Intraoral papillary endothelial hyperplasia: case discussion with supportive histochemistry and immunohistochemistry

A.R. Raghu* / S. Tandon** / N.N. Rao*** / R. Singh**** / V.K. Rekha*****

An intraoral mass of eight months duration in a six year-old girl was diagnosed as papillary endothelial hyperplasia. Histologically, the tissue was characterized by the unusual endothelial cell proliferation, which is significant, as papillary endothelial hyperplasia resembles angiosarcoma and possible over-treatment thereafter. Clarification of this unusual lesion based on histological findings with supportive histochemical staining and immunohistochemistry in the light of clinico-pathological correlation is discussed. This lesion warrants better documentation of the clinical behavior with regular monitoring.

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INTRODUCTION

Proliferative vascular lesions span a spectrum from reactive hyperplasias to neoplastic lesions including both benign and malignant variants.[1] Hyperplasias comprise a heterogeneous group of vascular proliferations that eventually show a tendency to regression. pyogenic granuloma, bacillary angiomatosis, intravascular papillary endothelial hyperplasia, verruga peruana are some of these.[2] Intravascular papillary endothelial hyperplasia (IPEH) is usually a cutaneous lesion thought to represent a peculiar manifestation of an organizing thrombus, the prime significance being the microscopic resemblance to angiosarcoma and possible misinterpretation there after.[3] Lesions of IPEH occurring in the head and neck area appear as subcutaneous red or blue nodules, which are usually confined, to the luminae of preexisting vessels or vascular malformations.[4] Histologically, papillary fronds lined by proliferating endothelium occurring *de novo* in organizing venous thrombi, in preexisting hemangiomas or phlebectasias[5] are seen. Orally, lesions are frequently seen on the lips,[31] followed by tongue.[6] The presentation is usually solitary, but rare cases of multiple nodules have also been reported.[7] However, the nature and the onset of papillary endothelial hyperplasia have aroused some controversy.

The case described here is one occurring on the lateral border of the tongue in a child with considerable complexity in the histological appearance. Clarification of this unusual lesion based on histological findings, histochemical staining and immunohistochemistry in the light of clinico-pathologic correlation is discussed.

CASE REPORT

A six- year- old girl was referred to the Department of Pedodontics, College of Dental Surgery, Manipal, for a swelling of eight months' duration, which was apparently asymptomatic with a slight increase in size from the time, it was first noticed. There was no history of

* A.R. Raghu, Associate Professor, Department of Oral Pathology, Manipal College of Dental Sciences, Manipal - 576 104, India.

Email - aparagh@yahoo.com, raghu.ar@cods.manipal.edu
Voice - 0820-2571201Extn22204
Fax - 0820 - 2571966

** S. Tandon, Professor and Head, Department of Pedodontics and Preventive Dentistry, Manipal College of Dental Sciences, Manipal - 576 104, India.

Email: drtandons@yahoo.com
Voice: 91 -820-2571201Extn22173
Fax: 91 -820 - 2571966

*** N.N. Rao, Professor and Head, Department of Oral Pathology, Manipal College of Dental Sciences, Manipal - 576 104, India.

Email: oralpath@cods.manipal.edu
Voice: 91 -820-2571201Extn22204
Fax: 91 - 820 - 2571966

**** R. Singh, Post Graduate Student, Department of Pedodontics and Preventive Dentistry, Manipal College of Dental Sciences, Manipal - 576 104, India.

Email: rashmis16@yahoo.com
Voice: 91 -820-2571201Extn22173
Fax: 91 -820 - 2571966

***** V.K. Rekha, Associate Professor, Department of Pathology, Kidwai Memorial Institute of Oncology, Bangalore, India.

Voice: 91-984-5117670

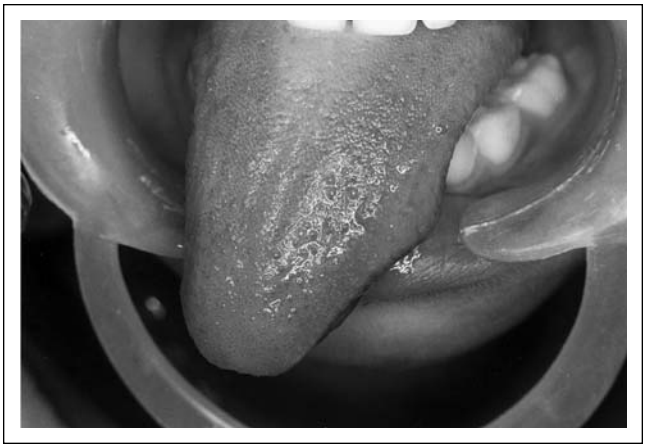

Figure 1. Preoperative view of the ovoid swelling on the left lateral border of tongue

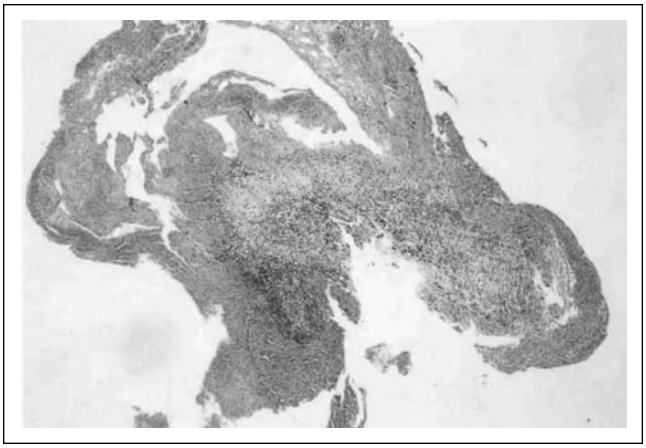

Figure 2. Photomicrograph in low power examination showing a circumscribed mass with cellular elements stained with haematoxylin and eosin stain - (4x)

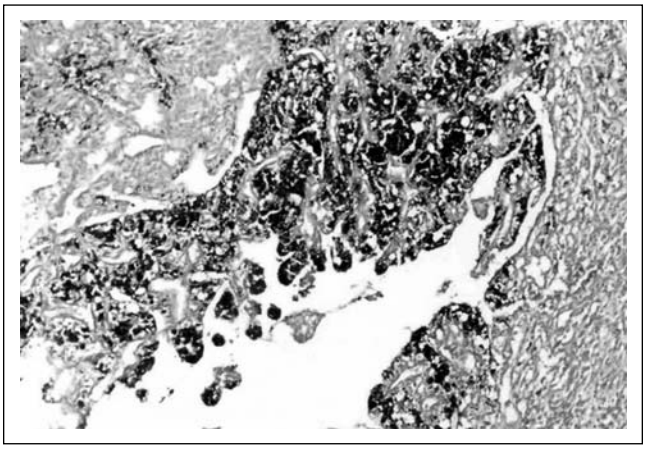

Figure 3. Photomicrograph showing deposition of hemosiderin demonstrated with Perl's Prussian blue - (20x)

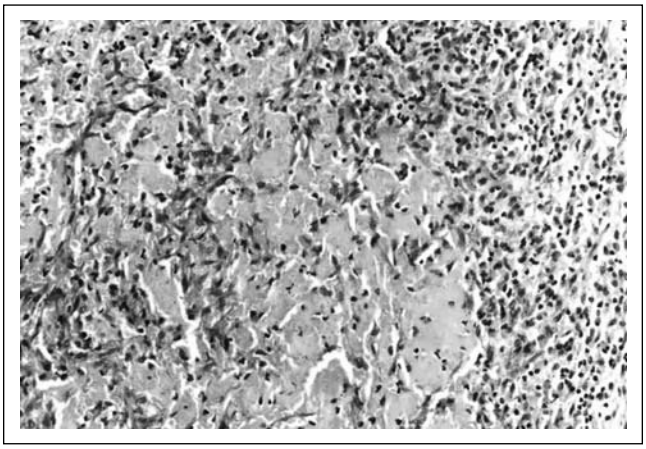

Figure 4. Photomicrograph of thrombotic material containing varying amounts of fibrin and RBCs recognized with Martius scarlet blue - (20x)

trauma, spontaneous bleeding or seizure. The peripheral blood smear revealed a slight eosinophilia of about 8%. All other tests were unremarkable.

On examination, an ovoid bluish swelling measuring about 1.0x1.0cm was noted without any tenderness on palpation or blanching on pressure. The swelling was elastic in consistency and somewhat movable under an intact mucosa (Figure 1). A clinical diagnosis of hemangioma with a differential diagnosis of mucocele was made, subsequent to which a biopsy was performed.

The surgical specimen received measured about 0.7x0.8x0.8cm and was brown in color. The 5µm thick formalin fixed paraffin embedded sections were stained with hematoxylin and eosin. When the initial observations were not confirmatory additional sections were stained with periodic acid Schiff stain (PAS), Perls Prussian blue (PPB) and Martius Scarlet blue (MSB). Immunohistochemical staining for factor VIII antigen was performed to confirm the vascular nature of the lesion.

Low power microscopic examination revealed a somewhat circumscribed mass comprised of vascular spaces admixed with cellular areas (Figure 2). No overlying squamous epithelium was noted. Prominent hemorrhagic areas with an inflammatory component comprised of lymphocytes and eosinophils were noted. Admixed closely were vascular spaces lined by single layer of flat endothelial cells. In some foci, cells with intracytoplasmic vacuoles lining indistinct vascular lumen were noted. Arranged randomly were few spindle shaped cells merging into the surrounding fibrin. Some of the spindle cells had elongated nuclei, ill-defined cytoplasmic borders occasionally lining slit like vascular spaces. Interstitial areas contained few areas of PAS positive hyaline globules probably reflecting areas of sulphated mucin activity.

Deposition of hemosiderin could be demonstrated in hemorrhagic areas with positive Perls Prussian Blue reaction. (Figure 3). Granulation tissue with endothelial cells having a large round or vesicular nucleus and indistinct eosinophilic cytoplasm formed the main bulk.

Few cells exhibited mitotic activity, nor were areas of prominent necrosis seen suggestive of malignancy. At the periphery, papillary fronds lined by endothelial cells extending from the surrounding pseudocapsule formed an extensive network of slit like spaces (Figure

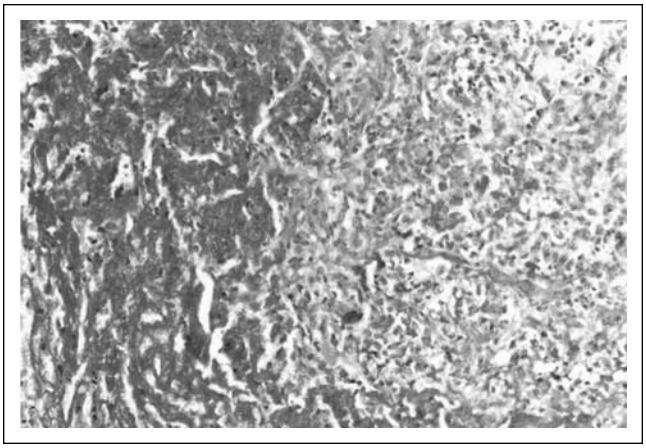

Figure 5. Photomicrograph showing papillary fronds lined by endothelium extending from the surrounding fibrous capsule forming slit like spaces - (20x)

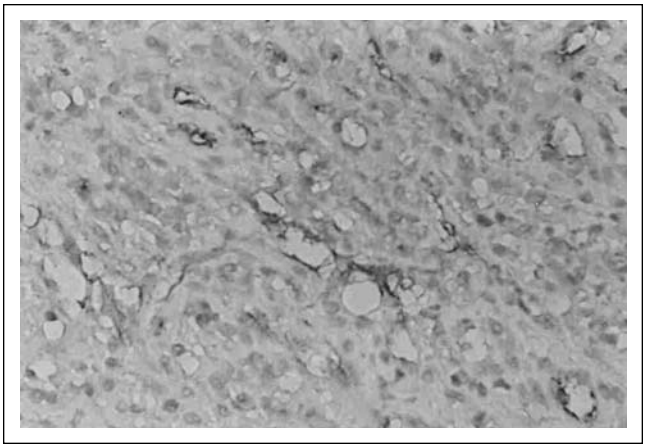

Figure 6. Photomicrograph of immunohistochemical staining for VIII antigen - (40x)

4). This thrombotic material consisting of fibrin and extravasated RBCs was recognized with Martius Scarlet blue (MSB) stain (Figure 5).

The immunohistochemical staining for Factor VIII antigen confirmed the endothelial nature of these proliferations (Figure 6). The histological features were most consistent with Papillary Endothelial Hyperplasia.

DISCUSSION

Papillary Endothelial Hyperplasia is a non-neoplastic reactive process first described by Masson,[8] who observed this peculiar endothelial proliferation in a thrombosed hemorrhoidal vein. In his original description, Masson regarded it as a true neoplasm that displayed degenerative changes including necrosis and thrombosis as it outgrew its blood supply.

However, Henschen[9] believed it to be a primary endothelial proliferation occurring in response to inflammation and stasis in a vascular bed. The term "Papillary Endothelial Hyperplasia" was first coined by Clearkin and Enzinger.[11] History of trauma is not usually elicited as in our case and biopsy is required to establish a diagnosis. In its pure form the lesion is small, containing clotted blood and surrounded by a fibrous pseudocapsule containing residual smooth muscle or elastic tissue of the pre existing vessel wall,[11] another feature that was observed in the present case. The vessels of small caliber are the usual site of its occurrence and there is a consistent association with thrombin material lending support to the idea that these are unusual organizing thrombi.[12,13] The debate whether PEH is a primary lesion with subsequent thrombus formation or an unusual manifestation of thrombosis continues and the etiology of PEH has yet to be confirmed.

This peculiar tumor-like process lacks specific clinical characteristics and its diagnosis must be based on microscopic examination, which is characterized by papillary proliferation of endothelial cells forming vascular channels, commonly associated with thrombus.[14] The in-growth of endothelial cells then subdivides the partially collagenized thrombus into coarse clumps. The florid endothelial proliferation, which is exclusively intravascular in location, suggests an exaggerated attempt at thrombus re-canalization.[12]

The proliferative activity in endothelial cells is perhaps mediated by angiogenic factors which may act directly on vascular endothelial cells, stimulating growth and locomotion by elaborating Fibroblast Growth Factor (FGF) and Transforming Growth Factor (TGF) or indirectly by mobilizing host cells such as macrophages to release growth factors.[15]

The current case in particular illustrated that the areas of florid papillary endothelial proliferation depicted a more recent organization and the papillae merging with the central granulation tissue represented the earliest stages in the organization of blood clot as confirmed by Martius scarlet blue staining. Thus the granulation tissue base could probably be the source of endothelial cell. Kreutner *et al.*[16] first made these observations in the light and electron microscopic study of intra vascular papillary endothelial hyperplasia.

Immunophenotyping of the endothelial cells in Papillary Endothelial Hyperplasia when compared with conventional intravascular organizing thrombi showed a similar progression in that they are initially positive for ferritin, then acquire vimentin positivity and display FVIII-rAg positivity in advanced ("mature") lesions. This suggests that intravascular endothelial hyperplasia is closely related to organizing thrombi.[13] The rounded or spindle cells occasionally seen as solid groups close to papillary fronds which may not react with factor VIII antigen are most likely histiocytes.[7]

The mechanism behind an exaggerated response of this neoplastic "actor" has been revealed by northern blot and immunoblot studies which showed 5-10-fold increase in basic fibroblast growth factor transcripts (7.0 and 3.7 kb) and a 10-20-fold increase in immunoreactive basic fibroblast growth factor protein compared

to that exhibited by non-IPEH organizing thrombi and cavernous hemangiomas.

These results suggest that the pathogenesis of IPEH involves an autocrine loop of endothelial basic fibroblast growth factor secretion stimulating endothelial cell proliferation.[12]

Papillary endothelial hyperplasia (also known as Masson's pseudoangiosarcoma) is thus an incidental finding within thrombosed dilated blood vessels or vascular tumors.

Hashimoto *et al.*[7] have described three forms of Papillary Endothelial Hyperplasia.

A. A primary or pure form in which the lesion arises in a dilated vessel,
B. A mixed or secondary form in which the lesions exist in preexisting vascular proliferations such as hemangioma, pyogenic granuloma or an arteriovenous malformation,
C. Extra vascular origin in hematomas.

Rare extravascular forms occur and can closely mimic angiosarcoma[17] histologically.

However, in angiosarcoma the anastomosing vascular channels are more irregular with the endothelial cells exhibiting cytological atypia with abnormal mitotic figures. Angiosarcoma also grows with an infiltrative pattern and invades the surrounding tissues unlike PEH, which tends to be well circumscribed.

Soft tissue hematomas generally resolve but may persist and develop into slow-growing, organized masses. A pseudocapsule and a predominantly necrotic central cavity, with foci of newly formed capillaries, histologically characterize them. These have been called chronic expanding hematomas or Masson's papillary endothelial hyperplasia. These lesions can mimic vascular neoplasms and must be considered in the evaluation of expanding soft tissue vascular malformations.[18]

Based on these observations and because of the complexity in histological presentation, one can reaffirm that such vascular presentations may represent the biological expression of one disease or a closely related group of diseases. Pyogenic granuloma, spindle cell hemangioma, epitheliod hemangioendothelioma and Dabska's tumor were considered in the differential diagnosis.

Pyogenic granuloma occurs commonly in the oral cavity. It appears as an exophytic growth in low power and the basic lesion is a lobular hemangioma set in a fibromyxoid matrix. Characteristically, the overlying epithelium almost meets at the base of the lesion. Typically, the lesion is well circumscribed with central feeding vessels and lobules of capillary sized vessels branching off from it, often accompanied by atypical cytological features such as marked plumpness of the endothelium and mitotic activity.[19,20,21,22]

Intravascular forms of epitheliod hemangioma may cause diagnostic problems. The characteristic pathological appearance of this tumor (also called angiolymphoid hyperplasia with eosinophilia (ALE)) is that of a proliferation of well formed small to medium sized vessels lined by histiocytoid or epitheliod endothelial cells with scalloped borders that protrude into the lumen. The stroma is fibro hyoid, comprised of inflammatory infiltrate, which contains eosinophils in particular, and lymphocytes in follicles.[23-25]

Spindle cell hemangioma is a benign, frequently multifocal lesion composed of spongy cavernous sinuses and spindled areas resembling Kaposi's sarcoma. However, they contain epitheliod endothelial cells lining vascular spaces, which are frequently vacuolated. The lesion shows an association with thrombi at various stages of organization with minimal hemosiderin deposits. Necrosis, cytological atypia , mitotic figures or PAS positive hyaline globules are generally absent.[26,27]

PEH should be distinguished from Endovascular Papillary Angioendothelioma (EPA) also known as Dabska-type hemangioendothelioma. The endothelial cells in EPA are hobnail, cuboidal or columnar. Although papillary endothelial proliferation with a central hyaline core is one of the most characteristic feature of EPA,[28] it has a distinctive histological pattern of anastomosing vascular channels with intravascular outpouchings, forming glomeruloid papillations.[29] Also proliferating endothelial cells of EPA differentiate towards "high" endothelial cells suggesting a close functional interaction with endovascular and stromal lymphocytes.[30]

CONCLUSION

The lesion presented here was Papillary Endothelial Hyperplasia, which was superimposed on a pre-existing vascular lesion for the lesion did not resolve following surgery, suggesting a possible mixed presentation with an underlying true vascular proliferation.

Features that aided its recognition and differentiation from a sarcoma included the constrained growth, absence of tissue necrosis, and the intimate association with thrombotic material. There was both architectural and cytological diversity. In some areas the lesion was markedly cellular while in other areas it was marked by endothelium lined papillary fronds with hyaline cores. As Papillary endothelial hyperplasia can be engrafted upon other vascular lesions, such as pyogenic granuloma or hemangioma, identification of an obviously benign vascular lesion in the background is important in determining subsequent behavior.

The treatment of pure IPEH is simple surgical excision, while that of the secondary form necessitates determination of the associated vascular lesion. Excision is curative in the former although recurrence has been reported with the mixed forms, possibly due to

incomplete excision or re-growth of the underlying vascular malformation.7,14

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