Primary Intracranial Sarcoma, DICER1-Mutant Presenting as a Pineal Region Tumor Mimicking Pineoblastoma: Case Report and Review of the Literature

Nalin Leelatian, MD, PhD1, James Goss, MD1, Devang Pastakia, MD2, Michael C. Dewan, MD3, Matija Snuderl, MD4, and Bret C. Mobley, MD1

1Department of Pathology, Microbiology and Immunology, Vanderbilt University Medical Center, Nashville, Tennessee, USA
2Department of Pediatrics, Vanderbilt University Medical Center, Nashville, Tennessee, USA
3Department of Neurological Surgery, Vanderbilt University Medical Center, Medical Center North, Nashville, Tennessee, USA
4Department of Pathology, NYU Langone Health and School of Medicine, New York, New York, USA

To the Editor:

Primary pineal tumors encompass a diverse group of tumor types that are relatively rare compared to other primary neoplasms of the central nervous system. The histopathology of primary pineal tumors can range from well-differentiated pineocytomas to poorly differentiated, highly aggressive pineoblastomas with primitive, embryonal morphology. In the pediatric population, pineoblastomas comprise a large majority of pineal region tumors. Recent methylation profiling has revealed 4 distinct molecular subgroups among pineoblastoma or germ cell tumor. The patient underwent a paramedian suboccipital craniotomy for right lateral supracerebellar approach with near-total tumor resection; thin disease adherent to the left internal cerebral vein was unresected.

The tissue was fixed in 10% neutral buffered formalin, paraffin-embedded, and routinely processed for microscopic examination. The hematoxylin and eosin (H&E)-stained, 5-μm-thick sections revealed a neoplasm composed of densely packed spindle cells with moderately pleomorphic nuclei and high nuclear-to-cytoplasmic ratios with diffuse, fascicular (Fig. 1C), and focal nodular (Fig. 1D) growth patterns. Mitotic activity was conspicuous. The tumor cells at the periphery of the nodules were immunoreactive for desmin (Fig. 1E, F). SMA labeled pericytes surrounding blood vessels but was negative in the tumor cells (Fig. 1G). No tumor cell immunoreactivity for myogenin was found (Fig. 1H). GFAP (Fig. 1I) labeled glial cells with reactive morphology. No convincing synaptophysin reactivity was seen in tumor cells (Fig. 1J). p53 labeled only rare cells, consistent with a wild-type pattern (Fig. 1K). The Ki67 proliferation rate was variable with regions of moderate and high labeling (Fig. 1L).

DNA methylation profiling was performed. When compared to a sarcoma reference dataset, the tumor clustered best with a reference class of “sarcoma, rhabdomyosarcoma-like tumors,” corresponding to “primary intracranial sarcoma, DICER1-mutant” according to the current WHO classification (4), with a class assignment calibrated score of 0.99. No apparent copy number alterations were identified (Fig. 2A). Next-generation sequencing was performed and revealed 2 distinct DICER1 mutations (Fig. 2B). The first mutation was a nonsynonymous single-nucleotide variant in exon 24 involving the hotspot RNase IIIb domain (c.G5125A:p.D1709N, allele frequency of 37%). The second mutation was a frameshift deletion in exon 15 (c.2361delT:p.F787fs, allele frequency of 48%). This frameshift mutation was subsequently confirmed to be of germline origin.

While the radiologic and initial histopathologic H&E findings were highly suggestive of a pineoblastoma, the lack of neuroepithelial differentiation by GFAP and synaptophysin immunohistochemistry raised the possibility of an unusual tumor type. A subset of tumor cells in this case demonstrated desmin immunoreactivity, similar to previously reported in pineoblastomas, 2 of which show a strong association with either DICER1 mutation or DICER1 cancer predisposition syndrome (1–3).

Here, we describe an unusual case of a rare DICER1-associated malignant neoplasm in a 3-year-old girl with no significant medical history. She presented with acute morning headaches, emesis, lethargy, and leftward gaze deviation. MRI revealed a 3-cm hemorrhagic and enhancing pineal region mass (Fig. 1A), which demonstrated slight T2 hyperintensity on T2/FLAIR weighted images (Fig. 1B). The mass showed anterior exophytic extension into the posterior third ventricle, posterior extension into the quadrigeminal cistern, and lateral extension into the left thalamus. The radiologic differential diagnosis included primary pineal neoplasm such as pineoblastoma or germ cell tumor. The patient underwent a paramedian suboccipital craniotomy for right lateral supracerebellar approach with near-total tumor resection; thin disease adherent to the left internal cerebral vein was unresected.

Microsatellite analysis was performed and revealed 2 distinct DICER1 mutations (Fig. 2B). The first mutation was a nonsynonymous single-nucleotide variant in exon 24 involving the hotspot RNase IIIb domain (c.G5125A:p.D1709N, allele frequency of 37%). The second mutation was a frameshift deletion in exon 15 (c.2361delT:p.F787fs, allele frequency of 48%). This frameshift mutation was subsequently confirmed to be of germline origin.
FIGURE 1. Preoperative MRI findings and histopathologic characteristics of the tumor. (A) Preoperative postcontrast T1 and (B) T2/FLAIR sequences MRI images. H&E sections of the tumor demonstrating (C) diffuse/fascicular (image obtained at 60X) and (D) nodular (image obtained at 40X) growth patterns. Immunohistochemical stains (images obtained at 40X) for (E, F) desmin, (G) SMA, (H) myogenin, (I) GFAP, (J) synaptophysin, (K) p53, and (L) Ki67. H&E, hematoxylin and eosin.

FIGURE 2. DICER1 mutation hotspots and anatomic locations of primary intracranial sarcoma, DICER1-mutant. (A) Copy number variation profiling results of the current reported case. (B) Structure of the DICER1 gene with reported mutations in primary intracranial sarcoma, DICER1-mutant. The 2 mutations reported here are highlighted. (C) Frequency of primary intracranial sarcoma, DICER1-mutant based on anatomic locations. The pineal region case is reported here.
DNA methylation profiling was critical for the diagnosis for this case, especially given the overlapping DICER1 mutation hotspots seen in intracranial sarcoma. DICER1-mutant and pineoblastoma (8, 9). The DICER1 p.D1709N mutation identified here has been previously reported in intracranial sarcoma, DICER1-mutant (5, 6, 10–12), as well as in pineoblastoma (9). However, DICER1 p.F787fs mutation has only been reported in the setting of pineoblastoma (8); its prevalence in intracranial sarcoma, DICER1-mutant beyond this case, or in the setting of DICER1 cancer predisposition syndrome is currently unknown.

After surgery, the patient received 3 cycles of vincristine, high-dose methotrexate, etoposide, cyclophosphamide, and cisplatin according to the Children’s Oncology Group (COG) study ACNS0334 protocol. She also received 3 cycles of ifosfamide, carboplatin, and etoposide (ICE) therapy. She subsequently received autologous stem cell transplantation after the second and third cycles of ICE therapy and focal radiation to the tumor bed. A follow-up MRI showed continued decrease in the extent of the enhancing pineal region tumor.

Most of the reported intracranial sarcoma, DICER1-mutant cases presented with supratentorial lesions, specifically within the cerebral hemispheres (Fig. 2C, 87%; 5–7, 10–15). A minority of cases involving infratentorial sites and leptomeninges have been reported (5, 6). To our knowledge, the case presented here is the first case of primary intracranial sarcoma, DICER1-mutant, that presented as a primary pineal region tumor. Notably, primary pineal region alveolar rhabdomyosarcoma has also been previously reported (16). Therefore, this case demonstrates that sarcomas, including primary intracranial sarcoma, DICER1-mutant, should be included in the differential diagnosis of primary pineal neoplasms. Moreover, DNA methylation can aid in the distinction between different types of sarcomas, as well as tumors of different histogenesis, that carry identical mutations.

COMPETING INTERESTS
The authors have no duality or conflicts of interest to declare.

REFERENCES
15. Sakaguchi M, Nakano Y, Honda-Kitahara M, et al. Two cases of primary supratentorial intracranial rhabdomyosarcoma with DICER1 mutation which may belong to a “spindle cell sarcoma with rhabdomyosarcoma-like feature, DICER1 mutant”. Brain Tumor Pathol 2019;36:174–82