Undifferentiated small round cell sarcoma

According to the current WHO classification, undifferentiated round cell sarcomas are characterized by relatively monotonous round to ovoid cytomorphology, with a high nuclear to cytoplasmic ratio, and no distinct line of differentiation, lacking consistent genetic abnormalities. However, as they most often resemble Ewing sarcoma, for practical and treatment purposes, round cell undifferentiated sarcomas have been regarded as 'Ewing sarcoma-like' and are often managed similarly to the Ewing sarcoma family of tumors. In contrast to classic Ewing sarcoma, round cell undifferentiated sarcomas lack the pathognomonic translocations involving the EWSR1 gene on chromosome 22 fused to a member of the ETS transcription factor family, either FLI1 [1)]

CIC-rearranged sarcoma is a high-grade sarcoma, most often harboring CIC:: DUX4 fusion, and is characterized by a distinct round cell histology, co-expression of ETV4 and WT1, and a specific DNA methylation class.

They fall under the Ewing sarcoma group of cancers. Although historically grouped with Ewing sarcomas, these tumors are genetically distinct and tend to be more aggressively metastatic than Ewing sarcomas on average.

Satomi et al. reported a brain tumor with ATXN1:: DUX4 that had an indistinguishable phenotype and DNA methylation profile from CIC-rearranged sarcoma. A 40-year-old man presented with a 5 cm hemorrhagic mass in the right frontal lobe of the cerebrum. The tumor was resected and histologically showed a dense proliferation of relatively monomorphic round cells with multifocal myxoid changes. Immunohistochemically, the tumor was diffusely positive for ETV4, WT1, and DUX4. Through classic histomorphology and immune profile, the tumor was provisionally diagnosed as CIC-rearranged sarcoma. However, no CIC fusions or mutations were identified using CIC break-apart fluorescence in situ hybridization (FISH) or FoundationOne CDx. Despite multiple surgeries and adjuvant chemoradiation therapy, the patient succumbed 16 months after presentation. RNA exome sequencing detected an in-frame intraexonic ATXN1 (exon 9):: DUX4 (exon 1) fusion, which was validated by reverse transcription-polymerase chain reaction and ATXN1 FISH assay. Upon DNA methylation analysis, the tumor matched with CIC-rearranged sarcoma both by the Deutsche Krebsforschungszentrum classifier and t-distributed stochastic neighbor embedding. Along with a recent report of a similar pediatric brain tumor, the present case suggests that ATXN1::DUX4 is a recurrent alternative molecular event in the sarcoma type that is presently defined by CIC rearrangement, which prompts an expansion of the tumor concept [2)].

1)
Delattre O, Zucman J, Plougastel B, Desmaze C, Melot T, Peter M, Kovar H, Joubert I, de Jong P, Rouleau G, et al. Gene fusion with an ETS DNA-binding domain caused by chromosome translocation in human tumours. Nature. 1992 Sep 10;359(6391):162-5. doi: 10.1038/359162a0. PMID: 1522903.
2)
Satomi K, Ohno M, Kubo T, Honda-Kitahara M, Matsushita Y, Ichimura K, Narita Y, Ichikawa H, Yoshida A. Central nervous system sarcoma with ATXN1::DUX4 fusion expands the concept of CIC-rearranged sarcoma. Genes Chromosomes Cancer. 2022 Jun 17. doi: 10.1002/gcc.23080. Epub ahead of print.

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