Ewing’s Sarcoma/Primitive Neuroectodermal Tumor of the Uterine Corpus

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Ewing’s sarcoma (ES)/primitive neuroectodermal tumor (PNET) is defined as a round cell sarcoma that shows varying degrees of neuroectodermal differentiation. The term PNET was first introduced by Hart and Earle in 1973. 

CASE REPORT

A 23-year-old Korean woman presented with irregular vaginal bleeding and low abdominal pain. Ultrasonography and magnetic resonance imaging of the pelvis revealed a huge intramural mass of the uterus, measuring 8.4 cm in diameter. Bilateral adnexal abnormality or significant lymphadenopathy was not identified. Total abdominal hysterectomy, bilateral salpingo-oophorectomy, and lymph node dissections were done.

Grossly, the uterus was slightly enlarged, measuring 6 × 13 × 8 cm. On opening the uterus, there was a mass arising from the anterior wall of the uterus, bulging out into the endometrial cavity with an area of ulceration on the endometrium. The cut surface of the uterus showed an unencapsulated but relatively well-circumscribed intramural tumor, measuring 9 × 7.5 cm (Fig. 1). The tumor showed a homogeneous gray-tan, solid, and fish-fleshy appearing cut surface with no conspicuous necrosis or hemorrhage. The tumor abutted the endometrium and serosal surface of the uterus. Both ovaries and salpinges were grossly unremarkable without any enlargement or tumor identified.

Microscopically, the tumor was composed of relatively uniform small round-to-oval neoplastic cells arranged in a diffuse sheet or solid nesting pattern of growth with intervening fibrous septa throughout the myometrium. The tumor invaded the endometrium focally but did not involve the serosal surface of the uterus. There were numerous areas of lymphatic tumor invasion and a metastatic tumor implant on the surface of the left ovary, but there was no evidence of metastatic tumor in the pelvic lymph nodes. The tumor cells had scanty cytoplasm with indistinct cytoplasmic border, round-to-oval nuclei of stippled chromatin pattern, and inconspicuous nucleoli (Fig. 2). Mitoses, apoptotic bodies, and focal areas of necrosis were frequently found (22/10 high power fields of mean mitotic count). Pseudorosettes were also frequently present but no malignant glandular areas were identified within or adjacent to the tumor.

On immunohistochemical examination the tumor cells showed diffuse strong positivity for cluster of differentiation 99 antigen (CD99) and neuron-specific enolase (NSE) in a membranous pattern and Friend leukemia virus integration 1 (FLI-1) in a nuclear pattern. The tumor cells were focally positive for vimentin but negative for c-kit, WT-1, CAM5.2, chromogranin, synaptophysin, CD56, CD10, CD3, CD20, leukocyte common antigen, desmin, and myogenin (Fig. 3). Electromicroscopic study showed a variable number of glycogen particles in a dispersed pattern and there were primitive intercellular and synaptic-like junctions. We also performed dual-color fluorescence in situ hybridization (FISH) analysis with a break-apart rearrangement probe. In normal cells, a combined two-signal pattern is seen, reflecting intact regions; we found separated single green
Uterine Ewing’s Sarcoma/Primitive Neuroectodermal Tumor

Fig. 1. (A) The uterus is slightly enlarged, measuring 6 × 13 × 8 cm. On opening the uterus, there is a mass arising from the anterior wall of the uterus, bulging out into the endometrial cavity with an area of ulceration on the endometrium. (B) The cut surface of the uterus shows an unencapsulated but relatively well-circumscribed intramural tumor, measuring 9 × 7.5 cm. The tumor shows a homogeneous gray-tan, solid, and fish-fleshy appearing cut surface with no conspicuous necrosis or hemorrhage. The tumor abuts the endometrium and serosal surface of the uterus.

Fig. 2. (A) The tumor is composed of relatively uniform small round-to-oval neoplastic cells and arranged in a diffuse sheet or solid nesting pattern of growth with intervening fibrous septa throughout the myometrium. The tumor invades the endometrium focally but does not involve the serosal surface of the uterus. (B) The tumor cells have scant cytoplasm with an indistinct cytoplasmic border, round-to-oval nuclei of stippled chromatin pattern, and inconspicuous nucleoli. Pseudorosettes are also frequently present but no malignant glandular areas are identified within or adjacent to the tumor.
and single orange signal patterns and identified rearrangement in the tumor. On the basis of the FISH results, we performed reverse transcription polymerase chain reaction (RT-PCR) and confirmed the products of \textit{EWS-FLI1} fusion transcript with 330 bp.

**DISCUSSION**

ES/PNET is defined as a round cell sarcoma that shows varying degrees of neuroectodermal differentiation. The term PNET was first introduced by Hart and Earle in 1973 to describe a group of small round cell tumors that appeared to be derived from fetal neuroectodermal cells with variable degrees of neuroectodermal differentiation.\(^1\) ES and PNET are regarded as two extremes of a morphologic spectrum of the same tumor entity. Their classification depends on the degree of differentiation of their neuroectodermal components. ES with no evidence of neuroectodermal differentiation lies at one end of the spectrum and PNET with clear evidence of neuroectodermal differentiation at the other. ES/PNET shows characteristic signature translocations involving the ES gene (\textit{EWSR1}, Ewing sarcoma breakpoint region 1) at 22q12.2 and various erythroblastic transformation specific (ETS)-family transcription factor genes, the most common of which is \textit{FLI1} at 11q24.1–q24.3.\(^2\) \textit{EWSR1} is a ubiquitously expressed gene encoding a multifunctional protein that regulates multiple cellular processes, while \textit{FLI-1} is a transcription factor that plays a role during vascular development and in lymphoid function.\(^3\) The resulting fusion genes act as an oncogenic transcription factor. Cases of ES/PNET in the female genital tract are rare. Such tumors are found in the ovary,\(^4\) vulva,\(^5\) vagina,\(^6\) cervix,\(^7\) and uterine corpus.\(^8\)

On the basis of microscopic examination the differential diagnosis of ES/PNET of the uterine corpus includes poorly differentiated endometrioid carcinoma, stromal sarcoma, small cell neuroendocrine carcinoma, and lymphoma, which are composed of sheets of cytologically malignant small cells with little or no

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**Fig. 3.** The tumor cells show diffuse strong positivity for CD99 (A) and neuron-specific enolase (D) in a membrane pattern and FLI-1 (B) in a nuclear pattern. The tumor cells are focally positive for vimentin (C).
cases and t(7;22), t(17;22) and t(2;22) in less than 1% of cases.

Recently, EWSR1 (22q12), a dual-color, break-apart rearrangement probe using FISH analysis (Abbott Laboratories, Abbott Park, IL, USA), has been commercially available, and its diagnostic value in ES/PNET is well-established. However, due to the presence of the t(11;22) translocation in other tumor types such as desmoplastic small round cell tumor, FISH results should be interpreted in light of the morphology and immunohistochemical profile.

At initial diagnosis, the tumor is often already at an advanced stage in most patients. In addition, there is no uniformity in the treatment of ES/PNET in the uterus. Total hysterectomy with bilateral salpingo-oophorectomy, with or without chemotherapy and/or radiotherapy, is the usual course of treatment provided. In this case, the patient underwent surgical resection and six courses of chemotherapy. The patient is still alive with no evidence of recurrence or metastasis after operation in December 2012, and chemotherapy with ifosfamide.

Conflicts of Interest
No potential conflict of interest relevant to this article was reported.

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