Vulvar Rhabdomyosarcoma in an Adult Female Patient: A Case Report and Review of Literature

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ABSTRACT

Vulvar Rhabdomyosarcoma (VR) is a rare gynecological cancer primarily found in children. This case report discusses the diagnosis, treatment, and management complexities of a 19-year-old patient with a slow-growing vulvar lesion.

A 19-year-old female with obesity and non-alcoholic fatty liver disease presented with a left vulvar lesion measuring 11 x 7 x 7 cm that was noticed five months ago. Core needle biopsy of the lesion revealed findings consistent with rhabdomyosarcoma. A Positron Emission Tomography-Computed Tomography (PET-CT) scan showed a hypermetabolic 8.3 x 6.7 x 6.7 cm mass in the left vulvar area, extending to the vagina, rectal wall, and anal region along with enlarged left inguinal lymph nodes.

The patient was treated with the Intergroup Rhabdomyosarcoma Study-IV (IRS-IV) protocol for 16 weeks with vincristine, dactinomycin, and cyclophosphamide. Concurrent chemoradiotherapy was administered between weeks 9-14, followed by continuation chemotherapy until week 28. Interim PET-CT scan prior to concurrent chemoradiotherapy revealed a reduced mass size to 3.8 x 2.8 cm and resolved left inguinal lymphadenopathy.

Despite completing treatment, the patient reported persistent back pain and mobility issues three weeks later. A subsequent PET-CT scan showed hypermetabolic lesions at vertebral locations C6, T9, T12, and L1-L3, along with the left ischium and bilateral femoral shafts. Thoracic vertebrae biopsy confirmed rhabdomyoblasts. Patient underwent palliative radiotherapy and spinal stabilization then proceeded with second line therapy with 1 cycle of Gemcitabine-Docetaxel but showed progression of symptoms described as persistent bleeding (hematuria) and neutropenia. Further diagnostics done to the patient showed possible bone marrow involvement. Unfortunately, the patient expired owing to symptoms of cancer progression.

The management of adult-onset VR presents a significant therapeutic challenge, largely attributable to the scarcity of clinical trials and tailored treatment regimens for this specific age group. Outcomes documented in existing literature for adult VR cases present with recurrence, disease progression, and mortality. The treatment landscape in adults is complicated by comorbidities which may influence both the therapeutic choices and outcomes. Given these intricate challenges, this case echoes the need for research efforts aimed at developing management protocols specifically designed for adults with VR.

Keywords: vulvar mass, rhabdomyosarcoma, adolescent, young-adult

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INTRODUCTION

Sarcomas are malignancies derived from the mesenchymal cell origin. They can occur in any age but are more common in the pediatric, adolescent, and young adult population,[1] The most common malignancies associated in the young adult population are rhabdomyosarcoma (RMS), synovial sarcoma, Ewing sarcoma, and osteosarcoma.[2]

Vulvar cancers comprise 5% of gynecologic malignancies but only 1-3% of these cases are sarcomatous in origin. According to the Surveillance, Epidemiology, and End Results (SEER) database, the most common vulvar sarcoma type is the dermatofibrosarcoma (27%) while rhabdomyosarcomas only consist of 5.7% in incidence.[3] Due to the very aggressive nature along with the high potential for metastases and recurrence, patients diagnosed with vulvar rhabdomyosarcoma present with a median survival of nine months, rendering a poor prognosis for these patients.[4]

Vulvar rhabdomyosarcoma (VR) is a rare gynecological neoplasm usually associated with children. To date, there are only five published cases of VR in adults based on the literature review. This case report discusses a 19-year-old patient presenting with a five-month history of a slowly growing left vulvar lesion.

CASE PRESENTATION

The patient is a 19-year-old female who presented with a slowly growing lesion in the left vulva measuring 11 x 7 x 7 centimeters (cm) by palpation and consulted the Philippine General Hospital Cancer Institute. There were no associated symptoms of weight loss, vaginal bleeding nor other palpable pelvic masses. Digital rectal examination was unremarkable. Patient does not have any comorbidities aside from obesity and non-alcoholic fatty liver disease. She also has an unremarkable family history and personal/social history.

Further work-ups in order to determine the etiology of the mass were carried out. Common etiologies of vulvar masses in this age group include benign causes such as Bartholin's cyst or abscess. A transperineal ultrasound was done showing a left solid vulvar mass from the 2 o'clock to 6 o'clock region measuring 6.28 x 4.61 x 4.59 cm.

A core needle biopsy of the lesion which showed tumor cells distributed in sheets and nests. The described cells have indistinct borders, hyperchromatic, round to ovoid nuclei, and scanty eosinophilic cytoplasm with atypical mitotic figures present resembling rhabdomyoblasts (Figure 1). Immunohistochemistry studies showed that the tumor cells were positive for desmin and myogenin but negative for smooth muscle actin (SMA) and pancytokeratin (Figure 2), confirming that the results are histologically compatible with rhabdomyosarcoma. A pelvic Magnetic Resonance Imaging (MRI) was requested to determine the extent of involvement of the tumor which showed a 7.4 x 5.4 x 7.1 cm heterogeneously enhancing lobulated mass with restricted diffusion involving the left vulva and perineum, as well as two enlarged left inguinal lymph nodes, the larger of which measures 2.3 x 2.6 x 2.4 cm. A Positron Emission Topography-Computed Tomography (PET-CT) scan was subsequently requested for metastatic work-up which showed an 8.3 x 6.7 x 6.7 cm enhancing soft-tissue mass in the left vulvar region with extension to the vagina, anterior rectal wall, left ischiorectal fossa, and anal region (partial extension) with a Standardized Uptake Value (SUV) value of 11.9. Taking into account the histopathologic and radiologic results of the patient, the patient is diagnosed as a case of VR Stage III.

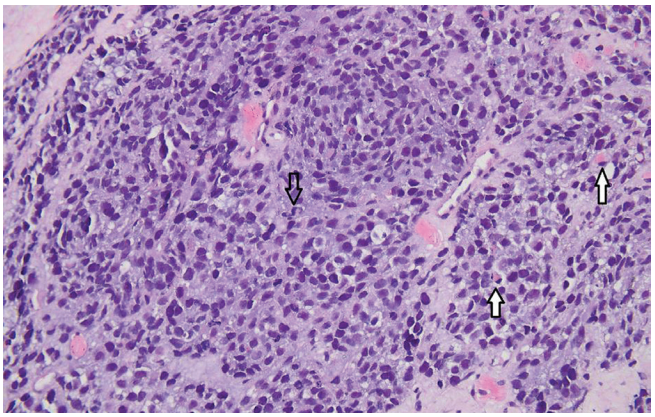

Figure 1. The tumor is composed of small cells distributed in sheets and nests. The cells have indistinct borders, hyperchromatic, round to ovoid nuclei, and scanty eosinophilic cytoplasm. Atypical mitotic figures are present *(black arrow)*. Cells with dense eosinophilic cytoplasm and eccentrically located nuclei *(white arrow with black outline)* resemble rhabdomyoblasts (Hematoxylin and eosin stain; 400x magnification).

The patient was started on the International Rhabdomyosarcoma Study – IV regimen[5] (Figure 3) consisting of vincristine 1.5mg/m2, dactinomycin 0.015 mg/kg/day, and cyclophosphamide 2200 mg/m^2 with sodium 2-mercaptoethane sulfonate (Mesna), with pegfilgrastim support and prophylactic antibiotics (co-trimoxazole, acyclovir, and fluconazole).

At the start of the first chemotherapy session (week 0), the vulvar mass measured approximately 8 x 6 x 2 cm by palpation. By week 4 of the regimen, the mass had decreased in size by 3 x 3 x 3 cm and was non-palpable on internal examination. A repeat PET-CT scan (Figure 4) done prior to week 9 of the regimen confirmed the significant decrease in the size and metabolism of the mass along the left side of the vulva. It currently measured 3.8 x 2.8 cm, from the previous 7.6 x 5.6 cm (re-measured in the prior study using approximately the same planes) with an SUV max of 3.0 from the previous 11.9. There was also resolution of the previously observed left inguinal lymphadenopathy. At this point, there were no fluorodeoxyglucose (FDG)-avid lesions at the abdominopelvic area and inguinal lymph nodes.

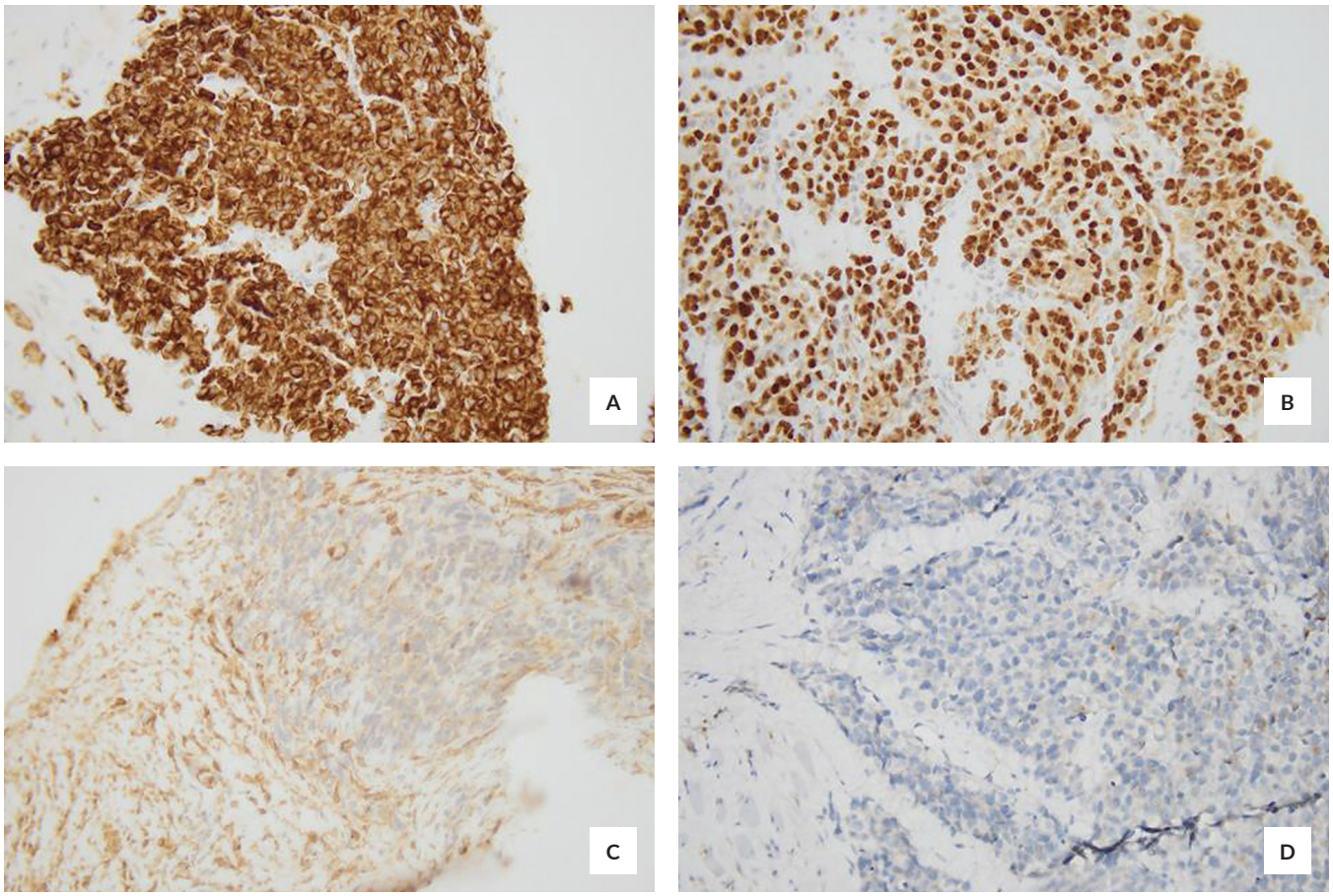

Figure 2. Immunohistochemistry strains. **(A)** Tumor cells strongly positive for Desmin (200x magnification), **(B)** Tumor cells strongly positive for Myogenin (200x magnification), **(C)** Focal positive in smooth muscle actin (200x magnification), **(D)** Tumor is negative for cytokeratin (200x magnification).

Induction Phase (Week 0-16)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Vincristine (1.5 mg/m^2)	■	■	■	■	■	■	■	■	■	■	■	■	■				■
Dactinomycin (0.015 mg/kg/day)	■			■			■										■
Cyclophosphamide (2200 mg/m^2)	■			■			■			■			■				■
Radiation Therapy (IMRT)										■	■	■	■	■	■		
Continuation Phase (Week 20-28)	17	18	19	20	21	22	23	24	25	26	27	28					
Vincristine (1.5 mg/m^2)				■	■	■	■	■	■				■	■	■	■	■
Dactinomycin (0.015 mg/kg/day)				■			■						■	■	■	■	■
Cyclophosphamide (2200 mg/m^2)				■			■						■	■	■	■	■

Figure 3. Intergroup Rhabdomyosarcoma Study IV (VAC regimen).[5]

Adapted from Intergroup rhabdomyosarcoma study-IV: results for patients with nonmetastatic disease by Crist WM, Anderson JR, Meza JL, Fryer C, Raney RB, Ruymann FB, et al. Intergroup rhabdomyosarcoma study- IV: results for patients with nonmetastatic disease. In: Boyiadzis MM, Frame JN, Kohler DR, Fojo T. Hematology Oncology Therapy, 2nd ed. pp. 1127. New York: McGraw-Hill Med;2014.

During the course of her induction chemotherapy, the most common side effects she experienced were nausea, vomiting, and generalized weakness. She also reported amenorrhea that started after week 1 of the chemotherapy. The aspartate aminotransferase (AST) and alanine aminotransferase (ALT) serum levels were being monitored regularly and the dosages of the chemotherapeutic drugs were adjusted accordingly. The highest recorded value was five times the upper limit despite the absence of any symptom of hepatitis such as jaundice, fever, and abdominal pain. Patient was also seen by gastroenterology service for clearance prior to resuming chemotherapy during that time.

During weeks 9-14, the patient underwent concomitant chemotherapy and radiation therapy (RT) as part of the

regimen. The risks and benefits of RT had been previously explained to the patient and her father including the possibility of infertility resulting from the significant exposure of her gonads to radiation as well as offering possibilities for fertility preservation. The family opted to proceed with the RT.

A total dose of 3600 centiGray (cGy) in 20 fractions (180 cGy/fx) to the pre-chemotherapy volume and 5040 cGy in 28 fractions (180 cGy/fx) for 42 days by 6 MV linear accelerator using Intensity-Modulated Radiation Therapy (IMRT) was given. The rationale for IMRT was to improve the conformality of the prescribed RT dose to the target volume, sparing more non-target tissues from high-dose radiation by the implementation of a response-based radiation treatment volume that targets the pre-chemotherapy tumor volume to an intermediate dose before "*coning down*" to boost the post-chemotherapy tumor volume to full dose. With this technique, delayed onset of RT allowed for continued tumor response to induction chemotherapy and facilitated further reduction in high-treatment volumes, which may reduce acute and late toxicities of treatment.[5] The patient was simulated using a hip-fix immobilization device with both arms positioned over the chest and both knees extended. The scan range was taken from above the liver down to the proximal femur and were acquired using 3 mm slice thickness. Relevant organs at risk for adverse reactions included the bladder, rectum, and femoral heads with doses within the recommended constraints as shown in Figure 5A. Typical target optimization was achieved with 95% and 98% of the planning target volume receiving 3600 cGy and 5040 cGy, respectively, as depicted in Figure 5B.[6]

The patient completed the concurrent chemotherapy and radiation, and is currently undergoing continuation chemotherapy (weeks 20-28). After completing treatment, the patient reported persistent back pain and mobility issues after three weeks. During the time of consult, patient did not yet present with any signs of neurological deficits. A post-treatment PET-CT scan showed an ill-defined non-FDG avid soft tissue mass in the left side of the vulva with diffuse FDG-tracer uptake measuring 3.8 x 2.7 cm with hypermetabolic lesions noted at vertebral locations C6, T9, T12, and L1-L3, along with the left ischium and bilateral femoral shafts (Figure 6). Thoracic vertebrae biopsy confirmed rhabdomyoblasts, indicating disease progression.

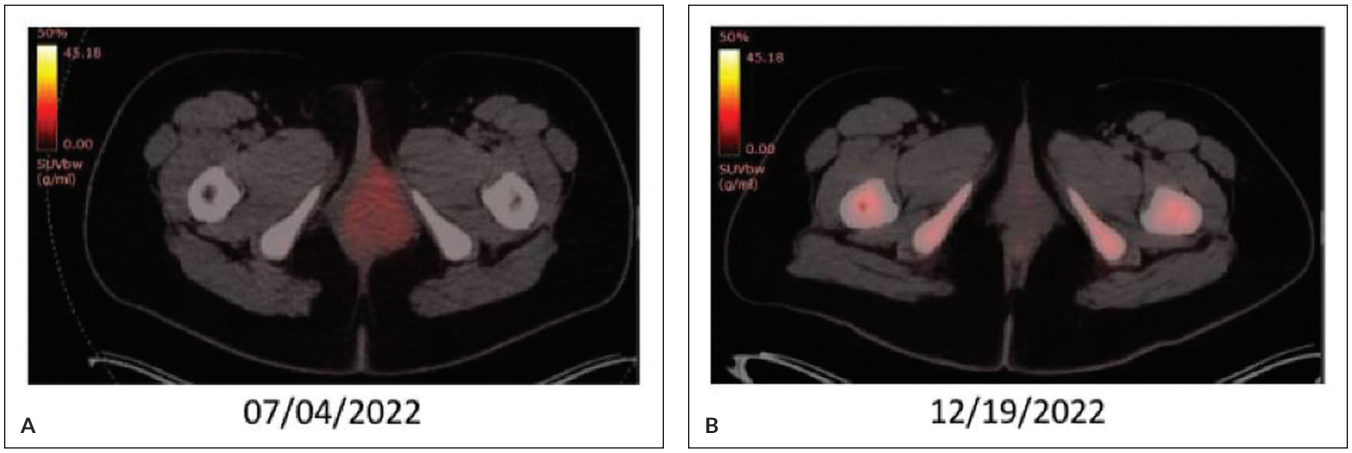

Figure 4. PET-CT result comparison of the pelvic area. **(A)** July 2022, **(B)** December 2022.

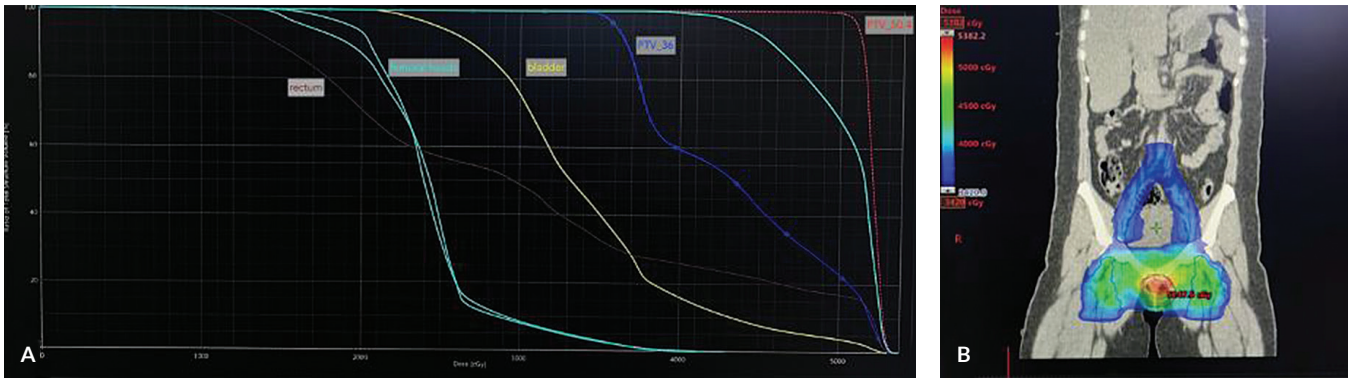

Figure 5. **(A)** Dose volume histogram showing 95% isodose of 3600 cGy *(blue line)* and 98% isodose of 5040 cGy *(red line)*, **(B)** Dose color wash in coronal view of the radiation therapy plan showing the heterogeneity of the dose distribution.

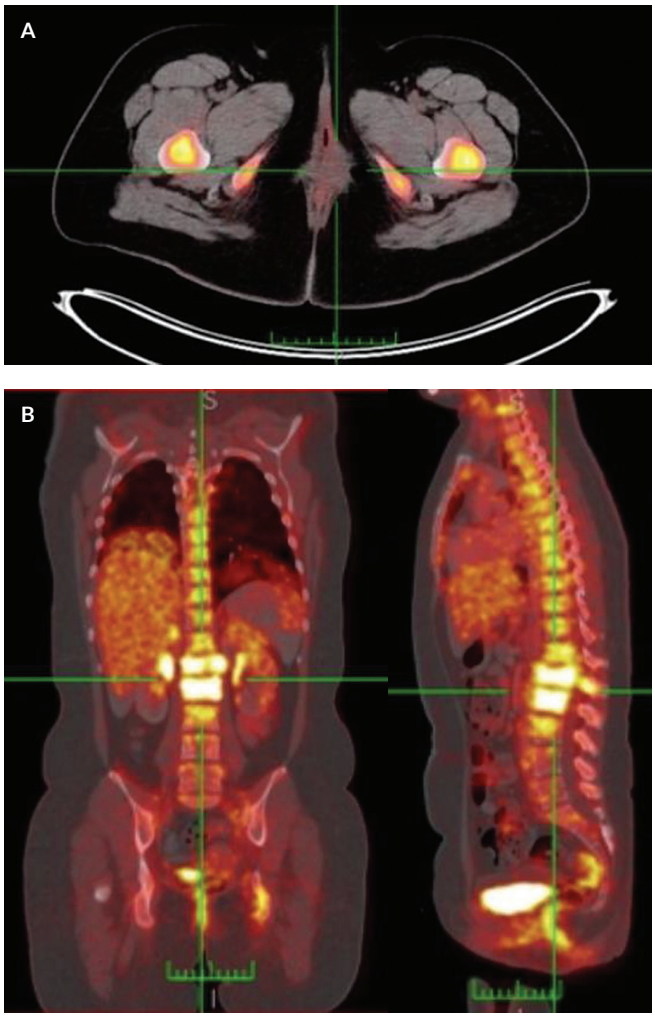

Figure 6. (A) Post-treatment PET-CT scan showing a non-FDG-avid vulvar lesion, **(B)** Coronal and sagittal view of the post-treatment PET-CT scan showing hypermetabolic lesions in the vertebrae.

Patient underwent palliative radiotherapy for the affected vertebrae with spinal stabilization due to the onset of leg weakness causing immobility. She also underwent second line therapy with 1 cycle of Gemcitabine-Docetaxel but showed progression of symptoms described as persistent bleeding (hematuria) and neutropenia. Further diagnostics done to the patient showed possible bone marrow involvement. Unfortunately, the patient expired owing to symptoms of cancer progression.

DISCUSSION

Embryonal rhabdomyosarcoma (ERMS) is a malignant soft tissue tumor with morphological and immunophenotypic features of embryonic skeletal muscle. It is the most common subtype of rhabdomyosarcoma, with around one third of cases occurring in children aged less than five years. ERMS also constitute 20% of all adult rhabdomyosarcomas. In terms of pathogenesis, genomic studies of ERMS have identified somatic driver mutations involving the RAS pathway (NRAS, KRAS, HRAS, NF1, FGFR4), involving effectors of PI3K (PTEN, PIK3CA), or in genes that control the cell cycle (FBXW7, CTNNB1). In addition, expression studies have identified markers that distinguish FOXO1 fusion-negative rhabdomyosarcoma (HMGA2 and EGFR overexpression) from FOXO1 fusion-positive rhabdomyosarcoma (AP-2β and P-cadherin overexpression).[7]

On gross examination, ERMS usually forms poorly circumscribed, fleshy, pale-tan masses that impinge on its adjacent organs.[7] Microscopically, ERMS contain primitive mesenchymal cells in various stages of myogenesis, recapitulating embryonic skeletal muscle. By immunohistochemistry, ERMS are essentially always positive for desmin, a cytoplasmic intermediate filament expressed in neoplasms with myogenic differentiation, although the extent of positivity may be variable. Skeletal muscle-specific markers such as myogenin (MYF4) and MYOD1 are also positive in essentially all cases. Muscle specific actin (MSA) and SMA (smooth muscle actin) are frequently positive. Ultimately, essential to the diagnosis of ERMS is the presence of primitive round and spindle cells with scattered differentiated rhabdomyoblasts showing positive for desmin and heterogeneous nuclear staining for myogenin and/or MYOD1.

Diagnosing ERMS based on morphology alone can be difficult since primitive round and spindle-shaped rhabdomyoblasts may also be seen in other entities. The main differential diagnosis would be alveolar rhabdomyosarcoma (ARMS), particularly the solid variant. Histologically, solid ARMS is composed mainly of small, round undifferentiated cells without an alveolar pattern. Solid ARMS is composed of densely packed groups or masses of tumor cells that resemble the round cell areas of ERMS but demonstrate a more uniform appearance.[8] In addition, the immunoprofile of ARMS is similar to other RMS which demonstrate desmin, myogenin, and MYOD1 positivity. The lack of FOXO1 gene rearrangements may help distinguish poorly differentiated ERMS from solid ARMS.[7]

In the investigation of vulvar masses, it is important to ascertain whether the lesion is benign or malignant in order to triage its proper treatment. Since vulvar lesions tend to be asymptomatic and discovered only upon self-examination, correct and timely diagnosis is important. Most common benign lesions are Bartholin gland cysts/ abscess, epidermoid cysts, and angiomas. While the most common malignant vulvar lesions vary depending on the age group, squamous cell carcinoma is the most common histologic subtype while sarcomas, albeit relatively less common, are more prevalent in the younger age group.[9,10]

The chemotherapy protocol used in this case is the three-drug chemotherapy regimen from the Intergroup Rhabdomyosarcoma Study-IV (IRS-IV). In this study,

Table 1. Summary of the Five Cases of Adult Vulvar Rhabdomyosarcoma Seen during Literature Review

Study	Patient	Intervention	Outcome
Wang 2023	24 y/o pregnant	Internal iliac embolization and chemotherapy	Progression
He 2022	20 y/o stage I ARMS	Surgery → adjuvant chemotherapy	Recurrence
Bhattacharyya 2015	21 y/o	Multimodality (?)	(?)
Reisner 2014	20 y/o (metastatic)	Surgery → chemotherapy (VAC)	Ongoing chemotherapy
Issam 2020	25 y/o	Chemotherapy (VDC)	Mortality

ARMS – alveolar rhabdomyosarcoma, VAC – vincristine, dactinomycin, cyclophosphamide, VDC – vincristine, doxorubicin, cyclophosphamide

patients were classified as low or intermediate risk. Low-risk patients possess tumors located at favorable sites (head, neck, and genitourinary; excluding the orbit, eyelid, parameningeal, bladder, and prostate), completely resected / microscopic residual, and tumors <5 cm at unfavorable sites but were completely resected. Intermediate-risk patients are those with local or regional tumors.

The patient has regional metastases and is thus classified as intermediate-risk. She was given vincristine, dactinomycin, and cyclophosphamide with concurrent radiotherapy at weeks 9-14 of the regimen. Researchers report a 3-year failure-free survival rate of 83% when using the three-drug regimen.[11,12]

RT is a considered a critical component of multimodality approach for pediatric rhabdomyosarcoma (RMS). The current standard of care is the induction chemotherapy followed by concurrent chemoradiation for patients with unresected disease, those with microscopic or gross residual disease after surgery, and for all patients with alveolar histology.[13,14] This is also supported by Children's Oncology Group (COG) STS committee, where studies have shown high rates of local failure for vaginal tumors when local control with radiotherapy is omitted.[15]

According to IRS Protocol, no routine RT is recommended for patients clinically grouped as Group I favorable histology tumor. Patients with a Group II favorable histology tumor should receive RT at Week 2. Patients with a Group III favorable histology tumor and those with a Group I–III unfavorable histology tumor should receive RT at Week 6. In terms of RT doses, Group II and Group III tumors should receive 41.4 Gy and 41.4-50.4 Gy, respectively, depending on whether the tumor size was <5 cm or ≥5 cm.[11]

A total of five case reports (Table 1)[16-20] based on the literature search showed poor results in adult patients with vulvar rhabdomyosarcoma. The table summarizes outcomes from various case studies on the treatment of adult vulvar rhabdomyosarcoma. In the 2023 study by Wang, a 24-year-old pregnant patient received internal iliac embolization and chemotherapy, which unfortunately led to disease progression. He et al. in 2022 reported on a 20-year-old with stage I alveolar rhabdomyosarcoma (ARMS) treated with surgery and adjuvant chemotherapy, resulting in recurrence. Bhattacharyya in 2015 discussed a 21-year-old patient who underwent an unspecified multimodality treatment, with no disclosed outcomes in the journal. Reisner's 2014 study involved a 20-year-old with metastatic disease managed with surgery and VAC chemotherapy (vincristine, actinomycin, and cyclophosphamide), and the case was marked by ongoing chemotherapy at the time of the report. Lastly, Issam in 2020 detailed a case involving a 25-year-old treated with VDC chemotherapy (vincristine, doxorubicin, and cyclophosphamide), which ended in mortality. These cases highlight the varying therapeutic approaches and outcomes for this rare malignancy in the adult population.

There are limited therapeutic options for rhabdomyosarcoma cases outside of combination chemotherapy and radiotherapy. A study by Miwa et al. highlighted possible therapeutic options such as trabectedin, tyrosine kinase inhibitors, and immune checkpoint inhibitors.[21] A phase 2 trial using trabectedin was given to children with recurrent rhabdomyosarcoma. The results of the trial failed to demonstrate a robust response to the disease with only one patient showing partial response and another with stable disease after 2 cycles of treatment.[22] The use of immunotherapy in this setting has also been dismal. In a phase 1 and 2 trial evaluating the Programmed death-1 inhibitor (PD-1) nivolumab in multiple malignancies in children and young adult population, a total of 12 rhabdomyosarcoma cases were recruited in the study which showed no objective response. What is important to consider here though is that only nine of the 12 patients in the rhabdomyosarcoma cohort underwent PD-L1 testing and only one case has a positive PD-L1 level (1%).[23]

Ethical considerations were thoroughly reviewed before initiating treatment in this case, with the principle of non-maleficence and double effect being of paramount importance. The healthcare team prioritized ensuring that the benefits of treatment significantly outweighed the associated risks and that the intent of treatment primarily based for the benefit of the patient. In alignment with the principle of autonomy, the patient was informed of the potential risks and benefits in undergoing the recommended treatment plan.

A key aspect of the ethical discussion was the potential impact of long-term complications of cancer treatment such as: fertility, secondary malignancies, and neuropathy. The use of multiagent therapy with alkylating agents and exposure to pelvic radiation is associated with amenorrhea, decrease ovarian reserves, and uterine dysfunction thereby, increasing the risk for infertility. Options such as ovarian and embryo cryopreservation are the recommended options for fertility preservation, but access and price to these are the

primary barriers for patients in our resource-limited setting. The risk for secondary malignancies are higher in patients with rhabdomyosarcoma, in a study analyzing the SEER database, rhabdomyosarcoma survivors have an increased incidence of malignancies at the bones, joints, heart, breast, male genital organs, and central nervous system. The use of vincristine is associated with neuropathy in 34.6% of patients administered with the drug. Recognizing that cancer treatment could have long-term consequences for the patient's health is part of the holistic management of the patient.[24-28]

This approach underscores the importance of respecting the patient's right to make informed decisions about their future reproductive potential. By integrating a comprehensive discussion on the treatment and its effects, the healthcare team not only adhered to ethical standards but also addressed the patient's holistic well-being, considering both the immediate and long-term implications of treatment.

CONCLUSION

The management of adult-onset VR presents a significant therapeutic challenge, largely attributable to the scarcity of clinical trials and tailored treatment regimens for this specific age group. Outcomes documented in existing literature for adult VR cases present with recurrence, disease progression, and mortality. The treatment landscape in adults is complicated by comorbidities which may influence both the therapeutic choices and outcomes. Given these challenges, this case reinforces the need for research efforts aimed at developing management protocols specifically designed for adults with VR.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

All authors declared no conflicts of interest.

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