

Jaw angiosarcoma

First case, with massive intraosseous localization,
described in Italian literature



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Maria Giulia Cristofaro*, Amerigo Giudice*, Francesco Conforti**, Valeria Zuccalà*,
Ida Barca*, Davide Caruso, Mario Giudice*

*Department of Oral and Maxillofacial Surgery, University «Magna Graecia», Catanzaro, Italy

**Department of Pathological Anatomy, University Magna Graecia, Catanzaro, Italy

Jaw angiosarcoma. First case, with massive intraosseous localization, described in Italian literature

Angiosarcoma (AS) is a rare non-epithelial malignant neoplasm arising from neoplastic vascular degeneration of endothelial cells. It usually occurs in soft tissue and skin. The incidence, according to American authors, is 1% of all soft tissue sarcomas. About 50% of AS is localized in head and neck region (scalp and face skin) and represents less than 1% of all malignancies of this district; the primitive intra-oral localization is rare, even rarer intraosseous development of AS in jaw bones.

The Authors report a case of a mandibular intraosseous angiosarcoma with different peculiarities: the rarity of the location and mode of occurrence; in addition they have focused on clinical-histopathological and immunohistochemical characteristics.

KEY WORDS: Angiosarcoma, Jaws Introduction, Oral cavity

The angiosarcoma is a rare malignant mesenchymal tumor that usually occurs at the level of soft tissue and skin¹. The incidence, according to American authors, is 1% of all soft tissue sarcomas. Particularly in head and neck area is localized predominantly in the scalp, skin (face region), and the intra-oral localization is rare and even rarer is the localization in jaw bones²⁻⁴.

The case of intraosseous angiosarcoma of the mandible presented by the authors, first described in Italian literature, presents a double feature: the rarity of the location and mode of occurrence. The authors have focused also on the clinical, pathological and immunohistochemical characteristics of the tumor.

Case report

The patient MM, aged 49, was admitted to the UO Maxillofacial Surgery of the «Magna Graecia» University of Catanzaro in March 2011 for the presence of an expansive vegetating lesion of the entire mandibular body in alveolar region 35-38, previously performed within an avulsion of 37 in February of same year. The patient reported a massive bleeding following a dental extraction, which forced him to immediate admission to the nearest emergency center, where it was carried out for an emergency treatment with blood transfusion (three units of blood) and compressive sutures. Resigned in the following days due to increased volume of the lesion, occurrence changes in sensitivity (hypoesthesia) of lips (bottom left) and by the spontaneous bleeding episodes, the patient performed CT-DentalScan which showed large osteolytic lesion interesting to the whole left mandibular region (31 to 38), with erosion of vestibular cortical at the two premolars and molars (region 34-35). The patient, admitted to our unit, also reported

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Correspondence to: Maria Giulia Cristofaro, Cattedra di Chirurgia Maxillo-Facciale, Facoltà di Medicina e Chirurgia, UMG di Catanzaro, Viale Europa 1, 88100 Germaneto di Catanzaro, Italy (E-mail: Cristofaro@unicz.it)

other concurrent systemic diseases (paroxysmal atrial fibrillation, hypertensive heart disease, diabetes mellitus type II, grade I obesity, hypercholesterolemia, hyperthyroidism) in drug treatment with cardiodinamic and metabolic balce very precariuos. Locoregional and physical examination showed facial asymmetry due to the presence of swelling in the left hemimandible region. Inspection of oral cavity showed us a lesion of about 3x2, 5x1, 5 cm, corresponding to the premolar-molar area with an elastic consistency, easily bleeding, bad defined margins, light red with bluish patches on the surface and disappearance of the vestibular fornix (Fig. 1). In correspondence with the previous avulsion, and



Fig. 1: Intra-oral view.

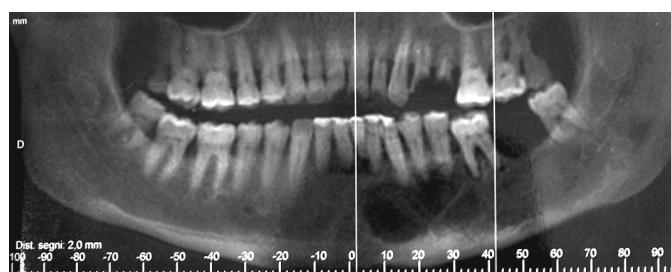


Fig. 2: Pre-operative OPT.

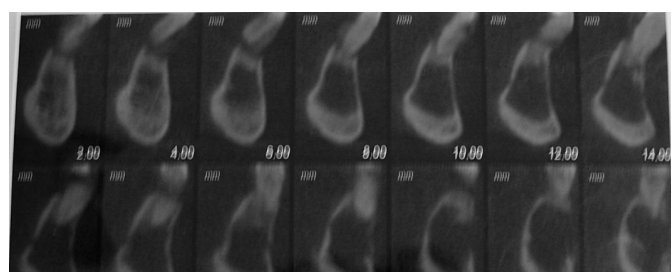


Fig. 3: CT Dentalscan.

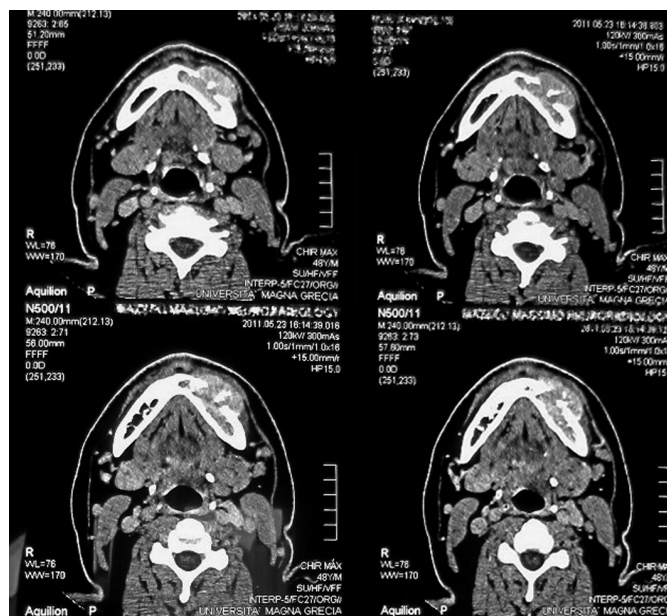


Fig. 4: Facial CT.

more precisely in reg.35-38, it showed a vegetans lesion, ulcerated and easily bleeding. On neck palpation we found an increase of cervical lymph node volume of level I and II (left side) apparently unharmed other organs and systems explored. Subjected to instrumental tests (neck and SAT ultrasound, OPT, Dental-scan, head and neck CT scan), were shown the involvement of soft tissues at the site of erosion of the cortical left mandibular region and some lymph nodes in the submandibular area with no other lymphadenopathy (Figg. 2, 3, 4). The biopsy report gave as a "malignant mesenchymal tumor type (suspected angiosarcoma)" and, therefore, was a planned surgery-chemotherapy.

The advice radiotherapy excluded the radiation treatment.

After stabilizing the patient, hemodynamically, for his other disease he was submitted to surgery.

The surgical procedure in the first phase involved the prior ligation of external carotid artery at its origin and therefore the ostectomy left hemimimandibolar section from symphysis to condylar base, with removal of perilesional lymph nodes (levels I-II). The minus bone was reconstructed with an metallic endoprosthesis of titanium (picture). Reconstruction with revascularized free flaps (fibula) has not been used and for concomitant peripheral vascular disease and for the patient decision, knowing the risks that its complex pathology of systemic and peripheral disease could result in the immediate future.

Histological examination showed a vascular proliferation with florid complex anastomosed and short intraluminal papillary formations, limits are poorly defined, infiltrative growth aspects, the cells showed mild atypia and a low mitotic activity; and the overlying oral mucosa



Fig. 5



Fig. 6



Fig. 7



Fig. 8

Figs. 5, 6, 7, 8: Intra-operative view :mass view, subtotal hemimandibulectomy and reconstruction.

appeared to us ulcerated with the presence of granulation tissue (Figs. 9-10). Immunohistochemistry gave negative for epithelial markers (cytokeratin-clone AE1/AE3-, p63) and positivity for vascular markers (CD31), confirming the diagnosis of low-grade angiosarcoma (Table I). There were no signs of cancer in the lymph nodes removed. The patient was discharged on the tenth day in good

clinical and surgical conditions. The inspections took place on a monthly basis and he is still under control. Two months after surgery (first instrumental control) with ultrasound, head and neck CT scan and total body CT scan showed no signs of local recurrence or metastatic regions in the areas examined (Figs. 11, 12). Currently the patient is undergoing chemotherapy.

TABLE I - Antibodies and protocols for immunohistochemistry

Antigen/Clone	Company	Dilution
CK Cocktail/ AE1/AE3	Novocastra	1:100
CD 31/ JC70A	Dako	1:40
P63/ BC4A4	Ab Cam	1:100



Fig. 9

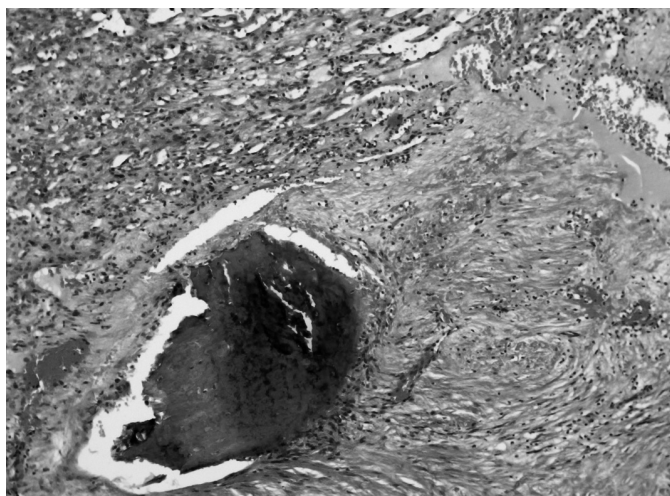


Fig. 10

Fig. 9, 10: The lesion consists of an unencapsulated proliferation of anaplastic endothelial cells enclosing irregular luminal spaces, bone tissue infiltrating.

Discussion

Sarcomas are a heterogeneous group of malignancies arising from malignant degeneration of cells originated from embryonic mesodermal sheet. Represents only 1%



Fig. 11: Post-operative clinical-strumental evaluation.



Fig. 12: Post-operative OPT.

of all the malignant neoplastic diseases with more than 50 different subtypes^{5,6}, which are derivated from different structures as bone, cartilage, muscle (smooth or striated), skin, fat, synovial tissue, blood vessels (blood or lymph), nervous tissue, etc. which leads to a great variety and potential histopathologic ubiquity anatomy of onset. Risk factors for the onset of sarcomas are a previous radiation therapy, exposure to certain chemicals such as vinyl chloride and arsenic, chronic lymphedema, bone infarcts, some syndromes (S. Gardner, S. Li -Fraumeni syndrome, tuberous sclerosis, hereditary retinoblastoma, Neurofibromatosis Type 1), although most cases are unable to identify a unique determining cause^{7,8}. The most relevant prognostic factor for sarcomas is, without doubt, the histological grading; the first grading proposed grading was done in 1939 by Broders (for the fibrosarcoma)⁹; Russell in 1977 gave an important contribution in the drafting of TNM sarcomas with a large study of over 1000 cas-

es¹⁰. There are three common types of systems used for grading sarcomas (NWT, NCI, FNCLCC) ranging from 2 to 4 classes of grading. NWT: a 2-degrees (high and low) easy for surgery, but with an ambiguous statement in respect of intermediate grading type of sarcomas; NCI system assigns a grade from 1 to 3, it is considered the best approach for predictability response to therapy and survival rate; the FNCLCC system presents 4 degrees, but for most sarcomas, this system does not add anything more to NCI for the minimum difference between grades 1 and 2.

The main criteria used for classifying the various grading systems, and variously estimated between them, are the histologic type, cellularity, the mitotic index and tumor necrosis, depth of tumor site. In the classification of sarcomas, defined as "generally high-grade" will include: synovial sarcoma, angiosarcoma, rhabdomyosarcoma, Ewing sarcoma, malignant fibrous histiocytoma, osteosarcoma extraosseous, and in those defined as "generally low-grade" myxoid liposarcoma, well-differentiated liposarcoma, dermatofibroma protuberans, desmoid sarcoma, other sarcomas such as fibrosarcoma, leiomyosarcoma, often need a more careful evaluation of the grading in relation to this case. The frequency of occurrence for site we can highlight that sarcomas is higher against the extremities (50%), the trunk and peritoneum (40%), however is extremely lower than incidence in head and neck region (10%)^{7,12}, demonstrating a high range differentiation: smooth or striated muscle (leiomyosarcoma, rhabdomyosarcoma), adipocyte (liposarcoma), cartilage (chondrosarcoma), bone (osteosarcoma), fibroblast (dermatofibrosarcoma), endothelial (angiosarcoma), etc.

From all of those Sarcomas who have a relative preference for the district are the head and neck rhabdomyosarcoma in children, cutaneous angiosarcoma and sinusal hemangiopericytomas (the latter is specific for this anatomical region) The angiosarcoma (AS) is a rare non-epithelial malignant neoplasm arising from neoplastic vascular degeneration of endothelial cells⁸; of this disease we can distinguished two distinct subtypes heman-giosarcoma and lymphangiosarcoma, they are different but prognosis and therapeutic approach are the same, and therefore often included in a single denomination of angiosarcoma^{1,8,13}.

It can occur at any anatomical site, typical is the skin and abdominal viscera. According to american authors, the angiosarcomas constitute only 1% of all soft tissue sarcomas with a prevalence of 2-3 cases every 100000 people. Most patients with this disease died of lung metastasis or local extension.

About 50% of all AS is localized in head and neck region at the level of scalp and face skin¹⁴, and represents less than 1% of all malignancies of this district^{8,15,16}, but with a high morbidity and mortality¹⁷⁻¹⁹. The oral cavity in angiosarcomas comprise less than 5% of the total cases reported in literature for this this neoplasm (19).

The first described case in 1923 by HJ Banks- Devis was an hemorrhagic angiosarcoma of the maxilla²⁰.

Sites of involvement in oral cavity are lips, tongue, mouth floor, cheeks palate and mandible¹⁸. Intraosseous development of AS is occasionally rare in humans and animals is allowed (though not uncommon in dogs) therefore the sites of greatest bone involvement are the femur and tibia, followed by the pelvis, spine and upper limb bones.

In head and neck primary intraosseous localization is more exceptional²¹ (the first case describe was in 1948 with involvement of the petrous portion of temporal bone)²² and even more rare is in intraosseus maxillary bone^{2,3,14,18,19,22,23}, and among these those with mandibular localization. All ages, sex and nationality may be affected by this disease even though the highest incidence occurs around the fifth decade of life.

The etiology of this disease remains unknown although several hypotheses have been examined^{8,24}. Clinically, the intraoral angiosarcomas (of soft tissue) are usually described as a circular or oval bluish nodules, often ulcerated surface, not very mobile on superficial palpation, lazy but capable of spontaneous bleeding as in the case report described³. In fact, the lesion presented with a bluish-red knots of the hemi-mandibular body with extension to the left buccal mucosa, bleeding for easy opening and closing mouth movements.

Often, their recognition is difficult, both entering the differential diagnosis with other vascular neoplasms such as malignant epithelioid hemangioendothelioma, Kaposi's sarcoma, malignant melanoma with benign processes including inflammatory disease²⁵. For the diagnosis of angiosarcoma remains fundamental histopathological examination, the tumor cells are often positive for CD31, CD34 and vWF (it is the most specific vascular markers but is positive only in the minority of angiosarcomas), while CD31 is positive in more than 90% of angiosarcomas (relatively high specificity and sensitività), especially for the poorly differentiated forms, where these can not be present, additional markers are needed, such as nuclear markers Fli- 126.

The treatment of choice for this type of disease is a wide surgical resection of the tumor^{2,16,24}, with or without chemotherapy and / or radiotherapy^{2,27}. Elective lymph node dissection is not indicated except in presence of a clinical evident involvement². In the case presented by the authors the lateral-cervical lymph node exision in level I was performed for the presence of unstructured submandibular lymph nodes ipsilateral to the lesion, even by an intraoperative clinical evidence of lymph nodes impairment. Our surgical behavior is also derived from the consideration that the lymph node metastasis indeed occurs in 3% of cases of localization in bone and 10% instead of the localization in soft tissue angiosarcomas for head and neck district distant metastases (28% of cases) involves, in order of frequency the lung, bones, CNS, and liver⁸.

Riassunto

L'angiosarcoma è un raro tumore mesenchimale maligno che solitamente insorge a livello dei tessuti molli e della cute e, secondo una casistica americana, costituisce solo l'1% di tutti i sarcomi dei tessuti molli. La sua localizzazione primaria intra-orale è rara ed ancora più rara è la localizzazione intra-ossea a carico delle ossa mascellari.

Gli Autori presentano il caso clinico di un paziente di anni 49 giunto alla nostra osservazione per la presenza da oltre un mese di una lesione espansiva a carico dell'intero corpo mandibolare con formazione vegetante a carico della mucosa della cresta alveolare regione 35-38, sede di precedente estrazione (avulsione di 37), in seguito alla quale era stato ricoverato nel più vicino presidio di pronto soccorso per episodio emorragico. A causa dell'aumento volumetrico della lesione eseguiva la TC-Dentascan che evidenziava vasta lesione osteolitica interessante l'intera branca orizzontale sinistra, dalla regione 31 ad oltre la regione 38, con erosione della corticale vestibolare in corrispondenza dei due premolari, regione 34-35.

Al momento del ricovero l'esame obiettivo loco-regionale evidenziava asimmetria del volto per la presenza di tumefazione in regione emimandibolare sinistra e modico aumento di alcuni linfonodi cervicali, soprattutto a sinistra a livello I-II. All'ispezione endorale si apprezzava una neoformazione di circa 3 x 2,5 x 1,5 cm, di consistenza fibroelastica coinvolgente quasi l'emimandibola sinistra e, in corrispondenza della pregressa avulsione, e più precisamente in reg. 35-38, si evidenziava una lesione vegetante e ulcerata, facilmente sanguinante.

Gli esami strumentali e in particolare la TC cervico-facciale evidenziavano il coinvolgimento dei tessuti molli nella sede di erosione della corticale vestibolare dell'emimandibola sinistra ed alcuni linfonodi parzialmente destrutturati in sede sottomandibolare e latero-cervicale sinistra (livello II).

Il prelievo biotico dava come referto "lesione tumorale maligna di tipo mesenchimale (sospetto angiosarcoma)" e, pertanto il paziente veniva sottoposto a intervento chirurgico di sezione osteotomica dell'emimandibola sinistra dalla sinfisi alla base del collo condilare, con asportazione dei linfonodi perilesionali (livelli I-II), e ricostruzione con una endoprotesi metallica in titanio.

L'esame istologico mostrava una proliferazione vascolare florida con lumi complessi anastomizzati e brevi formazioni papillari endoluminali, a limiti mal definiti ed aspetti di crescita infiltrativa; le cellule mostravano atipia ed attività mitotica non spiccata; l'immunoistochimica dava negatività per i marcatori epiteliali (citocheratina-clone AE1/AE3-, p63) e positività per marcatori vascolari (CD31), confermando la diagnosi di angiosarcoma. Non evidenza di neoplasia nei linfonodi asportati.

I controlli clinici e strumentali sono avvenuti con cadenza mensile ed è tutt'ora sotto controllo e in trattamento polichemioterapico.

Il caso clinico descritto dagli Autori è da ritenersi particolare per essere, da un punto di vista patogenetico, a partenza endo-ossea in un segmento scheletrico della testa-collo ancora più particolare, cioè la mandibola. Lo sviluppo intraosseo degli AS è eccezionalmente raro sia negli umani che negli animali domestici (anche se non infrequente nel cane).

Come nel nostro caso, per la diagnosi di angiosarcoma rimane fondamentale l'esame istopatologico. Il trattamento di elezione per questo tipo di patologie è l'ampia resezione chirurgica della neoplasia, associata o meno a chemioterapia e/o radioterapia. La dissezione elettiva dei linfonodi non è indicata, se non in presenza di coinvolgimento clinicamente evidente. La metastatizzazione linfonodale infatti avviene nel 3% dei casi di localizzazione ossea ed invece nel 10% delle localizzazioni dei tessuti molli.

Referencers

1. Fisher C: *Soft tissue tumor*. In: LeBoit PM, Burg G, Weedon D, Sarasin A (eds): *World health organization classification of tumours. Pathology and genetics of skin tumours*. Lyon: IARC Press; 2006.
2. Loudon JA, Billy ML, DeYoung BR, Allen CM: *Angiosarcoma of the mandible: A case report and review of the literature*. *Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics*. 2000; 89:471-76.
3. Favia G, Lo Muzio L, Serpico R, Maiorano E: *Angiosarcoma of the head and neck with intra-oral presentation: A clinico-pathological study of four cases*. *Oral Oncol*, 2002; 38:757-62.
4. Abbas K, Arash K: *Mandibular pathologic fracture as a first sign of disseminated angiosarcoma: A case report and review of literatures*. *Oral Oncology Extra*, 2005; 41:178-82.
5. Lahat G, Lazar A, Lev D: *Sarcoma Epidemiology and Etiology: Potential environmental and genetic factors*. *Surg Clin N Am*, 2008; 88:451-81.
6. Bree R, Valk PVD, Kuik DJ, Diest PJV, Doornaert P, Buter J, et al.: *Prognostic factors in adult soft tissue sarcomas of the head and neck: A single-centre experience*. *Oral Oncol*, 2006; 42:703-09.
7. Brennan MF, Singer S, Maki RG: *Sarcomas of the soft tissue and bone*. In: DeVita VT Jr, Hellman S, Rosenberg SA (eds): *Cancer: Principles and Practice of Oncology*. Vols. 1 & 2. 8th ed. Philadelphia, Pa: Lippincott Williams & Wilkins, 2008: 1741-833.
8. Fletcher CD, Unni KK, Mertens F: *World health organization classification of tumors: Tumors of soft tissue and bone*. Lyon, France: IARC Press, 2002.
9. Broders AC, Hargrave R, Meyerding HW: *Pathological features of soft tissue fibrosarcoma: With special reference to the grading of its malignancy*. *Surg Gynecol Obstet*, 1939; 69:267.
10. Russell WO, Cohen J, Cutler S, et al: *Staging system for soft tissue sarcoma. Task Force on Soft Tissue Sarcoma. American Joint Committee for Cancer staging and end results reporting*. Chicago: American College of Surgeons, 1980.
11. Kandel RA, Bell RS, Wunder JS, et al: *Comparison between a 2- and 3-grade system in predicting metastatic-free survival in extremity soft-tissue sarcoma*. *J Surg Oncol*, 1999; 72:77.

12. Sturgis EM, Potter B: *Expression of a lymphatic endothelial cell marker in benign and malignant vascular tumors*. Human Pathology, 2004; 35(7):857-61.
14. Fedok FG, Levin RJ, Maloney ME, Tipirneni K: *Angiosarcoma: Current Review*. Am J Otolaryngol, 1999; 20(4):223-31.
15. Singh RP, Grimer RJ, Bhujel N: *A heterogeneous group of sarcomas with specific behavior depending on primary site: A retrospective study of 161 cases*. Ann Oncol, 2007; 18:2030-36.
18. Fanburg-Smith JC, Furlong MA, Childers EL: *Oral and salivary gland angiosarcoma: A clinicopathologic study of 29 cases*. Mod Pathol, 2003; 16:263-71.
19. Frick WG, McDaniel K: *Angiosarcoma of the tongue: Report of a case*. Br J Oral Maxillofac Surg, 1988; 46(6):496-98.
20. Banks-Davi HJ: *Haemorrhagic Angiosarcoma of upper jaw*. Proc R Soc Med, 1923; 16 (Laryngol Sect):49.
21. Hindersin S, Schubert O, Cohnen M, Felsberg J, Schipper J, Hoffmann TK: *Angiosarcoma of the temporal bone*. Laryngorhinootologie, 2008; 87(5):345-48.
22. Kikade JM: *Angiosarcoma of the petrous portion of the temporal bone: Report of a case*. Ann Otol Rhinol Laryngol, 1948; 57(1):235-40.
23. Medina BR, Martinez Barba E, Vidal Torres A, Mendez Trujillo S: *Gingival metastases as first sign of a primary uterine angiosarcoma*. Br J Oral Maxillofac Surg, 2001; 59(4):46-71.
23. Oliver AJ, Gibbons SD, Radden BG, Busmanis I, Cook RM: *Primary angiosarcoma of the oral cavity*. Br J Oral Maxillofac Surg, 1991; 29(1):38-41.
24. Fukushima K, Dejima K, Koike S, et al.: *A case of angiosarcoma of the nasal cavity successfully treated with recombinant interleukin-2*. Surgery, 2006; 134(5):886-87.
25. Mücke T, Deppe H, Wolff K-D, Kesting MR: *Gingival angiosarcoma mimicking necrotizing gingivitis*. Br J Oral Maxillofac Surg, 2010; 39(8):827-30.
26. Folpe AL, Chand EM, Goldblum JR, Weiss SW: *Expression of Fli-1, a nuclear transcription factor, distinguishes vascular neoplasms from potential mimics*. Am J Surg Pathol, 2001; 1 25: 1061-66.
27. Pacheco IA, Alves APNN, Mota MRL, et al.: *Clinicopathological study of patients with head and neck sarcomas*. Brazilian journal of otorhinolaryngology, 2011; 77(3):385-90.

Commento e Commentary

Prof. GIORGIO IANNETTI
Ordinario di Chirurgia Maxillo-Facciale
Università "La Sapienza" di Roma

L'angiosarcoma intraosseo mandibolare rappresenta una localizzazione di estrema rarità, per cui riteniamo doverosa la comunicazione di tale evenienza alla comunità scientifica.

Nelle classificazioni delle lesioni osteolitiche primarie della mandibola l'angiosarcoma intraosseo non viene quasi mai citato, esponendo lo specialista a possibili errori diagnostici e di trattamento.

Anche un accertamento fondamentale come l'esame bioptico può presentare dei rischi di emorragie difficilmente controllabili.

Questo articolo offre alcuni interessanti spunti per il dibattito interdisciplinare sulle patologie neoplastiche testa-collo:

– la gestione delle lesioni potenzialmente emorragiche, quando sia indispensabile una arteriografia con embolizzazione selettiva della massa;

– la pianificazione della demolizione e della successiva fase ricostruttiva, che dovrà sicuramente tenere presente la prognosi e la qualità di vita residua, considerazioni che devono essere fatte anche quando la microchirurgia ricostruttiva sembra ormai una procedura routinaria.

* * *

Intraosseus mandibular angiosarcoma is a an exceptional evenience; therefore it deserve a mention to the scientific community.

Seldom is intraosseus mandibular angiosarcoma cited within osteolitic mandibular lesions causing a lack of knowledge that may expose specialists to a misunderstanding of the proper diagnosis and treatment. In those cases, even a bioptic examination may provoke serious bleeding.

This paper provides a starting point for discussion about the management of this disease and represents an in-depth contribution on the head and neck pathology. In particular, about the possibility of the selective embolization of the neoplasm after arteriographic examination in order to handle emorragic risk.

Moreover, great attention has been focused on the proper management of the oncologic resection and reconstruction; in fact prognostic outcomes and quality of remaining life should be always considered, even if microsurgical recostruction appear to have become routine.

