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Case Report

Benign cyst or malignancy? A six-year-old with primitive small round cell sarcoma of the right buttock: a case report

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ABSTRACT

A six-year-old male presents with mass on his right buttock. After surgical resection, he was found to have a primitive small round cell sarcoma, high grade with CIC-DUX4 fusion gene. Treatment started with compressed regimen of VDC/IE (compressed Ewing protocol). There was initial improvement in visual appearance of the buttock/wound site but recurrence of the tumor occurred despite extensive surgical resection along with metastases to the lungs and bone which progressed and eventually led to death. This case adds to the collective knowledge regarding the CIC-DUX4 type of pediatric neoplasms and provides insight for future chemotherapy protocols.

Keywords: Primitive small round cell sarcoma, Pediatric sarcoma, Gluteal mass, Pelvis mass, CIC-DUX4, Metastasis

INTRODUCTION

Sarcomas are a rare and complex group of malignant tumors originating from connective tissue and are rarer in the pediatric population than other malignancies. Because of this, it is often difficult to not only identify the exact type but also to provide a targeted treatment without delay of diagnosis.

Within pediatrics, there have been several reported cases of non-rhabdomyosarcoma soft tissue sarcoma (NRSTS) or undifferentiated round cell subtype (URCS). There are many different diagnoses under this category leading to a lack of defined treatment protocols.

Recently, there have been increasing cases of sarcomas with the CIC-DUX4 fusion gene with survival rates for these malignancies low. This is especially seen with tumors larger than 5 cm, unresectable tumors, and/or evidence of metastasis.[1].

CASE REPORT

A previously healthy six-year-old male presented to his pediatrician's office with concern for a pea-sized "bump" on his right buttock. There was no color change, pain, or associated symptoms. Persisting over a few weeks, an ultrasound showed probable sebaceous cyst. It was described as an ovoid, well-defined relatively hypoechoic lesion measuring 1.1×0.7×1.1 cm without increased blood flow. After months of observation the lesion significantly increased in size and he was referred to pediatric surgery.

A magnetic resonance imaging/magnetic resonance angiography (MRI/MRA) was ordered with concern for an arteriovenous or lymphatic malformation and showed a subcutaneous mass in the right gluteal muscle that measured 4.0×2.6×4.6 cm. He did not have any fevers, bone pain, weight loss, or adenopathy. Figure 1 shows the clinical and radiographic progression during the timeline reported with consent provided by parents. A primary debulking procedure was done showing a more solid-like

mass. Due to its rapid increase in size, a repeat resection was done in an attempt for gross total resection.

Pathology showed markers negative for sarcoma on next generation sequencing (NGS). Despite this, final diagnosis after specialized workup was primitive (undifferentiated) small round cell sarcoma, high grade. Tissue sample was sent out for more detailed analysis and determined it to be a round cell undifferentiated sarcoma with CIC-DUX4 gene rearrangement through fluorescence in situ hybridization (FISH) analysis. The tumor cells were notably negative for lymphoma markers and shows relevant markers for sarcoma diagnosis (Table 1). Morphology of the tumor cells were consistent with CIC-rearranged sarcomas.

Positron emission tomography (PET) was completed following resection and showed the pelvic mass measuring 4×4×1.7 cm with a bilobed appearance, as well as a lung nodule measuring 10×9 mm. Repeat computed tomography (CT) for staging was performed while awaiting a final pathologic diagnosis which showed that the mass doubled in size, measuring 11.3×5.9×5.4 cm and engulfed part of the coccyx and bordered the right bladder base. It also revealed multiple lung nodules bilaterally ranging 2-11 mm, showing progression to all lobes, as well as two enlarged inguinal lymph nodes measuring about 2 cm on the right and 1.3 cm on the left.

Table 1: Lymphoma-related and sarcoma-related immunohistochemistry markers for tissue sample.

Parameters	CD3	CD4	CD20	CD34	CD45	TdT	C-KIT	MUM-1	MPO
Lymphoma	-	-	-	-	-	-	-	-	-
	CD99	**S100**	**INI1**	**Desmin**	**CD56**	**WT1**	**FLI1**	**EMA**	**EWSR1**
Sarcoma	+	-	-	-	+	ND	+	-	-

ND=not done

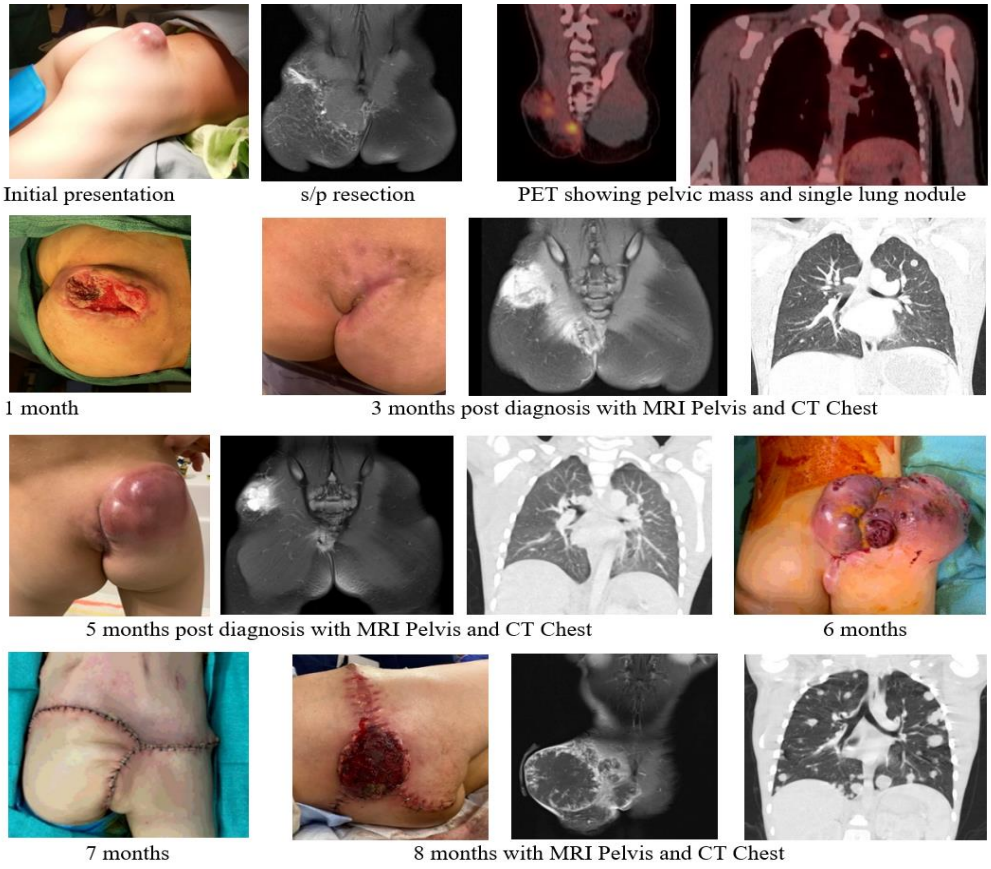

Figure 1: Timeline of clinical and radiographic.

Upon discussion with pediatric sarcoma experts, he was started on the compressed regimen chemotherapy protocol (VDC/IE) about 1 month after the first resection. He completed three cycles of chemotherapy and at the end of week 12 had repeat scans that showed a positive response to chemotherapy. Plan for local control was R0 versus R1 resection followed by radiation.

After eight cycles, repeat imaging five months following diagnosis showed continued positive response with interval decrease in tumor size to 8.2×6.0×2.1 cm and previously reported extension towards the ischiorectal and ischioanal fossa decreased in size, too. Inguinal lymph nodes also showed positive response. While waiting for surgical planning, he received another cycle of VDC and a cycle of VIT for disease control prior to the extensive surgery.

Seven months following diagnosis, he had an R1 surgical resection, with surgeon noting a 30×20 cm tumor of the right gluteal region. The procedure included removal of majority of the right buttock with resection of the superior gluteus maximus muscle and a small portion of pelvic floor muscles, removal of lymph nodes in the groin, placement of a colostomy, and reconstruction of the right buttock. Though extensive, he tolerated the procedure well and discharged home shortly afterwards for recovery.

Over the next few weeks, the patient had increasing pain and swelling to the right knee, as well as pain to the surgical site. Plain films showed a lytic lesion in the posterior, medial, distal femoral metaphysis, likely bony metastasis. Repeat CT chest at this time showed increasing lung nodules indicating progressive disease. He was then restarted on chemotherapy with cyclophosphamide and topotecan in addition to local radiation to the bony lytic lesion.

Three weeks after surgery, his primary tumor grew significantly, causing wound dehiscence. Due to progressive disease, the patient was admitted for pain management and palliative care, and the family decided to discontinue further treatment. Eight months following diagnosis, he died in the comfort of his home surrounded by family.

DISCUSSION

Soft tissue sarcomas in pediatrics are a rare entity, representing 7% of all pediatric cancers (with rhabdomyosarcoma at 4% and other soft tissue sarcomas at 3%).[2,3] With atypical initial presentation of the mass, as well as delay in diagnosis and overall challenging case histopathologically, there is concern about progression prior to starting adequate treatment. Within the last several years, there has been a push to identify these tumors with the CIC-DUX4 fusion gene as its own subset mainly for purposes of developing targeted treatment and to better understand the role these genetic factors play in prognosis. Because of this, a few case studies have been done to compare these specific diagnoses against other sarcomas.

The CIC gene is an important entity in the oncogenesis process. It is a transcription factor that would normally inhibit expression of ETV 1/4/5 (part of the ETS family and associated with cancer progression) and helps to regulate tyrosine kinase receptor pathways. DUX4 is a double-homeobox gene and responsible for activation of transcription factors. The fusion of CIC-DUX4 has been found responsible for tumor development and associated with metastatic capability by increasing the activity of CIC, allowing expression of ETV1/4/5.[4] In order to determine this diagnosis, samples must be sent to specialized labs for specific molecular studies which are not widely available. Recent studies aim to detect DUX4 through immunohistochemistry and in a series of five cases, showed diffuse, strong nuclear staining in all five CIC-DUX4 sarcomas and negative staining in 20 non-CIC-DUX4 tumors, which is helpful for potentially avoiding delayed diagnosis.[5] Other groups are looking at molecular targets that may affect the way CIC-DUX4 promotes tumor growth as a therapeutic strategy, specifically targeting some of the downstream expressed genes.[6]

According to Antonescu's series of 115 cases of CIC-positive sarcomas (average age 32 years, 22% pediatric cases), these tumors followed an aggressive clinical course with high rate of metastasis – the most common location being the lungs.[7] In comparison to Ewing sarcoma patients matched for age and stage to the CIC-positive sarcoma patients, 5 year OS rates were only 43% for CIC-positive versus 76% for Ewing sarcoma.

CONCLUSION

For patients with metastatic disease at presentation, there are even less options available including the unlikely possibility of gross total resection. Typically, they undergo multiple resections, several cycles of chemotherapy, and radiation that leave them with similar poor outcomes. A more targeted approach to this subset of sarcomas needs to be developed to improved survival rates.

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