

PRIMARY EPITHELIOID HEMANGIOENDOTHELIOMA IN THE CEREBELLUM: CASE REPORT WITH REFERENCE TO DRASTIC CHANGE IN THE WHO CLASSIFICATION

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SUMMARY – Epithelioid hemangioendothelioma is a rare vascular brain tumor. It develops from endothelial cells, usually in the liver, lung, bone and soft tissue. Primary localization of this tumor in the intracranial space is very uncommon; only 47 cases have been described in the literature. This tumor was initially classified as grade I (benign) in the World Health Organization (WHO) 2007 classification. In 2016, this tumor was re-classified as grade III (malignant). Herein, the first case report of epithelioid hemangioendothelioma in the cerebellum of a male patient is presented. Complete surgical excision was done. No adjuvant therapy was administered. Magnetic resonance imaging performed 2 years after the surgery continued to show no recurrence of the tumor. To our knowledge, this is the first report of cerebellar location of this rare tumor. In addition, the authors report drastic re-classification of the epithelioid hemangioendothelioma from the benign tumor (WHO 2007) to a malignant one (2016), which significantly changes postoperative management and follow up of this brain neoplasm.

Key words: *Hemangioendothelioma, epithelioid; Brain neoplasms; World Health Organization; Cerebellum*

Introduction

Epithelioid hemangioendothelioma (EHE) is a rare and uncommon vascular tumor of the brain^{1,2}. Malignant characteristics of EHE are invasion, recurrence and metastasis, and these characteristics are more pronounced in the intracranial space. It accounts

for less than 0.02% of all brain tumors. Only 47 cases of this tumor have been reported intracranially, with only 6 cases in the posterior cranial fossa, outside of the cerebellum (two in pediatric population). None of the posterior fossa cases was totally removed; five had subtotal resection and one only biopsy. No primary localization of EHE in the cerebellum has been reported so far³.

In this case report, the authors describe the first EHE of cerebellar location with radical tumor resection. In addition, we report drastic change in the classification of this tumor from benign (World Health

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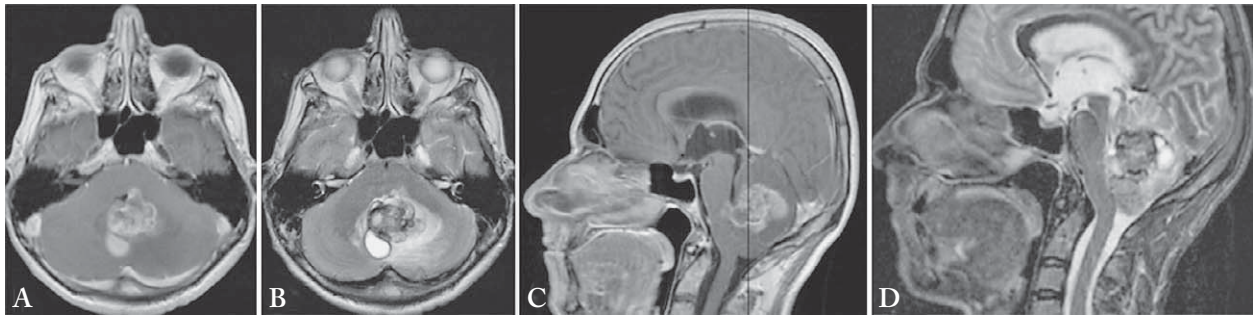


Fig. 1. Preoperative MRI. Axial and sagittal scans showing a tumor mass in the cerebellum only partially involving the brain stem: (a) axial post-contrast T1; (b) axial T2; (c) sagittal post-contrast T1; (d) sagittal T2 MRI images.

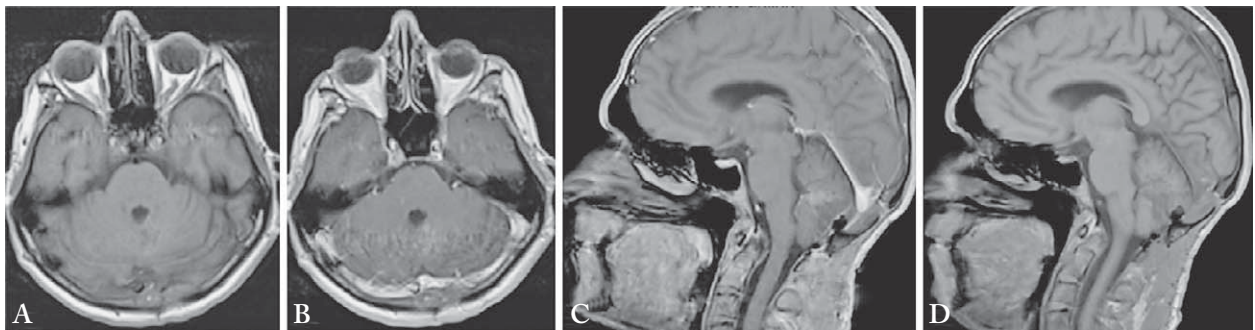


Fig. 2. MRI scans at three months postoperatively showing completely resected tumor: (a) axial T1; (b) axial post-contrast T1; (c) sagittal contrast T1; (d) sagittal non-contrast T1 MRI images.

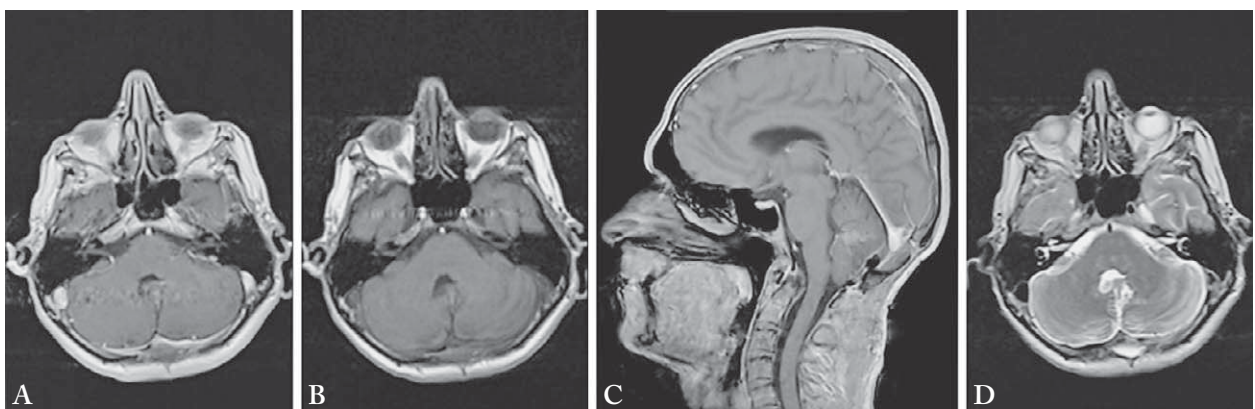


Fig. 3. Postoperative MRI (2 years) showing no recurrence of the tumor; (a) axial post-contrast T1; (b) axial non-contrast T1; (c) sagittal post-contrast T1; (d) axial T2 MRI images.

Organization (WHO) classification 2007) to malignant (WHO classification 2016).

Case Report

A 34-year-old male patient was admitted to the University Clinical Center of Sarajevo with a 20-day

history of progressive headache and vomiting. The patient reported fatigue, weight loss in the past month and vertigo. Examination showed gait difficulties due to vertigo and fatigue. Physical and neurological examination was normal without nuchal rigidity. Non-contrast magnetic resonance imaging (MRI) of the brain visualized an irregular heterogeneous signal in-

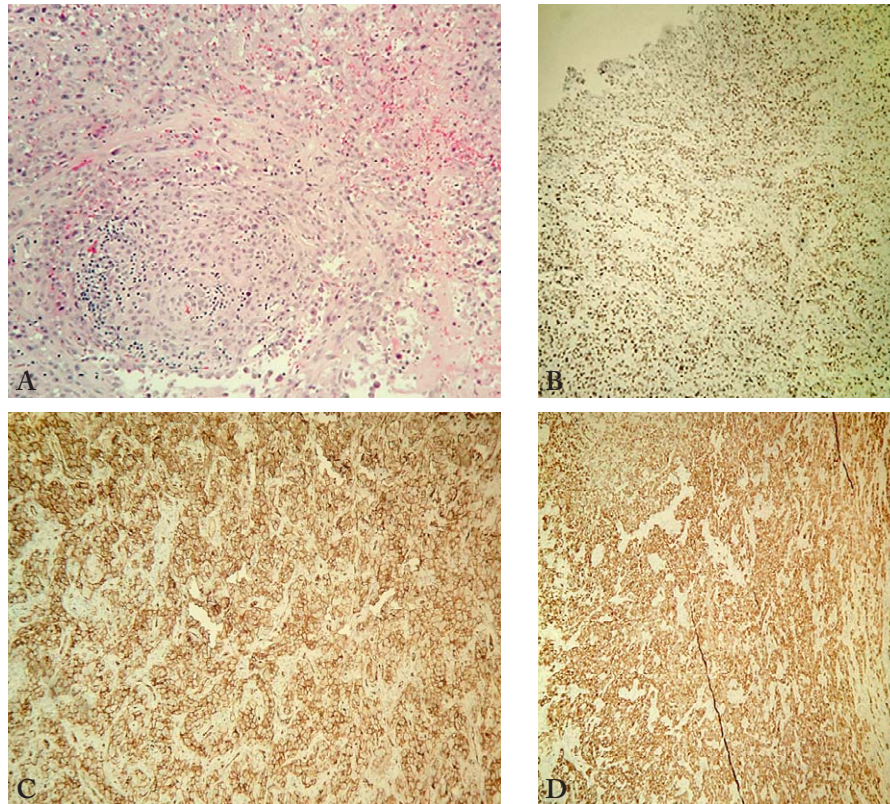


Fig. 4. (a) Microscopically, epithelioid-appearing cells were distributed in cords or nests. The tumor cells had oval or round nuclei and variably eosinophilic cytoplasm, and some contained cytoplasmic vacuoles. Some cells formed small intracellular lumina with occasional red cells included. Cellular pleomorphism was significant, and rare mitotic figures were present; (b) immunohistochemically, the tumor was positive for anti-ERG (E26 oncogene homolog); (c) the tumor was strongly and diffusely positive for CD31; (d) immunohistochemically, the tumor was strongly and diffusely positive for panCK (AE1/AE3) (magnification X100).

tensity area in the midline within the cerebellum, compressing the fourth ventricle and propagating towards the brain stem at the level of medulla oblongata and parasagittal left side of the pons. Within this zone, there was an area of T1 hyperintensities, and several T2 marginally hypointense areas representing probable hemorrhages. Post-contrast MRI showed occasional opacification. The size of the lesion measured 38x44x37 mm (Fig. 1).

The patient underwent surgery in prone position the next day after admission. Median suboccipital craniotomy was performed, followed by telovelar microsurgical approach. The tumor appearance was gray-blue, and it was highly vascular, with hard and soft parts. The usual microsurgical technique with gross total tumor resection was employed. After tumor re-

moval, hemostasis was performed, dura mater was closed in watertight fashion, then bone flap was positioned and fixed. The patient was extubated immediately after the surgery, and was without any new neurological deficit (Figs. 2 and 3).

The tumor was composed of short strands or solid nests of round to slightly spindled endothelial cells with abundant glassy eosinophilic cytoplasm with well-defined cell borders, and round to ovoid, bland, often vesicular nuclei with small central nucleoli (Fig. 4). These cells showed intracytoplasmic lumina containing erythrocytes. Tumor cells were negative for CK7, CK20, PAX8, TTF1, CDX2, epithelial membrane antigen, glial fibrillary acidic protein, S100, and showed strong and uniform immunoreactivity for endothelium-specific markers CD31, CD34 and for ERG. There were foci

Table 1. Reported cases of intracranial epithelioid hemangioendothelioma, partially or completely located in posterior cranial fossa

Case	Authors and year	Age (yrs) /sex	Side/location	Excision	Adjuvant therapy	Follow up period/outcome
1	Chen <i>et al.</i> , 1997	3/M	Cervico-medullary	Subtotal	Chemo	Tumor decrease (4 yrs)
2	Tamman <i>et al.</i> , 1997	4/M	Cerebellopontine angle	Subtotal	Radio	Tumor stable (2 mo)
3	Rushing <i>et al.</i> , 1998	38/F	Clivus	Biopsy	Radio	N/A
4	Watanabe <i>et al.</i> , 2003	55/F	Lower petroclival region	Subtotal	Radio	Tumor stable 1 yr
5	Zheng <i>et al.</i> , 2012	44/F	Lower petroclival region	Subtotal	None	Tumor stable 1.5 yrs
6	Drazin <i>et al.</i> , 2013	62/M	Mastoid/posterior fossa	Subtotal	Radio after recurrence	Recurrence 2 surgeries in 8 yrs

Chemo = chemotherapy; Radio = radiotherapy; N/A = not available

of necrosis. The findings of a tumor of endothelial cells showing a focally solid pattern of growth, histiocytoid cytology, and lacking aggressive features of angiosarcoma indicated a diagnosis of EHE.

After the surgery, the patient was discharged home in neurologically intact condition. Postoperative MRIs of the brain did not show any evidence of residual or recurrent tumor. Considering the new WHO classification of the central nervous system (CNS) tumors (2016) and changing of tumor grading from grade I to grade III, the patient was called to discuss adjuvant therapy, which he rejected.

Discussion

Epithelioid hemangioendothelioma is an uncommon tumor that accounts for 1% of all vascular tumors and the most common primary location of which is in soft tissues, bone, lung and liver. It is rarely located intracranially, primarily within the skull base, dura, or brain parenchyma, accounting for <0.02% all brain tumors^{1,2}. Localization of EHE in the posterior fossa seems to be extremely rare according to a systematic review by Barger *et al.*³. In this work, 47 intracranial EHE cases are described, none located in the cerebellum. Only 6 cases of EHE were located in the posterior cranial fossa, outside of the cerebellum (Table 1)³. None was radically resected; five were removed subtotally and biopsy was performed in one case. In addition, in our search of the English literature (PubMed and Google Scholar databases), no cerebellar location has been reported.

Epithelioid hemangioendothelioma is a tumor that is clinically and histologically similar to both benign

hemangioma and angiosarcoma; it has some characteristics of a malignant tumor, such as invasion, recurrence and metastasis. Concerning the 2016 WHO Classification of Tumors of the CNS, EHE is classified as mesenchymal, non-meningothelial tumor grade III⁴. It is interesting that in the 2007 WHO classification, EHE is classified as grade I neoplasm. This new classification changes drastically the postoperative oncologic treatment regarding adjuvant therapy.

Histologic differential diagnosis and characteristics of EHE

Differential diagnosis of brain EHE includes metastatic carcinoma, epithelioid sarcoma, chondroma and choroid meningioma^{4,6-9}. Epithelioid angiosarcoma may also be considered in differential diagnosis in cases of EHE with increased nuclear atypia. Epithelioid sarcoma (ES) is sometimes considered in differential diagnosis because of the immunophenotypic overlap. ES has strong keratin expression and EMA positivity, approximately 50% of ES are positive for CD34. EHE has a growth pattern of capillary sized channels lined by endothelial cells, with stroma rich in lymphocytes and histiocytes. Its cells contain relatively abundant eosinophilic cytoplasm, which may be vacuolated. In general, the nuclei are round or occasionally indented or vesicular, and show only minor atypia. Mitoses and limited necrosis may be seen. Small intracytoplasmic lumina (blister cells) are seen, but well-formed vascular channels are typically absent. Immunohistochemical studies (e.g., for CD31 and ERG) confirm the endothelial nature of these tumors. Approximately 90% of EHE harbor recurrent t(1;3)(p36;q25) translocation, which results in WWTR1-CAMTA1 fusion¹⁰.

A novel WWTR1-CAMTA1 gene fusion is a consistent abnormality in EHE of different anatomic sites^{11,12}.

Hemangioendothelioma is characterized by myxoid and hyalinized stroma, and angiosarcoma by irregular vascular or sinusoid channels, atypical mitosis, solid growth pattern, and typically foci of necrosis are present^{2,4-7}, while chondroma and choroid meningioma are microscopically showing cords and nests of epithelioid cells and growth pattern with extracellular chondroid material⁴. Epithelioid sarcoma has a higher level of nuclear atypia and often develops in distal extremities, with round eosinophilic cells surrounding cores of necrotic debris. Metastatic carcinoma has greater atypia and is positive for cytokeratins⁴. Definitive diagnosis of EHE is confirmed with positive endothelial cell markers CD31, CD 34 and factor VII-associated antigen, as in our case where the EHE was positive for CD31 and CD34, which confirmed the diagnosis^{2,4,10-14}. Another important characteristic and molecular marker of EHE is chromosomal translocation resulting in WWTR1-CAMTA fusion, which is unique for EHE, and can help confirm EHE in overlapping cases^{7,13-17}.

Treatment options

Treatment protocols for intracranial EHE are not well established because of its rare occurrence. The treatment of choice is complete excision of EHE^{1,7,10,11,18-24}. In our case, complete surgical excision without any radiotherapy and chemotherapy was performed. In all reported cases, approximately 60% of all EHE were completely removed, but none of those with cerebellar location¹. Pre- and postoperative adjuvant therapies are now recommended for EHE if complete resection is not possible because of the invading nature of the tumor to local tissues due to vascularity of EHE, where bleeding and blood loss can cause patient death, or in case of metastasis or multiple tumors^{1,6}. Some authors recommended preoperative embolization of the lesion to prevent profuse bleeding¹. Experience with radiotherapy in the management of EHE is very poor, as it was used in only few cases to date. Zheng *et al.*¹ report that only 13 patients underwent radiotherapy for intracranial EHE and only one case for tumor bed after total removal^{1,6}.

Given the possibility of higher radiotherapy morbidity and the lack of strong data supporting it over

chemotherapy, the latter is likely a better first option for adjuvant treatment than radiation. However, no chemotherapeutic agent has been shown to consistently influence tumor shrinkage but a number of those do seem to prevent further growth to a certain extent, albeit inconsistently. Traditionally, interferon alpha has been used, the rationale being that it inhibits endothelial growth and thus may be effective against a tumor derived from endothelial tissue²⁵. A number of other antiangiogenic medications have also been utilized. In a recent review of 36 patients with EHE treated with antiangiogenic therapy (thalidomide, lenalidomide, sorafenib, or bevacizumab alone or in combination), six patients experienced partial response, 14 stable disease, and 16 progressive disease²⁶. Radiotherapy seems to have similar rates of success; out of seven patients in the literature with intracranial EHE who received adjuvant radiotherapy, one had tumor shrinkage, three had stable tumor, and three experienced recurrent tumor growth and symptoms^{1,3}. Some treatment options with chemotherapy may result in better outcome, especially for metastatic and multiple cases^{25,26}.

It is important to note that our patient was operated in 2015 when the WHO classification of CNS tumors from 2007 was used, according to which EHE was classified as grade I. Considering the new WHO classification from 2016, according to which the same tumor is now designated as malignant (grade III), the patient was called for an interview for additional therapy, but he refused it. Interestingly, this tumor in this new calibration has changed drastically from benign grade I to malignant grade III. This should be considered in long-term follow up of EHE patients and neurosurgeons should be aware of this.

Despite the new grading score and with limited experience with radio- and chemotherapy of intracranial EHE, gross total resection remains the treatment of choice. Adjuvant treatment should be considered, but long-term experience on larger patient population is lacking¹. In our case, MRI at 2-year follow up showed that resection was complete without recurrence and no adjuvant treatment so far.

Conclusion

Epithelioid hemangioendothelioma is an uncommon and rare primary intracranial vascular tumor. The localization of this tumor in the cerebellum has not

been described before; no radical tumor resection of this tumor has been accomplished so far in this location. Histopathologic and immunohistochemical characteristics of the tumor are essential for the diagnosis of EHE. Complete surgical excision is a recommended treatment, with scrutinized long-term follow up by MRI screening. Adjuvant treatment should be strongly considered despite the lack of experience with it. Neurosurgeons treating or following up EHE patients should be aware of the drastic change in its classification from benign (WHO 2007) to malignant (WHO 2016).

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Sažetak

PRIMARNI EPITELOIDNI HEMANGIOENDOTELIOM U MALOM MOZGU: PRIKAZ SLUČAJA UZ OSVRT NA DRASTIČNU PROMJENU U KLASIFIKACIJI SZO

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Epitelioidni hemangioendotheliom je rijedak vaskularni tumor mozga. Nastaje iz endotelnih stanica, obično u jetri, plućima, kosti i mekom tkivu. Primarna lokalizacija ovoga tumora u intrakranijskom prostoru je veoma rijetka; samo je 47 slučajeva opisano u literaturi. Ovaj tumor je isprva bio klasificiran kao gradus I (dobročudan) u klasifikaciji Svjetske zdravstvene organizacije (SZO) iz 2007. godine. U 2016. godini ovaj tumor je klasificiran kao gradus III (zloćudan). Autori opisuju prvi slučaj epitelioidnog hemangioendothelioma u malom mozgu kod muškog bolesnika. Izvršena je potpuna kirurška ekscizija. Adjuvantna terapija nije ordinirana. Nalaz magnetske rezonance 2 godine nakon operacije pokazao je da nema povratka tumorske mase. Prema našem saznanju, ovo je prvi prikaz lokalizacije ovoga rijetkog tumora u malom mozgu. Također, autori upućuju na drastičnu promjenu u klasifikaciji epitelioidnog hemangioendothelioma od dobroćudnog tumora (SZO, 2007.) do zloćudnog (2016.), koja zasigurno mijenja poslijeoperacijski pristup i praćenje ove neoplazme mozga.

Ključne riječi: *Hemangioendotheliom, epitelioidni; Moždani tumori; Svjetska zdravstvena organizacija; Mali mozak*