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CASE REPORT

Pediatric Alveolar Rhabdomyosarcoma of the Leg: A Case Report and Review of Literature

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ABSTRACT

Rhabdomyosarcoma is the most common soft tissue sarcoma in the pediatric population and makes up for 5% of all pediatric cancers. We present the clinical course of a 4-year-old female patient with metastatic alveolar rhabdomyosarcoma. During the initial treatment, the patient experienced multiple disease recurrences. Over the course of 3 years, she received a combination of chemotherapy and radiation therapy before undergoing a knee disarticulation after second disease recurrence. After surgical control, she was disease free for at least 6 months before her third recurrence. A third round of salvage therapy did not prove effective and she ultimately had rapid progression of her disease. Treatment was eventually stopped, and palliative measures were pursued; the patient was placed on comfort care measures and home hospice care.
Level of Evidence: V; Case report.
Keywords: Alveolar rhabdomyosarcoma; Pediatric cancer; Cancer recurrence.

INTRODUCTION

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in the pediatric population and makes up for 5% of all pediatric cancers [1]. RMS is a solid tumor that is highly aggressive and has high malignant potential. It is derived from mesenchymal tissues and has multiple subtypes, of which embryonal and alveolar (ARMS) are the most prolific [2]. ARMS is typically the more aggressive subtype and the primary site can stem from multiple organ systems; however, ARMS of the extremities has one of the worst prognoses. ARMS typically presents as a non-painful, progressively enlarging soft tissue mass that may disrupt tissue and structures as the mass enlarges [3]. In most cases, ARMS is associated with a chromosomal translocation of either t(1;13)(p36;q14) or t(2;13)(q35;q14) with a resulting PAX7:FOXO1 or

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PAX3:FOXO1 gene fusion product, respectively. The resultant product has been linked to prognostic significance [4]. Diagnosis is confirmed with biopsy and treatment consists of a multi-faceted approach involving chemotherapy, local radiation therapy and local control with surgery. The following case details the treatment course of a 4-year old female who presented with metastatic ARMS with multiple disease recurrences throughout the course of her treatment.

CASE PRESENTATION

A 4-year-old female with no past medical history presented to the clinic after her parents incidentally noticed the presence of a new, non-painful mass in the posterior left leg. No systemic signs or functional impairment were apparent. Physical exam demonstrated a firm, deep-seated mass in the posterior compartment of the leg and left popliteal fossa fullness. She had full non-painful ROM of the left hip, knee and ankle. There was no axillary, inguinal, popliteal, or epitrochlear lymphadenopathy. Labs were significant for an elevated ESR at 41 mmol/h while C-reactive protein and lactate dehydrogenase were within normal limits.

Over the course of the next month, initial imaging (Figure 1) demonstrated a 5.3 x 5.0 cm lobulated mass that infiltrated the posterior and anterior compartment of the distal left lower extremity; fascial layers did not appear disrupted, however. A similarly enhancing mass 2.3 cm in diameter within the left popliteal fossa was observed as well (Figure 2). There was no evidence of metastasis or acute processes on CT of the chest, abdomen, and pelvis. Biopsy revealed a small round blue cell tumor and confirmed the diagnosis of RMS. Cytogenetic evaluation revealed DNA FISH probe positive for FOXO1 (FKHR) rearrangement and samples were also positive for Desmin and Myogenin with immunohistochemical staining. Genomic

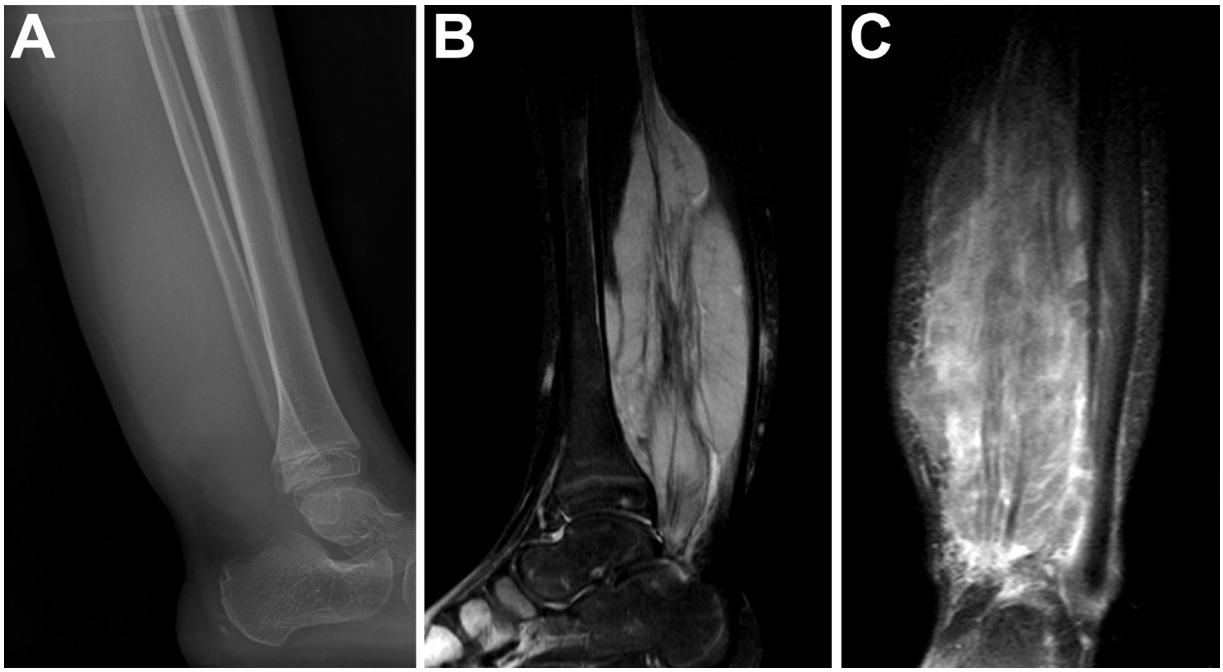

Figure 1. (A) X-ray of her left leg at initial presentation. Large soft tissue prominence is visualized in the posterior compartment. (B) MRI showing extensive T2-weighted lobulated lesion of the posterior compartment with some extension in the anterior compartment. (C) Heterogenous contrast uptake is seen throughout the mass.

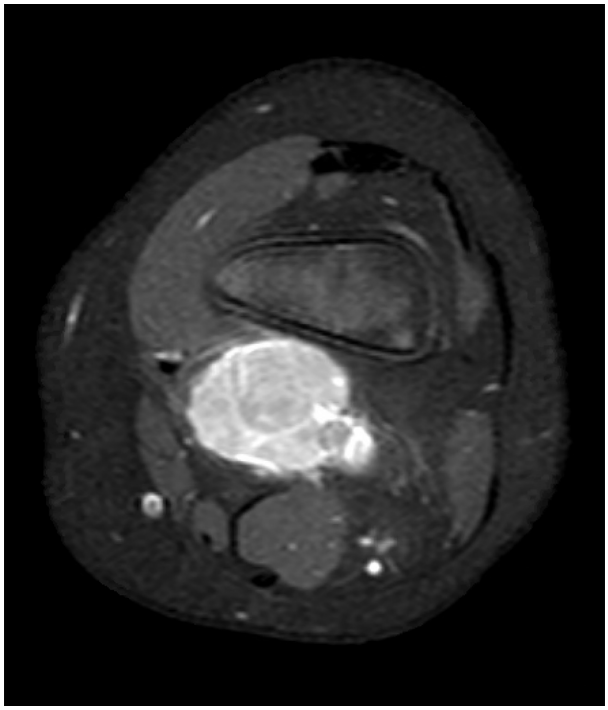

Figure 2. Heterogenous and lobulated mass seen within the popliteal fossa on initial MRI.

testing of biopsy sent to an outside laboratory confirmed the presence of PAX3-FOXO1 mutation. The initial PET scan (Figure 3A) revealed multiple, hypermetabolic lymph nodes, the largest up to 7 mm, in the left inguinal region; a bone scan was negative for disseminated osseous malignancy. Biopsy of the PET positive inguinal nodes was negative for metastatic disease. However, bone marrow biopsy of the bilateral iliac crests demonstrated infiltration of the right iliac crest with atypical, hyperchromatic cells arranged in clusters and small sheets; the left iliac crest showed no signs of infiltration, but samples of both left and right iliac crests displayed hypocellular (80%) bone marrow.

Due to the extent of metastases and infiltration, she had Stage 4 and Clinical Group 4 disease according to the Children's Oncology Group (COG) and Intergroup

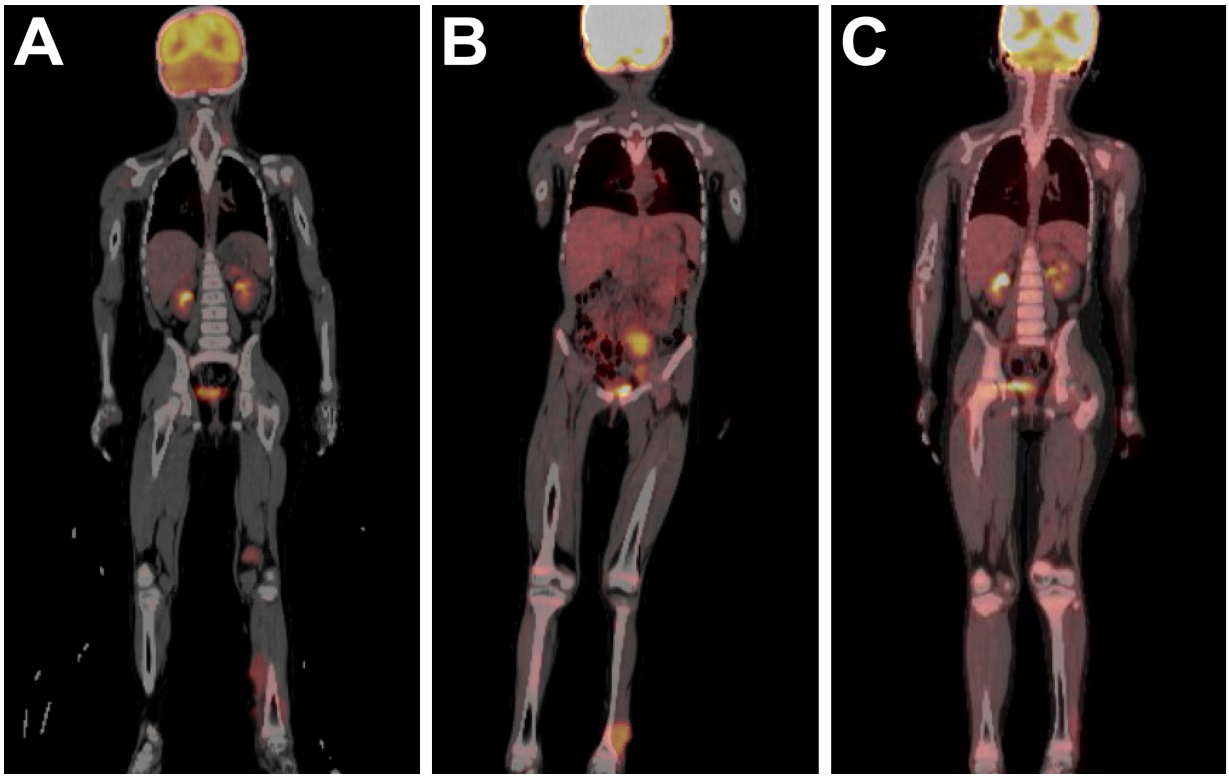

Figure 3. (A) Initial PET: hypermetabolic activity in the left lower extremity within the leg and popliteal fossa. (B) First recurrence PET: hypermetabolic activity at the primary site in the leg as well as left iliac nodes not observed in previous imaging. No increased activity is observed at the location of the previous popliteal metastatic site. (C) Second recurrence PET: increased signal in the lateral left leg. No distant disease was observed.

Rhabdomyosarcoma Study (IRS) criteria, respectively. The institution's pediatric tumor board recommendation consisted of initiation of treatment with induction chemotherapy following the Children's Oncology Group Study ARST0531 regimen which began six weeks after initial presentation. This regimen consisted of alternating cycles of vincristine/actinomycin D/cyclophosphamide (VAC) and vincristine/irinotecan (VI).

Ten week PET and CT scans showed a favorable response to therapy, but also revealed new areas of sclerosis involving the spine and sternum indicative of widespread osseous metastatic disease previously unidentified. Local control consisting of radiation and/or surgery was further deferred. At seven months, there was no demonstrated PET evidence of metabolically active residual or metastatic malignancy and no evidence of new metastatic disease in the chest, abdomen or pelvis. Scans obtained four weeks after completion of chemotherapy were negative for residual/recurrent or metastatic disease. Thirteen months after initiation of chemotherapy, Proton Radiation Therapy (RT) was delivered by an outside institution to the primary tumor site in the left leg including the popliteal metastatic deposit. A total of 5,040 cGy was delivered with minimal sequela consisting of radiation dermatitis which resolved; the sternum and vertebrae were not treated with RT at that time. Post-RT restaging imaging showed no evidence of disease and she returned to normal activities and school.

First recurrence: The patient presented to the clinic three months after RT with persistent pain in her left ankle after falling at school. There was interval development of a nodule on the lateral aspect of the leg above the ankle; imaging confirmed

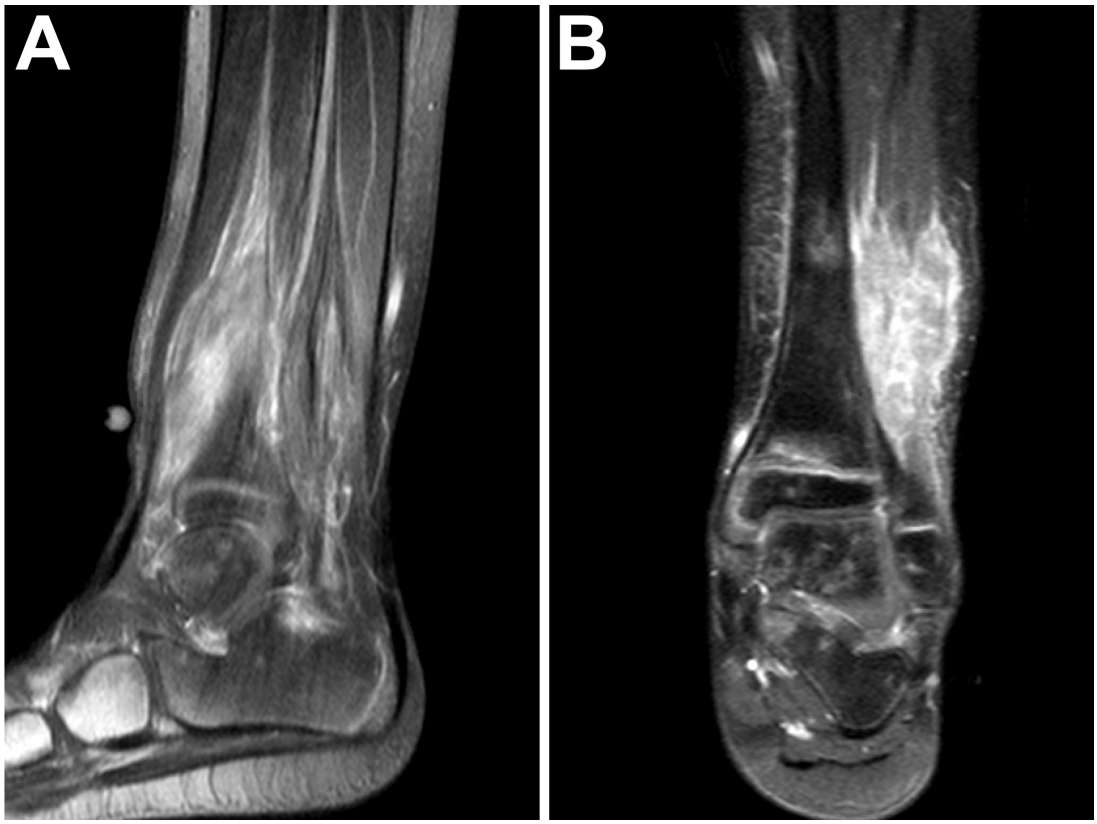

Figure 4. (A) Post-contrast T1-weighted sagittal view of first recurrence at the primary site in the left leg. (B) Patchy, heterogenous contrast uptake is seen in the coronal section.

disease recurrence and development of a 6.0 x 3.3 x 2.3 cm soft tissue mass in the distal left leg and new left iliac chain adenopathy on PET scan (Figures 3B and 4). Repeat chest CT and bone marrow biopsies were negative at this time. Upon completion of staging, salvage chemotherapy using the ARST0921 regimen (vinorelbine, temsirolimus, and cyclophosphamide) was initiated. Within twelve weeks of therapy initiation, there was a favorable response with resolution of the left iliac chain adenopathy and minimal remaining hypermetabolic activity at the primary site of recurrence. Orthopedic oncology deferred surgical local control again at this time and Radiation Oncology recommended against repeat RT of the left distal lower extremity. Six months following salvage therapy initiation, repeat scans demonstrated continued response and minimal residual increased metabolic activity in the distal left lower extremity. The ARST0921 regimen was completed after twelve 3-week cycles.

Second recurrence: MRI obtained one week following completion of first salvage therapy demonstrated recurrence of disease in a new location, her left flexor hallucis longus muscle (Figure 3C and 5). Needle core biopsy of the left distal extremity was performed by interventional radiology and confirmed recurrent rhabdomyosarcoma. PET/CT and bone marrow biopsies were negative for metastatic disease. After discussion with the family regarding options for local control, an additional salvage chemotherapy was initiated one month later; therapy consisting of two 3-week cycles of topotecan and carboplatin followed by alternating 3-week cycles of carboplatin/etoposide and topotecan/cyclophosphamide for 6 total cycles.

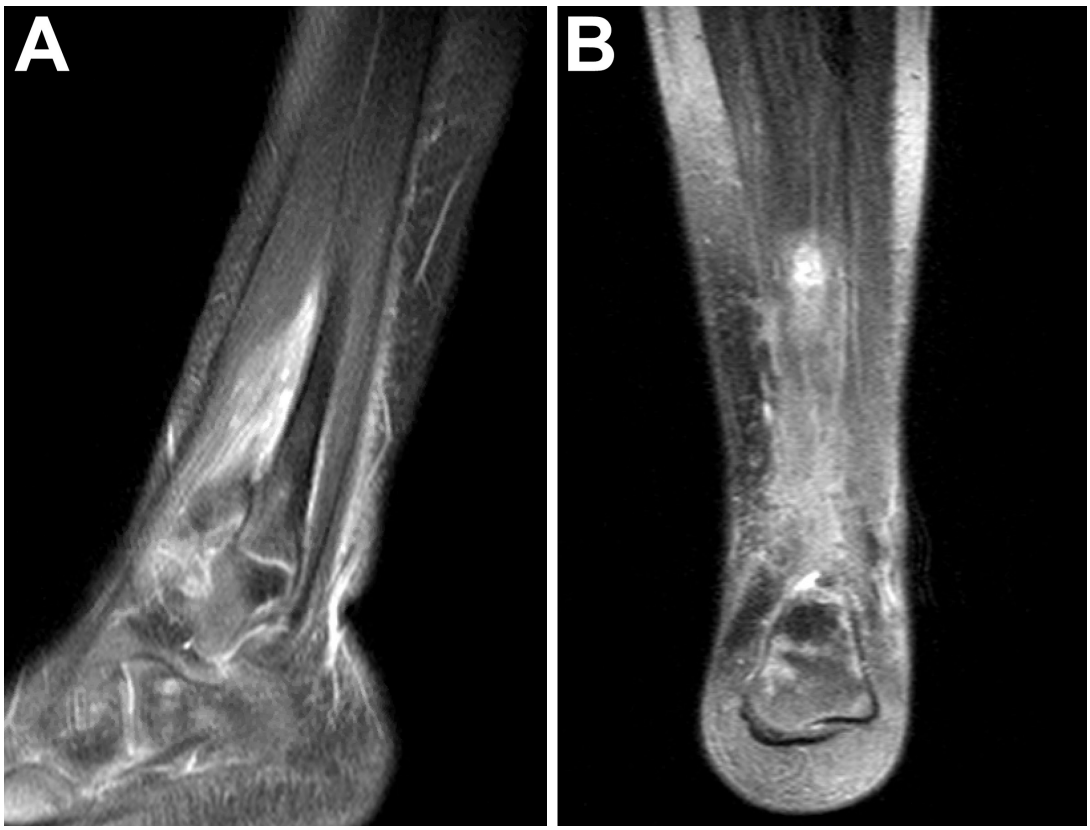

Figure 5. (A) Sagittal view showing hyperintense signal in the anterior compartment with second recurrence at the primary site in the left leg. (B) Area of increased T2 signal with enhancement in the posterior compartment and flexor hallucis longus muscle seen with second recurrence.

PET/CT and bone marrow examination performed one month after initiation of second salvage therapy revealed disease localized to the distal left lower extremity and no evidence of metastatic disease. Reassuring imaging and scans favored consideration of surgical local control; three months after initiation of second salvage therapy, orthopedic oncology performed a through-knee amputation of the left leg. Pathology revealed skin and soft tissue margins free of tumor, with the tumor 10.1 cm from the nearest skin margin. She did very well post-operatively and made very good progress in mobility. She then completed the remaining second salvage therapy regimen for 6 weeks post-operatively. Imaging following completion of salvage therapy revealed a concerning 5 x 2 mm nodule in the left lower lung lobe; maintenance chemotherapy was started (6 cycles of vinorelbine and oral cyclophosphamide x 28 days) three weeks later. Repeat PET/CT imaging at the start of maintenance cycle four showed mild, nonspecific tracer uptake at the distal left leg stump, considered to be inflammatory changes secondary to prosthesis use, and the absence of the previously identified pulmonary nodule seen on the most recent scan. She did well after the left knee disarticulation, returned to school, and was fully ambulatory using her left leg prosthetic device.

Third recurrence: Eight months post-operatively and at the end of her 6 months of maintenance chemotherapy, PET/CT and CT chest were obtained. Unfortunately, the new imaging revealed multiple new metastatic osseous lesions in the right eighth rib and bilateral femurs. Extensive MRI imaging detailed: an expansive (approximately 2.9 x 5.7 cm) lytic lesion involving the right eighth posteromedial rib, a new sub-4-mm right lung base nodule, abnormal femoral metaphyseal marrow signal bilaterally, but the absence of metastatic spread to the brain (Figures 6-7). Incisional biopsy

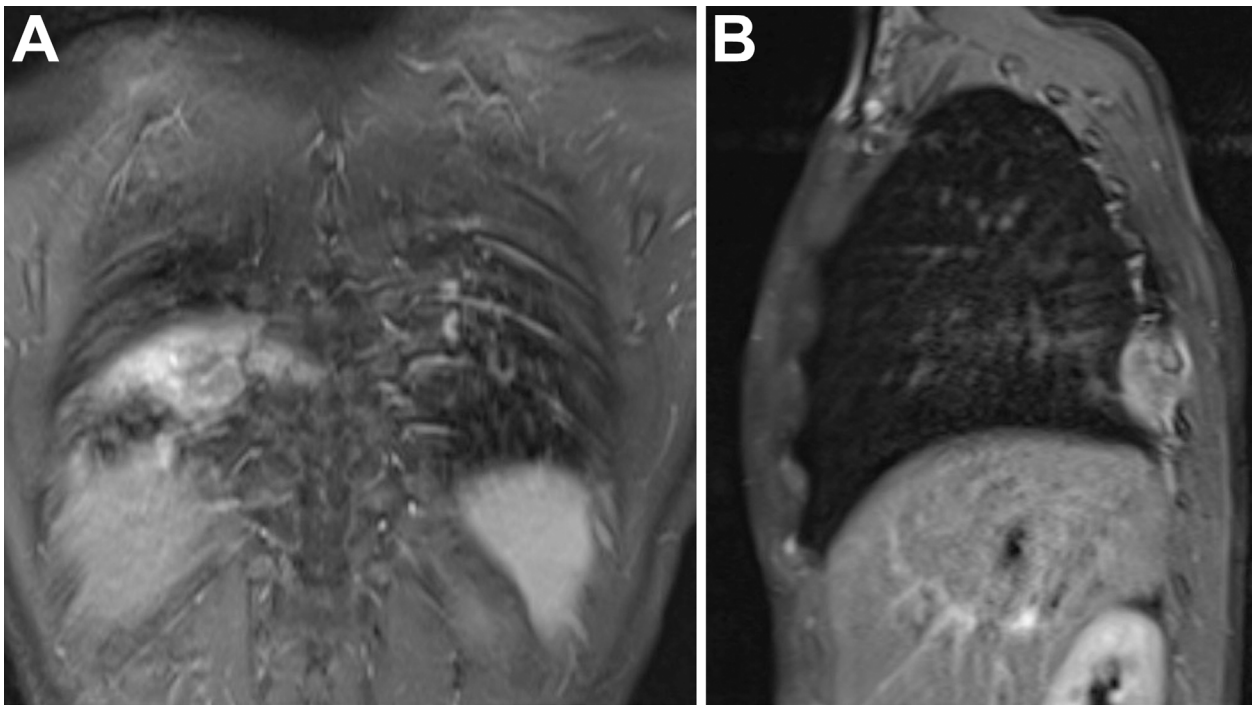

Figure 6. (A) Post-contrast T1 weighted coronal MRI of chest. The large metastatic lesion of the right posteromedial eighth rib is seen. (B) Post-contrast T1 weighted MRI showing a sagittal view of the rib lesion.

of the right distal femur metaphysis confirmed recurrent alveolar rhabdomyosarcoma and specimen samples were sent for genetic testing for possible clinical trial inclusion. At this time, the patient's parents opted for further treatment while attempting to maintain her current lifestyle. After completion of the first cycle of the third salvage treatment with gemcitabine and docetaxel, she received palliative radiation to the symptomatic right rib lesions. Although radiation provided some relief, the metastatic lesions in her lower extremities were rapidly progressing. She was no longer able to ambulate independently, with or without her prosthesis, and experienced severe, unremitting bilateral leg pain refractory to oral opioid medication. During a follow up visit 1 week after radiation, she was admitted to the pediatric inpatient service for significant hypercalcemia (19.1 mg/dL) and pain management. X-ray and MRI imaging confirmed a pathologic fracture of her distal right femoral metadiaphysis, although, no intervention was pursued (Figure 8A-B). After lengthy discussion with the patient's family, her parents opted for hospice care; she was discharged three days later to home hospice care with her family and comfort care measures only.

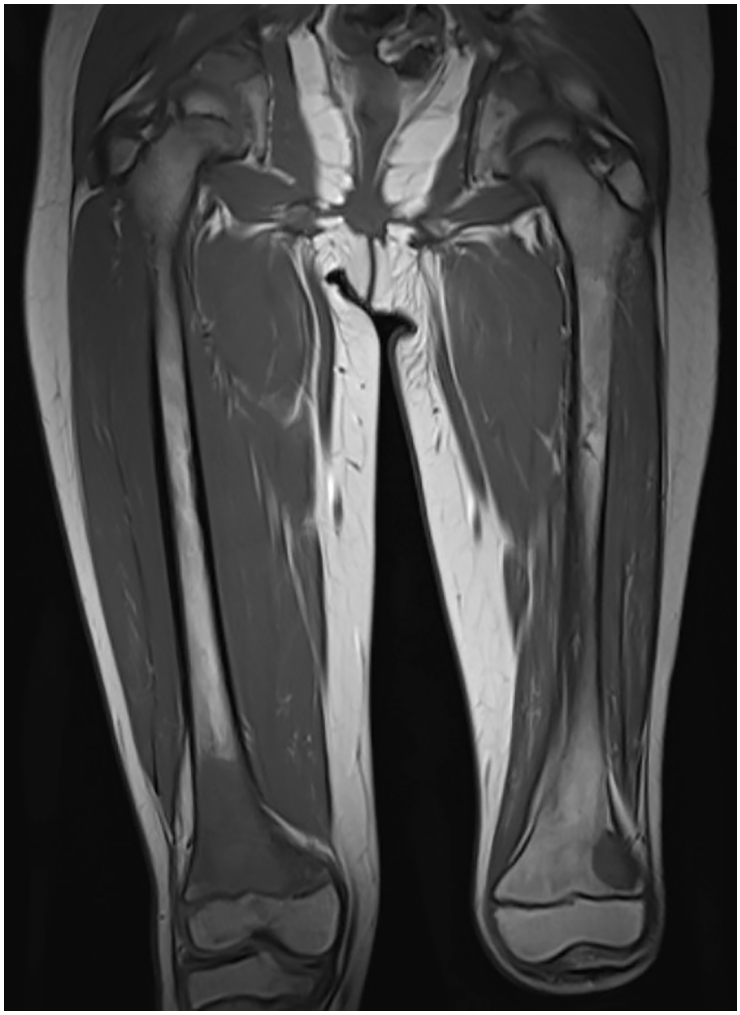

Figure 7. Coronal T1 of the bilateral femurs. Metastatic infiltration of the bilateral femoral metaphyses is seen. The left femoral metaphysis has a well-defined, eccentric circular lesion and the right femoral metaphysis has widespread infiltration that extends into the diaphysis.

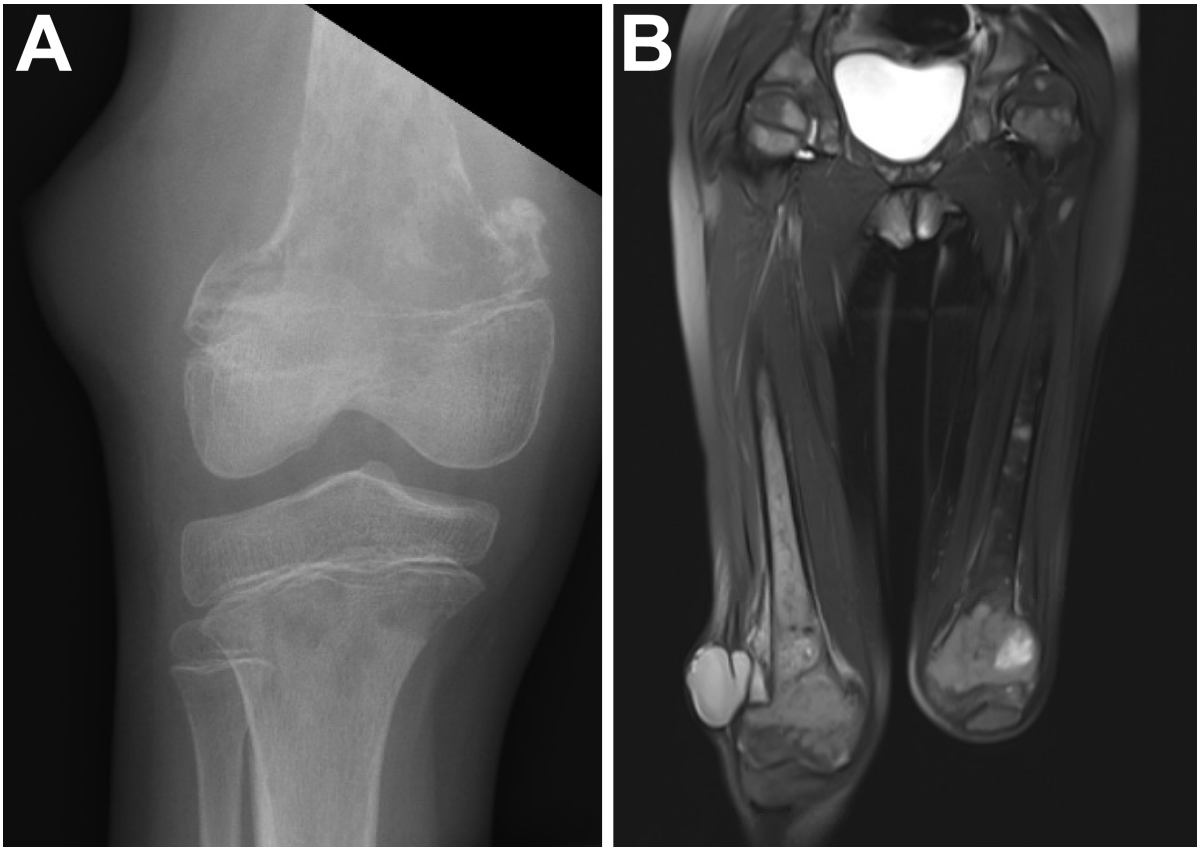

Figure 8. (A) X-ray of her right knee on hospital admission. Minimally displaced fracture of the distal metadiaphysis is visualized. Associated soft tissue swelling secondary to hematoma and moth-eaten appearance of metastatic lesion is also seen in femur diaphysis and tibia. (B) MRI of the bilateral lower extremities revealing significant disease burden and acute process in the right distal femur demonstrating pathologic fracture, adjacent hematoma and suspected bone infarction in the right femur shaft.

DISCUSSION

Our patient had multiple poor prognostic indicators: alveolar histology, PAX3-FKHR gene fusion, tumor location (extremity), tumor >5 cm, metastatic disease at presentation, and multiple local and distant recurrences [4,5]. She was Stage 4 or Clinical Group 4 at the time of diagnosis and within the very high risk treatment group.

The alveolar subtype accounts for 20% of rhabdomyosarcoma cases and approximately 44-50% of extremity RMS tumors have alveolar histology [1,3]. The distal portion of an extremity and the lower extremities are the more common extremity locations [1]. ARMS is located on the extremities in approximately 20% of RMS cases and typically follows a very aggressive course with an unfavorable outcome [3]. Of the 127 patients with metastatic disease in the IRS-IV trial, the most common sites of metastases were the lungs (39%), bone marrow (32%), lymph nodes (30%), and bones (27%) [6]. Of note, our patient had presumed or confirmed metastatic disease within all four of these locations throughout the course of her disease. In primary extremity disease, the rate of regional lymph node involvement is high, more so with recurrence; 38% of patients who had relapsing disease in IRS-IV had disease recurrence in lymph nodes [7]. Although biopsy

of her inguinal nodes at initial presentation were negative for metastases, new PET positive illiac nodes were observed with the first recurrence. Distal recurrence was presumed to have occurred in these lymph nodes; however, a biopsy was never done since these lymph nodes responded to therapy.

Patients with metastatic or stage IV ARMS have up to a 25% 5-year overall survival. Disease recurrence of ARMS is frequent with approximately 30% of patients experiencing disease relapse, commonly in lung and bone marrow [1,3]. Recurrence imparts a significant decrease in the rate of overall survival, which falls below 10% [8]. Among patients with the alveolar subtype and one or more recurrences, as in this patient, 5-year overall survival was as low as 5% with median survival typically less than 10 months from first recurrence [8].

The majority of ARMS patients have a PAX-FKHR fusion positive tumor. 23% of ARMS tumors are fusion negative, 55% are PAX3-FKHR fusion positive, and 22% are PAX7-FKHR positive [4]. In a multivariate analysis, Sorenson, et al. showed that patients with metastatic disease and PAX3-FKHR fusion positive tumors had significantly decreased estimated 4-year overall survival of 8% when compared to 75% overall survival with metastatic PAX7-FKHR fusion positive tumors [4]. When taken with the prevalence of the PAX3-FKHR fusion, a significant number of patients with metastatic disease will have very poor overall survival [4]. It has been postulated that fusion gene status in lower risk groups is an independent predicting factor of both disease recurrence and death, with decreased 5-year event free survival and overall survival [9]. However, it was found that fusion positive status plays less of a role than clinical features when staging and risk-stratifying patients with metastatic disease [10].

New chemotherapy regimens for rhabdomyosarcoma are frequently evaluated. VAC is the typical backbone, with newer regimens substituting or adding additional cycles of chemotherapeutic agents. Newer multiagent therapy regimens, such as ARST0431, with more toxic agents, have failed to show significant improvement in ARMS 5 year event free survival when compared to IRS-IV trials [11]. In patients with recurrence, ARST0921 using temsirolimus has shown promising results due to increased event free and overall survival when combined with vinorelbine and cyclophosphamide [5]. Temsirolimus is active against the mammalian target of rapamycin (mTOR) pathway activated in RMS and ARST0921 represents the tangible benefits of targeted molecular therapy in conjunction with cytotoxic therapy in treatment resistant disease [5].

Cases of relapsing and refractory RMS are typically treated with different regimens [12]. For this patient's second recurrence, agents that she had not been previously exposed to were chosen. Second salvage therapy followed the Italian Soft Tissue Sarcoma Committee's (STSC) regimen involving two upfront cycles of topotecan-carboplatin and then six total cycles of alternating between topotecan-cyclophosphamide and carboplatin-etoposide [12]. This regimen had shown 5-year overall survival rates of 17%, a slight increase when compared to 10% 5-year overall survival observed in patients with relapsing disease [12]. After completion of the Italian STSC regimen for refractory RMS, she was placed on maintenance therapy. Per European Pediatric Soft Tissue Sarcoma Study Group (EpSSG), in high risk patients with alveolar histology and without metastasis, maintenance

therapy consisting of vinorelbine and cyclophosphamide improved 5-year overall survival compared to no further treatment [2]. Although studies to evaluate merit of maintenance therapy in patients with metastatic disease are still in progress, the above maintenance regimen had shown promise in our patient with no evidence of disease for at least 6 months. This 6-month window afforded her the opportunity to return to school and normalize some aspects of her life. Although imaging had confirmed absence of macroscopic disease and the resolution of the left lung nodule during maintenance therapy, this sarcoma is extremely aggressive as demonstrated by the rapid progression of disease. Multiple new metastases had progressed within the two months between cycle 4 and 6 of her maintenance therapy.

Salvage therapy with gemcitabine and docetaxel has shown promise in pediatric patients with relapse or refractory sarcomas [13]. Higher dose gemcitabine (1,000 mg/m^2) and docetaxel (100 mg/m^2) demonstrated an objective response rate of 50% with relapsed/refractory pediatric sarcomas, although most cases were of Ewing sarcoma and none of rhabdomyosarcoma [13]. However, when using the gemcitabine and docetaxel at lower doses, 675 mg/m^2 and 75 mg/m^2, respectively; only 1 out of 5 patients with rhabdomyosarcoma had progression of his or her disease [14]. In patients with rhabdomyosarcoma treated with gemcitabine and docetaxel salvage therapy, there was overall clinical benefit in more than half of the patients, considering stable disease to be of clinical benefit [14]. After her confirmed third recurrence, our patient was placed on this regimen combined with radiation therapy. A priority influencing this treatment strategy was to maintain her current quality of life, something this regimen has demonstrated [13].

CONCLUSION

This case report detailed the clinical course of a very resilient, young patient with a very poor prognosis from initial evaluation. She had metastatic disease of an aggressive sarcoma with multiple distant and local recurrences. After 2 recurrences, chemotherapy and radiation were able to localize gross disease creating the opportunity for local surgical control. She had no evidence of disease for at least 6 months after knee disarticulation, over three years from initial presentation. Every treatment effort was made throughout the course of treatment, but her clinical course underlines the extremely aggressive and unremitting nature of alveolar rhabdomyosarcoma.

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