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Rare Adult Subtype of Rhabdomyosarcoma, a Common Childhood Soft Tissue Carcinoma

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Abstract

Rhabdomyosarcoma is a malignant soft tissue sarcoma of primitive mesenchymal cells, showing varying degrees of striated skeletal muscle cell differentiation. It is a very common cancer of childhood and adolescence, but rarely seen in the adult population. Here, we present a case of a 33-year-old male presented with a poorly differentiated desmin positive alveolar rhabdomyosarcoma in the left arm. The prognosis of alveolar rhabdomyosarcoma in adults is very poor, frequently detected at advanced stages or with metastases. The alveolar subtype in particular has been found to have a more aggressive course with a high rate of metastasis. Recent studies have shown that using pediatric treatment guidelines resulted in better survival outcomes and local control, but the survival rates are still below that of the pediatric population. Newer studies are looking into using specific molecular markers for more targeted therapy in hopes of further improving survival rates in the adult population.

Keywords

Rhabdomyosarcoma, Pediatric Oncology, Medical Oncology

Introduction

Rhabdomyosarcoma (RMS) is one of the typical tumors of childhood and adolescence, making up 50% of soft tissue sarcomas, with an incidence rate of 4.3 cases per million people younger than 20. It is rarely seen in the adult population, accounting for <1% of adult solid tumor malignancies and 3% of all adult soft tissue sarcomas. It typically presents as a painless, enlarging mass or with symptoms related to the primary lesion. It can present with pain due to compression of nearby neural structures.[1-3] The prognosis of RMS in children is better compared with the adult population, having a 5-year survival of 5% to 15% with local therapy to 47% to 62% with multimodal therapy.[4] The 5-year survival overall is 27%.[5] It has been shown that when pediatric guidelines are implemented in adult cases, the prognosis is better but it still does not reach the survival rate that is seen in the pediatric population. This could potentially be due to the increased incidence of poor prognostic indicators in adult cases when compared with pediatric cases or the increased risks or chemotherapy adverse events in the adult population.[4,6]

Case Presentation

A 33-year-old male without significant medical history presented to our clinic with a mass in his left arm. He first noticed this mass in early 2020; however, due to the Covid-19 pandemic he was unable to seek medical attention until 6 months later. He denied pain and the mass did not disrupt activities of daily living. He denied weight loss, fatigue, change in appetite, headache, chest pain, abdominal pain, nausea, vomiting, diarrhea, constipation, night sweats, fevers, and chills. An expedited workup was started with an x-ray and ultrasound of the mass which led to recommendations for a magnetic resonance imaging (MRI) of the left arm. MRI of the left arm revealed an 8 cm maximum diameter multiseptated hemorrhagic lesion within the medial aspect of the triceps muscle within the distal arm as seen on Figures 1 to 3. Interventional radiology-guided biopsy was done and revealed patchy nuclear staining for MyoD1 and was also positive for desmin and vimentin. It was negative for the following stains: smooth

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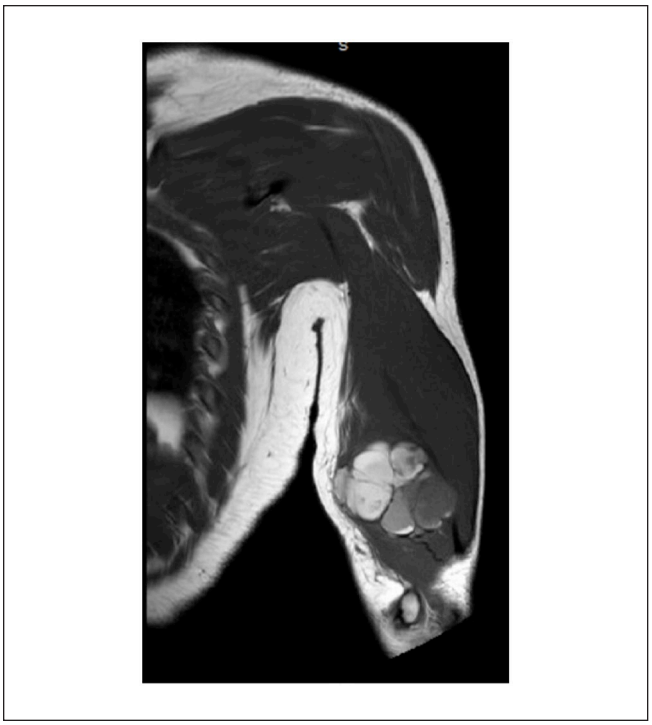

Figure 1. Magnetic resonance imagin of the left arm (coronal view); 8 cm maximum diameter multiseptated hemorrhagic lesion within the medial aspect of the triceps muscle within the distal arm.

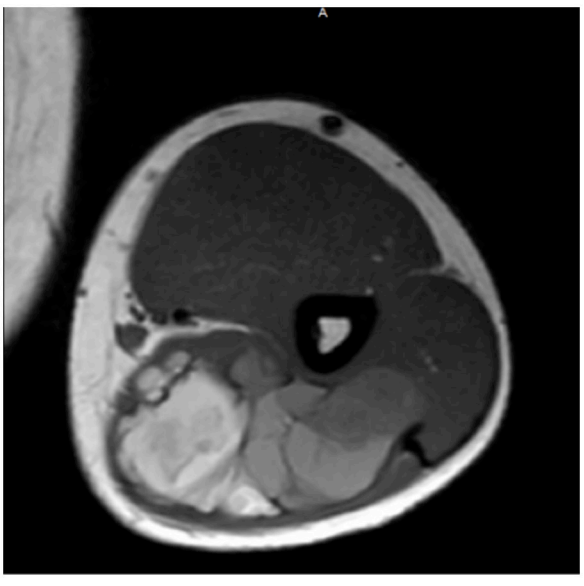

Figure 2. Magnetic resonance imagin of the left arm (Axial view); 8 cm maximum diameter multiseptated hemorrhagic lesion within the medial aspect of the triceps muscle within the distal arm.

muscle actin (SMA), muscle-specific actin (MSA), myogenin, neuron-specific enolase (NSE), muscle creatine kinase (MCK), S100, and CD45. These findings are consistent

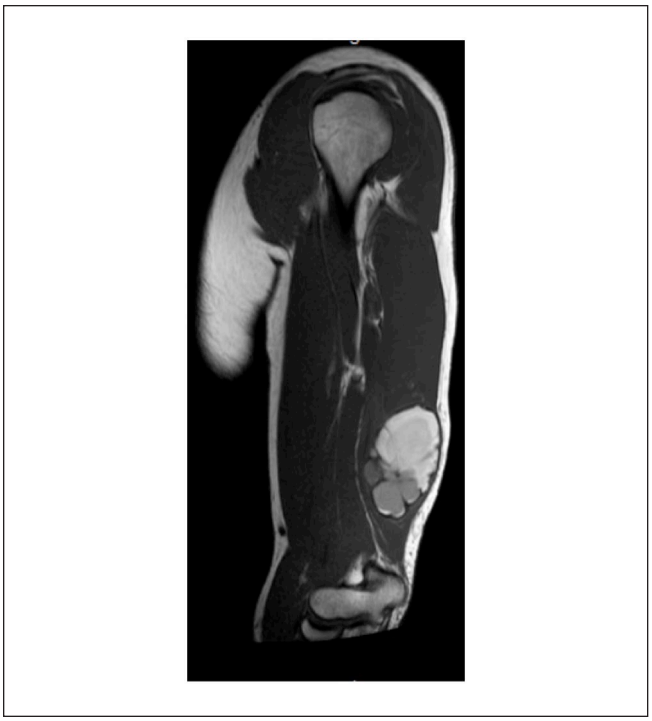

Figure 3. Magnetic resonance imagin of the left arm (Sagittal view); 8 cm maximum diameter multiseptated hemorrhagic lesion within the medial aspect of the triceps muscle within the distal arm.

with poorly differentiated desmin positive sarcoma—alveolar RMS. The morphologic features are more consistent with the alveolar subtype than the embryonal. Additional imaging significant for computed tomographic (CT) scan of chest without contrast revealed multiple pulmonary nodules seen within the lungs bilaterally significant for metastatic disease as seen on Figure 4. Chemotherapy started with VAC/IE (vincristine, adriamycin, cyclophosphamide, alternating with ifosfamide, etoposide), and Mesna.

Discussion

Rhabdomyosarcoma (RMS) is a common cancer of childhood and adolescence, comprising 50% of soft tissue sarcomas. Incidence is greatest in people less than 20 years old, the incidence rate being 4.4 cases per 1 million.[3] However, it is very rare in adults, making up about $<1\%$ of adult solid tumor malignancies and only 3% of all adult soft tissue sarcomas.[2] It typically presents as a painless, enlarging mass or with symptoms related to the primary lesion.[1,2] It can present with pain due to compression of nearby neural structures. The most common locations are the head and neck region, genitourinary tract, and extremities.[2] The most common site is the head and neck region in children, comprising 25% of the cases, and the extremities in adults, comprising 26% of the cases.[3] In children, RMS often co-occurs with defects

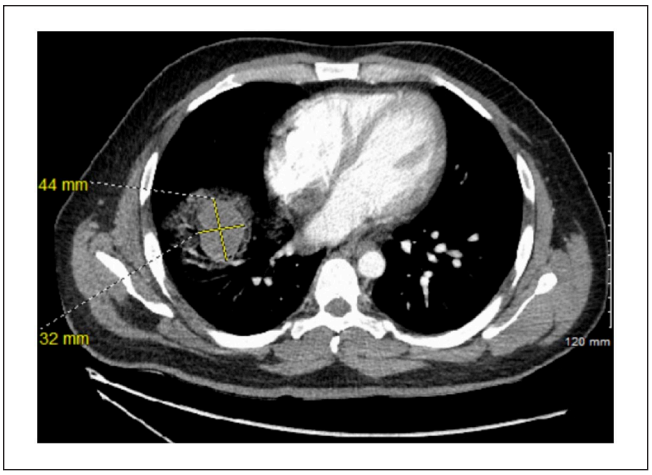

Figure 4. Right lower lobe anterior soft tissue nodular density 4.4 × 3.2 cm and surrounding right lower lobe anterior infiltrate; several metastatic bilateral lung nodules.

of the central nervous system, urogenital, gastrointestinal, and circulatory systems, and melanocytic nevi.[7] The risk factors for pediatric RMS include low socioeconomic status, in-utero radiation exposure, accelerated in-utero growth, and familial syndromes such as Nanoon, Li-Fraumeni, Neurofibromatosis, and Beckwith-Wiedemann.[8]

The two most common types of RMS are alveolar (ARMS) and embryonal (EMRS), with ARMS being more common in the adult population.[6] On histology, RMS can have highly differentiated cells; cell architecture can be round or ovoid in nature, containing an abundance or lack of acidophilic cytoplasm with fibrillar structures and eccentric nuclei. ARMS can present with poorly differentiated rhabdomyoblasts with scant cytoplasm and enlarged nuclei or can resemble poorly differentiated giant multinucleated cells. ERMS can also present with rhabdomyoblasts of heterogeneous appearance; round cells with hyperchromatic nuclei and basophilic cytoplasm can be found in low-density regions.[7] Positive nuclear staining for MyoD1 protein and Myogenin (Myf4) on immunohistochemistry is the gold standard of diagnosis as the expression of myogenin in >50% of neoplastic cells strongly suggests a diagnosis of ARMS.[7] In addition to histological classification, it has recently been shown that molecular markers can be used to classify tumors. Molecular markers can improve pretreatment risk stratification of RMS, which has the potential to significantly decrease mortality. The ARMS subtype is associated with PAX3-FOXO1 or PAX7-FOXO1 fusion proteins, with PAX7-FOXO1 demonstrating superior overall survival.[9]

Incidence of metastasis in ARMS, in particular, is directly proportional to tumor volume; 13% if less than 5 cm, 31% of between 5 cm and 10 cm, and 74% in greater than 10 cm.[10] Distant metastasis is quite common. The common sites of metastases are bone, bone marrow, lung, and distant lymph nodes.[6] Lung metastases are the most common, usually bilateral and diffuse at diagnosis.[11,12]

The treatment of RMS includes chemotherapy, radiotherapy, and surgical resection.[10-12] It has been shown that tumor negative margins and pre- and postsurgical radiotherapy yield a better clinical outcome. In ARMS specifically, lymph node prophylactic radiotherapy is given due to its high rate of metastasis. Chemotherapy is rarely used in early disease but is frequently used in advanced states and RMS with metastases. If the tumor is too large to have negative surgical margins, chemotherapy is administered because larger tumors have a higher incidence of metastasis in ARMS.[10] Multimodal therapy in line with the pediatric RMS treatment guidelines yielded better survival and local control.[11] It was seen that when surgery and radiation therapy were combined with chemotherapy, using doxorubicin, ifosfamide, and vincristine resulted in 55% overall and 64% disease-free survival in 2 years.[12] If the disease continues to progress while on chemotherapy, it is an ominous sign.[12] Newer studies are looking into using molecular markers for targeted therapy, but chemotherapy remains the mainstay of treatment.[7]

As mentioned before, PAX3-FOXO1 is linked to a poorer prognosis compared with PAX7-FOXO1 positive RMS. The fusion protein has been shown to be essential in ARMS tumorigenesis; targeting the fusion protein or inactivating downstream genes/signal pathways can likely halt tumor progression.[9] The FGFR4 signaling pathway, a target of PAX3-FOXO1, plays an essential role in myogenesis and is expressed in a majority of RMS tumors. Targeting this pathway can also potentially halt ARMS tumorigenesis.[9] Additional clinical targets include insulin-like growth factor 1 (IGF1) and anaplastic lymphoma kinase (ALK) receptors, whose transcription is enhanced by PAX3-FOXO1.[13]

In children, the 5-year survival rate is 5% to 15% with local therapy and 47% to 62% with multimodal therapy.[4] The overall survival of both ARMS and ERMS in adults is 18 months. The 5-year survival overall is 27%, for localized disease is 36%, and for metastatic disease is 11%.[5] RMS in an adult has a worse prognosis than in a child, with an overall survival rate of 20% to 40%.[3] Increasing age above 35 years old is associated with decreased survival from all subtypes.[1] In addition to older age, poor prognostic factors include size >5 cm, pleomorphic and alveolar subtypes, extremity location fusion gene positivity, infiltrative tumor, and metastatic presentation.[5,12] Particularly in the alveolar subtype, the expression of AP2i and P-cadherin indicate a poor prognosis. In the embryonal subtype, hyperdiploid tumors and those that express Epidermal growth factor receptors (EGFR) and fibrillin-2 have a favorable prognosis.[7]

As stated earlier, when adults are treated with the pediatric RMS guidelines, they have better outcomes. However, the survival rate is still not as high as that in the pediatric population.[4,6] One reason for this could be due to the

unfavorable clinical presentation in adults. Adults are more likely to have the alveolar subtype, regional lymph node involvement, and distant metastases at the time of diagnosis. Clinical features in adults with metastases are particularly aggressive. It is also thought that the worse prognosis could be due to medication noncompliance, mainly because of chemotherapy-related side effects.[6]

Conclusion

The prognosis of alveolar RMS in adults is very poor. Current treatment modalities for adults follow pediatric treatment guidelines. However, survival rates are still below that of the pediatric population. Newer studies are looking into using specific molecular markers for more targeted therapy in hopes of further improving survival rates in the adult population. This case is to inform clinicians of the rare adult subtype of common childhood cancer and highlight the importance of further research regarding its treatment modalities.

Authors' Note

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Verbal informed consent was obtained from the patient for their anonymized information to be published in this article.

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