

# Malignant Odontogenic Tumors: An Update on Selected Tumors

Mary S. Richardson · Susan Muller

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**Abstract** This is an update on selected odontogenic malignancies. The article deals with aspects of recognized odontogenic carcinomas, odontogenic sarcoma and a yet unrecognized entity, sclerosing odontogenic carcinoma. Odontogenic malignancies are exceedingly rare, complicating a thorough understanding of the biologic behavior, reproducible standardized diagnostic criteria, appropriate classification and clinical management. Without the knowledge of the tumor's biologic behavior, adequate clinical management is difficult and patient outcomes uncertain. The histopathologic features are emphasized as well as the more recent biomarker findings. These recent advances may facilitate further understanding of this group of malignancies and provide useful stratification to guide patient management.

**Keywords** Odontogenic malignancies · Odontogenic carcinoma · Jaws · Molecular markers

## Introduction

Odontogenic neoplasms derive from epithelial and mesenchymal remnants of the tooth germ that are classified into benign and malignant tumors [1]. The malignant odontogenic neoplasms are extremely challenging to study due to their rarity and complexity of their classification (Table 1). Most of what we know regarding these

malignant neoplasms is acquired from either case reports or small case series. The limited number of cases complicates establishing standardized diagnostic criteria and tumor clinical characterization [2–4]. Despite advances in molecular investigations, with the rare exception, the diagnosis is based primarily on a constellation of histopathologic features. It must be recognized that a diagnosis of primary odontogenic malignancy is rendered only after appropriate clinical and imaging workups fail to detect a primary tumor at another site [3]. The purpose of this article is to provide an update of selected malignant odontogenic tumors, but is not intended as a comprehensive review of the individual entities.

## Metastasizing Ameloblastoma

By definition, metastasizing ameloblastoma (MetAm) is the term used for a cytologically benign ameloblastoma (AB) that metastasizes but maintains the characteristic benign cytologic features of the parent tumor [1]. A combined review of the literature and clinicopathological investigation reported the metastasis is most often a late occurrence (18 years average time) after treatment of the primary jaw tumor [5]. Ameloblastomas (AB) are 1 % of all tumors found in the oral cavity [6], while metastatic ameloblastoma (MetAm) is estimated to occur in <2 % of AB [7]. The MetAm displays similar clinical behavior to the ameloblastoma, namely indolent but persistent growth. The metastasis usually follows multiple local recurrences of the parent tumor and possible routes include hematogenous, lymphatic, aerogenous, or passive transplant secondary to surgical manipulation [2, 5]. Some have postulated adequate primary resection of the parent tumor may decrease the incidence of MetAm [7, 8].

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M. S. Richardson (✉)  
Department of Pathology and Laboratory Medicine, Medical  
University of South Carolina, 165 Ashley Ave, EH 303D4,  
Charleston, SC 29425, USA  
e-mail: richardm@muscc.edu

S. Muller  
Emory University School of Medicine, Atlanta, GA, USA

**Table 1** WHO histological classification of odontogenic tumours [1]*Malignant tumours*

## Odontogenic carcinomas

- Metastasizing (malignant) ameloblastoma
- Ameloblastoma carcinoma—primary type
- Ameloblastoma carcinoma—secondary type (dedifferentiated), intraosseous
- Ameloblastoma carcinoma—secondary type (dedifferentiated), peripheral
- Primary intraosseous squamous cell carcinoma—solid type
- Primary intraosseous squamous cell carcinoma derived from keratocystic odontogenic tumour
- Primary intraosseous squamous cell carcinoma derived from odontogenic cysts
- Clear cell odontogenic carcinoma
- Ghost cell odontogenic carcinoma

## Odontogenic sarcomas

- Ameloblastic fibrosarcoma
- Ameloblastic fibrodentino- and fibro-odontosarcoma

The most common site of MetAm metastasis is the lung (78 %). The majority of pulmonary metastasis is bilateral (71 %) with involvement of bronchial spaces and/or pulmonary parenchyma [5]. A few reported patients with pulmonary deposits have developed a tumor-associated hypercalcemia [9]. The reported median survival times after metastasis range between 3 months and 5 years, although the longest survival reported is 37 years without treatment for the pulmonary lesions [5–7]. Less frequently, cervical lymph node metastases have been reported [5, 6, 9–11]. Others reported unusual rare sites of metastasis including vertebrae, skull, small bowel, brain, kidneys and heart [6, 8, 10]. The potential to metastasize has not

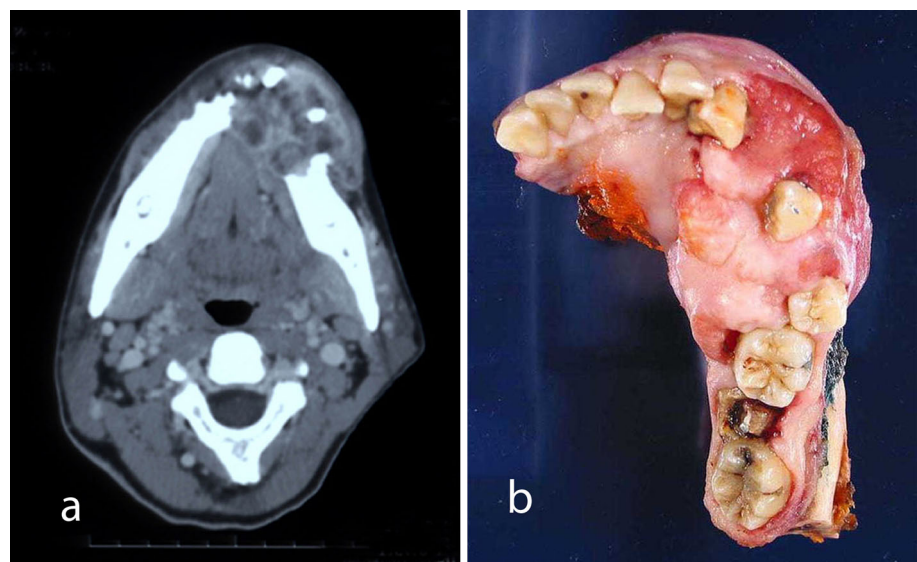
correlated with histologic subtype or pattern [5] while the molecular signature of ameloblastoma that leads to metastasis is still unclear [12, 13]. The exact events in the metastasis cascade of MetAm are elusive.

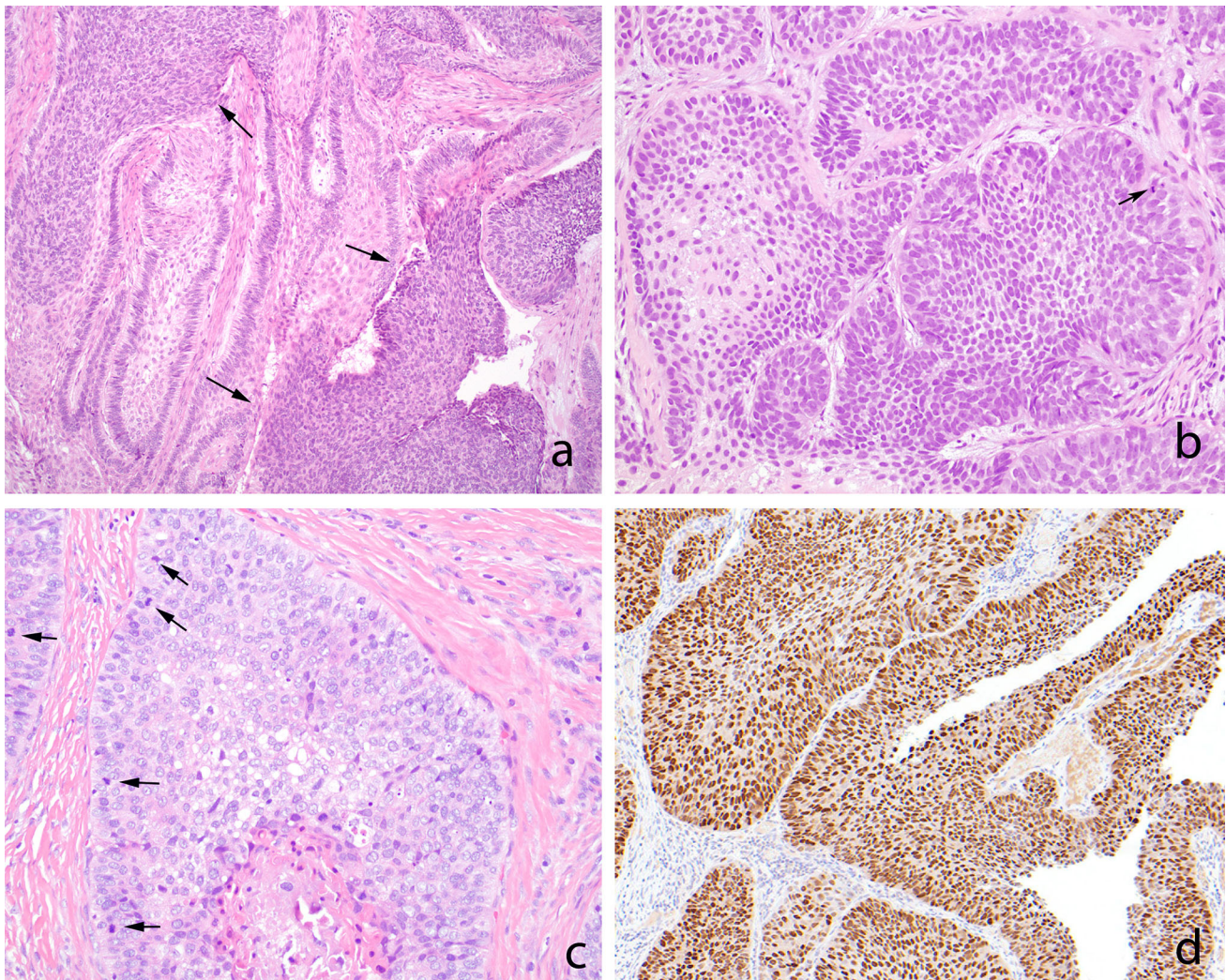
**Ameloblastic Carcinoma**

The term ameloblastic carcinoma (AC) refers to a malignant odontogenic neoplasm with histologic features of ameloblastoma with overtly malignant cytologic features, regardless of the presence or absence of metastasis [1]. Features of malignancy would include nuclear pleomorphism, readily identified mitotic activity (2 mitoses in a high power field in a high grade area), focal necrosis and nuclear hyperchromasia [14]. AC is rare with <100 cases in the literature [2, 14, 15]. The demographics of AC are similar to ameloblastoma, located most often in the posterior mandible and both genders affected equally, but AC is primarily seen in the elderly. The imaging and radiographic findings show an ill-defined radiolucency, often with cortical bone perforation (Fig. 1).

The majority of AC appears to develop de novo, but rare cases develop in pre-existing AB (secondary) [2, 14]. The carcinoma grows in the architectural arrangement of sheets, islands, or trabecular epithelium. The cells range from round, spindled to tall columnar with notable pleomorphism. Although ameloblastic differentiation may be focal or subtle, areas of peripheral palisading and “reverse nuclear polarization” away from the basement membrane are seen. In contrast, cytologically malignant epithelial odontogenic tumors are seen without sufficient differentiation to subclassify as AC; objective established criteria for the minimal degree required to separate odontogenic

**Fig. 1** Ameloblastic carcinoma: **a** X-ray computed tomographic axial image of the mandible demonstrating a large destructive multilocular lesion of the right anterior mandible. **b** Gross image of the resected specimen





**Fig. 2** **a** Malignant transformation of ameloblastoma to ameloblastic carcinoma (*arrows*). There is increased cellularity and loss of reverse polarity. **b** Ameloblastic carcinoma exhibiting cellular pleomorphism, hypercellularity and mitoses (*arrow*). Focally reverse polarity can be

identified. **c** High power microscopic image show numerous mitoses (*arrows*) along with central necrosis. **d** SOX2 immunopositivity in ameloblastic carcinoma (*image courtesy of Dr. Y. Leo Lei*)

carcinoma from AC are not available. Peri/endoneural and vascular invasion support a diagnosis of AC. Necrosis is frequently present (Fig. 2). No single feature is by itself a determinant of malignancy. Thus, AB with a limited atypia or intermediate grade cytologic features are often designated as “atypical ameloblastoma” (AA), posing a challenge to stratify from AC so the patient is rendered the appropriate therapy.

Aneuploidy is more common in AC and is considered a strong predictor of malignant potential [16]. One study reported a high frequency of allele loss in ameloblastic tumors, however, no significant difference between benign and malignant tumors was found to aid in stratification [13].

More recently a study explored using SOX2 (sex determining region-Y-related high mobility group box2) immunohistochemical nuclear staining as a marker to

identify areas in high-grade transformation in ameloblastic neoplasms [17]. The investigators used a scoring system with two parameters, percent of nuclei staining and intensity of staining. They found diffuse nuclear staining to be a sensitive (76.9 %) and specific (86.4 %) marker of high-grade transformation in AC. Prior to this study the proliferative marker Ki-67 has been found to be markedly higher in AC than AB. The investigators concluded that use of SOX2 in conjunction with Ki-67 would aid in separating AC from AB and AA [17] (Fig. 2).

### Clear Cell Odontogenic Carcinoma

Clear cell odontogenic carcinoma (CCOC) an unusual malignant tumor of putative odontogenic origin (postulated

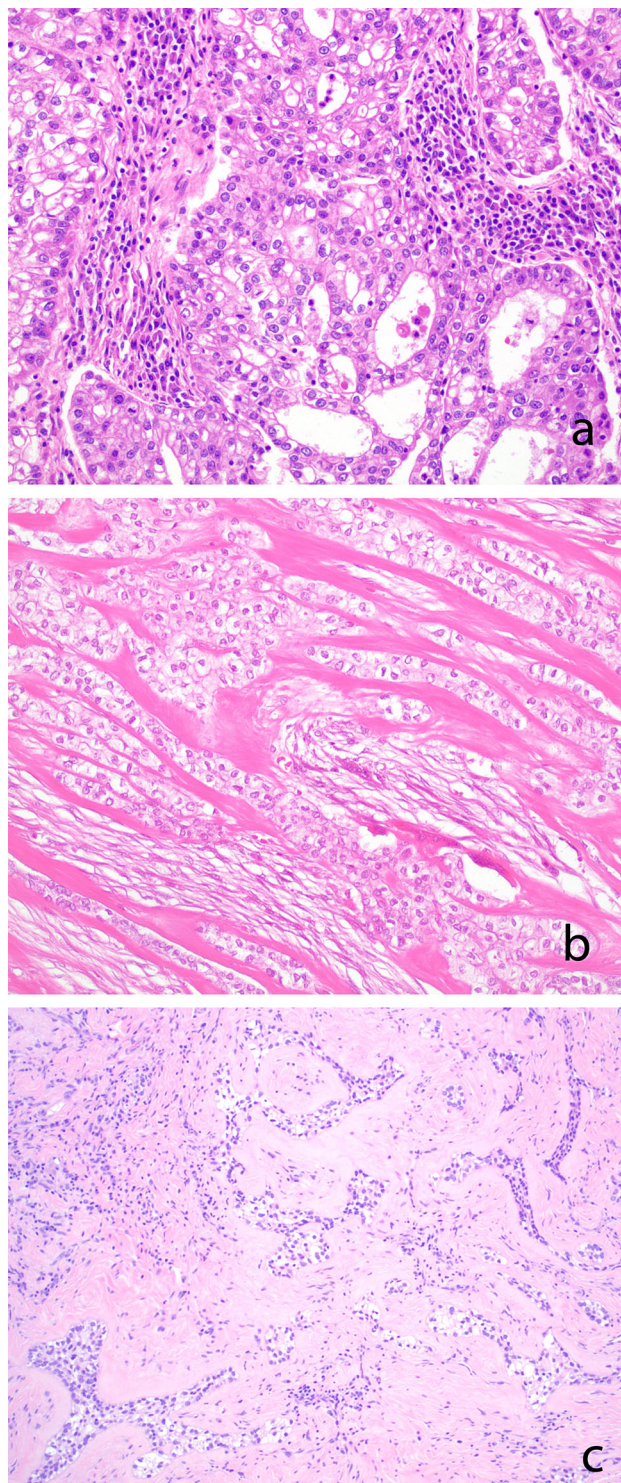
to be from dental lamina) is considered a distinct entity [1]. Currently there are approximately 74 reported cases in the English literature [18, 19]. Hansen originally described it in 1985 as a benign but aggressive lesion, centrally located in the jaws, under the guise of clear cell odontogenic tumor [20]. Subsequent case reports and small series included additional clinical follow-up that documented the capacity of this neoplasm for local destructive growth with invasion of medullary bone, nerves, lymphatics, as well as regional lymph node and distant metastases (pulmonary, bone) [21–23]. The World Health Organization reclassified the tumor in 2005 as an odontogenic carcinoma (Table 1).

The neoplasm affects patients of a wide age range but most often is seen in the sixth decade. There is a preponderance of female patients and CCOC is most often located in the mandible (84 %, mandible-to-maxilla 7:1) [24]. Establishing this tumor as a primary carcinoma, however, requires the exclusion of more common clear cell lesions in the jaws (metastatic carcinoma, salivary gland tumors and other odontogenic lesions).

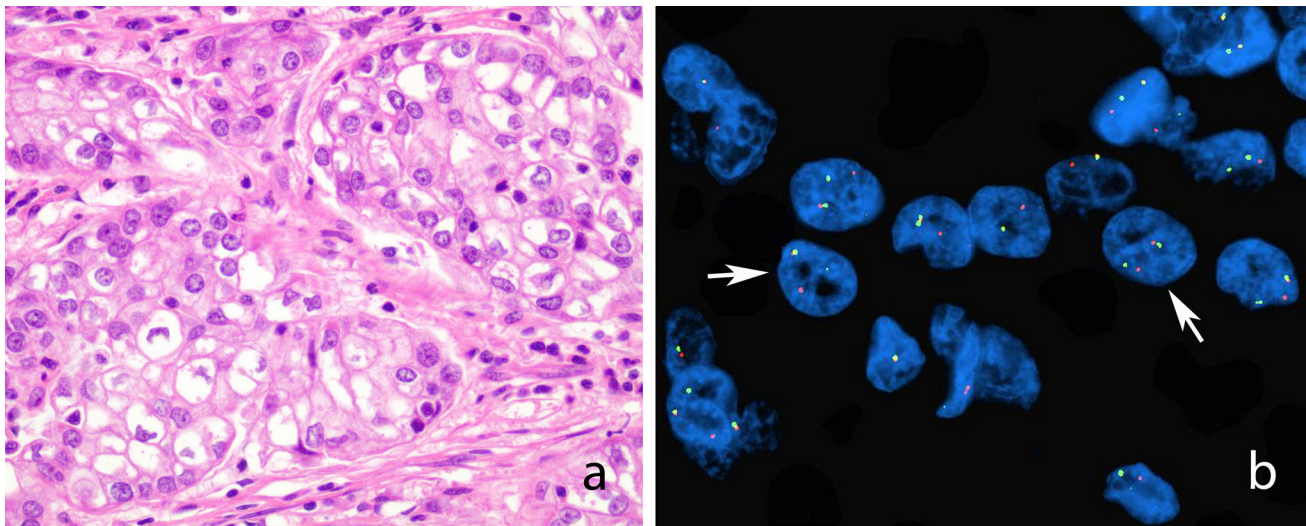
The histomorphology of the perimeter of the tumor is infiltrative which may explain the frequent radiographic appearance of a poorly delineated radiolucency [2]. Three histomorphologic growth patterns of this carcinoma are described. One pattern shows a biphasic pattern with oval and linear nests of clear cells with a peripheral rim of hyperchromatic polygonal cells with cytoplasmic eosinophilia. Another pattern is monomorphic, comprised entirely of nests and islands of only clear cells. The third, and least common, is an ameloblastomatous pattern with clear cells arranged in islands with peripheral palisading columnar cells with vague reverse polarization of the nuclei. In all patterns, the epithelial islands and nests are embedded within a heavily hyalinized to fibrocellular stroma. Stromal amyloid is not detected [25] (Fig. 3).

Many of the early surgical treatments for this particular neoplasm took the form of a curettage or enucleation. A review of the literature found consistently higher local recurrent rates for curettage/enucleation (80 %) than for resection alone (43 %) [24]. Long-term follow up is necessary for these patients since metastases can occur years later after primary resection. Patients who died of the tumor developed distant metastases [23].

The immunohistochemical profile of CCOC is positive for cytokeratins (AE1/AE3, CK19), p63, epithelial membrane antigen (EMA), while negative for CK-7, S-100 protein, smooth muscle actin, calponin, human melanoma antigen (HMB45), glial fibrillary acidic protein, and vimentin. The hyalinized stroma in CCOC is negative for



**Fig. 3** Clear cell odontogenic carcinoma showing a variety of histologic patterns: **a** ameloblastomatous pattern with islands of clear cells with peripheral palisading columnar cells; **b** sheets of clear cells with collagenized stroma; **c** nests and cords of clear cells surrounded by sclerotic stroma



**Fig. 4** **a** High power image of clear cell odontogenic carcinoma illustrating the marked pleomorphism and eosinophilic cytoplasm. **b** Detection of *EWSR1* gene rearrangement using dual-color break-

apart fluorescent in situ hybridization (FISH) indicated by *split red* and *green* signals present in the cells (arrows) (image courtesy of Dr. Elizabeth Bilodeau)

Congo red reactivity. The immunoprofile certainly supports a squamous origin [25].

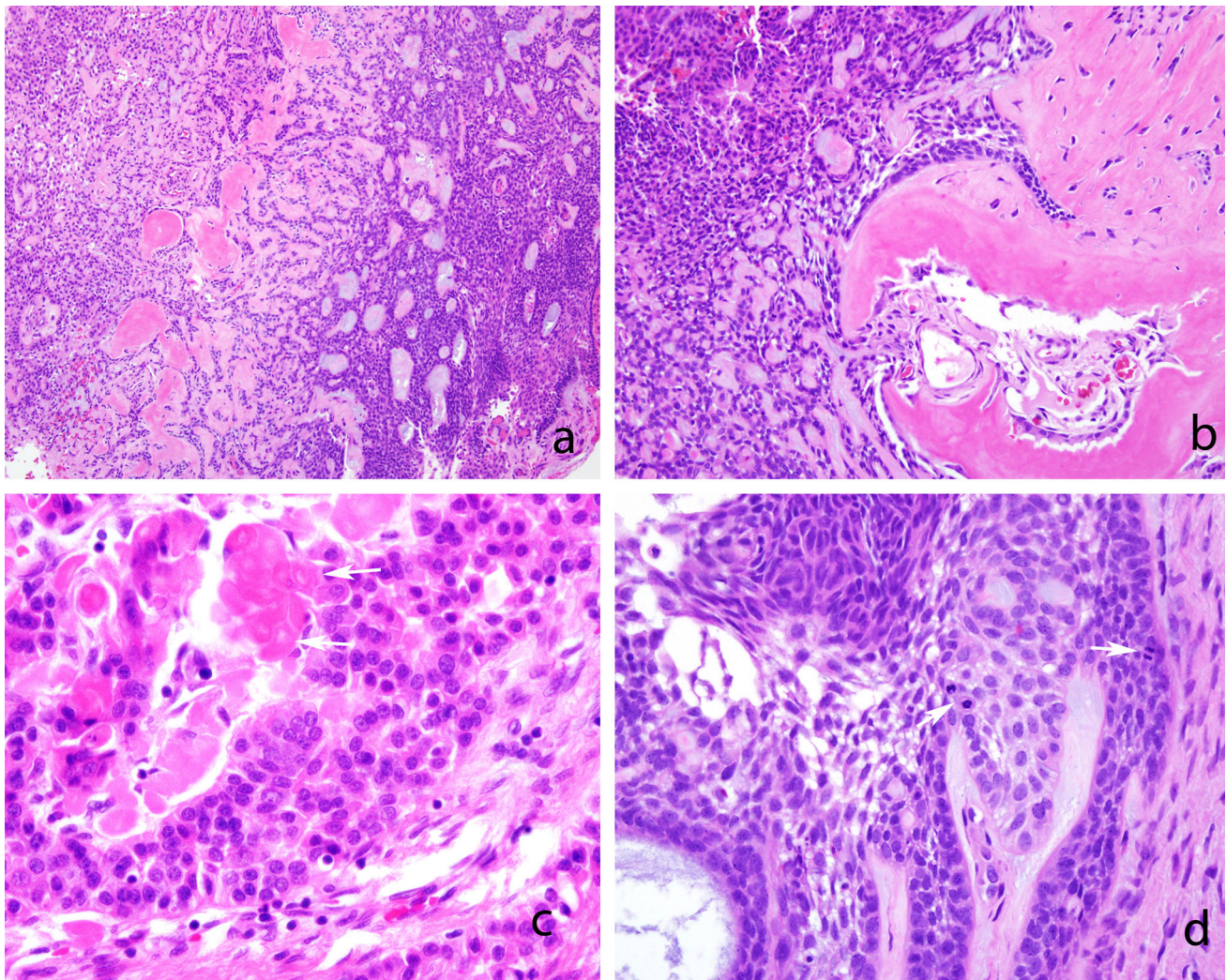
Included in the differential diagnosis of the carcinoma is hyalinizing clear cell carcinoma of salivary gland (HCCC). Most recently, a number of comparative studies of HCCC salivary origin and CCOC were undertaken in an effort to readily distinguish these two carcinomas. The difficulty in confidently separating these two entities to resolve a differential diagnosis of clear cell carcinoma in the gnathic area has become apparent [25]. Overlap of clinicopathologic features, tumor growth patterns, cytomorphologic features as well as immunophenotypic profile is now documented. This juxtaposition of features strongly suggests that distinction may not be possible [25]. Only two items allowed separation, location and peripheral palisading within epithelial islands, a feature seen in only about half of the CCOC cases [25]. Interestingly, this later feature in an earlier case report of HCCC in the jaws stated the absence of peripheral palisading was the reason for classifying their tumor as HCCC [26]. A follow-up study to the immunophenotype study documented a biological molecular link between CCOC and HCCC of salivary origin. Recently it has been recognized that HCCC has a *EWSR1-ATF1* translocation [27] (Fig. 4). In a study of CCOC and HCCC using molecular testing by FISH, several cases of CCOC had *EWSR1* rearrangement and one case tested, did have the *EWSR1-ATF1* translocation [28]. Now a subset of the CCOC is identified that harbors the *EWSR1-ATF1* translocation, thus demonstrating also a molecular overlap between HCCC and CCOC. The frequency of *EWSR1* rearrangement was 83 % [28]. Whether CCOC represents a central form of HCCC is speculative but plausible [28].

Others contend CCOC can be considered an odontogenic analog of HCCC [29].

### Ghost Cell Odontogenic Carcinoma

Ghost cell odontogenic carcinoma (GCOC) is an uncommon malignant epithelial odontogenic neoplasm. It is defined by the WHO as an odontogenic carcinoma with features of calcifying cystic odontogenic tumor (CCOT) and/or dentinogenic ghost cell tumor (DGCT) [1]. These tumors represent a heterogeneous group with variable clinical and radiologic presentations as well as variable histopathologic features [30]. The initial description of this tumor was in 1985 [31]. Since the WHO 2005 classification, another fourteen cases have been added to the literature [32]. GCOC affects a wide age range with a peak in fourth and fifth decades, more common in males (male:female 4:1) and maxilla is the common location (maxilla:mandible 2:1). The reported cases suggest this tumor may be most common within Asians [32]. Clinical presentation is similar to other carcinomas in this site (loose teeth, pain swelling, paraesthesia). Radiographically this lesion is a poorly defined radiolucency with mixed radio opacities.

The name GCOC reflects the histomorphology with identification of malignant rounded epithelial islands with mitoses readily identified. Ghost cells show aberrant keratinization where the eosinophilic cytoplasmic cell borders remain and only a faint outline of the nucleus remains (Fig. 5). The presence of ghost cells may vary in amount, sometimes requiring extensive examination of tumor



**Fig. 5** **a** Low power image of ghost cell odontogenic carcinoma. Eosinophilic dentinoid material is seen in the central field surrounded by a proliferation of hyperchromatic epithelial cells with a superficial resemblance to ameloblastoma. **b** Dentinoid material adjacent to the

epithelial component. **c** Proliferation of ghost cells (*arrows*). **d** Hyperchromatic and pleomorphic ameloblastoma-like epithelial cells with mitoses (*arrows*)

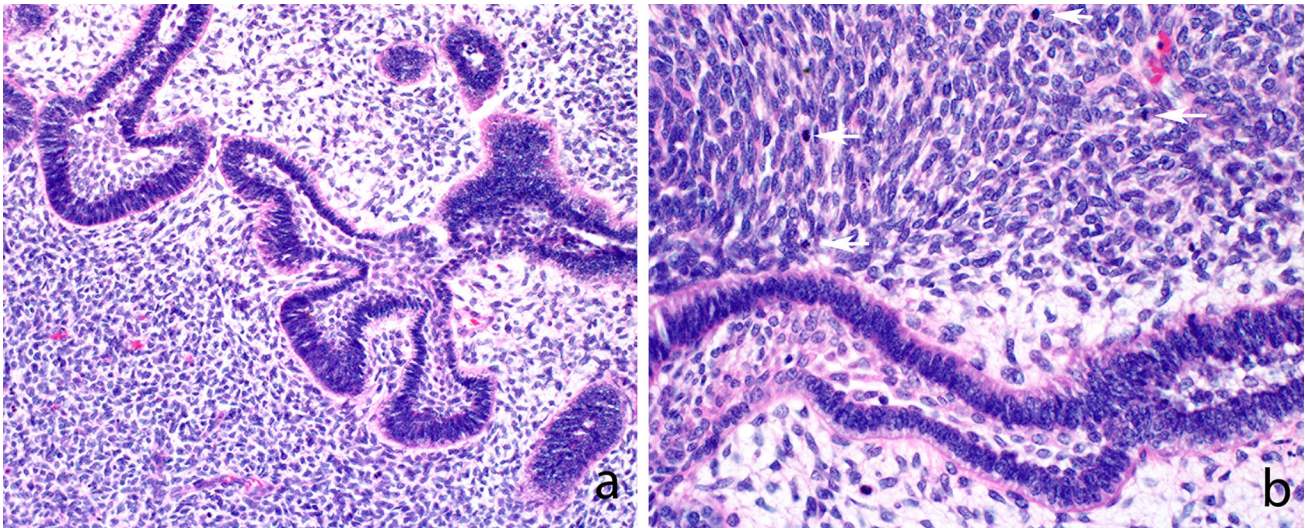
samples. Dysplastic dentin may be present reflect. Necrosis is usually present. Osseous destruction with permeation into adjacent tissue is often seen [33].

Four proposed mechanisms explain the histogenesis of odontogenic carcinoma. First, GCOC arises secondary to a benign calcifying cystic odontogenic tumor (CCOT). Second, GCOC arises from a dentinogenic ghost cell tumor (DGCT) or arises from any other odontogenic cyst. Lastly, it arises *de novo* [4, 32]. This latter mechanism accounts for 40 % of the reported cases of GCOC [32]. The *de novo* sequence, however, may include cases where an undiagnosed primary lesion was replaced by GCOC [32].

Diagnostic criteria have been established in GCOC but there is a wide spectrum of solid and cystic growth patterns, histologic diversity and variable biologic behavior, indolent or locally aggressive [34]. A number of studies have looked at

proliferative markers (Ki-67), syndecan-1 in tumor cells and matrix metalloproteinase (MMP-9) expression in adjacent stroma to aid in assessing recurrent tumors in malignant transformation, with limited success [34, 35]. Discriminating GCOC from benign calcifying odontogenic cyst may be difficult. Some reports have noted stromal MMP-9 staining and Ki-67 index (>20 %) to be significantly stronger in GCOC, indicating a proliferative activity associated with malignancy [32]. The nucleated cells next to the ghost cells in GCOC stained for cytokeratins, involucrin and BCL-2 associated X protein (BAX) suggesting some role in the osteolytic process [32, 34]. These studies are not conclusive at this time.

Surgical management of this carcinoma remains extensive resection with clear surgical margins (0.5 cm). The 5-year survival rate is 73 % [34]. Local, regional, and distant metastases are rare [36].



**Fig. 6** **a** Ameloblastic fibrosarcoma demonstrating a biphasic growth pattern. Benign odontogenic islands and cords of cuboidal to columnar epithelium surrounded by stroma showing increased

cellularity. **b** The malignant stroma shows pleomorphism, hyperchromasia and mitoses (arrows) (images courtesy of Dr. Angela Chi)

### Ameloblastic Fibrosarcoma (AFS)

Ameloblastic fibrosarcoma is a rare biphasic odontogenic sarcoma composed of a benign epithelial component intermingled within a hypercellular malignant mesenchymal stroma [1]. Other entities, such as ameloblastic fibrodentinosa sarcoma or fibro odontosarcoma, are included in the odontogenic sarcoma category and have, in addition to the above, dentin or enamel tissues present. Ameloblastic fibrosarcoma is considered the malignant counterpart of ameloblastic fibroma [1, 37].

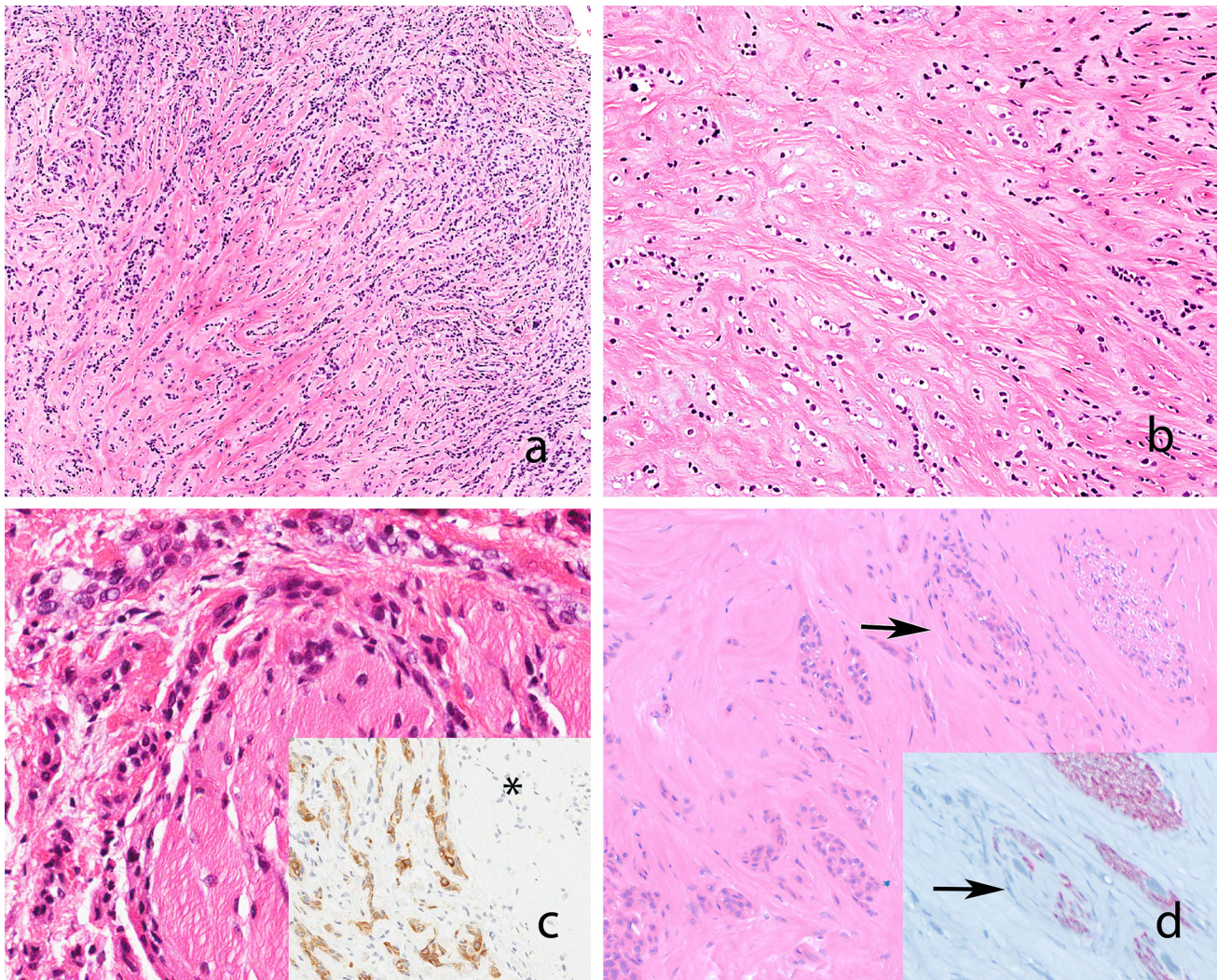
The mean age at presentation for reported cases of AFS is 27 years and the mandible is the most common site. The clinical presentation is often because of a painful facial mass. On imaging, the tumor is a destructive expansile radiolucent jaw mass with ill-defined borders. Interestingly, about half of these tumors arise in a recurrence of a previous AF and the mean age of AF is about 10 years younger (14.6 years) than for AFS [37–39]. AFS is considered a locally aggressive neoplasm with a low incidence of metastasis (4 %). In the reported cases the recurrence rate for this tumor is 37 % and the mortality rate 19 % [39].

On gross examination the tumor is cystic or solid. Histopathologic features are admixed sarcomatous mesenchyme and benign ameloblastic epithelial component. The epithelium in AFS is composed of anastomosing strands and cords of branched benign odontogenic epithelium, frequently showing peripheral palisading that resembles the developing enamel organ (Fig. 6). The malignant mesenchymal cells vary from hyperchromatic spindle to stellate with notable mitotic activity. The sarcomatous element is usually positive for BCL2, p53 protein, with a

high proliferative index for Ki-67 [40]. At this time no molecular marker is available to aid in identifying those AF prone to malignant transformation as AFS.

### Sclerosing Odontogenic Carcinoma

This tumor was described after the current 2005 WHO classification of odontogenic carcinomas (Table 1). In 2008, Koultas et al. [41] proposed as a distinct entity “sclerosing odontogenic carcinoma”. The initial report contains three cases, each neoplasm presenting as an expansile intragnathic mass that radiographically was an ill-defined radiolucency [41]. The tumor cells are characterized by infiltrating “single file” thin cords and strands of polyhedral epithelial cells. The cytologically bland cells showed infrequent mitotic activity and rare areas of epithelial cells containing large cytoplasmic vacuoles. Cords and strand of cells streaming within a stroma of dense sclerosis is the hallmark of SOC (Fig. 7). The authors described the cords of cells as “reminiscent of odontogenic rests”. Although the cytologic features appeared bland, the tumor showed extensive local infiltrative growth into muscle and nerves. Necrosis was not a feature. All patients in the initial series were treated with extensive surgery, and in one instance adjuvant radiation therapy. None of these patients have had a recurrence (3.6, 5, 12 years. follow-up) and none of the patients developed metastasis. The lack of metastasis was problematic for the classification as a malignant tumor [41]. The immunohistochemical profile of the tumor cells shows positive cytokeratin markers (CK5/6, CK19, weak staining CK7), membranous staining for



**Fig. 7** **a, b** Low and high power images of sclerosing odontogenic carcinoma illustrating a tumor infiltrating in single file composed of thin cords and strands. The cells are cytologically bland and are surrounded by dense sclerotic stroma (images courtesy of Dr. Fredrik Petersson). **c** Sclerosing odontogenic carcinoma infiltrating muscle.

The tumor cells are positive for CK19 by immunohistochemistry highlighting the muscle (\*) infiltration (inset) (images courtesy of Dr. Ioannis Koulas). **d** High power image shows perineural invasion (arrow) highlighted by S100 immunohistochemistry (inset) (images courtesy of Dr. Elizabeth Bilodeau)

E-cadherin and nuclear p63 staining. The tumor cells are negative for CK20, carcinoembryonic antigen (CEA) and CAM 5.2 [41, 42].

As noted by the original authors, additional case and series reports are needed to study the biology of this tumor process. There are now seven reported cases in the literature [41–45]. Six of the seven cases have been associated with perineural infiltration [42]. Five of the seven cases were initially treated with resection [41, 43, 44]. In one case the tumor was associated with a benign fibro-osseous lesion and initially treated with curettage. This patient had a recurrence 8 months later comprised of the epithelial neoplasm and underwent resection [45]. The most recent patient was treated with enucleation only and has had no recurrence in 12 months [42]. No case at this time has

reported lymph node involvement or distant metastasis. Other primary tumors of the maxillofacial region enter the differential diagnosis for SOC after metastases have been excluded, calcifying epithelial odontogenic tumor (CEOT), desmoplastic ameloblastoma, CCOC and epithelial-rich variant of central odontogenic fibroma (ERCOF) [41, 42]. In a recent case, rearrangement for *EWSR1* was tested for exclusion of CCOC and no re-arrangement was found [42]. Another yet unreported case has also been assessed for *EWSR1* rearrangement and is negative (unpublished data, personal communication Dr. Bilodeau).

Pathologists need to be aware of the features of “sclerosing odontogenic carcinoma”, however, due to our limited knowledge of the biologic behavior of SOC, this entity will require review for appropriate inclusion within the



next WHO classification of odontogenic tumors [1]. This neoplasm is a matter of international discussion as additional cases are needed to further its phenotypic characterization [2, 46, 47].

## Conclusion

In conclusion, the characterization of this group of malignancies will continue to evolve as additional cases are reported in detail. Our knowledge of application of molecular mechanisms and use of protein expressions to facilitate useful clinical stratification of and within these entities is just beginning. The addition of CCOC to the EWSR1 rearranged tumor spectrum leads that transition in tumors currently classified under odontogenic malignancies. The use of markers such as SOX-2 to identify routine benign tumors or atypical odontogenic tumors at risk for malignant transformation must continue. All of these applications will require studies to validate clinical utility. These molecular markers will have an impact on our classification schemes and potentially impact therapeutic decisions.

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