CASE REPORT

Two cases of primary supratentorial intracranial rhabdomyosarcoma with *DICER1* mutation which may belong to a "spindle cell sarcoma with rhabdomyosarcoma-like feature, *DICER1* mutant"

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Abstract

Rhabdomyosarcoma is the most common soft-tissue sarcoma affecting children and adolescents. It is defined as a malignant neoplasm characterized by morphologic, immunohistochemical, ultrastructural, or molecular genetic evidence of primary skeletal muscle differentiation, usually in the absence of any other pattern of differentiation. Primary intracranial rhabdomyosarcoma (PIRMS) is an extremely rare neoplasm, with only 60 cases reported in the literature, and generally has poor prognosis with an overall survival of only 9.1 months. The *DICER1* gene encodes an RNA endoribonuclease that plays a key role in gene expression regulation through the production of small RNAs. Herein, we report 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 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.

Keywords Rhabdomyosarcoma · DICER1 · SCS-RMSlike-DICER1 · Supratentorial · Hematoma

Introduction

Rhabdomyosarcoma is defined as a malignant neoplasm that shows morphologic, immunohistochemical, ultrastructural, or molecular genetic evidence of primary skeletal muscle differentiation, usually in the absence of any other pattern of differentiation. Rhabdomyosarcoma is the most common soft-tissue sarcoma in children and adolescents and

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is classified into two major subtypes, namely, embryonal and alveolar, based on distinct clinicopathological features, genetic alterations, and prognosis. The most common site of involvement is the head and neck region (~40%; including the nasal cavity, parameninges, and orbit), followed by the urogenital tract (~25%; most commonly in the paratesticular region in adolescents), and the extremities (~20%). Primary intracranial rhabdomyosarcoma (PIRMS) is an extremely rare neoplasm, with only 60 cases reported in the literature, and generally has poor prognosis, with an overall survival of only 9.1 months [1]. However, several recent studies have reported prolonged survival with the use of multi-modality treatment [1–3].

The *DICER1* gene, which is located at 14q32.13, encodes an RNA endoribonuclease that plays a key role in gene expression regulation through the production of small RNAs [4]. *DICER1* syndrome (OMIM: 601200) is a rare genetic disorder that predisposes individuals to the development of tumors, both benign and malignant, including pleuropulmonary blastoma, cystic nephroma, multinodular goiter, ovarian Sertoli-Leydig cell tumor, embryonal rhabdomyosarcoma, and other rare tumor entities. This disease primarily affects individuals in the pediatric and adolescent age range. The two-hit hypothesis based on the second somatic mutations in the RNase IIIb domain of the *DICER1* gene has been proposed as a mechanism responsible for causing rare tumors [5].

Genetically, alveolar rhabdomyosarcoma usually carries specific chromosomal translocations that produce PAX3- or PAX7-FOXO1 fusion genes, whereas embryonal rhabdomyosarcoma is commonly characterized by loss of heterozygosity at 11p15.5 and gains of chromosomes 2, 8, and 12 in varying combinations [6, 7]. The *DICER1* mutation in rhabdomyosarcoma is reported in embryonal rhabdomyosarcoma and originates within the urogenital tract, especially the uterine cervix, which is an uncommon site for rhabdomyosarcoma [8–14]. Histological features of rhabdomyosarcoma of the uterine cervix included cartilaginous nodules in nearly half of the cases [15].

Herein, we reported two cases of supratentorial PIRMS with somatic *DICER1* mutation that caused intracerebral hematoma in a 10-year-old girl (patient #1) and a 29-year-old male (patient #2). The former case has followed a long-term course of 5 years.

Clinical summary

Patient #1 is a 10-year-old girl who was referred to the hospital because of sudden onset of severe headache and upper extremity paralysis. She experienced vomiting and dressing apraxia 2 months prior and had surgery for evacuation of hematoma in the right parietal lobe. Upon admission to our institution, cranial CT and magnetic resonance imaging (MRI) revealed a hematoma in the same area, measuring 6.0 cm × 6.0 cm × 6.0 cm, with perifocal edema (Fig. 1a, b, c). A neoplasm was identified during the second operation for evacuation of hematoma, and the initial pathologic diagnosis was malignant tumor, NOS. Whole-body CT scan, FDG-PET scan, and bone marrow biopsy results were normal. She was administered with vincristine and focal radiotherapy on suspicion of primitive neuroectodermal tumor; treatment was later changed to a stronger chemotherapeutic regimen. Recurrence occurred 2 months later, and tumor excision was performed. Combined radiotherapy (50.4 Gy) and multi-agent chemotherapy comprising doxorubicin, etoposide, and cisplatin were given based on the final diagnosis of rhabdomyosarcoma and the enhanced lesion in the excisional cavity on MRI. Positive therapeutic response was observed for 41 months until the second recurrence. The tumor was incompletely excised during the subsequent recurrence because of infiltration of a large vein; therefore, gamma knife therapy was initiated. Disease recurrence adjacent to the resection cavity was observed on follow-up imaging at 16 months after the second tumor resection. The third tumor resection was recently performed and confirmed the recurrence of rhabdomyosarcoma. At 68 months from the initial therapy, the patient is alive under treatment.

Patient #2 is a 29-year-old male who presented right-sided hemiparesis. Brain CT scan showed a 7.5 cm left parietal lobe mass with internal bleeding that causes ventricular rupture (Fig. 1d). MRI revealed that the mass appeared hypo-intense on T1-weighted images and hyper-intense on T2-weighted images (Fig. 1e, f), and heterogeneously enhancement on contrast enhanced using gadolinium. The tumor was removed completely by craniotomy. The patient received chemoradiotherapy with vincristine, focal radiation of 32.4 Gy, and craniospinal radiation of 23.4 Gy. Afterwards, the patient underwent VAC chemotherapy comprising vincristine, actinomycin D, and cyclophosphamide, and alive with no evidence of recurrence at 11 months after disease onset.

Pathological findings

Microscopic features of the two cases were similar; results showed sarcomatous neoplasms that were highly cellular with brisk mitotic activity and admixed with large pools of hemorrhage. The tumor cells were composed of diffuse proliferation of immature spindle and ovoid cells that were arranged in fascicular and storiform patterns (Fig. 2a, h). Individual cells exhibited marked cytologic atypia with pleomorphic nuclei, and multi-nucleated giant cells were often observed (Fig. 2b, j). Focal clusters and scattered rhabdomyoblasts, characterized by large round
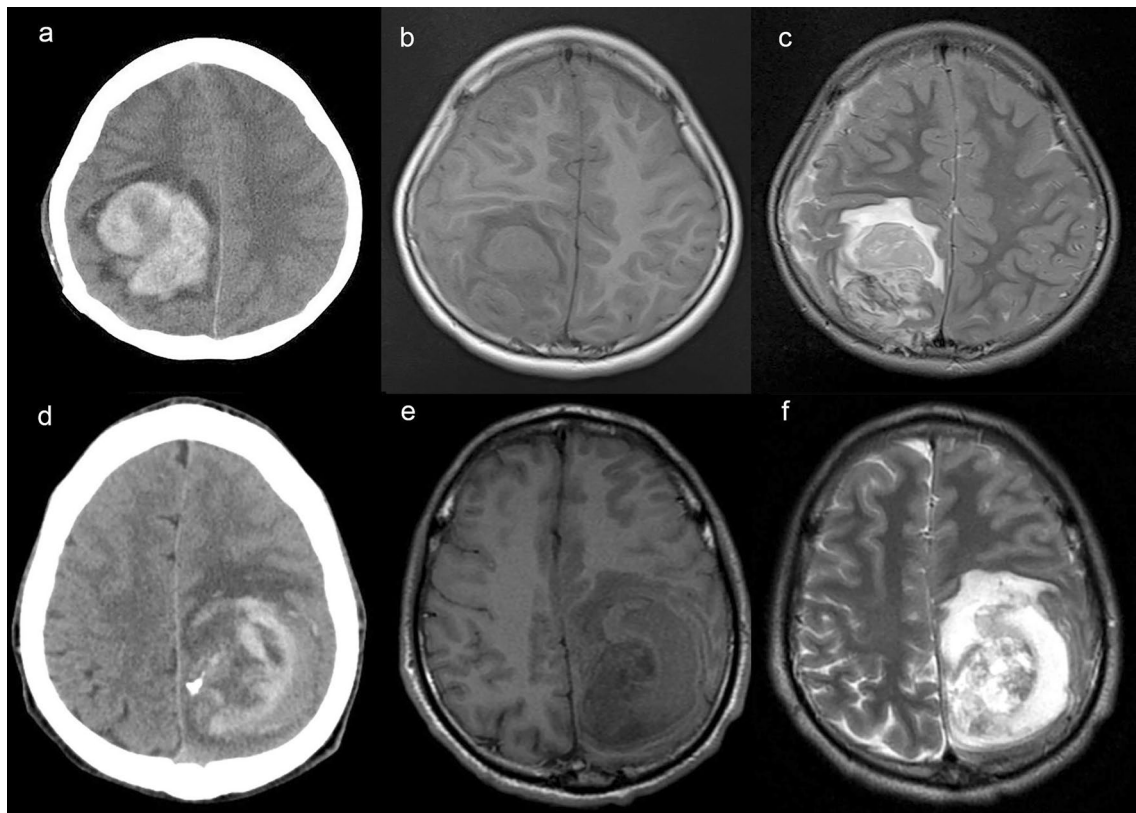
Fig. 1 Radiological images of intracranial rhabdomyosarcoma; patient #1 (**a–c**) and patient #2 (**d–f**). The hematoma in the right parietal lobe (measuring 6.0 cm×6.0 cm×6.0 cm) with edema was revealed on CT (**a**), and was observed to be iso-intense on the T1-weighted image (**b**) and hyper-intense on the T2-weighted image (**c**), suggesting acute stage of hematoma. A left parietal lobe mass with a diameter of 7.5 cm (**d**). MRI revealed that the mass was hypo-intense on the T1-weighted image (**e**) and the hyper-intense on T2-weighted image (**f**), suggesting acute stage of hematoma
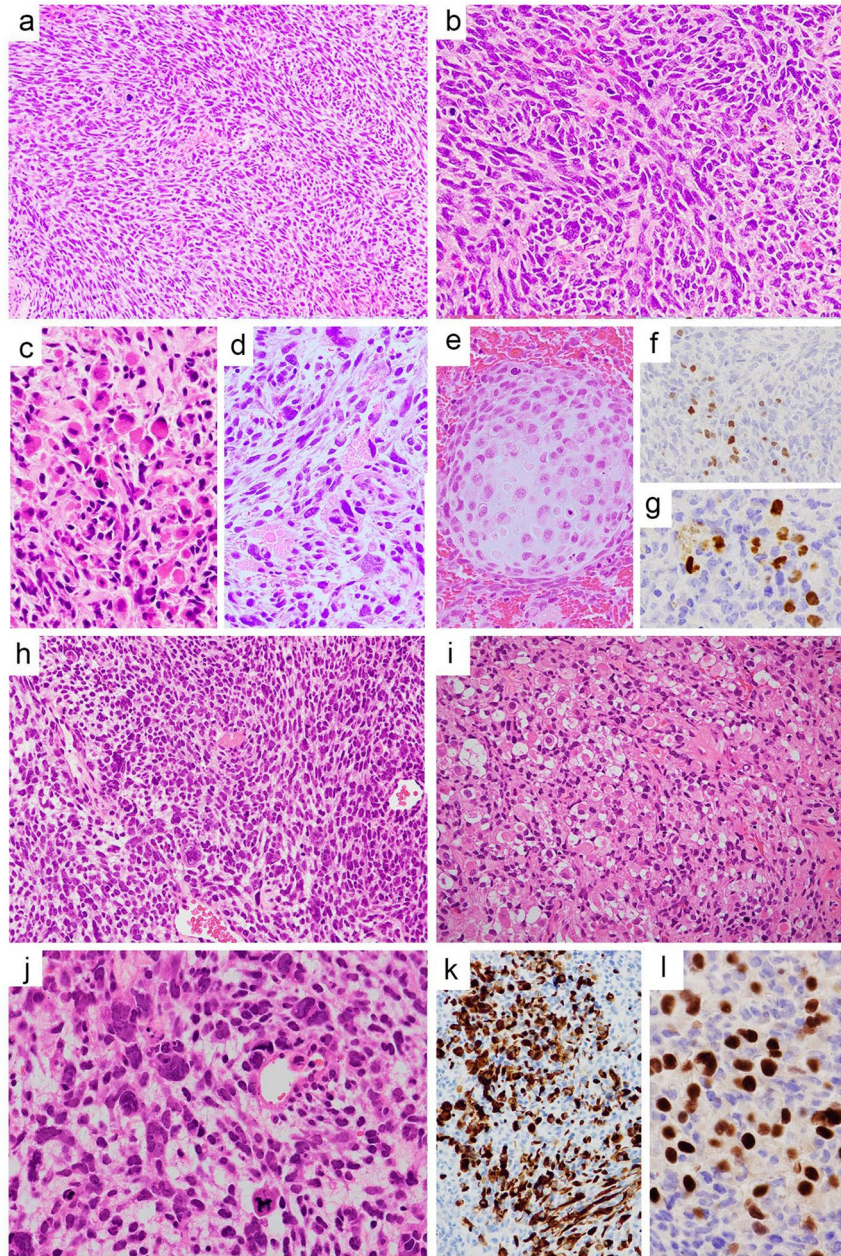
or oval eosinophilic cells with eccentric nuclei and abundant eosinophilic granular cytoplasm, were also noted (Fig. 2c, i). Patient #1 showed tumor cells with eosinophilic cytoplastic globules near the site of hemorrhage (Fig. 2d). Patient #1 showed myxoid area and a small focus of cartilaginous differentiation (Fig. 2e). Reticulin staining revealed abundant intercellular basement membrane deposition. Immunohistochemistry results showed that the tumor cells were diffusely and strongly positive for vimentin. Focal positivity for muscle markers, including desmin (Fig. 2f, k), HHF-35, myogenin (Fig. 2g, l), and myoglobin, were apparent in tumor cells with eosinophilic cytoplasm. Myoglobin staining was highly specific to rhabdomyoblast. Immunoreactivity for α-SMA varied; signals were scattered in patient #1 and were present in 30% of tumor cells in patient #2. INI1 expression was retained. Staining for S-100 protein, GFAP, synaptophysin, EMA was negative. In both cases, the sarcomas showed differentiation from undifferentiated cells to rhabdomyoblast; therefore, the tumors were histologically diagnosed as rhabdomyosarcoma.

Molecular analysis

Somatic *DICER1* and *TP53* mutations

DNA was extracted from fresh frozen tumor and non-tumor brain tissues in patient #1 and formalin-fixed and paraffin-embedded (FFPE) tumor tissues in patient #2 using DNeasy Blood and Tissue Kit (Qiagen, Tokyo, Japan) and GeneRead DNA FFPE Kit (Qiagen, Tokyo, Japan), respectively. Sanger sequencing of the RNase IIIb domain of DICER1 was performed using the following primer sets: forward, 5′-CCC CTCAGATTGTTACCAGC-3′; reverse, 5′-CGTTTTGAA CAGCACTAACCTC-3′ and forward, 5′-TCTGAGGAG GATGAAGAGAAAG-3′; reverse 5′-CGTTTTGAACAG CACTAACCTC -3′. As for tumor, DNA extracted from patient #1 target sequencing of all coding exons of the 93 selected brain tumor-related genes (Supplementary Table 1) was performed as previously described [16].

Non-synonymous mutations in the DICER1 RNase IIIb domain were detected in both tumor samples. These mutations included c.5425G>A, p.G1809R in patient #1 and
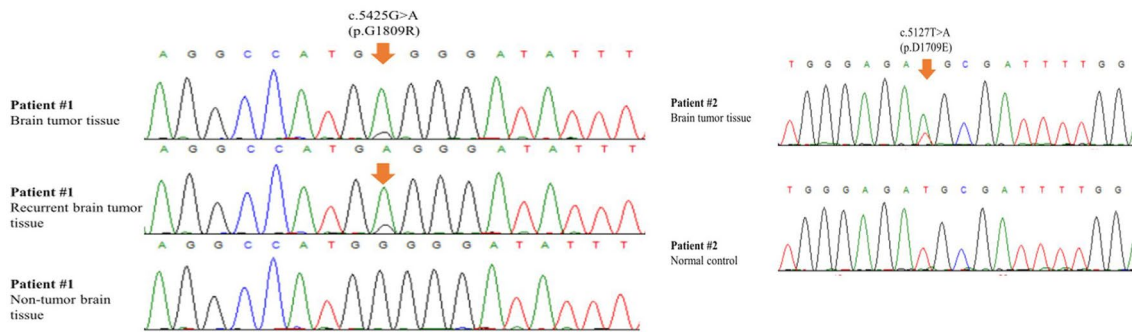
◀**Fig. 2** Microscopic and immunohistochemical analyses of intracranial rhabdomyosarcoma; patient #1 (**a**–**g**) and patient #2 (**h**–**l**). Diffuse proliferation of immature spindle cells arranged in a fascicular pattern (**a**, **h**). At high magnification, the tumor cells exhibited pleomorphic nuclei and eosinophilic cytoplasm (**b**, **j**). Frequent mitosis and scattered multi-nucleated giant cells were observed. Focal clusters of rhabdomyoblasts characterized by eccentric nuclei and abundant eosinophilic granular cytoplasm were noted (**c**, **i**). Patient #1 showed tumor cells with eosinophilic cytoplastic globules (**d**) and a small focus of cartilaginous differentiation (**e**). Focal positivity for desmin in the cytoplasm of tumor cells (**f**, **k**). Focal positivity for myogenin in the nuclei of tumor cells (**g**, **l**). *DICER1* RNase IIIb mutations in PIRMS (**m**). c.5425G>A, p.G1809R somatic mutation in patient #1. The same mutation was detected during both onset and recurrence. The c.5127T>A, p.D1709E mutation in patient #2

c.5127T>A, p.D1709E in patient #2 (Fig. 2m). In patient #1, no variant was detected in all coding exons of *DICER1* in non-tumor control tissues. In patient #2, only tumor DNA was available, while the non-tumor control sample was not available. The somatic mutation c.569C>T, p.P190L in TP53 was also detected in patient #1.

Discussion

Recently, Koelsche et al. proposed a new entity of intracranial sarcoma, "spindle cell sarcoma with rhabdomyosarcoma-like features, *DICER1* mutant (SCS-RMSlike-DICER1)'' based on the result of methylation analysis of 22 primary intracranial sarcoma cases [17]. As represented by the nomenclature, histologically rhabdomyoblasts or rhabdomyoblast-like cells were observed in all cases and most tumor cells were spindle shape, although supplier diagnosis of these 22 cases were variable including sarcoma NOS (*n* = 15), malignant tumor NOS (*n* = 2), embryonal rhabdomyosarcoma (*n* = 1), gliosarcoma (*n* = 1), glioblastoma (*n* = 1), mesenchymal chondrosarcoma (*n* = 1), and PNET (*n* = 1) [17]. *DICER1* hot spot mutations were detected in 21/22 cases and TP53 mutations in 12/22 cases [17]. Following this report, however, Lee et al. presented another cases of primary intracranial sarcoma which display the same molecular characteristics as "SCS-RMSlike-DICER1″ but different morphological characteristics: they harbor *DICER1* mutation and "SCS-RMSlike-DICER1" methylation pattern, but were morphologically characterized as pleomorphic rather than predominantly spindled or round cell with myogenic differentiation [18]. Accordingly, the authors proposed a broader term "Primary intracranial sarcoma, *DICER1*-mutant". Thus, the definition of the newly proposed entity of intracranial sarcomas with *DICER1* mutation, whether or not these tumors truly form a single entity despite the histological diversity, remains controversial.

In the present study, we reported two cases of supratentorial PIRMS harboring *DICER1* mutation. In both cases,

the tumors were characterized by immature spindle and ovoid cells with polymorphism and multi-nucleated giant cells, and showed clear skeletal muscle differentiation based on morphological and immunohistochemical analyses. Differential diagnosis, including other brain tumors that occasionally showed skeletal muscle components, such as medulloblastoma, atypical teratoid/rhabdoid tumor, gliosarcoma, anaplastic meningioma, and germ cell tumor, were excluded from the site and the immunohistochemistry results. The tumor samples from the present two cases harbored somatic hot spot mutations within the DICER1 RNase IIIb domain, namely, p.G1809R (c.5425G>A) in patient #1 and p.D1709E (c.5127T>A) in patient #2; these mutations were previously described as somatic mutations in intracranial sarcoma, pleuropulmonary blastoma, cystic nephroma, Sertoli–Leydig cell tumors, rhabdomyosarcoma of the ovary, and other *DICER1*-related neoplasms (Table 1) [4, 10, 12, 17, 19]. For patient #2, only tumor tissue was available without a paired normal sample; thus, the somatic versus germ line status of the identified *DICER1* mutation could not be determined. On the other hand, the mutation in patient #1 was confirmed to be somatic. As recognized in previous reports, primary intracranial sarcomas with *DICER1* mutation showed a diverse histologic spectrum, ranging from cases presenting immature cells to cases with distinct differentiation into skeletal muscle; latter cases were similar to the features observed in our two cases.

The clinical features and behaviors of intracranial sarcoma harboring *DICER1* mutations have not been previously investigated because of limited cases and follow-up sessions that are insufficient to derive reliable conclusions. In the present study, both cases were young and showed supratentorial tumors causing intracerebral hematoma. In 28 cases of intracranial sarcoma with *DICER1* mutations, including our two cases, the age distribution ranged from 0 to 76 years with a median age of 13 years, and the gender distribution was almost equal between females (*n* = 15) and males (*n* = 13) [17, 18, 20, 21]. A total of 26 cases had supratentorial tumor locations, except for two cases, in which the tumors were located in the cerebellopontine angle and cerebellum. Intratumoral hemorrhage was observed in all six cases in which image finding were mentioned, and it is considered that there is a feature easy to accompany bleeding. Previous studies have reported that PIRMS is commonly seen in infants and young children and the most common site of involvement in children is the cerebellum unlike adults in whom a supratentorial predilection [22–24]. In 60 cases of PIRMS, the age distribution ranged from 0 to 68 years with a median age of 18 years; 70% of cases were less than 18 years old, and M:F ratio was 1.3:1. The tumor located in supratentorial in 32, infratentorial in 20, supra-infratentorial in 3, and pineal are in 5 [1–3, 17, 22–36]. Intracranial hemorrhage,

Table 1 Case list of intracranial sarcoma with *DICER1* mutation

Case	Age/Sex	Location	Dicer1 mutation	TP53 mutation	Supplier diagnosis	Rhabdomyoblast	Cartilaginous nodule	Immunohistochemistry			References
								Desmin	Myogenin	α-SMA	
1	–/M	CNS not otherwise specified	c.5425G>A; p.G1809R	Not detected	Primitive neuroectodermal tumor	Focal	Absent	NA	NA	NA	Koelsche et al. [17]
2	8/F	Fronto-parietal lobe	c.5428G>C; p.D1810H	Not detected	Glioblastoma	Sparse	Absent	Sparse	Neg	Sparse	Koelsche et al. [17]
3	12/F	Frontal lobe	c.1870C>T; p.R624X; c.5438A>C; p.E1813A	Not detected	Mesenchymal chondrosarcoma	Sparse	+	Sparse	Focal	Patchy	Koelsche et al. [17]
4	0/F	Cerebellum	c.4999G>T; p.E1667X; c.5425G>A; p.G1809R	c.321_322insTAAC; p.S108_S109delinsX	Embryonal rhabdomyosarcoma	Present	Absent	Focal	Focal	Focal	Koelsche et al. [17]
5	9/F	Parietal lobe	c.5425G>A; p.G1809R	Not detected	Malignant tumor NOS	Focal	Absent	Focal	Focal	Focal	Koelsche et al. [17]
6	9/F	Parieto-occipital lobe	c.5113G>A; p.E1705K	Not detected	Malignant tumor NOS	Sparse	Absent	NA	NA	NA	Koelsche et al. [17]
7	44/M	Leptomeningeal supratentorial	c.5437G>A; p.E1813K	c.86C>A; p.A29D	Sarcoma NOS	Sparse	Absent	Focal	Neg	Focal	Koelsche et al. [17]
8	6/F	Frontal lobe	c.5437G>A; p.E1813K	Not detected	Sarcoma NOS	NA	NA	NA	NA	NA	Koelsche et al. [17]
9	6/M	Fronto-temporal lobe	c.5163T>A; p.Y1721X; c.5439G>T; p.E1813D	Not detected	Sarcoma NOS	NA	NA	NA	NA	NA	Koelsche et al. [17]
10	76/F	Parieto-occipital lobe	c.5437G>C; p.E1813Q	Not detected	Sarcoma NOS	Sparse	Absent	Sparse	Neg	Sparse	Koelsche et al. [17]
11	5/M	Parietal lobe	c.5113G>A; p.E1705K	c.421C>T; p.R141C	Sarcoma NOS	Sparse	Absent	Neg	Neg	Focal	Koelsche et al. [17]
12	6/M	Fronto-parietal lobe	c.5113G>A; p.E1705K	c.347G>A; p.R116Q	Sarcoma NOS	Sparse	Absent	Focal	Neg	Patchy	Koelsche et al. [17]
13	6/M	Parietal lobe	c.5113G>A; p.E1705K; c.5729G>T; p.R1910Q	c.335G>A; p.G112D; c.448C>T; pR150W	Sarcoma NOS	Sparse	Absent	Sparse	Neg	Sparse	Koelsche et al. [17]

Table 1 (continued)

Case	Age/Sex	Location	Dicer1 mutation	TP53 mutation	Supplier diagnosis	Rhabdomyoblast	Carti-laginous nodule	Immunohistochemistry			References
								Desmin	Myogenin	α-SMA	
14	6/F	Parietal lobe	c.5104C>T; p.Q1702X / c.5113G>A; p.E1705 K	c.193G>T; p.V65L / c.338G>A; p.G113D	Sarcoma NOS	Sparse	Absent	Sparse	Neg	Patchy	Koelsche et al. [17]
15	6/M	Frontal lobe	c.5113G>A; p.E1705 K	c.273G>A; p.W91X	Sarcoma NOS	Sparse	Absent	Focal	Sparse	Patchy	Koelsche et al. [17]
16	3/F	Parietal lobe	c.5425G>A; p.G1809R	c.334G>A; p.G112S	Sarcoma NOS	Present	Absent	Focal	Focal	Focal	Koelsche et al. [17]
17	5/F	Parieto-tempotal lobe	c.5125G>A; p.D1709 N	c.434G>T; p.C145F	Sarcoma NOS	Sparse	Absent	Neg	Neg	Patchy	Koelsche et al. [17]
18	2/F	Fronto-temporal lobe	c.3313_3314insCA; p.K1105 fs / c.5125G>A; p.D1709 N	Not detected	Sarcoma NOS	Focal	Absent	Sparse	Neg	Sparse	Koelsche et al. [17]
19	5/M	Frontal lobe	c.5113G>A; p.E1705 K	c.329G>C; p.R110P	Sarcoma NOS	Focal	Absent	Sparse	Neg	Focal	Koelsche et al. [17]
20	10/F	Fronto-parietal lobe	c.5437G>A; p.E1813 K	c.338G>A; p.G113D	Sarcoma NOS	Focal	Absent	Neg	Neg	Sparse	Koelsche et al. [17]
21	9/M	Cerebellopontine angle	c.5113G>A; p.E1705 K	c.193G>A; p.V65 M	Sarcoma NOS	Absent	Absent	Sparse	Neg	Patchy	Koelsche et al. [17]
22	20/M	Frontal lobe, left	c.5437G>A; p.E1813 K	c.713G>T; p.C238F	NA	Absent	Absent	Patchy	Neg	Neg	Lee et al. [18]
23	11/F	Parietal lobe, left	c.5425G>A; p.G1809R / c.2436+1G>A; p.Q812 fs	c.272G>A; p.W91*	NA	Absent	Absent	Patchy	Neg	Neg	Lee et al. [18]
24	19/M	Frontal lobe, right	c.5113G>A; p.E1705 K / c.5365-1G>A; p.E1788 fs	c.772G>A; p.E258 K	NA	Absent	+	Focal	Neg	Neg	Lee et al. [18]
25	12/F	Fronto-parietal lobe, right	c.1870C>T; p.R624X / c.5438A>C; p.E1813A	NA	NA	NA	+	+	+	NA	Das et al. [20]

Table 1 (continued)

Case	Age/Sex	Location	Dicer1 mutation	TP53 mutation	Supplier diagnosis	Rhabdomyoblast	Cartilaginous nodule	Immunohistochemistry			References
								Desmin	Myogenin	α-SMA	
26	4/M	Temporal lobe, left	c.5125G>A; p.D1709 N del(14)(q32.13q32.2)	c.844C>T; p.R282 W	High-grade spindle-cell sarcoma with myogenous differentiation	Absent	NA	Focal	NA	NA	Kock et al. [21]
27	10/F	Parietal lobe	c.5425G>A; p.G1809R	c.569C>T, p.P190L	Malignant tumor NOS, Rhabdomyosarcoma	Sparse	+	Focal	Focal	Patchy	This case
28	29/M	Parietal lobe	c.5127T>A; p.D1709E	NA	Rhabdomyosarcoma	Focal	Absent	Focal	Focal	Focal	This case

M male, *F* female, *NA* not available

not usually seen in CNS sarcoma, was also previously described in PIRMS [1, 22, 26, 27, 36]. PIRMS has poor prognosis, with an overall survival of only 9.1 months; however, several recent studies reported prolonged survival with the use of multi-modality treatment [1–3]. The two patients in this study multimodal treatment, including surgery, chemotherapy, and radiation, well worked.

In summary, we reported two cases of PIRMS harboring *DICER1* mutations. Although methylation profiling was not performed, both cases shared clinical and pathological characteristics in common with recently proposed methylation entity "SCS-RMSlike-DICER1" [17]. Our cases provide further evidence of the link between primary intracranial sarcoma and *DICER1* mutation which may form a distinct entity.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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