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Red exophytic mass of the maxillary anterior gingiva

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CASE REPORT

79-year-old male presented to his general dentist with a red and ulcerated exophytic growth between his maxillary left lateral incisor and canine (Figure 1A). The patient denied any paresthesia or pain associated with the lesion and had no evidence of cervical lymphadenopathy. He denied fever, chills, nausea, vomiting, diarrhea, constipation, or recent weight change. The patient reported a history of smoking a pack of cigarettes a day for approximately 30 years but reported quitting about 25 years ago. He did not report any

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history of using smokeless tobacco, and he reported drinking approximately two glasses of wine per day. His health history was significant for chronic hypertension, COPD, moderate asymptomatic aortic stenosis, Alzheimer's disease, prostate cancer treated with prostatectomy in 2006, a left bronchopleural fistula treated with lobectomy in 1994, and right lung pneumonia in 2012.

Due to the presence of a faulty composite restoration on the distal of the lateral incisor, the patient's dentist suspected that the soft tissue lesion represented reactive granulation tissue and replaced the restoration. Since the lesion did not resolve within three weeks after replacing the restoration, the patient was referred to a periodontist for further evaluation and surgical debridement of several teeth near the lesion. At the time of debridement in February 2014, the periodontist (SW) biopsied the soft tissue mass measuring 9 mm × 6 mm × 3 mm. The lesion extended from the buccal aspect to the palatal aspect of the associated maxillary gingiva, but a periapical radiograph (Figure 1B, made prior to the restoration) of the region, as well as a panoramic radiograph (not shown), did not reveal any bone involvement. The clinical impression was that of a reactive lesion, most likely a pyogenic granuloma.

DIFFERENTIAL DIAGNOSIS

The clinical differential diagnosis for a well-demarcated red gingival lesion without bone involvement includes pyogenic granuloma, peripheral giant cell granuloma, hemangioma and less commonly, Kaposi's sarcoma, angiosarcoma and metastatic disease. Pyogenic granuloma (PG) was favored as the initial clinical diagnosis because of the red, ulcerated appearance of the gingiva adjacent to a faulty restoration. PGs are reactive lesions, arising from various stimuli, including chronic irritation, injury, hormones, and drugs [1], and usually occur on the interdental papilla and facial gingiva.[2] They commonly appear as lobulated, exophytic nodules, often with a pedunculated base. The color can range from red to purple, often appearing hemorrhagic or ulcerated. They can vary in size from a few millimeters to 2–4 cm. PGs are often slow growing, asymptomatic, and usually only an aesthetic concern for patients. Although they commonly arise during pregnancy, men are affected in nearly one-third of cases.[1,2,3]

Another exophytic, nodular lesion commonly found on the gingiva is the peripheral giant cell granuloma (PGCG). PGCG is a tumor-like growth that most likely occurs in response to irritants in the gingival tissues.[3] Clinically similar to pyogenic granulomas, they can vary in size from a few millimeters to as large as 5 cm. Bone resorption characterized as a "cupping defect" can be seen with PGCGs; however, smaller lesions may not show any radiographic changes. As with pyogenic granulomas, PGCGs have are more prevalent in female patients. [1,2,3]

When considering gingival nodules, peripheral ossifying fibroma should also be included in the differential diagnosis. These reactive lesions are generally firm, pink, and can grow between 1 and 6 cm in size. They are slow-growing and can be sessile or pedunculated. Patients are often asymptomatic unless the nodule becomes ulcerated from trauma. A reactive lesion, peripheral ossifying fibromas occur more frequently in young adults, and females are affected more often than males.[1,2,3]

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Kaposi's sarcoma (KS) can present as a red, exophytic growth in the oral cavity. KS, a vascular neoplasm caused by infection with human herpesvirus 8, is observed in the following contexts: (1) classical type—observed in older men of Italian, Jewish or Slavic ancestry--progresses slowly and rarely presents with intraoral lesions; (2) endemic type—a relatively common neoplasm of young adults and children in sub-Saharan Africa; (3) iatrogenic type—seen in recipients of solid organ transplants; and (4) epidemic subtype—AIDS-related. The patient's history was not consistent with KS; in addition, the patient did not have any other skin or intraoral lesions.

Rarely, gingival enlargements mimicking a pyogenic granuloma can also represent metastatic disease; the gingiva is the most common location for oral soft tissue metastases. Common primary sites include lung, renal, and breast, and in a majority of cases, the patient presents with a history of malignancy. Although prostate cancer is common in men and was diagnosed in 2006 in our patient, metastatic lesions from the prostate are usually found in bone, and not in intraoral soft tissues. Due to the red clinical appearance of this lesion and its location adjacent to a faulty restoration without bone involvement, these options were considered but ranked lower in the differential diagnosis.

DEFINITIVE DIAGNOSIS AND MANAGEMENT

Histopathological examination revealed a nodular proliferation of large pleomorphic and atypical epithelioid cells with multilobulated and, in areas, hyperchromatic nuclei (Figure 2). The neoplastic cells contained abundant eosinophilic cytoplasm. In areas, tumor cells lined irregular interanastomosing channels infiltrating surrounding tissues that contained a mild to focally moderate mixed inflammatory cell infiltrate; scattered mitotic figures (including atypical mitotic figures; Fig 2d) were noted throughout the specimen. Based on these histological findings, the differential diagnosis included poorly-differentiated carcinoma, epithelioid sarcoma, large B-cell lymphoma, high-grade angiosarcoma, and melanoma. Immunohistochemistry was positive for vimentin, CD31, and ERG, supporting endothelial differentiation. Tumor cells were negative for CD20, CD30, high molecular weight keratin CK903, cytokeratin wide-spectrum (AE1:AE3 cocktail), MNF-116, S100 and CD34 (Figure 3). Coupled with the morphology, the diffuse intense staining of ERG (nuclear) and CD31 with focal accentuation of the cytoplasmic membrane supported a diagnosis of angiosarcoma. Lack of staining with the AE1:AE3 cocktail, MNF-116 and CK903 excluded a diagnosis of carcinoma and epithelioid sarcoma; lack of staining with S100 rendered a diagnosis of melanoma less likely; and CD20 negativity ruled out large B-cell lymphoma. We also considered Kaposi sarcoma, but in light of the clinical presentation as a single lesion in a relatively healthy patient and prominent cellular pleomorphism and vasoformation that were not typical for KS, we favored a diagnosis of angiosarcoma. A test for Kaposi's sarcoma-associated herpesvirus, however, was not performed. The location, clinical findings (no immunosuppression) and morphologic features argued against bacillary angiomatosis; specifically, the degree of pleomorphism and increased mitotic activity were beyond that seen in bacillary angiomatosis.

The patient was then referred to the University of Michigan Department of Oral and Maxillofacial Surgery/Hospital Dentistry for further evaluation and treatment. Additional

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radiographic evaluation, including a head and neck CT scan, confirmed the lack of bone involvement. A comprehensive work-up for metastatic disease was negative. The patient was determined to be stage 1 (T1N0M0) according to International Union Against Cancer and American Joint Committee on Cancer (UICC/AJCC) classification scheme.

His case was presented at a multidisciplinary sarcoma board, and the recommended treatment was primary surgical resection with maxillary obturator rehabilitation due to the small size of the lesion, and possible adjuvant radiotherapy to decrease the risk of recurrence. The patient did not desire to undergo any systemic chemotherapy, and the sarcoma board did not believe it would be necessary if adequate margins could be achieved intraoperatively without significant disfigurement and morbidity. The tumor was resected one month after initial diagnosis (Figure 4A). Ultimately, the maxillary right central incisor through the maxillary left second premolar were included in the wide local excision, but this was not easily predicted preoperatively (Fig 4B). Histological examination of all surgical specimens revealed tissue margins free of tumor. A maxillary surgical obturator was delivered at the time of surgery (Figure 4C). A new maxillary interim obturator was delivered two weeks post-operatively and modified as needed to accommodate post-operative tissue changes. The patient received a total of 60 Grays of radiation following surgery, with fractions delivered once daily, five times per week over the course of six weeks.

Three months after the surgical procedure, the patient was admitted to the Emergency Department for difficulty breathing and hypoxia and expired one month after admission due to respiratory distress presumably unrelated to his angiosarcoma diagnosis.

DISCUSSION

Primary sarcomas of the oral cavity are extremely rare. Among 11,250 head and neck malignancies reviewed by Gorsky and Epstein in 1998, only 139 (1.24%) were sarcomas and only 16 (0.14%) were in the oral cavity.[4] Angiosarcoma, also known as hemangioendotheliosarcoma, accounts for 1% of all sarcomas and 2% of soft-tissue sarcomas.[5] These endothelial cell malignancies of vascular or lymphatic origin can arise anywhere in the body; however, they most commonly present as tumors on the scalp of elderly Caucasian men.[4,6,7] A study conducted at the Oral and Maxillofacial Pathology Department of the Armed Forces Institute of Pathology determined that oral and salivary gland angiosarcomas represent approximately 1% (29 cases out of a total of 2,139) of all angiosarcomas.[8] There have been only 35 reports of primary oral angiosarcoma in the English literature over the past 20 years.[9] We report an unusual case of primary angiosarcoma of the maxillary gingiva submucosa that clinically resembled a reactive lesion of the gingiva.

Histologically, angiosarcomas can vary from well-differentiated neoplasms with vascular channels lined by atypical endothelial cells with few mitoses to poorly-differentiated neoplasms composed of solid sheets of epithelioid or spindle cells exhibiting brisk mitotic activity. Poorly-defined vascular spaces, multilayered endothelial lining and papillary projections into the vascular lumen may also be observed. Hemorrhage, necrosis, and

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lymphocytic infiltration are common features.[6] One hallmark of poorly differentiated angiosarcoma is fragmented erythrocytes within intracytoplasmic vacuoles. [9,10] Epithelioid angiosarcoma (EA) is a rare and highly aggressive variant that has an epithelial morphology and cytokeratin positive immunohistochemistry; thus making it difficult to distinguish from a poorly differentiated carcinoma. [7,11]

Angiosarcomas require immunohistochemical analysis to differentiate them from similar-appearing neoplasms, such as poorly-differentiated carcinoma, epithelioid sarcoma, large B-cell lymphoma, and melanoma. CD31 and CD34 are the most commonly used markers to support a diagnosis of angiosarcoma. However, CD34 is expressed in a variety of mesenchymal tissues and neoplasms, including epithelioid sarcoma and undifferentiated pleomorphic sarcoma and has a relatively low sensitivity for angiosarcomas, with approximately 40% of neoplasms demonstrating lack of expression.[12,13] CD31, although highly specific, is also negative in a subset of angiosarcomas and may be positive in other neoplasms such as undifferentiated pleomorphic sarcomas. Erythroblast transformation specific related gene (ERG) is a proto-oncogene highly expressed in endothelial cells, and numerous studies have demonstrated ERG to have exceptionally high sensitivity and specificity for vascular differentiation in angiosarcomas.[12–15] ERG can be used in conjunction with CD31 and CD34 to support a diagnosis of angiosarcoma.[12, 13]

Further IHC analysis for poorly-differentiated angiosarcomas typically reveals expression of mesenchymal markers, such as vimentin, and endothelial markers, including von Willebrand factor, agglutinin 1, and vascular endothelial growth factor (VEGF). The absence of melanoma markers such as S-100 protein, human melanoma black-45 (HMB45), and melanoma antigen are critical for distinguishing angiosarcoma from melanoma. [6] Negative expression of epithelial markers, including AE1:AE3, help rule out carcinoma, epithelioid sarcoma, and EA. Lack of expression of CD20 can help rule out large B-cell lymphoma.

Angiosarcomas are staged according to UICC/AJCC staging system, which is based on the TNM (tumor–node–metastasis) staging system. However, all angiosarcomas are considered high-grade by definition, so histological grading is not used in staging.[6]

Most angiosarcomas arise *de novo* but they may develop from benign vascular lesions.[16] The fiveyear survival rate is 35%, and approximately 50% of patients die within 15 months of diagnosis.[6,17] Currently, no randomized clinical trials and few prospective trials comparing treatment modalities for angiosarcoma exist. Most reports of angiosarcoma treatment in the literature are case reports and retrospective case series. Thus, the gold standard treatment protocol for angiosarcoma follows the guidelines outlined by the National Comprehensive Care Network (NCCN).

Angiosarcoma has a strong tendency to recur and metastasize. This case is particularly unique because the clinical presentation of the tumor combined with its relevant dental history strongly suggested a diagnosis of an inflammatory/reactive lesion such as a pyogenic granuloma. The lesion was properly identified as an angiosarcoma only because it was biopsied by a clinician who insisted on a definitive histopathological diagnosis before proceeding with treatment.

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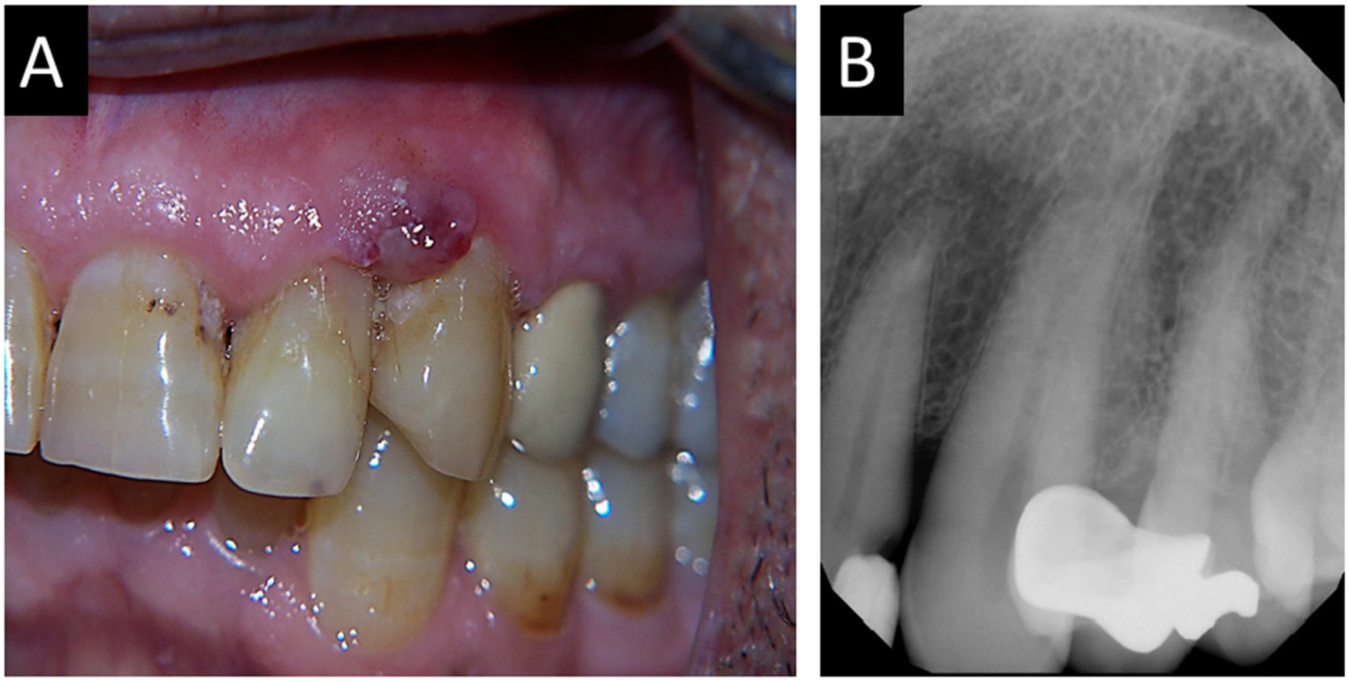

Figure 1. Clinical and radiographic findings at initial presentation

A) An exophytic, erythematous lesion on the free gingival margin and papilla associated with the maxillary left lateral incisor and canine, and measuring approximately 9mm × 6mm × 3mm. B) Periapical radiograph of the region showing no evidence of bone involvement

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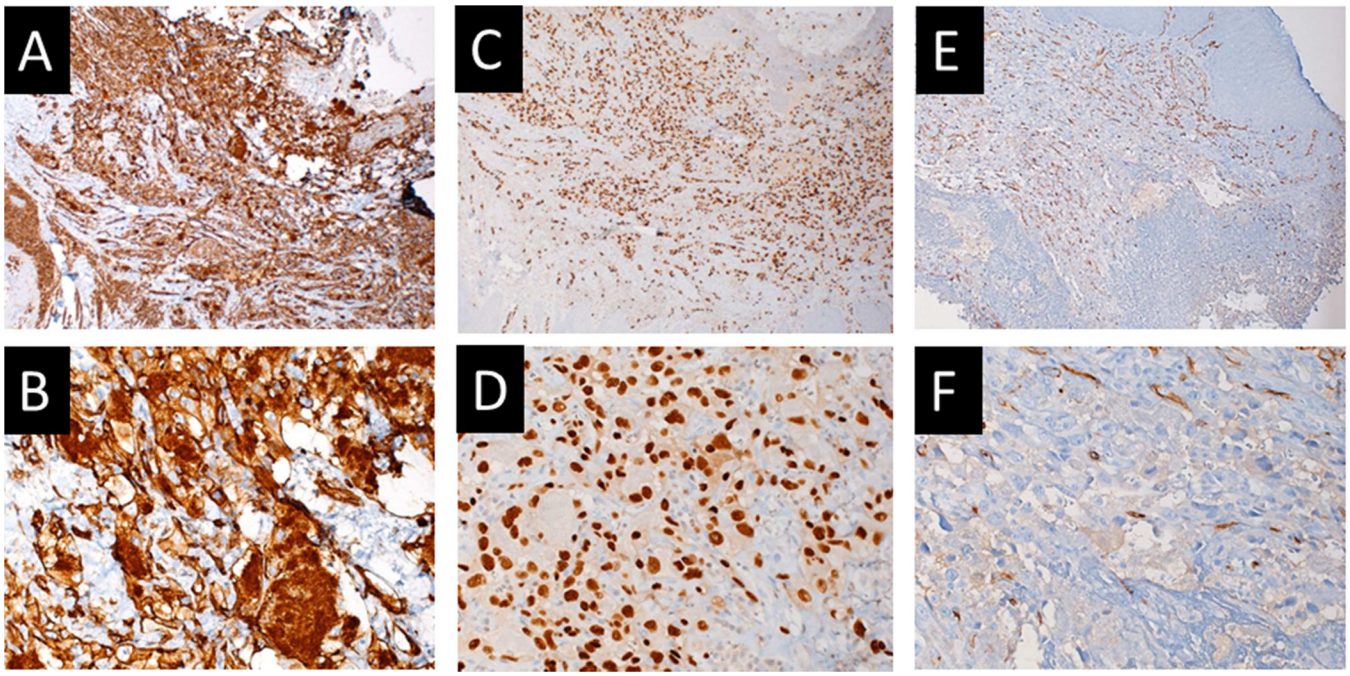

Figure 2. Histopathological features

A. (*H&E, 4x original magnification*) Low-power image of the lesion demonstrating a nodule surfaced by epithelium. B (*H&E, 20x magnification*) Infiltrative, neoplastic cells seen within the fibrovascular connective tissue lining irregular and poorly-formed vascular channels. C (*H&E, 40x magnification*) Pleomorphic, multilobulated, and atypical neoplastic cells exhibiting an increased nuclear to cytoplasmic ratio, hyperchromatic nuclei, and prominent nucleoli. D (*H&E, 40x magnification*) Atypical mitotic figures and prominent intracytoplasmic lumens. *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM01097*

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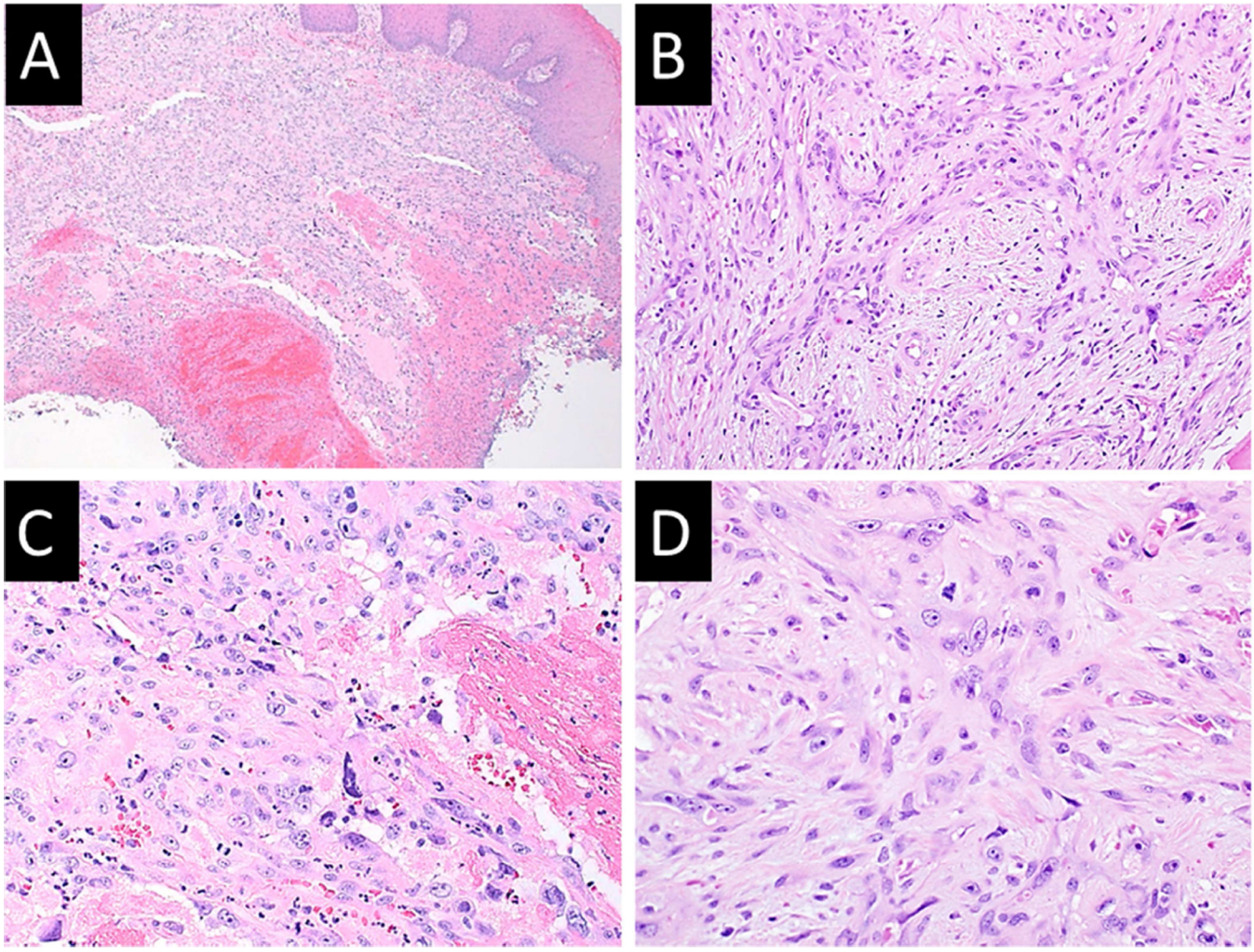

Figure 3. Representative immunohistochemical images of angiosarcoma

A and B) (*CD31, 10x and 40x magnification, respectively*) Diffuse, strongly positive cytoplasmic expression of CD31; *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM01072.* C and D) (*ERG1, 10x and 40x magnification, respectively*) Diffuse, strongly positive nuclear expression of ERG1; *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM01073.* E and F) (*CD34, 10x and 40x magnification, respectively*). The tumor cells were negative for CD34. *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM01074.*

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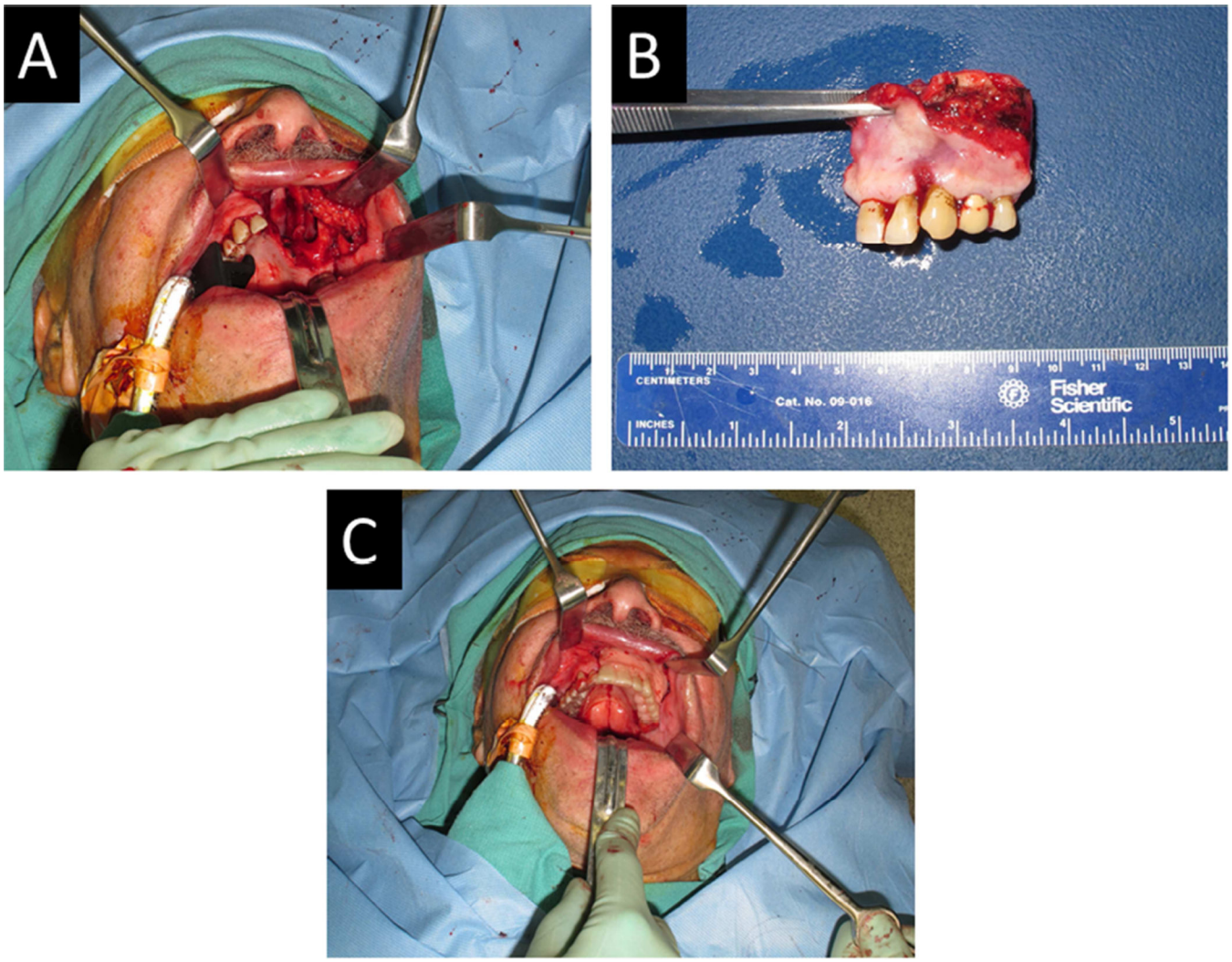

Figure 4. Intra-operative photographs demonstrating the resection specimen and obturator placement

A) Subperiosteal dissection with 2 cm margin around the lesion. B) The resection specimen, measuring 4.4cm × 4.0cm × 1.9cm, included the left maxillary central incisor through the left maxillary second premolar; the right maxillary central incisor was extracted separately. C) Resection completed and obturator in place.