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Comprehensive Treatment of Myeloepithelioma of the Central Nervous System in Adults: A Case Report and Literature Review

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► ***Case Report***

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ABSTRACT

Medulloepithelioma (MEPL) of the central nervous system (CNS) was once considered as a rare malignant embryonic tumor of the nervous system. The new classification of central nervous system tumors classified it as an Embryonal tumor with multilayered rosettes (ETMR), and its diagnosis depends on immunophenotype and molecular detection in addition to histology. This kind of tumor rarely occurs in adults, and the best treatment is uncertain. This case reports a case of adult MEPL, which mainly shows numbness of limbs. Magnetic resonance imaging (MRI) of the head showed a well-defined tumor near the meninges of the parietal lobe with small cystic changes, which was unevenly enhanced on enhanced scanning. The patient's local recurrence was confirmed within 18 months after complete resection of the tumor by simple operation, and radiotherapy and chemotherapy were given after the second operation. There was no disease progress 32 months after operation. According to our report, it can be speculated that operation, craniospinal radiotherapy (CSI) plus tumor bed boost and high dose chemotherapy are of great value to improve the prognosis of MEPL/ETMR.

INTRODUCTION

MEPL of the central nervous system is a rare, malignant primary embryonic tumor of the nervous system [1]. Before the revision of the World Health Organization (WHO) classification of tumors in the CNS, MEPL did not determine a specific gene phenotyping and was considered an independent tumor entity different from other embryonic tumors, (WHO grade IV), whose diagnosis was mainly based on morphological analysis [2, 3]. With the development of molecular biology of brain tumors, C19MC gene amplification or fusion of chromosome 19q13.42 is considered to be a special clinicopathological entity feature of the embryogenic tumor [4]. In the classification of CNS tumors in 2016, tumors with C19MC site change of 19q13.42 and histologic characteristics of MEPL were classified as "ETMR, C19MC change", while those without C19MC site change were still diagnosed as "MEPL" and classified as other embryonic tumors [5]. In the fifth edition of WHO classification of CNS tumors in 2021, embryonic tumors (ETANTR), ependymoblastomas (EBLs), and MEPL with different organizational forms belong to the same molecular entity, which is collectively called the ETMR [6]. The diagnosis of ETMR depends on immunophenotype and molecular tests in addition to histology. The diagnosis of ETMR depends on immunophenotype and molecular tests in addition to histology. This type of tumor tends to occur in children under 8-10 years of age and rarely in adults [3,7], resulting in poor prognosis due to rapid subarachnoid cell proliferation and high recurrence rate. Because clinical data are limited, current treatment recommendations are based on data from small, mostly retrospective patient cohorts. Surgery, radiotherapy and chemotherapy are the main treatment methods, but the optimal regimen is uncertain. The younger age of onset brings limitations and challenges to radiation therapy. We report a case of MEPL in an adult who recurred 18 months after complete resection of the tumor by simple surgery, and radiotherapy and chemotherapy were given after the second operation. There was a relatively long no disease progress after operation. The findings of our case study suggest that gross total resection (GTR), CSI plus tumor bed boost and high dose chemotherapy are of great value to improve the prognosis of MEPL/ETMR.

CASE PRESENTATION

The patient, male, 21 years old, was hospitalized in neurosurgery of our hospital in April 2019 due to " limb numbness for 1 week". MRI (Siemens, 3.0T, Verio, Germany) showed that the left parietal lobe was occupied, adjacent to the meninges (Gadoteridol injection, Prohance, Germany), and the enhancement was significantly enhanced (Contrast agents:

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Gadoteridol injection, Prohance, Germany), with patchy non-enhanced areas and obvious peritumoral edema (figure 1). After improving the relevant examinations, the "deep supratentorial lesion resection" was performed, and the tumor was completely removed. See in the operation, the tumor was located below the arachnoid membran, about 2.5×3.5×2.5cm, with a capsule, no obvious adhesion to the dura, but local adhesion to the surrounding brain tissue. Pathological pathology: MEPL (figure 2); immunohistochemical (Ventana NEXES Automated Immunohistochemistry System, Fuzhou Maixin Biotech Co.Ltd.Fuzhou, China：CKP (+); Epithelial membrane antigen (EMA) (-); Vimentin (+); Glial Fibrillary Acidic Protein (GFAP) (-); S-100 (scattered+); Syn (+); NSE (scattered+); CD99 (-); Ki-67 (index: 70%). The patient did not receive adjuvant treatment after operation. 18 months after operation, the patient suffered from limb numbness again, and was re-examined in a local hospital, suggesting local recurrence of the tumor. The patient underwent tumor removal in Beijing Tiantan Hospital on January 27, 2021. The tumor is rich in blood supply, with unclear boundaries and a size of 4×3.5×3cm. Total tumor resection was performed. Pathological diagnosis, MEPL. 40 days after surgery, the patient received postoperative concurrent chemoradiotherapy (CCRT) in our department (referring to the radiotherapy and chemotherapy protocol for high-risk medulloblastoma). Radiotherapy (VMAT-Elekta Synergy, England): CSI, 36 Gy, 20 times segmentation (3-dimensional conformal radiation therapy, 3D-CRT); followed by a boost to the tumor bed (Intensity modulated radiation therapy, IMRT), 20Gy, 10 times segmentation (figure 3). Concurrent chemotherapy with vincristine for injection (Shenzhen Wan Le Pharmaceutical Co. LTD) 1.5 mg/m^2 was performed on day 1, once every 7 days for 5 cycles. One month after radiotherapy, cyclophosphamide for Injection (75 mg/m^2 d1-2) (Endoxan, Germany), CisplatinInjection (75 mg/m^2 d1) (Jiangsu Haosen Pharmaceutical Collection Co. LTD) and Vincristine Fulfate for Injection (1.5 mg/m^2 d1, 8) were given as adjuvant chemotherapy, repeated every 4 weeks for 7 cycles. In the actual treatment, the single dose of vincristine was 2 mg. In the fourth, sixth and seventh cycles, vincristine was stopped on the eighth day and chemotherapy was stopped on the eighth cycle due to the patient's bone marrow suppression of 3 degrees and neurotoxicity of 2 degrees. According to the evaluation criteria for common adverse events of cancer treatment version 5.0, the patient's bone marrow suppression was 3 degrees, mainly manifested in leukopenia and neutropenia; nausea and vomiting was 2 degrees; neurotoxicity was 2 degrees, manifested as numbness of hands and feet; constipation was 2 degrees; weakness was 1 degree. Recombinant human granulocyte colony-stimulating factor (Qilu Pharmaceutical Co. LTD) is used to treat leukopenia. All adverse reactions were gradually alleviated after chemotherapy. Patients were followed up regularly, including general conditions and whole brain and spinal cord MRI. At present, 55 months after the first discovery of the lesion, 32 months after the second operation, and 24 months after adjuvant chemoradiotherapy, the patient is generally in good condition, with a Konzern Produktionsystem (KPS) score of 100, no obvious neurological dysfunction, and no recurrence or cerebrospinal fluid dissemination on MRI.

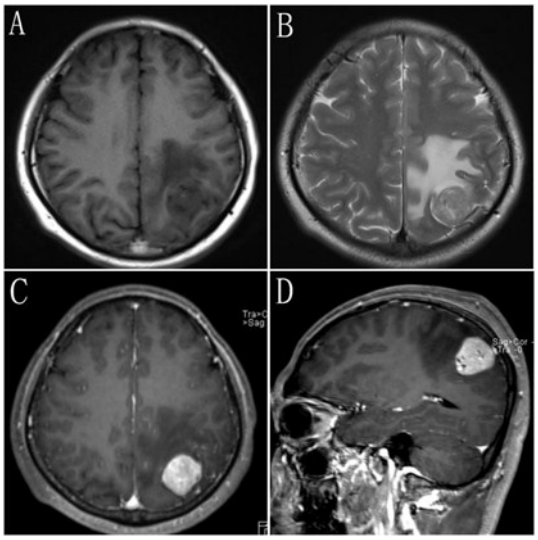

Figure 1. MRI plain scan and enhancement. A type of round mass was found in the left parietal lobe with clear boundary and size of 28×25×29mm. TIWI **(A)** shows uneven low signal and T2WI **(B)** shows uneven high signal. Contrast-enhanced scan **(C, D)** shows obvious enhancement of the lesion with spot-like areas without enhancement, compression of adjacent brain tissue, and large fluid signal shadows around the lesion.

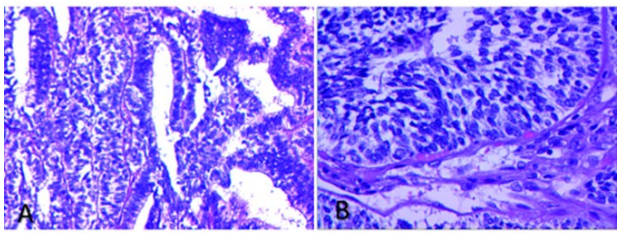

Figure 2. Histopathological findings (Hematoxylin-eosin staining, on high power): the tumor tissue is composed of various heteromorphic cells, arranged into shapes of irregular glandular tubes, capsules and sheets, showing biphasic differentiation changes, irregular karyomorphism, abundant chromatin, easy to see division images, chrysanthemum-like structures seen in some parts.

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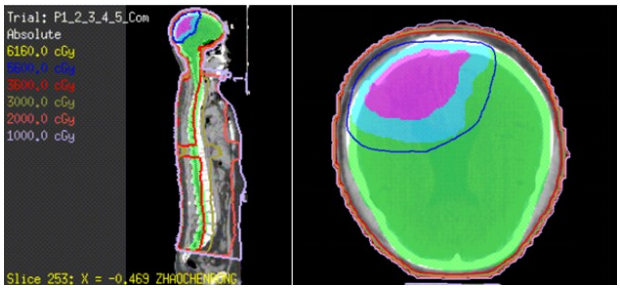

Figure 3. Radiotherapy planning CT (Treatment Planning System, Monaco). The planning target volume(PTV)of CSI (green color wash image) was administered 36 Gy (shown in red isodose line). The planning gross tumor volume of the tumor bed (PGTVtb) (baby blue color wash image) was administered 54 Gy (shown in blue isodose line). Note: The gross tumor volume of the tumor bed (GTVtb (rose red color wash image) with a margin of 1cm in three dimensions formed the Clinical Target Volume (CTV); CTV with a margin of 0.3 cm in three dimensions formed the PGTVtb.

DISCUSSION

Medulloepithelioma (MEPL) of the CNS, is a rare, malignant primary embryonic tumor of the nervous system. Typical MEPL histology is characterized by trabeculae and tubular structures similar to neural tubes, and pseudostratified neuroepithelia and poorly differentiated neuroepithelia are usually seen around the lumen [3]. Tumor cells are closely arranged, nucleoli are deeply stained, cytoplasm is rare, and nuclear division is common. Immunologic studies show that [1, 8,9]: there are abundant vimentin in the primordial epithelia of MEPL, most of which are highly expressed in LIN28A, Integrase interactor-1(INI-1) is immunopositive, GFAP, synaptophysin and EMA are immunonegative, and Ki-67 immune markers are generally high. In the fifth edition of the WHO classification of CNS tumors in 2021, ETANTR, EBLs and MEPL were all classified as ETMR and divided into three molecular subtypes (C19MC mutation, DICER1 mutation and NEC subtype) [6]. Amplification or fusion of the C19MC site at 19q13.42 is the most common genetic abnormality in ETMR, with about 90% of cases present, and biallelic mutations in the miRNA processing gene DICER1 are the second most common, occurring in about 5% of cases [10, 11]. LIN28A is generally highly expressed in ETMRs, which supports the diagnosis of ETMR, but it is not specific, and other high-grade tumors can also occur [9]. The diagnosis of this case mainly depends on histomorphology and immunochemistry, while the current diagnosis of ETMR depends on histology, immunophenotyping and molecular testing. ETMR with MEPL morphology are relatively rare [10] and express LIN28A, but a large number of tumors do not carry C19MC changes [1].

Intracranial MEPL tends to occur in children under 8 to 10 years old, with a peak of 6 months to 5 years old, and is very rare in adults [3, 7]. Due to the poor prognosis caused by rapid subarachnoid spread of tumor cells and high recurrence rate, the overall median survival time is 5 months [1]. The patients' clinical manifestations are mainly related to the location and size of the tumor, with focal neurological dysfunction, seizures and cranial hypertension, including nausea, vomiting and sleepiness. The first recurrence pattern in most ETMR patients is local tumor regeneration, while a few patients can have extensive spread of pial metastases, with occasional systemic metastases outside the central nervous system [4].

Intracranial MEPL often occurs around the supratentorial ventricles, and can also be found in the sellar region, suprasellar, infratentorial and lateral ventricles [2,12,13]. The tumor boundary is usually clear and lobulated, CT mostly shows low density or equal density, MRI T1 weighted image (T1WI) shows uneven iso - low signal, T2 weighted image (T2WI) shows uneven iso - high signal. With the progression of the disease, irregular flaky or tuberous cystic degeneration, necrosis and calcification are common in the tumor, and tumor stroke is rare. Tumors can invade and compress the surrounding brain parenchyma, resulting in swelling, but also break through the meninges and invade the adjacent skull, and subarachnoid dissemination can occur. After enhancement, most of the lesions showed uneven enhancement, but some MEPL did not enhance [14]. MEPL imaging lacks specificity, and cystic changes may be a common feature, but the proportion of cystic lesions is uncertain and cannot be distinguished from other cystic and solid tumors. This case is an adult patient; the main clinical manifestations are numbness of the limbs. The tumor was located in the parietal lobe, adjacent to the meninges, with clear boundaries, visible cystosis, obvious enhancement of the solid part (enhanced MRI), and obvious peritumoral edema, which was misdiagnosed as meningioma.

Due to the rarity of MEPL, the current literature is mostly case or small sample retrospective studies. In recent years, some scholars have carried out ETMR overall case analysis, generally recommending maximum safe resection, radiotherapy and chemotherapy adapted to age and risk as the main treatment. A pooled analysis of data from 67 patients concluded that GTR and therapeutic radiotherapy were independent favorable factors for PFS and overall survival (OS) [14]. Hurwitz [15] showed higher OS in GTR, high-dose chemotherapy and radiotherapy in univariate and multivariate analyses of 38 patients with ETMR. However, at present, the best treatment plan for the disease has not been determined. GTR is the key to prognosis, and surgical resection can alleviate the symptoms of intracranial hypertension and provide an opportunity for adjuvant treatment. Tumor cells infiltrating brain tissue suggest poor survival prognosis. It has been reported that

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extended resection to 1 cm of surrounding brain tissue or including infiltrating tissue can improve the prognosis of patients [16]. For patients with local recurrence, second operation is still the main treatment method [17].

The role of therapeutic radiotherapy is relatively clear; most cases survive longer after postoperative therapeutic radiotherapy. CSI and CSI plus local boost, and the radiotherapy dose was 20-68Gy [14,18]. Because MEPL can spread throughout the whole central nervous system, CSI is recommended in most literature. Bouhoula *et al*. [19] analyzed 44 cases of MEPL, believing that the best treatment may be GTR and therapeutic radiotherapy (in the first stage, CSI was 35Gy, 21 segments; in the second stage, focal radiotherapy was given to the tumor bed 20Gy, 12 segments). Müller *et al*. [18] gave chemoradiotherapy to MEPL patients with tumor residual after surgery, and achieved long-term survival. The treatment included CSI 36Gy (hyperfrit radiotherapy twice daily, 1 Gy each time), residual focal boost to 68Gy, simultaneous chemotherapy with vincristine weekly, and 8 cycles of adjuvant chemotherapy (cisplatin, Lomustine and vincristine). Jaramillo *et al*. [20] also introduced proton radiation therapy for ETMR cases, the CTV after CSI was described as GTV (tumor bed and residual lesion) expansion of 1cm, and it was believed that proton radiotherapy could reduce early and late radiotherapy adverse reactions, which may be helpful for radiotherapy in young children. A retrospective analysis of 228 ETMRs suggested that GTR and early therapeutic radiotherapy may be critical for long-term survival (> 36 months) in patients with ETMR [21]. Although the tendency to metastasize may indicate benefits from CSI treatment, ETMR occurs mostly in young children, so a balance needs to be struck between the potential benefits of radiotherapy and the high risk of neurocognitive function impairment. It has been reported that postoperative focal radiotherapy has also achieved long-term survival. Matsumoto *et al*. [16] gave a 6-year-old children with MEPL stereotactic radiotherapy (20 Gy) in the 1 cm area of the surgical edge, and achieved disease-free survival of more than 5 years. A small series (5 patients of ETMR) reported positive results for GTR, focal radiotherapy, modified IRS-II regimens and various concomitant drug treatments [22]. Some people have explored the use of intrathecal chemotherapy on the basis of focal radiotherapy to prevent pial dissemination, and achieved positive results [21]. There is a lack of data comparison between focal radiotherapy and CSI plus tumor bed boost.

At present, chemotherapy is mostly based on a variety of intensive combinations of other embryonic tumor treatments. It has been reported that ETMR patients without radiotherapy can obtain an extension of survival by complete resection and high-dose chemotherapy [11, 23]. Gualano *et al*. [24] reported a 5-month ETMR child whose tumor shrank after DFCI-IRS-III induction chemotherapy, and then underwent tumor resection, achieving long-term survival. A prospective P-HIT study of 30 patients with ETMR showed that after carboplatin/etoposide induction and high-dose chemotherapy, the 5-year OS was 47%, compared with 8% after other treatments [23]. There are also reports of active chemotherapy combined with autogenous bone marrow transplantation (ABMT) as an adjunct treatment for intracranial MEPL [1]. With the understanding of ETMR, new targeted drugs are also constantly being explored clinically [10].

Whether age is a prognostic factor is unclear, the relatively older patients reported [14, 18] all survived longer, possibly due to the implementation of operation, radiotherapy and aggressive chemotherapy. In both MEPL and ETMR case reports, adult patients are very rare, and there is a lack of comparison of diagnosis, treatment, and prognosis between adults and children. Adult patients are very rare in previous case reports of both MEPL and ETMR, and there is a lack of comparison of diagnosis, treatment and prognosis between adult and child groups. In this case, we reported an adult MEPL, which recurred within 18 months after the first operation (GTR) without adjuvant therapy. A longer survival period was obtained after secondary operation (GTR) and active postoperative chemoradiotherapy. Surgery and radiotherapy are still the main treatment methods for patients with local recurrence who have not received radiotherapy before. We recommend CIS plus tumor area boost in relatively elderly patients. In our case, after GRT, the patient was given CSI (36Gy) plus tumor bed (the CTV was expanded 1cm outside the tumor bed area) boost to 56Gy, and synchronous vincristine chemotherapy weekly. This radiotherapy protocol is safe and effective in this case, but the relatively clear target range and therapeutic dose need more case analysis and summary.

The main novelty of this study was that adult myeloid epithelioma is rare and rarely reported. At present, most of the literature reports are cases or small sample review studies. Surgery, radiotherapy and chemotherapy are the main treatment methods, but the specific treatment plan is not clear. Many studies do not describe the radiotherapy target area and dose in detail. In this case, simultaneous postoperative chemoradiotherapy and adjuvant chemotherapy were given to the patient after the second tumor resection, and a longer PFS was achieved, suggesting that postoperative radiotherapy and chemotherapy are beneficial to survival. In this paper, the target area and dose of radiotherapy, chemotherapy regimen and adverse reactions of patients are described in detail, and the literature of radiotherapy regimen is reviewed.

In conclusion, MEPL of the CNS in adults is rare

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and rarely reported. In the latest classification of CNS tumors, MEPL is classified as ETMR, and its diagnosis depends on histological examination and genetic screening. There are currently no large-scale clinical studies of ETMR, so the best treatment for ETMR is still being explored. In this case, a rare adult myeloid epithelioma was reported. After the second surgical resection, CCRT and chemotherapy were given, and a longer PFS was obtained, suggesting that postoperative radiotherapy and chemotherapy were beneficial to survival. The postoperative chemoradiotherapy regimen given in our case is safe and effective, and can be considered as a postoperative adjuvant therapy for relatively elderly patients. However, more clinical data are needed to demonstrate the effectiveness of this protocol in the future.

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Ethics approval and consent to participate: This case report was reviewed and approved by the Ethical Committee of the Second Hospital Affiliated to Lanzhou University, Lanzhou, China (Approval number 2023A-806 of December 12, 2023). Written informed consent was obtained from the patient.

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Authors' contributions: JL and YL designed the study and performed the experiments, JL collected the data, YL analyzed the data, JL and YL prepared the manuscript. All authors read and approved the final manuscript.

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