Primary intracranial sarcoma with DICER1 mutation

Patients with DICER1 predisposition syndrome have an increased risk to develop pleuropulmonary blastoma, cystic nephroma, embryonal rhabdomyosarcoma, and several other rare tumor entities. In this study, we identified 22 primary intracranial sarcomas, including 18 in pediatric patients, with a distinct methylation signature detected by array-based DNA-methylation profiling. In addition, two uterine rhabdomyosarcomas sharing identical features were identified. Gene panel sequencing of the 22 intracranial sarcomas revealed the almost unifying feature of DICER1 hotspot mutations (21/22; 95%) and a high frequency of co-occurring TP53 mutations (12/22; 55%). In addition, 17/22 (77%) sarcomas exhibited alterations in the mitogen-activated protein kinase pathway, most frequently affecting the mutational hotspots of KRAS (8/22; 36%) and mutations or deletions of NF1 (7/22; 32%), followed by mutations of FGFR4 (2/22; 9%), NRAS (2/22; 9%), and amplification of EGFR (1/22; 5%). A germline DICER1 mutation was detected in two of five cases with constitutional DNA available. Notably, none of the patients showed evidence of a cancer-related syndrome at the time of diagnosis. In contrast to the genetic findings, the morphological features of these tumors were less distinctive, although rhabdomyoblasts or rhabdomyoblast-like cells could retrospectively be detected in all cases. The identified combination of genetic events indicates a relationship between the intracranial tumors analyzed and DICER1 predisposition syndrome-associated sarcomas such as embryonal rhabdomyosarcoma or the recently described group of anaplastic sarcomas of the kidney. However, the intracranial tumors in our series were initially interpreted to represent various tumor types, but rhabdomyosarcoma was not among the typical differential diagnoses considered. Given the rarity of intracranial sarcomas, this molecularly clearly defined group comprises a considerable fraction thereof. We, therefore, propose the designation “spindle cell sarcoma with rhabdomyosarcoma-like features, DICER1 mutant” for this intriguing group [1)]

ETMR, pineoblastoma, primary intracranial sarcoma, and pituitary blastoma should be considered rare phenotypes of the DICER1 syndrome, and families should be counseled and screened for associated tumors. ETMR and primary intracranial sarcoma had a higher risk of relapse. GTR and radiotherapy appeared to improve the OS of patients with DICER1-mutant malignant intracranial tumors [2)].

DICER1-associated central nervous system sarcoma (DCS) without evidence of other cancer-related syndromes is rare. Though the morphology of DCS was highly variable, the immunophenotype was the predominant myogenic phenotype. Other lineage markers were consistently negative.

Case presentation: We report a case of DCS with neurogenic differentiation proved by immunohistochemical staining and whole-exome sequencing (WES). An 8-year-old female patient presented with 8-day history of headache, nausea and vomiting. Magnetic resonance imaging (MRI) revealed a heterogeneous mass in the left parietal lobe. The patient underwent the craniotomy via left parietal approach to resect the tumor completely. Histologically, the tumor predominately showed fibrosarcoma-like spindle cells with obvious cytoplasmic eosinophilic globules. Immunohistochemically, the tumor stained positively for DICER1, Desmin, and several neurogenic markers. DICER1 somatic hotspot mutation was confirmed by WES, as well as TP53 and RAF1 mutations which were commonly found in DCS, and other sarcoma-associated genes including AR,

AXL and ETV5 mutations. Subsequently, the result of Gene Ontology (GO) analysis showed that the mutated genes in this case were involved in neuron development. All of these findings indicated the diagnosis of DCS with neurogenic differentiation. Postoperatively, the patient received high-dose radiotherapy (60 Gy) and chemotherapy. There was no MRI evidence of tumor recurrence at the 21-month postoperative follow-up.

Conclusions: This unusual DCS case with neuronal differentiation is an important addition to the immuno-phenotypic spectrum of DCS. Although the prognosis for DCS is poor, gross tumor resection with high dose radiotherapy and chemotherapy may assist in prolonging survival [3)].

A child had been followed since infancy by our multi-disciplinary neuro-oncology clinic with annual magnetic resonance imaging (MRI) under the presumed diagnosis of encephalocraniocutaneous lipomatosis (ECCL), with clinical features including nevus psiloliparus, scalp lipoma, nodular skin tag on and coloboma of the eyelid, cortical atrophy and meningeal angiomatosis. At the age of 4, she was found to have a large temporoparietal lesion causing elevated intracranial pressure requiring surgical resection. Histopathological exam of the tumor was suggestive of an intracranial sarcoma. Sequencing analysis of the tumor revealed mutations in DICER1, KRAS and TP53. Subsequent germline testing confirmed DICER1 syndrome and revealed an insignificant FGFR1 variant at a low frequency. Methylation profile of the tumor showed the tumor clustered most closely with sarcoma (rhabdomyosarcoma-like), confirming this tumor to be a primary DICER1-sarcoma. Compared to the previously reported cases, our unique case of primary DICER1-sarcoma also demonstrated neurofilament and chromogranin positivity, and genomic instability with loss of chromosome 4p, 4q, 8p, 11p, and 19p, as well as gains in chromosome 7p, 9p, 9q, 13q, and 15q on copy variant analysis. The detailed sequencing and methylation information discovered in this unique case of DICER1-sarcoma will hopefully help further our understanding of this rare and emerging entity [4)].

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two cases of PIRMS with somatic DICER1 mutation showing morphological and immunohistochemical evidence of primary skeletal muscle differentiation; the two cases share common clinical features, including young age, supratentorial tumor, and onset of intratumoral bleeding. Although methylation profiling was not performed, both cases shared clinical and pathological characteristics in common with the recently proposed methylation entity “spindle cell sarcoma with rhabdomyosarcoma-like features, DICER1 mutant (SCS-RMSlike-DICER1)''. Our cases provide further evidence of the link between primary intracranial sarcoma and DICER1 mutation which may form a distinct entity [5)].

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