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Paranasal Sinus Embryonal Rhabdomyosarcoma Metastasizing to Breast and Ovary on PET/CT—A Case Report with the Review of Literature

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Abstract

Rhabdomyosarcoma (RMS) is a malignant soft tissue tumor of skeletal muscle origin. The head and neck, urinary tract, and extremities are the common sites of origin. Embryonal, alveolar, pleomorphic, and spindle/sclerosing are subtypes. It is more common in childhood and rare among adults. The incidence and risk factors for this disease are mainly largely unknown. RMS is sporadic in most instances; however, it is attributed to familial syndromes in some situations—its metastasis to the lungs, bone marrow, and lymph nodes. Breast and ovary involvement is scarce. Diagnostic workup mainly includes contrast-enhanced computed tomography (CECT) and magnetic resonance imaging (MRI). However, ^{18}F-fluro-deoxyglucose positron emission tomography (^{18}F-FDG-PET/CT) and PET/MRI are increasing contribution to providing functional insights about tumor biology and improving the diagnostic accuracy of the imaging workup. This report presents a case of the neck's embryonal RMS metastasizing simultaneously to the breast and ovary. PET/CT imaging revealed the unusual pattern, further validated by histopathology.

Keywords
- embryonal rhabdomyosarcoma
- metastasis
- breast
- ovary

Introduction

Rhabdomyosarcoma (RMS) is designated as the most frequently reported soft tissue sarcoma in children, accounting for more than 50% of soft tissue sarcomas. RMS can appear at any age, although 87% of patients present at an age younger than 15 years. It rarely affects adults.[1] Less than 1% of all malignancies are soft tissue sarcomas, and 3% of all soft tissue sarcomas are RMS.[2] It affects 4.3 cases per one million under 20 years of age annually.[2] RMS cells resemble skeletal muscle progenitor cells despite being derived from nonskeletal tissues.[3] RMS is divided into four clinical categories based on its histopathology—embryonal RMS (ERMS), alveolar RMS (ARMS), pleomorphic RMS (PRMS), and spindle cell and sclerosing RMS. ERMS accounts for most cases and has a favorable prognosis, but ARMS is clinically aggressive due to a propensity for metastasis and recurrence.[4] ERMS and ARMS are the most common histologies in children, but PRMS is nearly exclusively seen in adults. Furthermore, PRMS is more resistant to chemotherapy than ERMS and ARMS. RMS in older patients is associated with a poorer prognosis than in younger patients. They present with the primary tumor unfavorable and a more aggressive histologic subtype. Although the etiology and specific risk factors for RMS are unknown, in utero radiation exposure, faster in utero growth, low socioeconomic background, and parents who use recreational drugs during pregnancy all augment the chance of RMS. It usually presents as an isolated disease but has been linked to certain familial syndromes, including neurofibromatosis type I, Noonan syndrome, Li-Fraumeni syndrome (p53 mutations), Beckwith-Wiedemann syndrome, and Costello syndrome (HRAS mutations).[5]

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The location of the initial tumor, age at presentation, and metastatic disease influence the presenting signs and symptoms. The head and neck region, the genitourinary tract, and the extremities are common sites for origin. The tumor may originate in the orbit, para meningeal sites (middle ear, nasal cavity, paranasal sinuses, nasopharynx, infratemporal fossa), and other sites (scalp, parotid gland, oral cavity, pharynx, thyroid, and parathyroid glands). These tumors are most commonly ERMS and rarely spread to regional lymph nodes.[6] Genitourinary tract RMS mainly arises in the prostate and bladder. They present as hematuria, urinary tract infection, and features of obstruction. In females, the vagina, cervix, and uterus are common sites. Vaginal RMS mainly presents as bleeding or discharge per vaginum and is more common at a younger age, whereas uterine and cervical RMS is more common in older females.[7] The third most prevalent site of RMS is the extremities. These tumors usually appear as a painful lump or swelling with or without erythema of the surrounding skin in adolescents. The ARMS subtype accounts for about half of all extremities RMS.[6] The trunk, intrathoracic area, perineal–perianal region, and biliary system are less common sites. RMS most frequently metastasizes to the lung, followed by bone, bone marrow, and lymph nodes. Usually, 25% of the patients present with metastatic disease at the time of diagnosis. Visceral organ metastases are rare. There have been reports of primary RMS in the liver, brain, trachea, heart, and breast.[8]

Case Presentation

A 20-year-old female patient presented with a complaint of pain and swelling over the right side of the neck for 2 months. It was insidious in onset and progressively increased in size. She had swelling and bulging of the right eye and a diminution of vision for 1 month. On examination, she had multiple enlarged conglomerated lymph nodes over the right upper side of the neck and extending up to the posterior triangle of the neck. Contrast-enhanced computed tomography (CECT) of the head and neck was suggestive of a large, necrotic soft tissue mass lesion in the right maxillary, ethmoid, and sphenoid sinuses. It extended into the nasal cavity with the maxilla and cribriform plate erosion, and multiple cervical lymph nodes were also noted. Lymph node biopsy suggested ERMS. Immunohistochemistry (IHC) revealed tumor cells were positive for vimentin, desmin, Myogenin, and CD99 (paranuclear dot-like positivity) and negative for LCA, CD3, CD20, cytokeratin, synaptophysin, chromogranin, and terminal deoxynucleotidyl transferase. Ki67 index was approximately 50 to 60%. Baseline ^{18}F-fluro-deoxyglucose positron emission tomography (^{18}F-FDG-PET/CT) could not be done due to the ongoing coronavirus disease 2019 pandemic. She was further treated with 20 gray/5 fractions (#) palliative radiotherapy (RT) to the orbit; post palliative RT, ^{18}F- FDG-PET/CT was performed. ^{18}F-FDG-PET/CT was performed intravenously after injecting 370 Megabecquerel (MBq) 18F-FDG (IV). Whole body PET/CT images were acquired 45 minutes after the FDG injection.

^{18}F-FDG-PET/CT revealed FDG avid soft tissue mass in the right paranasal sinuses (►**Fig. 1A**) eroding the medial wall of the orbit. Solitary skeletal metastasis was noted on the right iliac bone and multiple bilateral cervical lymph nodes. The patient received three cycles of vincristine, dactinomycin, and cyclophosphamide (VAC) chemotherapy. Interim PET/CT showed a residual mass in the paranasal sinuses with cervical lymph nodes. Previously seen lesions showed partial treatment response (►**Fig. 1B**). She received three more

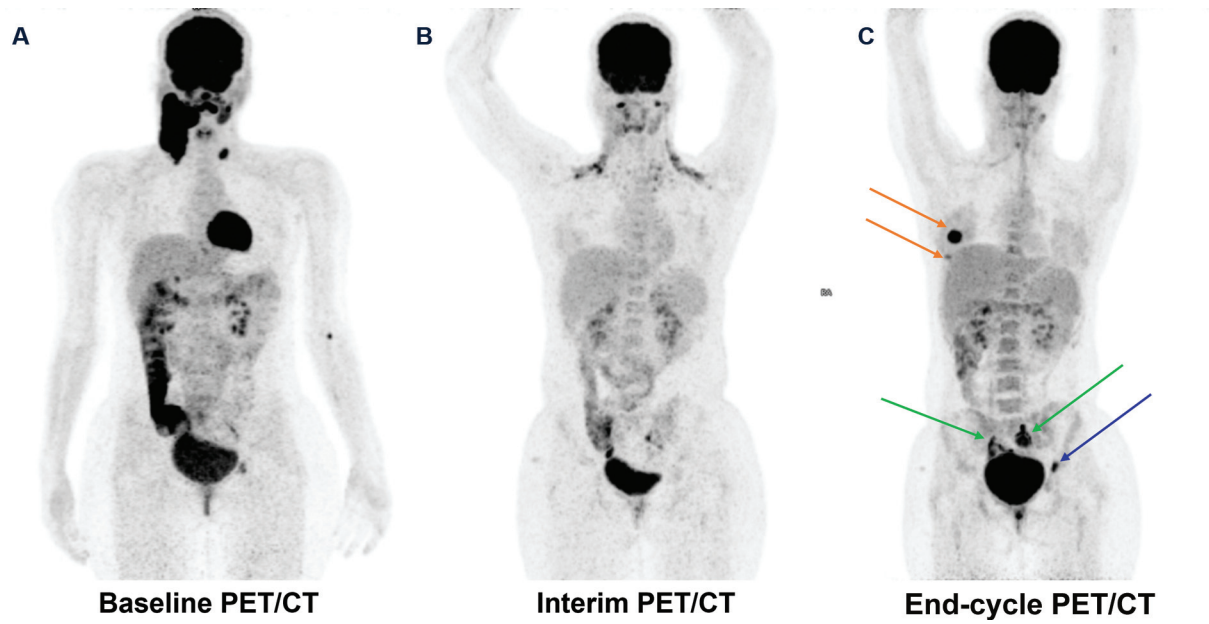

Fig. 1 Maximum intensity projection images of baseline positron emission tomography/computed tomography (PET/CT) reveal (**A**) flurodeoxyglucose (FDG) avid thickening involving paranasal sinus (PNS) and adjacent areas. Interim PET/CT (**B**) reveals no significant residual disease in the neck. End-cycle PET/CT (**C**) for treatment response reveals FDG avid metastatic involvement of right breast (red arrow), bilateral ovary (green arrow), and FDG avid lesion in left iliac bone (blue arrow).

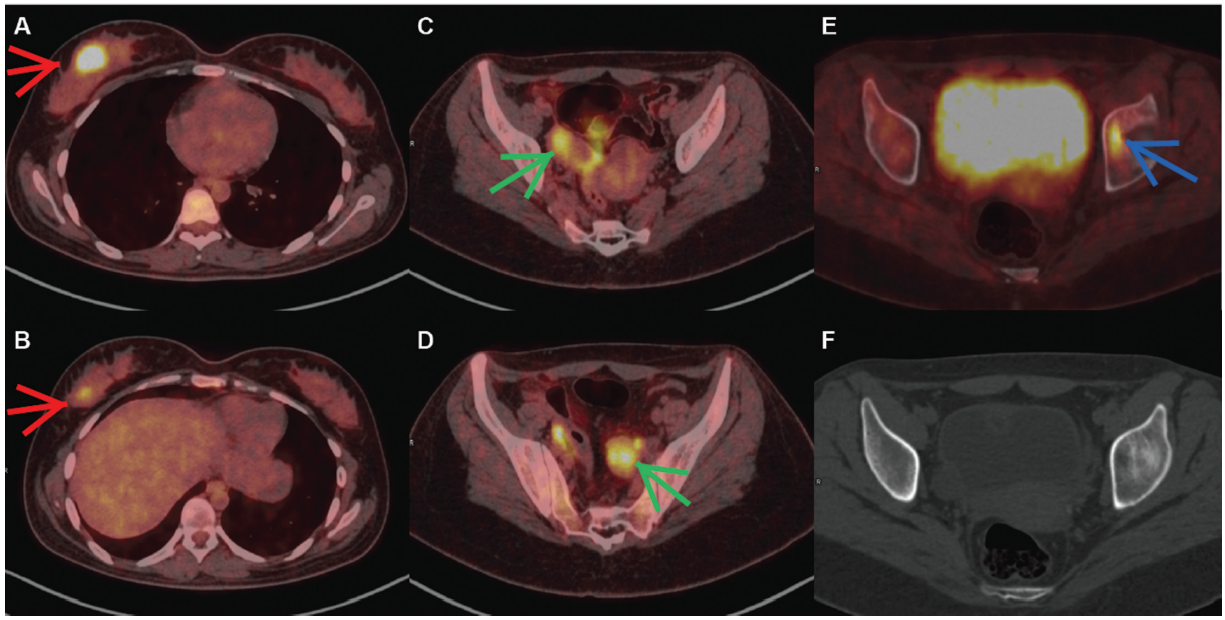

Fig. 2 End-cycle response positron emission tomography/computed tomography (PET/CT) fused images reveal flurodeoxyglucose (FDG) avid multiple lesions in the right breast (**A**, **B**); FDG avid lesions in the bilateral ovary (**C**, **D**), and FDG avid lesion in the left iliac bone (**E**) corresponding to axial CT image (**F**) reveal lytic lesions in the left iliac bone.

cycles of VAC chemotherapy and was referred for end-cycle PET/CT for treatment response. PET/CT revealed FDG avid and nonavid residual cervical lymph nodes. FDG avid soft lesions were noted in the right breast parenchyma and ovaries (►**Figs. 1C, –2A–D**). Also, metastatic lytic and sclerotic skeletal lesions were noted (►**Fig. 1C**, ►**Fig. 2**). The overall impression was suggestive of disease progression. Fine-needle aspiration cytology and histopathological examination (HPE) with immunohistochemistry suggested metastatic ERMS from both sites. The patient refused further treatment and was lost to follow-up.

Discussion

RMS is the most common soft tissue sarcoma in children. On the contrary, it is an uncommon neoplasm in adults and older population.[1] ERMS predominantly affects children in their first 5 years of life, but it may occur at older ages. ERMS typically occurs in and around the head, neck, bladder, vagina, prostate, and testicles. However, only a few primary cases are reported from the liver, brain, trachea, heart, and breast.[5] Two subtypes of ERMS are botryoid and spindle cell RMS. Sarcoma botryoides present as a grape-like lesion, particularly in the vagina or bladder. Botryoid and spindle cell RMS tends to have a better prognosis than conventional ERMS.

Lung, bone marrow, and lymph nodes are specific metastatic sites for RMS.[2] Metastasis to the breast and ovary is very rare. Our case, unfortunately, had HPE and IHC confirmed both breast and ovarian metastases. Breast metastases from RMS are exceptional, with an incidence of 6%.[9] Bilateral involvement is between 8 and 25%.[10] They occur mainly in adolescent girls, with the most primary tumors in the extremities.[9,10] The alveolar type has a strong connection with breast deposits. Breast metastases are believed to arise due to increased vascularity and rapidly growing mammary tissue at puberty.[9,10] Metastatic, as well as primary involvement of the ovary, is infrequent in RMS. We reviewed the literature for RMS metastasizing to the breast and ovary in the pediatric population (from age 0 to 18 years) and found 12 studies reporting breast metastasis, but ovarian metastasis was not reported (►**Table 1**). Out of 54 patients, only one was male, and the rest were female, demonstrating female predominance.

In most cases, the primary site was the extremity, followed by pelvic structures. Paranasal sinus as a site for primary was noted in eight (15%) cases. Out of 54 cases, 49 (90%) reported an alveolar variety of RMS; the embryonal variant was found in only a single case. Two studies showed the PET/CT utilization for metastasis detection and response evaluation. Most studies reported mortality in the follow-up period.

In our case, FDG-PET/CT revealed solitary skeletal metastasis in the baseline scan, and following chemotherapy, interim PET/CT revealed residual disease with partial treatment response. However, the patient developed further recurrence and ovarian breast metastasis demonstrated by FDG-PET/CT.

The diagnostic evaluation of a suspected RMS involves determining the primary disease extent and the presence of metastatic dissemination. A thorough physical examination should be carried out, with particular attention paid to the lymphatic structures in the region. A total blood count with differential, serum electrolytes, blood urea nitrogen, and liver function tests should be conducted along with serum creatinine, phosphorus, magnesium, uric acid, and calcium. Hypercalcemia due to bone absorption can develop in people with bone metastases, albeit uncommon. Bilateral bone

Table 1 Reported cases of rhabdomyosarcoma metastasis to the breast in the pediatric population ($n = 54$)

Sr no.	Authors (y)	No.	Age/sex	Primary site	Histology	PET	Outcome
1	Howarth[16] et al (1979)	6	11.5–16 F($n = 5$) M($n = 1$)	Extremity	Alveolar ($n = 6$) Mix ($n = 1$)	N	All died at 1–16 mo from breast metastasis
2	Bohman[17] et al (1982)	3	15–18 All F	Extremity, orbit, mandible	NA	N	NA
3	Copeland[18] et al (1985)	3	13–15 All F	Perineum	Alveolar	N	All died at 7–27 mo from diagnosis
4	Pettinato[19] et al (1989)	2	14–17 All F	NA.	Alveolar ($n = 1$) Embryonal ($n = 1$)	N	NA
5	Chan et al[20] (1991)	2	14–15 All F	Pelvis, perirectal	Alveolar	N	NA
6	Rogers et al[21] (1994)	2	12–16 All F	Perineum, extremity	Alveolar ($n = 1$) Primitive ($n = 1$)	N	All died of PD
7	Kwan et al[22] (1996)	2	14–15 All F	Extremity	Alveolar	N	Died with PD
8	Hays et al[23] (1997)	19	12–21 All F	Extremity ($n = 8$) Nasopharynx and paranasal sinus ($n = 7$) Trunk ($n = 4$)	Alveolar	N	Died with PD ($n = 3$) Alive with disease ($n = 3$) No evidence of disease ($n = 3$)
9	Vishnevskaia[24] et al (2004)	2	14 All F	Widespread metastasis	Alveolar	NA	Died within 3 mo–1.5 y
10	D'Angelo[25] et al (2010)	7	13-16 All F	Extremity ($n = 3$) vagina ($n = 1$) breast ($n = 1$) retroperitoneal ($n = 1$)	Alveolar	NA	All dead at 15–48 mo
11	Kebudi[26] et al (2017)	3	13–14/F	Extremity, perineum, sphenoid sinus	Alveolar	Y ($n = 3$)	Died with PD
12	Audino[27] et al (1995)	3	14–16 All F	Extremity	Alveolar	Y ($n = 3$)	Died($n = 1$) In remission($n = 2$)

Abbreviations: F, female; M, male; mo, month; *n*, number; N, no PET/CT done; NA, not available; PD, progressive disease; PET/CT, positron emission tomography/computed tomography; Y, PET/CT done.

marrow aspiration and iliac crest biopsies should be performed in the absence of abnormal peripheral blood counts or apparent bone metastases. Plain radiographs of the primary site and CT scans of the primary and adjacent structures should be done. Magnetic resonance imaging or ultrasonography helps determine the disease extent in malignancies of the extremity or head and neck region. ^{18}F-FDG-PET/CT can accurately detect tumor lesions extent and metabolic activity, aiding staging and evaluating therapy response in many malignant tumors. As a complement to staging, restaging, and response assessment of metastatic RMS, PET/CT imaging has steadily increased in use in the last decade.[11,12] HPE and IHC are necessary for confirming the diagnosis. In our case, FDG-PET/CT revealed solitary skeletal metastasis in the baseline scan. Interim PET/CT revealed residual disease with partial treatment response. However, the patient relapsed with unusual metastasis to the breast and ovary.

Treatment for RMS requires a multidisciplinary approach, including surgical excision with or without RT and chemotherapy. The prognosis of this disease depends upon the location of the metastatic burden and the treatment received[13] standard chemotherapy regimen in North America is VAC.[14] In Europe, the backbone consists of ifosfamide vincristine and actinomycin D.[14] A randomized trial showed no apparent difference in patient outcomes between the two treatment combinations.[14] VAC/IVA has remained the same chemotherapy regimen since it was developed four decades ago, despite changes in duration, dosage, and method of administration.[15] An open-label phase 3 trial (EpSSG RMS 2005) unambiguously showed that doxorubicin addition to the standard IVA backbone did not enhance patient

outcomes. Because of cardiotoxicity (especially in younger patients), there is a lack of rationale for its continued inclusion in the chemotherapy regimen. Disease progression is noted despite continuing a VAC-based chemotherapeutic regimen. Metastatic RMS has a poor prognosis. Multimodal chemotherapy, RT, mastectomy, and bilateral oophorectomy approaches depend on a patient's condition. Literature regarding the treatment protocol for such patients is very scarce.

Conclusion

RMS being a pediatric soft tissue sarcoma commonly metastasizes to lung, bone, and lymph nodes. The alveolar variety of RMS is more frequent than other types. Few cases of breast metastasis have been reported in the past; however, ovarian metastasis is not documented. We reported a rare case of ERMS metastasizing to the breast and ovary. This case also highlights the importance of the ^{18}F-FDG-PET/CT in the treatment response evaluation and disease monitoring.

Declaration of Patient Consent

The patient gave written consent; in the form the patient consents to have images and clinical information published. The patient acknowledges that his or her name or initials will not be publicized.

Conflict of Interest

None declared.

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