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Non-rhabdomyosarcoma

Roshni Dasgupta, MD, MPH[a,*], David Rodeberg, MD[b]

[a] Division of Pediatric General and Thoracic Surgery, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave, Cincinnati, Ohio 45229
[b] Department of Surgery, Brody School of Medicine, East Carolina University, Greenville, North Carolina

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ABSTRACT

Pediatric non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) are a heterogeneous group encompassing more than 50 different histological diagnoses arising from primitive mesenchymal tissue. Together, they comprise about half the soft tissue sarcomas diagnosed in children and young adults. Despite each histologies relative rarity, their management schema is similar among the different NRSTS histologies. Surgical management is an important component of the multimodal treatment strategy of all these tumors. Resection with negative margins, while maintaining function, plays an important role as a primary treatment of these patients as well as diminishing the risks of local and distant recurrence.

Introduction

Pediatric non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) are a heterogeneous group encompassing more than 50 different histological types. Similar to rhabdomyosarcoma, these tumors arise from primitive mesenchymal tissue. NRSTS comprise about half the soft tissue sarcomas diagnosed in children and young adults, accounting for 250–300 cases per year within the United States. Despite each tumor's relative rarity, there are several common management strategies that are used. Surgical management is an important component of the multimodal treatment strategy. Complete resection with negative margins decreases rates of local recurrence and improves overall survival in these patients.

Epidemiology

Soft tissue sarcomas in the pediatric, adolescent, and young adult population account for about 8% of all pediatric cancers.[1] About half of soft tissue sarcomas are NRSTS. The Surveillance, Epidemiology, and End Results (SEER) data from 1975 to 2012 show that NRSTS appear to be more common than rhabdomyosarcoma in adolescents and young adults.[2] Both environmental and genetic factors have been implicated in the development of NRSTS.

Genetics

Several genetic syndromes have been associated with the development of NRSTS. Patients with Li-Fraumeni syndrome have an increased risk of developing NRSTS as well as bone sarcoma, rhabdomyosarcoma, breast cancer, brain tumors, and acute leukemia secondary to p53 gene suppression.[3] Neurofibromatosis type 1 (NF1) has also been associated with the development of malignant peripheral nerve sheath tumors originating from benign neurofibromas.[4] Patients with Werner's syndrome have spontaneous chromosomal instability resulting in an increased incidence of soft tissue sarcomas.[5] Furthermore, individuals with germline mutations of the retinoblastoma gene (RB1) have an increased risk of soft tissue sarcomas especially leiomyosarcomas.[6]

Environmental

There are several environmental factors that have been associated with the development of NRSTS. Exposure to radiation may predispose to the development of malignant fibrous histiocytoma, occurring as a secondary malignancy within a previously radiated site.[7] Leiomyosarcomas have also linked to Epstein–Barr viral (EBV) infections in patients with HIV disease.

Pathogenesis

There are two primary divisions within NRSTS tumors from a genetic perspective—tumors that contain widespread instability within the genome and those tumors with specific chromosomal aberrations. The tumors with chromosomal rearrangements often code for a chimeric fusion protein which is thought to drive genesis of the tumor.[8] This resulting fusion can aid in diagnosis of the tumor by polymerase chain reaction (PCR). Recent insights into the pathogenesis of pediatric NRSTS have been made with the

* Corresponding author.
E-mail address: Roshni.Dasgupta@cchmc.org (R. Dasgupta).

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Table 1
Genetics of selected non-rhabdomyosarcoma tumors.

Histology	Genetic disorder	Genes involved
Alveolar soft part sarcoma	t(X;17)(p11.2;q25)	ASPL-TFE3
Clear cell sarcoma	t(12;16)(q13;p11)t(2;22)(q33;q12),t(12;22) (q13;q12)	ATF1/EWS, EWSR1/CREB1
Dermatofibrosarcoma protuberans	T(17;22)(q22;q13)	COLIAI-PDGFb
Desmoplastic small round cell tumor	t(11;22)(p13;q12)	EWS-WT1
Desmoid fibromatosis	Trisomy 8 or 20, loss of 5q21	CTNNB1 or APCC mutations
Epithelioid hemangioendothelioma	T(1;3)(p36;q25)	WWTR1/CAMTA1
Hemangiopericytoma	t(12;19)(q13;q13.3) and t(13;22)(q22;q13.3)	
Infantile fibrosarcoma	t(12;15)(p13,q25)	ETV-NTRK3
Malignant peripheral nerve sheath tumor (MPNST)	17Q11.2 loss or rearrangement 10p, 11q, 17q. 22q	NF1
Malignant rhabdoid tumor	Inactivation SMARCB1	SMARCB1
Synovial sarcoma	t(X;18)(p11;q11)	SSX-SYT

delineation of tumor associated genetic aberrations.[9] Identification of chromosomal abnormalities expressed by NRSTS tumors may also lead to the development of treatment strategies that are more targeted to each specific type of tumor (Table 1).[10]

Historically this diverse group of tumors has been treated similarly based on location, size, stage, grade, and completeness of resection. The integration of genetic data will be essential in creating a personalized treatment regimen for patients with these rare tumors in order to provide the best outcome for the individual cancer patient.

Presentation

The clinical picture of a child presenting with a NRSTS is again quite variable and is dependent on the anatomic location of the tumor, its size, and the histological subtype. While masses may develop in any part of the body, NRSTS most commonly presents in the trunk and extremities. Children will often develop symptoms secondary to local invasion or compression of anatomical structures and systemic symptoms such as weight loss; night sweats, however, are rare. Extremity masses are often noted after trauma or another incidental event.[11] Paraneoplastic-type symptoms such as hypoglycemia have been noted to occur with several tumor types including hemangiopericytoma, fibrosarcoma, and solitary fibrous tumor, likely secondary to increased levels of pro-insulin growth factor.[12,13] Ferrari et al. noted that the median interval between the development of symptoms and diagnosis was 2 months, and this interval was longer in adolescents and longer in NRSTS patients than in patients with rhabdomyosarcoma. Longer symptom interval also negatively affected overall survival.[14]

Assessment

Imaging

Any suspicious lesion should undergo imaging to help further characterize the mass. A plain film is often done as the primary imaging modality to detect bony involvement or tumor calcifications often noted in synovial sarcoma or extra-skeletal osteosarcoma. Magnetic resonance imaging (MRI) is generally considered to be the imaging modality of choice due to the excellent soft tissue resolution which can aid in diagnosis, operative planning, and prognostication.[15]

Staging with a computed tomographic (CT) scan of the chest to detect lung metastases is necessary. In addition, fluorine-18-fluorodeoxyglucose (FDG) positron emission tomography (PET), or PET/CT can be used for further staging information. In rhabdomyosarcoma, PET/CT has been judged superior to either bone scan or CT alone in the identification of nodal, bone, and bone marrow disease.[16]

Biopsy

For tumor masses that possess clinical and radiologic features that are suspicious of a malignancy, a histologic diagnosis must be obtained. Adequate tissue must be available to help classify the type of NRSTS tumor since often several diagnostic techniques including immunohistochemistry, fluorescence in situ hybridization (FISH), and cytogenetics are required to determine the diagnosis. Tissue may be obtained by open surgical biopsy or core needle biopsy methods. Due to the type and amount of tumor generally needed for diagnosis, a fine needle aspirate biopsy is not adequate. Core biopsy and or open biopsies can be used to ensure an adequate sample is obtained and should be oriented in a way that the biopsy tract can be resected at the time of the definitive surgical procedure. Excisional biopsies should only be done for small superficial lesions less than 3 cm.[17]

Lymph node evaluation

Lymph node metastases are common (up to 30%) in synovial cell sarcoma, epithelioid sarcoma, and clear cell sarcoma.[18] These diagnoses require lymph node evaluation for adequate staging. Sentinel lymph node biopsy is considered the preferred method for the evaluation of lymphatic node spread. Several studies have shown that sentinel lymph node biopsy in children can be done safely and successfully.[19,20]

Clinical staging and grouping

Staging

Clinical staging is important in determining the most effective therapy for patients diagnosed with NRSTS, as well as prognosticating outcome. The TNM staging of NRSTS is a collaborative effort with the American Joint Committee on Cancer (AJCC) and the International Union against Cancer. This is a pre-treatment staging system and is determined by the site and size of the primary tumor, degree of tumor invasion, nodal status, and the presence or absence of metastases. This primary purpose of this staging system is to determine the extent of tumor before any therapy (Table 2).

Clinical group

The extent of residual disease after the resection is an important prognostic factor in NRSTS and highlights the importance of skilled surgical resection. Clinical group assignment is determined based on the completeness of surgical excision and the evidence of