Small blue round cell tumors (SBRCTs) are a heterogeneous group of tumors affecting children and young adults that are often difficult to diagnose due to overlapping morphologic, immunohistochemical and clinical features. With current molecular testing it has become apparent of an increasing number of SBRCTs lacking the canonical EWSR1-FLI1 fusion typical of ES. This subset of undifferentiated round cell tumors has become the focus of significant investigation and debate recently, as on one hand they share significant overlap at morphologic, immunophenotypic and clinical levels with classic Ewing sarcoma, but display different genetic signatures, complicating diagnosis and clinical management.

Ewing sarcoma (ES) is the prototypical small round cell sarcoma molecularly characterized by fusions between EWSR1 and a gene of the ETS family of transcription factors. An EWSR1-FLI1 fusion is detected in 90% of cases, while a t(21;22)(q22;q12), resulting in an EWSR1-ERG fusion, is the 2nd most common abnormality, accounting for 5-10% of the cases. The molecular landscape of round cell sarcoma with Ewing-like morphology has been further expanded by the discovery of fusions of EWSR1 with alternative non-ETS partners; with EWSR1-NFATc2 fusion being one of the more common events in this class, being associated with the amplification of the fusion transcript.

About two-thirds of EWSR1-negative SBRCTs are associated with CIC-DUX4 related fusions, while another smaller subset with BCOR-CCNB3 X-chromosomal paracentric inversion. SBRCTs with CIC-DUX4 fusions result from either a t(4;19)(q35;q13) or a t(10;19)(q26;q13). The CIC-DUX4 fusion appears functionally unrelated to EWSR1-ETS and the reported distinct gene signature and immunoprofile of CIC-DUX4 sarcomas suggest a pathogenesis distinct from ES. The morphologic appearance of CIC-DUX4-sarcomas is less monotonous compared to classic ES, with slight nuclear pleomorphism, vesicular chromatin with focally prominent nucleoli, more abundant cytoplasm, areas of spindling and myxoid matrix formation with prominent stromal edema. Clinically, CIC-DUX4-positive tumors are highly aggressive, arising almost exclusively in deep soft tissue of young adults.

The second group of SBRCTs with ES-like morphology harbors a fusion between BCOR (encoding the BCL6 transcriptional co-repressor) and CCNB3 (encoding the testis-specific cyclin B3), resulting from an X-chromosomal paracentric inversion, which links the entire BCOR coding sequence to the CCNB3 exon. Although BCOR-CCNB3 positive sarcomas share with ES certain similarities, such as clinical presentation in children and skeletal location, and some morphologic and immunohistochemical overlap, they show a distinct gene expression profile and distinct copy number changes from classic ES. Combined clinicopathologic data of 50 cases reported to date indicate a predominant occurrence in males (M:F ratio, 39:11), a median age at diagnosis of 13 years (range 2-44), and a preferential location within
bone (34/50; 68%). RT-PCR or 3-color FISH assay techniques for detection of BCOR-CCNB3 fusions or CCNB3 immunohistochemistry are excellent and reproducible tools for diagnosis of these tumors. As whole transcriptome sequencing has become more accessible and applied to an increasing number of undifferentiated round cell sarcomas for novel fusion gene discovery, new genetic abnormalities have been recently identified, further expanding the genetic spectrum of round cell sarcomas. First, novel BCOR gene rearrangements have been reported in 9.5% of fusion negative SBRCTs, either as BCOR-MAML3 or ZC3H7B-BCOR. The ZC3H7B-BCOR fusion has been previously described in other tumor types, such as endometrial stromal sarcoma and ossifying fibromyxoid tumor. Furthermore, a significant proportion of SBRCTs occurring in infants were recently shown to have internal tandem duplication (ITD) in the last exon of BCOR or less commonly a YWHAE-NUTM2B/E fusion, as previously described in clear cell sarcoma of kidney (CCSK). As previously documented in CCSK, a high BCOR up-regulation was also detected in the SBRCT with either BCOR-ITD or YWHAE-NUTM2B/E fusion. These results suggest that despite the 2 different genetic abnormalities, this infantile subset of SBRCT shares a common core of BCOR mRNA overexpression, which may trigger a similar downstream pathway. Furthermore, a transcriptional BCOR up-regulation was also found in the BCOR-MAML3 and BCOR-CCNB3 round cell sarcomas. These findings suggest different mechanisms of BCOR overexpression, either through conventional gene fusions or ITD, and may emerge as a critical molecular event in these URCS.

Whether these newly identified genetic entities represent stand-alone categories of tumors or should be subsumed under the ES family of tumors is still a matter of debate. At present, the number of reported cases carrying a CIC-DUX4 or BCOR-CCNB3 fusion is still limited. Nevertheless, distinction of these SBRCT subsets appears important from a clinical and therapeutic point of view to allow prospective therapeutic management with selection of proper chemotherapeutic regimens or target-specific therapy.

REFERENCES


