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Suprasellar epithelioid hemangioendothelioma: Case report and review of the literature

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Abstract

Background: Epithelioid hemangioendothelioma (EHE) is a rare sarcoma of vascular origin, which is clinically and histologically intermediate between benign hemangioma and angiosarcoma. It is most commonly found in the liver, lung, and bone, however, 46 intracranial cases have been reported in the literature, of which this is the fifth reported suprasellar tumor.

Case Description: A 45-year-old woman developed progressive lethargy, somnolence, and memory decline over the course of 6 months. On computed tomography (CT), she was found to have a large hypothalamic mass and underwent subtotal resection via a bifrontal craniotomy.

Conclusions: While primary intracranial EHE is an uncommon presentation of a rare tumor, the suprasellar region does not seem to be an unusual location when it does occur. Prognosis is generally good, and may be better for primary intracranial disease than that for EHE originating elsewhere. Surgery is the first line of therapy, with variable benefit from adjuvant chemotherapy or radiation when total resection is not possible. Chemotherapeutic approaches in current use are directed at preventing endothelial proliferation.

Key Words: Epithelioid hemangioendothelioma, intracranial, suprasellar, review, vascular tumor

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INTRODUCTION

Epithelioid hemangioendothelioma (EHE) is an uncommon neoplasm of vascular origin which may arise in a number of locations; most frequently the liver, lungs, and bones but also intracranially.[3] While less aggressive than angiosarcoma, it may metastasize and in some cases demonstrates quite rapid growth.[17] Management is centered on surgical resection with adjuvant chemotherapy, usually with antiangiogenic agents.[46] We herein present a case of EHE arising in the suprasellar region in a 45-year-old woman, summarize previously published cases of intracranial EHEs, and review the literature on the clinical course and management of EHE.

CASE DESCRIPTION

Over the course of six months, a 45-year-old Vietnamese woman with a history of type 2 diabetes mellitus and hyperlipidemia became progressively lethargic, somnolent,

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and forgetful. Originally thought by her physicians to have an endocrine issue, she was diagnosed with an intracranial mass on computed tomography (CT) scan when her husband found it difficult to arouse her at home and brought her to a local emergency department. She was referred to our institution for neurosurgical evaluation, at which time she was sleeping 16 hours a day, and was noted to ask the same questions repeatedly, forgetting the answers each time. She had gained 25 pounds during the months prior to the presentation. She did not complain of headaches or visual changes, and had no symptoms of diabetes insipidus. Her last menstrual period had been 3–4 years prior to presentation. Neurological exam was unremarkable [Extraocular movements were intact, visual fields were full, and there was no nystagmus. Muscle strength was 5/5 throughout, reflexes were brisk and symmetric, and gait was normal-based. There was no dysmetria or pronator drift.]

Magnetic resonance imaging (MRI) with contrast was obtained, revealing a 3.6 × 3.7 × 3.2 cm lobulated, heterogeneous, fluid-attenuated inversion recovery hyperintense, and avidly enhancing hypothalamic mass extending into the anterior third ventricle [Figure 1]. The patient underwent subtotal resection via bifrontal craniotomy. Intraoperatively, the tumor was found to be rubbery and vascular, and it appeared continuous with portions of the hypothalamus and optic nerves. Postoperative course was notable for a triphasic water balance response and new-onset adrenal insufficiency treated with hydrocortisone. She also developed new psychiatric symptoms including paranoia and irritability beginning approximately 1 month postoperatively.

Pathology

Histologic examination demonstrated a predominantly epithelioid neoplasm with areas of spindled cytology with a dense inflammatory infiltrate [Figure 2a]. The tumor demonstrated several architectural patterns, including retiform [Figure 2b], chordoid [Figure 2c], and strands, often embedded in a myxoid matrix, giving an appearance reminiscent of chordoma at low power. At high power, many cells demonstrated intracytoplasmic lumina [Figure 2d] with occasional erythrocytes. The tumor was sharply demarcated from the surrounding brain, with reactive changes, including gliosis and accumulation of Rosenthal fibers, suggesting slow growth [Figure 2e]. The tumor cells were strongly and diffusely positive for CD34 [Figure 2f], and more focally positive for CD31 [Figure 2g], FLI-1, and factor VIII, compatible with a tumor of endothelial origin; however, there was only scattered reactivity for Erg [Figure 2h]. An immunostain for SMA [Figure 2i] to rule out a fibroblastic process or leiomyosarcoma were negative, and an immunostain for ALK-1 performed to exclude inflammatory pseudotumor was negative. Immunostains for EMA [Figure 2j], progesterone receptor, and S-100 were negative, which are less compatible with diagnoses of chordoid meningioma, chondrosarcoma, and chordoma. Immunostains for Oct-4 and PLAP performed to exclude a germ cell tumor were negative. Immunostains for cytokeratins CAM 5.2 and AE1/3 were performed to exclude a neoplasm of epithelial origin, and demonstrated only focal immunoreactivity, and an immunostain for TTF-1 was performed to exclude a metastatic carcinoma from a lung or thyroid primary was negative. Immunostains for CD163, CD3, CD20, and CD68 [Figure 2k-m] highlighted a marked lymphohistiocytic infiltrate throughout the tumor, however, immunostains for CD15 and CD30 were negative, arguing against a lymphoproliferative disease such as Hodgkin lymphoma, and an immunostain for CD1a to exclude a histiocytic process such as Langerhan's cell histiocytosis was negative. Immunostain for Ki-67 shows scattered positivity, demonstrating the moderate proliferative characteristics of this tumor [Figure 2n]. An immunostain for glial fibrillary acidic protein [Figure 2o] is negative in the tumor cells, but highlights the sharp demarcation of the tumor from the adjacent brain.

DISCUSSION

Epithelioid hemangioendothelioma (EHE) is a rare sarcoma of vascular origin which is clinically and histologically intermediate between benign hemangioma and angiosarcoma. It can present at any age but most commonly presents in the fourth and fifth decades.[3] A slight overall predilection for females

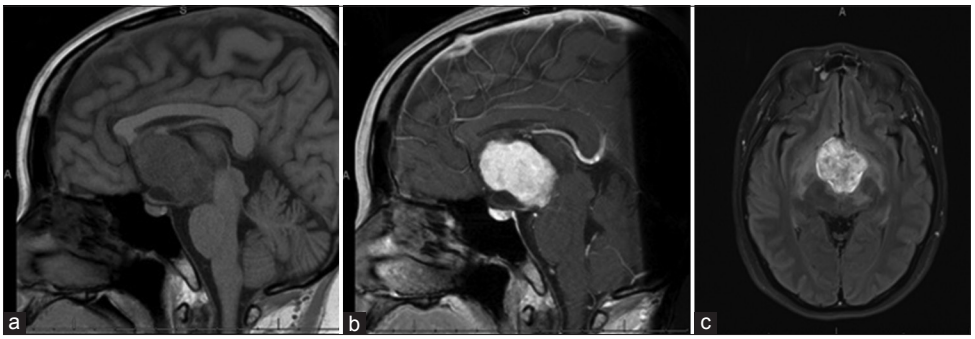

Figure 1: (a) Sagittal T1 precontrast, (b) sagittal T1 postcontrast, (c) axial fluid-attenuated inversion recovery

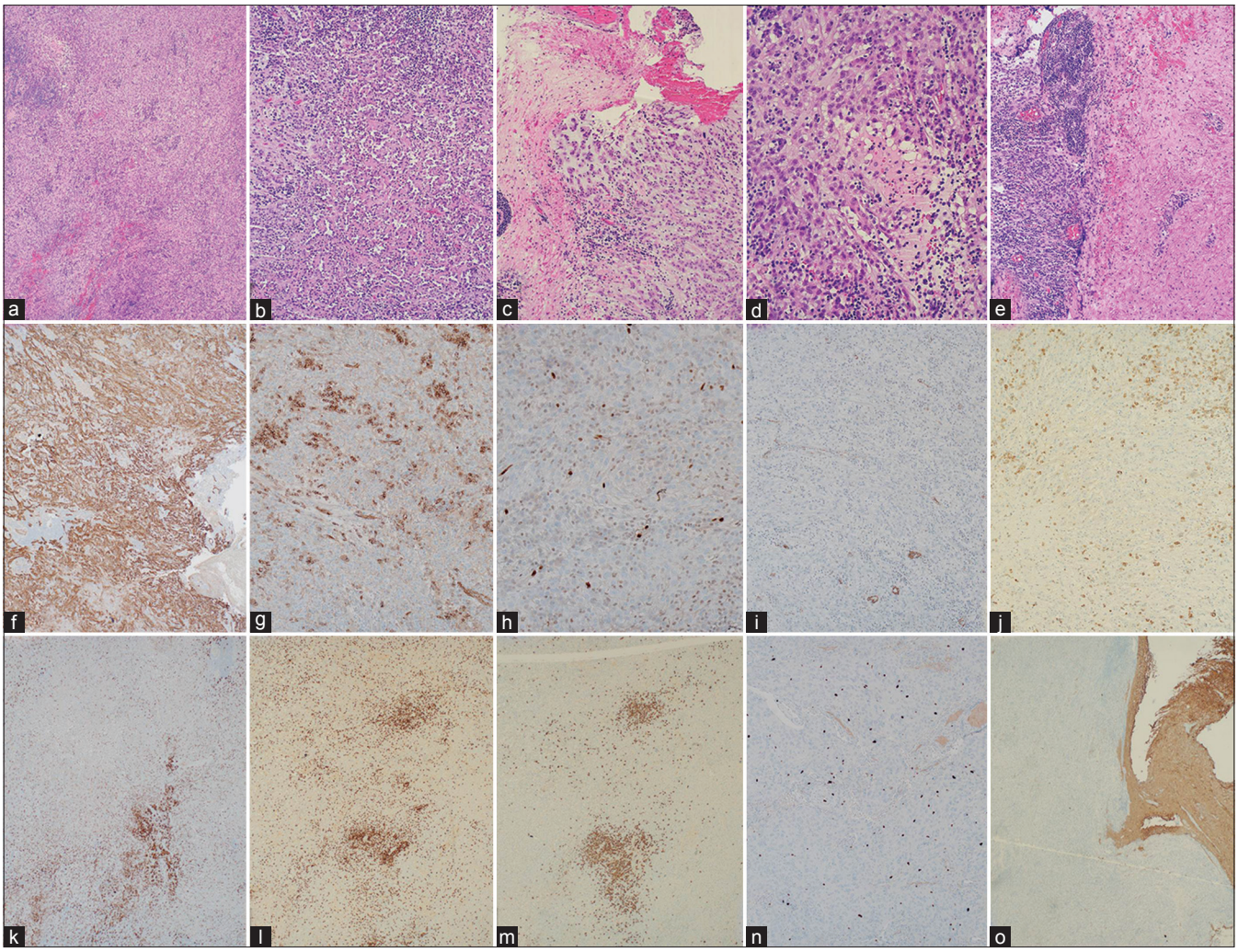

Figure 2: (a) Hematoxylin and Eosin (H and E), low power, (b) H and E, medium power, (c) H and E, medium power, (d) H and E, medium power, (e) H and E, low power, (f) CD34, (g) CD31, (h) Erg, (i) SMA, (j) EMA, (k) CD163, (l) CD3, (m) CD20, (n) Ki-67, (o) GFAP

has been reported, however, the majority of intracranial cases have occurred in males.[3] The pathophysiology of tumor development is poorly understood, though the fusion of the *WWTR1* gene, part of the hippo signaling pathway, to the CAMTA1 tumor suppressor gene via a t (1;3) (p36;q25) translocation seems to be present in most cases.[3] EHE is most commonly located in the liver, lung, and bone, though 46 previous cases of intracranial EHEs have been reported in the literature [Table 1]. This is the fifth reported case of EHE occurring in the suprasellar region, suggesting that while rare, this is not an unusual location for the tumor to arise. The patient's symptoms, however, were quite different from previous suprasellar EHEs, which presented with headache and visual loss;[4] loss of libido and asthenia;[15] headaches, ptosis, and diplopia;[32] and headache, diplopia, and visual loss.[1]

Radiologically, EHEs typically demonstrate uniform contrast enhancement on CT, which in at least one case led to misdiagnosis as a meningioma.[50] On MRI, the lesion may be isointense, hyperintense, and/or heterogeneous on precontrast T1 and there is intense enhancement with contrast.[15] The tumor may appear hyperintense and/or heterogeneous on T2. The differential diagnosis based on MRI may include choroid glioma or an ectopically located craniopharyngioma.

The clinical course of EHE is usually somewhat indolent compared to other sarcomas; overall, 5-year survival is 73% (Lau 2011) vs 35% for angiosarcoma.[17,23] Only five patients with intracranial EHE reported in the literature died from tumor complications, three of whom had multiorgan system disease. 20–30% of EHEs metastasize hematogenously to other organs.[3] While EHEs elsewhere in the body present with multiple tumors in the same organ system, in up to 50% of cases (shown by a recent study to be monoclonal local metastases rather than synchronous primaries), primary intracranial EHE appears to be unifocal.[11] The seven reported cases of multiple intracranial lesions were all associated with EHE of other organs and were likely metastases.[19,20,28,32,38,41,45]

Table 1: Reported intracranial epithelioid hemangioendothelioma

	Authors	Age/ sex	Side/location	Excision/ bleeding	Adjuvant therapy	Follow-up	Other organ involvement
Adult cases							
1	Pearl *et al*.[32]	36 M	R/fronto-parietal	Biopsy (1st op/term)	Radiation	Improvement; tumor decrease	
2	Pearl *et al*.[32]	73 M	Suprasellar	Subtotal	Radiation	Improvement; tumor stable	
3	Kepes *et al*.[19]	58 M	L/temporal	Resection	None	NA	Liver
4	Kepes *et al*.[19]	74 M	L/temporal	Resection	None	NA	
5	Hurley *et al*.[18]	23 F	Multiple	Total (x2)	None	Recurrence (6y); A (10y)	Heart
6	Nora *et al*.[28]	28 F	R/frontal	Total	None	Symptom free and tumor stable (30m)	
7	Nora *et al*.[28]	62 M	L/frontal	Total	None	Symptom and tumor free (1y)	
8	Puca *et al*.[35]	27 M	R/temporal	Total (x2; 1st op terminated)	Radiation and VE	Symptom and tumor free (18m)	
9	Phookan *et al*.[33]	36 F	R/cavernous sinus	Total	None	Disabled and tumor free (4m)	
10	Fryer *et al*.[13]	61 M	R/fronto-parietal	Total	Radiation	Recurrence (8w); D (6m)	
11	Golash *et al*.[14]	33 M	L/frontal	Total (x2; 1st op terminated)	None	Symptom and tumor free (2m)	
12	Rushing *et al*.[37]	38 F	Clivus	Biopsy	Radiation	NA	
13	Tancredi *et al*.[41]	20 F	Bilateral frontal	Total	Chemo	Alive (3y)	Skull
14	Palmieri *et al*.[30]	20 F	Bilateral parietal	Total	Chemo	Symptom free and tumor stable (30m)	Bone
15	Chan *et al*.[5]	20 M	L/frontal	Total	None	Symptom and tumor free (2y)	
16	Koh *et al*.[20]	26 F	L/sphenoid bone	Total (x2)	Failed VE	Improvement	
17	Watanabe *et al*.[45]	55 F	Petroclival	Subtotal	Radiation	Improvement and tumor stable (1y)	
18	Kubota *et al*.[21]	24 F	R/parieto-occipital	Total (x2; 1st op terminated)	Radiation and VE	Symptom and tumor free (9y)	
19	Baehring *et al*.[4]	49 F	Suprasellar	Subtotal	None	Improvement and tumor stable (6m)	
20	Hamlat *et al*.[15]	53 M	Suprasellar	Biopsy (1st op/ term)	Radiation and Chemo	Improvement and tumor stable (21m)	
21	Endo *et al*.[10]	69 M	Multiple	Subtotal	Chemo	Recurrence (1.5m); Death (3m)	
22	Fernandes *et al*.[12]	27 M	L/temporal	Subtotal	None	Recurrence (3m); Death (8m)	
23	Yeo *et al*.[48]	55 M	L/multiple	Total (frontal tumor)	NA	NA	
24	Parajon *et al*.[31]	58 M	R/sphenoid bone	Total	None	Symptom and tumor free (1y)	
25	Wong *et al*.[47]	50 M	L/multiple	Total	None	NA	
26	Zhang *et al*.[49]	57 F	L/temporal	Total	Radiation	Recurrence (2w); tumor decrease (2m)	
27	Sumrall *et al*.[39]	31 F	Multiple	Total (largest tumor)	Radiation and Chemo	Tumor stable (11y)	Scalp, liver, skull, lung
28	Zheng *et al*.[50]	25 M	R/temporo-parietal	Total	None	Symptom and tumor free (5m)	
29	Zheng *et al*.[50]	44 F	Petroclival	Subtotal	None	Symptom free and tumor stable (1.5y)	
30	Ma *et al*.[25]	58 F	Clival	Subtotal	Gamma knife radiotherapy	No recurrence or metastasis (6m)	
31	Ahmed *et al*.[1]	42 F	Sellar/suprasellar	NA	NA	NA	
32	Rocha Oliveira *et al*.[36]	37 F	L paracentral w/ concurrent lung involvement	Total	Sunitinib	Slight RLL paresis and tumor free (14m)	Lung
33	Drazin *et al*.[9]	62 M	L Mastoid/posterior fossa	Total	Rad following recurrence	Recurrence; symptom improvement and tumor free after 2nd resection (8y)	

Contd...

Table 1: Contd...

	Authors	Age/ sex	Side/location	Excision/ bleeding	Adjuvant therapy	Follow-up	Other organ involvement
34	Tsuchiya *et al*.[43]	24 F	Numerous bilateral lesions; also lung and liver	Biopsy	Rad	Death (4m)	Lung, liver
35	Medina *et al*.[26]	52 M	Temporal bone-posterior fossa; multiple bone mets	None	Chemo/rad	Death	Bone
36	Pacheco *et al*.[29]	37 F	L Sphenoid greater wing	NA	NA	NA	
37	Present case	45 F	Suprasellar	Subtotal			
Pediatric cases							
1	Llena *et al*.[24]	2w M	R/temporo-occipital	Total	NA	Death (1d)	
2	Taratuto *et al*.[42]	4y M	R/parietal	Subtotal	None	Tumor stable (6y)	
3	Chow *et al*.[7]	4m M	R/fronto-parietal	Subotal (x4)	None	Recurrence (x2); disabled (28m)	
4	Chen *et al*.[6]	7y F	R/gasserian ganglion	Total	None	Tumor free (5y)	
5	Chen *et al*.[6]	3m M	Cervico-medullary	Subtotal	Chemo	Tumor decrease (4y)	
6	Tamman *et al*.[40]	4y M	L/cerebellopontine angle	Subtotal	Radiation	Tumor stable (2m)	
7	Hodaie *et al*.[16]	4m M	L/temporal	Total	None	Symptom and tumor free (1y)	
8	Venizelos *et al*.[44]	11m M	R/parieto-temporo-occipital	Total (x2)	None	Recurrence (6m); tumor free (30m after operation #2)	
9	Mohan *et al*.[27]	15y F	R/fronto-temporo-parietal	Total	Radiation	Recurrence (3w); Death (4w)	
10	Aniba *et al*.[2]	3y F	L/orbital-nasal-cavernous sinus	Subtotal	None	Recurrence (2m); Death (2m4d)	

M: Male, F: Female, w: Weeks, m: Month, d: Days, L: Left, R: Right, op: Operative

Despite the generally slow disease progression, some EHEs are quite aggressive and efforts have been made to determine prognosis based on tumor characteristics; an analysis of 49 patients with EHEs arising in soft tissue found 5-year disease-specific survival to be 59% among patients with tumor size >3 cm and >3 mitotic figures/50 HPFs and 100% for other patients.[8] While this study was not undertaken in intracranial EHEs, it suggests our patient may have a relatively unfavorable prognosis given the size of her tumor and could benefit from some form of adjuvant therapy.

Treatment

The cornerstone of EHE treatment is surgical resection of the tumor. Recurrence is rare after total resection; a recurrence rate of 13% has been published.[46] Total resection of the tumor was not possible in our patient; this is frequently the case because intracranial EHEs often aggressively invade the surrounding tissue.[50] Bleeding is also a concern; while the transformed endothelium in these tumors tends to obliterate the vessel lumen such that EHEs are not as grossly or microscopically vascular as hemangiomas, in one review of reported cases, 16% of resections were aborted due to hemorrhage.[5] Total resection was possible in approximately 60% of published intracranial EHE cases. Subtotal resections tend to lead to regrowth and adjuvant therapy is likely indicated in these cases, particularly with large residual tumors and higher-grade histology, as discussed above. Options for adjuvant treatment include chemotherapy, radiation, and vascular embolization.[21]

Given the higher long-term morbidity of radiotherapy and the lack of strong data supporting one over the other, chemotherapy is likely a better first option for adjuvant treatment than radiation. No chemotherapeutic agent has been shown to consistently effect tumor shrinkage but a number do seem to prevent further growth, 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 tissue.[41] A number of other antiangiogenic medications have also been utilized. Sumrall *et al*. published the case of a patient with intracranial, cutaneous, hepatic, and pulmonary EHE which had been refractory to treatment with Adriamycin + ifosfamide, cisplatin chemoembolization, and IFN-α but stabilized with lenalidomide.[39] This derivative of thalidomide is thought to inhibit vascular endothelial growth factor and enhance the antitumor T-cell response, and do so with a more favorable side effect profile than thalidomide or IFN-α. Other, newer antiangiogenic

treatments have been reported to be effective against EHE, including capecitabine + bevacizumab,[23] Pazopanib,[38] and sunitinib.[34] In a recent review of 36 patients with EHE treated with antiangiogenic therapy (thalidomide, lenalidomide, sorafenib, or bevacizumab alone or in combination), 6 experienced a partial response, 14 stable disease, and 16 progressive disease.[38] Metronomic cyclophosphamide therapy has also been used.[22]

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 a stable tumor, and three experienced recurrent tumor growth and symptoms.[50] Vascular embolization has mostly been used in a neoadjuvant manner to reduce tumor size preoperatively.

CONCLUSION

While primary intracranial EHE is an uncommon presentation of a rare tumor, the suprasellar region does not seem to be an unusual location when it does occur. Prognosis is generally good, and may be better for primary intracranial disease than for EHE originating elsewhere. Surgery is the first line of therapy, with variable benefit from adjuvant chemotherapy or radiation when total resection is not possible.

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Conflicts of interest
There are no conflicts of interest.

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