Case Report
Clinical and pathological features of desmoplastic ameloblastoma: a literature review with three case reports

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Abstract: Desmoplastic ameloblastoma is a rare variant of benign odontogenic tumors. Our objective was to describe the clinical and pathological features of desmoplastic ameloblastoma. Three cases of desmoplastic ameloblastoma that were treated in the authors’ department were reviewed and analyzed along with radiological and histological data. The findings obtained from pathological examinations of two solid ameloblastomas served as controls. Moreover, 91 desmoplastic ameloblastoma cases in the literature were reviewed. Desmoplastic ameloblastoma is most commonly observed in the anterior and premolar regions of the mandible and maxilla, with a radiolucent and radiopaque appearance. After surgical resection, no recurrence was observed. On pathological examination, desmoplastic ameloblastoma was present in irregular and compressed epithelial islands scattered among massive stroma. In the epithelium, desmoplastic ameloblastoma expressed CK19 weakly to strongly and TGF-β1 moderately to strongly, while vimentin was expressed strongly in the stroma. However, solid ameloblastoma tumors had strong CK19 expression, weak to strong TGF-β1 expression, and negative to weak vimentin expression. The review of the literature was in agreement with our cases. Desmoplastic ameloblastoma has distinctive clinical and pathological features compared with solid ameloblastoma, and it might originate from an earlier odontogenic epithelium precursor or transition from ectomesenchyme.

Keywords: Desmoplastic ameloblastoma, cytokeratin 19, solid ameloblastoma, transforming growth factor β1, vimentin

Introduction
Ameloblastoma is a benign odontogenic epithelium tumor with slowly growing, a high risk of recurrence and local invasive behavior [1]. It comprises about 1% of all tumors and cysts of the jaws [2]. According to the 2005 World Health Organization classification of odontogenic tumors, ameloblastomas can be classified into four different categories as follows: solid ameloblastoma (SA), peripheral ameloblastoma, unicuspic ameloblastoma and desmoplastic ameloblastoma (DA) [3].

Desmoplastic ameloblastoma is a rare variant of ameloblastoma and was initially described by Eversole in 1984, presenting with clinical, imaging, and histological features that are distinct from those of more common types of ameloblastomas.

Clinically, DA usually occurs in the anterior or premolar regions in the mandible or maxilla, with localized swelling and teeth movement. This lesion most commonly occurs between the ages of 17 and 72 years with a male predilection. After suitable operation, the prognosis of DA is better than SA [1, 5, 6]. DA occasionally shows a “ground-glass” appearance, which presents as diffuse and mixed radiolucent and radiopaque lesion [7] in radiograph.

Histologically, DA is characterized by pronounced collagenous stroma and small nests of odontogenic epithelium. Several “hybrid lesion” cases have been reported with a combination
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Case reports

Case 1: A 49-year-old woman presented with a painless enlarged swelling in the right suborbital region that had persisted for 2 months. Panoramic film and cone beam computed tomography (CBCT) scans revealed a mixture of ill-defined radiolucency and radiopacity, 3.4 cm × 2.7 cm × 2.0 cm, involving the alveolar bone in the 15-21 region (Figure 1). Removal of the tumor and resection of the bone around the tumor were performed.

Case 2: A 35-year-old woman complained of a painless mass that had been present for several months. Radiography showed two lesions in the mandible. One was a tumor in the 35-44 region, with honeycomb-like bone expansion. The other lesion was completely radiolucent and located in the 37-38 region (Figure 2). Because of the extensive tumor invasion, the patient received a partial mandibulectomy and mandible reconstruction with a free fibula osseous flap.

Case 3: A 39-year-old man reported a painless swelling in the left mandible that had been present for more than 10 years but showed significant recent enlargement. Panoramic film and CBCT examinations indicated mandible destruction from 36 to 42, with root absorption at 34, 35, and 36 (Figure 3). This patient received radical treatment and reconstruction similar to that performed in case 2.

Pathological examination

After formalin-fixation and paraffin-embedding, specimens from the three DA cases were cut into 4-µm-thick sections and stained with hematoxylin-eosin (H&E stain). Moreover, immunohistochemical staining was performed to evaluate CK19, vimentin, and transforming growth factor β1 (TGF-β1) expression levels. Briefly, sections were heat-treated in Tris-EDTA buffer (pH 9.0) at 120°C for 10 min. Endogenous peroxidases were blocked with 0.9% hydrogen peroxide, followed by incubation with 1% bovine serum. Monoclonal antibodies, including CK-19 (Cell Signaling Technology, USA), vimentin (Cell Signaling Technology, USA) and TGF-β1 (Cell Signaling Technology, USA), were used for overnight incubation at 4°C. Biotinylated anti-mouse/anti-rabbit antibody and streptavidin-per-

Figure 1. Radiological images of case 1. (A) Panoramic film and (B) coronal view of the cone beam computed tomography (CBCT) scan. Buccal cortical expansion and honeycomb presentation are visible in the right premolar and canine regions of the maxilla.
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oxidase complex were used as the secondary antibody. Staining was finished with a 3,3'-diaminobenzidine substrate. Immunohistochemical staining was observed and classified using a 4-grade scale as follows: negative (no positively stained cells), weakly positive (positively stained cells ≤ 25%), moderately positive (25% < positively stained cells ≤ 50%); strongly positive (positively stained cells > 50%).

Two SA specimens were analyzed using the same procedure as controls. The three DA cases and two SA cases were labeled as DA1, DA2, and DA3 and SA1 and SA2, respectively.

Figure 2. Radiological images of case 2. A, B. Panoramic film and coronal view of the CBCT scan before the operation. A dominant labial swell and “soap bubble” lesion in the anterior part of mandible are visible. A completely radiolucent lesion is located in the left mandibular molar region, which was diagnosed as a dentigerous cyst histologically. C, D. Panoramic films 3 and 30 months after operation, respectively.

Figure 3. Radiological images of case 3. A, B. Panoramic film and coronal views of the CBCT scan before the operation. A giant lesion invading the mandible from 36-42, with root absorption and a combination of radiolucent and honeycomb presentation is visible. C, D. Panoramic films 3 and 10 months after operation, respectively.
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Review of the literature

The authors performed a search on MEDLINE and reviewed a total of 91 cases of DA and data on immunohistochemical features reported in 26 papers that were reported in the literature from 1993 through 2016.

Results

General results of 3 cases in the authors’ institution

Clinically, the three cases showed DAs in the anterior and premolar regions of the mandible and maxilla, with radiolucent and radiopaque appearances. After surgical resection, cases 2 and 3 have been disease-free for 24 months and 7 months, respectively. Unfortunately, we lost touch with the patient from case 1 after only 2 months of follow-up.

Microscopically, the three DA tumor specimens contained typical histologic DA features. The tumors contained variably desmoplastic stroma and narrow epithelial nests that were separated and compressed by extensive collagenous fibers (Figure 4A). Interestingly, we found a dentigerous cyst, which was separated from the tumor, in the 37-38 region in case 2. A conventional SA appearance was seen in the control group.

The immunohistochemical expression data of CK19, vimentin, and TGF-β1 in DA and SA are listed in Table 1. Both DA and SA epithelium strongly expressed CK19, except for one DA tumor with only slightly positive staining (Figure 4C, 4D). TGF-β1 was differentially expressed in both locations and showed different intensity levels of staining in DA and SA specimens. DA and SA specimens. In peripheral epithelium nest cells, DA specimens were positively stained and SA specimens were negative for TGF-β1, while reciprocal staining was observed in stellate cells (Figure 4E, 4F). Vimentin was intensely expressed in DA stroma, but its expression was weak or absent in SA stroma (Figure 4G, 4H).

Table 1. Immunohistochemical expression of CK19, vimentin, and TGF-β1

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>CK19</th>
<th>TGF-β1</th>
<th>Vimentin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Peripheral cells</td>
<td>Stellate cells</td>
</tr>
<tr>
<td>DA</td>
<td>±(DA1); ++(DA2&amp;3)</td>
<td>+(DA1); +(DA2&amp;3)</td>
<td>-(DA1~3)</td>
</tr>
<tr>
<td>SA</td>
<td>+(SA1&amp;2)</td>
<td>-(SA1&amp;2)</td>
<td>±(SA1); +(SA2)</td>
</tr>
</tbody>
</table>

Negative (-): no positively stained cells; Weakly positive (±): positively stained cells ≤ 25%; Moderately positive (+): 25% < positively stained cells ≤ 50%; Strongly positive (++): positively stained cells > 50%. DA: desmoplastic ameloblastoma; SA: solid ameloblastoma. The case number is indicated in brackets.
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Table 2. Review of the immunohistochemical features of 91 desmoplastic ameloblastoma patients in the literature: 1993 through 2006

<table>
<thead>
<tr>
<th>Study and year of publication</th>
<th>Case (n)</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Position</th>
<th>Immunohistochemical staining</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bologna-Molina et al. [33] 2015</td>
<td>2</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Glypican-1 (+)</td>
</tr>
<tr>
<td>Siar et al. [34] 2015</td>
<td>3</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Podoplanin (±)(+), E-cadherin (+), β-catenin (+), CD44v6 (±)(+), Jagged1 (±)(+), Jagged2 (-), Deltal (±)(+)</td>
</tr>
<tr>
<td>Khalil et al. [35] 2015</td>
<td>1</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Twist (+)</td>
</tr>
<tr>
<td>Siar et al. [36] 2014</td>
<td>4</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Snail (++), Slug (±)(+), SIP1 (±)(+), Twist (±)(+)</td>
</tr>
<tr>
<td>Ramesh et al. [12] 2014</td>
<td>1</td>
<td>45</td>
<td>F</td>
<td>Max</td>
<td>CK10 (+), CK13 (+), CK14 (+), CK16 (+), CK17 (+), CK18 (+), CK19 (+), CK20 (+)</td>
</tr>
<tr>
<td>Siar et al. [37] 2013</td>
<td>5</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>PCNA 80.94% ± 10.4, Ki-67 1.9% ± 1.24</td>
</tr>
<tr>
<td>Siar et al. [38] 2012</td>
<td>8</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Wnt1 (±)(+), Wnt2 (+), Wnt3 (±)(+), Wnt4 (+), Wnt5 (-), Wnt6 (-), Wnt7 (-), Wnt8a (-)(+), Wnt8b (-)(+), Wnt10a (-)(+), Wnt10b (-)</td>
</tr>
<tr>
<td>Krishna et al. [39] 2012</td>
<td>3</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>MDM2 (+)</td>
</tr>
<tr>
<td>Siar et al. [40] 2010</td>
<td>10</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Notch1 (±)(+), Notch2 (-), Notch3 (±)(+), Notch4 (±)(+)</td>
</tr>
<tr>
<td>Bologna-Molina et al. [14] 2010</td>
<td>1</td>
<td>66</td>
<td>1</td>
<td>1</td>
<td>CK1 (+), CK5 (+), CK6 (+), CK10 (+), CK13 (+), CK14 (+), CK16 (+), CK18 (+), CK19 (+), CK20 (+), laminin V (+)(+), type IV collagen (+)(+), S-100 (+)(+), SMA (+), Bcl-2 (+), p21 (-)</td>
</tr>
<tr>
<td>de Medeiros et al. [23] 2010</td>
<td>4</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Fibronectin (-)(+), tenasin (+)(+)(+)</td>
</tr>
<tr>
<td>Bologna-Molina et al. [41] 2009</td>
<td>4</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>CD138 (+), Ki-67 1.5%</td>
</tr>
<tr>
<td>Kumamoto et al. [42] 2008</td>
<td>3</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Bid (+), Bir (±)(+), Bad (+)(+), Noxa (+), Puma (+), Fas (+)</td>
</tr>
<tr>
<td>Kumamoto et al. [43] 2007</td>
<td>4</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>IGF1 (+)(+), IGF2 (+)(+), IGF receptor (+)</td>
</tr>
<tr>
<td>Dos et al. [8] 2006</td>
<td>1</td>
<td>36</td>
<td>1</td>
<td>1</td>
<td>Fibronectin (+), tenasin (-)</td>
</tr>
<tr>
<td>Kumamoto et al. [10] 2002</td>
<td>4</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>HGF (+), c-Met (+), TGF-β (+)(+)(+), TGF-β receptors (+)(+)(+)</td>
</tr>
<tr>
<td>Nagatsu et al. [46] 2002</td>
<td>3</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Type IV collagen α1&amp;α2 (+)(+)</td>
</tr>
<tr>
<td>Fukumashi K et al. [15] 2002</td>
<td>3</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>CK1 (+), CK13 (+), CK19 (±)(+)</td>
</tr>
<tr>
<td>Kumamoto et al. [9, 47] 2001</td>
<td>4</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>anti-FasL (±), caspase-3 (+)(+)(+), ssRNA (-)(±)(±), amelogenin (-), CK19 (+)</td>
</tr>
<tr>
<td>Takata et al. [16] 1999</td>
<td>7</td>
<td>17-48</td>
<td>1</td>
<td>1</td>
<td>Type IV collagen (+)(+), TGF-β (+)(+)</td>
</tr>
</tbody>
</table>

Negative (-): no positively stained cells; Weakly positive (±): positively stained cells ≤ 25%; Moderately positive (+): 25% < positively stained cells ≤ 50%; Strongly positive (++): positively stained cells > 50%. CK, cytokeratin; EMA, epithelial membrane antigen; F, female; HGF, hepatocyte growth factor; IGF, insulin-like growth factor; M, male; Mand, mandible; Max, maxilla; MDM2, mouse double minute 2 homolog; NA: not available; PCNA, proliferating cell nuclear antigen; SMA, smooth muscle autoantibody; XIAP, X chromosome-linked inhibitor of apoptosis protein; TGF, transforming growth factor.
General results of cases in literature

Immunohistochemical characteristics of 91 cases with DA collected from 26 reports are presented in Table 2. CK19 in DA was mildly or moderately expressed and only a few cases were negative [11-15]. Vimentin [12] and TGF-β1, [10, 16] usually showed moderate or strongly positive staining. The review of literature was consistent with our results above.

Discussion

DA is rare, accounting for only approximately 0.9%-13% of ameloblastoma patients [17]. Sun [5] summarized 115 DA cases, showing that DA prefers the anterior or premolar regions in the mandible or maxilla (91.7%), and it is rarely found in the mandibular molar region (8.3%). The mandible is slightly more susceptible than the maxilla (54.9% vs. 45.1%). Furthermore, Philipsen [18] reported that DA occurs in patients at an average age of 42.9 years. The three cases we described are consistent with these epidemiological characteristics.

Li [17] classified DA radiographs into three subtypes. The osteofibrosis type, which comprises almost half of DA tumors, is radiolucent and radiopaque in appearance, with the so-called “honeycomb” or “soap bubble” features. The radiolucent type, which has a completely radiolucent appearance, is somewhat analogous to odontogenic cysts. The compound type is a rare subtype with both radiolucent and radiopaque features combined with a large radiolucent change. Analyzing CBCT coronal figures, Luo [19] discovered that DA has a characteristic buccal bony expansion, which is distinct from the observed buccal-lingual expansion in SA. Cases 1 and 2 were both typical osteofibrosis type DAs, while case 3 was compound type DA. All three cases expanded in the buccal area.

Curettage and resection are both major treatments for DA [6]. However, because of limited DA case reports and a lack of understanding of DA biological behavior and prognosis, there are no defined strategies for DA treatment. Sun [5] examined 69 cases and found an overall recurrence rate of 15.9% and a time-to-recurrence of 36.9 months on average. Furthermore, their results suggested that curettage results in a higher potential of recurrence than resection, which may be because of the lesions’ ill-defined boundaries. In our study, patients underwent resection to prevent residual tumor. The patients from cases 2 and 3 have remained disease-free so far.

For cases showing severe and extensive bone destruction, reconstruction with free composite tissue flaps after osteotomy can contribute to quality of life and appearance. Cervelli [20] and Mijiti [21] reported two DA cases with free fibula osseous flaps used for immediate reconstruction. The patients from cases 2 and 3 in our study, who underwent reconstruction with free fibula osseous flaps, had a satisfactory recovery and appearance after surgery.

Histologically, DA exhibits irregular and compressed epithelial islands scattered among massive desmoplastic stroma, which consists of a large number of fibroblasts and extensive type I collagen [22, 23]. The distinct DA appearance suggests that it might have a different origin from common ameloblastoma [24]. To investigate differentiation and the relationship between the tumor epithelium and stroma, we examined the epithelial marker CK19, the stromal marker vimentin, and the extracellular matrix formation-related marker TGF-β1 by immunohistochemical staining.

The expression of cytokeratins, including CK19, correlates with the differentiation of tumor epithelium in ameloblastoma [25]. CK19, a typical cytokeratin marker, has also been used to estimate the degree of epithelial differentiation in ameloblastoma. Fukumashi [15] and Pal [13] suggested that DA may form in early stages of tooth development because CK19 expression is lower in DA than that for other ameloblastoma types. Case 1 exhibited poor CK19 expression, indicating that the tumor was probably derived from immature odontogenic epithelium.

TGF-β has various biological functions, including epithelial-mesenchymal transition induction and extracellular matrix formation enhancement by stimulating fibroblasts, among other roles [26, 27]. TGF-β and its major isoform TGF-β1 are differentially expressed in different types of ameloblastoma [27, 28]. Takata [27] found that DA tumor cells produced a lot of TGF-β, which induced desmoplastic stroma synthesis. TGF-β1 immunohistochemical expression in our...
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cases was consistent with the previous reports. Furthermore, we found TGF-\(\beta_1\)-positive cells on the outer layer of the epithelial islands, which contacted stroma directly. The peripheral cells likely secreted TGF-\(\beta_1\) and stimulated fibroblasts to synthesize large quantities of collagen.

Vimentin, a type of intermediate filament, is found in mesenchymal cells. Ramesh [12] and Sherlin [29] reported that DA have high vimentin expression with mass collagen formation. We found the same results in our immunohistochemical experiments and hypothesized that fibroblasts were possibly active during proliferation and collagen synthesis. Moreover, DA exhibited no stromal cellular atypia, distinct from odontogenic epithelial tumors with ectomesenchymal tissue, such as that found in ameloblastic fibroma [30].

The desmoplastic mechanism underlying DA has still not been elucidated. In contrast with normal ameloblastoma, DA is hypothesized to derive from ectomesenchyme because of its poorly differentiated epithelium, its extensive desmoplastic stroma, and the observation of mesenchymal-epithelial transitions in long bone ameloblastoma, also called adamantinoma [7, 31].

Based on our literature review and analysis, we can conclude that DA has prominent clinical and pathological features, which are distinct from conventional ameloblastoma.

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Disclosure of conflict of interest

None.

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