Primary epithelioid angiosarcoma of the temporal bone with initial presentation of otalgia

Di Ai, MD, PhD^a, Riyam T. Zreik, MD^a, Frank S. Harris, MD^b, Gerhard Hill, MD^c, and Yuan Shan, MD, PhD^a

^aDepartment of Pathology, Scott & White Medical Center, Temple, Texas; ^bDepartment of Neurosurgery, Scott & White Medical Center, Temple, Texas; ^cDepartment of Otolaryngology, Scott & White Medical Center, Temple, Texas

ABSTRACT

Primary angiosarcoma of the bone is exceedingly rare. Here, we report a case of epithelioid angiosarcoma arising from the right temporal bone in a 57-year-old woman who presented with otalgia that was refractory to conventional treatment.

KEYWORDS Angiosarcoma of the skull; epithelioid angiosarcoma; otalgia

Epithelioid angiosarcoma is a rare malignant vascular neoplasm that most frequently occurs in the dermis, soft tissue, or vessel-rich organs. Primary angiosarcoma of the skull is even rarer. We present a case of epithelioid angiosarcoma arising from the right temporal bone that was confirmed by biopsy.

CASE REPORT

A 57-year-old woman presented with mild to moderate otalgia without hearing loss of 9 months' duration. Conservative treatment including antibiotics, nonsteroidal antiinflammatory drugs, and eardrops was used with no improvement. The right external auditory canal (EAC) was narrowed by a soft tissue swelling arising from the lateral/posterior aspect of the EAC. Computed tomography (CT) of the head demonstrated a $2.6 \times 2.1 \times 1.6$ cm solid and cystic mass (*Figure 1*) with trabecular and cortical bone destruction of the right temporal bone and extension into the anterior mastoid tip and superior aspect of the cartilaginous EAC. The solid component of the mass extended inferiorly towards the tegmen tympanum and extended through the temporal bone laterally and into the mastoid region. Magnetic resonance imaging (MRI) also demonstrated a $4.8 \times 4.4 \times 3.2$ cm enhancing mass within the right temporal lobe with peritumoral edema and mild midline shift (*Figure 2*). No other masses or lymphadenopathy was seen on head, neck, and chest imaging. A right EAC biopsy was performed. Microscopically, the malignancy was composed of sheets of highly atypical epithelioid cells with poorly formed vascular channels lined by atypical

epithelioid cells. Numerous mitotic figures were noted. Immunohistochemistry demonstrated focal CD31 expression along with diffuse expression of Fli-1 and ERG (*Figure 3*). The malignant cells were negative for CD34, GFAP, S100, inhibin, RCC, CD10, CK7, CK20, and desmin. The Ki-67 proliferation index was 80%. The biopsy was diagnosed as high-grade spindle cell neoplasm most consistent with epithelioid angiosarcoma.

A temporal craniotomy was performed 10 days following the EAC biopsy due to progressively worsening ear pain and onset of leg weakness and saddle anesthesia. The large mass within the right temporal lobe was evacuated to lower the intracranial pressure. The mass was observed to be attached to the surface of the brain with focal invasion into the brain. Grossly, a $4.2 \times 2.9 \times 1.3$ cm aggregate of tan-white soft lobulated fragments was removed containing brain tissue intermixed with hemorrhage. Microscopically and immunohistochemically, the tumor cells were similar to those observed in the EAC biopsy, and the diagnosis of epithelioid angiosarcoma was made. Next-generation sequencing was negative for the WWTR1-CAMTA1 fusion that is seen in epithelioid hemangioendothelioma. Following surgery, the patient's symptoms of otalgia, leg weakness, and saddle anesthesia were resolved. Postoperative positron emission tomography/CT showed a markedly hypermetabolic region of activity within the right temporal bone with extension inferiorly to involve the mastoid and adjacent extracranial soft tissues to include the right middle ear, consistent with residual malignancy. There was no evidence of distant metastatic disease. Adjuvant chemotherapy

Figure 1. Neck CT with contrast revealing a mass-like structure in the right auditory canal, measuring $2.6 \times 2.1 \times 1.6$ cm, which consists of a cystic-appearing area (red thin arrow) and a solidly enhancing area (red thick arrow).

and radiotherapy were administered for 12 months. At 12-month postsurgery follow-up imaging, the disease was stable.

DISCUSSION

Otalgia is a complaint seen frequently in general practice. However, otalgia secondary to a tumor is very rare. The incidence of middle ear and temporal bone tumors is estimated to be 1 in 5000.¹ Patients with cancers in this region may report symptoms of otalgia or dysphagia, and some are asymptomatic.² Symptoms, including oropharyngeal symptoms, facial paresis or paralysis, dizziness, progressive onset of hearing loss, and immunosuppressed status, when present, should prompt a more detailed history, physical examination, and radiographic imaging.²

In the case presented here, the patient reported approximately 9 months of mild to moderate otalgia without any other symptoms that would have prompted additional workup. In such an indolent case, conventional treatments would be attempted as first-line treatments. Only when conservative therapies failed did a more thorough workup occur, including CT and MRI. Physicians should be aware that in cases of refractory otalgia following conservative treatment, other etiologies such as malignancy should be considered.

Epithelioid angiosarcoma is a very rare and highly aggressive endothelial cell malignancy.³ The majority of epithelioid angiosarcomas occur in deep soft tissue⁴ and in elderly patients, with a male predominance. However, epithelioid angiosarcoma does occasionally arise from vessel-rich organs^{5–8} and large caliber vessels.⁹ Epithelioid angiosarcoma arising from the skull is rarely reported in the literature (*Table 1*). Yamada et al reported one epithelioid angiosarcoma case that originated from the left temporal bone with subdural hematoma as the initial presentation without invasion into the EAC.⁸ Cui et al reported one case that most likely originated from the right mastoid process and/or right external canal with right facial nerve paralysis and otalgia as the initial symptoms.¹⁰

Figure 2. Brain MRI revealing a $4.8 \times 4.4 \times 3.2$ cm enhancing mass (red thin arrow) containing both solid and cystic components with peritumoral edema (red thick arrow) and mild right to left shift of the septum pellucidum of 6 mm. There were also some lytic bone destructions involving the posterior superior aspect of the right mandibular fossa.

The typical histology of epithelioid angiosarcoma includes anastomosing vascular channels lined by large atypical malignant cells with hyperchromatic nuclei and sheets of malignant epithelioid cells with abundant eosinophilic cytoplasm and round nuclei with prominent nucleoli. Hemorrhage and/or necrosis is commonly seen, and the mitotic rate is elevated.^{3,4} Immunohistochemistry is often required for diagnosis. Epithelioid angiosarcoma is positive for vascular markers including CD31, CD34, Fli-1, and ERG. CD31, although more specific, is usually weakly to focally expressed in most cases. CD34 is sensitive but less specific and is positive in 40% to 100% of cases. Nearly 50% of epithelioid angiosarcomas demonstrate keratin positivity, and EMA is only rarely positive.³ Because of focal keratin positivity, other endothelial markers, such as Fli-1 and ERG, should be used to differentiate epithelioid angiosarcoma from other malignancies such as epithelioid sarcoma, which is also keratin positive. Epithelioid sarcoma is negative for Fli-1,^{3,4,11} while ERG has similar positivity in both angiosarcoma and epithelioid sarcoma.¹² The high proliferative index of MIB-1 has been shown to be an adverse prognostic factor in angiosarcoma.¹³

Histologic features of epithelioid angiosarcoma may mimic metastatic carcinoma, melanoma, mesothelioma, epithelioid sarcomas, or epithelioid hemangioendothelioma. Metastatic carcinoma does not express endothelial markers. Melanoma is positive for S100, Melan-A, and HMB-45 and negative for vascular markers. Mesothelioma will stain for WT-1 and D2-40. Epithelioid sarcoma will not express endothelial

Figure 3. Immunohistochemistry results for the lesion in the right auditory canal mass (400×): (a) hematoxylin and eosin staining; (b) CD31 (+); (c) CD34 (–); (d) ERG (+); (e) Fli-1 (+); (f) Ki-67 (proliferation index = 80%).

Table 1. Reported cases of primary epithelioid angiosarcoma from skull and mid ear

Case/author	Age/sex	Tumor location at diagnosis	Clinical presentation	Past history	Metastasis	Treatment	Status (months after surgery)
1. Yamada et al ⁸	75/M	Left temporal bone	Worsening numbness and weakness in the right leg	Colon and gastric adenocarcinoma	Lung	Surgery, radiotherapy*	Died (4)
2. Present	57/F	Right temporal bone	Otalgia for 9 months	COPD, anxiety	External canal and brain	Surgery, chemoradiotherapy	Alive (12)
3. Cui et al ¹⁰	65/F	Right mastoid, right external canal	Right facial nerve paralysis and otalgia for 4 months	None	No	Surgery	Died (9)

F indicates female; M, male; COPD, chronic obstructive pulmonary disease.

*Radiotherapy was terminated prematurely due to rapidly progressing pulmonary metastases.

markers either, though it typically expresses EMA.¹¹ Epithelioid hemangioendothelioma is a low-grade vascular neoplasm with less atypia and rather low mitotic activity (<2 mitoses per 10 high-power fields).¹⁴

Epithelioid angiosarcoma is an extremely rare variant of angiosarcoma. It can originate from bone and the central neural system. However, epithelioid angiosarcoma from a skull origin is even rarer. To the authors' knowledge, only two cases that originated from the skull have been described in the literature.^{8,10} Our case was unique in that otalgia was the sole symptom at initial presentation. Due to the indolent course and rarity of an epithelioid angiosarcoma from skull origin, it is very unusual for a clinician to list skull malignancy on the top of the differential diagnosis list.

- Conley JJ. Cancer of the middle ear and temporal bone. *N Y State J Med.* 1974;74(9):1575–1579. PMID:4527067.
- Harrison E, Cronin M. Otalgia. *Aust Fam Physician.* 2016;45(7):493–497. PMID:27610432.
- Hart J, Mandavilli S. Epithelioid angiosarcoma: a brief diagnostic review and differential diagnosis. *Arch Pathol Lab Med.* 2011;135(2):268–272. PMID:21284449.
- Calonje JE, Fletcher CDM. Vascular tumors. In: Fletcher CDM, ed. *Diagnostic Histopathology of Tumors*, 4th ed. Philadelphia: Elsevier, 2013:68–70.
- Hendry S, Forrest C. Epithelioid angiosarcoma arising in an adrenal cortical adenoma: a case report and review of the literature. *Int J Surg Pathol.* 2014;22(8):744–748. doi:10.1177/1066896914532541. PMID:24771258.
- Rotellini M, Vezzosi V, Bianchi S. Epithelioid angiosarcoma of the thyroid: report of a case from an Italian non-alpine area and review of the literature. *Endocr Pathol.* 2015;26(2):152–156. doi:10.1007/s12022-015-9372-9. PMID:25935446.
- Hasegawa T, Fujii Y, Seki K, et al. Epithelioid angiosarcoma of bone. *Hum Pathol.* 1997;28(8):985–989. doi:10.1016/S0046-8177(97)90016-2. PMID:9269837.
- Yamada Y, Inamasu J, Moriya S, et al. Subdural hematoma caused by epithelioid angiosarcoma originating from the skull. *Head*

- Neck Pathol.* 2013;7(2):159–162. doi:10.1007/s12105-012-0389-9. PMID:22843419.
9. Goldblum JR, Rice TW. Epithelioid angiosarcoma of the pulmonary artery. *Hum Pathol.* 1995;26(11):1275–1277. doi:10.1016/0046-8177(95)90205-8. PMID:7590704.
 10. Cui Y, Bi LR, Zhang Y, Du B. [One case of epithelioid angiosarcoma of the middle ear]. *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi.* 2013;48(10):851–852. PMID:24406188.
 11. Miettinen M, Fanburg-Smith JC, Virolainen M, Shmookler BM, Fetsch JF. Epithelioid sarcoma: an immunohistochemical analysis of 112 classical and variant cases and a discussion of the differential diagnosis. *Hum Pathol.* 1999;30(8):934–942. doi:10.1016/S0046-8177(99)90247-2. PMID:10452506.
 12. Miettinen M, Wang Z, Sarlomo-Rikala M, Abdullaev Z, Pack SD, Fetsch JF. ERG expression in epithelioid sarcoma: a diagnostic pitfall. *Am J Surg Pathol.* 2013;37(10):1580–1585. doi:10.1097/PAS.0-b013e31828de23a. PMID:23774169.
 13. Meis-Kindblom JM, Kindblom LG. Angiosarcoma of soft tissue: a study of 80 cases. *Am J Surg Pathol.* 1998;22(6):683–697. doi:10.1097/00000478-199806000-00005. PMID:9630175.
 14. Kempson RL, Hendrickson MR. An approach to the diagnosis of soft tissue tumors. *Monogr Pathol.* 1996;38:1–36. PMID:8744273.