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CASE REPORT

Medulloepithelioma with heterologous osteoid component: a case report and review of literature

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Abstract

Purpose Medulloepithelioma is a rare brain tumor that has been classified as embryonal tumor with multilayered rosettes (ETMR) if it harbors C19MC amplification. In rare instances, it shows evidence of heterologous differentiation.

Methods We report a case of a 10-year-old female who presented with headache, squint, and minimal left sided weakness of 1 week duration.

Results Microscopy revealed a small round blue cell tumor with focal glandular and tubular differentiation. In one focus, well-developed osteoid was identified. The tumor labeled with LIN28A immunostain.

Conclusions Unusual features can be encountered in medulloepithelioma which should be in the differential diagnosis of CNS embryonal tumors. Full description of the case with review of the literature and comparison between cases with and without heterologous elements is presented.

Keywords Medulloepithelioma · Embryonal tumor with multilayered rosettes · LIN28A · Cytogenetics · Brain tumors

Introduction

Medulloepithelioma of the central nervous system (CNS) is a rare embryonal tumor typically arising in young children. It is classified as grade IV and carries a poor prognosis. Defining histopathologic features include a pseudostratified primitive neuroepithelium organized in papillary, tubular, or trabecular structures and surrounded by an external limiting membrane, a picture which mimics the primitive neural tube [12]. In rare cases, mesenchymal components and melanin pigmentation have been reported [2, 4, 15, 21, 23].

Recently, the combination of C19MC oncogenic miRNA amplification and high LIN28A expression has been revealed as a specific hallmark for a subset of CNS primitive neuroectodermal tumors (PNET) characterized by the presence of "ependymoblastic" rosettes, namely ependymoblastoma, embryonal tumor with abundant neuropil and true rosette (ETANTR), and occasionally, medulloepithelioma [10, 22]. Accordingly, the term PNET has been dropped off and replaced with "embryonal tumor with multilayered rosettes" (ETMR), C19MC-altered [10, 18, 22]. It is worthy of note, however, that if a tumor shows the characteristic features of medulloepithelioma in the absence of C19MC amplification [22], or when copy number at the 19q13 C19MC locus has not been tested, a diagnosis of medulloepithelioma remains valid [13].

Owing to its rarity, optimal management of medulloepithelioma remains uncertain. The 3-year survival rate is only 30% [16]. Gross total resection (GTR) and high-dose radiotherapy may have a role in improving survival, along with high-dose chemotherapy (HDCTX) [9, 15, 19].

Case report

A 10-year-old female patient presented with headache of 1-week duration followed by squint with minimal left-sided weakness. MRI showed a peripheral, large lobulated, mainly solid heterogeneously enhancing mass with a

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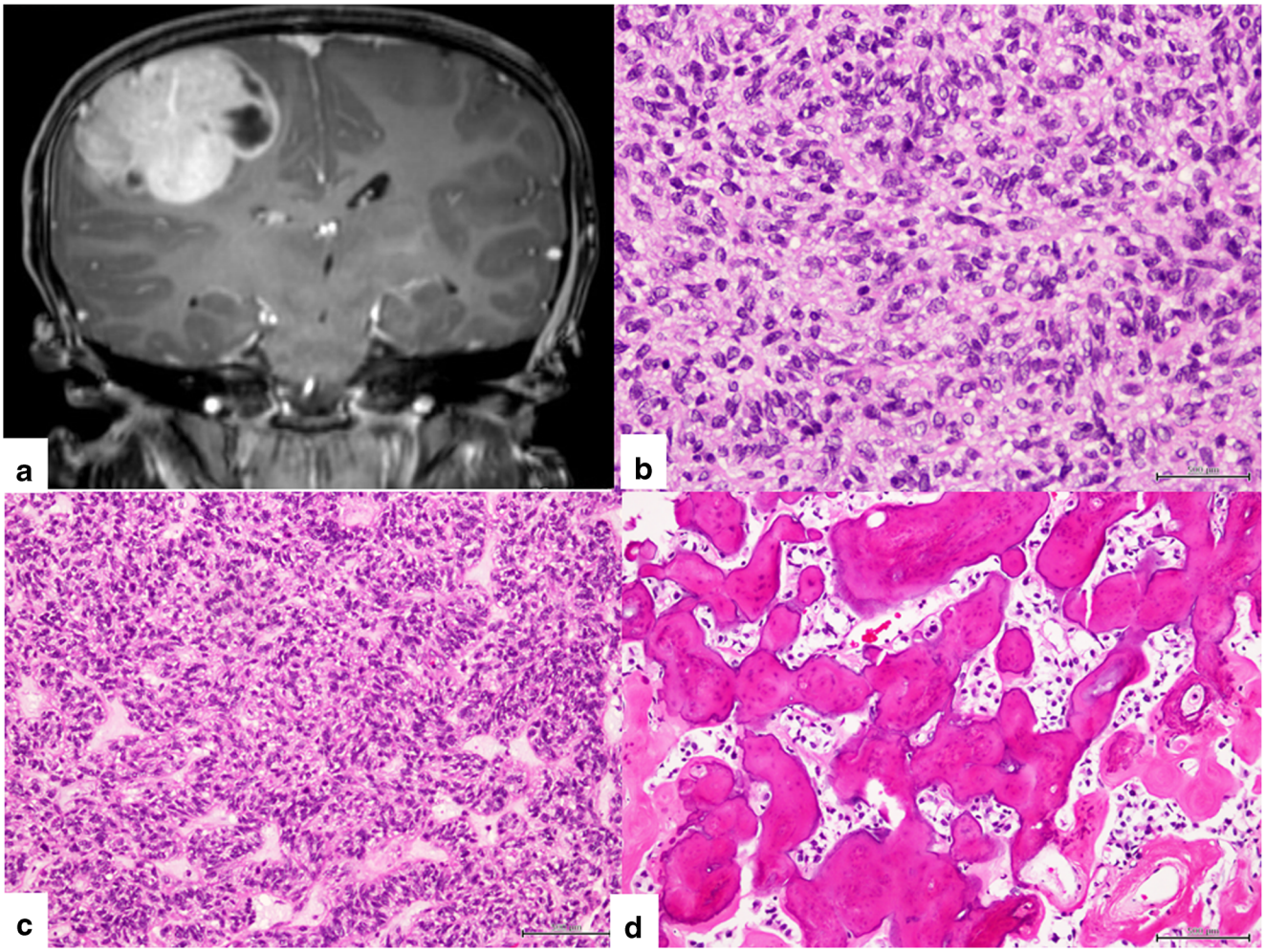

Fig. 1 **a** Contrast-enhanced brain MRI for the brain showing a large lobulated mainly solid heterogeneously enhancing mass with a small cystic component at the right parietal lobe. It is located peripherally involving the cortex. The outline of the mass is fairly well-defined. **b** Areas within the tumor composed of sheets of small round blue cells (H&E, ×40). **c** In other foci there was evidence of rosettes and glandular differentiation (H&E, ×40). **d** In one focus, clear osteoid formation was evident (H&E, ×40)

small cystic component in the right parietal lobe involving the cortex (Fig. 1a). The posterior aspect of the mass showed a signal void on T2 and a hyperintense signal on T1 (not shown) suggestive of calcification. She underwent GTR followed by radiotherapy (craniospinal irradiation of 36 Grays/20 fractions followed by a boost of 18 Grays/10 fractions to the tumor bed) and then received 3 cycles of cisplatin and etoposide followed by 7 cycles of vincristine and cyclophosphamide, based on the POG 9031 protocol. The patient is still alive without evidence of disease 30 months after the diagnosis.

Morphologically, the tumor was composed of sheets of embryonal cells with increased mitosis and apoptosis (Fig. 1b). Rosettes were focally identified. This pattern merged gradually into foci of columnar cells with oval nuclei arranged in vague trabecular and pseudo-glandular patterns (Fig. 1c), resting on a basement membrane as highlighted with Period-acid-Schiff (PAS) special stain and Collagen IV immunostain (Fig. 2a, b). A separate focus showed prominent perivascular hyalinization mounting into ossification (Fig. 1d), corresponding to the area of calcification detected radiologically. No other heterologous component could be identified despite extensive sampling.

The tumor cells were strongly immunoreactive for vimentin and nestin, and focally for EMA and cytokeratin (AE1/AE3). They were negative for SALL4, synaptophysin, GFAP, and CK-MNF. ATRX, INI-1/BAF-47, and BRG-1 immunostains were retained. LIN28A immunostain was diffusely strongly positive (Fig. 2c). Ki-67 proliferative index approached 30% (Fig. 2d). No cytogenetic or molecular testing was performed. The final diagnosis was a LIN28A positive embryonal tumor, with features consistent with medulloepithelioma with heterologous component.

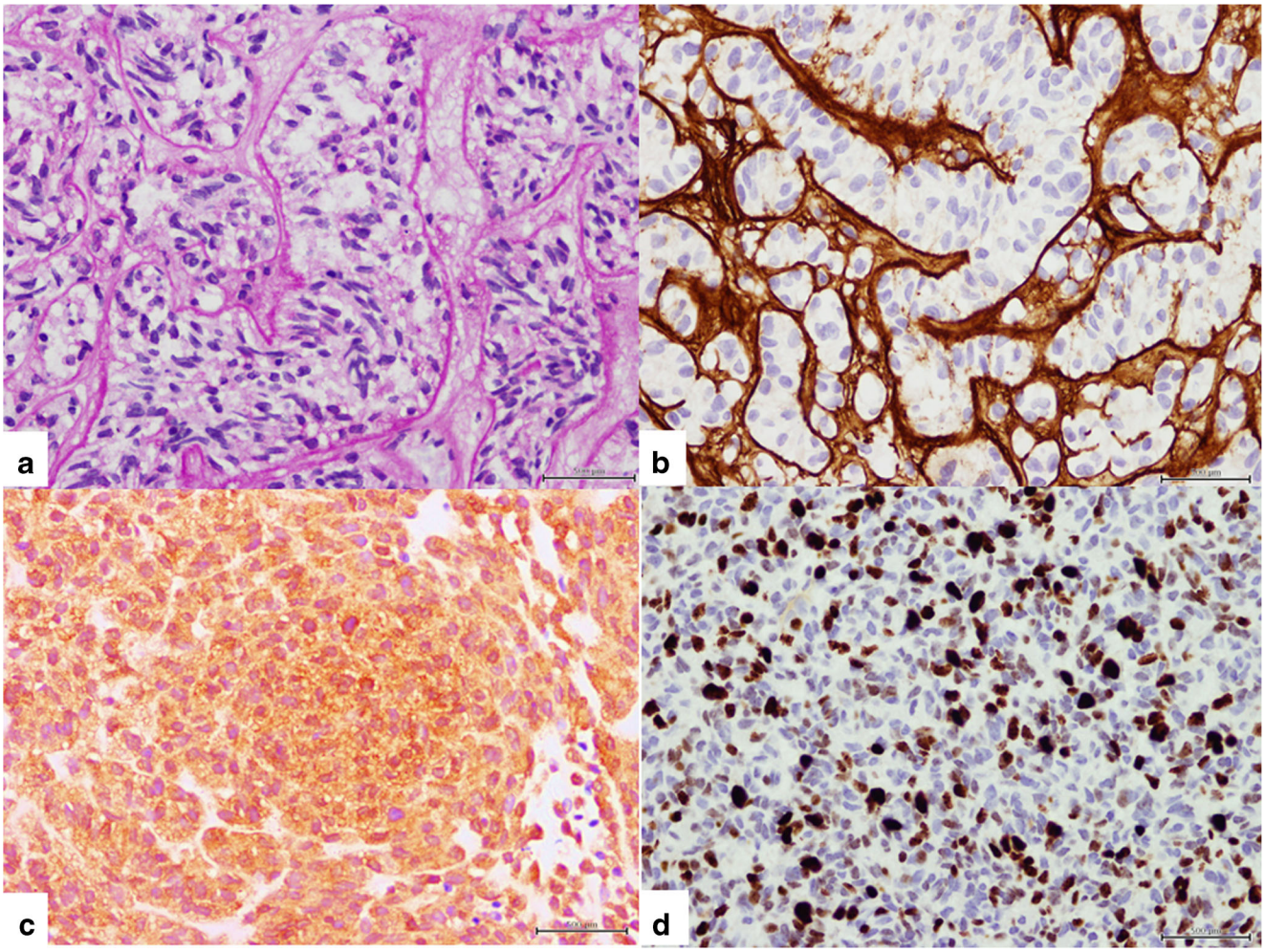

Fig. 2 **a** PAS and **b** Collagen IV immunostain highlighting the basement membrane within the tumor. **c** LIN28A are strongly diffusely positive in the tumor cells. **d** Ki-67 proliferative index is increased. (All images are ×40)

Discussion

First described in 1926 by Bailey and Cushing, medulloepithelioma remains a rare tumor with less than 55 reported cases. On literature review, it occurs primarily in infants and young children with an average age of 4.7 years (median 30 months). While five cases presented before 6 months, with at least two being congenital, six (11%) cases affected children older than 10 years of age. Both genders are affected almost equally. Supratentorial location predominates (70%). When comparing tumors without and with heterologous differentiation, younger age (43 vs. 68 months) and infratentorial predominance (53 vs. 15.6%) were noted in those without heterologous differentiation. While infratentorial location has been considered a poor prognostic factor; GTR, negative CSF, and adjuvant chemoradiation appear to be more important determinants of the outcome. Moftakhar et al. noted that the degree of differentiation did not affect the overall, but the recurrence free survival [14].

Although the presence of neuroglial differentiation is common, mesenchymal differentiation is only reported in a minority of cases (Table 1). This included less mature stromal elements resembling primitive mesenchyme [4]. Similar elements were also described in the case by Davie in 1932 [5], although later reexamination of this tumor by Russel revealed focal primitive rhabdomyoblastic differentiation, leading her to relabel the case as a teratoma [20]. The more mature mesenchymal elements, such as the osteoid area in the current case, usually occur as separate foci easily demarcated from their neighboring structures. This was well demonstrated in the case reported by Auer and Becker, which strikingly exhibited the entire spectrum of neuroepithelial differentiation, with islands of skeletal muscle, cartilage, and bone alongside areas of ependymal, astroglial, oligodendroglial, and neuroblastic differentiation [2]. Osseous differentiation as described in this case has not been previously reported other than as the focus described by Auer and Becker.

Despite occurring more frequently than medulloepithelioma, heterologous differentiation in other forms ETMR is even rarer.

Table 1 Summary of the medulloepithelioma cases with heterologous components since 1983

Author	Age	Symptom	Sex	Location	Surg	RTX	CTX	OS (mo)	Component
Auer (1983)	30 mo.	Fever, cough, vomiting	F	Left parieto-occipital	PR	Yes	None	11	Neuronal, glial, ependymal, mesenchymal (cartilage, osteoid, rhabdomyoblastic)
Molloy (1996)	32 mo.	Headache, lethargy, vomiting	NA	Frontal lobe	GTR	Yes	Yes	10	Neuronal, glial, mesenchyme (not specified)
Ramesh (2014)	17 yr.	Right-sided weakness, headache, vomiting	F	Left parietal lobe	Yes	Yes	NA	> 14	Mesenchyme (not specified)
Current case	10 yrs.	Headache, squint, left-sided weakness	F	Right parietal lobe	GTR	Yes	Yes	> 13	Osteoid

Abbreviations: *mo* month, *yrs.* years, *F* female, *M* male, *Surg* surgery, *GTR* gross total resection, *PR* partial resection, *NTR* near total resection, *STR* subtotal resection, *CTX* chemotherapy, *RTX* radiotherapy, *OS* overall survival, *NA* not available

Cases with dominant neurocytic or glial differentiation have been described [6, 17]. We previously reported rhabdomyoblastic and melanocytic differentiation in a case of ETANTR [1]. Since then, only two more cases of ETANTR with mesenchymal elements were described, both in the form of sarcomatoid areas immunopositive for actin, one of which contains nests of epithelioid cells [3, 7].

Although bearing a strong histological resemblance, ocular medulloepithelioma is distinct from CNS-based medulloepithelioma [8], as recent molecular analysis has proven them to be biologically distinct [11]. Interestingly, heterologous elements are frequently present in ocular medulloepithelioma, mainly in the form of hyaline cartilage, thus their classification into teratoid and nonteratoid [24].

In conclusion, we report a case of medulloepithelioma with heterologous differentiation. GTR and chemo-radiotherapy might have accounted for the long-term survival. Heterologous differentiation does not appear to adversely impact the outcome.

Compliance with ethical standards

Conflict of interest None.

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