemic chemotherapy consisting of cyclophosphamide, vincristine and epirubicin were administered. We regularly followed her hemogram, liver function test and brain MRI. Brain MRI performed 18 months after the operation showed neither residual tumor nor recurrent tumor.

Discussion

Ewing sarcoma and PNET were regarded as distinct in the past. Recently, studies have shown that the small round-cell tumors seen in both tumor types share common phenotypic and molecular features, supporting the concept of a single tumor category. Therefore, the term Ewing sarcoma/PNET family of tumors is currently employed.[6–8]

Ewing sarcoma/PNET are now defined as a group of small round-cell sarcomas that show varying degrees of neuroectodermal differentiation.[8–10] Ewing sarcomas are tumors that lack evidence of neuroectodermal differentiation when assessed by light microscopy, immunohistochemistry, and electron microscopy; PNET are tumors that show neuroectodermal features when evaluated by 1 or more of the above modalities.[9,10]
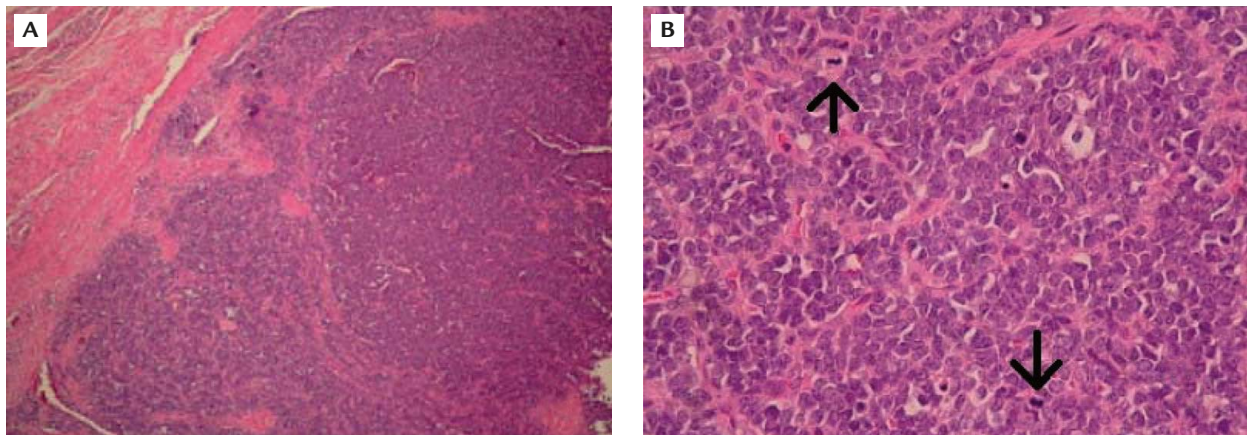
Figure 1. (A) Solid sheet growth pattern of Ewing sarcoma/PNET in the scalp. (B) The tumor is composed of uniform small, round, hyperchromatic cells with scant amphophilic cytoplasm and mitotic figures (arrows).

Extraosseous Ewing sarcomas can arise in the soft tissues of the chest wall, extremities, paravertebral and retroperitoneal regions, pelvis and abdomen, skin, visceral organs, head and neck,[4,5,7,10,11] but rarely occur in the female genital tract.[2–5] To date, only 4 cases of primary vaginal extraosseous Ewing sarcoma/PNET have been reported in the English literature (Table 1),[2–5] and none of them showed evidence of metastasis.

The diagnosis of Ewing sarcoma/PNET is based on histologic, immunohistochemical, and ultrastructural features. Uniform small round cells with round nuclei containing fine chromatin, scanty clear or eosinophilic cytoplasm with glycogen content, and indistinct cytoplasmic membranes are common microscopic features of Ewing sarcomas.[9,11,12] Although the presence of glycogen in a round-cell tumor was considered to be diagnostic of Ewing sarcoma, it is now known that Ewing sarcoma may be glycogen-negative.[12] In cases of PNET, the tumors comprise small- to medium-sized cells with moderate amounts of cytoplasm, variable glycogen content, and variable degrees of neuroepithelial differentiation.[11]

Immunohistochemical markers currently used in the diagnosis of Ewing sarcoma/PNET family of tumors include MIC2 (also designated CD99), neurofilament proteins, neuron-specific enolase, vimentin, and HBA-71.[1,6,11,13] CD99 is expressed in the membranes of nearly all Ewing sarcoma/PNET tumors.[6,11] Notably,
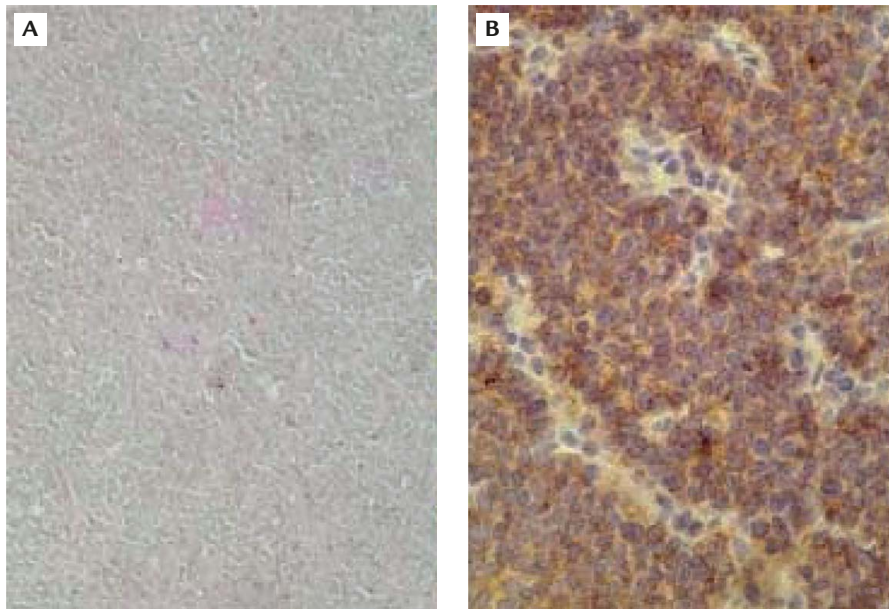
Figure 2. (A) Periodic acid-Schiff stain: the tumor cells are negative for glycogen granules in the cytoplasm. (B) Immunohistochemistry stain: the tumor cells have strong and diffuse membranous staining for CD99.
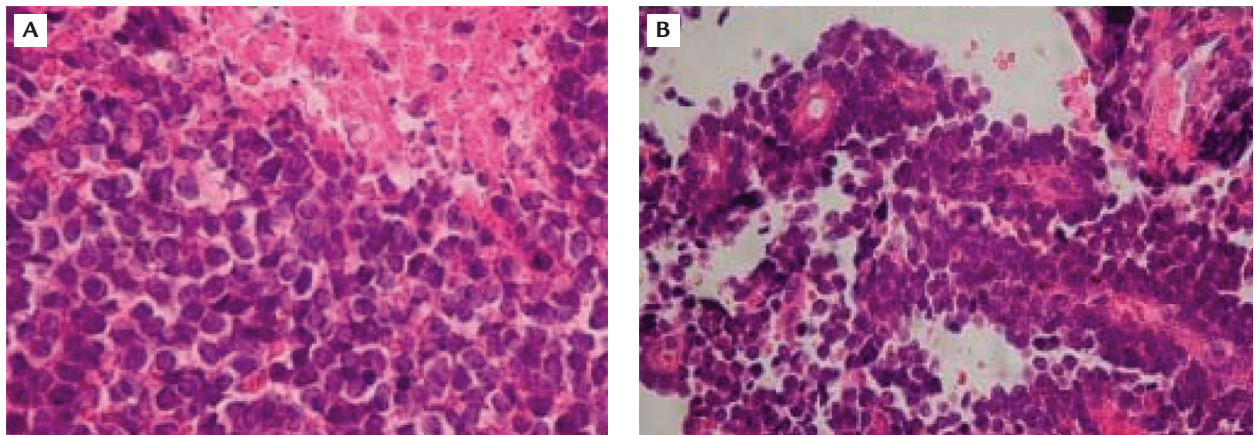
Figure 3. The histology of the vaginal tumor (A) is similar to that of the scalp tumor (B). Tumor necrosis (A) and focal pseudopapillary formation are noted.

Table 1. Clinicopathologic features of reported cases of vaginal Ewing sarcoma/PNET

Authors	Age (yr)	Size (cm)	Initial diagnosis	Final diagnosis	Treatment for vaginal lesion	Confirmatory immunohistochemistry	Metastasis	Follow-up (mo)
Farley et al.[3]	35	4	ES	ES	SE+C/T+R/T+IBT	HBA-71	No evidence	NED, 48
Vang et al.[4]	35	3	ES	ES	SE+C/T+R/T	CD99	No evidence	NED, 19
Gaona-Luviano et al.[5]	34	4	ES	ES	SE+C/T+R/T+IBT	CD99	No evidence	NED, 20
Liao et al.[2]	30	5	ES	ES	SE+C/T+R/T	CD99	No evidence	NED, 36
This case	27	6	UC	ES	SE+R/T	CD99	Cranial metastasis 13 mo after initial treatment	NED, 18 (after cranial surgery)

ES = Ewing sarcoma; UC = undifferentiated carcinoma; SE = surgical excision; C/T = chemotherapy; R/T = radiotherapy; IBT = vaginal cylinder intracavitary brachytherapy; NED = no evidence of disease.

MIC2 expression has been detected in other tumors, including lymphoblastic lymphoma and related leukemias,[9,11,14] rhabdomyosarcoma,[11] small cell carcinoma,[15] Merkel cell carcinoma, mesenchymal chondrosarcoma, and synovial sarcoma. However, MIC2 expression is a highly sensitive and reliable marker for the diagnosis of Ewing sarcoma/PNET when used as part of a panel of immunohistochemical stains, despite the lack of complete specificity.

The diagnosis in our patient was revised from undifferentiated carcinoma to Ewing sarcoma/PNET based on the results of immunohistochemical staining. Combined treatment with surgical resection, radiotherapy and chemotherapy resulted in a favourable outcome.

References

1. Dehner LP. Primitive neuroectodermal tumor and Ewing's sarcoma. *Am J Surg Pathol* 1993;17:1–13.
2. Liao X, Xin X, Lü X. Primary Ewing's sarcoma-primitive neuroectodermal tumor of the vagina. *Gynecol Oncol* 2004;92:684–8.
3. Farley J, O'Boyle JD, Heaton J, Remmenga S. Extraosseous Ewing sarcoma of the vagina. *Obstet Gynecol* 2000;96:832–4.
4. Vang R, Taubenberger JK, Mannion CM, Bijwaard K, Malpica A, Ordonez NG, Tavassoli FA, et al. Primary vulvar and vaginal extraosseous Ewing's sarcoma/peripheral neuroectodermal tumor: diagnostic confirmation with CD99 immunostaining and reverse transcriptase-polymerase chain reaction. *Int J Gynecol Pathol* 2000;19:103–9.
5. Gaona-Luviano P, Unda-Franco E, González-Jara L, Romero P, Medina-Franco H. Primitive neuroectodermal tumor of the vagina. *Gynecol Oncol* 2003;91:456–8.
6. de Alava E, Gerald WL. Molecular biology of the Ewing's sarcoma/primitive neuroectodermal tumor family. *J Clin Oncol* 2000;18:204–13.
7. Soulard R, Claude V, Camparo P, Dufau JP, Saint-Blancard P, Gros P. Primitive neuroectodermal tumor of the stomach. *Arch Pathol Lab Med* 2005;129:107–10.
8. Dagher R, Pham TA, Sorbara L, Kumar S, Long L, Bernstein D, Mackall C, et al. Molecular confirmation of Ewing sarcoma. *J Pediatr Hematol Oncol* 2001;23:221–4.
9. Hadfield MG, Quezado MM, Williams RL, Luo VY. Ewing's family of tumors involving structures related to the central nervous system: a review. *Pediatr Dev Pathol* 2000;3:203–10.
10. Carvajal R, Meyers P. Ewing's sarcoma and primitive neuroectodermal family of tumors. *Hematol Oncol Clin N Am* 2005;19:501–25.
11. Khoury JD. Ewing sarcoma family of tumors. *Adv Anat Pathol* 2005;12:212–20.
12. Horowitz ME, Tsokos MG, DeLaney TF. Ewing's sarcoma. *CA Cancer J Clin* 1992;42:300–20.
13. Kennedy JG, Frelinghuysen P, Hoang BH. Ewing sarcoma: current concepts in diagnosis and treatment. *Curr Opin Pediatr* 2003;15:53–7.
14. Riopel M, Dickman PS, Link MP, Perlman EJ. MIC2 analysis in pediatric lymphomas and leukemias. *Hum Pathol* 1994;25:396–9.
15. Lumadue JA, Askin FB, Perlman EJ. MIC2 analysis of small cell carcinoma. *Am J Clin Pathol* 1994;102:692–4.