A case of primary CNS embryonal rhabdomyosarcoma with PAX3-NCOA2 fusion and systematic meta-review

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Abstract

Purpose Primary central nervous system (CNS) rhabdomyosarcoma is a rare mesenchymal tumor predominantly seen in children and associated with a poor outcome. We report a case of primary CNS rhabdomyosarcoma with PAX3-NCOA2 fusion and present a systematic meta-review of primary CNS rhabdomyosarcoma to characterize this rare tumor.

Methods We present the case of a 6-year-old boy with primary CNS rhabdomyosarcoma in the posterior fossa. In a systematic meta-review, we compare the demographic data of primary CNS rhabdomyosarcoma with data of rhabdomyosarcoma at all sites from the SEER database and analyze clinical factors associated with survival outcome.

Results Our patient underwent gross total resection and received vincristine, actinomycin-D, cyclophosphamide with early introduction of concurrent focal radiation and remained alive with no evidence of disease for 2 years after the end of therapy. Histopathological review revealed embryonal-type rhabdomyosarcoma, and whole-transcriptome analysis revealed PAX3 (EX6)-NCOA2 (EX12) fusion. In all, 77 cases of primary CNS rhabdomyosarcoma were identified through the meta-review. The demographic data of primary CNS rhabdomyosarcoma were similar to data of rhabdomyosarcoma at all sites. Overall and event-free survival outcomes were available for 64 and 56 patients, respectively, with a 3-year OS of 29.0% and a 3-year EFS of 25.7%. The group that received trimodal treatment exhibited better survival outcomes, with a 3-year OS of 57.4% and a 3-year EFS of 46.3%.

Conclusions Primary CNS rhabdomyosarcoma shares common histological, molecular, and demographic features with non-CNS rhabdomyosarcoma. A trimodal treatment approach with early introduction of radiation therapy may result in favorable survival outcomes.

Keywords Primary CNS rhabdomyosarcoma · PAX3-NCOA2

Introduction

The first cases of primary central nervous system (CNS) rhabdomyosarcoma were described in the 1950s [1, 2]. The biology is not well understood, and whether this tumor is a rare variation of other CNS tumors or the CNS is a rare location of rhabdomyosarcoma has been debated [3, 4]. In the WHO 2016 classification of CNS tumors, primary CNS rhabdomyosarcoma is characterized by histological features of undifferentiated small cells and positive immunostaining...
for desmin and myogenin [5]. Generally, the prognosis of primary CNS rhabdomyosarcoma is poor, although successfully treated cases have been reported [6, 7].

Recently, molecular characterization of this rare tumor has revealed several features shared with non-CNS rhabdomyosarcoma. Multiple groups have reported cases of primary CNS rhabdomyosarcoma that harbor a DICER1 mutation, which is commonly seen in embryonal rhabdomyosarcoma at genitourinary sites [8–11]. PAX3-NCOA2 fusion in non-CNS rhabdomyosarcoma was also reported in a case of alveolar rhabdomyosarcoma of the pineal gland [12].

Here, we report the case of a 6-year-old boy with histologically defined embryonal rhabdomyosarcoma in the posterior fossa that was positive for PAX3-NCOA2 fusion and negative for DICER1 mutations. We also conducted a systematic meta-review of primary CNS rhabdomyosarcoma to better characterize the clinical features and treatment approach of this tumor.

Materials and methods

DNA extraction, Sanger sequencing, and whole-exome sequencing

The genomic study was approved by the institutional review board, and parental consent was obtained prior to the study. Using a QIAamp DNA Mini Kit (QIAGEN), germline DNA and tumor genomic DNA were extracted from peripheral blood during remission and fresh-frozen tumor samples at diagnosis, respectively. Sanger sequencing of DICER1 was performed and the sequence from exon 2 to exon 27 was compared with a known wild-type sequence, as described in a previous report [13]. For whole-exome sequencing, library construction was performed with a SureSelect Human All Exon Kit v6 (Agilent Technology). Enriched fragment libraries were then sequenced in a HiSeqX system (Illumina). Sequence alignment and detection of gene mutations and structural variations were performed using Genomon v.2.6.3 (https://github.com/Genomon-Project/).

RNA extraction and whole-transcriptome sequencing

Total RNA was extracted from tumor cells at diagnosis using an RNAsy Mini Kit (QIAGEN). For paired-end whole-transcriptome sequencing, we used a NEBNext rRNA Depletion Kit (Human/Mouse/Rat) with RNA Sample Purification Beads and the NEBNext Ultra II Directional RNA Library Prep with Sample Purification Beads (NEW ENGLAND Biolabs) followed by paired-end cluster generation and sequencing using DNBSEQ-T7 (BGI). Sequence alignment and structural variation calling were performed using the Genomon pipeline.

Review of primary CNS rhabdomyosarcoma in the literature

We searched PubMed for articles published in English and without time restrictions. Key words were “central nervous system” or “cerebral” or “cerebellar” or “brain” or “spine”, and “rhabdomyosarcoma” and “primary”. Studies unrelated to CNS tumors and those that discussed CNS metastasis of rhabdomyosarcoma originating from other sites were excluded. Articles that discussed primary CNS rhabdomyosarcoma were reviewed in detail. Rhabdomyosarcoma arising from the meninges was excluded. Cases that were not found by the initial search and that were described in the reviewed articles were included if appropriate. In the survival analysis, only cases with descriptions of relevant information, i.e., time from diagnosis to death, time from diagnosis to relapse, and treatment modalities at the first diagnosis, were analyzed. The process of inclusion/exclusion is detailed in the PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow chart (Fig. 2).

Surveillance, epidemiology, and end results (SEER) database

To compare data of primary CNS rhabdomyosarcoma cases in the literature to rhabdomyosarcoma data of a large cohort, we used the SEER database. The database information and software that were included in the analysis are described below. Surveillance, epidemiology, and end results (SEER) program (www.seer.cancer.gov) SEER*Stat Database: Incidence—SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, November 2018 Sub (1975–2017 varying)—Linked To County Attributes—Total U.S., 1969–2017 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2019, based on the November 2018 submission. Surveillance Research Program, National Cancer Institute SEER*Stat software (seer.cancer.gov/seerstat) version 8.3.9.

Statistical analysis

The log-rank test and Kaplan–Meier survival analysis were performed to identify prognostic and predictive factors of survival outcome. R package version 3.5.0. was used for the analysis.
Results

Our case

A previously healthy 6-year-old boy presented with a one-month history of ataxia and gait disturbance. Physical examination revealed mild dysmetria of the left side and no findings suggestive for cancer predisposition. His family history was not significant for cancer or cancer predisposition. An MRI of the brain revealed a heterogeneously enhanced T1 hypointense, T2 isointense lesion measuring 53 mm in diameter at the left pontine-cerebellar angle and enlarged ventricles. MRI of the spine was negative for metastasis and disseminated disease. Selective catheter embolization of the left anterior inferior cerebellar artery (AICA) that was feeding the tumor was performed as previously described [14]. Then, the patient underwent gross total resection (GTR) of the tumor.

Histopathological review of the tumor revealed a mixture of small round cells and spindle cells. Immunostaining was positive for desmin, myogenin and MyoD, which is consistent with the diagnosis of embryonal-type rhabdomyosarcoma. Fluorescence in situ hybridization (FISH) and PCR for the PAX3/7 genes were performed to detect fusions with FOXO1, which are characteristic of alveolar-type rhabdomyosarcoma, and the results were negative. To verify the primary tumor site, chest CT, abdominal MRI, and whole-body PET-CT were performed and revealed no evidence of tumors outside the CNS. Sanger sequencing of DICER1 and whole-exome sequencing revealed no pathological mutations, whereas whole-transcriptome analysis showed the PAX3-NCOA2 fusion at the 5' end of exon 6 of PAX3 (NM_181461) and the 3' end of exon 12 of NCOA2 (NM_1321712). This fusion gene was verified by RT-PCR and Sanger sequencing (Fig. 1).

Four weeks after GTR, vincristine, actinomycin-D, cyclophosphamide (VAC) chemotherapy was initiated. Within two weeks from the start of chemotherapy, focal radiation consisting of a 45 Gy photon beam in 30 fractions delivered to the tumor bed was initiated; actinomycin-D was omitted during radiation therapy. VAC therapy was continued for 39 weeks, which is common in intermediate-risk non-CNS rhabdomyosarcoma. Total doses of 42 mg/m² vincristine, 0.54 mg/kg actinomycin-D, and 30.8 g/m² cyclophosphamide were administered according to COG D9803 protocol without any grade III or IV nonhematological adverse events. Through the course of treatment, the patient’s activity level was maintained, and he had a Lansky performance score of 90. MRI performed at 26 months from the end of therapy revealed no evidence of disease.

Clinical features of primary CNS rhabdomyosarcoma in the literature

We identified 55 articles and 77 cases of primary CNS rhabdomyosarcoma, including our patient (Fig. 2, Supplementary Table 1). Diagnosis was predominantly in children, but cases in adults were also found. A similar pattern of age distribution was observed in the large cohort of 5013 cases of rhabdomyosarcoma at all sites from the SEER database, which included only eight CNS cases (Fig. 3A). The male to female ratio was 1.3 to 1 for both primary CNS rhabdomyosarcoma and rhabdomyosarcoma at all sites. The anatomical distribution of primary CNS rhabdomyosarcoma showed no predilection toward the supratentorial or posterior fossa (Fig. 3B). The histological subtype of primary CNS rhabdomyosarcoma was described in 27 cases, with 19 (70.4%) cases of embryonal, 6 (22.2%) cases of alveolar, and 2 (7.4%) cases of the pleomorphic type. In the SEER database cohort, histological descriptions were found in 3598 cases, with 1883 (52.3%) cases of embryonal, 1100 (30.6%) cases of alveolar, 490 (13.6%) cases of pleomorphic, and 125 (3.5%) cases of the spindle cell type. Molecular characterization of primary CNS rhabdomyosarcoma was described in seven cases, five (three embryonal, two unspecified histology) of which had DICER1 mutations and two (one embryonal and one alveolar histology) of which had PAX3-NCOA2 fusions.

To clarify prognostic and predictive factors of survival, we examined age, sex, disease dissemination at diagnosis, treatment, number of treatment modalities, extent of surgical resection, extent of radiation and chemotherapy regimens. The log-rank test revealed that disseminated disease was a poor prognostic factor and that non-GTR and fewer than three treatment modalities were poor predictive factors (Table 1). All 12 long-term survivors (>24 months) who were treated with trimodal therapy of surgery, radiation and chemotherapy, received radiation prior to or concurrently with chemotherapy. The time from surgery to radiation was available in five cases and ranged from one to six weeks with a median of four weeks. Kaplan–Meier curves were generated based on available overall survival data of 64 patients and event-free survival data of 56 patients and showed a 3-year OS of 29.0% (95% confidence interval (CI) 18.4–45.6%) and a 3-year EFS of 25.7% (95% CI 15.3–43.1%) (Fig. 4). The group that received trimodal treatment yielded better survival outcomes than the group received fewer than three treatment modalities, with a 3-year OS of 57.4% (95% CI 40.2–82.1%, p-value < 0.0001) and a 3-year EFS of 46.3% (95% CI 28.9–74.1%, p-value < 0.0001).
Fig. 1 Case of primary CNS rhabdomyosarcoma with PAX3-NCOA2 fusion. A MRI revealed a left cerebellomedullary angle tumor with a low T1 signal and heterogeneous weak contrast enhancement. Histopathological review of the tumor revealed. B Small round cell tumor. C Spindle-shaped cells. D Desmin( +). E MyoD1( +). F Ki-67 index of 70% and FOXO1 translocation-negative. G Sanger sequencing verified the presence of PAX3-NCOA2 fusion
Fig. 2 PRISMA flow chart. PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow chart of the primary CNS rhabdomyosarcoma meta-review. *216 records were excluded at screening for the following reasons: non-CNS primary sites, non-rhabdomyosarcoma tumor types, no clinical case description, non-English language. **20 records were excluded at full-text review for the following reasons: non-CNS primary sites, non-rhabdomyosarcoma tumor types, rhabdomyosarcoma originated from the meninges, duplicated case from another manuscript. ***55 records were analyzed for demographic data. ****44 records with survival outcomes were analyzed for quantitative meta-analysis.

Fig. 3 Demographics of primary CNS rhabdomyosarcoma vs. all rhabdomyosarcoma. A Age distribution of patients with primary CNS rhabdomyosarcoma showed similarities with age distribution of patients with rhabdomyosarcoma at all sites in a large cohort from the SEER database. B Sites of primary CNS rhabdomyosarcoma were distributed across the CNS without predilection for a specific location. The number of cases at each site are indicated in parentheses.
Table 1 Prognostic/predictive factors of primary CNS rhabdomyosarcoma

|                      | OS N=64 | p value | EFS N=56 | p value |
|----------------------|---------|---------|----------|---------|
| Age (years)          | 0.50    | 0.15    |          |         |
| 15 or younger        | 39 (60.9%) | 35 (62.5%) |          |         |
| 16 or older          | 25 (39.1%) | 21 (37.5%) |          |         |
| Gender               | 0.58    | 0.10    |          |         |
| Female               | 27 (42.2%) | 24 (42.9%) |          |         |
| Male                 | 37 (57.8%) | 32 (57.1%) |          |         |
| Dissemination        | 0.006   | 0.01    |          |         |
| Localized            | 56 (87.5%) | 48 (85.7%) |          |         |
| Disseminated         | 8 (12.5%) | 8 (14.3%) |          |         |
| Treatment            | <.001   | <.001   |          |         |
| Surgery              | 18 (28.1%) | 11 (19.6%) |          |         |
| RT                   | 1 (1.6%) | 1 (1.8%) |          |         |
| Surgery + chemo      | 1 (1.6%) | 1 (1.8%) |          |         |
| Surgery + RT         | 16 (25%) | 16 (28.6%) |          |         |
| Surgery + RT + chemo | 28 (43.8%) | 27 (48.2%) |          |         |
| # of treatment modalities | <.001 | <.001 |          |         |
| Two or fewer modalities | 37 (57.8%) | 30 (53.6%) |          |         |
| Surgery + RT + chemo | 27 (42.2%) | 26 (46.4%) |          |         |
| Surgery              | 0.03    | 0.04    |          |         |
| GTR                  | 30 (46.9%) | 27 (48.2%) |          |         |
| Non-GTR              | 34 (53.1%) | 29 (51.8%) |          |         |
| Radiation            | (N=27)  | 0.85    | (N=27)  | 0.87    |
| Focal                | 13 (48.1%) | 13 (48.1%) |          |         |
| Extended field       | 14 (51.9%) | 14 (51.9%) |          |         |
| Chemotherapy         | (N=28)  | 0.50    | (N=27)  | 0.24    |
| VAC-based            | 13 (46.4%) | 13 (48.1%) |          |         |
| Others               | 15 (53.6%) | 14 (51.9%) |          |         |

p values < 0.05 are shown in bold

OS overall survival, EFS event-free survival, RT radiation therapy, Chemo chemotherapy, GTR gross total resection, Extended field Craniospinal irradiation or whole brain radiation, VAC vincristine + actinomycin D + cyclophosphamide, p values <0.05 are in bold

Discussion

Efforts to better understand primary CNS rhabdomyosarcoma have progressed, especially in the advancement of molecular studies. We discovered that our case harbors the PAX3-NCOA2 fusion, which was also recently described by Jour et al. [12]. PAX3-NCOA2 and PAX3-NCOA1 were reported in both embryonal and alveolar rhabdomyosarcoma of non-CNS sites [15, 16]. The PAX3-NCOA1 and PAX3-NCOA2 encode chimeric proteins composed of the paired-box and homeodomain DNA-binding domains of PAX3, and the CID domain, the Q-rich region and the AD2 domain of NCOA1 or NCOA2. Both fusion proteins showed transforming activity in experiments. Although our case harbors wild-type DICER1, which was confirmed by whole-exome and Sanger sequencing, DICER1 mutations have been reported in both primary CNS and non-CNS rhabdomyosarcoma [8–11, 17]. A case of primary CNS rhabdomyosarcoma with NF1 was also reported, and an association between NF1 and non-CNS rhabdomyosarcoma is known [18–20]. We then further revealed the demographic similarities between CNS and non-CNS rhabdomyosarcoma. These findings collectively support the hypothesis that the CNS is a rare location for rhabdomyosarcoma and that this tumor type is not a variation of other CNS tumors. The reason that the commonly observed PAX3/7-FOXO1 fusion genes have not been reported in CNS cases is still unknown. This might be related to the low incidence of alveolar type histology in reported primary CNS rhabdomyosarcoma cases. The WHO 2021 classification of CNS tumors introduces major changes that advance the role of molecular diagnosis integrated with established approaches of histology and immunohistochemistry [21]. Although DNA methylation data of our case is not available, the novel methylation-based profiling as a precise diagnostic tool has impacted pediatric brain and solid tumors [22, 23]. Further molecular characterization including DNA methylation of both CNS and non-CNS rhabdomyosarcoma is warranted [24].

Our meta-review confirmed that the survival outcome of primary CNS rhabdomyosarcoma is generally poor. As increasing evidence shows similarities with non-CNS rhabdomyosarcoma, it is reasonable to refer to existing data of non-CNS rhabdomyosarcoma when formulating treatment for primary CNS rhabdomyosarcoma. VAC chemotherapy or alternating VAC and vincristine plus irinotecan (VI) has been administered for intermediate-risk non-CNS rhabdomyosarcoma with a 4-year event-free survival of approximately 60% [25]. Our analysis did not demonstrate the superiority of VAC over other regimens. Concurrent focal radiation is commonly used for non-CNS rhabdomyosarcoma with some specific exceptions. Locoregional failure is the most common pattern of non-CNS rhabdomyosarcoma with an example of IRS-II study where 70–80% of relapses in groups I to III disease and 46% of relapses in group IV disease were locoregional [26]. The optimization of the dose and timing of radiation to improve locoregional control is currently under investigation [27–30]. Based on the analysis of prognostic and predictive factors of primary CNS rhabdomyosarcoma, a trimodal approach including maximum possible surgical resection, chemotherapy and radiation therapy is predicted to lead to relatively favorable outcomes. Although the data are limited, early introduction of radiation is applied primarily in long-term survivors. Early introduction of radiation therapy after surgery is a...
Fig. 4 Kaplan–Meier survival prediction of patients with primary CNS rhabdomyosarcoma. A Kaplan–Meier curves for overall survival and event-free survival are plotted. B The overall survival curve was stratified by the surgery + radiation + chemotherapy group (red solid line) and the fewer than three modalities group (blue dashed line). C Event-free survival curves were stratified by the surgery + radiation + chemotherapy group (red solid line) and the fewer than three modalities group (blue dashed line).
common practice in the treatment of CNS tumors and is also reasonable for primary CNS rhabdomyosarcoma. The survival analysis may be affected by publication bias that deviates the reported outcomes better although we took a systematic approach to minimize the potential biases.

Despite progress in understanding this rare tumor, some concerns remain and require further investigation. The age of the patient, location, and appearance of the primary CNS rhabdomyosarcoma on MRI can be misleading and clinicians may assume they are other CNS embryonal tumors. Accurate and timely diagnosis is critical in the formulation of a treatment plan, and a second opinion for the review of histopathology specimens in cases of uncertain diagnosis should be considered. Molecular studies have enabled clinicians to make this diagnosis and have decreased its turnaround time, which may aid in correcting the diagnosis. Penetration of the blood–brain barrier by chemotherapy drugs would be questioned if the same treatment as non-CNS rhabdomyosarcoma is applied to CNS tumors. The use of corticosteroids as antiemetics is a common practice in non-CNS sarcoma treatment and is discouraged for CNS tumors due to concerns about decreased drug penetration in the CNS. Given these concerns, it is essential that multidisciplinary specialists, including diagnostic radiologists, pathologists, molecular pathologists, oncologists specializing in sarcomas, and neuro-oncologists, work closely to manage patients with this rare tumor.

**Conclusion**

Primary CNS rhabdomyosarcoma shares common histological, molecular, and demographic features with non-CNS rhabdomyosarcoma. A trimodal treatment approach with early introduction of radiation therapy may result in favorable survival outcomes.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s11060-021-03823-6.

**Author contributions** Conceptualization: RT, KI; Methodology: RT, KI, YY, MK; Formal analysis and investigation: RT, YY, MY, HS, JI, HO; Writing original draft preparation: RT, KI, HO; Writing original draft preparation and supervision: RT, KI, HS, JI, HO; Writing review and editing: RT, HS, JI, HO, TM, MK, HS; Supervision: TM, MK, HS.

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**Data availability** The datasets generated during and/or analyzed during the current study are available in the Supplemental Table 1.

**Code availability** The software and codes used during the current study is available and shown in the method section.

**Declarations**

**Conflicts of interest** The authors have no conflicts of interests to declare that are relevant to the contents of this article.

**Ethical approval** The authors confirm that the current study was approved by the appropriate institutional review board and certify that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

**Consent to participate** The authors confirm that patient’s and/or parental/legal guardian’s consent was obtained for the participation in the study.

**Consent for publication** The authors confirm that patient’s and/or parental/legal guardian’s consent was obtained for publication.

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