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CASE REPORT

Epithelioid Hemangioendothelioma of the Head and Neck: Role of Podoplanin in the Differential Diagnosis

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Abstract Epithelioid hemangioendothelioma is an uncommon vascular tumor of soft tissue and bone that may rarely occur in the liver, lung and the head and neck. We present five new cases of epithelioid hemangioendothelioma of the head and neck region diagnosed and managed in one institution in order to define the phenotypic characteristics, podoplanin immunohistochemical staining and the biological outcome. Podoplanin is a transmembrane mucoprotein selectively expressed in lymphatic endothelium and recently in some vascular neoplasms. The patients were comprised of two male and three female patients ranging in age from 4 to 71 years. The lesions were found in the gingiva, submandibular region soft tissue, nasal cavity and tongue, and ranged in size from 0.7 to 2.5 cm. All tumors manifested infiltrative cords and nests of epithelioid cells with occasional spindle morphology in a myxoid stroma. Immunohistochemical analysis of vascular and epithelial markers showed strong and uniform cytoplasmic reactivity for podoplanin and variable intensity and staining of CD31 and lack of cytokeratin staining in tumor cells. Surgical treatment included simple and wide local excisions. Of the three patients with follow-up, one developed lymph node metastasis and one had no evidence of disease 10 months after surgery. The patient with multiple recurrences and LN metastases was additionally treated with chemotherapy and is under consideration for radiation therapy. Hemangioendothelioma of the head and neck is: (1) a low-grade malignancy with a tendency for local recurrence and regional lymph node metastasis, (2) complete excision with negative margins is the treatment of choice for localized disease and (3) podoplanin may be useful in differentiating epithelioid hemangioendothelioma from non-vascular tumors.

Keywords Epithelioid hemangioendothelioma · Podoplanin · Immunohistochemistry · Biological outcome · Differential diagnoses

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Introduction

Epithelioid hemangioendothelioma (EHE) is a generally low-grade vascular neoplasm, consisting of an epithelioid endothelial cell proliferation with distinctive myxohyaline stroma [1]. The tumor can arise in skin, bone or soft tissue or may have a primary parenchymal location, most commonly in the liver and lung [2–12]. Several examples at rare sites including the head and neck have previously been reported [13–18]. Regardless of origin, EHE may pose a diagnostic challenge due to the overlapping morphologic features with certain carcinomas, melanoma, and epithelioid sarcoma phenotypes [19–37]. This diagnostic difficulty may further be compounded by occasional expression of cytokeratin in these tumors [12]. The purpose of this study is to report five new cases of EHE in the head and neck region and to discuss the pertinent differential diagnoses and the expression of podoplanin in these tumors. To our knowledge, podoplanin expression in these neoplasms has not been previously investigated.

Materials and Methods

Five patients diagnosed with epithelioid hemangioendothelioma from 1996 to 2006 and originating in the head and neck region were identified from a review of the files of the Department of Pathology at M.D. Anderson Cancer Center. Clinical records and surgical pathology reports together with the follow-up information, were reviewed. In all cases, hematoxylin-and-eosin stained histologic preparations were available and were reviewed. In the four cases for which paraffin blocks were available, immunohistochemical studies were performed using the avidin–biotin-peroxidase complex method in a Dako AutoStainer (Carpinteria, CA). The primary antibodies used were mouse monoclonal antibodies to podoplanin (D2-40, Signet Laboratories, Dedham, MA, 1:50 dilution), CD31 (JC70A, Dako, 1:20), and cytokeratin (CAM 5.2, BD BioSciences, San Diego, CA, 1:25). The immunostaining was done using the LSAB2 peroxidase kit (Dako). To enhance the immunostaining for podoplanin and CD31, a heat epitope retrieval procedure was performed using a Black-and-Decker vegetable steamer. The buffer solution used was Tris-EDTA buffer, pH 8.0. Enzymatic pretreatment with 0.2% protease, type XXIV (Sigma Chemical Co., St. Louis, MO) in Tris buffer saline, pH 7.3, was used. The antigen–antibody immunoreaction was visualized using 3-amino-9-ethylcarbazole as chromogen. To evaluate the specificity of the antibodies, known positive and negative tissues were used as controls (Table 1).

Results

Patient Information

The patients included two males and three females who ranged in age from 4 to 71 years. The most common presentation was a submucosal or soft tissue mass. The locations of the lesions were the gingiva in two cases, the nasal cavity, tongue and submandibular soft tissue, one each.

Pathologic Findings

The tumors ranged from 0.7 to 2.5 cm in size. Histologically, the tumors appeared as encapsulated, predominantly epithelioid cellular proliferations with ill-defined boundaries (Fig. 1) embedded within a collagenous to fibromyxoid stroma. Cytologically, the tumor cells demonstrated moderate to ample eosinophilic to amphophilic cytoplasm with nuclei having irregular nuclear contours, coarse chromatin and prominent nucleoli (Fig. 1). A consistent feature in all cases was intracytoplasmic lumen formation in variable proportions (Fig. 2). Mitotic figures were rare. The pertinent pathologic features are summarized in Table 2.

Table 1 Antibodies utilized in staining of head and neck hemangioendothelioma

Antibody	Clone	Dilution	Source
Podoplanin	D2-40	1:50	Signet
CD31	JC 70 A	1:20	Dako
Cam 5.2	Zym 5.2	1:25	BD

BD: Becton Dickenson

Immunohistochemical Studies

Immunohistochemical studies were performed on four tumors with archival tissues. All four tumors showed strong and uniform membrane and/or cytoplasmic staining for podoplanin. CD 31 was also demonstrated in tumor cells and blood vessels but the staining was of variable intensity and heterogeneous (Fig. 1). Immunostaining for cytokeratin was negative in all four lesions.

Radiologic Findings

Radiographic evaluation by computed tomography (CT) was available in one case (case 3) which presented in the gingiva and showed underlying bone resorption of the maxillary cortex (Fig. 3).

Follow-up and Treatment

In case #1, the patient was initially treated with local excision but recurred after 3 and 5 years and was subsequently treated by wider excision and he is disease free at 10 years of follow up. The lesion in case #3 was locally excised twice at 1-year intervals. The lesion recurred for the third time after 4 years and was treated by excision and maxillectomy. The patient recently presented with a fourth local recurrence and lymph node metastases 5 years and 4 months from initial diagnosis. Case #4 presented with concurrent lymph node metastases and was treated by wide local excision and lymph node dissection. The patient is currently disease free at 10 months following surgery. The clinical features of our five cases of EHE arising in the head and neck are summarized in Table 3.

Discussion

The present study, for the first time, shows that podoplanin may play a role in the differential diagnosis of epithelioid

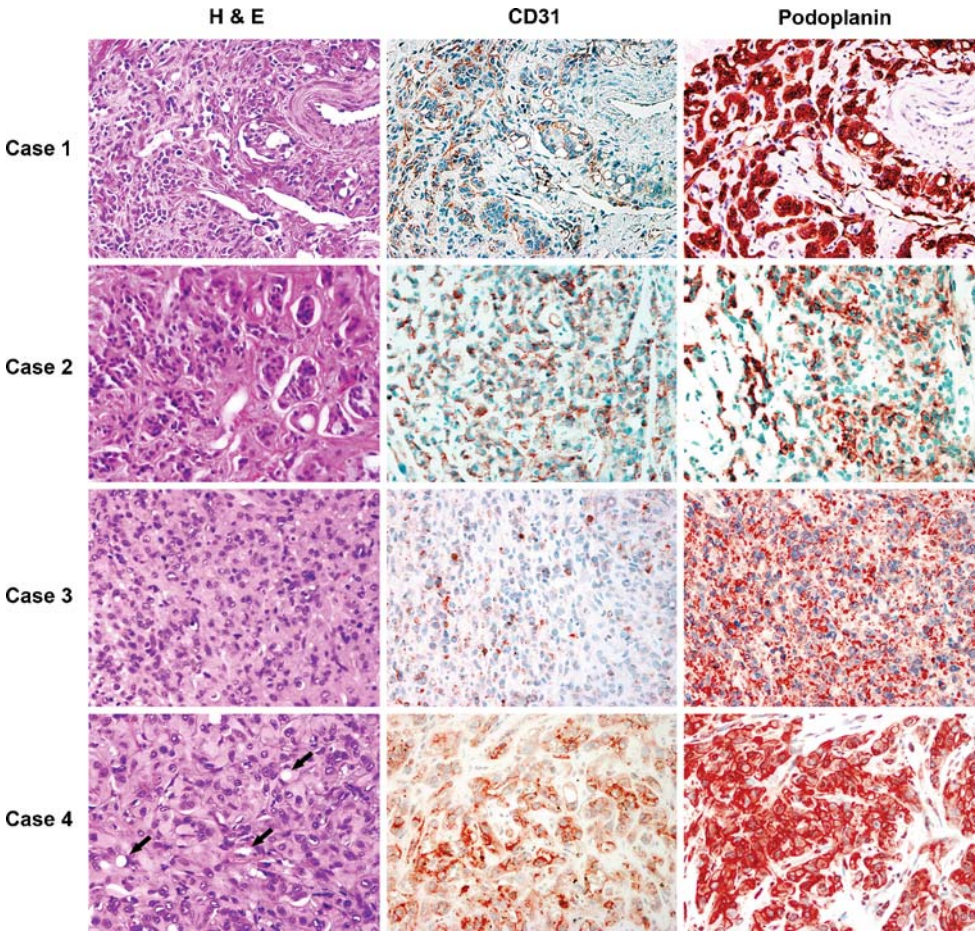

Fig. 1 Four cases of EHE stained with hematoxylin and eosin (H&E), CD31 and podoplanin. H&E sections of all four cases show epithelioid morphology with intra-cytoplasmic lumina, readily apparent in Case 4 (arrows). CD31 shows patchy expression compared to the diffuse, homogenous expression of podoplanin

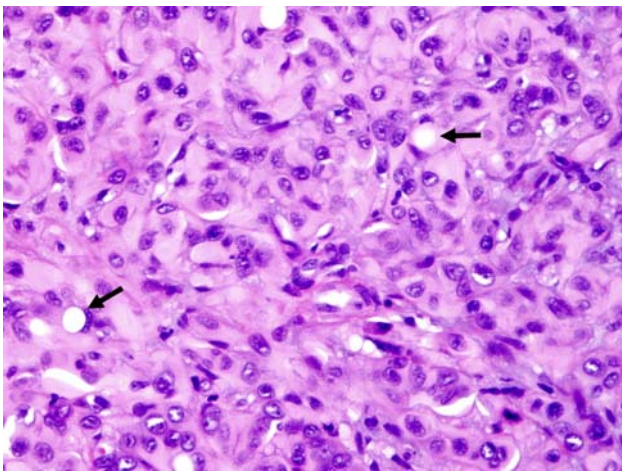

Fig. 2 A high power micrograph of case #4 illustrating the epithelioid features and the intra-cellular vaculation of tumor cells (arrows)

Table 2 Histopathologic findings in epithelioid hemangioendothelioma of head and neck

Case #	Stroma	Pleomorphism	Mitoses (#/10 HPF)	Spindle features	Necrosis
1	Fibrotic	Absent	<1	30%	Absent
2	Myxoid	Focal	=2	Absent	Absent
3	Fibrotic	Absent	=1	<5%	Absent
4	Fibrotic	Absent	<1	Absent	Absent
5	Fibrotic	Absent	<1	<5%	Absent

HPF = high power fields

hemangioendotheliomas originating in the head and neck. In contrast to the heterogeneous expression of traditional endothelial markers, all tumors exhibited homogenous and uniform cytoplasmic staining by podoplanin. Podoplanin is an intracellular protein reported to be expressed in lymphatic endothelium, alveolar type I cells, osteoblasts and peritoneal mesothelial cells but not in normal vascular endothelial cells [38]. In contrast, conventional endothelial markers (CD31, CD34, Factor VIII antigen) are expressed by both lymphatic and blood vessel endothelial cells [39]. Recently, podoplanin has been reported to be expressed in vascular neoplasms including Kaposi sarcomas [40], Kaposiform hemangioendotheliomas [41], hobnail hemangiomas [42] and a subset of angiosarcomas [43, 44]. Although we contend that podoplanin expression in our cases and other vascular neoplasms suggest an aberrant expression during vascular tumorigenesis, the possibility

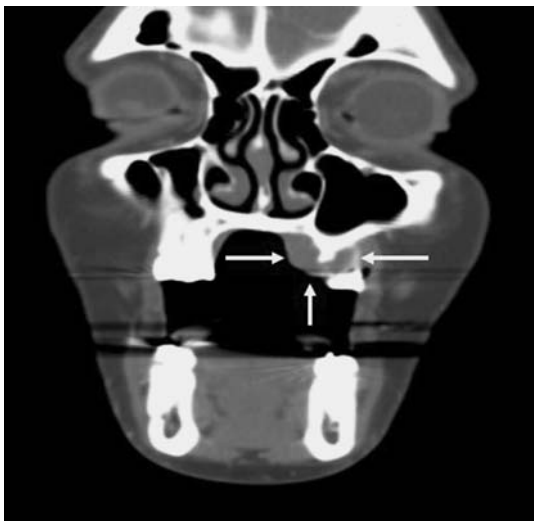

Fig. 3 Computed tomography (coronal view) of the maxillofacial area shows a soft tissue mass involving the left hard palate with erosion of the maxillary cortex (Case 3)

that some of these lesions originate from lymphatic origin cannot be entirely ruled out.

Histopathologically, all of our lesions manifested similar bland epithelioid cytomorphologic features and infiltrative patterns with the characteristic collagenous and myxoid stroma typically seen in EHE. Other studies, however, have reported increased mitoses, necrosis, spindle atypia and pleomorphism in some EHE [2]. We attribute the difference between these results to be the inclusion of the epithelioid form of angiosarcoma in some of the previous reports. In this study, however, two patients had lymph node metastases and experienced multiple recurrences. The multiple recurrences in some of these tumors may be related to their critical location within the head and neck region and the undefined boundaries leading to incomplete or inadequate excision. Complete excision with wide margins is, therefore, the recommended primary treatment for these lesions [18].

EHE in the head and neck may pose diagnostic difficulties, especially with certain types of carcinoma and epithelioid-forming sarcomas [18, 36, 37, 43]. This may rarely be complicated by aberrant expression of cytokeratin in some of these cases [12, 35]. The differentiation of EHE from epithelioid angiosarcomas is based mainly on the presence of marked cytologic atypia and pleomorphism and high mitotic rate in the latter tumor. Significant anaplasia and high mitotic rate (>5/10 HPF) should exclude the diagnosis of EHE. Epithelioid sarcoma may also be considered in the differential diagnosis of EHE. The low mitotic activity (<5/50 HPF), minimal pleomorphism, lack of necrosis and the presence of intracytoplasmic vascular lumen formation should distinguish EHE from epithelioid sarcoma [37]. Since epithelioid sarcomas commonly express cytokeratin and other epithelial markers [37, 45] and because EHE may occasionally express these markers [2], podoplanin may further aid in differentiating these tumors.

Clinically, the patients' characteristics in this study were similar to those previously reported (Table 4) [11, 14]. Tumors were most frequently located in the soft tissue of the head and neck, gingiva and tongue. Other sites previously cited included buccal mucosa, parotid gland, nasal cavity, floor of mouth, larynx and thyroid [21–27]. Treatment was mainly local excision with only one case also treated by radiation. Lymph node metastasis was encountered in only two of 43 cases previously reported and with the addition of two of our cases, a total of 4 of 48 (8.3%) cases had lymph node metastases. The collective data, including the present series, showed no mortality in patients with head and neck EHE. The availability of anti-angiogenic agents may play a role in future treatment of this entity. Radiation therapy is also under investigation as a treatment modality in patients with multiple recurrences and lymph node metastasis.

We conclude that epithelioid hemangioendothelioma of the head and neck is a low-grade malignancy with a tendency for local recurrence and regional lymph node metastases. Complete excision with negative margins is the treatment of choice and long-term follow up is recommended as local recurrences (25%) remain common. While

Table 3 Summary of clinical features of 5 cases of epithelioid hemangioendothelioma

Case #	Age (Years)	Sex	Site	Size (cm)	Treatment	Follow-up
1	4	M	Nasal Cavity	2.5	Excision	Rec. × 2, 3 & 5 years, NED 10 years
2	62	F	Neck	1.8	NA	NA
3	17	F	Gingiva	0.7	Excision, Maxillectomy, Chemo and XRT	Rec. × 4, LN Mets (within 5 years)
4	66	F	Gingiva with LN Mets	NA	WLE & LN dissection	NED (10 months)
5	71	M	Tongue	1.0	Excision	NA

Abbreviations: Chemo, Chemotherapy; Cm, Centimeter; F, Female; LN, Lymph node; M, Male; Mets, Metastases; Mo, Months; NA, Not available; NED, No evidence of disease; Rec. Recurrence; WLE, Wide local excision; XRT, Radiation therapy

Table 4 Clinicopathologic features of previously published epithelioid hemangioendotheliomas of the head and neck

Reference (#) (Year)	#'s of Cases	Age/ Gender	Size (cm)	Site	Treatment	Follow-up
2, 1997	5	30–65 years/4M-1F	0.4–4.0	ST, Cheek and Neck	SE	NED 42–60 months
13, 1986	1	NA/ M	NA	Gingiva	SE	NED 36 months
14, 1986	1	4–67 years/7M-5F	1.7–2.5	Neck ST, Gingiva	WLE and SE	LN mets-2 cases, Rec.-1 case
15, 1987	1	25 years/F	1.0	Palate	SE	NED 21 months
16, 1987	1	4 years/M	NA	Gingiva	SE	NA
17, 1991	2	36–45 years /1M-1F	0.2–1.5	Tongue, Gingiva	SE	Rec. 1 case
18, 2007	9	6–53y years/8M-1F	0.5–7.0	Tongue, FOM, Oral Cavity	WLE	Rec.-3 Cases NED 6–96 months
19, 1995	1	7 years/F	1.5	Gingiva	WLE	NED 48 months
20, 1996	1	46 years/M	1.0	ST, Cheek	SE	NED 36 months
21, 1998	1	44 years/F	3.7	Thyroid	Subtotal Thyroidectomy	NED 24 months
22, 1999	1	19 years/M	1.5	Larynx	SE	NED 36 months
23, 2000	1	48 years/F	2.0	Parotid	NA	NA
24, 2001	1	18 years/F	NA	Buccal Mucosa	SE Rec. WLE	Rec. 9 months NED 24 months
25, 2003	1	23 years/M	NA	Nasal Cavity	WLE	NED 12 months
26, 2003	1	81 years/M	2.0	Parotid	Total Parotidectomy	NED 7 months
27, 2004	1	28 years/M	NA	Parotid	Parotidectomy and LN dissection	NA
28, 2005	1	25 years/M	NA	Nasal cavity	WLE	NA
29, 2005	1	28 years/F	0.6	Gingiva	SE	NED 8 months
30, 2006	1	34 years/F	2.5	ST, Neck	SE	NED 84 months

Abbreviations: AWD: Alive With Disease; Cm: Centimeters; F: Female; LN: Lymph Node; M: Male; Mets: Metastases; NA: Not Available; NED: No Evidence of Disease; Rec: Recurrence; SE: Simple excision; ST: Soft Tissue; WLE: Wide Local Excision; #: Number; FOM: Floor of mouth

lymph node metastases are rare, clinical monitoring should include lymph node evaluation. Podoplanin, in addition to histologic features, may be used to differentiate EHE from non-vascular neoplasms, such as poorly differentiated carcinomas and epithelioid sarcomas.

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