
Spindle cell hemangioma (hemangioendothelioma) of the head and neck: case report of an unusual (or underdiagnosed) tumor

K.I. Tosios,^a I. Gouveris,^a A. Sklavounou,^a I.G. Koutlas,^b Athens, Greece, and Minneapolis, Minnesota

NATIONAL AND KAPOEDESTRIAN UNIVERSITY OF ATHENS AND UNIVERSITY OF MINNESOTA

Spindle cell hemangioma (SCH), also known as spindle cell hemangioendothelioma, is a unique vascular tumor with combined microscopic features of both a cavernous hemangioma and Kaposi sarcoma. It almost exclusively affects the dermis and subcutis of the distal extremities. A review of the literature disclosed only 5 cases of SCH reported in detail in the soft tissues of the head and neck. An additional case of SCH manifesting as a submucosal nodule in the upper lip of a 29-year-old woman is presented. Because this is the second case reported from the same institution, it is suggested that SCH is an underdiagnosed lesion. (**Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008;105:216-21**)

In 1986, Weiss and Enzinger¹ described a unique vascular tumor with combined features of both cavernous hemangioma and Kaposi sarcoma. The spindle cell hemangioendothelioma was considered to be an intermediate or low-grade malignancy, with a biologic behavior between a hemangioma and an angiosarcoma.¹ Subsequently, Fletcher et al.² and Imayama et al.³ presented evidence that spindle cell hemangioendothelioma is a nonneoplastic reactive vascular proliferation. Later Perkins and Weiss⁴ proposed the terms “spindle cell hemangioma” (SCH) for solitary lesions and “spindle cell hemangiomatosis” for multifocal lesions. This view was adopted by other authors.⁵

Spindle cell hemangioma is a relatively uncommon lesion, with fewer than 200 cases reported in the English-language literature up to 2006. It affects almost exclusively the dermis and subcutis of the distal extremities and rarely the proximal extremities, axilla, trunk, vulva, penis, spleen, pancreas, bones, and head and neck.^{1,4} Spindle cell hemangioma presents as a solitary tumor or as multiple nodules clustered within the same region.^{1,4} Its color is normal or bluish, its consistency firm, and it ranges in size from a few millimeters to a few centimeters, with most lesions being less than 2.0 cm.² It has a wide age distribution

with preference for young adults, and occasional lesions may be present from birth.^{1,4} There is no significant gender predilection,^{1,4,6} but solitary lesions tend to be more common in males and multifocal lesions in females.² Because the tumor is asymptomatic, with pain reported in just a few cases,⁷ it is usually present for many years before diagnosis.^{1,4}

To our knowledge only 5 cases of SCH in the soft tissues of the head and neck have been reported in detail.^{6,8-11} We present an additional case in the mucosa of the upper lip in a 29-year-old woman and review the literature on SCH of the head and neck.

CASE REPORT

A 29-year-old woman presented with a 1-year history of a slowly growing swelling in her upper lip. The lesion was not associated with local trauma or inflammation, and the patient's medical and dental histories were unremarkable.

Oral examination revealed a circumscribed submucosal nodule, approximately 1 × 0.7 cm, in the right upper lip. The covering mucosa was intact, with bluish discoloration, and on palpation the nodule was soft and not freely movable. No lymph nodes were detected on neck palpation. With the clinical diagnosis of mucocele, conservative surgical excision was performed under local anesthesia. Healing was uneventful. The patient was free of recurrence 3 years after treatment.

Grossly, the specimen was well demarcated, measured 1 × 0.7 × 0.5 cm, and had brown-black cut surfaces with white foci. The surgical material was fixed in buffered formalin, embedded in paraffin, and 5- μ m-thick sections cut and stained.

Microscopic examination showed a relatively well defined submucosal mass (Fig. 1), surrounded by fibrous connective tissue. The most conspicuous feature was the presence of irregular cavernous spaces lined by a single layer of endothelial cells that were flat or bulged into the lumens (Fig. 2). The

^aDepartment of Oral Pathology and Surgery, School of Dentistry, National and Kapoedestrian University of Athens.

^bDivision of Oral Pathology, University of Minnesota School of Dentistry.

Received for publication Dec 1, 2006; returned for revision Jan 21, 2007; accepted for publication Mar 13, 2007.

1079-2104/\$ - see front matter

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doi:10.1016/j.tripleo.2007.03.005

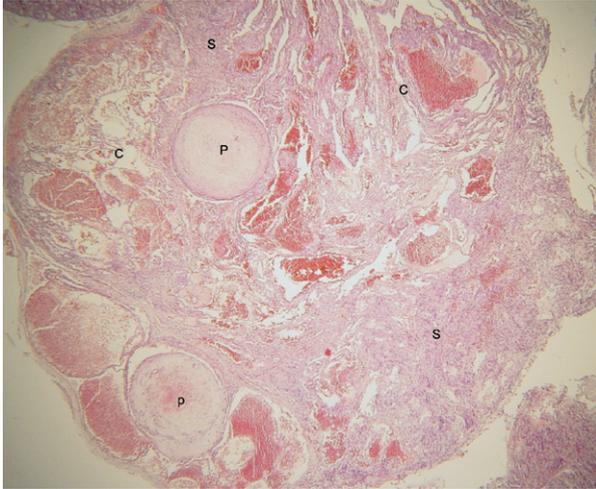


Fig. 1. Well defined submucosal mass with cavernous spaces (C), solid (S) areas, and large phleboliths (P) (hematoxylin and eosin stain, original magnification $\times 40$).

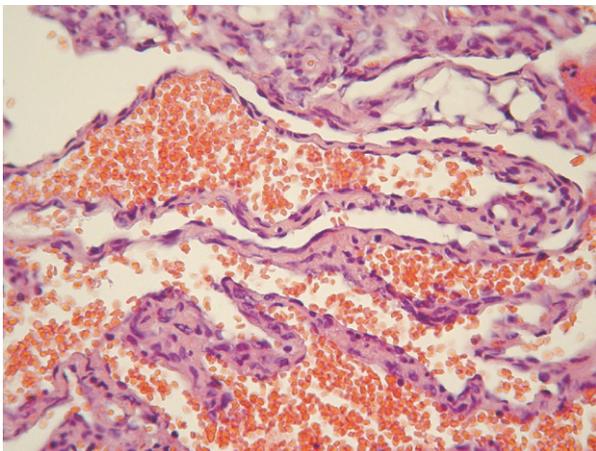


Fig. 2. Irregular cavernous spaces lined by flat endothelial cells (hematoxylin and eosin stain, original magnification $\times 400$).

spaces contained thrombi, phleboliths, and blood and were occasionally occupied by fronds or papillae of connective tissue, reminiscent of intravascular papillary endothelial hyperplasia (Fig. 3). Among the cavernous spaces were solid areas that showed proliferation of spindle-shaped cells with elongated and plump nuclei. They were arranged haphazardly or in short interlacing fascicles and occasionally delineated slit-like spaces (Fig. 4). Groups of epithelioid cells with round or oval nuclei and pale eosinophilic cytoplasm were also seen both in the cavernous spaces and in the solid areas. Some of the epithelioid cells contained large cytoplasmic vacuoles, which were interpreted as miniature lumina, that imparted on the cells a "clear" appearance (Fig. 5). Extravasated red blood cells and hemosiderin deposits were present.

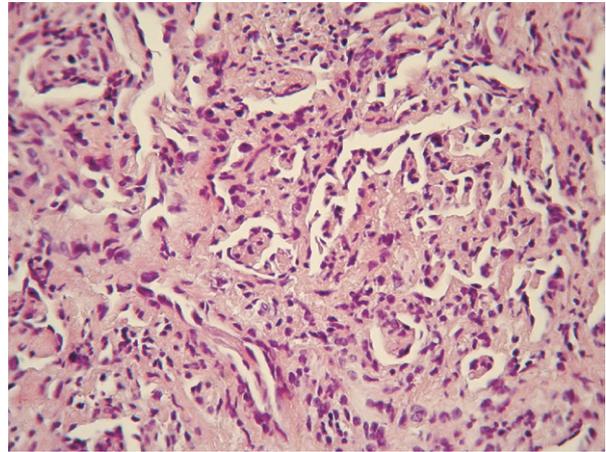


Fig. 3. Fronds or papillae of connective tissue reminiscent of intravascular papillary endothelial hyperplasia (hematoxylin and eosin stain, original magnification $\times 400$).

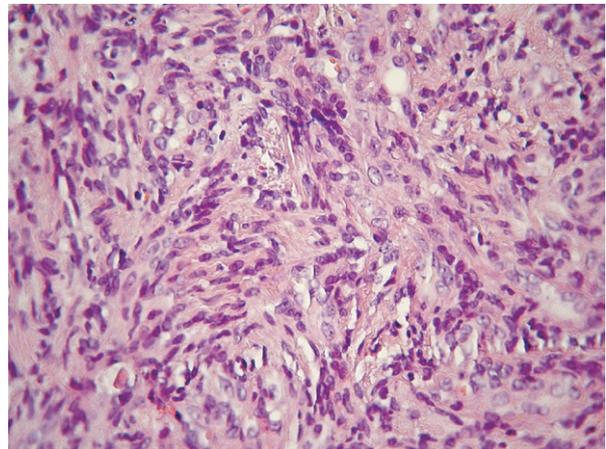


Fig. 4. Spindle-shaped cells in solid areas arranged in short interlacing fascicles and slit-like spaces (hematoxylin and eosin stain, original magnification $\times 400$).

Mitotic activity was low and areas of necrosis were not found. Histologic features were consistent with spindle cell hemangioma (hemangioendothelioma).

Immunohistochemistry was performed on formalin-fixed and paraffin-embedded tissue sections with antibodies for vimentin (LN6, dilution 1:50; Biogenex, San Ramon, CA), factor VIII (BGXO16A, 1:100; Biogenex), CD34 (QBEND/10, 1:20; Biogenex), smooth-muscle actin (1A4, 1:100; Biogenex), CD68 (PGM1, 1:30; Biogenex), estrogen receptor (1D5, 1:50; Dako, Carpinteria, CA), and Ki-67 (Mib-1, 1:30; Dako). Pretreatment with Antigen Retrieval Citra in a microwave oven was applied for the last two antibodies. Most cells reacted strongly for vimentin; CD34 and factor VIII reacted with endothelial cells lining the cavernous spaces, epithelioid cells, and cells lining slit-like spaces in the solid areas (Fig.

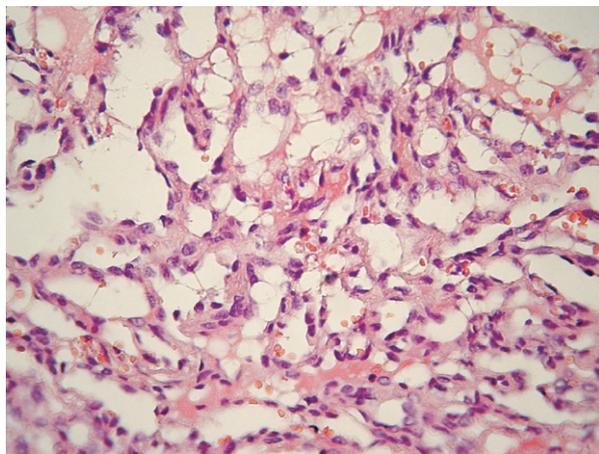


Fig. 5. "Clear" cells (hematoxylin and eosin stain, original magnification $\times 400$).

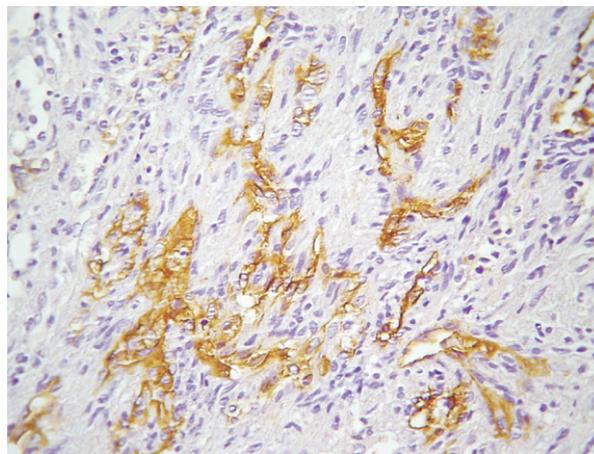


Fig. 6. CD34(+) cells in spindle cell areas (avidin-biotin-peroxidase, original magnification $\times 400$).

6). More CD34(+) than factor VIII(+) cells were seen. Smooth-muscle actin revealed the presence of small- to medium-sized vessels both in the cavernous and in the solid areas (Fig. 7) and decorated short bundles of spindle cells in the solid areas. A few CD68(+) cells were seen in the solid areas. There was no nuclear reactivity for estrogen receptors. The number of Ki-67(+) cells was $<5\%$.

DISCUSSION

Five cases of SCH of the head and neck have been described in detail in the English-language literature up to 2006. Their main clinical features, along with the present case, are presented in Table I. Four of the 78 cases of Perkins and Weiss⁴ were located in the head and neck, but because no clinical details were given they are not included in the table. Case 5 of Scott and Rosai¹¹ presented with multiple tumors on the ear, fingers, penis, and forearm in a 70-year-old man. Baron et al.⁸ reported an SCH on the left lateral nasal sidewall of a 17-month-old boy that recurred 2 years after surgical excision. In the case of Lade et al.,¹⁰ a large SCH at the posterior pharyngeal wall of a 25-year-old man, extending up to the epiglottis, was associated with difficulty in swallowing and night breathing as well as change in voice. Two intraoral SCH have been reported by Tosios et al.⁶ and Ide et al.⁹ in the mandibular vestibule of a 12-year-old girl and on the major palatine artery of a 55-year-old man, respectively.

Multifocal SCHs have been associated with Maffucci syndrome,^{1,4} Ollier disease,¹² chronic lymphoedema or Millroy disease,^{1,2} Klippel-Trenaunay syndrome,² von Willenbrand disease and acute myelomonocytic leukemia,¹¹ early-onset varicose veins,² and epithelioid hemangioendothelioma.¹

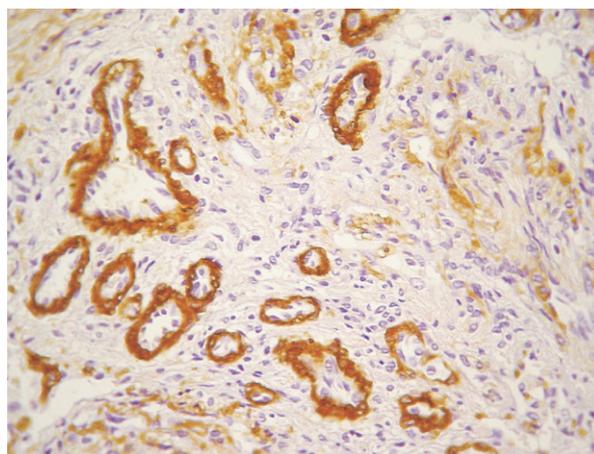


Fig. 7. Smooth-muscle actin-lined vessels in solid areas (avidin-biotin-peroxidase, original magnification $\times 400$).

Microscopically,^{1,2,4,11} SCH shows a biphasic pattern, with many cavernous vascular spaces and a solid cellular stroma, their relative proportions varying both between different lesions and within the same lesion. The cavernous spaces have thin walls, are lined by flat endothelial cells, and contain blood, thrombi, and phleboliths. The cellular zones are composed of spindle cells forming short interlacing fascicles and indistinct slit-like spaces. They are thought to represent stacks of collapsed cavernous vessels with intervening fibroblastic stromal cells.^{1,4} In accordance with this view, vascular spaces lined by CD34(+) or factor VIII(+) cells surrounded by smooth-muscle actin(+) cells were seen in the solid areas in the present case, whereas in an earlier study² similar spaces were lined by the basement membrane components laminin, collagen IV, and fi-

Table I. Main clinical features of 6 cases of spindle cell hemangioma of the head and neck

Author	Age	Gender	Duration (months)	Site	Maximum size (cm)	Follow-up (months)
Scott and Rosai ¹¹	70	M	recent presentation	ear (also fingers, penis, forearm)	NA	NA
Tosios et al. ⁶	12	F	NA	mandibular vestibule	1	LFU
Baron et al. ⁸	17m	M	13	lateral nasal sidewall	1	24 recurrence
Ide et al. ⁹	55	M	3	palate	1.2	12 FOD
Lade et al. ¹⁰	25	M	6	posterior pharyngeal wall	6	48 FOD
Present case	29	F	12	upper lip	1	36 FOD

F, female; M, male; NA, not available; FOD, free of disease; LFU, lost to follow-up.

bronectin. Round or polygonal epithelioid or histiocytoid cells may be interspersed singly or in small clusters among the spindle cells. Intracytoplasmic vacuoles in those cells are interpreted as “miniature lumens.” No significant nuclear atypia is found and mitotic activity is very limited.^{1,2,6} Occasionally, small folds or papillae of connective tissue lined by endothelial cells may form intravascular “roman bridges” in small vessels apart from the main tumor mass.⁶ Some lesions are entirely or partially contained within vessels, usually abnormal thick-walled veins,^{1,4,6} and large malformed vessels reminiscent of arteriovenous malformation may be seen in the periphery.^{2,4} The present lesion was not intravascular, and the lack of vessels in the periphery may be related to the conservative excision dictated by the benign clinical diagnosis.

Immunohistochemically, the lining cells and the vacuolated epithelioid cells are positive for vimentin,^{6,12} CD31,^{9,13,14} CD34,^{2,9,13,14} factor VIII-related antigen,^{1,2,6,7,12-15} *Ulex europaeus* I lectin,^{2,7,11,12,14} and HAM-56.^{6,7} In contrast, spindle cells are negative for endothelial markers^{1,7,11,13,14} and react for vimentin,^{6,9,12,13} and occasionally for actin,^{7,9,13} desmin,¹⁵ factor XIIIa,^{3,7} lysozyme, alpha-1-antithrypsine, MAC387, and HAM-56 antigen.^{6,7} The lesional cells do not react for S-100 protein, type IV collagen, cathepsin-B, cytokeratins, epithelial membrane antigen, or herpes virus 8 latent nuclear antigen-1.^{7,16} The present immunohistochemical findings are consistent with earlier reports. Limited CD68 positivity suggests that HAM-56(+) cells identified in earlier reports^{6,7} are of probable endothelial origin.

Immunohistochemical and ultrastructural findings^{1-3,7,11} support the endothelial nature of the lining cells and the vacuolated epithelioid cells. Spindle cells seem to comprise a heterogenous nonclonal cellular population, composed of various cell types that participate in the structure of the normal vascular wall.^{3,7} They present features of fibroblasts,^{3,7,9} pericyte-like cells,^{1,3,7,9} smooth muscle cells,^{3,15} macrophages,^{3,7} primitive mesenchymal cells,^{1,11,12} or cells with primitive endothelial differentiation.^{1,2,15}

The low proliferative activity of tumor cells^{1,2,6} was also confirmed in the present case. A G-banding cyto-

netic analysis in 1 case revealed a normal karyotype with rare nonsignificant aberrations.² Steroid receptor analysis in 2 cases was negative for estrogen and progesterone and positive for androgen and glucocorticoid receptors.¹

The differential diagnosis of SCH includes Kaposi sarcoma, cavernous hemangioma, epithelioid hemangioma, intravascular papillary endothelial hyperplasia, kaposiform hemangioendothelioma, and epithelioid and spindle cell hemangioma. Male predominance, occasional multifocal growth, location on the extremities, and predominance of spindle cells resemble Kaposi sarcoma, but that tumor rarely contains cavernous vessels with thrombi and phleboliths and lacks epithelioid cells, and the spindle cells react for the endothelial marker CD34.^{1,13} On the other hand, SCH does not present the hyaline globules seen in Kaposi sarcoma^{4,11} and does not express human herpes virus 8 latent nuclear antigen-1. Differentiation from cavernous hemangioma is based on the presence of spindle cells,¹⁵ whereas epithelioid hemangioendothelioma has a more solid appearance and lacks cavernous spaces with thrombi and phleboliths as well as spindle cell areas.¹⁰ As was seen in the present case, SCH may display areas similar to intravascular papillary endothelial hyperplasia, but the latter is more acellular, has many papillae, and does not present spindle and epithelioid endothelial cells.^{2,6} Kaposiform hemangioendothelioma forms distinct glomeruloid nests.¹⁷ The epithelioid and spindle cell hemangioma does not show cavernous vascular spaces, and the epithelioid cells tend to line well formed vascular spaces.^{18,19}

Multifocal and multiple lesions must also be differentiated from disseminated lobular capillary hemangiomas (DLCH) and epithelioid angiomatosis.¹¹ In DLCH, the lesions are more typical of capillary hemangiomas, and there are no dilated vascular spaces and spindle cell areas. The latter are also not seen in epithelioid angiomatosis, a form of histiocytoid hemangioma that involves internal organs of HIV-positive patients. So far, no patient with SCH has tested positive for HIV.

Unfamiliarity with the microscopic features of SCH and its similarity with hemangiomas may account for the paucity of reported cases in the head and neck. Because the present case is the second reported from

the same institution,⁶ it is suggested that SCH may be an underdiagnosed lesion.

Spindle cell hemangioma was originally reported as a neoplasm of intermediate malignancy,¹ but subsequently it was considered to be a reactive lesion^{2,3} or a benign neoplasm.⁴ Weiss and Enzinger¹ thought that the progressive growth, high recurrence rate, regional lymph node metastasis in 1 case, and certain microscopic features are consistent with a low-grade angiosarcoma or a neoplasm of intermediate malignancy. Long clinical course, multifocal growth, lack of true metastatic potential, examples of spontaneous regression, low proliferative activity, lack of mitoses and cellular atypia, intravascular location in many examples, and the nonclonal phenotype of spindle cells are not consistent with a malignant lesion.^{2-4,7}

Fletcher et al.² thought that the presence of clusters of abnormal vessels close to the tumor and a smooth muscle component within the tumor, as well as the association of some SCH with early varicosities, is indicative of a nonneoplastic and possibly reactive lesion. They proposed that SCH is caused by abnormalities of blood flow due to an arteriovenous shunt at the affected area, a view shared by some authors²⁰ and disputed by others.¹¹

Imayama et al.³ noticed that the endothelial cells in SCH present features indicative of deregulated angiogenesis, and the vessels have the ability to form different segments of the microvasculature. Therefore, they suggested that SCH is a reactive process associated with vascular damage. They also hypothesized that this behavior of the endothelium may facilitate thrombosis and that a cyclical process of repeated thrombosis and thrombus organization with new vascular proliferation may explain the pathogenesis of the lesion. The presence of areas reminiscent of intravascular papillary endothelial hyperplasia (considered to be an exuberant form of organizing thrombi), the strong positivity of lesional cells for vimentin and HAM-56, and the variable or multifocal positivity for endothelial cells antibodies that are also seen in intravascular papillary endothelial hyperplasia and conventional intravascular organizing thrombi support this view.⁶ Furthermore, SCH may arise after trauma, such as repeated injections or surgical excision.²⁰ Although no history of local trauma was elicited in the present patient, it should be remembered that the lip mucosa can be frequently traumatized.

Perkins and Weiss⁴ noticed that SCH resembles angiomatosis in the presence of abnormally engorged vessels, herniations, and intraluminal webs. Thus, they suggested that SCH is a benign vascular neoplasm, although they recognized that the distinction between a vascular malformation and a benign vascular neoplasm

can be arbitrary. In their view, alterations in blood flow could explain the biphasic appearance of the tumor. Cavernous vascular spaces are seen in areas where blood flow is adequate, whereas in solid areas diminished blood flow causes collapse of the vascular walls and proliferation of fibroblastic stromal cells.

Spindle cell hemangioma shows excellent prognosis after wide surgical excision. Owing to the possible coexistence of a vascular abnormality, preoperative angiographic examination has been advised.² More than 50% of patients may develop new lesions in the same anatomic region^{1,4} considered to be not recurrences but new primaries or continuous or multifocal intravascular growths.^{2,4} Recurrence may develop many years after the initial excision.¹

Local excision is the treatment of choice for most lesions, while postoperative radiotherapy, low-dose interferon α -2b, and intralesional and intra-arterial administration of recombinant interleukin-2 have been successful in treating and/or preventing recurrence of inaccessible or multiple SCH.^{1,21} The only case of regional lymph node metastasis of a SCH that occurred after 19 recurrences in 40 years is thought to represent radiation-induced malignant transformation into high-grade angiosarcoma.^{4,11} No patient has been reported to have died from the disease.

Spindle cell hemangioma is considered to be an unusual vascular tumor of the head and neck that is important to recognize to avoid misdiagnosis. Awareness of its diagnostic features is anticipated to increase the number of reported cases.

The authors acknowledge the skillful technical assistance of Mr. Georgios Babaliaris.

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Reprint requests:

Konstantinos I. Tosios
Department of Oral Pathology and Surgery
School of Dentistry
University of Athens
Greece
ktosios@dent.uoa.gr