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Diagnostic Approach to Paediatric Small Round Cell Tumors

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Introduction

Small round cell tumors (SRCT) is a term for tumors composed histologically of small round cells with scanty blue staining cytoplasm. SRCT predominate in childhood and adolescence and share similar morphological features of small undifferentiated round cells with nucleus occupying the entire cell volume and scanty indiscernable cytoplasm. This category includes a variety of tumors such as lymphoma, Ewings/ primitive neuroectodermal tumours (Ewings/ PNET), neuroblastoma, rhabdomyosarcoma (RMS), Wilm's tumor, retinoblastoma, desmoplastic small round cell tumor (DSRCT), hepatoblastoma, medulloblastoma and malignant neuroectodermal tumour of infancy.

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Accurate diagnosis of pediatric small-round-cell tumors has become increasingly crucial, as disparate approaches to therapy are used for distinct tumour types. In addition, as therapy is also tailored according to patient risk, it has become important to further classify tumors biologically. There have been significant changes in laboratory medicine with regard to the approach and investigation of pediatric tumor specimens.

Tissue sampling approach to paediatric tumors

The exact approach to obtaining tissue for diagnosis in paediatric tumors depends on a range of factors, including the anatomical site and patient age. While open surgical biopsies continue to provide adequate diagnostic material, with improvements in diagnostic capability from increasingly small tissue samples, the role of initial minimally- invasive-needle-core biopsy diagnosis has become of greater importance. Image-guided 'tru-cut' type

needle core biopsies and fine needle aspiration cytology provide much more limited diagnostic material as compared to the traditional open approach, but are associated with reduced morbidity.

Disadvantages of FNAC/ needle core biopsies

1. The material obtained may be unrepresentative of a large tumor.
2. There may be insufficient material to perform morphological studies or molecular analysis.

Specimens should ideally be received fresh in the laboratory immediately following the biopsy procedure, at which time the sample can be divided into aliquots for FISH and molecular studies such as RT-PCR, cytogenetic studies, fixed in glutaraldehyde for electron microscopy if required, and the remainder processed for routine fixation, paraffin embedding and sectioning for morphological examination and immunohistochemical staining.

Thoracic Masses

Neuroblastoma, lymphomas, PNET, DSRCT, RMS, comprise the SRCT seen in the thoracic cavity. Many of these tumours are symptomatic but few of them may be asymptomatic and are picked up on chest radiograph.

Abdominal Masses

The various SRCT which can be encountered in abdomen are neuroblastoma, Wilm's tumour, lymphoma, hepatoblastoma and PNET. A thorough physical examination should be carried out before proceeding with appropriate imaging studies. Plain abdominal x-ray films and ultrasonography of the abdomen should be obtained because these may be diagnostic and assist in determining the need for further tests such as abdominal CT and MRI.

SRCT involving the bone

Patients with bone tumors usually present with pain at the site of involvement. Patients with Ewing's sarcoma (ES) present with pain that may be intermittent initially but, over time, increase in severity and become constant. In some cases, there may be an associated soft tissue mass as tumor breaks through the periosteum and infiltrates the surrounding tissue. ES and its histological variants, small cell osteosarcoma- and mesenchymal chondrosarcoma should be considered in the list of differential diagnosis along with the hematopoietic malignancies.A careful review of radiographs of the involved bones may help in arriving at a provisional diagnosis.

Orbital Masses

In cases of facial or orbital tumors, a mass or swelling may be discernible. Orbital rhabdomyosarcomas may cause proptosis, as can lymphoma, neuroblastoma, and retinoblastoma.

When the results of the clinical and imaging studies point to the probability of a neoplasm, the next decision is selection of the most reliable method to establish the pathologic diagnosis. Though the large area of the tumor is composed of primitive appearing monomorphic small blue cell population, the morphological clues that are most useful in diagnosis are summarised below

Table 1: Morphological features of various SRCT

SRCT	Morphological features
Neuroblastoma	Lobulated tumour "Homer-Wright" rosettes, fine fibrillar material , occasional ganglion cells
Ewings/PNET	Cytoplasm of tumor cells frequently contain glycogen, geographic areas of necrosis and rosette formation by component round cells
RMS	Moderate blue cytoplasm , strap and tadpole cells and cellular and nuclear pleomorphism
Retinoblastoma	Flexner-Wintersteiner rosettes
Hepatoblastoma	Cells arranged in acinar pattern; epithelial and mesenchymal components
Wilm's tumour	Blastemal clusters, tubule formation, mesenchymal component
DSRT	Nests of round cells with palisading adundant desmoplastic stroma

Table 2: Immunohistochemical Panel for SRCT

IHC	ES/PNET	RMS	WT	NB	Lymphoma	DSRCT	MNTI
LCA	-	-	-	-	+	-	-
CD99	+	-	-	-	+	-	-
Desmin		+	-		-	+	-
Keratin	rare	rare	-	-	-	+	+
MyoD1/ Myogenin	-	+	-	-	-	-	-
NSE	±	-	-	+	-	-	+
S100	-	-	-	+	-	-	rare
WT1	-	+	+	-	-	+	
HMB45	-	-	-	-	-	-	+

ES : Ewing's sarcoma; PNET : Primitive Neuroectodermal tumor,RMS : Rhabdomyosarcoma, WT : Wilm's tumor, NB : Neuroblastoma, DSRCT : Desmoplastic Small round cell tumor, MNTI : Melanotic Neuroectodermal tumor of infancy

Table 3: Characteristic Molecular Genetic Alterations Associated with SRCT

Tumor	Translocation	Molecular Feature
PNET/Ewing sarcoma	t(11;22)(q24;q12) t(21;22)(q22;q12) + others	EWS-FLI-1 EWS-ERG +others
RMS	t(1;13)(p36;q14) t(2;13)(q25;q14)	PAX7-FKHR (FOXO1) PAX3-KHR(FOXO1)
DSRCT	t(11;22)(p13;q12)	EWS-WT1

There is a significant overlap of morphological features of various SRCT, making the diagnosis difficult only on the basis of morphology. Immunohistochemistry helps to make a diagnosis in such cases.

Many SRCT of childhood also exhibit highly characteristic cytogenetic abnormalities. However, accurate karyotyping of solid tumors is technically difficult, and successful cytogenetic analysis can be performed in only a subset of cases. Despite the technical limitations, detection of a cytogenetic abnormality can be an important diagnostic aid in some childhood cancers. Molecular approaches, including fluorescence *in situ* hybridization (FISH) and reverse transcription polymerase chain reaction (RT-PCR), have facilitated the detection of chromosome translocations and have provided the methodology necessary for fully characterizing the involved genes.

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