DICER1-associated central nervous system sarcoma with neural lineage differentiation: a case report

Kun Yao1†, Zejun Duan†, Jing Feng1, Changxiang Yan2 and Xueling Qi1*

Abstract

Background: 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 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 immunophenotypic spectrum of DCS. Although the prognosis for DCS is poor, gross tumor resection with high dose radiotherapy and chemotherapy may assist in prolonging survival.

Keywords: DICER1-associated central nervous system sarcoma, Neurogenic differentiation, Whole-exome sequencing, Case report, Radiotherapy

Background

Intracranial sarcomas are uncommon tumors with poor prognoses and mainly occur in adult patients [1]. They rarely affect children, which are often associated with syndromic disorders [2–4]. DICER1 syndrome is one of rare syndromic disorders with intracranial sarcomas, which always exhibits germline DICER1 mutations [5, 6]. Few studies reported rare cases of pediatric intracranial sarcoma involving somatic DICER1-mutants and without evidence of other peripheral tumors. Koelsche

†Kun Yao and Zejun Duan contributed equally and should be regarded as co-first authors.
*Correspondence: xszqxl169@mail.ccmu.edu.cn
1 Department of Pathology, Sanbo Brain Hospital, Capital Medical University, No.50 Xiangshan Yikesong Road, Haidian District, 100093 Beijing, China
Full list of author information is available at the end of the article

© The Author(s) 2022. Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated in a credit line to the data.
et al. reported a group of predominantly pediatric intracranial spindle cell sarcomas to be called “spindle cell sarcoma with rhabdomyosarcoma-like features, *DICER1* mutant (SCS-RMS like-DICER1).” In this study, the somatic *DICER1* mutation was detected in three of five cases [7]. In another study, Kamihara et al. reported six cases of “DICER1-associated central nervous system sarcoma (DCS),” in which three of six cases harbored somatic *DICER1* mutations instead of germline *DICER1* mutations [8]. Moreover, most of the reported cases showed highly variable morphology, but they were consistent with the positive of myogenic markers, while other lineage markers were consistently negative, such as GFAP, OLIG2, SOX10, SOX2, CD34, S100, EMA, and cytokeratin [5–10]. To the best of our knowledge, there is no report of DCS with the expression of neurogenic markers. Herein, we describe a rare DCS case with the somatic *DICER1* mutation and neural lineage differentiation, including clinical, imaging, pathological, molecular profiles and treatment.

**Case presentation**

An 8-year-old female presented to the neurosurgery department with intermittent headache, nausea and vomiting for 8 days. Neurological examination revealed no abnormalities. She had no familial cancer or extracranial tumor history.

**Neuroimaging**

The brain MRI revealed a heterogeneous mass in left parietal lobe which was predominantly hypointense on T1 (Fig. 1a), inhomogeneous hyperintense on T2 (Fig. 1b), and iso-intense on fluid attenuation inversion recovery (FLAIR) (Fig. 1c). After the administration of contrast, the mass displayed heterogeneous enhancement (Fig. 1d and e). The patient underwent a craniotomy via left parietal approach, which revealed a well-defined, soft, gray and gelatinous lesion attached to the falx cerebri (5 cm × 5 cm × 5 cm). The postoperative course was uneventful and postoperative CT scan showed that the intracranial tumor had been completely removed (Fig. 1f).

---

**Fig. 1** Preoperative and postoperative neuroimages of this DCS patient. Preoperative head MRI shows there is a heterogeneous intracranial mass. Axial T1-weighted MRI shows hypo-intense lesion in the left parietal lobe (a). Axial T2-weighted MRI shows inhomogeneous hyper-intense (b). Axial FLAIR image shows iso-intense (c). Axial and sagittal post-contrast T1-weighted MRI shows enhancement of the mass and the adjacent dura (d and e). Postoperative CT presents completely tumor resection (on the day after surgery) by axial CT (f). Postoperative MRI shows no tumor recurrence (19 months after surgery) which confirms on T1-weighted (g), T2-weighted (h), and axial coronal post-contrast T1-weighted (i).
Pathology and immunochemistry

Light microscopy examination revealed sarcomatous neoplasms predominantly presented with spindle-shaped cells in a fascicular pattern (Fig. 2a). There was a clear boundary between tumor and peripheral brain tissue (Fig. 2b). In some areas, a myxoid stroma matrix was found with a few multinucleated tumor giant cells (Fig. 2c). The nuclei of the tumor cells were with brisk mitotic activity (Fig. 2d). Prominent cytoplasmic eosinophilic globules were easily identified (Fig. 2e and f).

Immuno-histochemical staining was performed to diagnose and identify the direction of tumor differentiation by Ventana Benchmark Ultra automated stainer (Ventana, Tucson, Arizona, USA) (Fig. 3a-h, and Supplementary Table 1). Firstly, we labeled markers commonly used in the diagnosis of meningioma and non-astrocytic mesenchymal sarcoma. But the tumor cells were only stained positively for Vimentin and had focal expression of Desmin. Considering that the primary location of the tumor was intracranial, the diagnostic markers for neuroepithelial tumors were also stained. The tumor cells were stained positively for some neurogenic makers, for instance S100, Syn, MAP2, NFP, Nestin, CD56, and SOX2, which highlighted the neural lineage differentiation of tumor cells. However, the tumor cells were negative for GFAP, OLIG2, CgA, and SOX10. It also failed to provide strong diagnostic evidence. The possibility of rare tumors began to be considered. INI1 and BRG1 were retained. The DICER1 protein immunostaining was extensively positive in the tumor cells, indicating the high possibility of DICER1 mutation. Moreover, though the frequent nuclear positivity of TLE1, loss of H3K27me3 and loss of ATRX expression in DCS has been reported [8, 11], it was not observed in this case. In addition, the P53 expression was negative. The tumor cells displayed with a large amount of thin reticulin fibers (Fig. 3i). In summary, a diagnosis of primary intracranial spindle cell sarcoma with neurogenic and myogenic differentiation, possibly associated with DICER1 mutation, was favoured.

Next-generation sequencing

Next, WES was performed in surgical formalin-fixed paraffin-embedded (FFPE) tumor tissues and paired normal control (peripheral blood) in order to determine whether this patient harbored somatic DICER1 mutation and other genetic variants. In brief, WES analysis sequencing libraries were generated using Agilent SureSelect Human All Exon V6 kit (Agilent Technologies, CA, USA). DNA libraries were sequenced on Illumina Hiseq platform and 150 bp paired-end reads were generated and cleaned. The reads were mapped to the reference human genome b37 by Burrows-Wheeler Aligner (BWA) software [12]. The identification and filter of SNPs followed the workflow of GATK [13]. The parameters were set as default.

The somatic mutation of DICER1 p.E1813D (c.5439G > T, VAF: 76.47%) located within the Ribonuclease III domain

![Fig. 2](image) Histopathological features of the DICER1-associated central nervous system sarcoma. Histopathological features were similar with sarcomatous neoplasms. The tumor presented with spindle-shaped cells with a fascicular pattern of growth (the long arrow) (a). The interface of tumor and normal brain was well demarcated (the black line shows the interface) (b). Focal myxoid stroma matrix (the long arrow), a few multinucleated giant cells (the short arrows) (c), frequent mitoses (the short arrows) (d), and cytoplasmic eosinophilic globules (the short arrows) (e and f) were observed. Histopathological images were taken at a magnification of 100 x in a to c, 400 x in d to f.
was detected. The loss of heterozygosity (LOH) event in *DCIER1* was identified, which caused by deletion of the wild-type allele. And other mutations frequently mutated in DCS were detected, including *TP53* mutation (c. 560-2A > T, 81.29%) and *RAF1* mutation (p.R191T, 40.96%) which was predicted to cause activation of the MAP kinase signaling pathway. Moreover, several sarcoma-associated gene mutations were found, including *AR* mutation (p.G473del, 11.11%), *AXL* mutation (p.T45P, 8.11%), and *ETV5* mutation (p.F11Y, 33.33%). Hence, with *DICER1* mutation accompanied by LOH and several DCS frequent mutations detected by WES, a final diagnosis of DCS was established.

The result of analysis based on WES indicated that the tumor presented a high level of tumor mutational burden (TMB, 5.63 Mut/MB) as reported before [8], while showing no microsatellite instability (MSI). In addition to the mutations described above, 158 other somatic alterations were detected. To identify the potential molecular function of these variant genes, we performed Gene Ontology (GO) analysis using DAVID website [14]. The parameters were set as default. The result of GO analysis showed that mutated genes in this case were mainly involved in chromatin organization (*SATB1, ATAD2* and *CHD4*), neuron development (*TENM4, SECISBP2* and *HS6ST1*), and histone deacetylation (*SIN3B, CHD4* and *MTA2*) processes (Fig. 4). Meanwhile, RNA sequencing (RNA-seq) was performed as previously described [15], but we did not find any gene fusions.

**Post-operation**

Subsequently, the patient received postoperative radiotherapy (60 Gy/30f) with the following cyclophosphamide, doxorubicin and vincristine for the first, third, fifth and seventh chemotherapy cycles. In the second, fourth, sixth and eighth cycles, ifosfamide and etoposide were used for chemotherapy. After eight cycles (median duration of 21 days among cycles) of combination chemotherapy, brain MRI revealed no evidence of tumor recurrence at the 19-month follow-up (Fig. 1g-i). At the 21-month postoperative follow-up, no clinical symptoms were observed.
Discussion and conclusions

We here describe a case of DCS harboring somatic DICER1 hotspot mutation with neurogenic differentiation. Early reports have described that though the morphology of DCS was highly variable, spindle cell morphology was common with immunopositive myogenic markers (SMA, desmin, and myogenin) [7, 8]. Other lineage markers were consistently negative [7, 8]. In the current case, the tumor predominately showed fibrosarcoma-like spindle cells with brisk mitotic activity, including obvious cytoplasmic eosinophilic globules. These microscopic features were quite similar to previous reports [7, 8]. Unlike previous cases, this case showed the expression of neurogenic markers (S100, NFP, Syn, MAP2, CD56, Nestin, and SOX2) in addition to myogenic marker (Desmin). The GO analysis based on somatic mutations called by WES had indicated that several genes involved in neuron development were mutated, such as TENM4, SECISBP2 and HS6ST1. We have shown that this case had both neural characteristics and the potential for neural development. The neurogenic differentiation was found in DCS, and this testified the statement of "highly variable heterologous differentiation of DCS" on the other side.

Except for somatic DICER1 hotspot mutation, some other genetic alterations were detected in this patient. The TP53 mutation and other mutations related to the MAP-kinase pathway were frequent in SCS-RMS like DICER1 [7, 8, 10, 11]. TP53 mutation and RAF1 gene mutation, which were associated with MAP-kinase pathway, have been observed in the current case too. Furthermore, the patient also carried tumor-driving genes: AR, AXL and ETVS mutations. Recently, AXL has been proven to be a candidate for pathogenesis and therapeutic investigations in leiomyosarcoma [16] and osteosarcoma [17]. It was demonstrated that ETVS had oncogenic function on Ewing’s sarcoma [18]. This may be of interest because AXL and ETVS, confirmed sarcoma-associated genes in leiomyosarcoma, osteosarcoma and Ewing’s sarcoma growth, can be also detected in DCS cases [16–18]. Similar tumor-driving mutations in this DCS and other kinds of sarcoma suggested that there was also an inherent relationship between DCS and some other mesenchymal sarcomas.

Clinical experience with DCS is very limited. Some DCS cases without germline DICER1 variants and family history of DICER1-related tumors were presumed to represent sporadic disease [8]. It is worth noting that a few DCS cases without germline DICER1 variants may present de novo neoplasm in other organs besides intracranial sarcoma as time goes on [7]. In our case, however, no other diseases occurred during the 21 months of follow-up after surgery. Generally, even if the DCS patients without DICER1 germline mutation did not have any other diseases at the time of DCS, it is still required to pay close attention to their general and systemic examination in postoperative follow-up.

Sporadic reports of long-term cure indicate that achieving gross total resection, immediate postoperative focal radiotherapy, and prolonged combination chemotherapy may be of importance [8]. Effective regimens include cyclophosphamide, topotecan, ifosfamide, doxorubicin, vincristine and dactinomycin. We found that three of the DCS patients in the previous study who had been exposed to high dose rate radiotherapy (≥59.9 Gy) had relatively favorable prognosis [8]. In addition, this patient who had been undertaken gross tumor resection, high dose rate radiotherapy, and chemotherapy had no tumor recurrence at the 21-month follow-up. It suggested that the treatment of DCS should include gross total resection and combination of high dose rate radiotherapy (60 Gy) and chemotherapy.
In summary, this first report of DCS with neuronal differentiation extends the immuno-phenotypic spectrum of DCS. Although the prognosis for DCS is poor, gross tumor resection, high dose radiotherapy and chemotherapy may assist in prolonging survival. Long-term observation is essential to better elucidate the biological behavior of DCS with neuronal differentiation.

Abbreviations
DCS: DICER1-Associated central nervous system sarcoma; SCS-RMS: like-DICER1 mutant; WES: Whole-exome sequencing; RNA-seq: RNA sequencing; GO: Gene ontology; MRI: Magnetic resonance imaging; FLAIR: Fluid attenuation inversion recovery; FFPE: Formalin-fixed paraffin-embedded; BWA: Burrows-Wheeler Aligner; TMB: Tumor mutational burden; MSI: Microsatellite instability; VAF: Variant Allele Frequency; LOH: Loss of heterozygosity.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s13000-022-01252-1.

Additional file 1: Supplemental Table 1. The Primary antibodies for immunochemistry and corresponding staining results.

Acknowledgements

We are grateful for the cooperation of the patient’s family. We appreciate Dr. Liu Hailong for polishing up the article.

Patient consent
Written informed consent was obtained from the family member (mother) of the patient for the publication of any potentially identifiable images or data included in this article.

Authors’ contributions

The overall experimental design was conceived and supervised by Qi Xueling. Changxiang Yan provided the clinical materials and information. Yao Kun contributed to the analysis of the data and the final draft of the manuscript. Duan Zejun contributed to the analysis of the data and the figure. Feng Jing contributed to the analysis of the data and the final draft of the manuscript. All authors approved the final manuscript.

Funding

None.

Availability of data and materials

The data that support the findings of this study are available on request from the corresponding author.

Declarations

Ethics approval and consent to participate

The present study was conducted in accordance with the Declaration of Helsinki and under the guidelines of the institutional board on ethics of the Sanbo Brain Hospital, Capital Medical University, Beijing.

Consent for publication

All authors consent for publication.

Competing interests

All authors declare that they have no conflicts of interest.

Author details

1 Department of Pathology, Sanbo Brain Hospital, Capital Medical University, No.50 Xiangshan Yikesong Road, Haidian District, 100093 Beijing, China.

2 Department of Neurosurgery, Sanbo Brain Hospital, Capital Medical University, 100093 Beijing, China.

Received: 16 September 2021 Accepted: 15 September 2022

References

1. Zhang G, Xiao B, Huang H, Zhang Y, Zhang X, Zhang J, et al. Intracranial synovial sarcoma: a clinical, radiological and pathological study of 16 cases. Eur J Surg Oncol. 2019;45(12):2379–85. https://doi.org/10.1016/j.ejso.2019.08.015.

2. Kühlen M, Borkhardt A. Cancer susceptibility syndromes in children in the area of broad clinical use of massive parallel sequencing. Eur J Pediatr. 2015;174(8):987–97. https://doi.org/10.1007/s00431-015-2565-x.

3. McBride KA, Ballinger ML, Killick E, Kirk J, Tattersall MH, Eeles RA, et al. Li-Fraumeni syndrome: cancer risk assessment and clinical management. Nat Rev Clin Oncol. 2014;11(5):260–71. https://doi.org/10.1038/nrclinonc.2014.41.

4. Ripperger T, Bielack SS, Borkhardt A, Brecht IB, Burkhardt B, Calaminus G, et al. Childhood cancer predisposition syndromes-A concise review and recommendations by the Cancer Predisposition Working Group of the Society for Pediatric Oncology and Hematology. Ann J Med Genet A. 2017;173A(4):1017–32. https://doi.org/10.1002/ajmg.a.38142.

5. Schultz KAP, Williams GM, Kamihara J, Stewart DR, Harris AK, Bauer AJ, et al. DICER1 and associated conditions: identification of at-risk individuals and recommended surveillance strategies. Clin Cancer Res. 2018;24(10):2251–61. https://doi.org/10.1158/1078-0432.CCR-17-3089.

6. Kim J, Schultz KAP, Hill DA, Stewart DR. The prevalence of germline DICER1 pathogenic variation in cancer populations. Mol Genet Genomic Med. 2019;7(3):e555. https://doi.org/10.1002/mgg3.555.

7. Koelsche C, Mynakre M, Schimpf D, Bertero L, Serrano J, Sahm F, et al. Primary intracranial spindle cell sarcoma with rhabdomyosarcoma-like features share a highly distinct methylation profile and DICER1 mutations. Acta Neuropathol. 2018;136(2):327–37. https://doi.org/10.1007/s00401-018-1871-6.

8. Kamihara J, Paulson V, Breen MA, Laetsch TW, Rakheja D, Shulman DS, et al. DICER1-associated central nervous system sarcoma in children: comprehensive clinicopathologic and genetic analysis of a newly described rare tumor. Mod Pathol. 2020;33(10):1910–21. https://doi.org/10.1038/s41379-020-0516-1.

9. de Kock L, Priest JR, Foulkes WD, Alexandrescu S, An update on the central nervous system manifestations of DICER1 syndrome. Acta Neuropathol. 2020;139(4):689–701. https://doi.org/10.1007/s00401-019-01997-y.

10. Alexandrescu S, Meredith DM, Uдов HG, Alaggio R, Novello M, Ligon KL, et al. Loss of histone H3 trimethylation on lysine 27 and nuclear expression of transducin-like enhancer 1 in primary intracranial sarcoma, DICER1-mutant. Histopathology. 2021;78(2):265–75. https://doi.org/10.1111/his.14217.

11. Lee JC, Villanueva-Meyer JE, Ferris SP, Sloan EA, Hofmann JW, Hattab EM, et al. Expression and role of TYRO3 and AXL as potential therapeutical targets in neurofibromatosis type 1. Acta Neuropathol. 2019;137(3):521–5. https://doi.org/10.1007/s00401-019-01960-x.

12. Li H, Durbin R. Fast and accurate short read alignment with Burrows-Wheeler Aligner. Bioinformatics. 2009;25(14):1754–60. https://doi.org/10.1093/bioinformatics/btp324.

13. Terra. 1st ed. Sebastopol: O’Reilly Media; 2020.

14. Huang DW, Sherman BT, Lempicki RA. Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. Nat Protoc. 2009;4(1):44–57. https://doi.org/10.1038/nprot.2008.211.

15. Li Z, Jin Y, Zou Q, Shi X, Wu Q, Lin Z, et al. Integrated genomic and transcriptomic analysis suggests KRT18 mutation and MTAP are key genetic alterations related to the prognosis between astrocytoma and glioblastoma. Ann Transl Med. 2021;9(8):713. https://doi.org/10.21037/atm-21-1137.

16. Dantas-Barbosa C, Lesluyes T, Loarer FL, Chibon F, Treilleux I, Coindre JM, et al. Expression and role of TYRO3 and AXL, as potential therapeutical
targets in leiomyosarcoma. Br J Cancer. 2017;117(12):1787–97. https://doi.org/10.1038/bjc.2017.354.

17. Han J, Tian R, Yong B, Luo C, Tan P, Shen J, et al. Gas6/Axl mediates tumor cell apoptosis, migration and invasion and predicts the clinical outcome of osteosarcoma patients. Biochem Biophys Res Commun. 2013;435(3):493–500. https://doi.org/10.1016/j.bbrc.2013.05.019.

18. Kedage V, Selvaraj N, Nicholas TR, Budka JA, Plotnik JP, Jerde TJ, et al. An interaction with ewing’s sarcoma breakpoint protein EWS defines a specific oncogenic mechanism of ETS factors rearranged in prostate cancer. Cell Rep. 2016;17(5):1289–301. https://doi.org/10.1016/j.celrep.2016.10.001.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.