

CLINICOPATHOLOGIC CONFERENCE

An incidentally discovered radiolucency in the posterior mandible

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(Oral Surg Oral Med Oral Pathol Oral Radiol 2012;113:17-20)

CLINICAL PRESENTATION

A 61-year-old woman presented to the general dentist for routine dental treatment. Her medical history included diabetes mellitus managed with metformin, a negative history of tobacco, alcohol, or drug use, and unremarkable family history for neoplastic disease. Significant dental history included restorative treatment over several decades, and her third molars were extracted without periapical or pericoronal pathology at age 19 years. Clinical examination revealed a normocephalic atraumatic head with a normal range of mandibular movement, stable occlusion, and supple cervical region without lymphadenopathy. The intraoral examination revealed no evidence of any soft tissue pathology. The patient was asymptomatic, and the dentition was within normal limits. Panoramic radiographic examination revealed a large well circumscribed radiolucency distal to the second molar, within the ramus of the left mandible (Figure 1). The radiographic findings prompted an incisional biopsy. Computerized tomography revealed a less discrete osteolytic lesion centered well within the mandible that had also penetrated the lingual cortical plate (Figure 2).

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of a well circumscribed, noncorticated, radiolucent lesion of the retromolar region of the mandible comprises several classes of pathology, including odontogenic cysts and tumors, nonodontogenic tumors, and other nonneoplastic conditions.

A significant number of intrabony jaw lesions have their origin from the tooth-forming tissues, and therefore, odontogenic cysts and tumors are a logical place to start a differential diagnosis. Odontogenic cysts are more common than odontogenic neoplasms. Of the odontogenic cysts, odontogenic keratocyst (OKC; or

keratocystic odontogenic tumor) would be the most likely in the present case. Keratocysts affect the mandible ~75% of the time and exhibit a strong propensity for the posterior mandible and the ascending ramus.¹ The majority of OKCs are found in people between ages 10 and 40 years, and radiographic findings most often demonstrate a benign process with well corticated borders.¹ Additionally, a significant number of OKCs (38%) tend to be associated with an unerupted tooth or earlier extraction site.¹ Finally, from the odontogenic cyst category, neither a residual dentigerous cyst nor residual apical periodontal cyst would be considered, because those conditions were not present at the time of third molar extraction.

Odontogenic tumors often present as well circumscribed radiolucencies, which suggest that this lesion could be one of a variety of odontogenic neoplasms, such as ameloblastoma, odontogenic myxoma, and the outside possibility of a low-grade odontogenic malignancy. Many of the odontogenic tumors would be improbable based on demographic features. Odontogenic myxoma is found in the posterior mandible ~23% of the time with equal predilection for the maxilla and mandible, but the lesion in the present case did not demonstrate the “soap bubble” radiographic appearance spanning from the premolar region to the molars that is typical of a myxoma.² Yet, of the odontogenic tumors, ameloblastoma is the most likely in this case, given the location and presentation of the lesion in the posterior mandible. Excluding odontomas, ameloblastoma is the most common odontogenic tumor in general, and ~80% are found in the mandible, with the molar-ramus area affected between 39% and 66% of the time.^{3,4} The average age of diagnosis for ameloblastoma is middle to late 30s. Although our patient was significantly older, just over 10% of cases do affect patients in their seventh decade.^{3,4}

Notably, the lesion did not appear to be associated with a tooth, and accordingly, nonodontogenic pathology must be entertained in the differential diagnosis. Nonodontogenic mesenchymal neoplasms may include neurofibroma, desmoplastic fibroma of bone, and vascular lesions. Even though neurofibromas are most

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Received for publication Mar 19, 2011; returned for revision Jul 27, 2011; accepted for publication Aug 3, 2011.

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2212-4403/\$ - see front matter

doi:10.1016/j.tripleo.2011.08.007

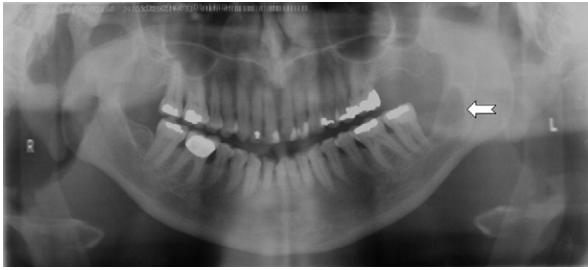


Fig. 1. Panoramic radiograph showing a 1.5×1.5 cm well defined and noncorticated radiolucent lesion, located within the ascending ramus of the left mandible (arrow).



Fig. 2. Computerized tomography reveals 1.5×1.5 cm osteolytic lesion within the ramus of the mandible. Lingual cortical plate destruction is apparent.

commonly found on the buccal mucosa or the dorsum of the tongue, these lesions may arise within the bone as well.⁵ In the present case, the location is favorable for desmoplastic fibroma, with 84% being found in the mandible and 70% of mandibular lesions affecting the ascending ramus.⁶ However, desmoplastic fibroma was not likely, because 84% occur in people <30 years old.⁶

Finally, lack of cortication and cortical perforation would raise the possibility of malignancy. Metastatic disease is usually symptomatic, but not uncommonly the oral metastasis can precede the discovery of the primary site. An intra-alveolar carcinoma, such as clear cell odontogenic carcinoma, may be feasible. Clear cell odontogenic carcinoma is quite uncommon, but reported demographic features, such as presenting in the mandible ~80% of the time, cortex perforation, soft tissue involvement, and age of the patient, make it a

possibility as well.⁷ Primary mucoepidermoid carcinoma (MEC) was also possible; despite its rarity, its favored site is the posterior mandible.⁸

DIAGNOSIS

A biopsy was performed by accessing the lesion from the crest of the alveolar ridge. Histologic examination revealed numerous nests and larger sheets of epithelial cells associated with both microcystic and macrocystic areas (Figure 3). The neoplastic cells were often polyhedral and in areas; mature squamous differentiation was noted. Well formed mucus cells were mixed with the epidermoid cells (Figure 4). Mitoses were rarely encountered, and perineural invasion, necrosis, and high-grade cytologic atypia were absent. A mucicarmine special stain demonstrated intracytoplasmic staining of the mucus cells (Figure 5). A positron-emission tomography (PET) scan showed no indication of metastatic disease throughout the body, nor suggestion of another primary neoplasm. A diagnosis of intraosseous MEC was made.

MANAGEMENT

Following confirmation from PET of no independent primary site, definitive surgical treatment commenced. The lesion was resected with 1-cm margins; the coronoid process and condyle were left intact. The buccal section was subperiosteal with the cortical plate intact. However, the lingual section was supraperiosteal to include the lingual mucosa, sacrificing the lingual nerve. Multiple frozen tissue samples were taken during the surgery to verify clear margins. The patient was placed in intermaxillary fixation in preparation for the second-stage surgery and to allow for accurate reconstruction of the mandibular discontinuity with the use of a stereolithographic model to contour the plate.

Following the harvesting of a bicortical bone graft from the iliac crest, the proximal segment of the ascending ramus and the distal portion of the body of the mandible were exposed. The mandibular discontinuity was reconstructed with a 2.3 mm Stryker Leibinger fixation plate. Postoperative recovery was uneventful.

The 12-month follow-up radiographic examination revealed osteogenesis; the donor tissue was well integrated into the recipient site, occlusion was stable, and the patient again could exercise the muscles of mastication to open 37 mm.

DISCUSSION

Primary intraosseous adenocarcinoma is rare and mainly confined to the jaws, particularly the mandible. The most frequent histopathologic type is MEC.⁸ Most often, central salivary malignancies are reported in either the body or ramus of the mandible.^{8,9} The 3 most

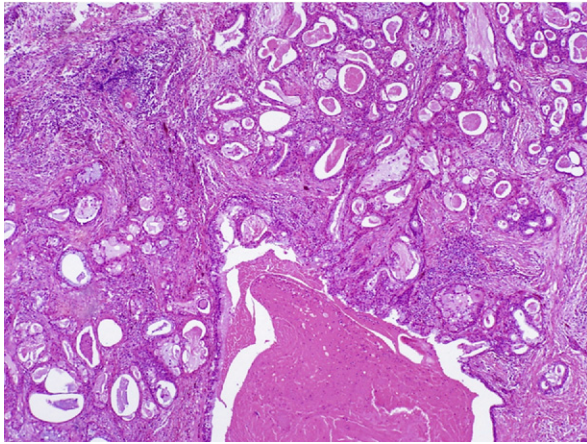


Fig. 3. Photomicrograph showing small infiltrating cords and islands of neoplastic epithelium with micro- and macrocystic areas. Hematoxylin and eosin stain. Original magnification $\times 13$.

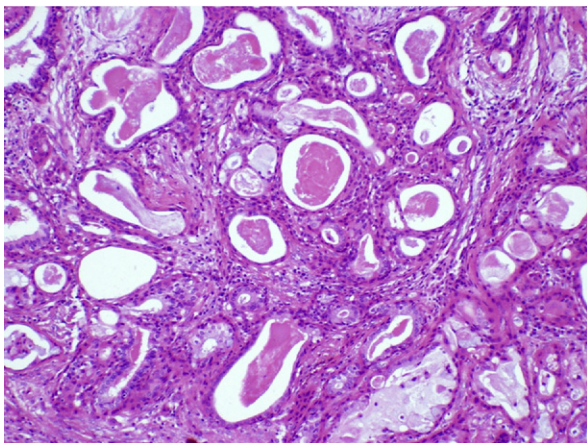


Fig. 4. Photomicrograph showing epidermoid cells mixed with larger more lightly staining mucus cells. Hematoxylin and eosin stain. Original magnification $\times 33$.

common subtypes of intraosseous adenocarcinoma are MEC, adenoid cystic carcinoma, and adenocarcinoma not otherwise specified, with MEC being the most prevalent.^{8,9} Fewer than 200 cases of central salivary gland tumors have been reported in the literature, the majority of which ($n = 135$) have been primary intraosseous MEC.⁹ The prevalence of intraosseous MEC is unknown.

The histogenesis of central salivary gland tumors has been widely debated. These malignancies may arise from developmental remnants of submandibular salivary gland, ectopic entrapment of retromolar minor mucous glands, glandular metaplasia of the epithelial cell rests of the dental lamina, or as an expression of the glandular potential of the epithelial lining of odontogenic cysts.⁸⁻¹⁰ Lack of details surrounding this particular case prevents the opportunity to rule out a history

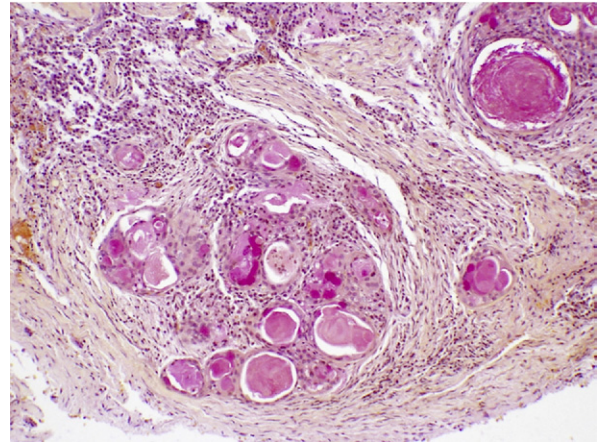


Fig. 5. Mucicarmine stain demonstrating mucus cells with bright red intracytoplasmic mucin. Original magnification $\times 33$.

of a previous cyst or to evaluate the development of the lesion. An odontogenic origin for central MEC is supported by the fact that between 32% and 48% of cases have been associated with an impacted tooth or an odontogenic cyst,^{8,11} although a recent report showed no correlation.⁹

Genetic analysis has demonstrated a subset of soft tissue and intraosseous MEC with the chromosomal translocation $t(11;19)$, resulting in the fusion transcript $CRTC1/MAML2$.^{12,13} Preliminary evidence suggests that this mutation imparts an increased likelihood of metastasis.¹² Additionally, the $TORC1/MAML2$ gene fusion has been reported in central MECs.¹⁴

Central MECs do not appear to have a significant gender predilection, although some series slightly favor female patients. They have been reported from the first to seventh decade of life but seem to have a predilection for middle age.^{8,9,11} The mandible is affected about 3 times more frequently than the maxilla with a predilection for the posterior mandible.⁸ Rarely are the anterior jaws affected. Many patients are asymptomatic, but as the neoplasm expands, pain and swelling are encountered.

Radiographically, central MEC presents as a unilocular or multilocular radiolucency, which may be either well or ill-defined. Many are remarkably well defined. The margins are generally noncorticated, but typically the cortical plate is intact.¹⁵

Retrospective case studies of intraosseous MEC have led some investigators to develop criteria for diagnosis, which include presence of an intact cortical plate.^{8,15} However, any central malignancy may perforate the cortex if untreated, which means that cortical perforation should not preclude a diagnosis of intraosseous MEC. Brookstone and Huvos⁸ proposed a clinical 3-stage system for classifying intraosseous MEC, in which the third stage includes cortical perforation and destruction of the

periosteum. These stages were recommended because a large tumor confined to the cortical plates undoubtedly would pose a better prognosis than a much smaller lesion that penetrated the cortical plate and invaded surrounding structures or demonstrated metastasis. In the same review, however, there appeared to be no association with grade of malignancy observed and prognosis with treatment.⁸ According to the proposed staging system, the present lesion would be classified as stage III, because the cortical plate was perforated.

Treatment may include either aggressive surgical resection or a more conservative approach.^{8,9} Retrospective analyses of intraosseous MEC suggest that en bloc resection is the best approach to prevent recurrence.⁹ More conservative treatment might include enucleation, curettage, or marsupialization, which may be supplemented with adjuvant therapy, such as radiotherapy, but risks for recurrence and osteoradionecrosis clearly exist with little added value.⁹

A systematic review of intraosseous salivary gland tumors showed that conservative treatment resulted in recurrence in 40% of cases, whereas aggressive surgical treatment yielded 4% recurrence.⁸ Survival of patients after 5 years is seldom addressed in the literature, but one group provided 2- and 5-year follow-up data after aggressive surgical treatment, reporting 100% survival rates.¹¹ A retrospective chart review indicated high survival with 1 death in a group of 20.⁹ Reports on metastasis vary greatly, with as little as 9% in a group of 66¹¹; however, another assessment of cases indicated that although none of the maxillary tumors metastasized, 39% of the mandibular cases were found to have metastatic cervical involvement before treatment.⁹ Cytogenetic analysis of soft tissue lesions demonstrated statistically significant correlation with *CRTC1/MAML2* fusion and metastasis,¹² but the same has yet to be observed for the intraosseous type. In our case, the patient presented without metastasis and without recurrence at 12 months after treatment.

In summary, the present case was of an intraosseous MEC, which presented as an asymptomatic, well circumscribed, noncorticated radiolucency of the retromolar region of the mandible. The differential diagnosis for a lesion with this presentation includes many classes of intrabony pathology, including primarily odontogenic cysts and tumors, but other nonodontogenic lesions as well. The histogenesis of intrasosseous MEC is debatable. Surgical resection is associated with a good prognosis.

The authors of this article owe gratitude to Dr. Malcolm Harris for his unique and selfless contributions, which undoubtedly improved the quality of the research herein.

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