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Rapidly progressing central-type primitive neuroectodermal tumor of the ovary: a case report

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Summary

Primitive neuroectodermal tumors (PNET) belong to a group of highly malignant tumors comprised of small round cells of neuroectodermal origin. These tumors can be either of peripheral-type (Ewing family tumors/PNET) or central-type. A number of case reports have described PNET involving the gynecologic organs and the prognosis is generally poor. The authors describe the case of a 53-year-old woman with a rapidly progressing central-type PNET of the ovary.

Key words: PNET; Primitive; Neuroectodermal; Ovary; Pelvic mass.

Introduction

Primitive neuroectodermal tumors (PNETs) of the female genital tract were first described by Hart and Earle in 1973 [1]. They described a group of small round cell tumors that appear to be derived from neuroectodermal cells. These cells are composed of differing degrees of neural, glial, and ependymal differentiation and may occur anywhere in the body. Precise diagnosis may be challenging with routine microscopy due to the non-specific histological features. According to the World Health Organization (WHO) there are two subclasses of PNET including central- and peripheral-type. Central PNETs usually involve the brain and spinal cord, whereas peripheral PNETs involve the sympathetic nervous system, skeleton, and soft tissues [2].

In general, PNETs of the female genital tract are exceptionally rare and often highly aggressive malignancies. To date there have only been a limited number of case reports of PNET of the female genital tract, whether peripheral- or central-type. The authors present a case of a widely metastatic and rapidly progressing central-type PNET arising in the ovary.

Case Report

The patient was a 53-year-old woman with past medical history of hypertension and asthma who initially presented to her primary care physician with symptoms of pelvic pressure. Pelvic ultrasound was performed on April 9, 2013 which showed a 3.5×1.8×3 cm soft tissue structure in the region of the right ovary. CA-125 level at that time was noted to be 6.4 U/ml (normal ≤ 35 U/ml). MRI of the pelvis on May 8, 2013 demonstrated a solid-appearing structure in the left adnexal region with an adjacent cyst.

The patient was referred to Gynecologic Oncology for management of the suspicious mass on May 9, 2013. On examination, the uterus was not enlarged and no pelvic mass was palpable, possibly due to the patient's body habitus. She was scheduled for laparoscopic bilateral salpingo-oophorectomy on May 28, 2013; however, before reaching that date, she required admission to the hospital for treatment of pneumonia. Repeat CT scan of abdomen and pelvis was performed on May 21, 2013 again showed a stable three-cm solid left adnexal mass with adjacent cystic structure. There was no evidence of metastatic disease. The patient's surgery was delayed to allow for resolution of the acute pulmonary process.

The patient was then lost to follow-up until she eventually presented with severe abdominal pain and acute renal failure on July 31, 2013 with a serum creatinine on admission elevated to 2.06 mg/dl (normal 0.7-1.3). On examination at that time, a large, fixed abdominopelvic mass was palpable and CA-125 was 88.7 U/ml (normal ≤ 35 U/ml). MRI of the abdomen and pelvis was performed and showed an ill-defined pelvic mass measuring 15.5×12.5 cm and causing bilateral hydroureteronephrosis. Preparations were made to take the patient to the operating room for surgery; however, prior to surgery, the patient again suffered acute respiratory decompensation and surgery was again postponed. No longer medically fit for surgery, a CT guided biopsy of the pelvic mass was performed on August 15, 2013. Results of this biopsy showed a malignant neoplasm with predominantly spindle cells and the immunohistochemistry was thought to be most consistent with synovial sarcoma. While awaiting final pathology, renal function continued to deteriorate necessitating bilateral nephrostomy tubes. During this time, she also developed symptoms of large bowel obstruction. She was medically optimized and taken to the operating room on August 29, 2013 for exploratory laparotomy and formation of a transverse loop colostomy. At the time of laparotomy, there was a large, fleshy, solid, white fixed pelvic mass with areas of necrosis and hemorrhage extending to above the pelvic brim and involving the pelvic sidewalls bilaterally, causing ureteral and large bowel obstruction. There was involvement of multiple intraperitoneal structures including the colon, fallopian tubes, ovaries, omentum, and small bowel. The tumor was determined to be unresectable, so transverse loop colostomy was performed to relieve the obstruction and right salpingo-oophorectomy

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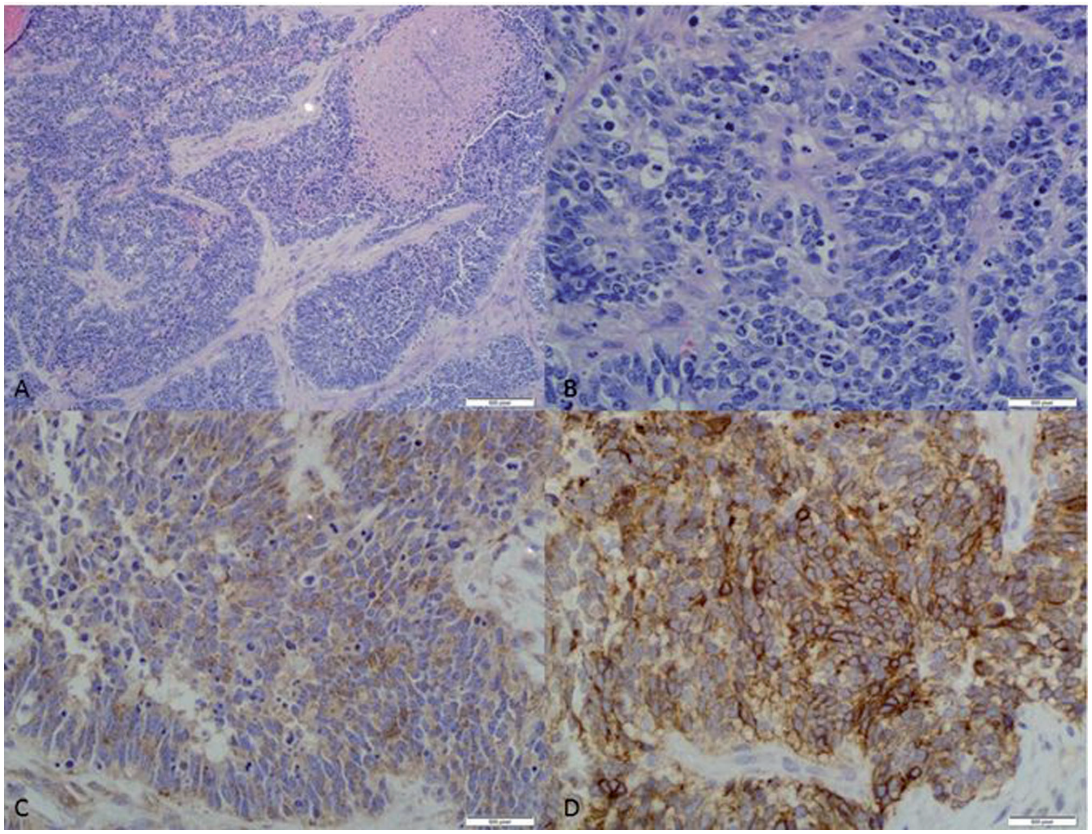

Figure 1. — A, High-grade neoplasm composed of small, round cells with extensive areas of necrosis (×10, H&E). B, (×40, H&E). C, Tumor cells are weakly-positive for AE1/AE3 and strongly express CD56 (D).

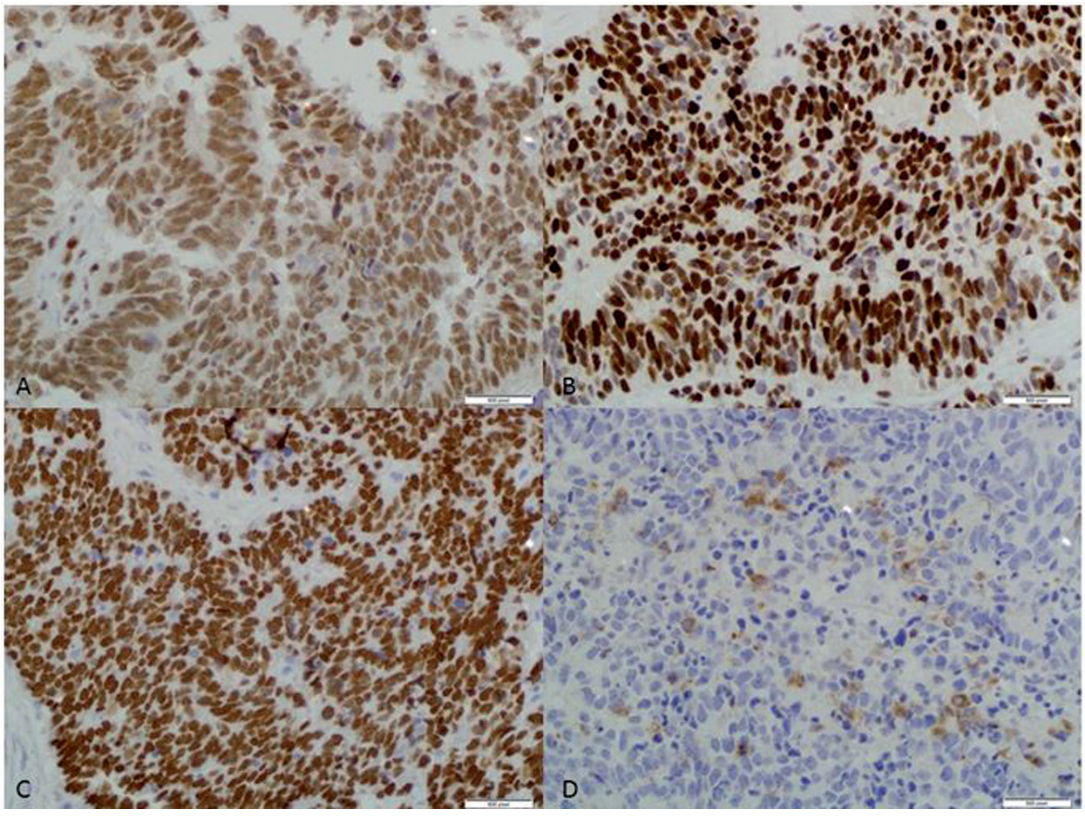

Figure 2. — The tumor expresses FLI-1 (A), p53 (B), SALL4 (C) with focal synaptophysin labelling (D).

was performed for diagnostic purposes only.

Following the surgery, due to severe deconditioning, the patient was slow to meet postoperative goals. She remained in the hospital while awaiting results of final pathology; however, prior to return of final pathology, the patient began to exhibit signs of altered mental status and experienced respiratory failure requiring intubation and ICU admission on September 9, 2013. While in the ICU, despite aggressive management, she suffered multi-organ system failure. Given the continued deterioration in the patient's status and the overall poor prognosis associated with this malignancy, the healthcare proxy made the decision to withdraw support and the patient died on September 26, 2013.

Pathology

Autopsy was performed showing a large 21×12×10 cm, three-kg white, solid, fleshy pelvic mass with extensive infiltration of the pelvic organs. There was approximately 1,000 ml of ascites, extensive peritoneal implants with invasion through the intestinal wall, as well as metastatic lesions involving the liver and lungs. No normal ovarian tissue was identified, and the uterus was surrounded by this mass which infiltrated the serosal surfaces.

Microscopically, the tumor appeared to be a high-grade malignant neoplasm with overall epithelioid growth pattern and abundant desmoplastic stroma. There were solid small round cells as well as spindle cell areas and focal columnar glandular differentiation. Immunohistochemical stains were positive for AE1/AE3 (focally weakly positive), CD56, FLI-1, p53, SALL4, and synaptophysin (focal). The tumor was negative for PanKeratin, CAM5.2, CK7, Calretinin, CD10, CD30, CD31, CD45 (LCA), CD99, Chromogranin, EMA, Inhibin, Myogenin, NF, GFAP, and WT1 (negative nuclear staining, but strong cytoplasmic staining). (Figures 1 and 2) Tissues submitted for fluorescent in-situ hybridization (FISH) for *EWSR1* translocation failed to grow in cell culture.

Discussion

PNETs of the female genital tract are extremely rare and aggressive tumors. These tumors, which are related to Ewing's family of sarcomas of the bone, have been reported to arise in any site within the female genital tract including ovaries and uterine body, and less commonly the cervix, vulva, and vagina [3]. To date, at least 89 cases of PNET associated with the organs of the female genital tract have been described in the English literature. Given the limited number of patients and the relatively poor prognosis, there are no standard guidelines for diagnosis, treatment, and management of PNETs [3].

Diagnosis of peripheral PNET is typically established based on gross pathology and microscopic architecture, supported by immunohistochemical (IHC) staining patterns, as well as identification of genetic defects associated with the Ewing family of sarcomas. Grossly, these tumors vary in size, but are typically large, mostly solid, yellow-white masses with no obvious capsule. Tumors may contain areas of hemorrhage and necrosis. Microscopically, tumor tissue demonstrates a malignant pattern of monomorphic small round blue cells with poorly to well-formed rosettes [3]. Most commonly positive IHC stains include CD99, NSE, vimentin, synaptophysin, and neurofilament. Testing for genetic mutations will show a balanced t(11;22)(q24;q12) translocation mutation in approximately 85% of tumors, resulting in abnormal fusion of the *EWS-FLI1* gene commonly seen in the Ewing family of sarcoma [3]. Tumors without rearrangement of the *EWSR1* gene should otherwise be descriptively characterized as central-type PNET. Central PNET is an embryonal tumor derived from the central nervous system. Ovarian neuroectodermal tumors with CNS-type differentiation (especially those associated with teratoma) have a germ cell origin [4]. Although there was no molecular confirmation of *EWSR1* translocation due to failure of cell culture, SALL4-positivity (germ cell tumor) as well as CD99-negativity supports the diagnosis of central-type PNET in this case.

In the reported literature there is often no distinction between peripheral- versus central-type PNET, and the clinical and prognostic importance is unclear. Due to the rarity of reported cases of all types of PNET, it is very difficult to determine an optimal treatment strategy. Proposed treatment options have included complete surgical resection [5], adjuvant chemotherapy [6, 7], and radiation [8] either alone, or in combination [9]. Unlike their less aggressive cousins (Ewing sarcoma), extra-skeletal PNETs are very aggressive with worse prognosis requiring early and aggressive multimodal treatment strategies. Recurrence rates following surgical resection alone have been reported as high as 80% to 90% [6]. These rates have been improved with the use of adjuvant chemotherapy [7]. In part, due to the rarity of this entity and the overall poor prognosis, the choice of adjuvant chemotherapy has varied widely in the reported literature. There is no consensus or recommended treatment regimen. Chemotherapeutic strategies have involved multi-agent regimens similar to those used for Ewing sarcoma (vincristine, doxorubicin, and cyclophosphamide ± actinomycin, ± iphosphamide, and etoposide), ovarian germ cell or stromal tumors (bleomycin, etoposide, cisplatin), and epithelial ovarian cancer (carboplatin, paclitaxel). Other single agent regimens which have been reported include: vinblastine, VP-16, docetaxel, irinotecan, thiotepa, tenisopid, and holoxan.

PNETs of the female genital tract are rare and behave aggressively. Prompt diagnosis and treatment involving surgical resection followed by adjuvant chemotherapy appear to give the patient the best chance at a good outcome. Further studies are necessary to better elucidate the most effective regimen for treatment of this rare disease.

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