

Extravascular type of intravascular papillary endothelial hyperplasia mimicking parotid gland neoplasia and the possible role of ferritin in the pathogenesis: A case report

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Abstract. Intravascular papillary endothelial hyperplasia (IPEH) is defined as a vascular lesion characterized by extensive proliferation of vascular endothelial cells. This lesion was first described by Pierre Masson in 1923 as intravascular hemangioendothelioma. The most frequent sites of involvement are the skin and subcutis. IPEH comprises ~2% of the vascular tumors of the skin and subcutaneous tissue and it has a predilection for the head, neck, trunk and the extremities. The diagnosis is based on histopathology. We herein present the second case of Masson's tumor of the parotid gland described in literature. The patient was a 70-year-old female. Magnetic resonance imaging revealed an irregular lesion with smooth margins, initially considered to be compatible with pleomorphic adenoma. Immunohistochemical analysis revealed positivity of the tumor cells for ferritin heavy and light chains, vimentin and CD31. The aim of the present study was to emphasize the immunohistochemical characteristics and briefly discuss the potential role of ferritin in the pathogenesis of IPEH.

Introduction

Intravascular papillary endothelial hyperplasia (IPEH), also referred to as intravascular angiomatosis, vegetant intravascular hemangioendothelioma, Masson's pseudoangiosarcoma or Masson's tumor, is a relatively uncommon vascular lesion caused by extensive proliferation of endothelial cells (1-3).

IPEH was first described in 1923 by Pierre Masson as an intravascular papillary proliferation formed within the lumen of an inflamed hemorrhoidal plexus in a male patient, and termed 'Hémangioendothéliome végétant intravasculaire' (4). IPEH comprises ~2% of the vascular tumors of the skin and subcutaneous tissue and it has a predilection for the head, neck, trunk and the extremities (5-7). The majority of the described cases in the head and neck were reported in the oral mucosa, lower and upper lips, tongue, gingiva, skin, subcutaneous tissue of the face and scalp, intracranium, orbit and ocular adnexa. Clinically, IPEH may simulate mucocele, hemangioma, lymphangioma, angiosarcoma, hematoma, Kaposi's sarcoma, hemangioendothelioma, thrombosed vein, phlebectasia, traumatic fibroma, melanoma, fibroepithelial polyp, non-odontogenic soft tissue infection, intramasseteric abscess, cysticercosis, benign neoplasms of smooth muscle origin, and reactive and neoplastic neural lesions, such as traumatic neuroma, neurofibroma and neurilemmoma (8-10). Radiologically, no specific findings have been found to be characteristic of IPEH.

The microscopic examination of IPEH is pathognomonic and immunohistochemical evaluation is not generally required for diagnosis (11). Useful points in the differential diagnosis are the lack of cellular anaplasia, necrosis, mitotic activity and nuclear atypia; most of the papillary structures are associated with thrombi, and the papillae are usually covered by no more than two endothelial cell layers. Additionally, the proliferative process occurs exclusively in the intravascular space (11). Hashimoto *et al* (12) classified IPEH into three types as follows: Type I (pure form), is the most common subtype and is characterized by dilated vascular spaces; type II (mixed form) occurs in pre-existing varices, capillary or cavernous hemangiomas, lymphangiomas, pyogenic granulomas, arteriovenous malformations and blue rubber bleb nevi; type III (undermined type) is the least common variant and is characterized by an extravascular location, developing in the bed of a hematoma, frequently associated with trauma.

Immunohistochemically, IPEH lesions are positive for CD31, CD34, vimentin, α -smooth muscle actin, factor VIII, XIIIa, type IV collagen, CD105, Ki-67 and ferritin (13,14). CD31 and CD34 are considered to be the most sensitive

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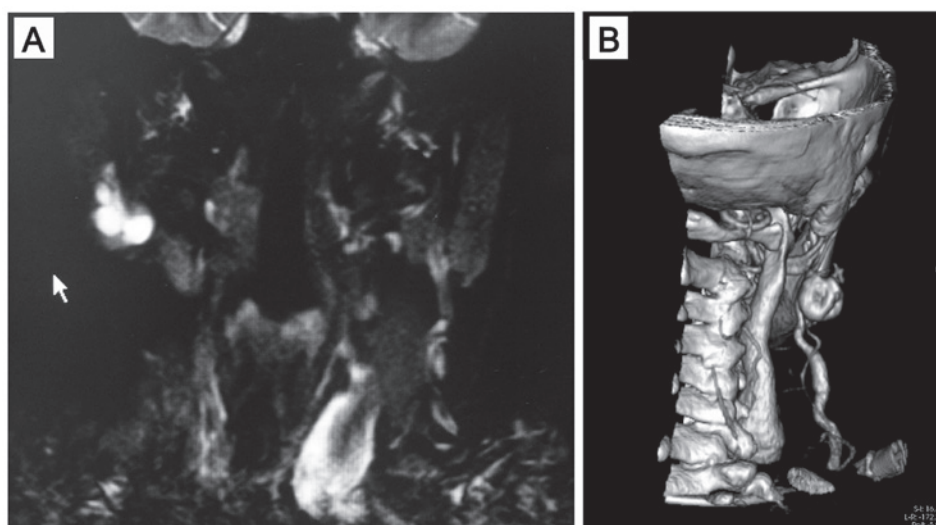


Figure 1. Radiological findings. (A) Magnetic resonance imaging revealed a lesion appearing as isointense on T1 sequences, heterogeneously hyperintense on long TR sequences, with homogeneous contrast enhancement. (B) Computed tomography-based three-dimensional reconstructed images showing the anatomical association of the lesion with the surrounding vessels.

markers indicating the vascular origin of the lesion, while staining for the other vascular markers may be variable. Ferritin is a ubiquitous protein involved in intracellular iron metabolism, due to its ability to sequester free iron in a non-toxic and bioavailable form (15). Two functionally and genetically distinct ferritin subunits exist: L-ferritin and H-ferritin, also referred to as light-chain and heavy-chain ferritin (FLC and FHC, respectively). A single ferritin complex may include both H and L subunits and the H:L ratio within a single complex may modulate its functional potential in a context-dependent manner. In addition to its intracellular form, ferritin is also an abundant protein in the circulation, as well as in the synovial and cerebrospinal fluids (16). Serum ferritin is associated with a higher risk for certain cancers, and higher levels are detected in several malignancies, including Hodgkin's lymphoma, neuroblastoma, lung, ovarian, pancreatic, intestinal, hepatic, gastric and breast cancers (17). The level of serum ferritin may also be modified by inflammation. Indeed, inflammatory cytokines may regulate the expression of ferritin on two levels: A transcriptional level (mainly H-ferritin) and a translational level (both H- and L-ferritin) (18). In addition, a number of authors suggested a critical role of ferritin in the regulation of angiogenesis, exerting a cytoprotective effect on endothelial cells (19). We herein present a new case of Masson's tumor in the parotid gland, which, to the best of our knowledge, is the second reported in the international literature.

Case report

A 70-year-old woman was admitted to the Unit of Oral and Maxillofacial Surgery, with a 5-year duration of a right parotid painless enlargement, causing facial asymmetry. Magnetic resonance imaging (MRI) and computed tomography-based three-dimensional (3D-CT) templating were used for preoperative planning.

The patient appeared to be in overall good health. On clinical examination, a lesion sized 2x1 cm was identified in the right parotid gland. The lesion was freely movable, tender on

digital palpation, non-fluctuant, rubbery in consistency, with well-defined margins, not fixed to the underlying or overlying structures. There were no signs of neurological abnormalities, such as facial paralysis. MRI revealed an irregular lesion with smooth margins, appearing isointense on T1 sequences, heterogeneously hyperintense on long TR sequences with homogeneous contrast enhancement, initially considered to be compatible with pleomorphic adenoma (Fig. 1A). 3D-CT-reconstructed images revealed an association of the lesion with the vessels (Fig. 1B). Extracapsular dissection of the lesion was performed under general anesthesia (20). On macroscopic examination, the resected specimen was a tender and brownish-red nodule, sized 2x1 cm.

Histological examination revealed a hemorrhagic area, forming an organized thrombus with areas of intravascular papillary formation, covered by flat to plump endothelial cells. No necrosis, mitoses or significant pleomorphism were identified (Fig. 2A and B). The morphological diagnosis was IPEH, type III variant. Immunohistochemical analysis revealed cell positivity for FLC, as well as FHC, vimentin and CD31 (Fig. 2C-F).

Discussion

The pathogenesis of IPEH remains unclear. Masson described IPEH as the result of endothelial cells proliferating into the vessel lumen, followed by obstruction and a secondary red infarct; in this description, Masson considered IPEH as a neoplasm (4). On the basis of IPEH incidence, with a male:female ratio of 1:1.3, a hormonal role has also been suggested (9). Subsequently, IPEH was defined as an uncommon benign, non-neoplastic vascular lesion, consisting of endothelial cell proliferation caused by a reactive process (21,22). In this context, significant attention has been directed to the association of IPEH with thrombus formation, with several hypotheses on the potential causative role in the thrombotic process. Levere *et al* reported elevated level of basic fibroblast growth factor (bFGF) in cases of IPEH when

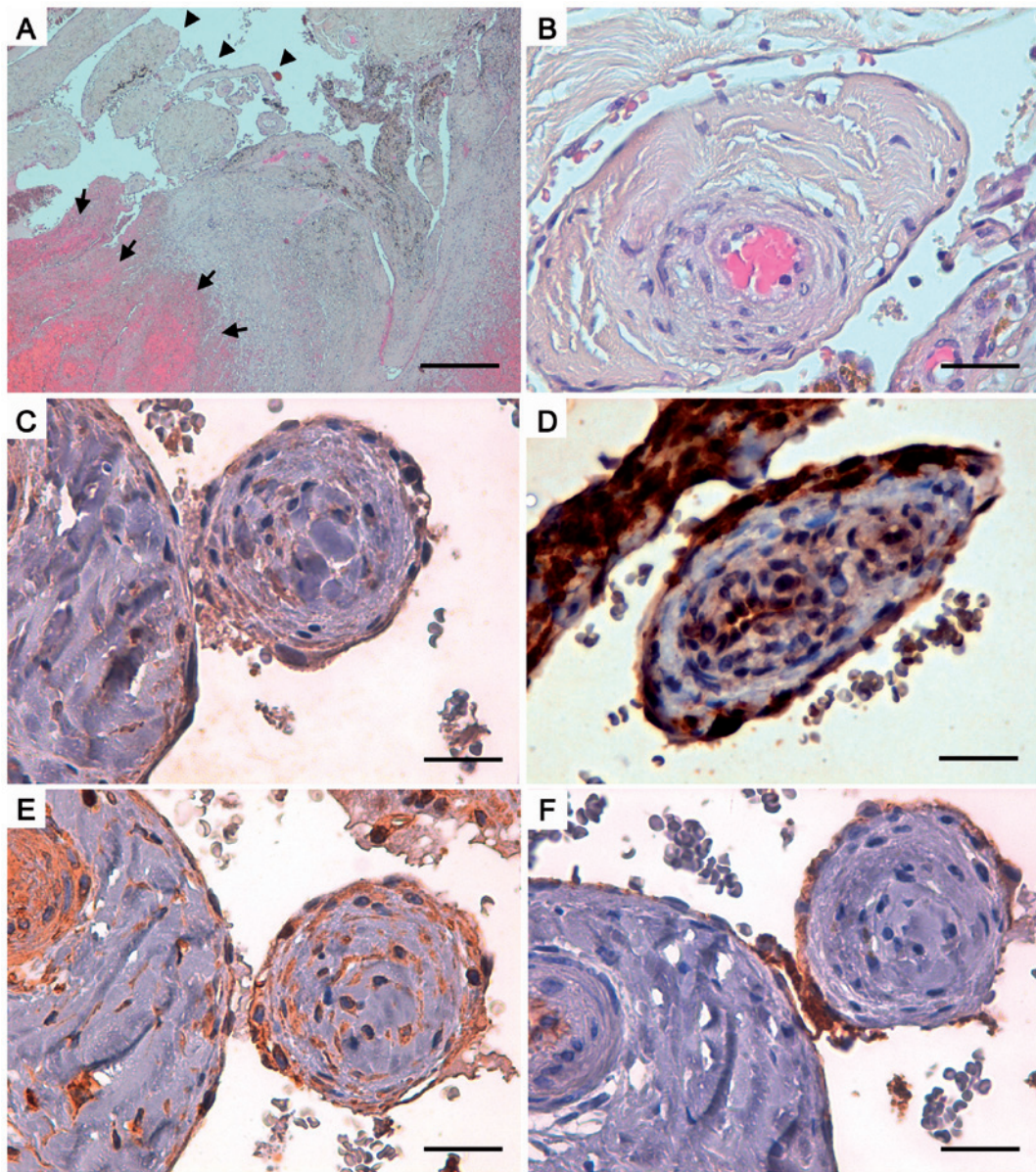


Figure 2. Histological findings. (A) Panoramic view of the lesion showing the papillary architecture (arrowheads). The arrows indicate the peripheral haemorrhagic area [hematoxylin and eosin (H&E) staining; magnification, x50]. (B) A detail of a papilla composed of a fibrinous core covered by plump endothelial cells (H&E staining; magnification, x600). A definitive brown staining on immunohistochemical analysis indicates positivity for (C) FHC, (D) FLC, (E) vimentin and (F) CD31; FLC staining was of particularly high intensity (magnification, x600). FHC, heavy-chain ferritin; FLC, light-chain ferritin.

compared with non-IPEH organizing thrombi; in addition, they suggested that bFGF was released by macrophages in response to trauma (23). A number of studies pointed to IPEH as an unusual form of thrombus that undergoes fragmentation, followed by active endothelialization of its fragments (24). Accordingly, Albrecht *et al* described the positivity of thrombus-lining cells for ferritin, vimentin and factor VIII-related antigen, indicating cells progressing from a histiocytic to an endothelial phenotype (25). In particular, ferritin positivity was reported in the earlier stages of lesion development, while vimentin and factor VIII-related antigen positivity have been reported in the final stage (5,26). Surprisingly, in the present case, the lesion exhibited simultaneous expression for vimentin, CD31 and both ferritin subunits. From the more recent literature, it appears that ferritin may modulate the balance between pro- and anti-angiogenic

factors. In particular, Tesfay *et al* demonstrated that ferritin was able to block the anti-angiogenic activity of two-chain high-molecular-weight kininogen (HKa), interfering with the anti-adhesive and anti-proliferative signaling of HKa. Furthermore, both FHC and FLC were able to counteract the inhibitory effects of HKa on the proliferation, adhesion, migration and viability of endothelial cells. The regulatory role of ferritin on angiogenesis has been confirmed by other studies, which suggest it to be primarily due to FLC (27). Accordingly, in our study, the intensity of FLC staining appeared to be higher compared with that of FHC staining. In conclusion, we herein report a rare case of Masson's tumor of the parotid gland, the second case described in literature to date. The immunohistochemical findings suggest the potential role of ferritin, not only in the pathogenesis, but also in the maintenance of IPEH. However, further investigations are

required in order to elucidate the precise role of ferritin in cell progression from a histiocytic to an endothelial phenotype.

References

1. Luce EB, Montgomery MT, Redding SW and Aufdemorte TB: Intravascular angiomatosis (Masson's lesion). *J Oral Maxillofac Surg* 46: 736-741, 1988.
2. Kuo T, Sayers CP and Rosai J: Masson's 'vegetant intravascular hemangioendothelioma': a lesion often mistaken for angiosarcoma: study of seventeen cases located in the skin and soft tissues. *Cancer* 38: 1227-1236, 1976.
3. Torne Escasany R and Umbert Millet P: Masson's pseudoangiosarcoma of the tongue: Report of two cases. *J Cutan Pathol* 12: 66-71, 1985.
4. Masson P: Hémangioendothéliome végétant intravasculaire. *Bull Soc Anat Paris* 93: 517-523, 1923.
5. Tosios K, Koutlas IG and Papanicolaou SI: Intravascular papillary endothelial hyperplasia of the oral soft tissues: Report of 18 cases and review of the literature. *J Oral Maxillofac Surg* 52: 1263-1268, 1994.
6. Hutcheson EL, Picarella EA, Blevins PK: Masson's tumor of the hand: a case report and brief literature review. *Ann Plast Surg* 69: 338-339, 2012.
7. Tedla M, Bežová M, Biró C, Tedlová E, Eng CY and Zeleník K: Intravascular papillary endothelial hyperplasia of larynx: Case report and literature review of all head and neck cases. *Otolaryngol Pol* 68: 200-203, 2014.
8. Moon WS, Chung GH and Hong KH: Intravascular papillary endothelial hyperplasia in a vascular lesion of the paranasal sinus. *Arch Pathol Lab Med* 124: 1224-1227, 2000.
9. Makos CP and Nikolaidou AJ: Intravascular papillary endothelial hyperplasia (Masson's tumor) of oral mucosa. Presentation of two cases and review. *Oral Oncol Extra* 40: 59-62, 2004.
10. Murugaraj V, Kingston GT, Patel M and Anand R: Intravascular papillary endothelial hyperplasia (Masson's tumour) of the oral mucosa. *Br J Oral Maxillofac Surg* 48: e16-e17, 2010.
11. Sarode GS, Sarode SC and Karmarkar SP: Oral intravascular papillary endothelial hyperplasia (Masson's tumor): A review of literature. *J Oral Maxillofac Surg Med Pathol* 26: 73-79, 2014.
12. Hashimoto H, Daimaru Y, Enjoji M: Intravascular papillary endothelial hyperplasia. A clinicopathologic study of 91 cases. *Am J Dermatopathol*. Dec;5(6):539-546, 1983.
13. Akdur NC, Donmez M, Gozel S, Ustun H and Hucumenoglu S: Intravascular papillary endothelial hyperplasia: Histomorphological and immunohistochemical features. *Diagn Pathol* 8: 167, 2013.
14. Guledgud MV, Patil K, Saikrishna D, Madhavan A and Yelamali T: Intravascular papillary endothelial hyperplasia: Diagnostic sequence and literature review of an orofacial lesion. *Case Rep Dent* 2014: 934593, 2014.
15. Zolea F, Biamonte F, Candeloro P, Di Sanzo M, Cozzi A, Di Vito A, Quaresima B, Lobello N, Trecroci F, Di Fabrizio E, *et al*: H ferritin silencing induces protein misfolding in K562 cells: A Raman analysis. *Free Radic Biol Med* 89: 614-623, 2015.
16. Meyron-Holtz EG, Moshe-Belizowski S and Cohen LA: A possible role for secreted ferritin in tissue iron distribution. *J Neural Transm Vienna* 118: 337-347, 2011.
17. Alkhateeb AA and Connor JR: The significance of ferritin in cancer: Anti-oxidation, inflammation and tumorigenesis. *Biochim Biophys Acta* 1836: 245-254, 2013.
18. Rogers JT, Bridges KR, Durmowicz GP, Glass J, Auron PE and Munro HN: Translational control during the acute phase response. Ferritin synthesis in response to interleukin-1. *J Biol Chem* 265: 14572-14578, 1990.
19. Tesfay L, Huhn AJ, Hatcher H, Torti FM, Torti SV and Ahmir A: Ferritin blocks inhibitory effects of two-chain high molecular weight kininogen (HKa) on adhesion and survival signaling in endothelial cells. *PLoS One* 7: e40030, 2012.
20. Cristofaro MG, Allegra E, Giudice A, Colangeli W, Caruso D, Barca I and Giudice M: Pleomorphic adenoma of the parotid: Extracapsular dissection compared with superficial parotidectomy-a 10-year retrospective cohort study. *Sci World J* 2014: 564053, 2014.
21. Henschen F: L'endovasculite proliférante thrombopoïétique dans la lésion vasculaire locale. *Ann Anat Path* 9: 113-121, 1932.
22. Csank GA and Curletti EL: Intravascular papillary endothelial hyperplasia: Challenge in diagnosis and vascular reconstruction-a case report. *Vasc Endovascular Surg* 32: 295-299, 1998.
23. Levere SM, Barsky SH and Meals RA: Intravascular papillary endothelial hyperplasia: A neoplastic 'actor' representing an exaggerated attempt at recanalization mediated by basic fibroblast growth factor. *J Hand Surg Am* 19: 559-564, 1994.
24. Buchner A, Merrell PW, Carpenter WM and Leider AS: Oral intravascular papillary endothelial hyperplasia. *J Oral Pathol Med* 19: 419-422, 1990.
25. Albrecht S and Kahn HJ: Immunohistochemistry of intravascular papillary endothelial hyperplasia. *J Cutan Pathol* 17: 16-21, 1990.
26. Katzman B, Caligiuri DA, Klein DM, Nicastrì AD and Chen P: Recurrent intravascular papillary endothelial hyperplasia. *J Hand Surg [Br]* 22: 113-115, 1997.
27. Coffman LG, Parsonage D, D'Agostino R Jr, Torti FM and Torti SV: Regulatory effects of ferritin on angiogenesis. *Proc Natl Acad Sci USA* 106: 570-575, 2009.