Intraosseous carcinoma of the jaws: A clinicopathologic review. Part II: Odontogenic carcinomas

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ABSTRACT: This is the second of a 3-part review of the clinicopathologic features of intraosseous carcinoma of the jaws (IOCJ). This part deals with odontogenic carcinomas, rare entities that are difficult to evaluate because of changes in classification/nomenclature, lack of standardized diagnostic criteria, and variable consistency of the existing literature. Endorsing a critical approach, problems are addressed and areas of uncertainty are highlighted. As in part I, we emphasize histopathologic features from a diagnostic point of view and also question the existence of some "distinct" entities. © 2012 Wiley Periodicals, Inc. *Head Neck* **35:** 902–905, 2013

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ODONTOGENIC CARCINOMAS

Metastasizing ameloblastoma

This is a diagnosis made in retrospect when an ameloblastoma of typical histologic appearance is followed by metastatic deposits of similar appearance. Metastases are most commonly to the lungs,[1] although cervical nodal deposits have been reported.[2,3] Since jaw ameloblastoma and metastases of ameloblastoma show typical benign histology, "metastasizing ameloblastoma" is outside the context of intraosseous carcinoma of the jaws (IOCJ) (in part I[4] we discussed the classification of IOCJ and detailed 2 categories: metastatic and salivary-type carcinomas). The entity, however, is in the current classification schemes of odontogenic carcinomas[1] and is considered here for the sake of completeness.

The pulmonary or nodal deposits may be regarded as metastasis by the hematogeneous or lymphatic route, respectively. Some pulmonary deposits may even be aerogeneous in origin and the possibility of passive transport and implantation to extraosseous sites during surgical manipulation cannot be excluded. Because the metastases almost always follow multiple primary site recurrences of the jaw tumor, and the average time from initial diagnosis of primary to diagnosis of "metastasis" is 18 years,[1,5] one would favor the biology to be passive transport and implantation. However, since many patients die of their metastatic tumor, it appears to represent active tumor spread.

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Ameloblastic carcinoma

This is a tumor of ameloblastic differentiation that has overtly malignant cytologic features. The designation applies whether or not metastases are present.[6] The tumor is very rare, with fewer than 70 reported cases.[7] Males and females are equally affected. Ameloblastic carcinoma (AC) mainly affects the elderly, although a wide age range has been reported.[8] Similar to ameloblastoma, most cases occur in the posterior mandible. The typical presentation is an ill-defined radiolucency, sometimes with focal radiopacities (representing dystrophic calcification), with cortical expansion leading to perforation and invasion of adjacent tissues.[8] This contrasts with the "soap-bubble" imaging appearance of ameloblastoma.

By definition, the essential histologic features of AC are: (1) epithelial plexiform strands and follicles (features that typify ameloblastoma), but with a malignant cytology (eg, nuclear and cellular pleomorphism, nuclear hyperchromatism, increased mitotic activity), and focal necrosis; and (2) at least a focal presence of peripheral ameloblast-like cells with palisaded arrangement and reverse nuclear polarity.[8] The presence of perineural/endoneural and/or vascular invasion supports a diagnosis of AC.[9] The histologic recognition of AC would therefore

seem straightforward. Difficulties, however, may occur depending on the relative extent of the diagnostic histologic features in a given biopsy specimen. There is no consensus on this and cases with limited or focal malignant cytology may overlap with an entity termed "atypical" or "proliferative" ameloblastoma (see the following text). A useful diagnostic adjunct may be the assessment of cycling cells by means of immunohistochemistry (IHC) with antibodies to Ki-67 or proliferating cell nuclear antigen (PCNA) and/or aneuploidy, which are higher in AC than ameloblastoma.[10,11] On the other hand, ameloblast-like cells may be sparse/absent in a single block, which may lead to a diagnosis of primary intraosseous squamous cell carcinoma (SCC) (see part III).[5]

Confusion with clear cell odontogenic carcinoma (CCOC) (see the following text) may also arise, since some ACs exhibit a clear cell population that may be prominent. Spindle cell variants of AC have also been reported,[12] which may further add to diagnostic problems. Confusion with metastasis seems less likely since the cellular arrangement of metastatic carcinomas/adenocarcinomas usually do not exhibit ameloblastomatous patterns. Some have also included basaloid squamous cell carcinoma and basal cell carcinoma in the differential diagnosis, but these are easily excluded on the basis of accurate clinical information and pathologic features.

The outcome of AC is considered poor, with death due to local extension and pulmonary metastases in 22% to 40% of patients.[9,13,14] Typically, aggressive surgical intervention is recommended.[9] Adjuvant radiotherapy should be considered and novel treatments such as carbon ion therapy may offer some hope for extensive local relapse or in cases suitable only for subtotal resection.[15] The limited experience, however, supports a need for caution and, ideally, therapeutic options should be individualized.

Finally, regarding pathogenesis, AC may arise de novo or within a histologically verified ameloblastoma. The latter is referred to as "AC, secondary type" (dedifferentiated or high-grade transformation ameloblastoma).[6] It is not known whether ameloblastomas showing occasional mitoses, but no other cellular atypia, represent incipient dedifferentiation/high-grade transformation. However, lesions showing increased mitotic activity and proliferation of peripheral basaloid cells, but lacking nuclear pleomorphism, neural/vascular invasion, and other histologic features of frank malignancy, have been regarded as reflecting an intermediate stage and designated as "atypical" or "proliferative" ameloblastoma.[16] In this context, it is tempting to speculate that the characteristic features of ameloblastoma are increasingly lost as dedifferentiation/high-grade transformation progresses, a fully dedifferentiated/transformed ameloblastoma being thus histologically difficult to distinguish from a primary intraosseous SCC. The extremely rare AC, secondary type, is mainly seen in the seventh decade, following a long history of ameloblastoma with multiple recurrences and sometimes after radiotherapy.[17] Patients present clinically with a rapidly growing mass with perforation of cortical bone and invasion of adjacent tissues. A possible explanation would again be dedifferentiation/high-grade transformation attributable to a sequence of molecular events, the last of which is rapid.

Clear cell odontogenic carcinoma

Although this is considered as a distinct entity,[18] it is probably one of the most difficult jaw lesions to establish/diagnose given the range of other primary and metastatic tumors that can have a clear cell component. Demographic features include a rare incidence (0.3% of 759 odontogenic tumors in a Chinese population),[7] a wide age range with a mean of 57 years, a preponderance of female patients (male:female ratio, 1:1.6) and location in the mandible (maxilla:mandible ratio, 1:7.7).[19,20] The most common presenting feature is jaw enlargement, often accompanied by mild pain and tooth mobility.[19] Sensory deficits are rare, which might be a diagnostic contrast to mandibular metastatic renal cell carcinoma (the archetype of clear cell metastases).[19] On imaging, CCOC appears as a poorly delineated, uni- or multicystic radiolucency, often leading to root divergence and resorption.[19,21]

Histologically, CCOC is nonencapsulated, invades medullary bone, and consists of solid, often angular, cellular aggregates of cells traversed by dense, fibrous septae. The tumor cell population is often biphasic, consisting of cells with clear or eosinophilic cytoplasm and dense nuclei. Cellular pleomorphism and mitotic activity are rare and when present, affect the eosinophilic cells. The ratio of clear to eosinophilic cells varies and, occasionally, the cellular aggregates almost exclusively consist of clear cells.[19] Glandular features are not obvious.

The histogenesis of CCOC and the nature of the clear cells are challenging.[22-24] Odontogenic embryonic residues as in primary intraosseous SCC-solid type, have been considered as sites of origin; again, although some of the residues consist of clear cells, this is speculative. Histochemically, the tumor clear cells contain diastase-sensitive PAS-positive granules[22,23] and show diffuse granular acid phosphatase, nonspecific esterase, and NADH diaphorase activity.[23] The features suggest that the tumor cells accumulate glycogen in their cytoplasm, which accounts for the clear appearance, and show lysosomal/cytosolic activities of unresolved nature. Immunohistochemically, the cells express CK19, epithelial membrane antigen, and filaggrin. They are usually negative for S-100 protein, glial fibrillary acidic protein, involucrin, vimentin, and smooth muscle actin.[23-30] Features of the profile can be reconciled with the cytoskeleton of various descendants of the basal layer of oral epithelium. Ultrastructural findings[23] include the presence of intracytoplasmic glycogen rosettes without well-developed Golgi apparatus, free tonofilaments, or secretory granules, supporting the theory of a nonglandular epithelial origin. Overall, the findings of the special investigations are incomplete and not particularly enlightening. The possibility that the clear cell appearance reflects an epigenetic change rather than an inherent phenotype cannot be excluded and, if so, would question the notion of a distinct entity.

CCOC is a diagnosis made only after excluding salivary neoplasms, other odontogenic tumors, and metastases.[31] Authors have listed salivary clear cell carcinoma, mucoepidermoid carcinoma (MEC), acinic cell carcinoma, clear cell oncocytoma, and epithelial-myoepithelial carcinoma as possible sources of confusion. In our opinion, the list is only partially meaningful. Clear cell

oncocytoma, a rare salivary gland neoplasm, has yet to be reported within jaws. In addition, acinic cell carcinoma largely consisting of clear cells is a rarity in salivary glands and not yet described as a primary intraosseous tumor. Mucosubstance histochemistry might identify a few mucous cells, suggesting a diagnosis of MEC with a "florid" clear cell component. Diagnosis of epithelial-myoepithelial carcinoma with a "florid" abluminal clear cell component has to rely on identification of occasional bilayered luminal structures showing the characteristic "biphasic" phenotype (eosinophilic, adluminal; "clear," abluminal). Accordingly, the real challenge seems to be distinction from salivary clear cell carcinoma, itself a rare and incompletely understood entity. The issue may thus be impossible to resolve and interpretation could reflect the opinions of individual pathologists. The importance of site (soft tissue vs bone) in resolving this issue is obvious.

Regarding odontogenic tumors, the clear cell variant of calcifying epithelial odontogenic tumor might also be considered. A thorough effort to seek out typical calcifying epithelial odontogenic tumor areas should be undertaken on multiple blocks/step-serial sections. Clear cell islands may also occur in developmental lateral periodontal cysts and gingival cysts of adults, but these rarely enter into the differential diagnosis.

Many CCOCs show aggressive clinical behavior.[19,22,24,28,30,32] Radical resection at diagnosis has been recommended since local enucleation tends to be followed by local recurrence and metastasis.[32,33] Adjuvant radiotherapy should be considered for cases with close or positive margins and nodal involvement.[34] In accord with practices related to other types of tumors, it has been suggested that low labeling indices for proliferation markers (Ki-67, PCNA) and little or no expression of p53 might predict a favorable prognosis.[29]

Ghost cell odontogenic carcinoma

Ghost cell odontogenic carcinoma is a histologically distinct odontogenic carcinoma. It is rare, with around 25 cases in the literature,[35] and is regarded as the malignant counterpart of the dentinogenic ghost cell tumor and the calcifying cystic odontogenic tumor, which is the solid and cystic variant of the lesion formerly known as the calcifying odontogenic cyst (Gorlin's cyst).[36] Ghost cell odontogenic carcinoma affects a wide age range, with a peak in the fourth and fifth decades, is more common in males (male:female ratio of 2.6:1), and in the maxilla (maxilla:mandible ratio of 2:1).[35] Clinical symptoms are similar to other IOCJs (pain, swelling, paresthesia, loose teeth), but on imaging, the poorly demarcated radiolucency is mixed with radiopacities.[35,37]

The pathogenesis is incompletely understood. Most commonly, the lesion presents de novo, but it may follow recurrence of a benign calcifying cystic odontogenic tumor, dentinogenic ghost cell tumor, or possibly, ameloblastoma or any other odontogenic tumor.[36] It is a matter of dispute whether tumors with ghost cells following recurrences of "ameloblastoma" are ghost cell odontogenic carcinomas or reflect appearance of a ghost-cell phenotype in an AC.

The definition of ghost cell odontogenic carcinoma is reflected in the histology. Pleomorphic, mitotically active cells that tend to be small and basaloid and arranged as nests, strands, and islands without obvious palisading, are intermingled with the distinctive diagnostic ghost cells. The latter may show dystrophic calcification or are associated with dentinoid material.[36] Necrosis is a frequent finding[38] and as well as infiltration of cancellous bone and marrow spaces, ghost cell odontogenic carcinoma may destroy cortical bone and invade surrounding connective tissue and muscle.

We feel that a diagnosis of ghost cell odontogenic carcinoma is straightforward when features of infiltrative growth, obvious cytologic malignancy, and abundant ghost cells are evident. In these cases, special studies might be unnecessary. It has, however, been suggested that IHC evaluation of cell proliferation and matrix metalloproteinase-9 protein in tumor parenchyma and stroma, respectively, could be helpful while assessing recurrent ghost-cell lesions because increased expression of these markers may indicate malignant transformation.[39,40] Difficulties may arise when only occasional ghost cells are present in an IOCJ and, depending on the pathologist, the tumor may be classified as ghost cell odontogenic carcinoma or AC with ghost cells (see earlier text). On these grounds, it is tempting to speculate that odontogenic carcinomas are part of a continuum rather than distinct entities. This has to be judged against site differences between AC and ghost cell odontogenic carcinoma (mandible vs maxilla, respectively).

Radical surgery combined with radiation therapy has been recommended but may be followed by local recurrence and/or metastases may occur in up to 50% of cases.[35,37,41-44]

Sclerosing odontogenic carcinoma

Sclerosing odontogenic carcinoma was proposed as a distinct entity in 2008 when 3 cases of apparent odontogenic carcinoma characterized by small nests and thin cords of small, cuboidal, and polygonal epithelial cells supported by a markedly sclerotic stroma were described.[45] The tumors appeared cytologically bland but showed extensive local infiltration of muscle and nerves and microscopic involvement of surgical margins that had been clinically judged to be free during surgery. Immunohistochemically, the tumor cells show positive cytoplasmic staining for CK5/6 and CK19, and e-cadherin; and positive nuclear staining for p63. Staining for CK20, carcinoembryonic antigen, and CAM5.2 are negative. Sclerosing odontogenic carcinoma has also been reported to be admixed with a benign fibro-osseous lesion of the mandible.[46]

We feel that caution should be exerted before endorsing "sclerosing odontogenic carcinoma" as a distinct entity. Further phenotypical characterization is desirable and, ideally, distinct criteria should be established to justify a unique classification. A wide variety of tumors show a sclerotic stroma, and the feature is regarded as a histologic variant, rather than indicating a unique tumor type. The designation "sclerosing odontogenic carcinoma" could be used as a descriptive term for an odontogenic carcinoma showing a sclerotic stroma.

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