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High-Grade Metastatic Pleomorphic Rhabdomyosarcoma in a TP53 Germline Mutation Patient: A Rare Presentation in Adults

Shervin Zoghi[1]*, Aaron Tsumura[1], Rashmi Verma[1] and Morgan Angus Darrow[2]

[1]Department of Hematology and Oncology at the University of California, Davis, USA

[2]Department of Pathology and Laboratory Medicine at the University of California, Davis, USA

ABSTRACT

Pleomorphic Rhabdomyosarcomas (PRMS) in adults are an exceptionally rare and aggressive soft-tissue tumor arising from undifferentiated mesenchymal cells. While more common in children, rhabdomyosarcomas in adults are associated with poorer outcomes and require immediate, aggressive intervention. Here we present a case of high-grade pleomorphic rhabdomyosarcoma of the left thigh in a 58-year-old male with metastases to the lungs and pelvis. Due to the limited diagnostic and treatment protocols of this rare disease and subtype, the goal of this case study is to highlight a comprehensive clinical approach to this disease.

***Corresponding author**

Shervin Zoghi, Department of Hematology and Oncology at the University of California, Davis, USA.

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Introduction

Soft tissue sarcomas constitute a subtype of malignant soft tissue tumors originating from primitive skeletal muscle cells. It predominantly affects children, with adult-onset cases being extremely rare. Sarcomas account for less than 1% of all adult solid malignant tumors, and less than 5% of these sarcomas are diagnosed as Rhabdomyosarcomas [1]. While they can occur at any site, almost 46% of all sarcomas are located at the thigh, buttock, and groin, followed by 18% in the torso, 13% in the upper extremity, 13% in the retroperitoneum, and 9% in the head and neck [2]. Generally, between 20-40% of patients with rhabdomyosarcomas experience metastatic disease burden [3,4]. The primary site of metastasis is to the lungs because of the abundant vasculature of these tumors and the hematogenous spread from their typical locations in actively contracting muscles [5].

Case Presentation

A 58-year-old male uninsured patient presented to the urgent care with a rapidly growing and painful large mass on the back of his left leg (Figure 1). He reported that it had been small and nontender for the past year, before starting to rapidly grow and cause pain as of two months prior to presentation. He denied weight loss, night sweats, dyspnea, and fever. The skin overlying the mass was fluctuant with mild erythema and warm to the touch. Complete laboratory workup was normal. However, a subsequent CT Abdomen/Pelvis demonstrated a posterior proximal thigh subcutaneous soft tissue mass measuring 13.3 x 11.4 x 12 cm, suspicious for a possible soft tissue sarcoma (Figure 2). An urgent referral at the UC Davis Cancer Center Clinic was placed and an ultrasound guided core biopsy along with further imaging were completed.

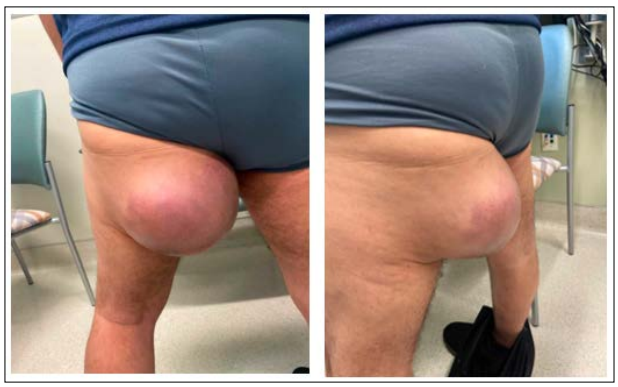

Figure 1: Initial Presentation of the Rhabdomyosarcoma on the Posterior Left Leg

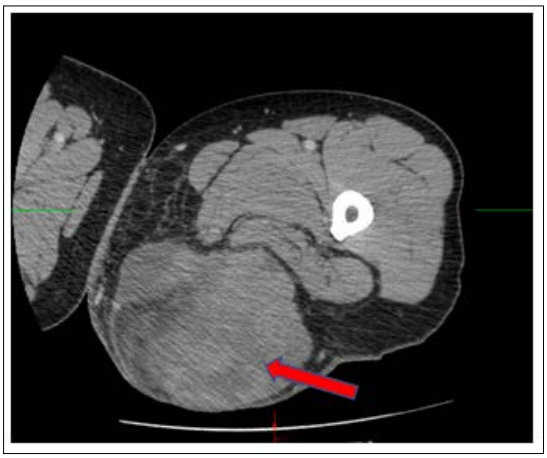

Figure 2: CT Abdomen/Pelvis at the Time of Diagnosis

Biopsy of the tumor, evaluated by the surgical pathologist, showed a highly cellular core with sheets of markedly pleomorphic malignant cells and numerous mitoses. There were prominent features of rhabdomyoblasts, which are composed of abundant eosinophilic cytoplasm, eccentric nuclei, and prominent nucleoli (figure 3). The desmin immunohistochemical stain, a generalized marker for both smooth and skeletal muscle differentiation, exhibited strong positive results as evidenced by the prominent brown staining (figure 4). The myogenin stain, a more specific marker for skeletal muscle differentiation, demonstrated nuclear staining as well (figure 4). Overall, these findings are consistent with a high-grade pleomorphic rhabdomyosarcoma. Further staging showed significant lymphadenopathy in the pelvis as well as a spiculated right apical lung nodule measuring 13x13mm on Chest CT (Figure 5), indicative of metastasis. A punctate right upper lobe nodule near the minor fissure and a 3mm left upper lobe nodule was also noted. Chromosomal analysis showed the presence of multiple abnormalities and apparent loss of 17p (loss of TP53 tumor suppressor gene), which are indicative of adverse prognosis.

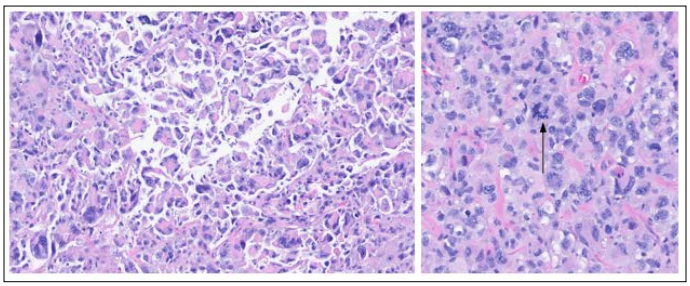

Figure 3: 400X Magnification Shows a Highly Cellular Core with Sheets of Pleomorphic Malignant Cells with Features of Rhabdomyoblasts. The Arrow Highlights Atypical Mitosis

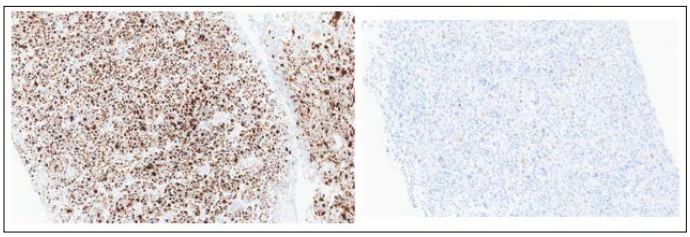

Figure 4: Desmin (left) and Myogenin (right) Immunohistochemical Stains

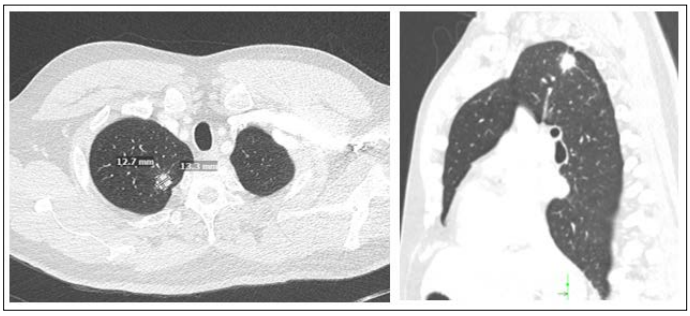

Figure 5: CT Chest Showing a Spiculated Right Apical Lung Nodule

Prior to initiating cycle 2 of AIM, the patient was found to be febrile with a purulent cellulitis overlying the tumor (Figure 6). He was given 10 days of antibiotics, starting with broad spectrum vancomycin and ceftriaxone, followed by doxycycline and Augmentin post-sensitivities results. After completing antibiotic therapy, the patient completed the following two cycles of AIM with minimal complications. After cycle 3 (Figure 7), this patient was discussed at the multidisciplinary sarcoma tumor board, with overall agreement that the patient's repeat staging imaging showed some improvements in the primary mass, now measuring about 13.7x15.6x14cm with significantly reduced malignant lymphadenopathy, and stability of the metastatic 13mm spiculated nodule at the right apex. Furthermore, after all six cycles of AIM are complete, the patient will undergo evaluation for surgical resection with possible neoadjuvant radiation.

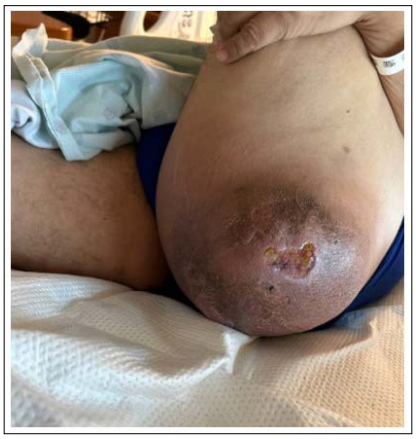

Figure 6: Secondary Cellulitis Infection Overlying the Tumor

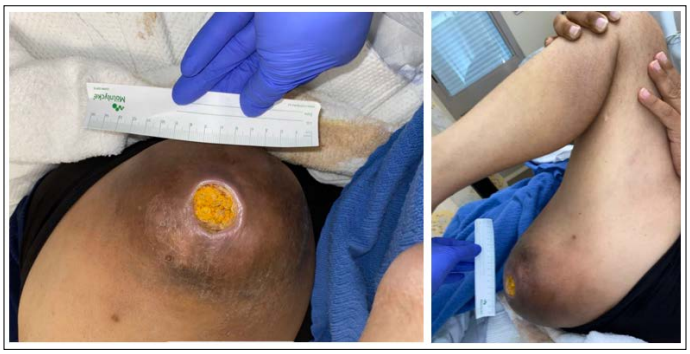

Figure 7: Tumor Images Post Cycle 3 of AIM Therapy

Discussion

The management of adult-onset metastatic sarcomas, with a particular emphasis on high-grade pleomorphic rhabdomyosarcomas, poses significant challenges due to the lack of established clinical guidelines, the few numbers of newly diagnosed cases, and the presence of diverse comorbidities and predispositions.

Currently, the standard of care for treatment of sarcomas generally requires either Doxorubicin or more aggressive AIM therapies. This was a point of discussion for the care team, as there is little guidance regarding what threshold warrants escalation to AIM. For this patient, the tumor size itself was not what constituted concern so much as it was the accelerated rapid growth described by the patient and depicted by CT scan.

There are a number of factors to consider when deciding to use AIM therapy. First and foremost, AIM is typically reserved for high-risk or advanced cases of rhabdomyosarcoma. It is more aggressive, particularly because of the addition of Ifosfamide, which increases the likelihood of potential complications such as myelosuppression and bladder toxicity – while the addition of Mesna helps to protect the bladder from hemorrhagic cystitis, careful monitoring is still warranted [6,7]. Thus, it's important to evaluate the patient's condition, tumor characteristics and disease extent before starting treatment. Secondly, AIM is more

challenging to administer because it generally requires inpatient care since the safety and feasibility in the outpatient setting has not been fully established.

However, a recent study by the University of Arizona Cancer Center attempted to transition AIM based chemotherapy to the outpatient setting for 21 patients for a total of 83 cycles and found that continuous outpatient infusion and care was in fact feasible, well-tolerated, and significantly cheaper [8]. While 71% of the patients were hospitalized at least once and 43% of them experienced neutropenic fever, the number of bed stays saved by transitioning was 390, for a cost savings of well over a million dollars [8]. With the development of new guidelines to the outpatient setting, many more patients will likely be receptive to receiving the AIM therapy.

After the completion of AIM therapy, the patient will undergo evaluation for surgical resection and neoadjuvant radiation. There are a number of additional considerations to consider during this process, such as the increased rates of flap failures due to delayed neovascularization in the flap. Histologically, the tissues undergoing radiation experience a decrease in the number and diameter of capillaries, affecting the transitional zone between the graft and tissue bed and causing vascular thrombosis and potential flap failure [9]. Radiation therapy has also been shown to induce a proinflammatory and prothrombic state due to increased vessel lesions [10]. These changes, coupled with the increased endothelial cell dehiscence, coagulation, fibrinolysis, leukocyte adhesion molecules, and NF-kB released in post-irradiated tissue beds, are clearly correlated with a statistically significant risk of failure [11,12].

Conclusion

In this report, we detail the case of a highly aggressive, metastatic pleomorphic rhabdomyosarcoma in an adult who has experienced rapid growth of tumor size and bulk symptoms. Based on the patient's clinical presentation and diagnostic workup, aggressive management using AIM combination chemotherapies and analgesics was warranted and has been successful in slowing down tumor growth and pain symptoms. While further treatment with surgical intervention and neoadjuvant radiation are critical, additional scrutinization for thrombosis and neovascular complications are necessary. As this case report has demonstrated, managing tumor growth and pain symptoms in adult sarcoma patients requires a multimodal, aggressive treatment plan.

Acknowledgement

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