A mixed form of intravascular papillary endothelial hyperplasia in an uncommon location: case and literature review

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Abstract

Intravascular papillary endothelial hyperplasia (IPEH) is an unusual benign, non-neoplastic vascular lesion that usually occurs in skin, but is uncommon in the oral cavity. Herein, we review the pertinent literature of oral IPEH and report a new mixed form. A 61-year-old man presented with an ulcerated nodule in the lingual portion of the gingiva related to the left mandibular canine. An excisional biopsy was performed presuming the clinical diagnosis of pyogenic granuloma. Histopathological analysis showed areas of granulation tissue consistent with pyogenic granuloma. But in addition, there were thin-wall dilated vessels with papillary projections of endothelial cells producing vascular channels, associated with an area of organizing thrombus. These microscopic findings led to the diagnosis of pyogenic granuloma associated with IPEH. The immunohistochemical reactions revealed a diffuse positivity of the vascular cells for CD-34 and smooth muscle actin antibodies. In addition, there was partial positivity for podoplanin and negativity for CD-105 in the IPEH areas. No signs of recurrence were observed after 6 months of follow-up. The most prevalent site of IPEH in the oral region is the lower lip. IPEH is slightly more common in women and exhibits peaks of prevalence between the fourth and sixth decades of life.

Keywords: intravascular papillary endothelial hyperplasia, Masson tumor

Introduction

Intravascular papillary endothelial hyperplasia (IPEH), also called Masson tumor, is an unusual benign, non-neoplastic, vascular lesion of the skin and subcutaneous tissue, which usually manifests as a small mass [1]. Microscopically, IPEH is characterized by a papillary proliferation of endothelial cells creating vascular channels, which may represent an unusual form of organizing thrombus [1]. In some cases, this lesion can histologically resemble an angiosarcoma [1-3].

IPEH is uncommon in the oral cavity, where it usually occurs in a distended vessel. It may be observed with or without other vascular lesions. The lips, buccal mucosa, and tongue are the most frequently involved sites [3]. Herein, we integrate the relevant literature of oral IPEH with a new case report and also discuss important features of this tumor.

Case Synopsis

A 61-year-old man with chronic periodontitis presented with a nodular soft tissue mass located in the lingual portion of the attached gingiva related to the left mandibular canine. Clinical examination revealed a nodule with reddish areas and a granular surface, measuring approximately 12x15x7mm (**Figure 1**). The nodule presented with a fibrous consistency and some ulcerated areas. Subgingival and supragingival calculus were present in the teeth

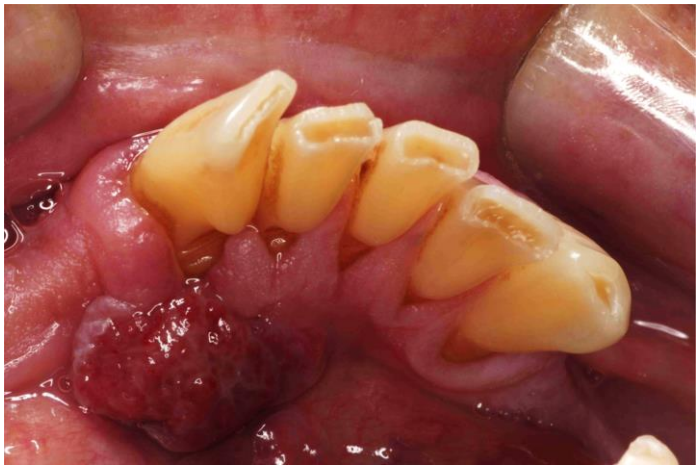

Figure 1. *Clinical photograph of the lesion, which presented as a nodule with reddish areas and granular surface.*

of the region. Two teeth were extracted during the excisional biopsy. The clinical impression was pyogenic granuloma.

Microscopic examination revealed a proliferative lesion composed of granulation tissue with numerous blood vessels (**Figure 2A**). Thin-walled vessels with dilated lumen were observed. One vessel exhibited a mixed thrombus with the presence of fibrin in some areas and red blood cells in others (**Figure 2B**) with some areas of organization. Adjacent to the thrombus and in other regions, papillary projections formed by connective tissue lined by a single layer of flattened endothelial cells (**Figure 2C**) could be seen. These papillary projections, which protruded into the vascular lumen, adhered to the vascular walls or were found floating in the lumen. Irregular channels formed, related to their fusion. Mitotic figures or pleomorphism were not observed. The fragments were partially covered by stratified squamous epithelium and a thick layer of fibrinopurulent exudate covered an ulcer area.

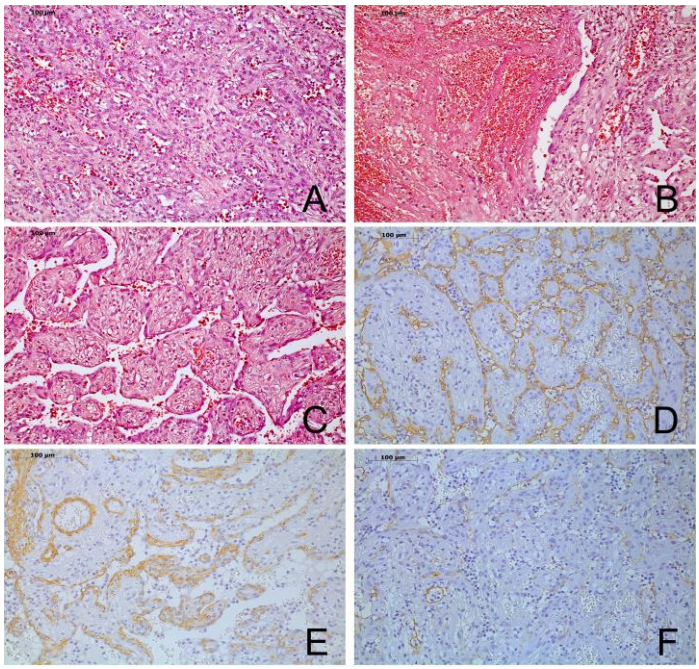

Figure 2. ***(A)*** *Some areas of the lesion presented a highly vascularized tissue characteristic of pyogenic granuloma, H&E.* ***(B)*** *In another site, inside a distended vessel, an organizing thrombus was observed, H&E, showing fibrin and leukocytes in some areas and red blood cells in others, near papillary projections, which were lined by single layers of flattened endothelial cells, H&E,* ***(C)****.* ***(D)*** *The vascular cells were positive for CD-34, and smooth muscle actin, ×,* ***(E)****.* ***(F)*** *Focal positivity for podoplanin was observed. Scale bar=100 µm.*

The microscopic findings led to the diagnosis of pyogenic granuloma associated with IPEH. Immunostaining of the specimen with primary antibodies against CD-34 (Clone QBEnd10-Dako, 1:50), smooth muscle actin (SMA, Clone 1A4-Dako, 1:200), podoplanin (Clone D2-40-Dako, 1:50), and CD-105 (Clone SN6h-Dako, 1:500) was performed. The immunohistochemical reactions revealed a diffuse strong positivity of the vascular cells for CD-34 (**Figure 2D**) and smooth muscle actin (**Figure 2E**). Partial positivity for podoplanin was observed (**Figure 2F**). The cells were positive for CD-105 only in the areas of pyogenic granuloma, whereas in the areas of IPEH they were negative. The patient has been followed and no recurrence occurred after 6 months (**Figure 3**).

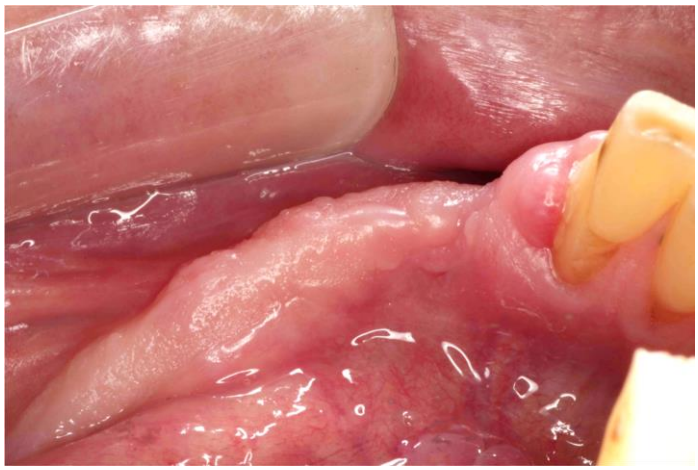

Figure 3. *Postoperative photograph showing no evidence of recurrence after 6 months of follow up.*

Case Discussion

IPEH is a benign non-neoplastic vascular lesion that was first described by Masson in 1923 as "vegetant intravascular hemangioendothelioma" [4]. Later, other names as "intravascular angiomatosis" [5, 6], "Masson pseudoangiosarcoma" [7], and "intravascular endothelial proliferation" [8] were used to designate this lesion. In 1976, Clearkin and Enzinger [1] used the name "intravascular papillary endothelial hyperplasia," which has predominantly been used until now [9, 10], since it was considered more descriptive and less confusing than others [2].

The origin of IPEH is not totally clear. It has been classified as a reactive process instead of a true neoplasm, once most researchers consider it as an unusual form of organizing thrombus [2, 8, 11, 12] characterized by exuberant endothelial growth. The thrombus may be fragmented as a result of intravascular pressure and thrombus contraction [12]. Inoue et al. suggested that its pathogenesis may be associated with some mechanical stimulus such as trauma or inflammation because they observed that many IPEH lesions occurred near to ulcerated areas without an organizing thrombus [10]. A previous study also has suggested that trauma could contribute to the development of this lesion [3]. In the present case, the patient presented with chronic periodontitis with sub and supragingival calculus, a risk factor for the development of the pyogenic granuloma. However, differing from the ulcerated cases investigated by Inoue et al. [10], in the present case the organizing thrombus was present and may have contributed to the pathogenesis of IPEH.

IPEH may occur as a primary event or as a part of another lesion [7]. A classification system for IPEH has been adopted: type I represents the primary (pure) form, characterized by the presence of the lesion in a distended vessel; type II or secondary (mixed) form shows an IPEH in preexisting hemangiomas [3, 10, 11] and pyogenic granulomas [3, 10]; type III indicates an extravascular location of the lesion, which is a rarely observed [11]. In this case, the lesion was type II.

A previous report showed that IPEH corresponds to 2% of vascular tumors of the skin and subcutaneous areas. Common regions affected are face, hand, fingers, and neck [2]. An electronic search was made in PubMed/Medline database and just 31 well-documented papers about intra-oral/lip IPEH have been published in the English language literature until November 2016 [3, 6, 7, 9, 10, 13-38], which resulted in 97 cases, including our case (**Table 1**). Considering all the cases and the current report, the most prevalent site was the lower lip followed by the buccal mucosa, upper lip, and tongue. Only 4 cases have been described in the gingiva, including the current report (**Table 1**). IPEH presented mostly as a nodule, mass, or swelling with red, blue, or purple color [6, 7, 13-15, 17-19, 23-28, 30, 31, 33-35, 37, 38]. Some lesions exhibited an ulcerated surface [3, 10, 19, 29]. A bilobulated [3] or multilobulated [21, 26] appearance was also reported. The size ranged from 0.2 to 4 cm with a mean size of 1.6 cm. IPEH occurred more commonly in women (1.37:1), with a mean age of 44.9 years-old (standard deviation = 16.67), (**Table 1**) and peaks of prevalence between the fourth and sixth decades of life (**Figure 4**). Some authors have suggested that the female predilection may be associated with hormonal factors, which could increase locally produced angiogenic growth factors to promote excessive endothelial proliferation [3, 39].

Clinical diagnosis of pyogenic granuloma, pleomorphic adenoma, mucocele [9], hemangioma, thrombosed vein, traumatic fibroma, and nevus [3]

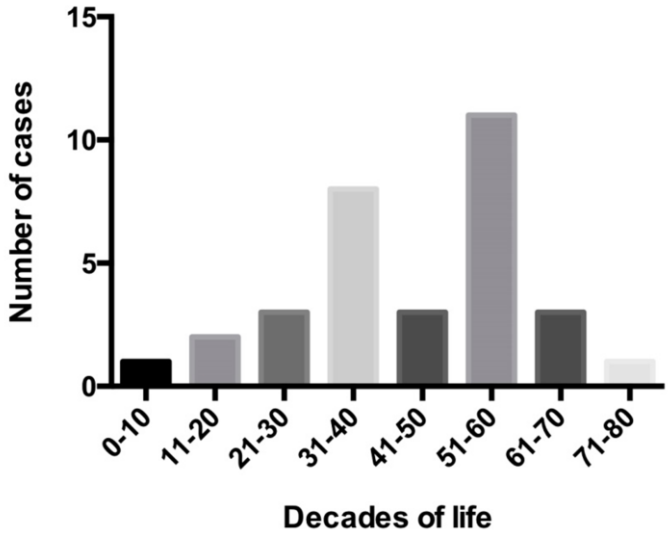

Figure 4. *Age distribution of intravascular papillary endothelial hyperplasia (n = 32 reports), showing peaks of prevalence between fourth and sixth decades of life.*

Table 1: *IPEH of the oral cavity and lip previously reported in the English language literature (present case included).*

Study	Age	Gender		Site	Size (cm)	Treatment	Recurrence
	Mean (range)	F	M		Mean (range)		
Kuo et al. (1976) [7]	40 (12-57)	2	2	1 BM, 3LL	0.87 (0.2-2)	Surgery	Absent (2), NR (2) (2)
Barr et al. (1978) [23]	36 (26-46)		2	2 LL	0.8 (0.6-1)	Surgery	Absent
Heyden et al. (1978) [16]	48		1	1 LL	1.2	Surgery	NR
McClatchey et al. (1978) [33]	37.6 (21-67)	1	2	1 LL, 1 UL, 1 LC	3 (1-4)	Surgery	Absent
Williams and MacDonalds (1982) [6]	52 (29-66)	2	1	1 BM, 1LL, 1 UL	0.66 (0.5-0.8)	Surgery	NR
Escanasy and Millet (1985) [28]	40 (38-42)	1	1	1 T	2	Surgery	Absent
Bowman et al. (1987) [14]	56 (45-67)		2	1 T	0.5 (0.5-1)	Surgery	NR
Luce et al. (1988) [31]	34.8 (25-54)	5		1 MV, 3 LL, 1 NR	0.5 (0.3-0.7)	Surgery	Absent
Buchner et al. (1990) [25]	53 (30-63)	9	7	2 MV, 3 BM, 6 LL, 3 T, 2 UL	0.9 (0.5-1.8)	Surgery	Absent
Bodner and Dayan (1991) [13]	60	1		1 MV	1	Surgery	NR
Renshaw and Rosai (1993) [19]	59.4 (35-83)	4	1	2 LL, 2 UL, 1 NR	NR	Surgery	Absent (3), recurrence (1), NR (1)
Stern et al. (1994) [36]	53			1 T	-	Surgery	Absent
Tosios et al. (1994) [3]	52.3 (24-83)	14	4	1 MV, 1 BM, 7 LL, 5 T, 3 UL, 1 LC	1.08 (0.7-2)	NR	NR
Courten et al. (1999) [27]	58 (28-77)	1	5	2 BM, 3LL, 1 UL	NR (0.5-2)	Surgery	Absent
Guillou et al. (2000) [29]	37		1	1 RP	1.5	Surgery	Absent
Matsuzaka et al. (2003) [17]	28		1	1 UL	NR	Surgery	NR
Devi et al. (2004) [32]	9 months		1	1 FM	-	-	-
Tokman et al. (2004) [38]	21	1		1 MV	4	Surgery	Absent
Wang et al. (2006) [21]	55	1		1 BM	3	Surgery	NR
Soares et al. (2008) [20]	58 (40-77)	2		1 BM, 1 UL	1	Surgery	Absent
Campos et al. (2009) [26]	50.6 (32-72)		3	2 LL, 1 LC	1.06 (1-1.2)	Surgery	Absent
Cohen et al. (2009) [15]	79		1	1 LL	2	₸Sotradecol® + surgery	Absent
Yonezawa et al. (2009) [37]	62	1		1 LL	1	Surgery	Absent
Bologna-Molina et al. (2010) [24]	70	1		1 BM	1	Surgery	Absent
Murugaraj et al. (2010) [18]	14	1		1 BM	1	Surgery	NR
Fontes et al. (2011) [9]	32	1		1 T	< 2	Surgery	Recurrence
Inoue et al. (2011) [10]	45.4 (13-81)	4	5	1 P, 1 BM, 1 LL, 1 T, 2 UL, 3 G	NR	NR	NR
Narwal et al. (2013) [34]	19	1		1 BM	3	Surgery	Absent

Guledgud et al. (2014) [30]	40		1		1 BM	3	Surgery	Absent
Sarode and Sarode (2015) [35]	54		1		1 LL	4	Surgery	Absent
Bajpai and Pardhe (2016) [22]	30		1		1 P	2	Surgery	Absent
Present case	61			1	1 G	1.5	Surgery	Absent
Total	44.9 (0.9-83)		56	41	2 P, 6 MV, 15 BM, 35 LL, 13 T, 14 UL, 3 LC, 4 G, 1 RP, 1 FM, 2 NR	1.6 (0.2-4)	-	-

F- female, M- male, P- palate, MV- mandibular vestibule, BM- buccal mucosa, LL- lower lip, T- tongue, UL- upper lip, LC- labial commissure, G- gengiva, RP- retromolar pad, FM- floor of the mouth, NR- not reported. ᵀ Sodium tetradecyl sulfate 3%

have been suggested in cases of IPEH. In the present case, the hypothesis was pyogenic granuloma because of the clinical appearance of the lesion, which presented with reddish and ulcerated areas, the gingival location, and the presence of inflammatory factors (periodontitis).

The diagnosis of IPEH must be based on histologic examination. Microscopically, it is characterized by papillary projections of endothelial cells producing vascular channels, which can be attached to the walls or appear as multiple isolated papillae, apparently floating in the lumen [2, 3, 7]. The papillary projections contain single layers of endothelial cells lining a dense hyalinized stroma that may represent capillaries. Sometimes, these papillary projections exhibit a large number of cells appearing to be coated by multiple layers of endothelial cells [7]. Slight pleomorphism, mitotic figures, and nuclear hyperchromasia may be observed [3].

The microscopic differential diagnosis of IPEH comprises some malignant and benign vascular tumors such as intravenous atypical vascular proliferation, malignant endovascular papillary angioendothelioma, and angiosarcoma [2, 3, 7]. The intravenous atypical vascular proliferation, which is also called epithelioid hemangioma [40], has been interpreted by some authors as a morphologic variant of angiolymphoid hyperplasia with eosinophilia [7]. This condition has been considered the most difficult confounder in the differential diagnosis of IPEH [2]. In both IPEH and intravenous atypical vascular proliferation, the endothelial growth is predominantly detected within the lumen of a blood vessel. Nevertheless, the proliferation in intravenous atypical vascular tumor is more solid, there is no formation of papillary projections, and it may extend into vascular walls and even out of vessels [7, 8]. Furthermore, intravenous atypical vascular tumor is not so closely linked with thrombus [8] and exhibits epithelioid cells. In our case, the presence of papillary projections, the non-epithelioid aspect of the cells, and the association of the lesion with a thrombus were highly indicative of IPEH.

Malignant endovascular papillary angioendothelioma or Dabska tumor, considered as a variant of angiosarcoma [2, 7], is a locally aggressive tumor with low metastatic rate [40, 41]. It is composed of lymphatic-like channels with papillary endothelial structures [40] and has been identified as a tumor in the differential diagnosis of IPEH [2, 3, 7, 41]. Dabska tumor shows channels coated by cuboidal endothelial cells with hyperchromatic nuclei that protrude into the lumen, leading to the "hobnail" appearance, characteristics that were not observed in the present case.

Angiosarcoma also has been suggested in the differential diagnosis of IPEH [2, 3, 7, 9, 12]. However, according to Amérigo et al., this has been overemphasized by authors. The clinical presentation of angiosarcoma (usually a large mass, with necrosis and ulceration) and the gross appearance (non-circumscribed and with infiltrating behavior) are highly suggestive of malignancy [2]. Microscopically, although angiosarcoma may show angiomatous zones of anastomosing channels coated by endothelial cells [42], they can be histologically distinguished from IPEH because the latter usually does not show accentuated pleomorphism, many mitoses, or foci of necrosis [2, 7, 9, 12]. In the present case no features resembling a malignant neoplasm were found. Moreover, IPEH usually is associated with a thrombus, which is not observed with angiosarcoma [3].

A diffuse positivity of the vascular cells for CD-34 and SMA was found after immunohistochemistry, which confirms the blood vascular origin of this lesion, also observed by previous studies [9, 10, 20]. Just a focal positivity for podoplanin, a marker of lymphatic endothelial cells [43], was observed in this case. Inoe et al. detected a partial positivity for podoplanin in IPEH and suggested that endothelial cells of lymphatic vessels could play a role in the formation of IPEH [10]. Positivity for CD-105, a powerful marker of neovascularization [44], was present in the areas of pyogenic granuloma, which was expected as previously reported [45], whereas the areas of IPEH were completely negative. This marker is an important aid to differentiate IPEH from angiosarcoma, since CD-105 is overexpressed in angiosarcoma associated endothelial cells [46].

The treatment for IPEH is the removal of the entire lesion. A previous study reported the use of Sotradecol® (sodium tetradecyl sulfate 3%) before the surgery to decrease the size of the lesion [26]. Two cases of oral recurrence have been described [9, 19], one of them associated with a lobular capillary hemangioma [19]. In this report, no evidence of recurrence was observed after 6 months of follow-up.

Conclusion

In summary, IPEH is an unusual benign, non-neoplastic, vascular lesion probably originating from a thrombus in organization. Most authors have considered that the main relevance of this lesion is its possible histological similarity with angiosarcoma. Herein, we review the pertinent literature and discuss the pathogenesis of IPEH as well as important clinical and microscopic features of this uncommon oral lesion.

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