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Case Report

A rare case of a peripheral Ewing sarcoma primitive neuroectodermal tumor of pelvic origin ☆,☆☆

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ABSTRACT

Primitive neuroectodermal tumors (PNET) represent malignant neuroectodermal tumors composed of small round cells. They can be differentiated between originating from the peripheral nervous system or the central nervous system. Peripheral PNET (pPNET) can be further subclassified as one of the Ewing family tumors (EFT). Although rare, EFT can originate in the female genital tract and pelvic region. Here, we present a case of a middle-aged female with PNET masses in her uterus, abdomen, and hepatic lobes. We discuss the diagnostic modalities, including immunohistochemistry, histopathology, and imaging findings associated with this rare malignancy.

Introduction

Primitive neuroectodermal tumor (PNET) can be classified according to both cell origin and location: central (cPNET) and peripheral (pPNET). According to World Health Organization (WHO) classification, Central PNET are defined as poorly differentiated neuroepithelial tumors often stem from neuronal, astrocytic, and ependymal lineages [1]. They can be classified based on their immunohistochemical and electron-microscopic features into the neuroblastic (medulloblastoma) and glial (ependymoma) subtypes [1,2].

Peripheral PNET tumors are neuroectodermal tumors that often involve the sympathetic nervous system, as well as bone and soft tissue [3]. These tumors often are in the soft tissues of the abdomen and lower limbs and currently they are considered part of a spectrum of round cell sarcoma, including Ewing's sarcoma (ES) [4]. Primary ovarian PNETs may be difficult to diagnose based on clinical presentation as they depend

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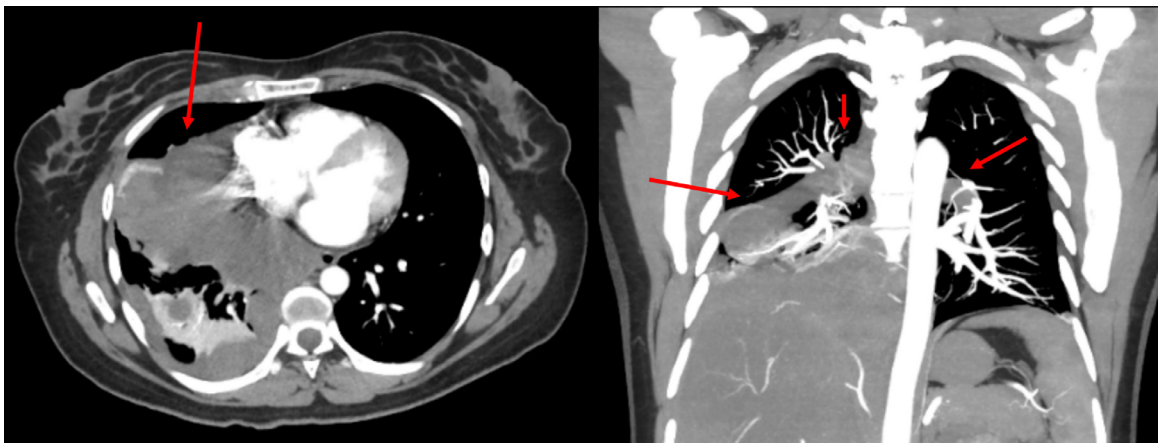

Fig. 1 – CT angiogram chest notable for large right perihilar mass contiguous with bulky mediastinal and hilar adenopathy with extension into the right middle lobe and right lower lobe as well as right pleural involvement (red arrows).

on mass effect [5]. Herein, we present a striking case of PNET originating in the pelvis.

Case presentation

A 32-year-old Hispanic multiparous female with no significant past medical or family history presented to the emergency department with a chief complaint of shortness of breath, chest, and abdominal pain. The patient endorsed pleuritic, non-radiating, right lower chest pain for 3 months prior. Her pain was associated with bilateral lower abdominal pain, dysmenorrhea, and menorrhagia. The patient reported 3 months prior to presentation, she had similar complaints and presented to an outside hospital. At that time, she underwent a computed tomography (CT) scan which demonstrated a uterine cyst and lung nodule. The patient then underwent a lung biopsy at the outside hospital; however, she was unaware of the result. The patient was lost to follow up for 3 months following this initial encounter.

In the emergency department, the patient's vitals were unremarkable. Initial laboratory studies were noncontributory; therefore, imaging was ordered for further investigation. CT angiogram of the chest was negative for pulmonary embolism; however, demonstrated a large perihilar mass along with bulky mediastinal and hilar adenopathy with extension into the right middle and lower lobe, with pleural involvement causing atelectatic changes in the lung and additional pulmonary nodules resembling metastatic implants (Fig. 1).

Repeat CT of the abdomen/pelvis with contrast demonstrated multiple heterogeneous bulky masses in the pelvis surrounding the uterus and adnexa with degrees of necrosis, multiple mesenteric masses in the left hemiabdomen and enlarged mesenteric lymph nodes, multiple masses, and implants along the right hepatic lobe consistent with carcinomatosis/metastasis (Fig. 2). The previous lung biopsy result was obtained and showed the presence of primitive neuroectodermal tumor (PNET)/Ewing sarcoma. A bone scan ordered at our facility showed no presence of osseous disease. A subsequent CT-guided biopsy of the pelvic mass was pursued at our facility to send additional tests concerning primary peripheral PNET/Ewing sarcoma of the ovary/female gynecologic tract vs primary central PNET.

The pathological report showed diffuse proliferation of small blue cells with focal rosette formation, and extensive tumor necrosis (Fig. 3). On immunostaining, the tumor cells were strongly positive for CD99, FLI-1, NSE, Vimentin, Synaptophysin (weak), and were negative for Chromogranin, Pancytokeratin, TTF-1, and Desmin (Fig. 3). These results were compatible with a PNET (either pPNET/Ewing or central PNET). FISH analysis for EWSR1 translocation was performed to confirm the diagnosis; however, resulted negative. Further immunohistochemical analyses were performed on the pelvic mass biopsy with a negative GFAP stain. Although a negative FISH analysis for EWSR1 rearrangement argued against peripheral PNET/Ewing sarcoma, the diagnosis of Ewing sarcoma/peripheral PNET was established given that rare variants can affect less common genes like FUS, BCOR, CCNB3, CIC, or DUX4.

The patient underwent multiple chemotherapy regimens (including 6 cycles of Vincristine sulfate, Dactinomycin, and Cyclophosphamide (VAC), followed by 6 cycles of Vincristine (VC), then 8 cycles of Ifosfamide, Carboplatin, and Etoposide with Mesna treatment (ICE) with Granix support) and progressed on treatment. Repeat imaging demonstrated progression of the disease as well as hydronephrosis, and the patient was initiated on Cabozantinib oral therapy. Due to further clinical progression, the patient and her family pursued hospice measures, and she expired shortly thereafter.

Of note, this case occurred during the COVID-19 pandemic. The patient tested negative for COVID-19 and vaccination status was unknown.

Discussion

In terms of gross pathology, this malignancy can be characterized as a gray or white mass with either poor or well-defined margins and soft texture [6]. Histologic characteristics of Ewing sarcoma include small, round, blue cells with round

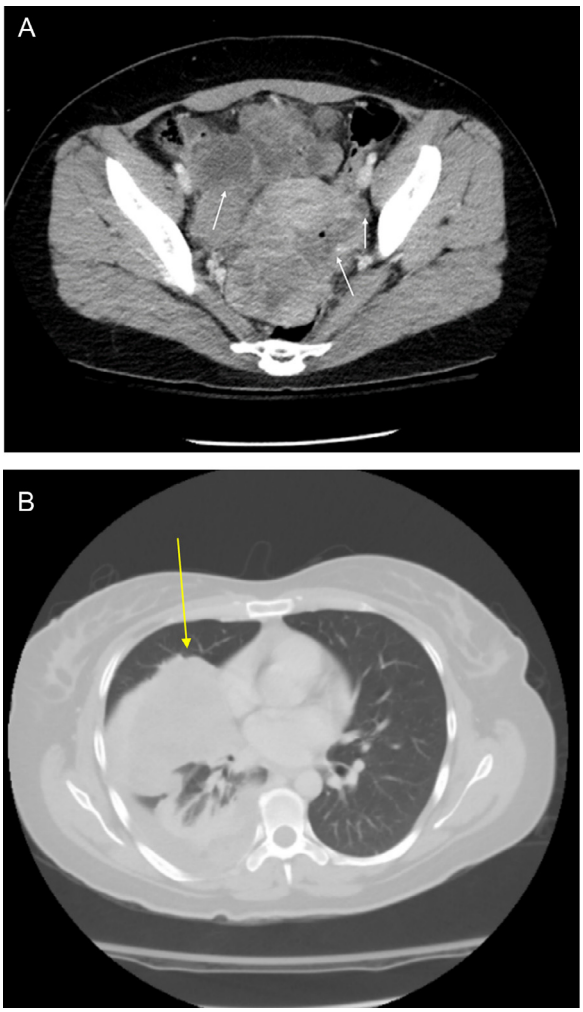

Fig. 2 – CT abdomen and pelvis with contrast demonstrating multiple heterogeneous bulky masses in the pelvis surrounding the uterus and adnexa (white arrows, A) as well as partial visualization of a lobulated heterogeneous mass involving the right lung base including involvement of the pleura with associated right basilar atelectasis/postobstructive changes (yellow arrows, B).

nuclei, approximately 10-15 micrometers in diameter, organized in crowded sheets in between a fibrous layer, with possible areas of necrosis [6]. These characteristic cells may develop "Homer-Wright Rosettes" with a pseudorosette arrangement surrounding blood vessels [6]. Cytogenetic evaluation is crucial for this disease in order to evaluate the patient's prognosis, with the majority of patients exhibiting reciprocal translocation of chromosomes 11 and 22 (t[11;22][q24;q12]) [6]. Immunohistochemical analysis may demonstrate positive stains for neurospecific endolase, Leu7, CD99, FLI-1 protein, vimentin, synaptophysin and MIC-2 gene product [6]. Our patient's histologic, and cytogenic findings demonstrated rosette formation with extensive tumor necrosis, with positive staining of vimentin, CD99, FLI-1, and synaptophysin with an absence of the traditional Ewing sarcoma translocation. Given our patient's negative findings of translocation, this made for an argument against peripheral PNET/Ewing sarcoma; however, given additional analysis with negative GFAP stain and given the rare variants demonstrated such as FUS, BCOR, CCNB3, CIC, or DUX4, primary peripheral PNET/Ewing sarcoma of the ovary was considered for our patient. A recent study demonstrated that patients found to have BCOR-CCNB3 fusion transcripts secondary to a X-chromosomal inversion were categorized with Ewing sarcoma-like morphology [7]. Given these findings and our patient's presentation, additional studies are warranted to further understand the significance of these rare variants and how they contribute to accurate diagnoses.

According to the European Intergroup Cooperative Ewing Sarcoma Studies (EI-CESS) trials, the Ewing sarcoma family of tumors (EFT) most commonly arises in long bones of the extremities like femur, humerus, tibia and fibula along with pelvic bones [8]. Some Ewing sarcomas arise in soft tissue. As compared to Ewing sarcoma of the bone, extraosseous Ewing sarcoma more commonly arises in older females, which is a consistent finding in our case presentation [9]. Initial signs and symptoms that patients commonly present with consist of localized pain and swelling that has been present over weeks to months [10]. Depending on the location of the tumor, patients can present with back pain or symptoms of radiculopathy with cord compression when the spine or sacrum are involved. About 20% of patients can present with systemic symptoms like fever, fatigue, and weight loss in extraosseous disease [11]. Additionally, in line with our patient's presentation, primary pelvic tumors are more likely to present with metastatic disease. Clinically evident metastases can present with higher lactate dehydrogenase levels, fever, an interval of fewer than 3 months between symptom onset and diagnosis, as well as age greater than 12 years [12]. Metastatic disease to the lung is the most common site of spread (70%-80%) and is the leading cause of death in patients with EFT [11].

Management of Ewing's Sarcoma includes consideration for chemotherapy, radiation therapy, and/or surgical intervention. Regardless of staging on initial diagnosis, systemic management is preferred in order to target metastatic disease, and long-term survival rates have increased from 10% to 60-70% with the utilization of multi-agent chemotherapy [13]. Specific agents which have demonstrated efficacy with this malignancy include Vincristine, Actinomycin-D, Doxorubicin, Cyclophosphamide, Ifosfamide, and Etoposide [13].

In terms of surgical management, initial reports have demonstrated efficacy in wide resection of the primary tumor; however, randomized trial data regarding this is limited [13]. This malignancy has been found to be chemosensitive and radiosensitive and therefore, limb salvage therapy may be attempted on a case-by-case basis [13]. For instance, if the surgical margins are deemed inadequate in pre-operative radiologic studies, radiation therapy may be considered an adjunct therapy, or amputation may be the only therapeutic option [13]. In summary, each patient's treatment plan should be individualized with risks versus benefits communicated for each treatment option. Our patient underwent multiple regimens including the recommended chemotherapy above; however, she, unfortunately, developed progressive disease with metastasis.

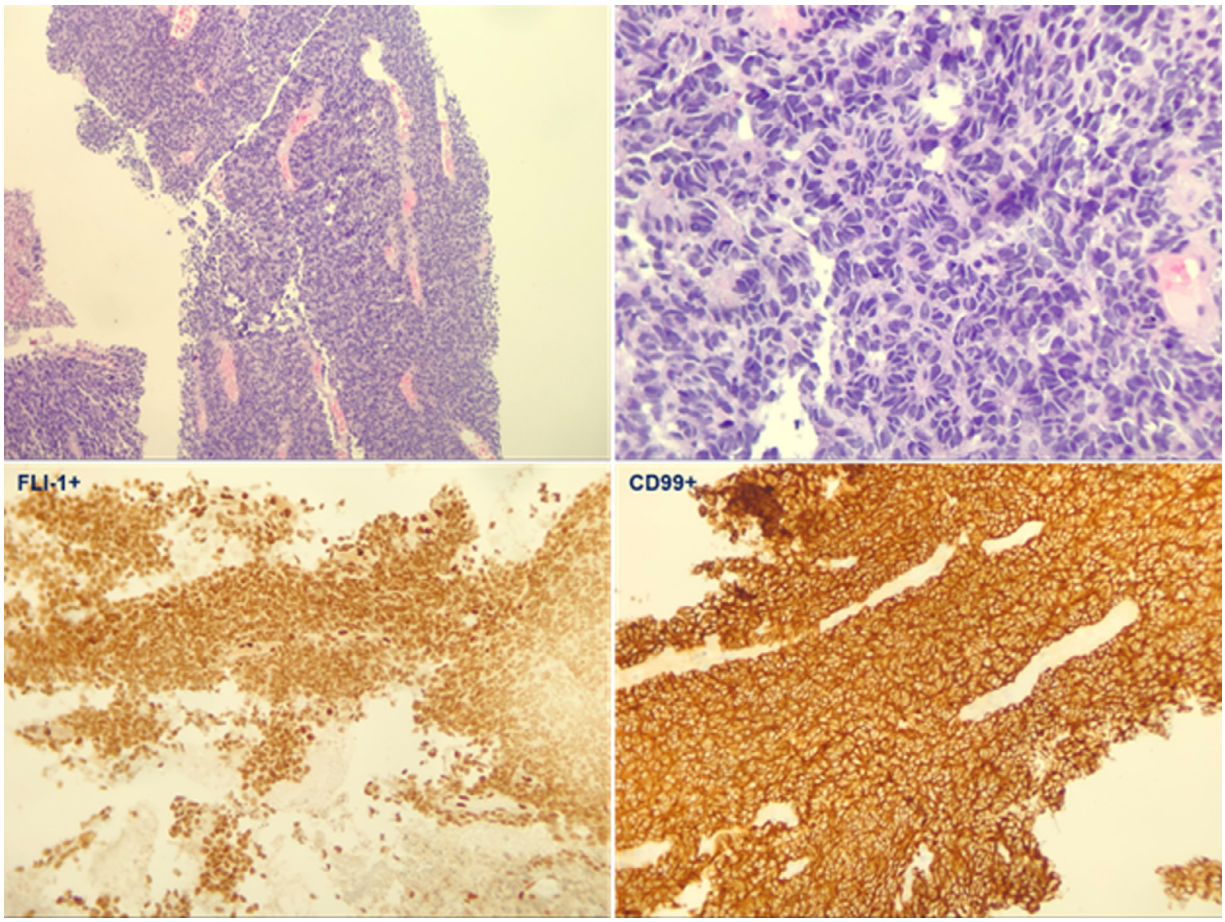

Fig. 3 – Pelvic mass biopsy (40× top left, 200× top right) demonstrated diffuse proliferation of small blue cells (best visualized at top right) with focal rosette formation, and extensive tumor necrosis, with high nuclear-to-cytoplasmic ratio with nuclear molding and dispersed chromatin, as well as CD99 and FLI-1 positivity consistent with primitive neuroectodermal tumor (PNET)/Ewing's sarcoma.

Conclusion

Ewing sarcoma pPNET represents a rare tumor that warrants additional research. As with our patient, this rare tumor should be considered when patients present with unusual ovarian masses, especially when patients are of reproductive age. For an accurate and fastidious diagnosis to be made, a multi-disciplinary method is helpful, and it is important to distinguish between pPNET versus central PNET to determine management. Subclassification can additionally be useful when determining prognostic features. Additional research is warranted to better understand this rare disease process to improve treatment for future patients.

Patient consent

Informed consent for publication of their case was obtained from the patient.

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