



Primary Intranodal Epithelioid Haemangioendothelioma in the Submandibular Region: A Case Report

Khilan Shukla^{1,2,3} · Touraj Taheri^{4,5} · Hooman Baghaie⁶ · Omar Breik¹

Received: 14 February 2024 / Accepted: 11 May 2024
© Crown 2024

Abstract

Epithelioid haemangioendothelioma (EHE) is a rare vascular tumour that primarily affects the liver, lungs and bone. It is very rarely described in the head and neck region, and is exceptionally uncommon within the submandibular region. We report a very rare case of EHE originating in a lymph node within the submandibular salivary gland of a 54-year-old female patient. The tumour was resected and the patient was regularly followed up, with no recurrence of disease at 24 months postoperatively. A review of existing literature, clinical and immunohistopathological features are discussed, which highlight the diagnostic dilemma, absence of consensus for management and appropriate surveillance method associated with EHE.

Keywords Epithelioid haemangioendothelioma · Submandibular gland · Malignancy · Head and neck surgery · Head and neck pathology

Introduction

Epithelioid haemangioendotheliomas (EHE) are a group of rare vascular tumours that primarily affect the liver, lungs and bones, with very rare incidence in the heart, spleen, breast, and in the head and neck [1]. After having been

previously termed intravascular bronchoalveolar tumour and histiocytoid haemangioma [2], the term ‘*Epithelioid haemangioendothelioma*’ was first definitively described in 1982 by Weiss and Enzinger [3], which allowed for its differentiation from other tumours of endothelial origin. EHE was initially considered a clinically intermediate condition between angiosarcoma and haemangioma, however is now recognised as distinct from these two conditions after identification of disease defining genes [4].

Nevertheless, due to its rarity and varied clinical and histological presentation, it is still commonly misdiagnosed [5, 6]. Several papers report EHE as having been initially misdiagnosed as epithelioid haemangioma, angiosarcoma, hepatocellular carcinoma, and sarcoma [7, 8], with one study noting as many as 60–80% of hepatic EHE being initially misdiagnosed [8].

The presence of EHE in the head and neck is considered very rare, however, given the propensity for misdiagnosis, it is possible that it is underreported in the literature. After systematically reviewing the English literature there are only eight cases [9–13] of EHE reported within the submandibular region since Weiss and Enzinger [14] defined the disease in 1982 (Table 1). It is an uncommon differential of a lump in the submandibular region, but should still be clinically and histologically excluded during the diagnostic process. We report a rare case of primary intranodal EHE in the right

✉ Khilan Shukla
K.shukla@griffith.edu.au
Touraj Taheri
Touraj.taheri@health.qld.gov.au
Hooman Baghaie
Baghaie.hooman@gmail.com
Omar Breik
Omar.breik@health.qld.gov.au

¹ Maxillofacial Surgery Department, Royal Brisbane and Women’s Hospital, Brisbane, Australia

² Griffith University, Gold Coast, Australia

³ James Cook University, Cairns, Australia

⁴ Pathology Department, Royal Brisbane and Women’s Hospital, Brisbane, Australia

⁵ School of Medicine, University of Queensland, Brisbane, Australia

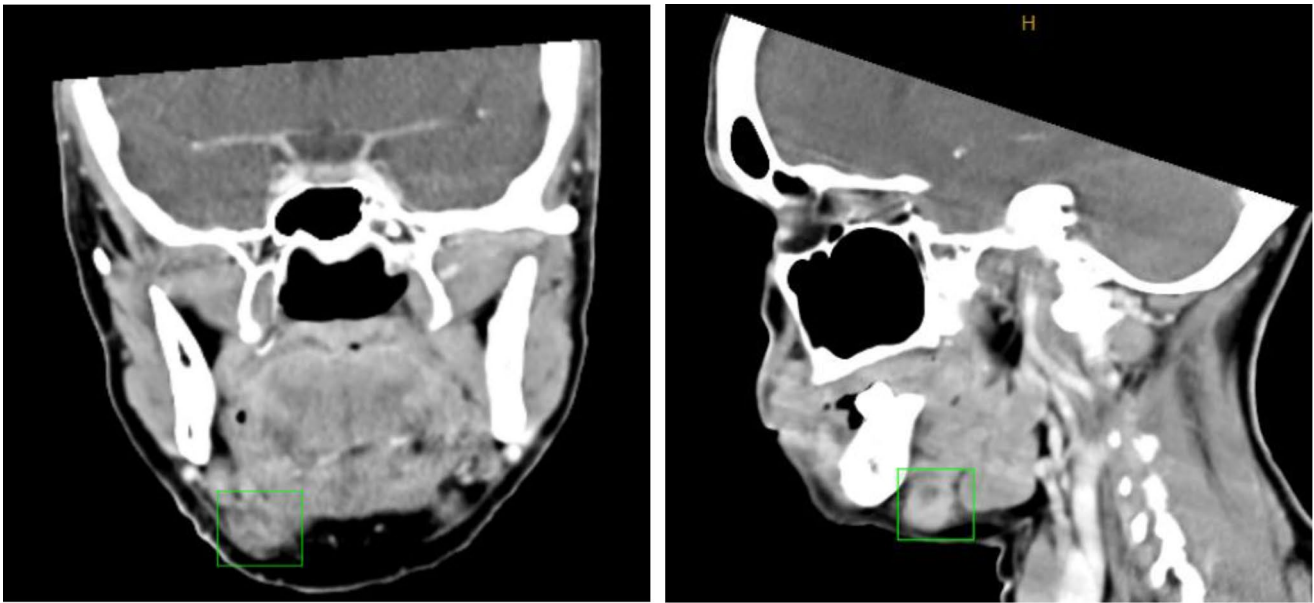
⁶ Maxillofacial Surgery Department, Westmead Hospital, Sydney, Australia

Table 1 Reports of EHE in the submandibular region

Study (Year)	Case(s)	Age + Sex (M/F)	Primary (P) vs. Metastatic (M)	Treatment	Follow up	Outcome
Ellis & Kratochvil (1986) ⁹	4	54 (F)	P	Surgical Excision	9 months	No recurrence
		50 (M)	P	Surgical Excision	N/R	N/R
		4 (F)	Unknown	Surgical Excision	N/R	N/R
		67 (M)	P	Surgical Excision	N/R	Residual tumour excised at 2 months
Naqvi et al. (2008) ¹⁰	1	62 (F)	N/A	N/A	N/R	N/R
Ranjit et al. (2015) ¹¹	1	25 (F)	P	Surgical Excision	N/R	N/R
Rigby et al. (2006) ¹²	1	N/A	P	N/A	N/R	N/R
Yoruk et al. (2008) ¹³	1	44 (F)	P	Surgical Excision	6 months	No recurrence

N/A: Not Available

N/R: Not Reported

**Fig. 1** CT scan demonstrating enlarged right submandibular lymph node with necrotic appearance

submandibular gland, which was managed surgically and had no evidence of clinical or radiological recurrence at 24 months.

Case Report

A 58-year-old woman was referred to our oral and maxillofacial surgery clinic with a 4-month history of a painful submandibular lump. The lump had not changed in size and she denied any dysphagia, odynophagia or odontogenic pain and did not report fevers, chills, or night sweats. She was otherwise in good health and did not smoke or drink alcohol. She reported removal of a benign parathyroid adenoma 11 years ago.

On examination, a firm 2 cm x 1 cm tender, non-mobile mass was noted in the right submandibular region. There

was no other cervicofacial lymphadenopathy, purulent intraoral discharge or any overlying cutaneous features of cellulitis. Her dentition was sound, and a dental radiograph did not reveal an odontogenic source for her presentation. A prior ultrasound examination ordered by her general practitioner revealed inflammation around the right submandibular gland, with no evidence of salivary calculi.

A IV contrast-enhanced computed tomography (CT) of her neck demonstrated an enlarged right submandibular lymph node, with central hypodensity and peripheral fat stranding, suggesting the presence of a necrotic node (Fig. 1). Fine needle aspiration biopsy (FNAB) was inconclusive with a mixed population of lymphoid cells in a background of blood. Follow up flow cytometry revealed no malignant cells.

Given the unusual and prolonged nature of the patient's presentation, there was a high degree of suspicion for a

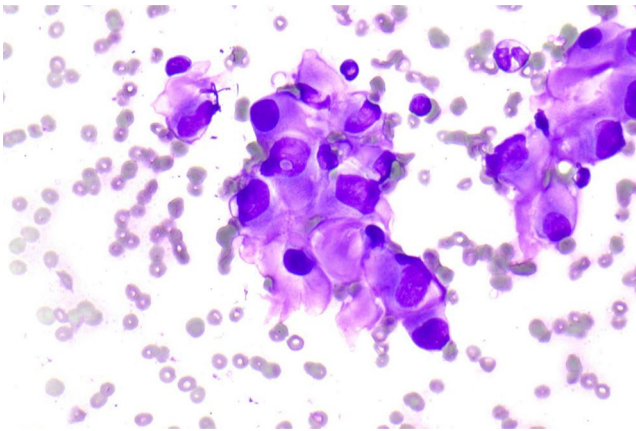


Fig. 2 Cytology demonstrating mild atypia of epithelioid and plasmacytoid cells. No mitosis or high grade atypia evident

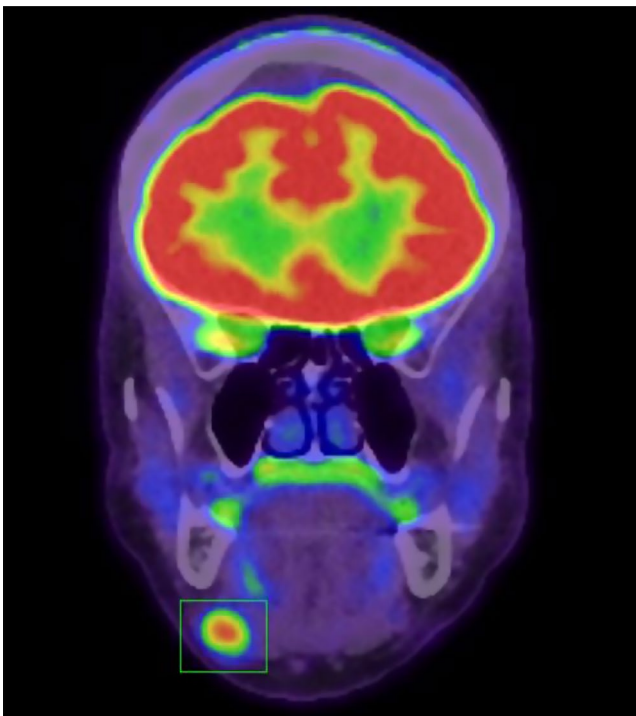


Fig. 3 FDG-PET scan demonstrating moderately avid lesion in right submandibular region

neoplastic process. A repeat FNAB was consequently completed which noted presence of epithelioid cells with low grade morphological features (Fig. 2).

A fluorodeoxyglucose positron emission tomography (FDG-PET) scan demonstrated moderate avidity (Fig. 3) of a primary intranodal tumour in the right submandibular gland, with no evidence of further nodal or metastatic disease. There was no tumour located within the salivary parenchyma. The possibility of a primary thyroid neoplasm with lymph node metastasis was considered, however a

subsequent ultrasound guided core biopsy revealed features consistent with EHE.

The core biopsy histology revealed classic features of epithelioid hemangioendothelioma presenting as an intranodal tumour. The tumour cells were round and epithelioid with mild nuclear pleomorphism, nil mitosis or necrosis and abundant eosinophilic cytoplasm. Some intracytoplasmic vacuoles with pseudo-lumen formation were noted. A myxoid stroma with hyalin change and small capillary channels was noted. The tumour cells were decorated by endothelial markers CD31, CD34 and ERG. Cytokeratin AE1/AE3 and S100 were negative. Histologic features from the resected specimen are demonstrated in Fig. 4.

After a multidisciplinary team discussion and review of her imaging and histopathology, the patient was treated by a right sided neck dissection of Level I to III nodes. The operative specimen histology yielded fourteen nodes with an isolated pathological node with focal extracapsular extension in Level IB. The Level II and III nodes were free of disease. Her recovery was unremarkable, and she was followed up clinically every 6 months, with biannual FDG-PET scans. She did not receive any adjuvant chemotherapy or radiotherapy and there was no clinical or radiographic evidence of recurrence at 24 months to date.

Discussion

Within the head and neck, haemangioendotheliomas account for fewer than 1% of vascular tumours. Four major types have been described - epithelioid, hobnail, polymorphous and kaposiform [13], with the epithelioid having the poorest prognosis due to its aggressiveness and potential for metastasis [15]. Recent advancements in genotyping have allowed for identification of disease defining gene fusions such as WWTRI/CAMTA1 and YAP1/TFE3 using fluorescence *in situ* hybridisation (FISH) [16, 17]. These establish EHE as a distinct entity and allow for its immunohistological differentiation from similar benign and malignant tumours. In our case, FISH for CAMTA1 could not be sourced, however this is not mandatory for diagnosis if other histological features suggest EHE [18, 19].

This case report detailed a clearly defined EHE originating in a lymph node within the submandibular gland. The reported age of incidence of EHE in the submandibular region ranges between 4 and 67 years, however appears to have a predilection for middle and older aged adults. The aetiology of this condition is still largely unknown [20]. The patient in our case was 58 years old, which is consistent with the majority of presentations.

Epithelioid haemangioendothelioma was reclassified from 'intermediate malignancy' to 'fully malignant' by the

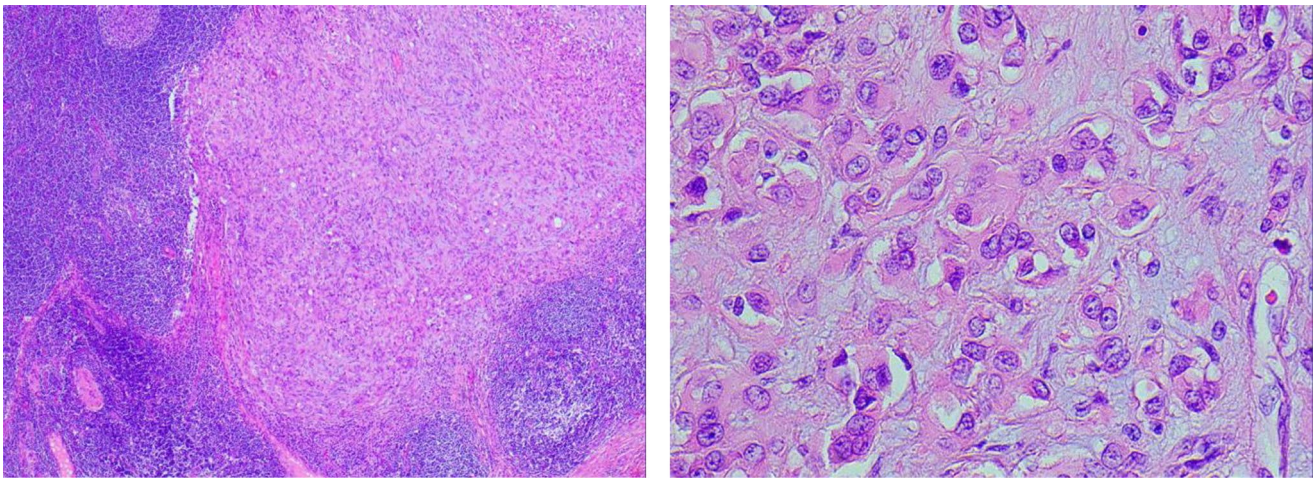


Fig. 4 Histopathology slides demonstrating cords or nests of epithelioid cells with cytoplasmic vacuolization and myxohyaline stroma. High power view (right) demonstrated abundant eosinophilic cytoplasm and intracytoplasmic vacuoles with pseudo-lumen formation

World Health Organisation in 2013 [21]. Due to its rarity, a standardised treatment protocol is still lacking for EHE, with several proposed treatment regimens based on the location and nature of the tumour. Localised lesions are typically treated with surgery, although chemotherapy and radiotherapy may also be used to reasonable effect. Alternate regimens that are reported in the literature include hormone therapy, thermoablation and transarterial chemoembolisation, however these are not well described or widely used [22, 23]. Historically, some authors utilised a ‘watchful waiting’ approach, with spontaneous regression and prolonged disease stability having been reported in very rare instances [24, 25]. As the tumour is now classified as ‘fully malignant’ and given the elevated risk of metastasis from head and neck tumours, treatment with curative intent is usually indicated, and active surveillance should only be considered for patients who are poor candidates for surgery or active treatment [26].

To date, there is a severe paucity of evidence to for a standardised approach to managing EHE in the head and neck. A recent consensus paper by Stacchiotti et al. (2021) [26] notes that surgery with curative intent is usually appropriate in cases of unifocal EHE. In the 8 available cases of EHE reported in the submandibular region (Table 1), 6 patients underwent surgical treatment with wide local excision [9, 11, 13], with insufficient data for the remaining 2 papers [10, 12]. None of these papers clearly described the location of the tumour as originating within a submandibular lymph node, however Yoruk noted presence of lymphoid tissue on FNAB [13]. Ellis and Kratochvil (1986) reported a patient case where residual EHE tumour required removal after 2 months. They also noted a second case of EHE in the submandibular region, with a similar tumour in the alveolar mucosa [9]. It was unable to be determined which specimen represented the primary tumour. Therefore, it is important

to conduct an appropriate clinical examination and investigations to rule out the possibility of a distant primary sites with metastasis to the head and neck, as metastatic lesions may be clinically and histologically indistinct from a primary tumour. In our patient, there was no additional tumour found on FDG-PET.

Unfortunately, the follow up of submandibular EHE was sparsely reported, and was six and nine months in the 2 patients where data was available. There remains a lack of available data regarding optimal frequency and follow up duration of EHE, however Stacchiotti et al. [26] suggest MRI of the primary site and whole-body CT scan 6-monthly for the first 5 years. They note that avidity on FDG-PET scans are usually mild-moderate, with increased avidity being proportional to the risk of progression and poorer survival [26]. In the current patient, as the initial lesion demonstrated avidity, and given the lack of an established screening protocol at the time of treatment, the patient was followed up with 6-monthly surveillance FDG-PET and did not display signs of recurrence at 24 months follow up. Original and subsequent imaging studies including CT scan and PET did not show a primary or secondary tumour in lung, liver, soft tissue or bone. Therefore this case can be interpreted as primary intranodal EHE in the right submandibular gland which has only been reported once before in the literature [13, 27].

Conclusion

Epithelioid haemangioma remains an uncommon presentation in the head and neck, and is especially rare in the submandibular region. Nonetheless, adequate investigation should be undertaken to exclude this condition during the diagnostic process of a submandibular lump. If

diagnosed, appropriate investigation should be undertaken to confirm whether it is a primary or metastatic lesion. Due to its rarity in the submandibular region, even if a lesion is presumed to be a primary tumour, surveillance may be required to ensure it is not a metastatic lesion. While the majority of localised EHE tumours in the head and neck are usually managed surgically, further research is required regarding the optimal imaging modality and surveillance of these lesions post-operatively. The follow up and monitoring of primary and metastatic EHE lesions in the head and neck would benefit from further investigation.

Funding Open Access funding enabled and organized by CAUL and its Member Institutions.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

References

- Mehrabi A, Kashfi A, Fonouni H et al (2006) Primary malignant hepatic epithelioid hemangioendothelioma. *Cancer* 107(9):2108–2121. <https://doi.org/10.1002/cncr.22225>
- Weiss SW, Ishak KG, Dail DH, Sweet DE, Enzinger FM (1986) Epithelioid hemangioendothelioma and related lesions. *Semin Diagn Pathol.* 1986;3(4):259–287
- Weiss SW, Enzinger FM (1982) Epithelioid hemangioendothelioma a vascular tumor often mistaken for a carcinoma. *Cancer* 50(5):970–981. [https://doi.org/10.1002/1097-0142\(19820901\)50:5<970::AID-CNCR2820500527>3.0.CO;2-Z](https://doi.org/10.1002/1097-0142(19820901)50:5<970::AID-CNCR2820500527>3.0.CO;2-Z)
- Tanas MR, Sboner A, Oliveira AM et al (2011) Identification of a disease-defining Gene Fusion in Epithelioid Hemangioendothelioma. *Sci Transl Med* 3(98):98ra82–98ra82. <https://doi.org/10.1126/scitranslmed.3002409>
- Din NU, Rahim S, Asghari T, Abdul-Ghaffar J, Ahmad Z (2020) Hepatic epithelioid hemangioendothelioma: case series of a rare vascular tumor mimicking metastases. *Diagn Pathol* 15(1):1–7
- Wiegand S, Dietz A, Wichmann G (2021) Malignant vascular tumors of the Head and Neck-which type of Therapy Works Best? *Cancers (Basel)* 13(24). <https://doi.org/10.3390/cancers13246201>
- Sardaro A, Bardoscia L, Petruzzelli MF, Portaluri M (2014) Epithelioid hemangioendothelioma: an overview and update on a rare vascular tumor. *Oncol Rev* 8(2):259. <https://doi.org/10.4081/oncol.2014.259>
- Neofytou K, Chrysochos A, Charalambous N et al (2013) Hepatic epithelioid hemangioendothelioma and the danger of misdiagnosis: report of a case. *Case Rep Oncol Med.* 2013
- Ellis GL, Kratochvil FJ 3 (1986) Epithelioid hemangioendothelioma of the head and neck: a clinicopathologic report of twelve cases. *Oral Surg Oral Med Oral Pathol* Jan 61(1):61–68. [https://doi.org/10.1016/0030-4220\(86\)90204-5](https://doi.org/10.1016/0030-4220(86)90204-5)
- Naqvi J, Ordonez NG, Luna MA, Williams MD, Weber RS, El-Naggar AK (2008) Epithelioid hemangioendothelioma of the head and neck: role of podoplanin in the differential diagnosis. *Head Neck Pathol* Mar 2(1):25–30. <https://doi.org/10.1007/s12105-007-0035-0>
- Ranjit P, Madhusudan PN, Suhaili DNP, Bickle IC (2015) Epithelioid Hemangioendothelioma of the Submandibular Region. *Philipp J Otolaryngol Head Neck Surg* 30(1):47–50
- Rigby MH, Taylor SM, Bullock MJ, Wright BA (2006) Epithelioid hemangioendothelioma of the submandibular triangle. *J Otolaryngol* Jun 35(3):194–195
- Yoruk O, Erdem H, Mutlu V, Erdogan F, Altas E, Kantarci M (2008) Epithelioid hemangioendothelioma of the submandibular gland. *Auris Nasus Larynx* Mar 35(1):157–159. <https://doi.org/10.1016/j.anl.2007.05.005>
- Salgarelli AC, Bellini P, Maccio L, Setti G (2016) Epithelioid hemangioendothelioma of the mandibular gingiva: a rare case of metastasis 4 years after radical excision and literature review. *J Oral Maxillofac Pathol* Jan-Apr 20(1):137–141. <https://doi.org/10.4103/0973-029x.180975>
- Singh S, Kumar S, Parmar K, Sharma A (2021) Epithelioid hemangioendothelioma of retroperitoneum: a sinister location. *Surg* 169(6):e19–e20
- Yang P, Zhang S, Yu C et al (2020) Fluorescence in situ hybridization for WWTR1-CAMTA1 has higher sensitivity and specificity for epithelioid hemangioendothelioma diagnosis. *Am J Transl Res* 12(8):4561–4568
- Shibuya R, Matsuyama A, Shiba E, Harada H, Yabuki K, Hisaoka M (2015) CAMTA1 is a useful immunohistochemical marker for diagnosing epithelioid haemangioendothelioma. *Histopathol* Dec 67(6):827–835. <https://doi.org/10.1111/his.12713>
- Fletcher C, Bridge JA, Hogendoorn PCW, Mertens F (2013) WHO classification of tumours of soft tissue and bone: WHO classification of tumours, vol 5. World Health Organization
- Thompson LDR, Franchi A (2018) New tumor entities in the 4th edition of the World Health Organization classification of head and neck tumors: nasal cavity, paranasal sinuses and skull base. *Rev Virchows Archiv* 472(3):315–330. <https://doi.org/10.1007/s00428-017-2116-0>
- Hanege FM, Uzun L, Yavuz C, Ozkanli S, Kurtgoz S (2016) Epithelioid hemangioendothelioma of the nasal septum. *B-ENT* Aug 12(2):155–157
- Doyle LA (2014) Sarcoma classification: an update based on the 2013 World Health Organization Classification of Tumors of Soft Tissue and bone. *Cancer* Jun 15(12):1763–1774. <https://doi.org/10.1002/cncr.28657>
- Singhal S, Jain S, Singla M et al (2009) Multifocal epithelioid hemangioendothelioma of liver after long-term oral contraceptive use—a case report and discussion of management difficulties encountered. *J Gastrointest Cancer* 40(1–2):59–63. <https://doi.org/10.1007/s12029-009-9083-x>
- Ohopj NP, Yousem SA, Sonmez-Alpan E, Colby TV (1991) Estrogen and progesterone receptors in Lymphangiomyomatosis, Epithelioid Hemangioendothelioma, and sclerosing Hemangioma of the lung. *Am J Clin Pathol* 96(4):529–535. <https://doi.org/10.1093/ajcp/96.4.529>
- Yousaf N, Maruzzo M, Judson I, Al-Muderis O, Fisher C, Benson C (2015) Systemic treatment options for epithelioid haemangioendothelioma: the Royal Marsden Hospital experience. *Anticancer Res* 35(1):473–480

25. Rosenberg A, Agulnik M (2018) Epithelioid hemangioendothelioma: update on diagnosis and treatment. *Curr Treat Options Oncol* 19:1–8
26. Stacchiotti S, Miah AB, Frezza AM et al (2021) Epithelioid hemangioendothelioma, an ultra-rare cancer: a consensus paper from the community of experts. *ESMO Open*. 2021;6(3):100170.
27. Vazzano JL, Patton A, Tinoco G, Iwenofu OH (2022) Primary intranodal epithelioid hemangioendothelioma with molecular confirmation. *Int J Surg Pathol* 30(5):557–563

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.