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Original

Intravascular papillary endothelial hyperplasia of the oral cavity

Harumi Inoue[1)], Yuji Miyazaki[1)], Kentaro Kikuchi[1)], Masahiro Fujinami[1)], Noriaki Yoshida[1)], Fumio Ide[1)], Hideaki Sakashita[2)] and Kaoru Kusama[1)]

[1)]Division of Pathology, Department of Diagnostic and Therapeutic Sciences, Meikai University School of Dentistry, Sakado, Japan
[2)]Division of Oral and Maxillofacial Surgery II, Department of Diagnostic and Therapeutic Sciences, Meikai University School of Dentistry, Sakado, Japan

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Abstract: To examine the pathogenesis of intravascular papillary endothelial hyperplasia (IPEH), a relatively uncommon benign, non-neoplastic vascular lesion, clinicopathological and immunohistochemical studies were performed. Paraffin-embedded tissue specimens of 78 vascular lesions were examined histologically, and 9 cases of IPEH were investigated immunohistochemically using antibodies against CD34, vimentin, factor VIII antigen, α-smooth muscle actin (α-SMA), podoplanin, CD105, and ki-67 antigen. A thrombus or ulcer was found near the sites of all IPEH specimens. Histologic examination revealed papillary proliferated endothelial cells located toward the lumen of enlarged blood vessels. Immunohistochemistry showed that CD34, α-SMA, and factor VIII antigen were positive in lining endothelial cells. Vimentin was positive in the mesenchymal components. Immunohistochemical staining for podoplanin and CD105 was partially positive. Labeling index was 4.7 to 9.2 in ki-67-positive cases. IPEH is believed to result from reactive proliferation of blood endothelial cells that is caused by an abnormal process of organization in thrombosed blood vessels. The pathogenesis of IPEH might be related to inflammation or mechanical stimulus such as irritation. (J Oral Sci 53, 475-480, 2011)

Keywords: intravascular papillary endothelial hyperplasia; hemangioma; thrombus; immunohistochemistry; podoplanin.

Correspondence to Dr. Harumi Inoue, Division of Pathology, Department of Diagnostic and Therapeutic Sciences, Meikai University School of Dentistry, 1-1 Keyakidai, Sakado, Saitama 350-0283, Japan
Tel: +81-49-279-2773
Fax: +81-49-286-6101
E-mail: harumi-i@dent.meikai.ac.jp

Introduction

Vascular tumors in the oral region have been traditionally described as hamartomas or malformations rather than as true neoplasms (1). Stout (2) stated that a vascular tumor, in contrast to a hamartoma, contained more endothelial cells than was necessary to line the lumina. Clinically, vascular lesions have a tumor-like appearance, due to endothelial proliferation in vessels and enlargement of vessels with secondary reactive change.

Intravascular papillary endothelial hyperplasia (IPEH) was first described in 1923 as Masson's tumor and is currently believed to be a relatively uncommon benign, non-neoplastic vascular lesion (3,4). IPEH is believed to be a reactive proliferation of blood endothelial cells caused by an abnormal process of organization in thrombosed blood vessels (5-8).

IPEH is often diagnosed as a malignant tumor such as an angiosarcoma, malignant endovascular papilloma, or malignant melanoma, owing to their clinical and pathologic similarities (9-11). With regard to differential diagnosis, it is thus extremely important for clinicians and pathologists to become familiar with this lesion. In

this study, we investigated the pathogenesis of IPEH by examining the clinical, histologic, and immunohistochemical characteristics of 9 cases of IPEH.

Materials and Methods

Paraffin-embedded tissue specimens of 78 vascular lesions were examined histologically, and 9 cases of IPEH were investigated immunohistochemically using antibodies against CD34, vimentin, factor VIII antigen,

Table 1 Clinical characteristics of 9 IPEH cases

Patient No.	Age (years)	Gender	Site	Clinical diagnosis	Accompanying histopathologic lesion	IPEH type	With thrombus	With ulcer
1	43	F	Tongue	Hemangioma	Thrombosis	I	○	
2	81	F	Lower lip	Hemangioma	Hemangioma	II	○	
3	71	M	Cheek	Tumor	Hemangioma	II		○
4	57	M	Upper lip	Inflammation	Hemangioma	II		○
5	40	M	Upper lip	Hemangioma	Hemangioma	II	○	
6	22	M	Gingiva	Epulis	Hemangioma	II		○
7	20	F	Gingiva	Epulis	Hemangioma	II		○
8	62	F	Gingiva	Tumor	Pyogenic granuloma	II		○
9	13	M	Hard palate	Tumor	Pyogenic granuloma	II		○

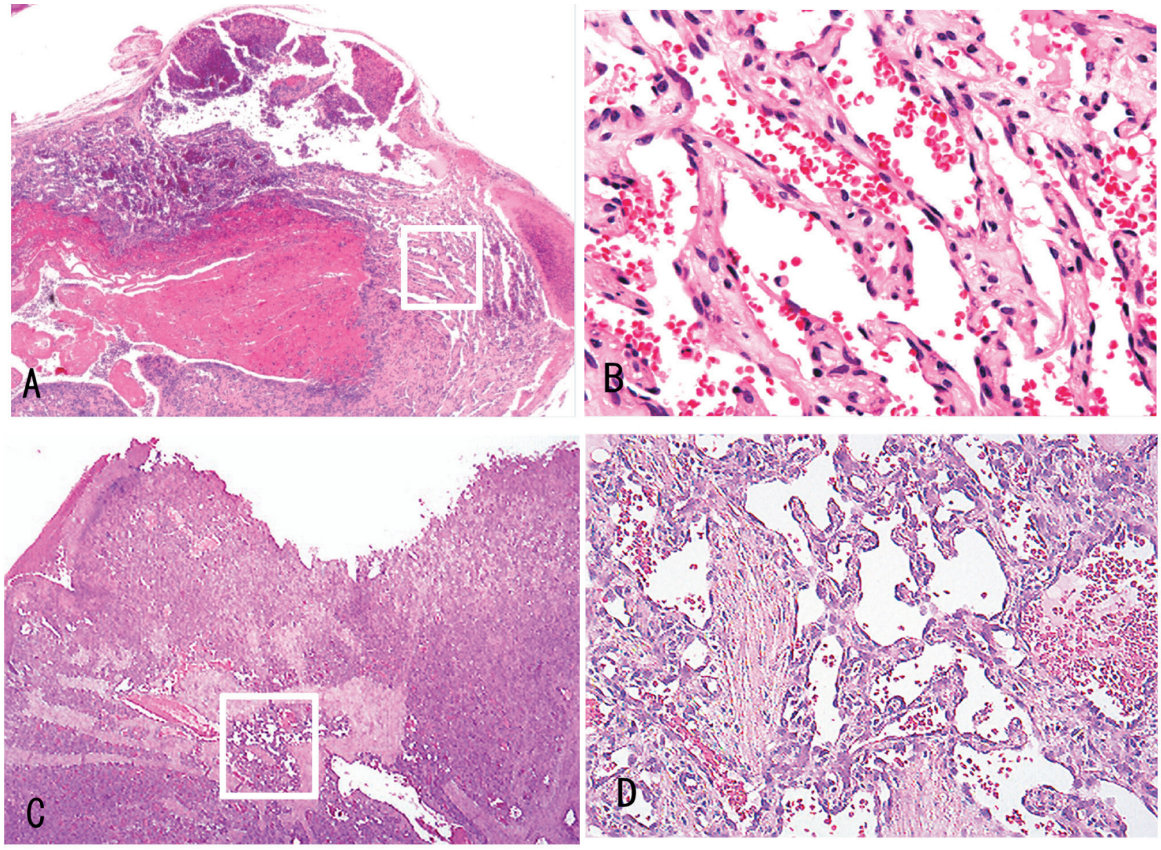

Fig. 1 Histopathologic features of IPEH.
A: Hematoxylin and eosin (HE) staining of IPEH in an organizing thrombus accompanied by a hemangioma (original magnification ×20), B: The cores of papillae consist of fibrous connective tissue and are lined by a single layer of endothelial cells (original magnification ×200), C: HE staining of IPEH near an ulcer accompanied by pyogenic granuloma (original magnification ×12.5), D: Papillary proliferation of endothelial cells towards the lumen of an enlarged blood vessel (original magnification ×100).

Table 2 Immunohistochemical reactivity for antigens in IPEH cases

Patient No.	CD34	Factor VIII antigen	α-SMA	Vimentin	Podoplanin	CD105	Ki-67 antigen
1	+	+	+	+	-	+	+ (8.0)
2	+	-	-	+	-	-	- (0.0)
3	+	-	+	+	+	+	+ (9.2)
4	+	+	+	+	-	-	+ (8.3)
5	+	+	+	+	+	-	+ (8.7)
6	+	-	+	+	-	-	- (0.0)
7	+	+	+	+	-	-	+ (9.0)
8	+	+	+	+	-	+	+ (7.2)
9	+	+	+	+	-	+	+ (4.7)
%	100	66.7	88.9	100	22.2	44.4	77.8 (%)

α-smooth muscle actin (α-SMA), podoplanin, CD105, and ki-67 antigen. The study protocol was reviewed and approved by the Research Ethics Committee of Meikai University School of Dentistry (A0832).

Tissue preparation

The tissue samples were collected from the Division of Pathology, Department of Diagnostic and Therapeutic Sciences, Meikai University School of Dentistry, and matching data for patient age, gender, and lesion site were obtained from information submitted with surgery request forms. Among a total of 3,343 diagnoses made at our department from January 2006 through July 2010, only 9 cases of IPEH were found in 78 vascular lesions. The paraffin-embedded tissue blocks were sliced into thin sections for subsequent histologic examination. The tissue sections were then stained with hematoxylin and eosin for histologic diagnosis.

Immunohistochemical examination

Each sample of the 9 cases of IPEH embedded in paraffin wax was sectioned and mounted on glass microscope slides. Deparaffinized sections were immersed in absolute methanol containing 0.3% (v/v) hydrogen peroxide for 15 min at room temperature to block endogenous peroxidase activity. After washing with running water and phosphate-buffered saline (PBS, pH 7.4), the sections were immersed in 0.01 M citrate buffer, pH 6.0, and heated in a microwave oven for 5 min at high voltage and then for 15 min at low voltage to increase the antigenicity of CD34, vimentin, factor VIII, α-SMA, CD105, and ki-67 antigen. All sections were then incubated in 2% (w/v) bovine serum albumin (BSA) to block nonspecific reactions. Appropriately diluted monoclonal antibodies against CD34 (NU-4A1; Nichirei, Tokyo, Japan), vimentin (SP20; Nichirei), α-SMA (1A4; Nichirei), podoplanin (D2-40: Dako North America, Inc., USA; supernatant, 1:100), and CD105 (Dako North America, Inc.; supernatant 1:10) were applied to each section for 1 h. Antibodies against factor VIII antigen (F8/86; Dako Denmark A/S, Denmark; supernatant 1:20) and ki-67 antigen (M1B-1; Dako) were applied for 30 min at room temperature. The sections were then incubated with peroxidase-labeled dextran polymer (Simple Stain MAX-PO; Nichirei Bio Inc., Tokyo, Japan) for 30 min, and the reaction products were visualized by immersing the sections in freshly prepared 0.03% diaminobenzidine solution containing 2 mM hydrogen peroxide for 6 to 8 min. Nuclei were lightly stained with Mayer's hematoxylin. As a negative control, serial sections were treated with 2% BSA-PBS instead of the primary antibodies and were confirmed to be unstained. Immunohistochemical reactivity for CD34, vimentin, α-SMA, podoplanin, CD105, factor VIII antigen, and ki-67 antigen was evaluated in the endothelial cells of IPEH and classified into 2 groups: negative and positive. The percentages of cases positive for each antigen are shown in parentheses. For ki-67 antigen, positive cells were counted and the labeling index is shown.

Results

Among the 78 vascular lesions that had been previously diagnosed as hemangioma (49 cases), pyogenic granuloma (15 cases), thrombosis (8 cases), epulis hemangiomatosa (6 cases), we observed 9 cases of IPEH (12% of vascular lesions). Six of the IPEH cases were associated with hemangiomas, 2 with pyogenic granulomas, and 1 with thrombosis. Among the 9 IPEHs, 3 were observed with a thrombus and 6 with an ulcer.

The clinical data for the IPEH cases are summarized in Table 1. Patient age ranged from 13 to 81 years (mean, 45.4 years). There were slightly more males (male:female

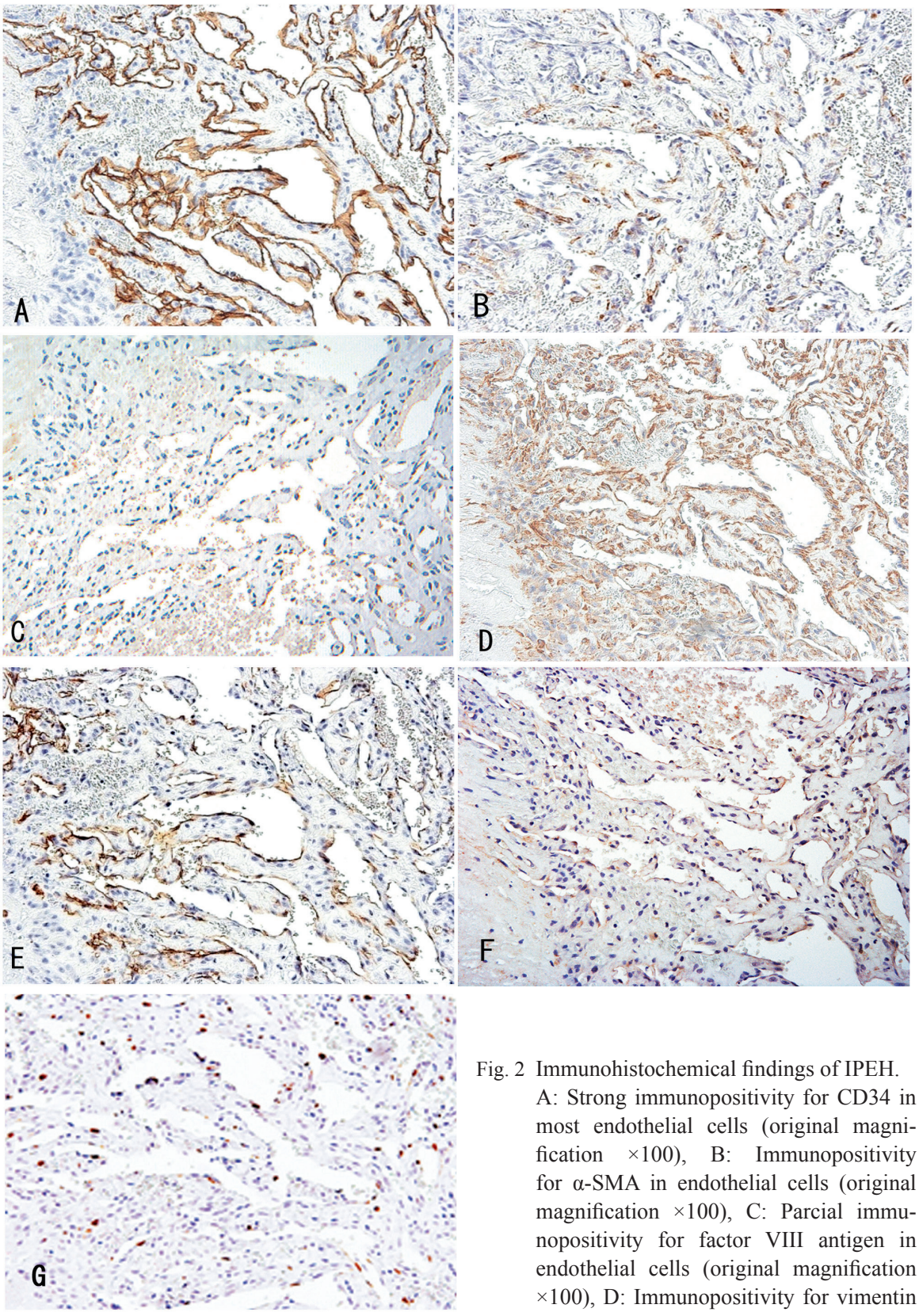

Fig. 2 Immunohistochemical findings of IPEH. A: Strong immunopositivity for CD34 in most endothelial cells (original magnification ×100), B: Immunopositivity for α-SMA in endothelial cells (original magnification ×100), C: Parcial immunopositivity for factor VIII antigen in endothelial cells (original magnification ×100), D: Immunopositivity for vimentin in lining of endothelial cells and stroma (original magnification ×100), E: Partial immunopositivity for podoplanin in endothelial cells (original magnification ×100), F: Partial immunopositivity for CD105 in endothelial cells (original magnification ×100), G: A few nuclei of endothelial cells were stained by ki-67 antibody (original magnification ×100).

ratio, 5:4), and the upper lip and gingiva were the most frequent sites.

Histopathologic findings

In cases of IPEH associated with thrombi, an organizing thrombus was observed in an expanded blood vessel. The endothelial cells proliferated in a papillary pattern towards the lumen of the enlarged blood vessel from the area of the organizing thrombus (Figs. 1A, B). In other cases, an ulcer was found near the area of IPEH formation (Figs. 1C, D). In cases associated with a thrombus or ulcer, the structure of papillary proliferation was covered with no more than 2 layers of endothelial cells, and no atypia or mitotic activity was seen around the cores of fibrous connective tissue, which were frequently hyalinized and hypocellular.

Immunohistochemical findings

The results of immunohistochemical staining for CD34, vimentin, α-SMA, podoplanin, CD105, factor VIII antigen, and ki-67 antigen in IPEHs are summarized in Table 2. In all cases, the lining endothelial cells were positive for CD34 and α-SMA (Figs. 2A, B). Factor VIII antigen was partially positive in endothelial cells in 6 of the 9 cases (Fig. 2C). Vimentin showed positivity in the mesenchymal component in all cases (Fig. 2D). A few cases were positive for podoplanin and CD105 (Figs. 2E, F). In 7 cases, ki-67 antigen was positive; however, the labeling index was 4.7 to 9.2 in those cases (Fig. 2G).

Discussion

In the present series, the upper lip and gingiva were the most frequent sites for IPEH. This finding was not consistent with previously reported cases, for which the most commonly affected intraoral site was the lower lip (6,7,12).

Traditionally, hemangiomas have been divided into capillary and cavernous types. The capillary type consists of numerous minute blood vessels and vasoformative tissue-mere rosettes of endothelial cells. The cavernous type consists of large blood-filled sinusoids (13). A mixture of the two types is often observed. In the present series, capillary hemangioma most often accompanied IPEH and was predominant in half of the cases, followed by cavernous hemangioma and then the mixed type.

H-E staining demonstrated numerous papillary processes located in the direction of the vascular lumen; the cells were covered by a single layer of endothelium. The absence of abnormal mitosis, cellular atypia, and necrosis, which are often indicative of malignancy, is a characteristic feature of IPEH (14-16). In this study, the labeling index was 4.7 to 9.2 in ki-67-positive cases. There was a tendency for the ki-67 labeling index to be higher in CD105-positive cases, which indicates proliferation of endothelial cells. Soares et al. (11) found that proliferative endothelial cells in IPEH were negative for CD105, suggesting that IPEH is an old reactive process and that it differs from the reactive process in pyogenic granuloma, in which all cells are positive for CD105. In the present study, CD105 was detected in 4 cases of IPEH, but the staining was not strongly positive. Therefore, IPEH is not likely to be a proliferative lesion comprising newly forming vessels. Positive staining for CD34, factor VIII antigen, and α-SMA suggests that IPEH is a lesion of blood vascular origin. Vimentin positivity showed that IPEH is of mesenchymal origin. Moreover, partial positivity for podoplanin indicated that the endothelial cells of lymphatic vessels might have a role in IPEH formation.

In a recently developed classification system for IPEH, type I is the primary (pure) form, in which changes are observed in a distended vessel; type II is the secondary (mixed) form that occurs in preexisting varices, hemangiomas, pyogenic granuloma, or lymphangiomas; and type III is an uncommon type with an extravascular location (7,12,17). In our series, 8 cases were type II and 1 was type I; none were type III.

IPEH is characterized by papillary proliferation of endothelial cells and is believed to be caused by an abnormal process of organization in thrombosed blood vessels. Nevertheless, we confirmed that the pathogenesis of IPEH is probably related to inflammation or some form of mechanical stimulus, such as irritation or trauma, because 6 of the IPEH cases were from samples of tissue near areas of ulcer formation, without an organizing thrombus. In the present study, proliferative lymphatic vessels were sometimes observed in an organizing thrombus, which suggests that lymphatic vessels might be involved in the process of thrombus organization.

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