Undifferentiated “round” cell (“Ewing-like”) sarcoma: not always so-round nor Ewing-like

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In this issue, Yamada and colleagues contribute their experience on a rare, yet increasingly important to recognize, subset of round cell sarcomas (“Ewing-like” tumors) with alternative fusion transcripts. They retrospectively examined a large cohort of unclassified sarcomas with a round cell component in their archives and confirm 10% to harbor *CIC-DUX4* or *BCOR-CCNB3* fusions or other *CIC* rearrangements. They further demonstrate that these tumors can have unusual morphological features like myxoid stroma and both spindled and epithelioid cells, which can cause diagnostic confusion.

Ewing sarcoma is the prototypical round cell sarcoma. Classically, these tumors involved the bones of young children though they can affect all ages and can also be extraskelatal, including primary to the skin [1]. These high-grade cellular tumors are composed of monotonous small round cells with a scant cytoplasm, though challenging-to-recognize rare variants have been described including adamantinoma-like, atypical variants with larger nuclei, hyalinized matrix, and even spindled cells. While not specific, these tumors characteristically have CD99 reactivity with a distinct membranous accentuation. They can express keratins (particular low molecular weight forms) in a patchy distribution and also S100 protein, which can cause confusion. Ewing sarcoma was the first sarcoma (and solid tumor) discovered to have a characteristic recurrent translocation involving *EWSR1* on 22q12 and *FLI1* on 11q24 in the vast majority of cases. The resulting fusion

combines the transcriptional activation N-terminus domain of *EWSR1* (a member of the TET family of RNA-binding proteins), with the ETS DNA-binding domain of *FLI1*, resulting in overexpression of *FLI1*. A small fraction of cases involve *ERG* on 21q22 instead of *FLI1*, and even rarer variants involve other ETS family members such as *ETV1*, *ETV4*, and *FEV*. Rarely, *FUS* is found to substitute for *EWSR1* in these tumors [1]. Not only is this fusion critical for tumorigenesis but it is also useful to confirm the diagnosis, particularly in small biopsies, and in unusual clinical, morphological, and immunohistochemical variants. While aggressive, these tumors are responsive to neoadjuvant chemotherapy.

However, it became increasingly recognized that a population of “small round cell” sarcomas, with many of the features of Ewing sarcoma, lacked rearrangements in *EWSR1*. These were termed “Ewing-like tumors” or undifferentiated round cell sarcomas, and despite lacking the characteristic translocation, patients were treated with Ewing sarcoma protocols given their similar morphology. In 2006, two cases of “Ewing-like” tumors were found to harbor rearrangement in *CIC* and *DUX4* [2]. This discovery was further validated in the testing of additional undifferentiated small round cell sarcomas with some series finding up to 68% of *EWSR1* negative round cell sarcomas to harbor *CIC* rearrangement [3, 4]. *CIC* is located on 19q13 and encodes for a protein that belongs to a family of HMG (high mobility group)-box transcription repressors, while *DUX4* is located on 4q35 and 10q26 and is known to play a role in transcription activation. In addition, rare cases show rearrangement involving *CIC* and *FOXO4* on Xq13 [5, 6], with some series reporting desmoplasia in these cases. Despite having morphological and immunohistochemical overlap (i.e., both can have a round cell component and can express CD99, Erg, and *FLI1*), they also have important differences from Ewing sarcoma, with atypical morphological features (including atypical nuclei, spindled, and myxoid

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areas) and express DUX4, WT1, calretinin, and MYC, while being negative for NKX2-2 [7–10]. Some studies have also shown that these tumor to have a more aggressive clinical course and be less responsive to traditional Ewing chemotherapy, making their distinction from Ewing Sarcoma clinically relevant [10, 11].

Shortly following the discovery of *CIC*-rearranged round cell sarcomas, a subset of “Ewing-like” tumors that lacked *CIC* rearrangement and *EWSR1* rearrangement, were found using RNAseq to have a different alternative *BCOR*-*CCNB3* fusion transcript [12]. This fusion is the result of a cytogenetically cryptic chromosomal X inversion translocation with *BCOR* located on Xp11.14 with *CCNB3* located on Xp11.22, resulting in overexpression of *CCNB3*. *BCOR* functions to interact with a corepressor of BCL6, a protein important for the formation germinal centers and apoptosis, while *CCNB3* encodes for cyclin B3, a member of the cyclin family important in cell cycle regulation. In addition, alternative fusions include *BCOR*-*MAML3* and *ZC3H7B*-*BCOR* has also been described [13]. While these tumors have some features of Ewing sarcoma, they also display atypical features, including spindle cells, with some cases mimicking synovial sarcoma or even malignant peripheral nerve sheath tumors. In some series, these tumors were found to predominantly occur in the soft tissue of adult male adolescents [14]. Behavior in these tumors is not as established given their rarity, with some studies showing no significant differences, while others suggesting that they may be more aggressive than Ewing sarcoma.

The concept of tumors that were originally termed “Ewing-like tumor” or now undifferentiated “round” cell sarcomas under the 2013 WHO classification is actively evolving. The discovery of alternative fusion transcripts and their subsequent increased recognition is allowing for better classification and study of these rare tumors. Although previously lumped as Ewing-like and “round cell” sarcoma, studies like Yamada and colleagues collectively show that these tumors also have distinct clinical, morphological, and immunohistochemical features and should no longer be considered necessarily as “Ewing-like” sarcoma or “round” cell sarcoma but acknowledged as their own separate entity. This distinction is important given their more aggressive clinical course and so that future therapeutic trials specific to these rare sarcomas can be developed. Their distinct nosocomial status will likely become firmly codified in the next WHO classification scheme. Until then, the use of appropriate molecular methods will allow an increased recognition and additional study.

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