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Complex management of a large retroperitoneal undifferentiated sarcoma encasing the abdominal aorta in a pediatric patient: a case report and review

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Abstract

Background Retroperitoneal undifferentiated sarcomas are rare, highly aggressive mesenchymal tumors with limited available treatment options. Surgical resection ± chemoradiation remains standard of care. However, in unique cases, challenging tumor biology, advanced tumor stage, and the morbidity required of an R0 resection can prohibit management and ultimate cure. Targeted therapies have an increasing role in this setting due to advances in molecular analytics.

Case presentation Herein, we describe the management of an 11-year-old female with a chemotherapy-refractory large retroperitoneal sarcoma encasing the infrarenal aorta with a large acquired aortic pseudoaneurysm. This is the first report describing the complex approach to a retroperitoneal *NTRK*-fusion (+) undifferentiated sarcoma confounded by an acquired aortic pseudoaneurysm in a pediatric patient. Preoperative considerations, intra-operative technique, postoperative management, adjuvant therapies and a brief review of the literature are discussed.

Conclusion Overall, a holistic understanding of the tumor biology and a cohesive multidisciplinary approach is integral to the care and long-term management of these cases.

Keywords Undifferentiated sarcoma, Acquired aortic pseudoaneurysm, Surgery, Chemoradiotherapy, Targeted therapy

Background

Soft tissue sarcomas (STS) form a heterogenous group of malignant mesenchymal tumors that account for up to 8% of all pediatric cancers [1, 2]. Pediatric non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) comprise approximately half of all STS diagnoses, accounting for up to 250–300 cases per year in the USA [1]. Undifferentiated sarcomas, a rare subset of NRSTs, are defined by their lack of clear differentiation characteristics on histopathologic analysis [3, 4]. They are highly mitotically active and composed of variable morphologic subtypes including round cell, pleomorphic, epithelioid and spindle cell variants [4]. Like other NRSTS lesions, undifferentiated sarcomas can present throughout the body, although they predominantly localize to the trunk [4]. Due to the nature of the retroperitoneum, retroperitoneal sarcomas can be large at presentation, with symptomatology resulting from displacement and/or obstruction of surrounding structures [2]. Clinical presentation varies based on tumor size, histologic subtype, and anatomic location. However, a study conducted by Ferrari et al., found the average interval between diagnosis and development

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of symptoms is approximately 2 months in pediatric patients [1, 5]. Upon diagnosis, surgical resection with a combination of neoadjuvant or adjuvant chemoradiotherapy remains the mainstay approach to the treatment of these tumors.

This report highlights an unusual case of a large retroperitoneal undifferentiated sarcoma encasing the infrarenal abdominal aorta with a large acquired aortic pseudoaneurysm. Given its complexity, a detailed review of the preoperative workup, intraoperative approach, and postoperative course will be discussed in this text. This will be the first report of its kind to describe the management of a retroperitoneal sarcoma associated with an abdominal aortic pseudoaneurysm in a pediatric patient.

Case presentation

An 11-year-old female presented for definitive management of a seven cm retroperitoneal mass encasing a large infrarenal abdominal aortic pseudoaneurysm and common iliac arteries. She had initially presented to an outside facility with a 1-month history of progressive back and right leg pain. Biopsies obtained were suggestive of a spindle cell sarcoma or a hemangiopericytoma. Her tumor was deemed inoperable by physicians at two outside hospitals; thus, she was started on multi-agent chemotherapy. Her disease was refractory to multiple cycles of doxorubicin, ifosfamide, etoposide, cytoxan, and vincristine followed by treatment with a tyrosine kinase inhibitor, Sorafenib. Disease progression ultimately resulted in poor nutrition, debilitating functional status, and failure to thrive. As such, she was transferred to our center for surgical resection and further multi-disciplinary care.

Pre-operative imaging revealed an enlarging heterogenous retroperitoneal mass invading the L3–L5 vertebral bodies associated with significant intra-abdominal mass effect and moderate bilateral hydronephrosis (Fig. 1). A dedicated computed tomographic (CT) angiogram identified a 7.2 cm × 6.9 cm × 7 cm retroperitoneal mass which had increased in size from 5.0 cm × 5.5 cm × 5.5 cm only approximately 2 months prior. This mass encased a large lobulated infrarenal acquired aortic pseudoaneurysm that extended inferiorly to immediately above the aortic bifurcation (Fig. 1). Biochemical analysis was not consistent with endocrinopathies and there was no evidence of overt metastatic disease.

After extensive multidisciplinary discussion between the pediatric medical oncology, surgery, urology, radiation oncology, as well as vascular surgery teams, the decision was made to attempt surgical resection of the tumor and aortic pseudoaneurysm with vascular reconstruction. Additionally, the patient's preoperative management required hematologic optimization as she was a Jehovah's witness. After a suboptimal response to Epoetin Alfa, she was started on iron dextran infusions which yielded a favorable response. Once medical optimization was achieved, we proceeded with surgical intervention.

Surgical technique

The patient was taken to the operating room by the pediatric surgery, pediatric urology, and vascular surgery teams. Once the patient was fully anesthetized, positioned and sterilely draped, bilateral ureteral stents were placed to aid in identification of the ureters during the case. The abdomen was accessed via a midline laparotomy. Upon entry, the pulsatile tumor was immediately

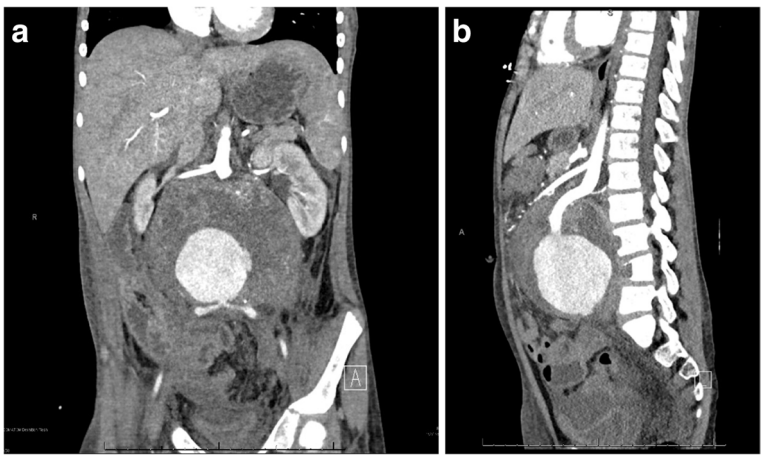

Fig. 1 **a** Coronal imaging demonstrating retroperitoneal sarcoma containing an acquired infrarenal aortic pseudoaneurysm which is displacing intraabdominal organs and renal vasculature. **b** Sagittal view of intraabdominal tumor containing an infrarenal abdominal aortic pseudoaneurysm. Evidence of invasion of spinous processes of the lumbar spine

visualized and found to be adherent to numerous structures including the small bowel and its mesentery. Proximal aortic control was obtained by dissecting the aorta at the esophageal hiatus and securing it with a Rummel tourniquet. Next, Cattell–Braasch and Kocher maneuvers were performed to mobilize the right colon, small bowel, duodenum, and pancreas off the tumor to gain adequate exposure to the tumor and distal aorta. The bilateral common, external, and internal iliac arteries were isolated for distal vascular control. The ureters were superficially encased by the tumor with no evidence of invasion into the kidneys and circumferentially dissected off the mass. The inferior vena cava (IVC) was then exposed and found to be encased and obstructed due to chronic compression by the tumor. Thus, the decision was made to ligate the IVC below the takeoff of the renal veins. Bilateral renal vasculature was identified and released from the tumor. After confirming adequate exposure of the mass and aorta, as well as proximal and distal vascular control, the aorta was transected proximally and distally at the level of the common iliac arteries. The tumor and aorta were carefully dissected and released en bloc (Fig. 2). After en bloc resection of the mass, it remained apparent that the tumor had invaded several vertebral bodies, consistent with pre-operative imaging. The decision was made not to resect these sites of bony invasion to prevent potential spinal cord injury or dural exposure, yielding an R2 resection status. Hemostasis was obtained and the patient was systemically heparinized prior to aortic reconstruction utilizing a 12×6 mm rifampin-soaked dacron aortobiiliac interposition graft. The graft was protected with a well vascularized omental pedicle flap. Care was taken ensure abbreviated aortic clamping times during the aortic resection and reconstruction. At the conclusion of the reconstruction, heparinization was reversed with protamine. An area of ischemic sigmoid colon was subsequently noted, most likely due to sacrificing multiple sigmoidal arteries during the course of the operation due to tumor encasement. A Hartmann's procedure was performed taking great care to prevent spillage that could potentially contribute to a vascular graft infection. The abdomen was closed primarily and the case concluded. The patient was then transferred to the intensive care unit for postoperative care.

Her post-operative course was initially complicated by a protracted ileus and debilitating large volume chylous ascites requiring multiple paracenteses. A peritoneovenous shunt (Denver shunt) was placed to maintain fluid status and revert ascitic fluid centrally. However, this yielded significant right heart strain, overload, and pulmonary edema, requiring re-admission to the intensive care unit for aggressive diuresis. She returned to the ward and was ultimately discharged home on post-operative day 42 after nutritional and functional optimization. Final pathology of the tumor was consistent with an undifferentiated sarcoma with rhabdoid morphology harboring a *STRN-NTRK2* fusion.

Upon discharge, she received a short course of chemotherapy followed by enrollment into an investigative international multi-center clinical trial (LOXO-TRK-15003) evaluating the efficacy of Larotrectinib (LOXO–101) in pediatric tumors harboring NTRK-fusions. Her residual disease responded favorably to adjuvant therapy with evidence of partial response (PR) per Response Evaluation Criteria in Solid Tumors (RECIST) after only her first cycle. Six months postoperatively, she underwent Denver shunt removal and ostomy reversal with an uneventful recovery. Interval follow-up imaging revealed sustained PR and eventual complete response (CR) by RECIST criteria. She has since completed 82 cycles of the trial agent with her 6-year surveillance scans showing no evidence of disease.

Discussion

Undifferentiated sarcomas, a heterogenous group of rare mesenchymal tumors, are largely a diagnosis of exclusion [6]. Initially described as malignant fibrous histiocytomas (MFH), these tumors were later formally categorized as undifferentiated sarcomas by the World Health Organization in 2013, an umbrella term encompassing all soft tissue sarcomas with an unclear line of differentiation [3, 4, 6]. On histopathology, they are generally CD117 and vimentin positive, sheet forming, high-grade tumors with multiple sites of necrosis [4, 6]. Diagnosis is challenging

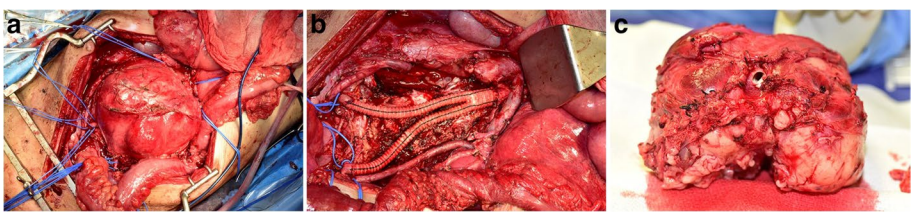

Fig. 2 **a** Intraoperative view of full exposure of the tumor and associated aortic pseudoaneurysm. **b** View of retroperitoneum after tumor resection and aortobiliac vascular reconstruction with dacron graft.. **c** En bloc retroperitoneal tumor specimen

and prognosis remains poor, with local recurrence rates between 19 and 31% and rates of metastasis at 30–35% [6, 7].

Nonetheless, the diagnosis and management of undifferentiated sarcomas mirror that of other NRSTS. Diagnostic work up and staging should commence with laboratory analysis and cross-sectional imaging to determine tumor size, organ invasion, and the presence of metastatic disease. Greater than 15% of patients have metastatic disease on presentation, with the most common site being the lungs, thus staging imaging must include radiographic analysis of the chest [8]. 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG) PET has become an increasingly attractive staging modality, although its utility as a surveillance tool remains unclear [8, 9]. This should be followed by a core or surgical biopsy to obtain adequate tissue for histologic, molecular, and cytogenic analysis [8, 10]. This is imperative as NRSTS encompass over 50 histologies, each of which have unique progression and response patterns to therapy [1].

Guidelines for staging and risk stratification of NRSTS in children remains a highly debated topic, as such, a uniform classification tool doesn't currently exist. Methods used for staging include the Cooperative Weinchteilsarkom Studiengruppe-2002-P protocol mainly used in Europe and the American Joint Committee on Cancer (AJCC) for sarcoma, a predominantly adult staging system frequently used by the Children's Oncology Group (COG). The Pediatric Oncology Group grading system and the system of the Fédération National des Centres de Lutte Contre le Cancer (FNCLCC) are more conventional grading tools for pediatric sarcomas [8]. A multi-institutional prospective trial of 529 patients with NRSTS below 30 years of age conducted by the COG (ARST0332) led to the development of a risk stratification tool based on tumor size, grade, and extent of surgical resection (low, intermediate, and high) (Table 1), to facilitate prognostication and inform clinical management [11].

Complete surgical resection, with or without perioperative chemoradiation therapy remains the standard of care in treatment of patients with undifferentiated sarcoma [1, 8, 10–12]. Surgical resection with negative microscopic margins (R0) has significant implications towards overall prognosis and survival; however, an R1 resection may be adequate in select low risk patients with low-grade disease [8]. An R0 resection is attainable in approximately 48% of patients, with decreasing frequency in more advanced disease [8, 11]. Primary re-excision should be pursued in patients with R1 or R2 resections if feasible, to avoid the need for adjuvant radiation and its subsequent long-term toxicity in pediatric patients [12]. Additionally, chemotherapy may be used to attain and maintain local disease control in the neoadjuvant and adjuvant settings, respectively [12–14]. As such, subset analysis of 32 pediatric patients with undifferentiated sarcomas included in the ARST0332 trial demonstrated a favorable 5-year overall survival at 77% with combination chemoradiotherapy and surgical resection for local control [4, 15]. Chemoradiotherapy also plays a significant role in the management of unresectable disease [8, 12, 16, 17]. The findings of the ARST0332 trial recommend sole surgical resection be provided to patients considered low-risk, and perioperative chemotherapy and/or radiation be implored for intermediate/high risk groups and/or patients deemed unresectable [11].

Molecular and cytogenic study of these tumors have proven vital in facilitating ongoing clinical trials for therapy development, as multiple NRSTS histologies are chemoresistant, limiting treatment options. Larotrectinib (LOXO-101), a highly selective small molecule inhibitor of neurotrophic tyrosine kinases (*NTRK*) genes and associated proteins, has demonstrated favorable results in phase I/II trials in both adult and pediatric patients with *NTRK* fusion-positive tumors [15]. Gene fusions involving *NTRK1, NTRK2, NTRK3* and their downstream oncogenic pathways, have been implicated in the pathogenesis of multiple adult and pediatric tumors, including pediatric sarcomas [15]. This alteration serves as an attractive therapeutic target and has been the focus of multiple trials. A multi-institutional phase I/II trial conducted from 2015 to 2017 utilizing Larotrectinib in 55 adult and pediatric patients with *NTRK*-fusion positive tumors revealed up to an 80% overall response rate, with 55% of patients remaining progression-free at 1 year [18]. As such, targeted therapy with Larotrectinib is incredibly promising in the setting of unresectable disease, or in achieving residual disease control after an R1 or R2 resection, as is the case with our patient. Further studies

Table 1 Risk stratification of patients with NRSTS

Risk status	Characteristics
Low risk	Non-metastatic; low-grade, or high-grade tumors < 5 cm; R0 or R1 resection
Intermediate risk	Non-metastatic; unresected tumor of any grade or size; R0 or R1 resection in tumors > 5 cm
High risk	Evidence of metastasis

as well as long-term follow up are necessary to determine which patients are the best candidates for these novel therapies. Early phase trials are currently ongoing evaluating the safety and efficacy of oral Larotrectinib in pediatric solid tumors (SCOUT trial [*NCT 02637687*]).

Overall, outcomes in this rare patient population are dependent on effective and early diagnosis, a comprehensive understanding of the pathology, and cohesive perioperative multidisciplinary care. Clinical trials on novel therapeutic targets are underway and could potentially diversify treatment options for these patients.

Abbreviations

STS	Soft tissue sarcomas
NRSTS	Non-rhabdomyosarcoma soft tissue sarcomas
CT	Computed tomography
IVC	Inferior vena cava
LOXO–101	Larotrectinib
PR	Partial response
CR	Complete response
MFH	Malignant fibrous histiocytomas
FDG	2-[^{18}F]-fluoro-2-deoxy-D-glucose
RECIST	Response Evaluation Criteria in Solid Tumors
AJCC	American Joint Committee on Cancer
COG	Children's Oncology Group
FNCLCC	Fédération National des Centres de Lutte Contre le Cancer
NTRK	Neurotrophic tyrosine kinases

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MET: study concept building, manuscript writing, design, formatting, manuscript review. JCJ: writing, editing, formatting, manuscript review. KM: editing, manuscript review. JTM: study concept building, study design, manuscript review. All authors read and approved the final manuscript.

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