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Pseudomyogenic Hemangioendothelioma: A Vascular Tumor Previously Undescribed in the Oral Cavity

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Pseudomyogenic Hemangioendothelioma: A Vascular Tumor Previously Undescribed in the Oral Cavity

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Abstract

The pseudomyogenic hemangioendothelioma (PMH) is a low-grade malignant vascular neoplasm of different tissue planes including skin and soft tissue. Primary tumors in the skeletal muscle and bone have also been diagnosed. The PMH was introduced into the WHO classification of tumors of soft

tissue and bone in 2013. This is the first description of oral involvement. A 21-year-old female presented with a 2-month old swelling of her gingiva. The swelling appeared red in color and was soft in consistency. A clinical diagnosis of a pyogenic granuloma was made and an incisional biopsy was submitted for histopathological evaluation. The lesion consisted of a proliferation of spindle and epithelioid looking cells. Cells were arranged in loose fascicles and sheets. Rhabdomyoblast-like cells were also seen. No mitotic figures were present. Lesional cells were reactive to cytokeratin AE1/AE3 and CD31. Lesional cell reactivity to S100 protein, HMB 45, SMA, Desmin and CD34 was negative. Following the diagnosis, a wide excision for clear margins was performed. No recurrence has been reported 2 years since the removal. The PMH is a cutaneous tumor that behaves in an indolent fashion. This is the first report of oral involvement by this neoplasm. Recognition of its histopathological features and immunohistochemical reactivity will prevent misadventures in the diagnosis of oral lesions.

Keywords

Pseudomyogenic, Hemangioendothelioma, Oral, Mucosal, Cytokeratin, CD31, Epithelioid sarcoma, Rhabdomyoblast

Introduction

In 1992, Mirra et al. [1] published five cases of an unusual tumor that they titled as “The fibroma-like variant of epithelioid sarcoma,” describing it as a “fibrohistiocytic/myoid cell lesion often confused with benign and malignant spindle cell tumors”. They justified the designation of the tumor based on the reactivity of the lesional cells to vimentin and low molecular weight cytokeratin. In 2003, Billings et al. [2] with the advent of newer immunohistochemical markers and antigen retrieval techniques, discovered a vascular lineage and proposed to rename this tumor as “epithelioid sarcoma-like hemangioendothelioma”. In an independent study, Hornick and Fletcher [3] named the tumor as “Pseudomyogenic (fibroma-like) variant of epithelioid sarcoma” and later in a series of 50 cases, they recognized the tumors indolent behavior and vascular origin and renamed it as “Pseudomyogenic Hemangioendothelioma” (PMH) [4]. A recurrent translocation (7;19) (q22;q13) was identified in 2011 [5]. In 2013, the WHO classification of tumors of soft tissue and bone included the pseudomyogenic hemangioendothelioma as a new entity under the group of vascular tumors [6].

The pseudomyogenic hemangioendothelioma presents as solitary or multiple nodules of the skin, typically in young adults [2, 4]. In a series of 50 cases, over 50% affected the distal extremity. Only 2 cases (4%) affected the skin of the face [4]. Although cutaneous presentation is most common, tumors have been diagnosed in the subcutis, skeletal muscles and bone [1, 2, 4]. The following case presented below is the first report of a pseudomyogenic hemangioendothelioma of the oral cavity.

Case Report

A 21-year-old female presented with a 2-month history of a slow growing mass of the anterior maxillary gingiva. The mass measured approximately 1.4 cm in its greatest dimension. It appeared red in color, and was soft in consistency. The working clinical diagnosis was a pyogenic granuloma. The clinician performed an incisional biopsy and submitted the tissue for microscopic examination and diagnosis.

Histopathological examination showed a partly ulcerated lesion consisting of plump spindle and epithelioid cells arranged in a loose fascicular and sheet-like pattern against a background of rich vascularity. Lesional cells appeared in close proximity to the surface epithelium (Fig. 1). While the cytoplasm was brightly eosinophilic, the cytoplasmic membranes were not clearly defined and the nuclei appeared elongated in the spindle cells and round to oval in the epithelioid cells. The chromatin appeared smudged (Fig. 2). Lesional cells with a rhabdoid or rhabdomyoblast-like appearance were seen (Fig. 3). Mitotic figures were not seen. The lesional cells were diffusely and strongly positive to cytokeratin AE1/AE3 (Fig. 4) and CD31 (Fig. 5). Lesional cells were non-reactive to S100, HMB 45, SMA, Desmin and CD34 antibodies. On the basis of the histopathological features and the immunohistochemistry, a diagnosis of a pseudomyogenic hemangioendothelioma was made. A recommendation for complete removal and frequent follow-up for recurrence was given. Following the diagnosis and recommendation, a wide excision for clear margins was performed. No recurrence has been reported 2 years since the removal.

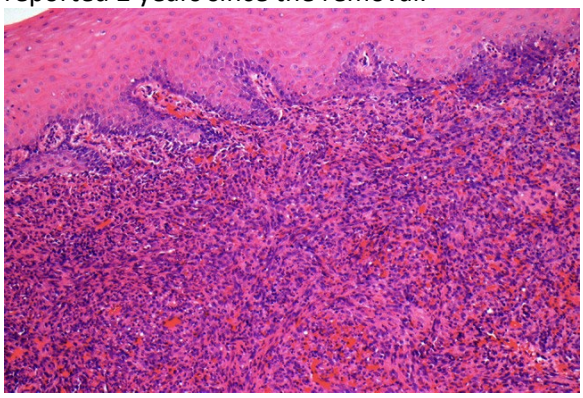

Fig. 1 A subepithelial proliferation of spindle and epithelioid cells. H&E 10×

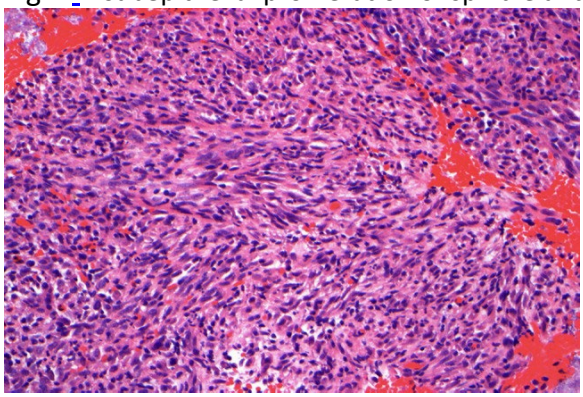

Fig. 2 Plump spindle cells are arranged in loose fascicles and sheets. H&E 20×

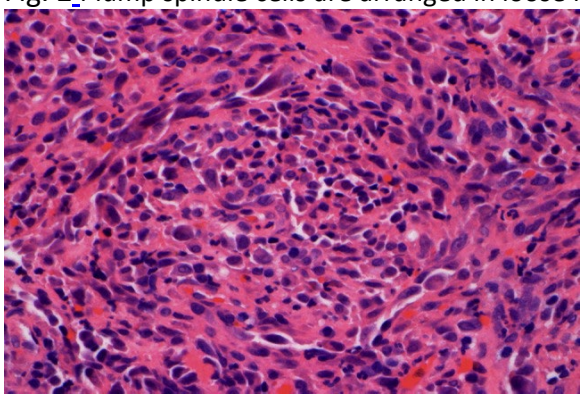

Fig. 3 Many rhabdoid and rhabdomyoblast-like cells are seen. There are no mitotic figures. H&E 40×

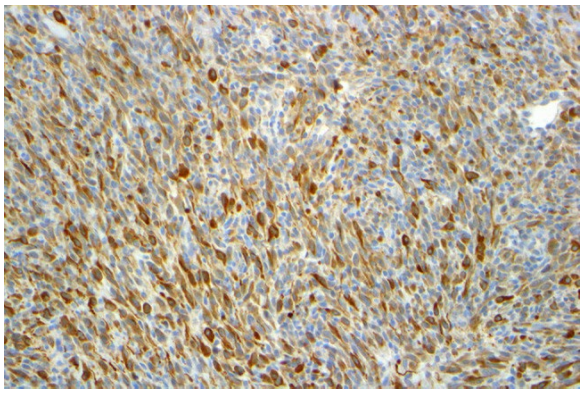

Fig. 4 Lesional cells are diffusely and strongly reactive to cytokeratin AE1/AE3

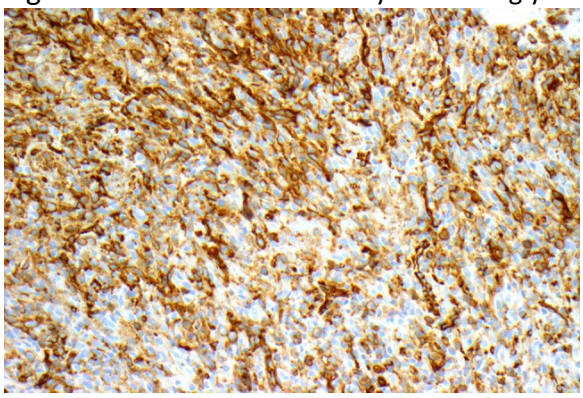

Fig. 5 Lesional cells are diffusely and strongly reactive to CD31

Discussion

Since the first description of the “Fibroma-like variant of Epithelioid Sarcoma” by Mirra et al. in 1992 [1], this neoplasm has undergone changes in name as its biologic behavior was established. Further, evolution in immunohistochemical markers and techniques resulted in the eventual identification of its vascular origin by Billings et al. [2]. The most recent terminology “Pseudomyogenic hemangioendothelioma” was coined by Hornick and Fletcher in 2011 [4].

Clinical Features

The PMH is a low-grade malignant neoplasm of vascular origin with a tendency to affect young adults. In the initial report of five cases by Mirra et al. [1], the youngest patient was 18 years of age and the oldest was 43 years of age, whereas the median age was 23 years in the series of seven cases by Billings et al. [2]. Hornick and Fletcher [4] found that 82% of patients were under the age of 40 years in their series of 50 cases. Each of these investigations found a male predilection, with a male to female ratio of 4:1 [1], 4:3 [2] and 4.6:1 [4] respectively.

The PMH typically affects the lower limb, arm, skin of trunk/chest and head and neck in decreasing order of frequency [1, 2, 4]. Tumors present as superficial and deep soft tissue masses [2, 4] and may involve the dermis, skeletal muscle and bone [4].

Lesions are frequently multifocal [4] and vary from 0.5 cms [1, 4] to 5.5 cms [4] in size. Pain is a variable feature and in the series of 50 cases by Hornick and Fletcher [4], 50% of patients complained of pain

associated with the tumors. The duration of symptoms may range from 1 to 24 months with a mean of 7 months [4].

The oral tumor in our case affected a 21-year-old female. The reported duration was 2 months. The tumor was painless and erythematous in appearance.

Histopathological Features

The histopathological features were identical in all cases in the series by Mirra et al. [1], Billings et al. [2] and Hornick and Fletcher [4]. The tumors infiltrated the surrounding dermis, fat and skeletal muscle. The tumors consisted of plump spindle cells with an eosinophilic cytoplasm. Epithelioid cells and rhabdoid and rhabdomyoblast-like cells were also seen. Cytoplasmic membranes were not well-defined. The nuclei were vesicular. Atypia was mild to moderate, with infrequent mitotic activity. The plump spindle cells were arranged in short loosely adherent fascicles and sheets. A focal storiform arrangement was also seen. Neutrophils infiltrated the tumor in variable numbers. Eight out of a total of 55 cases from both series [1, 4] showed foci of necrosis. Seven tumors showed vascular involvement [4].

The tumor in our patient showed a partially ulcerated surface and consisted of plump spindle and epithelioid cells in a well vascularized stroma. No Grenz zone was seen and tumor cells appeared in close proximity to the surface epithelium (Fig. 1). The cells were arranged in a loose fascicular and sheet-like pattern. The cytoplasm was brightly eosinophilic but the cytoplasmic membranes were not defined. The nuclei were elongated in the spindle cells and round to oval in the epithelioid cells. The chromatin appeared smudged although this may also be attributed to section thickness (Fig. 2). Rhabdoid or rhabdomyoblast-like cells were easily identified (Fig. 3). Mitotic figures were not seen.

Immunohistochemical Features

All tumors showed a strong, diffuse reactivity to cytokeratin AE1/AE3 [1, 2, 4]. The tumors were also strongly positive to vimentin [1, 2] and negative to desmin, myoglobin and S100 [1]. Due to its lack of specificity, vimentin as an immunohistochemical marker is no longer relevant and many laboratories do not offer this antibody. 5 of 6 [2] and 47% of cases [4] respectively were positive to CD31. One hundred percent of cases were positive to FLI-1 [2, 4]. CD31 reactivity was noted as being linear and membranous, thereby characterizing the cells as endothelial in origin [2]. All tumors were non-reactive to CD34, desmin and S100 [2–4]. In the series where other specified markers were used, EMA and muscle specific actin were negative [2], weak focal reactivity to CAM5.2 and SMA was seen in 60% and 33% of tumors respectively [4]. All 50 tumors expressed strong and diffuse nuclear reactivity to INI 1 [4].

The histopathological findings in our case influenced the selection of the immunohistochemistry antibody panel. The lesional cells were diffusely and strongly positive to cytokeratin AE1/AE3 (Fig. 4) and CD31 (Fig. 5). Lesional cells were non-reactive to S100, HMB 45, SMA, Desmin and CD34 antibodies. As there was no concern regarding an epithelioid sarcoma, INI 1 was not used.

A subset of PMHs show a t (7;19) (q22;q13) translocation [5]. In a later study, a fusion gene *SERPINE1-FOSB* resulting from a translocation between chromosomes 7 and 19 was discovered using mRNA sequencing, RT-PCR and interphase FISH analysis [7].

Differential Diagnosis

The differential diagnosis of a PMH includes benign and malignant tumors. This list includes spindle cell carcinoma, spitz nevus, spindle cell melanoma, benign fibrous histiocytoma, myofibroma, nodular fasciitis, leiomyoma, leiomyosarcoma, spindle cell rhabdomyosarcoma and monophasic spindle cell synovial sarcoma. While the epithelioid sarcoma has not been reported in the oral cavity, it will be included in the differential diagnosis here for two reasons.

1. The PMH was considered an epithelioid sarcoma until its recent separation as a distinct entity of vascular origin. Recognition of the PMH in the oral cavity and therefore its differentiation from the epithelioid sarcoma will prevent misadventures in diagnosis and management.
2. Nuclear reactivity to INI 1 is the key immunohistochemical event in the PMH that allows it to be differentiated from the INI 1 negative epithelioid sarcoma and therefore the INI 1 reactivity of the PMH should be viewed only in this context.

Sarcomatoid (spindle cell) carcinoma of the oral cavity is a diagnostically challenging tumor and may show no epithelial differentiation at either the histopathological or immunohistochemical level [8]. Those that show epithelial differentiation at the immunohistochemical level, express cytokeratins including AE1/AE3. However, these tumors do not express CD31 and FLI 1 [4]. Also, sarcomatoid carcinomas always show anaplastic features. Frank areas of epithelial differentiation and dysplasia of the surface epithelium may also be seen in many cases [8].

The head and neck is a common area affected by the Spitz nevus. These nevomelanocytic neoplasms of childhood may be entirely non-pigmented. A junctional or compound cellular distribution is useful in the differential diagnosis but many spitz nevi may lack this feature and be entirely dermal [9]. When present in the epithelium, the melanocytic theques show a retraction artifact from the adjoining epithelial cells. Also, pale pink basement membrane material known as Kamino bodies may also be seen in the epithelium in junctional and compound spitz nevi [9]. Nevus cells are spindled or epithelioid and arranged in vertically oriented nests. The cells become smaller in the deeper portions of the lesion and tend to loose pigment. Tumors show symmetry and mitotic activity is low to absent. Lesional cells are reactive to HMB45 with diminishing intensity as lesional cells move deeper into the connective tissue [9]. Melanoma may resemble spitz nevi but is typically asymmetric and shows prominent mitotic activity. They are uniformly, strongly positive to S100 and HMB45 staining throughout the lesion [9]. Approximately 4% of melanomas are positive to cytokeratin AE1/AE3 but are 100% negative to CD31 [10].

The benign fibrous histiocytoma (BFH) is a common dermal neoplasm. The BFH shows a storiform arrangement of slender spindled cells with entrapped bands of collagen. However, the cellular variant of the BFH shows a fascicular to sheet-like arrangement of larger eosinophilic spindled cells. Collagen entrapment may be present only at the infiltrative periphery. However, unlike the PMH, mitotic figures are readily identified in the cellular BFH [11]. Benign fibrous histiocytomas are negative to cytokeratin AE1/AE3 and CD31 [4].

The head and neck and particularly the oral cavity is a preferred site for the solitary myofibroma. The mean age at presentation is 26.6 years [12]. Tumors consist of irregular fascicles of plump spindle cells. Densely cellular areas alternate with relatively myxoid areas giving this tumor its characteristic biphasic

appearance. A prominent hemangiopericytoma-like vascularity may also be seen. Lesional cells are uniformly positive to smooth muscle markers SMA and muscle specific actin (MSA) and negative to cytokeratin [12].

Nodular fasciitis and related lesions including proliferative fasciitis and proliferative myositis were reclassified as tumors by the WHO in their 2013 classification of tumors of soft tissue and bone [6]. A recurring *MYH9-USP6* gene fusion product has been identified in 92% these neoplasms [13]. Nodular fasciitis is a neoplasm with a multinodular infiltrative periphery. Although cellular atypia is minimal, mitotic figures are easily identified. Plump spindled cells admixed with inflammatory cells are arranged in loose fascicles in a myxoid stroma. Osteoclast-like giant cells may also be seen. Tumor cells are positive for SMA and calponin and negative for smooth muscle myosin specific (SMMS), h-caldesmon, cytokeratin, FLI 1 and CD31 [4, 14].

Leiomyomas and leiomyosarcomas are smooth muscle tumors consisting of intersecting fascicles of eosinophilic spindle cells with elongated, blunt ended (cigar shaped) vesicular nuclei. Leiomyosarcomas are densely cellular and infiltrative with a high rate of mitotic activity. These tumors diffusely and strongly express reactivity to SMA but are negative for FLI 1 and CD31 [4, 14]. Diffuse and strong immunoreactivity to cytokeratin (11%) and EMA (6%) was noted in leiomyosarcomas in one study and this should be recognized as a serious pitfall in the differential diagnosis of malignant spindle cell tumors [15]. Specifically, oral leiomyomas mostly are of vascular smooth muscle origin and these angioleiomyomas are compact bundles of smooth muscle arising from and surrounding compressed vascular channels. These vascular channels may express FLI 1 and CD31 while the smooth muscles remain negative to these markers and express diffuse, strong reactivity with SMA [16].

Both, spindle cell rhabdomyosarcoma and monophasic synovial sarcoma are rare aggressive neoplasms composed of atypical spindle cells arranged in long intersecting fascicles. The tumors are hypercellular and tightly packed with little collagenous stroma. Mitotic activity is brisk. Spindle cell rhabdomyosarcomas are positive for desmin. Nuclear expression of myogenin or MYOD1 is a consistent and diagnostic feature [17]. Cytokeratin expression may be focal in the monophasic spindle cell synovial sarcoma and strong nuclear reactivity to TLE1 is seen [18].

The epithelioid sarcoma, like the PMH, arises over the distal extremities of young adults. Epithelioid and spindled cells gather in nodular aggregates around areas of necrosis. A solid pattern of growth may also be seen. These tumors express reactivity for cytokeratin and membranous CD34. PMHs are negative for CD34. A distinctive membranous CD31 reactivity as noted in the PMH is absent in the epithelioid sarcoma [19]. While the PMH expresses strong nuclear reactivity for INI 1, the epithelioid sarcoma is negative for this marker [4].

In the series of 7 cases by Billings et al. [2], 2 patients developed local recurrences and 1 patient developed regional soft tissue metastasis. No patient showed lymph node involvement or distant metastasis. In the larger series of 50 cases by Hornick and Fletcher [4], follow-up information was available for 31 patients. Eighteen of these 31 patients (58%) developed local recurrences in the form of solitary or multiple nodules. One patient showed regional lymph node involvement. One other patient developed dissemination of disease to the lungs, bones, skin over the scalp and axilla and the

gluteal soft tissue 16 years following excision of the primary tumor of the skin of the foot. The patient died of disease 1 year following discovery of disseminated lesions [4].

The majority of cutaneous tumors follow an indolent clinical course. A handful of cases exhibited a multifocal presentation and regional soft tissue involvement. The risk of lymph node and distant metastasis is small. Tumors are treated with a wide local excision and histopathological confirmation of clear margins [2, 4]. Four patients with extensive multifocal disease underwent amputations [4].

In conclusion, the pseudomyogenic hemangioendothelioma is a recently classified low-grade malignant soft tissue tumor of vascular origin [6]. It tends to affect young adults and the majority of cases are diagnosed affecting the skin and deep soft tissue of the extremities. Tumors affecting the skeletal muscle and bone have also been described [1, 2, 4]. Cutaneous lesions may be solitary or multiple. Histopathologically, the tumor consists of plump spindle and epithelioid cells. Rhabdoid looking cells are frequently seen. Lesional cells are cytokeratin AE1/AE3 and CD31 positive. Cytokeratin AE1/AE3 is the only strongly, diffusely reacting keratin type in this tumor [4, 6]. Reactivity to EMA, PAN-K (MNF116) and CAM5.2 is weak and focal [4]. They are non-reactive to S100 protein, HMB 45, SMA, Desmin, and CD34 antibodies [3, 4]. Lesional cell nuclear reactivity to INI 1 excludes the possibility of an epithelioid sarcoma [3, 4]. The tumor follows an indolent clinical course [2–4]. Recognition of the histopathological features and immunohistochemistry reactivity pattern of the tumor is emphasized. This is the first report of oral involvement. At this time, complete removal of oral tumors with clear margins and long-term follow-up for recurrence is recommended.

Compliance with Ethical Standards

Conflict of interest

The authors declare that they have no conflict of interest associated with this report.

Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors. UTHSC IRB 16-04954-NHSR.

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