Revista del Instituto Nacional de Cancerología

Vol. 46, Núm. 1
Enero-Febrero 2000
pp 58 - 63

Oral nodular endothelial hyperplasia. Report of cases and review of the literature

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ABSTRACT

Intravascular papillary endothelial hyperplasia (intravascular angiomatosis) is a lesion which several authors regard as a reactive phenomenon associated with such vascular alterations as hemangiomas, hematomas, varix, thrombi or dilated vessels while others consider it a neoplasm. An extensive review of the literature and a discussion of the previously reported points of view with a report of six new oral cases (including the first such lesion associated with an oral hematoma) is presented. As it is demonstrated, this process starts as a thrombus formation with initial proliferation of endothelial cells and it ends as an endothelial nodule of main intravascular location. The importance of distinguishing this lesion from angiosarcoma is stressed and their differences discussed. We propose that the correct name for this entity is "Nodular Endothelial Hyperplasia".

Key words: *Endothelial hyperplasia, intravascular endothelial hyperplasia, Masson's pseudoangiosarcoma, papillary intravascular endothelial hyperplasia.*

RESUMEN

La hiperplasia papilar endotelial intravascular (angiomatosis intravascular) es una lesión que diferentes autores consideran un fenómeno reactivo asociado a alteraciones vasculares como: hemangiomas, hematomas, várices, trombos o vasos dilatados; otros, en cambio, la consideran una neoplasia. En este artículo se presenta una revisión de la literatura, se reportan seis casos intrabucales (incluyendo el primer caso asociado a un hematoma) y se realiza una discusión de los diferentes puntos de vista que se han publicado. Como se demuestra en este trabajo, esta lesión comienza con la formación de un trombo con proliferación de células endoteliales y termina como un nódulo endotelial que se localiza principalmente a nivel intravascular. Se hace hincapié en la distinción de este proceso con el angiosarcoma y se discuten sus diferencias. Se propone que el nombre correcto para esta entidad es hiperplasia endotelial nodular.

Palabras clave: Hiperplasia endotelial, hiperplasia endotelial intravascular, pseudoangiosarcoma de Masson, hiperplasia papilar endotelial intravascular.

History. In 1922, Ewing[1] described a rare and somewhat obscure intravascular endothelioma in the corpus cavernosum. He also described some cases of encapsulated, slow growing subcutaneous tumors with abundant endothelial cells occurring in dilated varicose veins with previously obstructed circulation. These tumors grew in broad papillary masses formed by enlarged cells with hyperchromatic nuclei. He also described a papillary intravascular cellular proliferation of endothelium arising in a distended lymphatic vessel and a papillary growth in a cervical lymph node which was the seat of chronic lymph stasis, which he called Papillary Fibroendothelioma. In his book, Ewing[1] included in the term hemangio-endothelioma some rare endothelial entities such as endothelioma of the corpus cavernosum and an intravascular endothelioma arising in hemorrhoidal and other dilated veins. In his classification of endothelioma, the plexiform type grew in papillary projections from convoluted columns, suggesting the term papillary endothelioma. Before 1922, Ackerman[2] classified vascular tumors as intravascular, lymphangiomatous and interfascicularis. Ewing,[1] also pointed out that Schlagenhaufer[3] described such tumors arising in hemorrhoidal veins and in the ovary and that Kroemer,[4] described a large cystic lymphangioma in which endothelial cells were prominent. In 1923, Masson[5] reported an intravascular process he believed was a neoplastic lesion and which he called "Hémangioendothéliome végétant intravasculaire". Henschen,[6] described similar changes in nasal and laryngeal vessels which he considered a reactive phenomenon.

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Fecha de recepción 24/08/98. Fecha de aceptación 04/03/99.

Table I. Endothelial hyperplasia. Clinical findings of oral cases.

	Cases	
Location	*n*	*%*
Lips	38	60.32
Tongue	10	15.87
Buccal mucosa	9	14.28
Vestible	3	4.76
Commisure	1	1.59
Intraosseous	1	1.59
Not specified	1	1.59
Total	63	100.00
Gender distribution		
Female	30	47.60
Male	21	33.30
Not specified	12	19.00
Total	63	100.00
Female/male ratio		
This review	3/2.1	
Corio et al	1/2.5	
Buchner et al	1.2/1	

Review of the literature.- Rosai and Ackerman,[7] published three cases of intravascular alterations in dilated veins, one of which was in the lower lip. They recognized its relation to trauma, suggesting a reactive process associated with recanalization of blood flow through a thrombus. Salyer and Salyer,[8] grouped the major histologic features of this intravascular lesion in such a way that one could distinguish it from angiosarcomas. Clearkin and Enzinger,[9] reported ten cases in the head and neck area (one in the lip), but they did not present specific clinical features. They found this alteration associated with hemangiomas, small vascular malformations and large veins. In 1976, Kuo et al[10] published seventeen cases and described two types: A "pure" form arising in a dilated vascular space and a form associated with lesions such as pyogenic granulomas or hemangiomas. They considered that the "intravenous atypical vascular proliferation" of Rosai and Ackerman[7] was different from "Masson's pseudoangiosarcoma" proposed by them, since the former has a papillary growth with cells showing an epithelioid or histiocytic appearance while the latter showed a solid growth.

Finlayson and Nayak,[11] suggested that abnormal blood flow or intraluminal pressure could have been the stimulating factor in their reported cases. Its relation to thrombi were commonly reported.[11-14,15] As expected, this phenomenon is also associated with thrombi forming diseases.[14]

In animals, it is present in vascular tumors induced by an avian hemangioma retrovirus in fowls.[16]

Immunohistochemistry revealed that the endothelial cells in this lesion are positive for CD34,[17] factor VIII-related antigen,[16,18] factor VIII and factor XIIIa.[17] Cohen et al,[19] found that two of their three cases were CD34 negative, suggesting that endothelial cells in their lesions do not express CD34 antigen because they are mature cells.

Some authors[20,21] commented on the similarity between endothelial cells in pyogenic granuloma or granulation tissue and the cells of this lesion.

A review of the literature of intraoral lesions revealed that 63 reported cases of this lesion exist.[7,9,10,22-32] Of them, 38 were located in the lips,[7,9,10,22-26,29,31] 10 in the tongue,[25,27,29,32] nine in the buccal mucosa,[25,26,29] three in vestibule[28-30] and one in the commisure,[24] a non specified area[28] and intraosseous[18] respectively. The clinical demographics of those cases are summarized in *tables I* and *II*.

In an effort to clarify some of the questions regarding the development and etiology of this lesion we discuss some clinico-pathological aspects and report six new oral cases (four in the lips, two in the buccal mucosa), including the first intraoral case associated with a hematoma.

Table II. Age distribution of the reviewed cases.

	Cases	
Decade	*n*	*%*
11-20	1	1.6
21-30	7	11.1
31-40	4	6.4
41-50	10	15.9
51-60	5	7.9
> 60	8	12.7
Not specified	28	44.4
Total	63	100.0
	Age (years)	
	Range	*Average*
This review	12-83	46.4
Corio et al[39]	21-72	44.6
Buchner et al[43]	30-62	53.0

CASE REPORTS

All the lesions were removed as excisional biopsies. The patients were followed from 13 to seven years, with no clinical evidence of recurrence.

Case 1. We reviewed a 43 year old male presented with a raised four mm reddish lesion in the middle of the lower lip, which was present for eight weeks. The lesion was a dilated blood vessel with a luminal thrombus and a diffuse accumulation of endothelial cells with no vascular differentiation *(Figure 1)*. This lesion was reported out as a dilated blood vessel with early changes of endothelial hyperplasia.

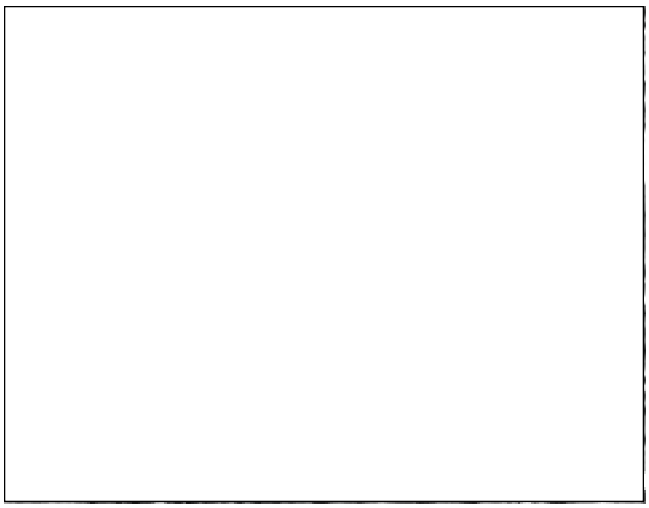

Figure 1. *Capillary vessel containing an intravascular nodule of endothelial cells. H and E (200 X).*

Case 2. During the clinical examination of a 63 year old male patient, the dentist discovered a raised lesion two mm long in his right buccal mucosa. It was said to be present for several months. Microscopic observation showed several dilated vascular channels, one of which had an organizing thrombus with papillary projections *(Figure 2)* and eosinophilic leukocytes. Diagnosis: Hemangioma with nodular endothelial hyperplasia.

Case 3. A 67·year old female, referred by a dental practitioner, presented a 1.0 cm round, pale pink lesion in her lower lip mucosa extending to the skin. It was multilobular, soft, asymptomatic and of 20 years' duration. Microscopic examination revealed two dilated blood vessels, one of which contained an organizing thrombus. The other showed abundant endothelial cells covering small intraluminal papillary projections. The center consisted of thrombotic material and the cellular mass was continuous with the endothelial vascular lining. Diagnosis: Blood vessels with nodular endothelial hyperplasia.

Case 4. Clinical examination of a 23 year old female patient, revealed a red lesion in the left buccal mucosa. Microscopic review of the lesion showed numerous blood vessels separated by thin septae of fibrous connective tissue. Several dilated channels showed organized thrombi, one of which was calcified. One of the vessels had an intraluminal nodular structure formed by endothelial cells *(Figure 3)*. Diagnosis: Hemangioma with nodular endothelial hyperplasia.

Case 5. A 50 year old female patient with a one cm raised purple lesion in the lower lip mucosa, said to be present for several years, was seen in the Oral

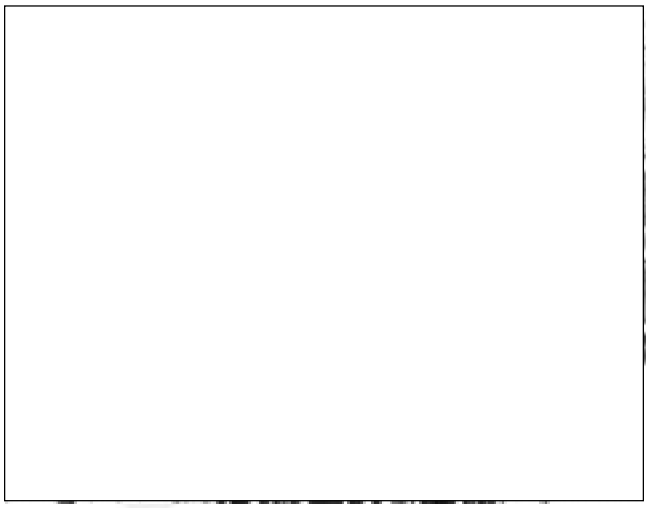

Figure 2. *Intraluminal thrombotic material showing numerous endothelial cells without signs of vascular formation. H and E (40 X).*

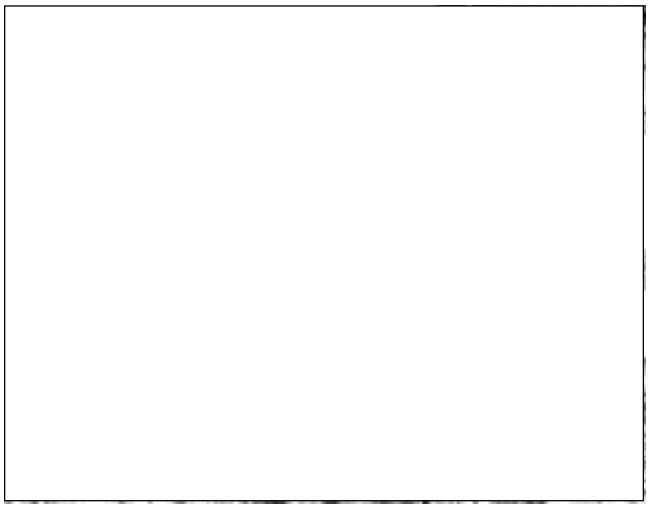

Figure 3. *Papillary projections in an organizing thrombus showing some channels lined by endothelial cells. H and E (100 X).*

Pathology Clinic. Microscopic examination of the lesion revealed several vascular channels, the largest of which contained four intraluminal mural proliferations formed by endothelial cells *(Figure 4)*. Two cellular masses had smooth surfaces and the other had small intraluminal peripheral papillae, a suggestion of vascular formation and numerous eosinophilic leukocytes. The final diagnosis was: Hemangioma with nodular endothelial hyperplasia.

Case 6. A 50 year old female patient presented with a red-violet, six cm, raised lesion in the border of the lower lip of several years duration. Microscopic examination of the lesion revealed an eosinophilic homogeneous material resembling a thrombus with papillary projections *(Figure 5)*. Diagnosis: Hematoma with nodular endothelial hyperplasia.

To date, no clinical signs of recurrence were seen in any patient.

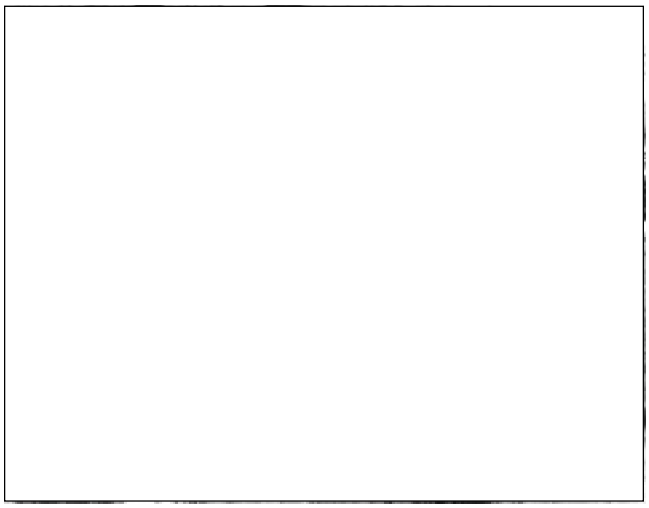

Figure 4. *Large vascular channel with four intraluminal nodules, two with peripheral papillary projections, and two with smooth surfaces. H and E (40 X).*

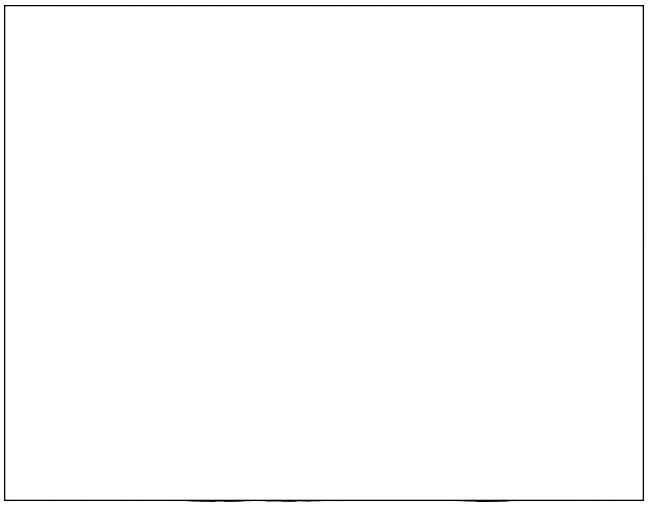

Figure 5. *Extravascular thrombotic material with endothelial papillary projections. H and E. (40 X).*

DISCUSSION

Since the first description of this lesion, it has been described under a variety of different names. Papillary fibro-endothelioma and intravascular endothelioma,[1] Papillary proliferation of the endothelium,[2] Papillary endothelioma,[4] Hémangioendothéliome végétant intravasculaire,[5] L'endovasculite proliférante trombopoiétique,[6] intravenous atypical vascular proliferation,[7] Intravascular angiomatosis,[8] Intravascular papillary endothelial hyperplasia,[9] Masson's vegetant intravascular hemangioendothelioma,[10] Masson's pseudoangiosarcoma,[10] Intravascular endothelial hyperplasia,[21] Masson's lesion,[15] and Papillary endothelial hyperplasia.[32]

Masson[5] considered this lesion to be an endothelial neoplasm with secondary thrombus formation. Later, Henschen[6] proposed that the changes were the result of a reactive and reparative response of the endothelium to inflammation and stasis within blood vessels.

This process can not be clinically diagnosed, but some features are characteristic. It is usually firm, tender, two to four cm masses, which have a blue or red color and are sharply demarcated and slightly elevated.[9,10] However, they can only be diagnosed by means of careful microscopic examination. Treatment of choice is surgical excision, but 14 recurrences have been reported to date.[7,9,10,12,13,31]

Recognition of this phenomenon is of critical importance since misdiagnosis as angiosarcoma or viceversa can occur[7-10,17,23,25,27,29] and it can be devastating for the patient.

It is important to note that as was stated by Salyer and Salyer,[8,33] the features which distinguish this lesion from angiosarcoma are: 1) The lesions are well circumscribed and have a predominately intravascular location. 2) Extravascular lesions are associated with hematomas. 3) Rare but normal mitotic figures occur. 4) There is a lack of cellular atypia. 5) There are no necrotic areas. 6) Cells do not invade the perivascular space. 7) Solid areas exist with or without vascular differentiation. 8) Papillary fronds are one or two cells thick. 9) Papillary structures are mainly supported by a core of thrombotic material.

We propose to eliminate "papillary" because in our case 3 (nodular growth), case 1 (diffuse) and case 5 (nodular and papillary growths) and those of other

authors.[7,10,12,22,25,29,34] showed that non-papillary and solid areas are present in this lesion. In view that our case 6, those cases of Salyer and Salyer,[8] Corio et al,[25] Kaufman and Stout,[35] Hashimoto et al,[12] and 18 cases reviewed by Pins et al,[36] all of them showing this process arising in hematomas, the term "intravascular" becomes highly inadequate. For this reason we suggest its elimination and the adoption of the shorter and more educated name "Nodular Endothelial Hyperplasia" (NEH) since all reported cases were nodular lesions.

The cases of Salyer and Salyer,[8,33] Clearkin and Enzinger,[9] Barr et al[23] and Rosai and Akerman,[7] called "intravenous atypical vascular proliferation", those of Kuo et al[10] labeled as "Masson's pseudoangiosarcoma", despite their apparent involvement, presence of nodular areas of endothelial proliferation, increase of the mitotic rate, hyperchromatism and occasional slight atypical appearance, they all should be considered as part of the microscopic spectrum of NEH.

In four of our cases, the nodules of hyperplastic endothelial cells were clearly associated with thrombus formation. The process probably starts with a recently formed thrombus and early endothelial proliferation occurs (case 1). Later, (case 2) papillary projections develop when endothelial cells cover the irregular surface of the thrombus. In the more advanced stage, thrombotic material is slowly resorbed and papillary projections become smaller (case 3). At an end stage, the thrombotic material is completely resorbed and only a nodule composed of endothelial cells remains (cases 4 and 5).

According to our results, we suggest that this condition starts as a thrombus with initial proliferation of endothelial cells and ends as a nodule, mainly in intravascular location. In our reported cases, the sequence of the events just described follows the clinical duration of the lesions. These results are in agreement with those of Albretch and Khan.[21] In some instances, irregularities of the thrombotic surface are seen as papillary projections or well-formed vascular channels. In two of our cases, as well as in other reports,[10,12,21,25,29,37] eosinophilic leukocytes were present. It is an interesting finding and a challenge for further research.

Sixty-three oral cases of NEH have been reported to date, 57 from the literature[7,9,10,18,22-32] and six in this paper. Thirty patients (58.8%) were females and 21 (41.2%) were males with a 3:2.1 female-male ratio (n = 51) [Table I]. Ages ranged from 12 to 83 years (n = 35, mean = 46.4 years) [Table II]. In this figure, the cases of Corio et al[25] and Buchner et al[29] are not included, since ages were not specified. 64.7% of the reviewed cases were in patients over 40 years of age.

The most common oral location was the lips, followed by tongue, buccal mucosa and oral vestibule. The results suggest that these lesions were associated with trauma, since more than 90% of the reviewed cases were located in frequently traumatized zones. All the patients were treated by surgical excision. In the oral area, only three recurrences in the lips were reported.[7,31]

To our knowledge, case 6 of our series is the first reported example of this condition arising in an intraoral hematoma. However, two similar cases in the head and neck area were presented by Corio et al,[25] although their exact location was not stated. No oral cases were presented in the review of the literature of NEH extravascular cases by Pins et al.[36]

ACKNOWLEDGMENTS

The authors are indebted to Barnet M., M.D. Levy for his review and criticism of the manuscript and acknowledge the technical assistance of Alejandra Greenham G., M.D. in the preparation of the slides. This work was prepared largely while the first author was a Visiting Scientist in the Biomineralization Department, Forsyth Dental Center. Boston, MA. He is grateful to Edgard C. Moreno, M.D. (Forsyth) and the *Fundación UNAM* (Mexico) for their support.

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