

## Fine Needle Aspiration Findings in Malignant Ameloblastoma: A Case Report and Differential Diagnosis

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*We present a case of malignant ameloblastoma presenting in the posterior mandible and cervical lymph nodes of an African American child. This case is somewhat unusual in that the patient was an adolescent and presented with metastatic disease. This partly clinical as well as cytologic diagnosis was facilitated by the presence of typical ameloblastoma cytology in multiple cervical lymph nodes adjacent to the histologically confirmed intraosseous ameloblastoma. Although cytology is helpful in diagnosing ameloblastoma, its features are by no means definitive as there are several cytologic mimics. A high index of suspicion is therefore necessary to confirm or exclude ameloblastoma when evaluating any jaw lesion and/or adjacent enlarged lymph nodes by cytologic examination. Adequate sampling is paramount to accurate diagnosis, and is especially important when attempting to distinguish ameloblastoma from ameloblastic carcinoma. Diagn. Cytopathol. 2009;37:586–591. © 2009 Wiley-Liss, Inc.*

**Key Words:** malignant ameloblastoma; fine needle aspiration

Ameloblastoma (AB) is defined as a benign, but locally aggressive epithelial odontogenic neoplasm arising in the jaw and having close resemblance to the enamel organ epithelium.<sup>1</sup> Although the most common odontogenic neoplasm, it accounts for only 1% of all jaw tumors. AB is slow growing and typically behaves in a benign fashion however, it is capable of local invasion and destruction. Tumors removed by curettage have a high tendency for recurrence.<sup>2</sup> The etiology of AB is still unknown but has

been linked to faulty regulation of the genes involved in tooth development.<sup>3</sup> On histology, AB contains epithelial islands that resemble the enamel organ. These islands consist of two principal, but distinct cell types; (1) the centrally located stellate-shaped cells, which resemble the stellate reticulum of the enamel organ in a developing tooth, and (2) the peripherally located ameloblast-like columnar cells, which exhibit peripheral palisading and reversed polarization of nuclei. Cellular pleomorphism, necrosis, and abnormal mitoses are not typical features of conventional AB.

Malignant or metastasizing AB (MAB) is extremely rare and accounts for fewer than 1% of ABs.<sup>1</sup> These tumors are histologically identical to conventional AB but are associated with metastasis.<sup>3</sup> The diagnosis of MAB is therefore a clinical one and is often made in hindsight, after the tumor has metastasized.<sup>4</sup> MAB should be distinguished from ameloblastic carcinoma (ABC) which is a true malignant neoplasm. ABC typically shows frankly malignant histologic features including nuclear pleomorphism, prominent nucleoli, abnormal mitoses, necrosis, and/or perineural invasion.<sup>1,4</sup>

We herein describe a case of MAB that presented in the posterior mandible of an African American child. This case is somewhat unusual in that the patient presented with metastatic disease involving adjacent submandibular lymph nodes, and had developed in an adolescent rather than an adult in whom it is more frequent. The diagnosis of malignant AB was based on histologic findings in the biopsy of the mandibular lesion and fine needle aspiration (FNA) findings in multiple enlarged cervical lymph nodes, both of which showed features consistent with AB.

### Case Reports

A 15-year-old African American male presented to an outside institution with a 1 month history of a non-tender,

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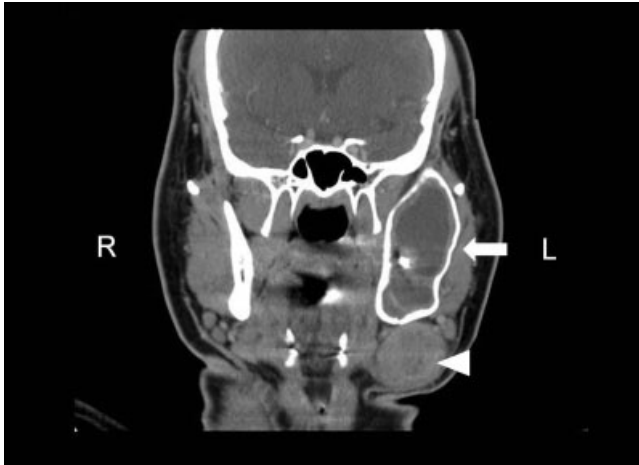
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**Fig. 1.** CT scan showing a 7 cm circumscribed unicystic lytic lesion involving the body, angle, and condyle of the mandible (see arrow). This was associated with enlarged submandibular cervical lymph nodes (arrow head).

slowly increasing, left facial swelling. On examination, a fixed, non-tender, expansile mass was identified in the left submandibular area. Oral examination revealed granular, erythematous mandibular gingival mucosa, in the region of the posterior mandibular molar teeth overlying the mass. The mandibular buccal and lingual plates were expanded, and the mandible was deviated to the right but there was no associated dysfunction or malocclusion. A computerized tomography (CT) scan revealed a  $7 \times 7 \times 3$  cm circumscribed, lytic lesion involving the mandibular body, angle, and condyle and coronoid processes (Fig. 1). This was associated with multiple enlarged left-sided levels I, II, and III cervical lymph nodes, ranging in size from 15 mm to 4.5 cm. The radiologic findings were felt to be consistent with an AB with likely metastatic disease to multiple cervical lymph nodes. An incisional biopsy of the mandibular mass was performed at an outside oral surgery clinic and was microscopically confirmed to be AB. The patient was then referred to the Medical College of Georgia for management. FNA was performed on two enlarged levels I and II cervical lymph nodes, and showed cytologic features consistent with metastatic AB. On the basis of the latter finding, a diagnosis of malignant AB was made. A left hemi-mandibulectomy and left cervical lymph node dissection were then performed.

### Materials and Methods

FNA was performed using 25-gauge needles and 10-ml syringes and material was collected as needle and syringe washes. Air-dried and alcohol-fixed smears were prepared and stained with the Diff-Quik (DQ), Papanicolaou (Pap), and hematoxylin and eosin (H&E) stains, respectively. Material was also submitted in phosphate buffered saline for cell block preparation, placed in 10% formalin, embedded in paraffin and stained with the H&E stain. On

examination of the surgical (resection) specimen, a well circumscribed partially cystic tumor was identified in the posterior region of the mandible. The tumor measured  $7 \times 7 \times 3$  cm and on sectioning showed a dense white cut surface with a large central cyst. Tissue sections were cut, fixed in 10% formalin, embedded in paraffin and cut 3–4 microns thick then stained with H&E.

### Cytologic Findings

The aspirates and cell blocks from both lymph nodes showed similar findings. Smears were hypercellular and composed of sheets, clusters, and singly disposed basaloid cells (Figs. C-1A and B). The basaloid cell clusters contained central loose spindled and stellate-shaped cells as well as peripherally arranged columnar cells with palisaded deeply-chromatic nuclei and clear cytoplasm (Fig. C-1C). These were morphologically consistent with ameloblast-like cells. Another interesting and striking low power finding was the arrangement of tumor cells in linear streams (Fig. C-1D). Cells had high nuclear to cytoplasmic ratios with oval to round, or spindled nuclei and scant pale cytoplasm (Fig. C-2A). Nuclear molding was also a prominent feature. Nuclei had fine powdery chromatin, small peripheral nucleoli (Fig. C-2B) and focal nuclear “holes”. There was minimal nuclear pleomorphism however, and rare mitotic figures were seen (Fig. C-2A). Occasional benign squamous cells, rosettes, and stromal fragments were also identified (Fig. C-2C). In addition, mature lymphocytes with standard maturation sequence and occasional lymphoglandular bodies were seen (Fig. C-2D). On low power, the lymphocytes were almost indistinguishable from the basaloid tumor cells. The cell block sections showed similar basaloid cells with high nuclear to cytoplasmic ratios, embedded in dense eosinophilic stroma (Fig. C-3A).

### Histologic Findings

The H and E-stained sections from the mandibular resection and biopsy specimens were composed of anastomosing islands and sheets of stellate and basaloid cells with a follicular and plexiform arrangement (Fig. C-3B). These were surrounded by dense fibrous stroma. The basaloid cells had high nuclear to cytoplasmic ratios with minimal atypia, while the more central stellate-shaped cells resembled the stellate reticulum in a developing tooth enamel organ (Fig. C-3C). Focal central squamous differentiation was also present. The peripheral ameloblast-like columnar cells had clear cytoplasm and elongated palisaded nuclei that were positioned away from the basement membrane (Fig. C-3C). The follicular arrangement of tumor cells closely resembled cellular aggregates within the cytologic smears (Fig. C-3D). There was no overt evidence of carcinoma. Left neck dissection revealed 2 of 45 positive lymph nodes.

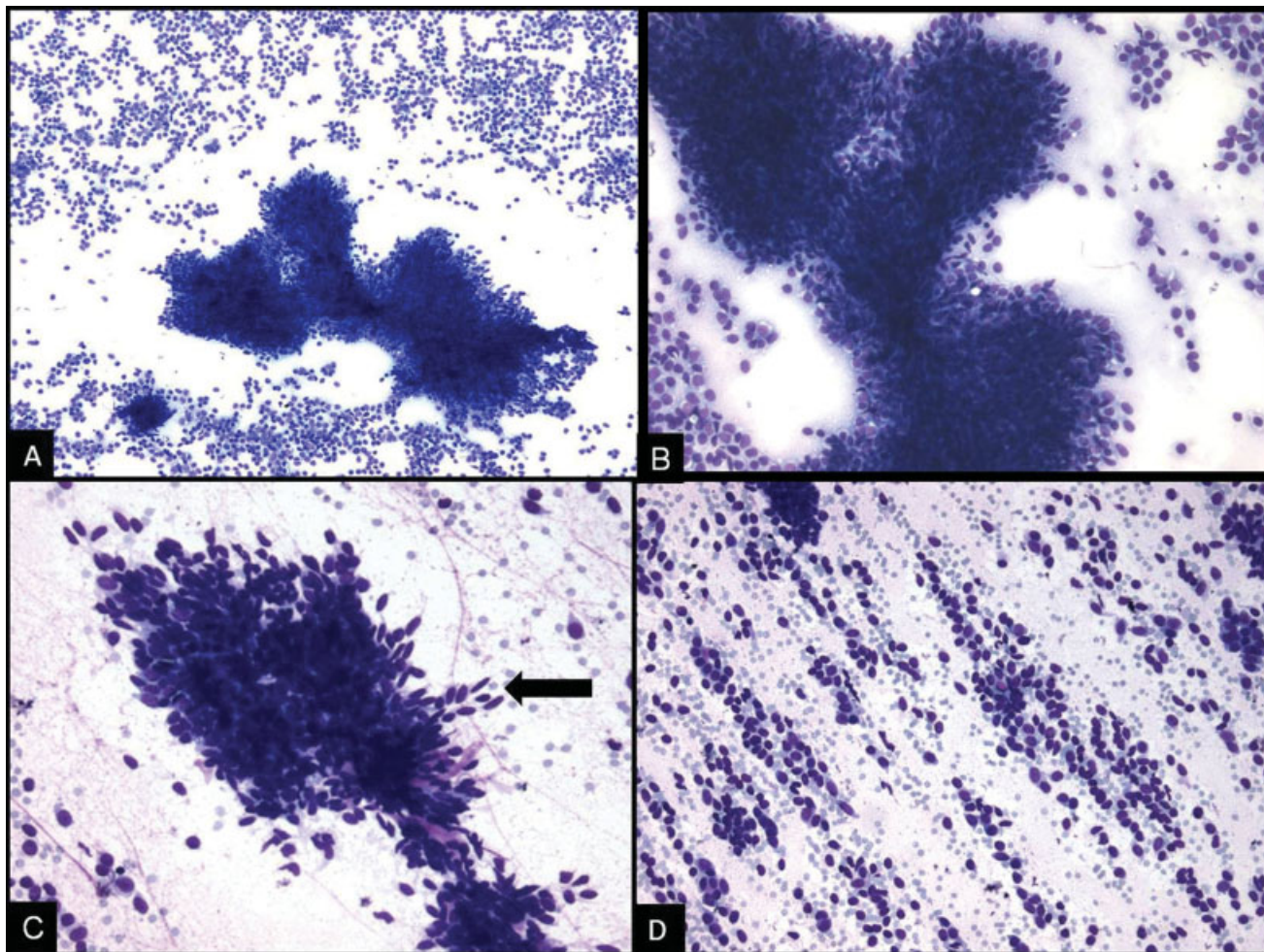


Fig. C-1

**Fig. C-1.** A. Hypercellular smear with clusters and singly disposed basaloid cells (DQ stain,  $\times 40$ ). B. Cluster of basaloid cells with central loose spindled stellate reticulum-like cells and focal peripherally palisading tumor cells (DQ stain,  $\times 100$ ). C. The elongated tumor cells which are present on the periphery of branching clusters (arrow) are consistent with ameloblasts (DQ stain,  $\times 200$ ). D. Smear showing linear streaming arrangement of single tumor cells (DQ stain,  $\times 200$ ).

## Discussion

AB is divided into two main types, the multicystic (MC AB) variant, which accounts for 80% of tumors and occurs in the mandible of adults<sup>5</sup> and the unicystic (UC AB) variant, which accounts for 10–15% and is more frequently observed in the posterior mandible of children and adolescents.<sup>1</sup> On X-Ray, MC AB has a multilocular “soap bubble” appearance,<sup>1</sup> whereas UC AB appears as a circumscribed unilocular “cyst-like” lucency, which often surrounds an unerupted tooth. The two most common histologic subtypes of AB are the follicular and plexiform variants. The follicular variant exhibits islands and sheets of stellate-shaped cells with central cyst formation. The plexiform subtype consists of anastomosing cords of stellate-shaped tumor cells with two to three layers of ameloblast-like cells peripherally. Various less frequent histologic subtypes are also described but these (as well

as the follicular and plexiform subtypes) have little clinical significance. The acanthomatous subtype of AB deserves special mention as in addition to its conventional AB histology it also exhibits extensive squamous differentiation and keratin formation, which may be mistaken for squamous cell carcinoma (SQCA).

Malignant or metastasizing AB is histologically identical to conventional AB but is associated with metastasis. The most common sites of metastasis include the lung and cervical lymph nodes.<sup>1</sup> In contrast, ABC has frankly malignant histology, and may also show areas of conventional AB.<sup>1,4</sup> ABC may arise de novo or as a transformation of conventional AB.<sup>5</sup> Most cases of MAB and ABC are diagnosed in adults and are aggressive tumors, with poor clinical outcome and 50% of patients documented in the literature have died of their disease.<sup>1</sup>

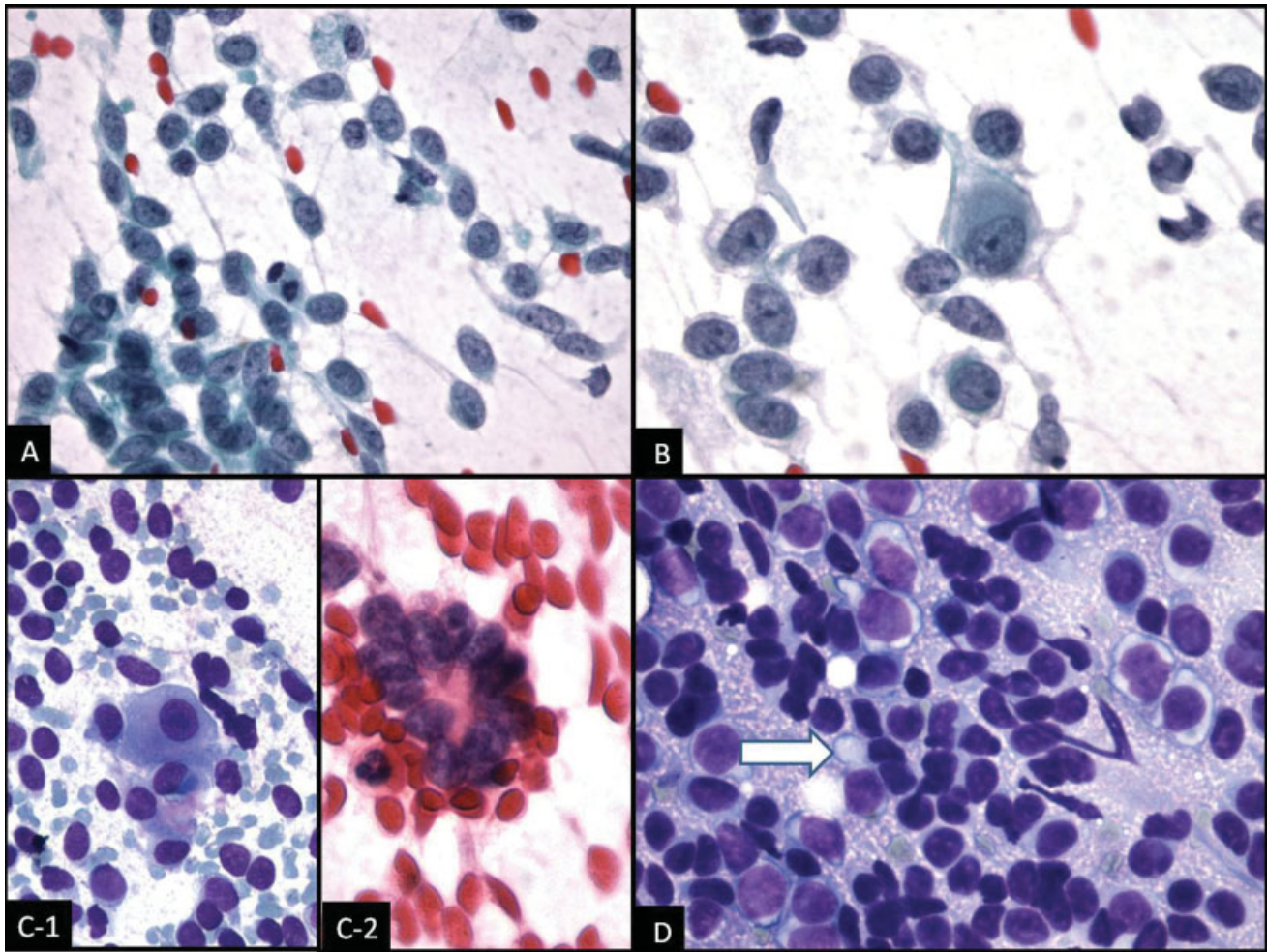


Fig. C-2

**Fig. C-2.** A. Smear showing tumor cells with high nuclear/cytoplasmic ratios, nuclear grooves, and focal nuclear molding. Columnar cells are present in the lower right and a single central mitotic figure is also present (Papanicolaou stain,  $\times 400$ ). B. Nuclei have fine powdery chromatin and small nucleoli. Note central benign squamous cell (Papanicolaou stain,  $\times 600$ ). C. Note centrally located benign squamous cell (C-1) (DQ stain,  $\times 200$ ) and rosette (C-2) (Hematoxylin and Eosin stain,  $\times 600$ ). D. DQ stain showing admixture of basaloid tumor cells, mature lymphocytes, and central lymphoglandular body (arrow) (DQ stain,  $\times 400$ ).

The cytologic diagnosis of conventional AB has been well documented in the literature.<sup>6-15</sup> In fact, Ucok et al. in their report of over 40 cases of AB found that preoperative FNA diagnosis of AB was not only possible but also an invaluable non-invasive tool for determining the need for, and type of, surgical management of these patients.<sup>14</sup> Despite its intraosseous location, AB is amenable to FNA, because the tumor often causes marked thinning of the overlying cortex. On cytology AB is characterized by (1) small basaloid cells with high nuclear to cytoplasmic ratios, minimal atypia, fine chromatin, variable nuclear molding, and spindling, (2) peripheral columnar-type cells with palisaded basophilic nuclei, and (3) benign squamous cells.<sup>11-13</sup> These squamous cells are more abundant in the acanthomatous variant of AB. Other less frequently reported cytologic findings include rosettes,

stromal fragments, and granular cells with abundant cytoplasm. The latter is seen in the granular cell variant of AB, which has also been definitively diagnosed on cytology.<sup>7</sup>

Although the cytology of conventional AB has been previously reported, only a handful of reports have described the cytologic features of malignant AB.<sup>10,15-17</sup> The first such report was by Levine et al. in 1981.<sup>10</sup> On cytology MAB is indistinguishable from conventional AB and unless identified in locations distant from the primary tumor cannot be classified as malignant on cytology alone. Because ABC shows frank malignant cytologic features, in addition to areas of conventional AB,<sup>4,5,18-20</sup> cytology alone can be used to distinguish this tumor from conventional AB and MAB. However, there are only isolated reports in the literature that describe the cytologic features of ABC.<sup>20,21</sup>

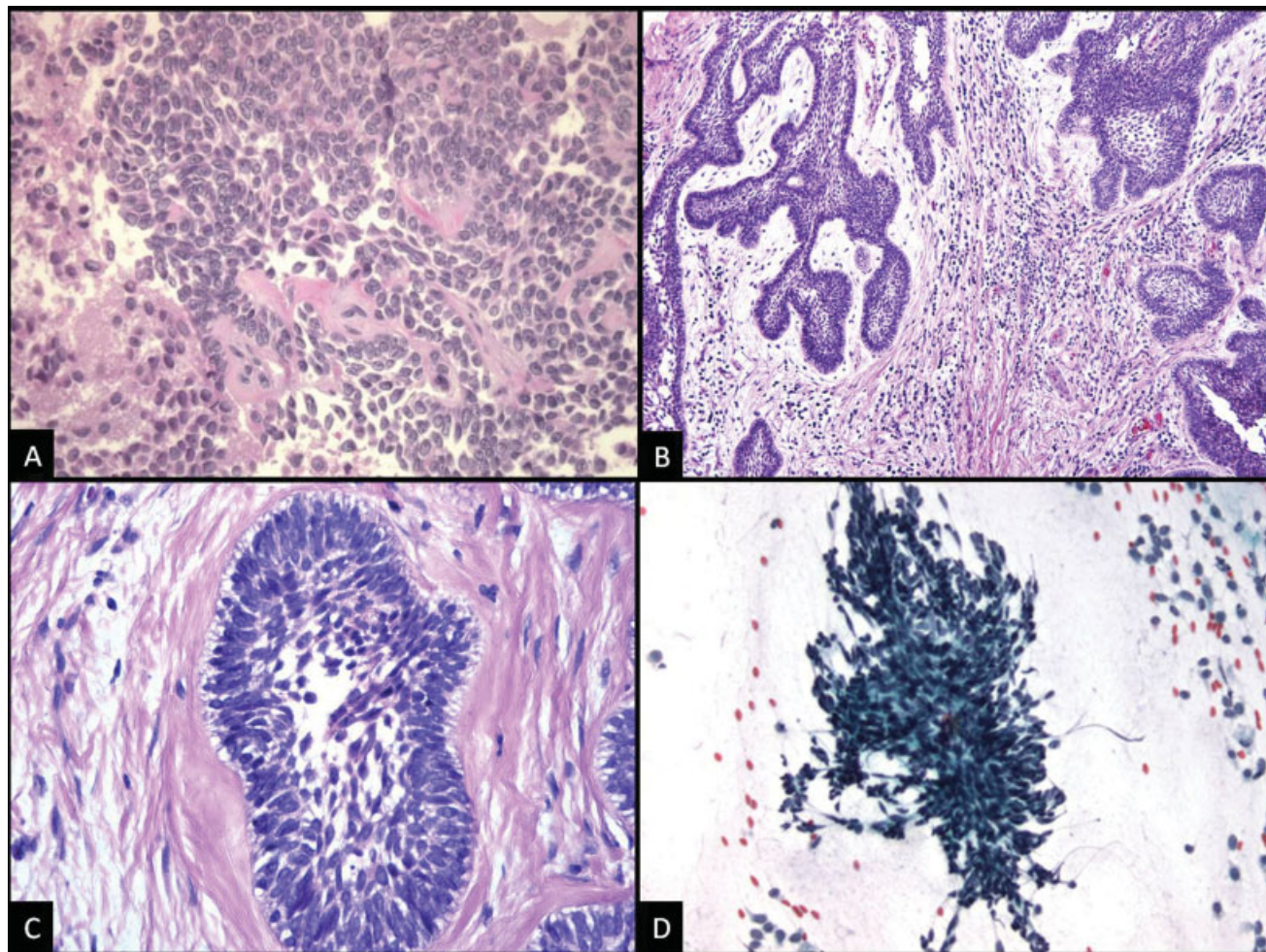


Fig. C-3

**Fig. C-3.** A. Cell block section showing basaloid tumor cells with surrounding dense stroma (Hematoxylin and Eosin stain,  $\times 400$ ). B. Tissue section from needle core biopsy of intraosseous tumor showing islands of tumor cells with both follicular and plexiform arrangement of cells (Hematoxylin and Eosin stain,  $\times 200$ ). C. Tissue section showing a cluster of tumor cells with central loosely arranged stellate reticulum and peripheral columnar ameloblasts (Hematoxylin and Eosin stain,  $\times 400$ ). D. Smear showing cluster of central spindled stellate reticulum and peripheral columnar ameloblasts (Papanicolaou stain,  $\times 200$ ).

Despite the obvious benefit of the preoperative FNA diagnosis of AB, MAB, and ABC there are several limitations to FNA. These include inadequate sampling due to extensive cyst formation within the tumor. This may lead to false-negative results which can be especially dangerous in ABC. Failure to identify frankly malignant tumor cells can lead to misclassification of ABC as conventional AB. In fact, there is one such report in the literature in which an FNA of ABC was read as negative because of “a geographic miss” of frankly malignant tumor cells.<sup>22</sup> The accurate preoperative diagnosis of AB is very important because it helps prevent unnecessary or suboptimal surgical management. Another limitation of cytology is its inability to distinguish conventional AB from MAB, without prior knowledge of metastatic disease.

Several differentials should always be excluded whenever basaloid cells of an intraosseous mandibular or max-

illary lesion are seen. These include small cell carcinoma, lymphoma, adenoid cystic carcinoma (ACC), poorly differentiated SQCA, and ameloblastic fibroma (AF). The small basaloid cells of AB may show prominent nuclear molding similar to that seen in small cell carcinoma however unlike small cell carcinoma the nuclei of AB have finely dispersed chromatin and not the typical “salt and pepper” chromatin pattern of small cell carcinoma. Malignant lymphoma may also resemble the basaloid cells of AB however unlike AB background smears of lymphoma show prominent lymphoglandular bodies, which would not be seen in AB. In our case, an interesting finding in the FNA of the submandibular lymph nodes was the presence of background lymphoglandular bodies. We attribute this finding to partial nodal involvement by AB with surrounding mature lymphocytes and their associated cytoplasmic fragments. This phenomenon could be a potential

confounding factor in the FNA diagnosis of AB. ACC is an aggressive salivary gland tumor that may also metastasize to bone. The solid variant of ACC where one sees fewer extracellular hyaline globules of basement membrane and abundant basaloid cells may look similar to AB. The identification of these basement membrane globules is probably the most helpful cytologic feature in distinguishing the two entities. Metastatic poorly differentiated SQCA with a predominant basaloid pattern and few keratinized cells may resemble the acanthomatous variant of AB. However, SQCA would have frankly malignant features, which would not be expected in conventional AB or MAB. Two additional differentials that are more specifically related to our case are metastatic lobular carcinoma of the breast and polymorphous low grade adenocarcinoma of salivary gland. These two differentials were considered because of the unique and striking linear arrangement of tumor cells in our patient's lymph node FNAs, a finding that has not been previously described in the cytology literature. The presence of spindle basaloid cells and squamous cells would not be expected in either of the latter two tumors and so distinction from AB is possible. AF is a primary intraosseous tumor that should be distinguished from AB. Both tumors show a predominance of basaloid cells with peripheral tumor cell palisading.<sup>23</sup> AF is also common in children and adolescents, as is UC AB. AF, however, has more stromal fragments than AB and this perhaps is the most helpful cytologic feature that may distinguish the two entities.

In summary, we present a case of malignant AB, which was diagnosed as such on FNA. This partly clinical as well as cytologic diagnosis was facilitated by the presence of typical AB cytology in enlarged cervical lymph nodes adjacent to a histologically confirmed mandibular AB. Although cytology is helpful in diagnosing AB it does not distinguish between conventional AB and malignant AB. Adequate sampling is also important when attempting to distinguish conventional AB from ABC. Because there are several cytologic mimics of AB, a high index of suspicion is always necessary when evaluating FNA material from jaw lesions and/or regional lymph nodes. The need for correlation of cytologic findings with clinical and radiologic information cannot be overstated.

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