

## Case Report

# Mandibular central leiomyosarcoma with high telomerase activity: a case report

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**Abstract:** Leiomyosarcoma is a malignant lesion of smooth muscle origin, and rare in the oral region. This report presents an extremely rare case of intraosseous leiomyosarcoma of the mandible. After visiting other general hospital, a 29-year-old man was referred to our hospital because of a pain in the left mandibular region with paresthesia of the left mental region. The left mandibular third molar had already been extracted in another hospital, and a brownish mass occupied the corresponding region. A panoramic radiograph showed osteolytic destruction around the left mandibular angle and ramus. A computed tomography scan and magnetic resonance image revealed perforation of the lingual and buccal cortex of the mandible. A non-epithelial malignant tumor was diagnosed from a biopsy specimen. Immediately, we resected the tumor and reconstructed the titan plate under general anesthesia. A final diagnosis of leiomyosarcoma was made from a surgical specimen based on findings showing a proliferation of hyperchromatic spindle cells, which were positive for the markers  $\alpha$ -smooth muscle actin, calponin, HHF35, and desmin. The S-100, epithelial membrane antigen, and cytokeratin markers were negative. The patient had 3 courses of adjuvant chemotherapy after the operation, and showed no evidence of recurrence during the follow-up at the outpatient clinic. However, 2 years after the first operation, lung metastases and local recurrence were detected. Additional chemotherapy was not effective. Finally, the patient died almost 3 years after the first operation.

**Keywords:** Leiomyosarcoma, intraosseous, immunohistochemistry, telomerase

### Introduction

Leiomyosarcoma is a malignant neoplasm derived from smooth muscle, and accounts for 5-10% of non-epithelial malignant tumors [1]. It generally appears in the uterus, digestive tract, or skin [1], and occurrence in the oral region is believed to be rare [2], with involvement of the mandible being particularly rare.

A certain amount of the reports of leiomyosarcoma can be found in the oral region. The leiomyosarcoma of tongue [3], maxillary region [4, 5], nasal sinus [6] and other site has been reported. However, leiomyosarcoma of with mandibular centrality can be found with difficulty. Herein, we report a case of leiomyosarcoma with mandibular centrality.

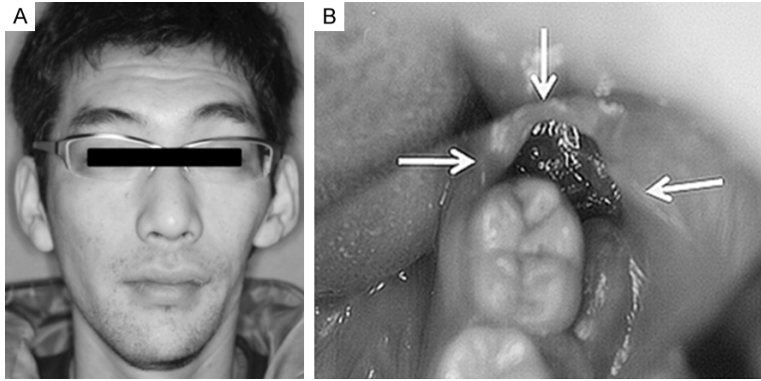
### Case report

A 29-year-old man with no significant medical history presented to the oral surgery depart-

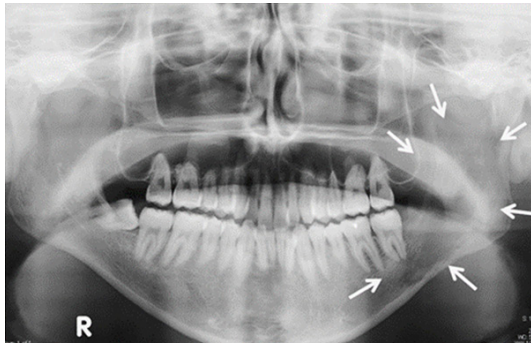
ment of a local hospital with the chief complaint of pain in the left mandibular third molar area. Panoramic radiography revealed an area with an indistinct boundary extending from the third molar region into the mandibular ramus, and mandibular osteomyelitis originating at the third molar was diagnosed. After administration of an anti-inflammatory agent, left mandibular third molar extraction and curettage under general anesthesia were planned. Because the mandibular tissue had a highly enhanced area, strongly suspected of being a neoplastic lesion after the extraction, only the biopsy was performed and the curettage was canceled. After the histopathological diagnosis of a non-epithelial malignant tumor, the patient was referred to our hospital for a complete evaluation.

The patient was of average build and height, with good nutritional status (**Figure 1A**). Reduced sensation was noted in the left mentum, but there was no significant cervical

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**Figure 1.** Figure of first visit to our hospital. A. Patient's frontal view. B. Oral cavity at initial diagnosis. A hyperplastic brownish tumor is visible in the left mandibular third molar extraction socket (arrow).

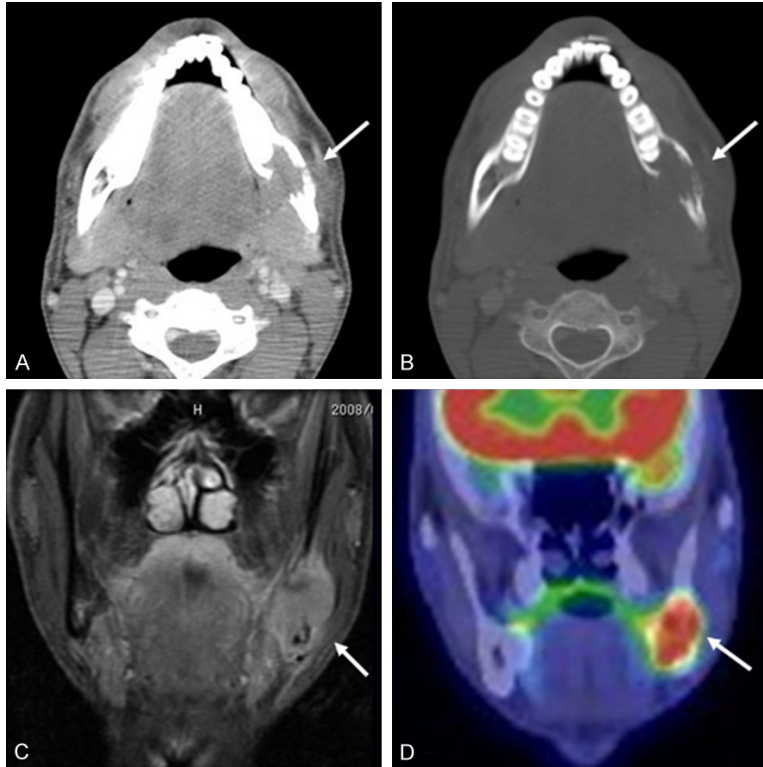


**Figure 2.** Panoramic radiograph at initial diagnosis. Radiograph revealing an area with an indistinct boundary, extending from the left mandibular body to the mandibular ramus, mandibular angle, and coronoid process (arrow).

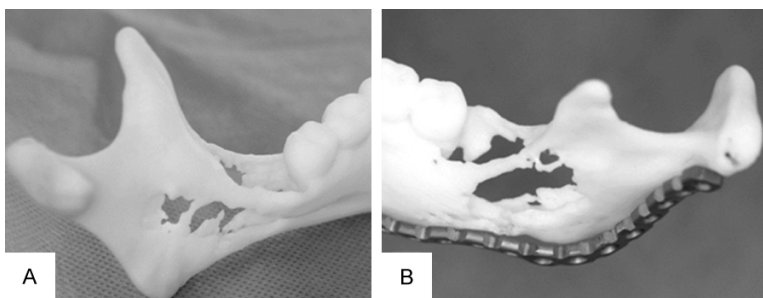
lymphadenopathy. A hyperplastic brownish solid tumor was observed in the left mandibular third molar extraction socket (**Figure 1B**). There was no trismus. Panoramic radiography showed bone resorption from the left mandibular third molar area to the mandibular angle and ramus (**Figure 2**). Contrast-enhanced computed tomography (CT) showed an osteoclastic lesion centering on the left mandibular retro-molar area, with destruction of cortical bone extending to the buccolingual side, and a soft tissue shadow invading the surrounding area (**Figure 3A, 3B**). Magnetic resonance imaging of the left mandibular body showed muscle tissue and isointense signals on a T1-enhanced image, and high signals on a T2-enhanced image; gadolinium contrast-enhanced imaging showed a solid tumor with an indistinct boundary and enhancement (**Figure 3C**). The tumor measured approximately 41 × 33 × 20 mm.

Positron emission tomography-CT showed fluorodeoxyglucose-enhanced uptake with a maximum standardized uptake value of 9.0 in the retro-molar area, which is believed to indicate centrality at the mandibular angle and ramus (**Figure 3D**). There was no evidence of cervical lymph node or systemic metastases.

After the initial diagnosis, we immediately performed a repeat biopsy of the left mandible. The result showed a high probability of leiomyosarcoma in the non-epithelial malignant tumor. In February, we performed a tumorectomy (mandibular region resection) and reconstructive surgery using a titanium plate. The resection was performed according to the imaging findings and a 3-dimensional stereoscopic model (**Figure 4A, 4B**). Although the anterior resection stump was originally planned for the distal canine area, we progressed further into the bone while performing rapid pathology tests, and the resection ultimately almost reached the midline. The resection extended to subcutaneous adipose tissue on the outer and rear sides, directly under the articular process on the upper side and the pterygoid muscle on the inner side (**Figure 5A-C**). The resection margin was 15 mm. While no tumor was apparent on the resection stump, histopathological progression toward the outside of the mandible was particularly advanced on the inner side; therefore, the safety margin for a non-epithelial malignant tumor was inadequate. To avoid local recurrence and remote metastasis, we proposed systemic chemotherapy for the patient. After obtaining consent, we performed postoperative adjuvant chemotherapy (cisplatin: 120 mg/body, doxorubicin hydrochloride: 50 mg/body, and caffeine: 2400 mg/body), for a total of three courses from April to June. Adverse events included hair loss and vomiting, as well as plate exposure in the area corresponding to the mandibular angle. After the completion of chemotherapy, we performed plate removal under general anesthesia, following which chewing, swallowing, and ingestion were possible, even though the jawbone was transected.



**Figure 3.** Imaging findings. A, B. Computed tomography scan showing an osteoclastic lesion centering on the left mandibular retromolar area, with cortical bone destruction extending to the buccolingual side, and a soft tissue shadow extending into the surrounding area (arrow). C. Gadolinium contrast-enhanced magnetic resonance image showing a solid tumor with enhancement and an indistinct boundary (arrow). D. Positron emission tomography-computed tomography scan showing enhanced fluorodeoxyglucose uptake with a maximum standardized uptake value of 9.0 and centrality localized to the mandibular angle (arrow).



**Figure 4.** Three-dimensional reality model. A. Inner side surface view; B. Outer side surface view and pre-venting titanium plate.

Histopathology involved hematoxylin-eosin staining and various immunohistological tests of the resected specimen. On hematoxylin-eosin staining, heterocysts arrayed in bundles with stained nuclei within spindle-shaped cells, and fibrous cytoplasm, were visible. High cell den-

sity, nuclear atypia, and nuclear fission images were also seen (Figure 6). Immunohistological staining results are shown in Figure 6 and Table 1. From these findings and surgical specimens, we diagnosed mandibular-origin leiomyosarcoma. Generally, sarcomas have lower levels of telomerase activity, however, this leiomyosarcoma has an abundant telomerase activity, which is one of the marker of cell proliferation (Figure 7).

Following satisfactory progress, the patient was discharged from the hospital in June, and returned to our department for regular outpatient follow-up. CT scans taken two years after the surgery revealed multiple metastases in the lungs. There was no response to additional chemotherapy, and the patient died about three years after the initial surgery.

### Discussion

Leiomyosarcoma is extremely rare among malignant tumors in the oral region [2], with few examples in the literature. Leiomyosarcoma in the oral region does not show clear differences according to gender or age, and may occur at various sites, including the gums, tongue, buccal mucosa, or mandible [7]. Moreover, cases with mandibular centrality are extremely rare. When leiomyosarcoma arises from the mandible, it is reasonable to assume that it is derived from surrounding vascular smooth muscle in the mandibular canal. In this particular case, as decreased sensation was noted in the mentum in the initial evaluation, the tumor was thought to originate from blood vessels in the mandibular canal or from surrounding branch-

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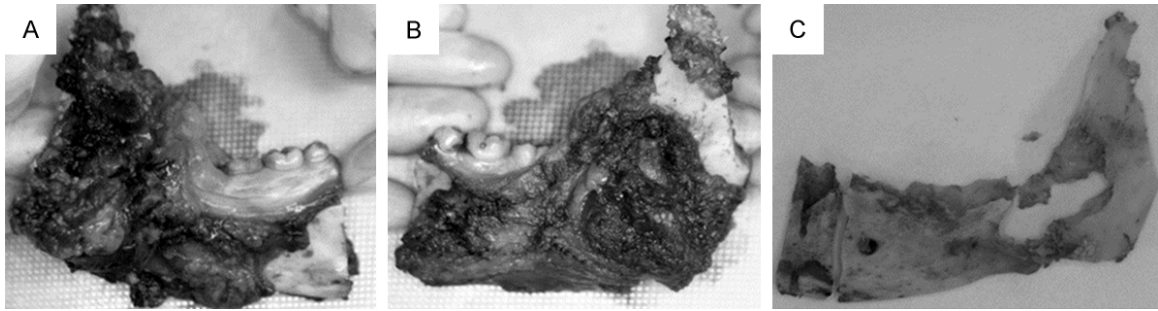
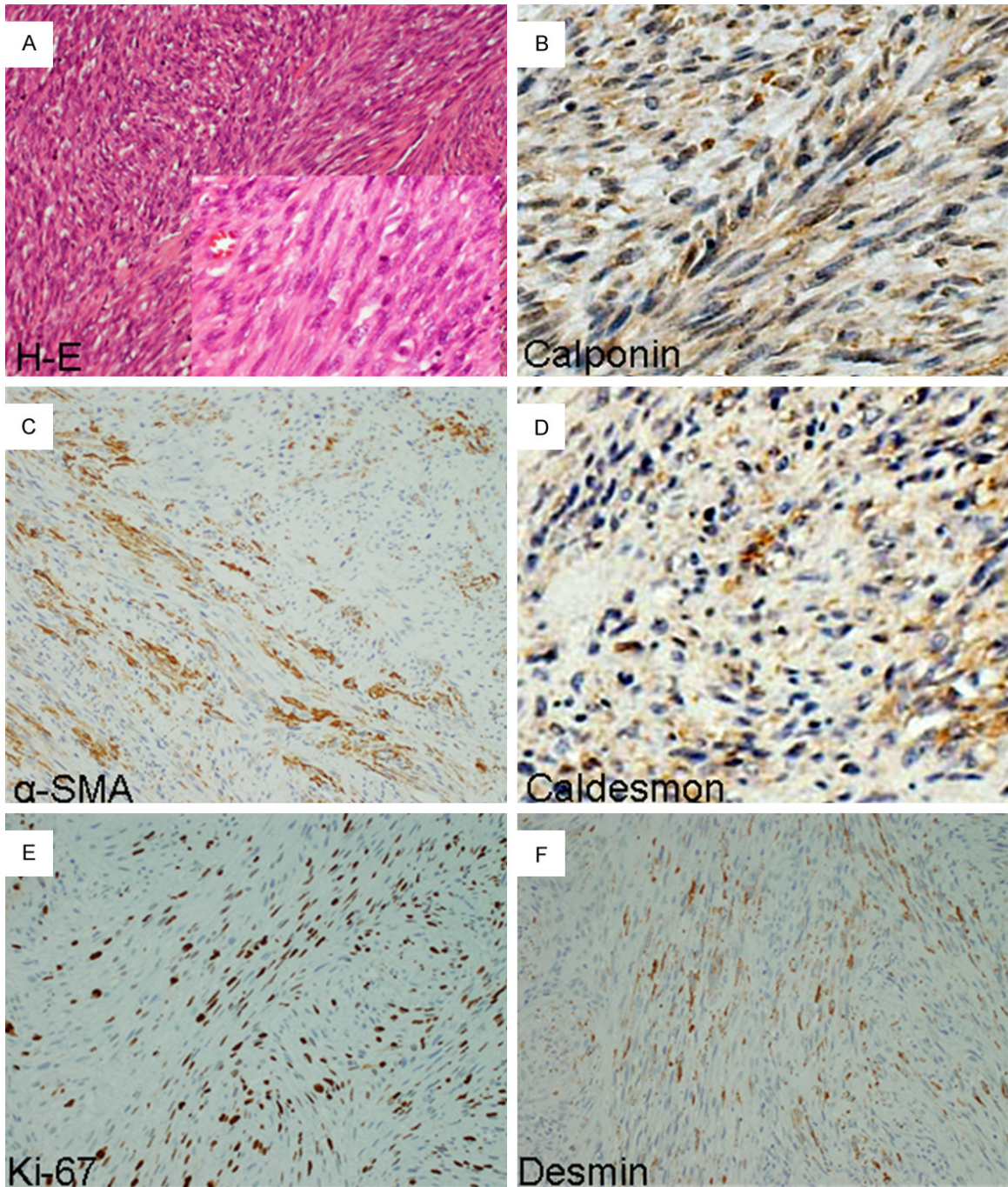


Figure 5. Resected specimen. A. Inner side surface view; B. Outer side surface view; C. Bone specimen.

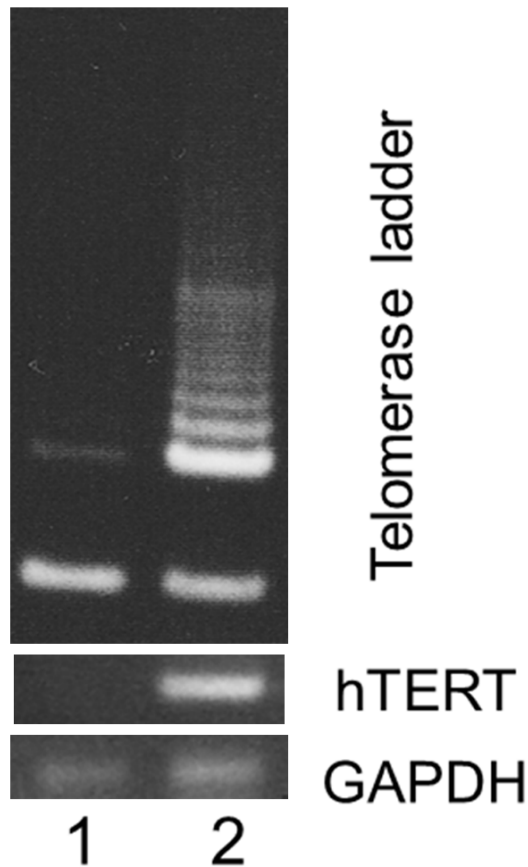


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**Figure 6.** Histopathological images. A. Hematoxylin and eosin staining ( $\times 100$ ); B. Calponin immunostaining ( $\times 100$ ); C.  $\alpha$ -smooth muscle actin immunostaining ( $\times 200$ ); D. Caldesmon immunostaining ( $\times 100$ ); E. Ki-67 immunostaining ( $\times 200$ ); F. Desmin immunostaining ( $\times 200$ ).

**Table 1.** Immunohistochemica

Markers	Reactivity
$\alpha$ -smooth muscle actin	+
Calponin	+
HHF35	+
Desmin	+
Caldesmon	+
Cytokeratin	-
Epithelial membrane antigen	-
S-100	-
CD34	-
CD246	-



**Figure 7.** Telomerase activity assay. Lane 1, The biopsy specimen. Lane 2, Negative control without template. The sample of lane 2 showed the typical ladder pattern of telomerase activity. hTERT is a catalytic subunit of telomerase, which is parallel to the telomerase activity.

es; however, the exact origin could not be identified.

In general, a definitive pathological diagnosis is extremely important for selecting an appropriate treatment method and determining the prognosis for non-epithelial malignant tumors. This is also important for soft tissue sarcomas because effective tissue-based chemotherapy regimens are available. While our case was a leiomyosarcoma, fibrosarcoma or osteosarcoma was also suggested. Therefore, immunohistological tests were necessary for differential diagnosis. While the cells were negative for epithelial markers such as cytokeratin or epithelial membrane antigen, they were positive for smooth muscle cell markers, such as  $\alpha$ -smooth muscle actin, calponin, HHF35, desmin, and caldesmon; thus, a definitive diagnosis of leiomyosarcoma could be made. Moreover, the proliferative marker is also useful information at the treatment of this kind of tumor. Ki-67 index was high. Moreover, this tumor has a telomerase activity and expressed hTERT mRNA [5, 8]. This indicated that this tumor has a great potential in tumor cell proliferation.

For leiomyosarcoma, the first choice for treatment is complete resection [9, 10], and the prognosis is expected to be particularly favorable when a wide initial resection is possible. Chemotherapy is adjunctive or palliative. In this particular case, while a wide mandibular resection including soft tissue was performed, the tumor invasion was more extensive than expected, and chemotherapy was performed to avoid postoperative recurrence or metastasis. We consulted an orthopedic surgeon for the chemotherapy regimen and administered drugs commonly used for leiomyosarcoma with the concomitant use of caffeine to augment cisplatin activity. With no definite residual tumor or remote metastasis, efficacy could not be determined.

Ethunandan et al. reported that the five-year survival rate for leiomyosarcoma in the oral region is about 55% [11]. However, the survival rate decreases for cases with bone invasion

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[11]. As the number of reported cases with mandibular centrality is small, we were unable to discern a trend, but these included extremely malignant cases in which metastasis to other organs had already occurred at the time of initial diagnosis. Unfortunately, although follow-up was conducted every three weeks, and imaging including positron emission tomography-CT was performed as needed, the patient developed respiratory failure due to lung metastasis, and died about three years after the surgery. Thus, as with many other sarcomas, the choice of initial treatment is critical, but control is extremely difficult when a recurrence or remote metastasis develops.

### Acknowledgements

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### Disclosure of conflict of interest

None.

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### References

- [1] Enzinger FM and Weiss SW. Soft tissue tumors. 3rd Edition. In: Enzinger FM, editor. St Louis: Mosby Co; 1995. pp. 491-510.
- [2] Farman AG and Kay S. Oral leiomyosarcoma. Report of a case and review of the literature pertaining to smooth-muscle tumors of the oral cavity. *Oral Surg Oral Med Oral Pathol* 1977; 43: 402-409.
- [3] Ahn JH, Mirza T and Ameerally P. Leiomyosarcoma of the tongue with multiple metastases: a case report and review of literature. *J Oral Maxillofac Surg* 2012; 70: 1745-1750.
- [4] Shokouh TZ, Taghipour Z, and Naser SS. Leiomyosarcoma of the maxilla in a 24-year-old man who initially presented with odontalgia, and suffered from tumour mismanagement. *BMJ Case Rep* 2013; 2013: bcr2013-200933.
- [5] Sumida T, Hamakawa H, Otsuka K and Tanioka H. Leiomyosarcoma of the maxillary sinus with cervical lymph node metastasis. *J Oral Maxillofac Surg* 2001; 59: 568-571.
- [6] Fitzpatrick SG, Woodworth BA, Monteiro C and Makary R. Nasal sinus leiomyosarcoma in a patient with history of non-hereditary unilateral treated retinoblastoma. *Head Neck Pathol* 2011; 5: 57-62.
- [7] Nikitakis NG, Lopes MA, Bailey JS, Blanchaert RH Jr, Ord RA and Sauk JJ. Oral leiomyosarcoma: review of the literature and report of two cases with assessment of the prognostic and diagnostic significance of immunohistochemical and molecular markers. *Oral Oncol* 2002; 38: 201-208.
- [8] Sumida T, Hamakawa H, Sogawa K, Sugita A, Tanioka H and Ueda N. Telomerase components as a diagnostic tool in human oral lesions. *Int J Cancer* 1999; 80: 1-4.
- [9] Mindell RS, Calcaterra TC and Ward PH. Leiomyosarcoma of the head and neck: a review of the literature and report of two cases. *Laryngoscope* 1975; 85: 904-910.
- [10] Brandjord RM, Reaume CE and Wesley RK. Leiomyosarcoma of the floor of the mouth: review of the literature and report of case. *J Oral Surg* 1977; 35: 590-594.
- [11] Ethunandan M, Stokes C, Higgins B, Spedding A, Way C and Brennan P. Primary oralleiomyosarcoma: a clinico-pathologic study and analysis of prognostic factors. *Int J Oral Maxillofac Surg* 2007; 36: 409-416.