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CASE REPORT

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Primary pineal alveolar rhabdomyosarcoma in an adult patient: a case report and literature review

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Abstract

Background The rarity of adult primary cerebral rhabdomyosarcoma (PCRMS) cases has necessitated the adoption of pediatric rhabdomyosarcoma (RMS) therapeutic protocols, highlighting a critical need for expanded treatment experiences to enhance prognoses.

Case presentation A 21-year-old female presented to our facility with a 20-day history of persistent headache, nausea, and vomiting, along with mild upward gaze palsy for the past 5 to 7 days. A brain magnetic resonance imaging (MRI) revealed a mass in the pineal region, extending into the third ventricle, measuring approximately 2.5 × 2.0 × 3.0 cm. The lesion exhibited mild irregular lobulation and heterogeneous enhancement. Intraoperatively, it displayed characteristics similar to high-grade gliomas, including a grayish appearance, abundant vasculature, firm texture, and indistinct margins adjacent to the bilateral thalamus. Pathology confirmed alveolar PCRMS with FOXO1 gene rearrangement. Whole-body imaging following pathological diagnosis showed no evidence of skull base infiltration or extracranial metastasis. Despite comprehensive multimodal treatment, including surgery, stereotactic radiotherapy, and chemotherapy, tumor recurrence occurred three months after initial surgery, and the patient unfortunately succumbed to the disease eight months after her initial diagnosis.

Conclusions Alveolar PCRMS in the pineal region, a distinct subtype of RMS, is exceptionally rare and typically associated with a bleak prognosis, suggesting unique tumor biology. A multidisciplinary and aggressive management approach is crucial. Further research into the molecular makeup of RMS in adults may pave the way for more effective, tailored treatments for this aggressive disease.

Keywords Rhabdomyosarcoma, Pineal gland, Alveolar, Histopathology, Case report

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Background

Rhabdomyosarcoma (RMS) represents a distinct class of soft tissue neoplasms characterized by undifferentiated skeletal muscle cells, originating through myogenic lineage differentiation during embryonal or fetal development [1]. RMS is predominantly diagnosed in children and commonly involves organs such as the prostate, bladder, and extremities. Notably, RMS is exceptionally rare in adults, comprising less than 0.001% of all adult sarcomas [2]. To date, only 24 cases of adult primary cerebral rhabdomyosarcoma (PCRMS) have been reported, typically associated with a poor prognosis, with the longest survival time being approximately 20 months [3].

The present study reports the seventh documented case of adult PCRMS localized to the pineal region, marking the second known instance of an alveolar-type RMS characterized by FOXO1 rearrangement. Moreover, it incorporates an appraisal of pertinent literature since 2000, concentrating on the clinical profiles, diagnostic criteria, and therapeutic approaches for adults with PCRMS. The objective is to enhance diagnostic accuracy, refine treatment approaches, and enhance prognostic outcomes for this challenging condition.

Search strategy

An advanced search was conducted in the Cochrane Library, Embase, PubMed, and Web of Science databases using the search terms "adult" AND "rhabdomyosarcoma" AND "brain" OR "cerebral" OR "head" OR "intracranial" OR "central nervous system". Only literature published in English was considered between January 1, 2000, and December 30, 2022. The references cited in the study were reviewed to obtain relevant information not found in the above retrieval. Two independent reviewers (TC and CD) independently screened all retrieved articles to ensure comprehensive retrieval.

The search yielded 35 articles, of which 23 were excluded for not meeting the inclusion criteria. The exclusions were primarily for the following reasons: two articles focused on pediatric cases (< 18 years), one was centered on the cerebellopontine angle region, one was related to meningeal RMS, and six pertained to maxillofacial region RMS. Additionally, six articles had inconsistent pathological diagnoses of RMS, and seven were reported prior to 2000. Ultimately, 12 articles were selected for further analysis.

The inclusion criteria were as follows: (a) studies wherein patients were pathologically diagnosed with PCRMS; (b) adult patients; (c) well-defined tumor location; (d) cases reported since 2000; (e) case reports, reviews, clinical articles. The exclusion criteria were as follows: (a) not meeting the diagnosis of PCRMS; (b) pediatric patients; (c) articles reported before 2001; (d) cases of meningeal, infratentorial, and extracranial RMS.

Case presentation

A 21-year-old female presented to our facility with a 20-day history of persistent headache, nausea and vomiting. She also experienced mild dyskinesia in upward eye movement over the past 5 to 7 days. The patient reported no history of visual disturbances, tinnitus, or hearing loss, and denied any symptoms of dizziness or balance issues. Following the onset of her symptoms, she received nonspecific symptomatic treatment (details unspecified) at a community hospital with minimal improvement. Her medical history is unremarkable, with no known family history of hereditary or infectious diseases; no history of unclean coitus. She has never smoked, consumed alcohol excessively, or substance abuse.

Neurological examination revealed mild bilateral upgaze palsy, convergence-retraction nystagmus, slight light-near pupillary dissociation. Slit-lamp biomicroscopy and tonometry showed no signs of papilledema, and there was no evidence of cerebellar ataxia or meningeal irritation.

A magnetic resonance imaging (MRI) examination revealed a mass lesion located in the pineal region, which extended into the third ventricle. The lesion exhibited irregular and lobulated margins with variable enhancement patterns, approximately $2.5 \times 2.0 \times 3.0$ cm in size, and was well-separated from adjacent structures, as demonstrated in Fig. 1A-C. Blood tests confirmed normal levels of α-fetoprotein (AFP) and β-human chorionic gonadotropin (β-HCG), ruling out the presence of a germ cell tumor. These findings narrowed the initial differential diagnoses to ependymoma and subependymal giant cell astrocytoma.

To address her symptoms and confirm a definitive diagnosis, the patient underwent a meticulous excision through a right-side transcallosal-hemispheric approach, achieving a complete excision without complications. Intraoperatively, the tumor exhibited texture consistent with a high-grade glioma, including a grayish-white appearance, abundant vasculature, and indistinct margins near the bilateral thalamus, without evidence of necrosis or hemorrhage. Pathological examination was conducted on the collected tissue samples. A postoperative MRI scan showed no residual tumor or contrast enhancement, confirming a successful procedure.

The histological examination revealed diffuse infiltration by spindle-shaped cells with features akin to rhabdoid-like cells, characterized by a high nuclear-to-cytoplasmic ratio, ample eosinophilic cytoplasm, coarse chromatin, pleomorphic nuclei, and increased mitosis. Hematoxylin and eosin (HE) staining demonstrated that the neoplasm lesion predominantly consists of short, spindle-shaped cells with either eosinophilic or clear cytoplasm, arranged in a storiform pattern (Fig. 2A). These neoplastic cells, medium in size and round to oval

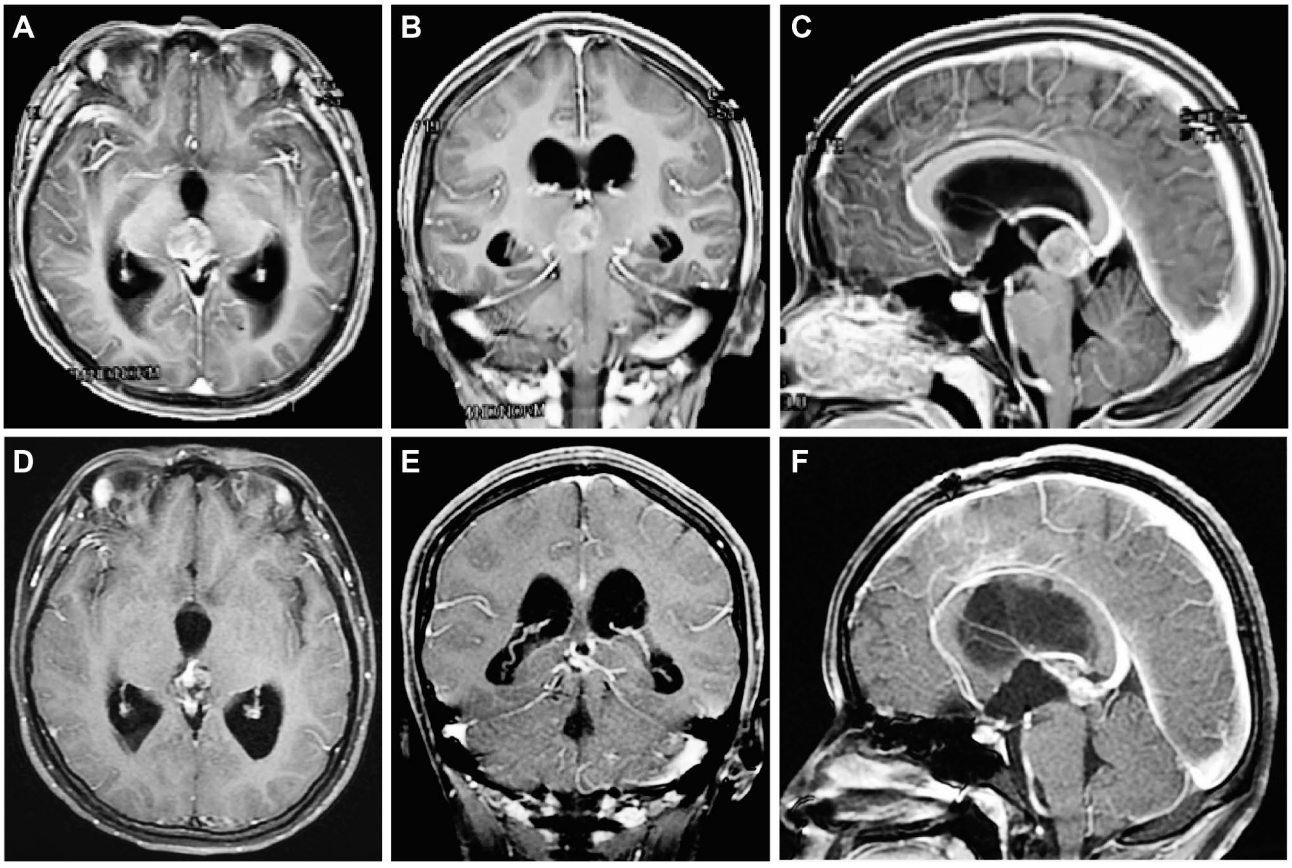

Fig. 1 Preoperative and postoperative MRI of a mass in the pineal region. Preoperative gadolinium-enhanced MRI scans in axial (**A**), coronal (**B**), and sagittal (**C**) planes revealed an irregular, heterogeneously enhancing, and lobulated mass located in the pineal area. This mass compressed the aqueduct and extended anteriorly into the third ventricle, resulting in hydrocephalus. Three months after surgery, gadolinium-enhanced MRI scans demonstrated complete removal of the lesion with no evidence of recurrence, while bilateral ventricular enlargement persisted (**D-F**)

in shape, were densely packed with well-defined borders. Notably, large cells resembling rhabdomyoblasts, marked by eccentric nuclei and abundant pink cytoplasm, were observed. Immunohistochemical staining exhibited extensive nuclear positivity for OLIG2 across all neoplastic cells (Fig. 2B), suggesting a potential association with a PAX3 gene fusion mutation. Desmin staining displayed diffuse positivity in the cytoplasm (Fig. 2C). Additionally, there was widespread and intense nuclear positivity for MyoD1 and myogenin (Fig. 2D, E), supporting differentiation into the myogenic lineage. The Ki-67 proliferation index reached 50% (Fig. 2F), reflecting a high level of proliferative activity within the neoplastic cell population. Collectively, these histological findings conclusively diagnosed the lesion as alveolar type PCRMS, thereby excluding other potential diagnoses such as primary germ cell tumors, atypical rhabdoid tumors, rhabdoid meningiomas, glioblastomas, carcinomas, and other sarcomas.

Following the pathological diagnosis, detailed imaging of the maxillofacial region, neck, chest, abdomen, pelvis, and thighs was conducted to assess any potential infiltration from the skull base, and to rule out the possibility of metastasis from extracranial masses. No evidence of spread was identified.

Given the aggressive nature of the lesion, a multidisciplinary neuro-oncology team reviewed the case. The patient then underwent stereotactic radiotherapy with a prescribed dose of 60 Gy, incorporating a volume-security margin and additional reinforcement of the surgical bed. Moreover, a chemotherapy regimen consisting of vincristine, dactinomycin, and cyclophosphamide was recommended. However, the patient did not fully adhere to the adjuvant therapy regimen.

Three months postoperatively, follow-up imaging detected no signs of tumor recurrence or metastatic spread (Fig. 1D-F). The patient reported satisfactory quality of life and maintained an excellent functional status. Despite these favorable outcomes, the patient ultimately died eight months after the PCRMS diagnosis, possibly due to rapid recurrence or the development of metastatic disease.

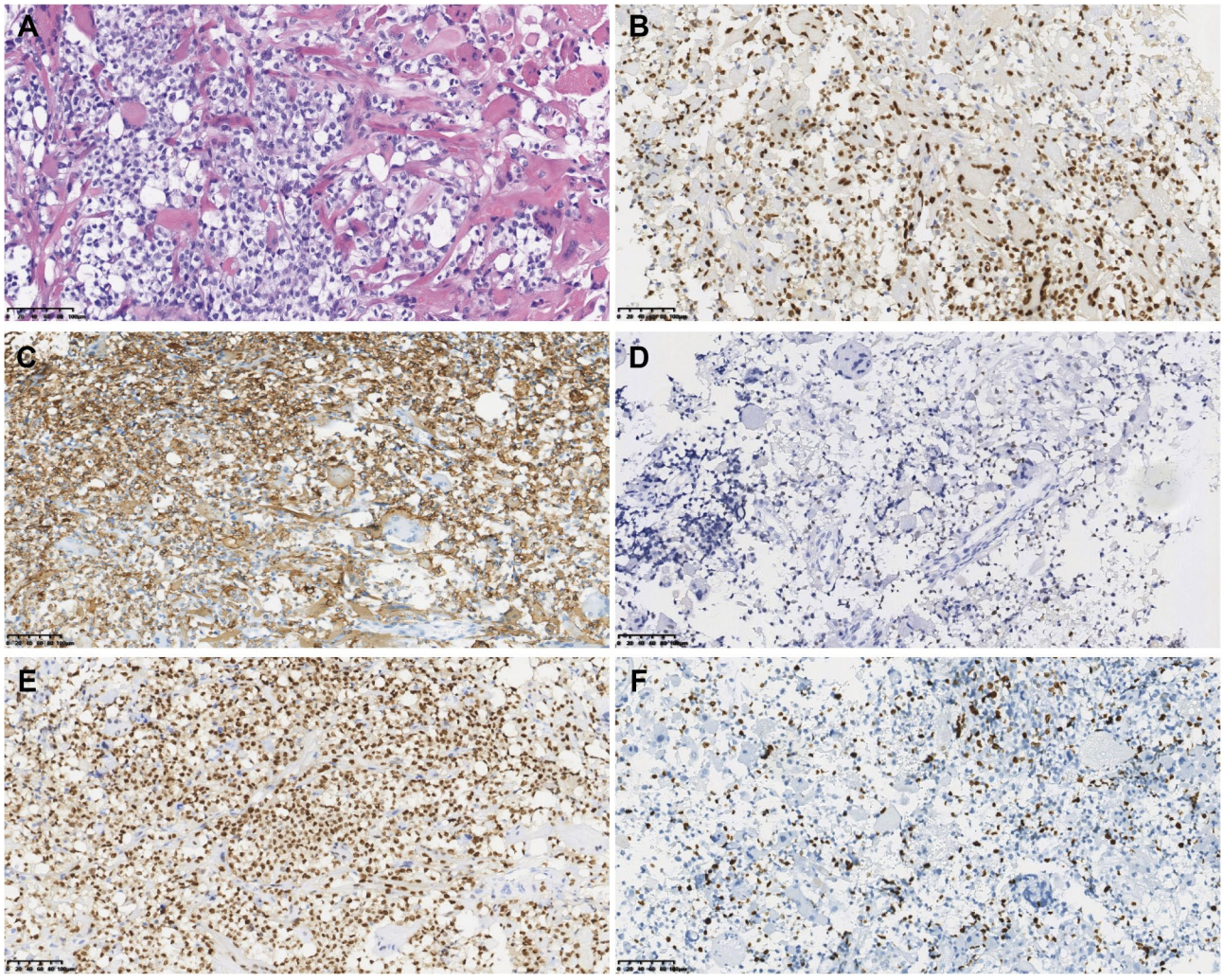

Fig. 2 Pathological diagnosis. **A** H&E staining (200×) revealed medium-sized, storiform-patterned spindle cells, with moderate atypia and clear boundaries. Prominent features included myo-epiblast-like cells with eccentric nuclei and distinctive pink cytoplasm. Immunohistochemistry, OLIG2 (**B**, 100×) showed partial positivity; desmin (**C**, 200×) revealed muscular differentiation; MyoD1 (**D**, 100×) and Myogenin (**E**, 100×) confirmed myogenic differentiation; Ki-67 (**F**, 100×) denoted high proliferative activity

Discussion and conclusions

The etiology of PCRMS remains unclear, with several hypotheses suggesting its neuroectodermal origin lacking neuronal or glial differentiation. Potential sources include heterotopias, multipotent or dedifferentiated mesenchymal cells, or central nervous system (CNS) teratomas [15]. In the pineal region, PCRMS may originate from nearby structures extending into the gland or directly from the gland itself [6].

Adult PCRMS shares a rhabdomyoblastic phenotype but exhibits significant diversity in clinical, morphological, and molecular attributes. Contrasting with the pediatric preference for infratentorial regions, PCRMS is more commonly diagnosed in supratentorial areas, particularly in the frontal and parietal lobes, affecting individuals aged 18 to 65 years. The average age of onset is 42.83 years for males and 33.14 for females, with no significant gender predominance. Of the 13 cases reviewed, 7 (54%) were identified in the pineal region, underscoring the entity's clinical significance in differential diagnosis for masses within this region (Table 1).

PCRMS exhibits highly aggressive behavior, impacting recurrence/metastasis and survival [8]. Our review shows that 53.85% of PCRMS patients survived beyond one year (Table 1). However, only 28.57% of cases in pineal region achieved this, with just two surpassing a two-year survival span. The interval from initial surgery to recurrence or metastasis averaged 6.5 months, ranging from 1 to 14 months. Local recurrence occurred in 46.15% (6 out of 13), while distant metastasis was observed in 7.69% (1 patient), indicating the increased risk of local recurrence. Distinctly, adults with PCRMS in the pineal gland exhibit a unique clinical profile, with 44% succumbing within

Table 1 Reported cases of primary cerebral rhabdomyosarcoma in adults since 2000

Author/Year	Age / Sex	Location	Subtype	Immunohistochemistry positive	Therapy	Survival (months)	Follow up (months)
Mitsuhashi T (2002) [4]	42/F	Left frontal	NA	Vimentin, myoglobin	TR	NA	NA
Grebe HP (2008) [5]	40/F	Right frontal	Embryonal	Desmin, muscle actin	SR, RT	> 11	Recurrence 3 month
Pirillo V (2011) [3]	51/F	Left parietal	Alveolar	GFAP, synaptophysin, vimentin, desmin	TR, RT	20	Recurrence 11 month
Lau SK (2015) [6]	33/F	Pineal region	NA	MyoD1, myogenin, INI1, desmin	SR	5	NA
Yu T (2015) [7]	18/M	Pineal region	NA	Desmin, myogenin	TR	5	NA
Scull C (2016) [8]	43/M	Pineal region	NA	Desmin, muscle-specific actin, INI1, myogenin	SR, RT	4	Recurrence 1 month
Desai KB 2019) [9]	51/M	Right temporal	Alveolar	Vimentin, CD56	Biopsy, RT	17	NA
Jour G (2019) [10]	22/F	Pineal region	Alveolar PAX3-NCOA2	Desmin, myogenin	PR, RT, CT	> 14	Recurrence 14 month
Pandey L (2020) [11]	44/M	Pineal region	NA	Desmin, myogenin, INI1	SR, RT, CT	6	Recurrence 2.5 month
Vijayaraghavan N (2021) [12]	23/F	Right frontoparietal	NA	Desmin, myoD1, GFAP	TR, RT, CT	14	NA
Xie L (2022) [13]	36/M	Pineal region	Alveolar FOXO1 gene rearrangement	Desmin, myoD1, Oligo2, INI-1, ALK, CD99, S100, Ki67(30–35%)	TR, TMZ	12	Recurrence 8 month
Mallereau CH (2022) [14]	65/M	Left frontoparietal	NA	Desmin, myogenin	TR, RT	> 12	Lung metastasis 6 month
Present case (2022)	21/F	Pineal region	Alveolar FOXO1(FKHR)	Desmin, myoD1, Oligo2, CD56, myogenin	TR, RT	8	NA

one year, a notable deviation from other brain tumors in the same region.

Several factors contribute to the generally poorer outcomes observed in adults with PCRMS. The aggressive nature of these tumors, often reflected by a high Ki-67 proliferation index, the difficulty in achieving complete surgical resection, and a propensity for rapid recurrence postoperative all significantly worsen the prognosis. Additionally, the occurrence of tumors in challenging locations, such as the pineal region and the presence of aggressive histological variants such as alveolar RMS with PAX3-FKHR fusion.

Diagnosing PCRMS poses significant challenges due to its uncommon occurrence, lack of a standardized grading system, and diverse presentation. Asymptomatic or atypical symptoms, such as headache, nausea, ataxia, diplopia, confusion, and facial paresis have been observed in previously reported cases [6, 8, 11, 13]. Lesions in the pineal region often present with early-onset symptoms such as hydrocephalus, and the classical Parinaud's triad. These symptoms are caused by the lesion obstructing the aqueduct and compressing the tectal plate, thereby disrupting cerebrospinal fluid flow. Occasionally, neoplasms in the hemisphere may manifest as tumor-related strokes, which are not typically associated with pineal region PCRMS [4].

Preoperative radiological evaluations often fail to provide distinct imaging features unique to PCRMS, complicating its differentiation from other brain malignancies. In cases of pineal region PCPMS, differential diagnoses based on imaging should include pineal parenchymal tumors, germ cell tumors, high-grade gliomas, lymphomas, metastases, and primitive neuroectodermal tumors. These tumors typically exhibit iso- to hypointense on T1- and hyperintense on T2-weighted MRI, with variable Gadolinium-enhancement patterns. Histological analysis is crucial for suggesting rhabdomyosarcoma, with imaging aiding in determining its primary or metastatic nature.

The primary diagnostic approach for RMS involves identifying a primitive tumor that tests positive for skeletal muscle lineage markers. Concurrently, it is important to exclude other neoplasms that may contain skeletal muscle components, such as atypical teratoid/rhabdoid tumors, medullomyoblastomas, gliosarcomas, teratomas with rhabdomyosarcomatous differentiation, germ cell tumors, and pinealoblastomas with rhabdomyoblastic features [11, 16]. Muscle-specific antigens, including actin, myoglobin, and desmin, are often evaluated to facilitate diagnosis. However, the specificity of these diagnostic criteria is limited, as evidenced by cases where desmin is positive in 11 patients (84.6%), reactive myogenin in 6 cases (46.2%), and vimentin in 3 cases (23.1%) (Table 1).

The World Health Organization (WHO) has classified RMS into four distinct subtypes: embryonal, alveolar,

polymorphic, and spindle cell/sclerosing [17]. The polymorphic subtype is the most prevalent. Notably, the alveolar subtype is distinguished by its aggressive behavior and a resemblance to lymphoma's round cell tumors. The determination of histological subtypes is crucial for guiding prognosis and developing personalized treatment plans. However, only 6 of 13 cases (46.15%) have achieved a definitive histological classification, including the current case.

In complex PCRMS cases, the detection of the FOXO1 gene fusion is essential. Approximately 80% of alveolar RMS cases involve PAX3-FOXO1 or PAX7-FOXO1 translocations, with PAX3-FOXO1 associated with higher Olig2 expression and poorer outcomes [18]. The remaining 20% of cases without these gene fusions exhibit clinical and morphologic features more akin to embryonal RMS, which is often seen in pediatric patients with a more favorable prognosis. Nonetheless, molecular genetic diagnosis in these cases remains infrequent, as evidenced by only 23.08% of cases (3 out of 13) in this study including the current case (Table 1).

Treatment strategies for adult PCRMS often mirror those employed for pediatric patients with extracranial RMS. Surgical approaches prioritize maximal tumor resection without compromising safety, a principle consistent with other neoplasms of the central nervous system. However, the complexity of the pineal region's anatomy often limits the extent of safe tumor resection. The reviewed cohort in our research showed that survival outcomes vary significantly based on treatment modality. Patients undergoing solely surgical resection experienced a mean survival of 5 months. Those receiving surgery combined with radiation therapy achieved a mean survival of approximately 10.28 months. Adding chemotherapy to this regimen further increased survival to about 11.33 months, highlighting the potential benefits of multimodal therapy in managing PCRMS.

Radiotherapy has been proven effective in treating pediatric RMS and other intracranial malignancies [19, 20]. This typically involves dosages and fractionation similar to those used for malignant gliomas, with a total dose ranging from 50 to 60 Gy, administered over approximately 30 sessions. However, well-defined treatment protocols for radiotherapy in adults with PCRMS are currently lacking. As for chemotherapy, there is no consensus on the optimal regimen for adults with PCRMS. Some multidisciplinary oncology teams may recommend either the VAC (vincristine, actinomycin D, cyclophosphamide) or ICE (ifosfamide, carboplatin, etoposide) chemotherapy regimens, based on a careful risk-stratification approach [21].

The research demonstrates its strengths through an in-depth literature synthesis, the development of robust diagnostic criteria, and comprehensive molecular analysis, which significantly enhances the study's clinical relevance and provides valuable insights for patient management. Furthermore, the study highlights the limitations posed by the lack of unified diagnostic and therapeutic approaches across diverse populations and through a broad period. Additionally, the absence of comprehensive long-term follow-up data hinders a deeper understanding of disease progression, recurrence patterns and prognosis, reducing the study's clinical utility in real-world clinical practice. Despite these limitations, the study provides a robust foundation for future research and underscores the importance of recruiting more representative cohorts to strengthen the generalizability of its conclusions.

Conclusions

PCRMS in the pineal region, a distinct subtype of RMS, is exceptionally rare and typically associated with a bleak prognosis, suggesting unique tumor characteristics. A multidisciplinary and aggressive treatment approach is crucial. Further research into the molecular makeup of PCRMS in adults may pave the way for more effective, tailored treatments for this aggressive disease.

Abbreviations

RMS	Rhabdomyosarcoma
PCRMS	Primary cerebral rhabdomyosarcoma
AFP	α-fetoprotein
β-HCG	β-human chorionic gonadotropin
HE	Hematoxylin and eosin
PR	Partial removal
SR	Subtotal removal
TR	Total removal
CT	Chemotherapy
RT	Radiotherapy
CNS	Central nervous system
WHO	World Health Organization

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Author contributions

Conception and Design YY, QM. Drafting the Manuscript TC, C D. Prepared figure and table YH L, TC. Final approval of completed manuscript all authors.

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Data availability

Data and materials are provided within the manuscript file.

Declarations

Ethics approval and consent to participate
Informed consent was obtained from the patient to publish this case, and approval for this study was provided by Research Ethics Committee of the West China Hospital of Sichuan University.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and the accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Competing interests
The authors declare no competing interests.

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