Case Report

A rare case of adult rhabdomyosarcoma with adnexal metastasis responding to non-conventional chemotherapy

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ABSTRACT

Rhabdomyosarcoma (RMS) is a pediatric soft tissue sarcoma having a rare incidence among adults. It is a highly chemo-radiosensitive tumor among the pediatric population but has poor biology in adults with dismal outcomes. Due to the rarity of adult RMS, there are no well-defined treatment guidelines for adult RMS and are mostly managed with pediatric-defined protocols but lack similar response. Here, we present the case of an adult female with extremely atypical metastatic site RMS which showed an extraordinary response to non-pediatric protocol, rather than adult sarcoma-based protocol. This might give an idea to have more research and trials in the future to implement adult sarcoma-based therapy among adult RMS cases.

Key words: Adult, Metastatic rhabdomyosarcoma, Rare

Rhabdomyosarcoma (RMS) is a pediatric sarcoma that rarely occurs in adults. RMS arises from the mesenchymal tissue and can occur at various sites in the body but the most commonly affected sites are the head and neck (35%), genitourinary tract (22%), and extremities (18%) [1]. RMS has an incidence of 4.5/million people, mostly who are younger than 20 years in the United States [1]. It is largely a disease of childhood but adult patients of RMS have rare incidences and are associated with poor overall outcomes [1]. In recent years, the 5-year overall survival rates of RMS in the pediatric population have significantly improved with a survival of 70% but the survival of adult populations with RMS is consistently lower with 5-year overall survival rates ranging from 40% to 54% [2]. Adult RMS differs from childhood RMS in terms of natural history, behavior, poor response to treatment, prognosis, and outcome. Risk-based treatment protocols are based on the initial staging, grouping, and histology of the tumor. The accepted treatment guidelines for childhood RMS include gross total resection with preservation of function, systemic chemotherapy for all, and radiation therapy for all with the exception of those with group I embryonal tumors [3,4]. In many pediatric studies, it is observed that age itself is a poor prognostic feature with children <10 demonstrating lower rates of survival than children 1–9 years of age [5]. Some of this difference in outcome between children and adults has been attributed to the increased incidence of poor prognostic features in adults such as unfavorable primary site, unfavorable histology, and higher rates of regional and distant spread [6]. The extent to which discrepancies in the treatment of the pediatric and adult population with RMS play a role in the lower survival rates among adults is unknown [7]. Unlike the pediatric RMS where the therapy and treatment protocols are well established with surgery, chemotherapy, with or without radiotherapy being the backbone, we lack well-defined treatment guidelines for adults. In most instances, pediatric protocols are used for therapy but in view of a rare entity, no randomized trials for the therapy of adult RMS are available.

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CASE REPORT

A 34-year-old premenopausal woman started noticing a swelling over her left distal foot, lateral to her little toe. It was first seen to be the size of a pea. The swelling was painless, non-fluctuant, and had no features of inflammation. Over a span of 2 months, there was a gradual increase in the size of the lesion and she noticed a similar swelling over her left lateral aspect of the neck. She also started noticing pain in her lower back which was dull aching and non-radiating, without any evident neurological deficits. Over a span of 3 months, her symptoms gradually increased. She also noticed low-grade dull aching pain in the lower abdomen more over the left side. She took some analgesics that gave her relief but soon the symptoms reappeared. She has no co-morbidities and a family history of cancer. She is married and has two kids. The youngest child was 6 years old with an uneventful obstetrical

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history. She had normal menstrual history with regular cycles and average flow. She mentions menorrhagia/dysmenorrhea since the past 2 cycles.

The patient came to the medical oncology department in view of abnormal swellings in her body. On examination, she was of the average build without any evident gross abnormality. She had mild-to-moderate pallor. She had stable vitals Eastern Cooperative Oncology Group performance status 0. Higher mental functions were normal with intact neurological parameters. The cardiorespiratory examination was within normal limits. On per abdomen examination, the abdomen was soft without any organomegaly. Her per rectal and per vaginal examinations were unremarkable. On musculoskeletal examination, there was a firm swelling of about 4×2 cm at the lateral border of the left little toe. It was non-tender, non-fluctuant, mobile to the horizontal plane, and attached to the overlying skin without any evident inflammatory feature. There was a similar swelling of about 6×4 cm located over the sternal head attachment of the left sternocleidomastoid muscle. There was no such evident swelling over any other anatomical sites. There was no evident lymphadenopathy. There was tenderness over the upper lumber vertebral level. The movement of forward bending was restricted, and the straight leg raise test was positive over the left side.

After a thorough physical examination, relevant laboratory investigations were done which suggested anemia (Hb 6.2 g/dL), without any evidence of blood loss and history of blood product support. Her lactate dehydrogenase (LDH) was high (1400 mg/dL). Rest laboratory parameters were within normal range.

The patient underwent whole-body fluorodeoxyglucose (FDG) positron emission tomography/computerized tomography (PET-CT) scan that was suggestive of FDG-avid right paratracheal, prevascular, AP window, subcarinal (size 1.1×2.3 cm, SUV max 9.9) mass noted. Spleen was enlarged (size 12.7 cm) with diffusely increased FDG update (SUV max 3.7) along with increased FDG update noted in the body of the pancreas (SUVmax 4.6). FDG-avid solid cystic lesions were noted in the bilateral adnexa. The left adnexal lesion was 2.4×2.6 cm SUVmax 8.6. The right adnexal lesion was 2.8×3.2 cm SUVmax 1.9. FDG-avid omental, serosal, and mesenteric mass deposits were noted. FDG-avid multiple lytic and marrow lesions with the same showing soft tissue components noted in bilateral skull bones, mandible, multiple cervicodorso lumbar vertebrae, bilateral humerii, bilateral scapula, bilateral clavicle, manubrium, multiple sites in ribs, multiple pelvic bone sites with the sacrum, and bilateral femur (Fig. 1). A provisional diagnosis of high-grade lymphoma was made with bone marrow infiltration, heeding to her age group and diffuse FDG uptake pattern on PET-CT scan.

An incisional biopsy from the neck lesion was done. The histopathology was suggestive of a small round blue cell tumor. The cells were typically arranged in loose and dense cellularity within a myxoid matrix, without any septa or interseptal nests of cells, or any discohesion. The cells were positive for desmin, muscle-specific actin, and Myo D and were found to be RMS (Fig. 2). The fluorescence *in situ* hybridization (FISH) for t (2;13)(q35;q14) and t (1;13)(p36;q14) was negative and had a normal karyotype. Based on the histopathology and FISH, a final diagnosis of embryonal RMS was made. A bilateral bone marrow biopsy and aspiration were done for a standard staging workup, and there was no evidence of any tumor cell infiltration.

After making a final diagnosis of high-risk metastatic RMS, she was planned for vincristine (1.5 mg/m^2), adriamycin (37.5 mg/m^2), cyclophosphamide (1200 mg/m^2) chemotherapy regimen with bone-directed therapy, zoledronic acid (4 mg), with Peg-GCSF support. She received the 1st dose after taking it for informed and written consent and explaining the immediate and long-term side effects. She tolerated the chemotherapy well and was discharged uneventfully. Following her 1st dose, she noticed a reduction in the size of her neck mass and an almost complete disappearance of her foot lesion. She received 4 cycles of the same regimen every 3 weeks. She did not complain of any Common Terminology Criteria for Adverse Events grade 3 or grade 4 toxicities except for Grade 2 iron-deficiency anemia which responded to parenteral and oral iron therapy. Following the completion of four cycles, she had complete clinical remission of the disease and underwent an FDG PET-CT scan which was suggestive of resolution of previously seen right supraclavicular, mediastinal nodes, and masses. The size of the spleen was reduced with a reduction in the FDG uptake. The pancreatic lesion also showed a reduction in uptake. There was a complete resolution of bilateral adnexal mass and peritoneal deposits. Metabolic resolution of skeletal lesions was noted, overall suggestive of a very good response to therapy (Fig. 3). The patient completed her 8 cycles till August 2023, and a repeat scan suggested maintaining a complete response. She is on observation and 3 monthly zoledronic acid. She is doing well and has no evidence of any new welling or abnormal findings.

DISCUSSION

RMS commonly affects children and adolescents but is rare in adults [8]. It is difficult to diagnose in adults due to its relatively rare occurrence and its significant clinical and biological heterogeneity. Thus, in 1972, the Intergroup RMS Study Group (IRSG) was established by three pediatric cooperative cancer study groups that combined their resources for further research. The IRSG along with other trials conducted by other international organizations has improved patient outcomes, identified prognostic variables, and developed risk-based treatments [9].

There are limited data available on the management of RMS in adults, due to its relative rarity. All patients require multimodal treatment planning (surgery, radiotherapy, and chemotherapy) and risk stratification.

Combination chemotherapy/systemic therapy is used to reduce the size of the primary tumor and to target the metastatic foci and is the mainstay treatment in children. In general, surgical resection is performed whenever feasible. The defined guidelines are mostly meant and inspired by the pediatric population. Age itself is a marker of high risk and poor prognosis in defined pediatric risk

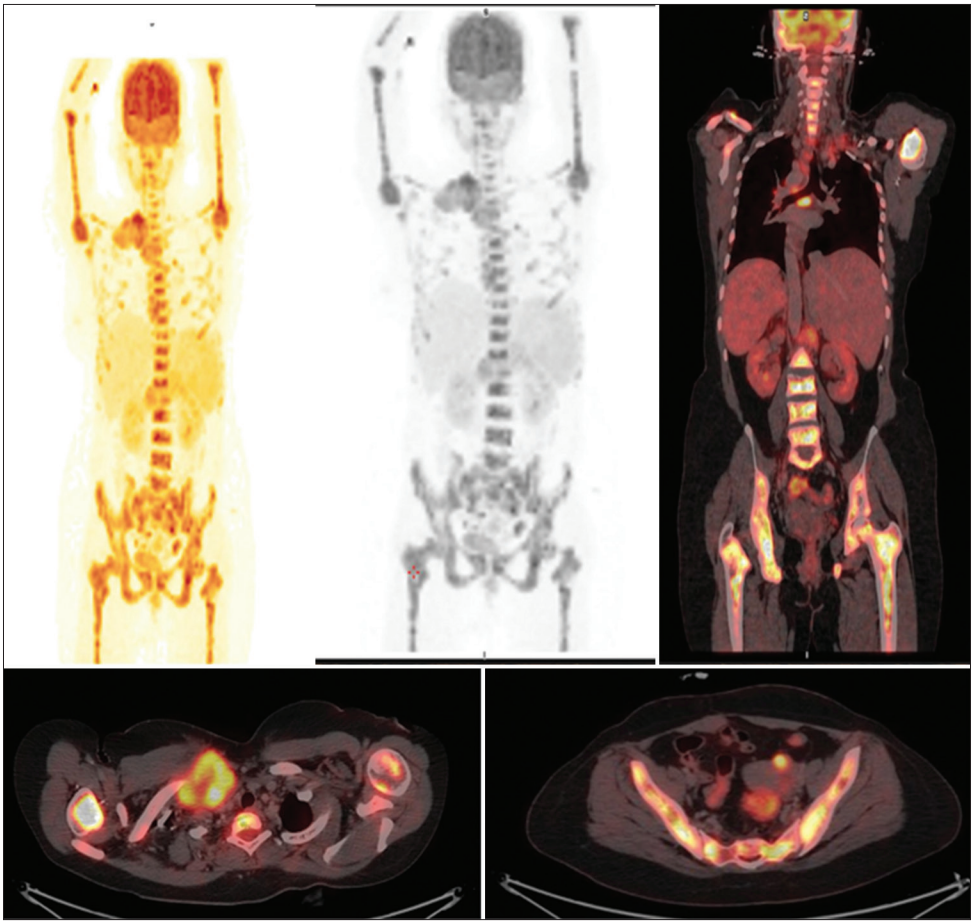

Figure 1: Whole-body fluorodeoxyglucose (FDG) positron emission tomography computerized tomography scan suggestive of extensive FDG-avid axial and extra-axial bone involvement. There is significant FDG uptake in bilateral adnexa, head-body of pancreas, spleen, and cervical LNs, overall stage IV disease

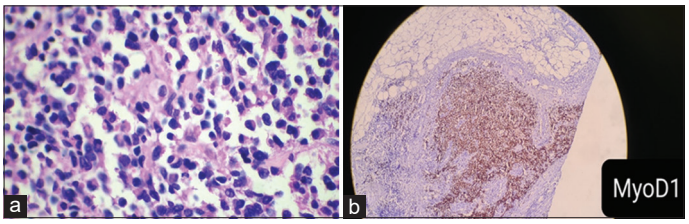

Figure 2: Histopathology and immunohistochemistry S/O small round blue cell tumor with MyoD1 positive

groups. Complete resection cannot be performed in most patients (as in our first case) due to the inconvenient location of the primary site of most RMSs. In the year 1960s, a combination regimen including vincristine, actinomycin, and cyclophosphamide was proven to significantly improve the response rate [10] and this became the standard chemotherapy regimen for pediatric non-metastatic RMS (intermediate or high-risk) [10]. This regimen is well tolerated, with easily manageable acute and chronic toxicities. The IRSG study showed that the 5-year failure-free survival rates of newly diagnosed low-risk RMS patients treated with vincristine and actinomycin were similar to those treated with vincristine, actinomycin, and cyclophosphamide (89% and 85%, respectively), suggesting vincristine and dactinomycin, suitable for low-risk RMS [11]. Omitting cyclophosphamide reduces the risk of secondary hematological diseases and infertility.

Chemotherapy regimens used in adult RMS are not separately defined and are usually derived from pediatric clinical trials. In the MD Anderson Cancer Center study, the 10-year overall, disease-free, and metastasis-free survival rates for adults with RMS treated with chemotherapy regimens including vincristine and cyclophosphamide with dactinomycin or doxorubicin were 47%, 45%, and 59%, respectively [12]. At present, agents such as carboplatin, irinotecan, topotecan, and vinorelbine have also shown significant efficacy in the treatment of pediatric patients with metastatic, relapsing, or refractory RMS [13,14].

Surgery is the primary treatment for patients with pleomorphic RMS (74% vs. 34% for non-pleomorphic histology), and the event-free survival rate was 37% for patients who underwent complete resection compared to 0% in patients with unresectable tumors [14]. The incidence of this type increases with age, and one of the historic dilemmas of this disease has been its true relationship with other types of RMS. Radiotherapy is beneficial to patients with advanced disease. It is typically used to control residual or bulky and microscopic deposits or when the tumor is located in an unfavorable site [15].

Historically, the risk stratification is well defined for pediatric RMS based on the histology, molecular type, age, and anatomical locations and the one falling into low/intermediate risk groups have a good prognosis; all patients with this rare tumor were

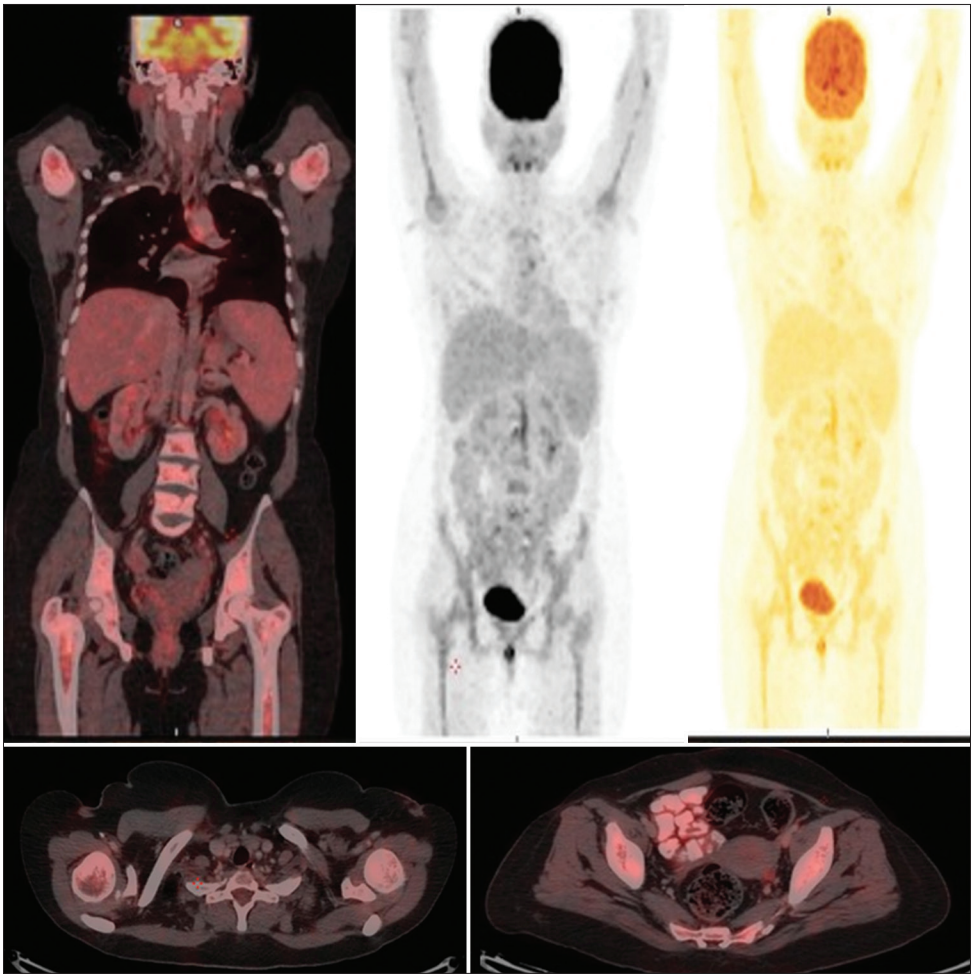

Figure 3: Whole-body fluorodeoxyglucose positron emission tomography computerized tomography after 4 cycles of chemotherapy results in a significant reduction of all metabolically active metastatic sites

believed to have a dismal prognosis [16]. However, this has not been shown in adults, who continue to have a very poor prognosis. It is paramount to recognize the disease as early as possible, but there are still some challenges in making a correct diagnosis.

The above-discussed case was unique in its presentation; the age was atypical to have a suspicion of RMS. The pattern of metastatic deposit is extremely rare, unlike the typical RMS where spread is hematogenous with common sites of metastases seen in the lung parenchyma, bones, loco-regional lymph nodes, liver, and brain, the above patient had adnexal metastasis, which has a very limited documentation in literature surge. The distant lymph nodes are involved in an atypical pattern looking like lymphomas. The FISH suggested embryonal RMS, which was supposed to behave in an indolent course and clinical presentation, but our patient had extensive metastatic disease, favoring against alveolar variant behavior. A multidisciplinary team discussion was made before starting the therapy and in view of the atypical presentation and aggressive picture of the disease, a non-pediatric inspired regimen was planned, including ifosfamide and etoposide with vincristine with IV bisphosphonate (zoledronic acid) and GCSF support. The response following the VIE chemo regimen was extraordinary with complete metabolic resolution and minimal tolerable toxicities.

Utilizing the ifosfamide and etoposide in the first-line setting for metastatic RMS was not elucidated in view of the extensive application of pediatric-inspired protocols but a case like the above might require a different approach and more intensive therapy. The limited information regarding this disease suggests that multiple adverse clinical factors may seem to converge in adults with RMS. Some studies have shown a more pronounced expression of multidrug-resistance proteins in adult patients and poor tolerance of adults to intensive treatment. These factors may be the reason for the poor prognosis of patients with RMS. In a SEER database analysis, the 5-year, 10-year, and 15-year survival rates including all patients were estimated to be 46%, 42%, and 41%, respectively. The results of children were significantly better than adults. The corresponding child survival rates were 61%, 58%, and 57%, and the adult survival rates were 27%, 21%, and 18%, respectively [17]. There is a discrepancy among patients with early stages and localized diseases, the 5, 10, and 15-year survival rates were much lower in adults (estimated at 47%, 36%, and 30%, respectively) than in children (82%, 80%, and 79%, respectively) [18]. These discrepancies might reflect differences in pathogenesis, and what is controversial is whether chemotherapy, the main therapy of pediatric RMS treatment, should be used in all adults with RMS [18]. In a retrospective study, adult patients

were more likely to show similar outcomes to children when receiving a treatment strategy more similar to adult STS, which is based on standard surgery-based treatment, usually supplemented with radiotherapy, but rarely with chemotherapy [19].

CONCLUSION

In conclusion, RMS is a rare soft tissue sarcoma in adults, with significant clinical and biological heterogeneity. There are many challenges to make a correct diagnosis and land on perfect management. Despite best efforts unlike the pediatric RMS, adult RMS is associated with poor outcomes on classical therapeutic options. The incidence of multidrug resistance protein is more expressed in adult patients, and their lower tolerance to intensive treatment may be the reason for poor prognosis in adults. Meanwhile, due to the limited information available about this rare disease, there are no definitive, optimal regimens for the treatment of RMS in adults. Additional studies on the management plan and the pathogenesis of RMS in adults are needed. Regimens inspired by adult sarcomas, like VIE can be further studied and evaluated, which can define better treatment guidelines among them.

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