Novel BCOR-MAML3 and ZC3H7B-BCOR Gene Fusions in Undifferentiated Small Blue Round Cell Sarcomas.

Small blue round cell tumors (SBRTs) are a heterogeneous group of tumors that are difficult to diagnose because of overlapping morphologic, immunohistochemical, and clinical features. About two-thirds of EWSR1-negative SBRTs are associated with CIC-DUX4-related fusions, whereas another small subset shows BCOR-CCNB3 X-chromosomal paracentric inversion. Applying paired-end RNA sequencing to an SBRT index case of a 44-year-old man, we identified a novel BCOR-MAML3 chimeric fusion, which was validated by reverse transcription polymerase chain reaction and fluorescence in situ hybridization techniques. We then screened a total of 75 SBRTs lacking EWSR1, FUS, SYT, CIC, and BCOR-CCNB3 abnormalities for BCOR break-apart probes by fluorescence in situ hybridization to detect potential recurrent BCOR gene rearrangements outside the typical X-chromosomal inversion. Indeed, 8/75 (11%) SBRTs showed distinct BCOR gene rearrangements, with 2 cases each showing either a BCOR-MAML3 or the alternative ZC3H7B-BCOR fusion, whereas no fusion partner was detected in the remaining 4 cases. Gene expression of the BCOR-MAML3-positive index case showed a distinct transcriptional profile with upregulation of HOX-gene
signature, compared with classic Ewing's sarcoma or CIC-DUX4-positive SBRCTs. The clinicopathologic features of the SBRCTs with alternative BCOR rearrangements were also compared with a group of BCOR-CCNB3 inversion-positive cases, combining 11 from our files with a meta-analysis of 42 published cases. The BCOR-CCNB3-positive tumors occurred preferentially in children and in bone, in contrast to alternative BCOR-rearranged SBRCTs, which presented in young adults, with a variable anatomic distribution. Furthermore, BCOR-rearranged tumors often displayed spindle cell areas, either well defined in intersecting fascicles or blending with the round cell component, which appears distinct from most other fusion-positive SBRCTs and shares histologic overlap with poorly differentiated synovial sarcoma.