

# Adenoid Ameloblastoma with Dentinoid

## A systematic review

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**ABSTRACT:** This article aimed to collectively present the demographic, clinical, radiographic and histopathological features as well as the treatment performed along with its outcome for all the cases of adenoid ameloblastoma with dentinoid (AAD) reported in scientific literature till date. Ameloblastoma and adenomatoid odontogenic tumours are the most common odontogenic neoplasms. However, AAD, a hybrid variant of the two lesions, is found to be extremely rare. The lesion comprises of characteristic histopathological features of ameloblastoma and adenomatoid odontogenic tumour and shares certain clinical characteristics with either of the entities. AAD may be considered to be present at the more aggressive end of spectrum of benign odontogenic neoplasms. Owing to the frequent tendency of the lesions to be underdiagnosed, careful histopathological screening of submitted biopsies is warranted. With the increase in number of reported cases in the recent years, it is likely to be included as a separate entity in the upcoming World Health Organization classification.

**Keywords:** Odontogenic Tumors; Adenomatoid Odontogenic Tumor; Adenoameloblastoma; Immunohistochemistry.

THE PROCESS OF ODONTOGENESIS INVOLVES complex molecular interactions. Disruptions in these interactions may result in a distinct spectrum of neoplasms, unique to the jaws, that are collectively termed odontogenic tumours (OTs).<sup>1</sup> The World Health Organization (WHO) has defined OTs as lesions derived from epithelial, ectomesenchymal and/or mesenchymal elements that are or have been a part of the tooth-forming apparatus.<sup>2,3</sup> Owing to their development from various components of the tooth-forming apparatus, OTs may present a considerable histopathological diversity.

Two or more distinct tumour entities may co-exist within the same lesion and are reported as hybrid tumours. Ide *et al.* defined these as lesions showing the combined histopathological characteristics of two or more previously recognised tumours and/or cysts of different categories.<sup>4</sup> These tumours have not been included in the 2017 WHO classification system of odontogenic neoplasms due to the inadequate number of reported cases.<sup>5</sup>

One such variant of the hybrid odontogenic tumour may exhibit the histological features of both ameloblastoma (AM) and adenomatoid odontogenic tumour (AOT). This hybrid odontogenic tumour was first reported by Slabbert *et al.* in 1992 as dentinoameloblastoma.<sup>6</sup> The diagnostic term adenoid ameloblastoma with dentinoid (AAD) was first reported by the Armed Forces Institute of Pathology in 1994 by Brannon.<sup>7</sup> Over time, various terminologies have been associated with the lesions, such as atypical plexiform ameloblastoma with dentinoid, ameloblastoma with features of dentinoid, hybrid ameloblastoma and

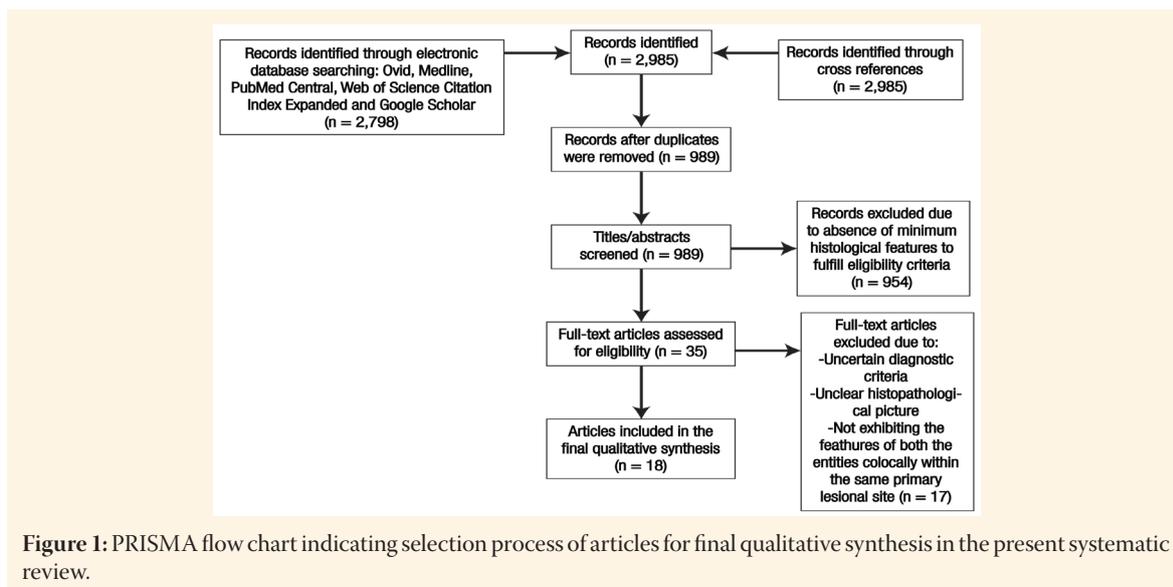
AOT originating within an unicystic ameloblastoma and atypical adenoid ameloblastoma.<sup>8–13</sup> As a result of the paucity of reported cases of the lesions, the data available regarding their pathogenesis, clinical behaviour, diagnosis and prognosis are limited.

The present systematic review aimed to collectively present the demographic details, clinical features, histopathological patterns, molecular markers, treatment performed and the outcomes of the cases of AAD found in the literature in English. Another objective was to improve the understanding of the lesions with respect to their clinical characteristics, varied histopathological morphology and prognosis.

This systematic review has been registered in the International prospective register of systematic reviews – PROSPERO (Record ID: [https://www.crd.york.ac.uk/prospero/display\\_record.php?RecordID=207062](https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=207062)).

## Methods

Case reports and case series of AAD were retrieved by a systematic search of scientific databases, including Ovid (Walter Kluwer, New York, USA), Medline (National Library of Medicine, Maryland, USA), PubMed Central (National Library of Medicine), Web of Science Citation Index Expanded (Clarivate Analytics, London, UK) and Google Scholar (Google, Mountain View, USA) with the keywords ‘Adenoid’ OR ‘Adenomatoid’ AND ‘Ameloblastoma’ AND ‘Dentinoid’. An additional search was performed using keywords ‘Hybrid’ AND ‘Odontogenic’ AND ‘Tumours’ and the retrieved literature was scanned to identify any cases reported with a name differing



**Figure 1:** PRISMA flow chart indicating selection process of articles for final qualitative synthesis in the present systematic review.

from AAD. Additionally, case reports and case series of AAD were also scanned from cross-references.

#### CRITERIA FOR SELECTION AND EXCLUSION

The case reports and case series of the lesions co-localised within the same primary lesion site, exhibiting the histopathological characteristics of both AM and AOT and available in English language were included in this review. However, lesions with uncertain diagnostic criteria, unclear histopathological characteristics and the absence of features of both the entities found co-locally were excluded from the review [Figure 1].

In order to be classified as AAD, a lesion should present characteristic histopathological features of both AM and AOT in association with extracellular dentinoid material. Therefore, the reported cases were included in this study if their histopathological pictures comprised a combination of at least one of the features of AM and AOT, respectively, along with dentinoid material [Table 1]. With respect to the AM component, any of the histopathological variants of solid/conventional AM as well as unicystic ameloblastoma (UAM), peripheral AM and metastatic AM were considered to be eligible for inclusion.

Overall, in terms of the labels used in the present systematic review for the respective histological features, the following definite diagnostic formula denoting the minimum criteria for a lesion to be considered as AAD was proposed:

AM-F / AM-P / UAM + AOT-S / AOT-D + DM

In addition to these minimum requisite features, lesions presenting other peculiar features, such as the

**Table 1:** Coded labels provided to various histopathological features in the present systematic review

Ameloblastoma component	
AM-F	Follicles of odontogenic epithelium with peripheral tall columnar ameloblast-like cells with reversal of polarity and central stellate reticulum-like cells in the form of follicles within a mature connective tissue stroma
AM-P	Odontogenic epithelium infiltrating into a mature connective tissue stroma in the form of interlacing strands or plexuses
UAM	Cystic lesion having lumen lined by tall columnar cells with hyperchromatic nuclei exhibiting nuclear palisading with reversal of polarity and cytoplasmic vacuolisation (Gorlin-Vickers Criteria) <sup>14</sup>
Adenomatoid odontogenic tumour component	
AOT-S	Sheets/islands/cords/whorling of spindle to ovoid shaped odontogenic epithelial cells
AOT-D	Duct-like structures lined by epithelial cells with eosinophilic material/cystic space in the lumen
AOT-R	Rosette-like structures consisting of two layers of low to tall columnar epithelial cells with eosinophilic material/cystic space centrally in the lumen
Dentinoid material	
DM	Extracellular homogenous eosinophilic material (dentinoid)
Other features	
CC	Presence of clear cells within the tumor islands in AOT component of the lesion.
GC	Presence of ghost cells within odontogenic epithelial nests/islands in the AOT component or within ameloblastomatous epithelium

AM = ameloblastoma; UAM = unicystic ameloblastoma; AOT = adenomatoid odontogenic tumour; DM = dentinoid material; CC = clear cells; GC = ghost cells.

**Table 2:** Summarised parameters of cases of adenoid ameloblastoma with dentinoid

Author and year of publication	Age in years	Gender	Duration	Arch	Side	Symptom	Radiographic feature	Histopathological feature	Special stains/IHC	Final diagnosis	Treatment (with number of recurrences)	Follow-up with NED
Slabbert <i>et al.</i> <sup>6</sup> (1992)	24	Male	N/P	Mn	Left	Swelling	UL RL	AM-F, AM-P, AOT-S, DM	Van Gieson + Masson's trichrome + Congo red – Alcian blue –	Dentinoame-loblastoma	WE	N/P
Matsumoto <i>et al.</i> <sup>8</sup> (2001)	19	Male	1 mo	Mn	Right	Swelling	WD UL RL	AM-P, AOT-S, AOT-D, DM	Mucicarmine + Alcian blue +	Atypical plexiform AM with dentinoid	Marsupialisation + enucleation; (1 rec after 2 yr); WE	2.5 yr
Evans <i>et al.</i> <sup>9</sup> (2004)	39	Male	N/P	Mn	CM	Swelling	WD UL RL	AM-P, AOT-S, AOT-D, DM, CC	N/P	AM with features of AOT	WE; WE + curettage enucleation + curettage (3 recs over a 16-yr period); SR	18 mo
Zhang <i>et al.</i> <sup>10</sup> (2006)	64	Female	16 mo	Mn	CM	Swelling + paresthesia	WD UL RL with RO clusters	AM-F, AOT-S, AOT-R, DM, GC	N/P	Hybrid odontogenic tumor characteristic of CCOT, solid multicystic AM and AOT	SR	3 yr
Jivan <i>et al.</i> <sup>12</sup> (2007)	40	Male	7 mo	Mn	CM	Swelling	WD UL RL	UAM, AOT-S, AOT-D, AOT-R, DM	Calretinin ++ in cystic lining	AOT originating within a unicystic AM	N/P	N/P
Ghasemi-Moridani <i>et al.</i> <sup>15</sup> (2008)	19	Female	2 mo	Mx	Right	Swelling	WD UL RL	AM-P, AOT-S, AOT-D, DM	N/P	AAD	Excision	N/P
Ide <i>et al.</i> <sup>16</sup> (2009)	44	Male	N/P	Mx	CM	N/P	WD UL RL	AM-P, AOT-S, AOT-D, AOT <sup>4</sup> , DM	Calretinin +	AAD	En; Excision; (3 recs over a 11-year period) Partial maxillectomy	8 yr
Sonone <i>et al.</i> <sup>17</sup> (2011)	35	Female	1 year	Mn	Right	Swelling + numbness	WD UL RL with RO foci	AM-P, AOT-S, AOT-D, AOT-R, DM, GC	Van Gieson +	AAD	SR	6 mo
Saxena <i>et al.</i> <sup>18</sup> (2012)	45	Male	2 wk	Mx	Left	Swelling	Diffuse RL	Congo red – AM-P, AM <sup>4</sup> AOT-D, AOT-S, DM	N/P	AAD	WE (3 recs) SR	N/P
Yamazaki <i>et al.</i> <sup>11</sup> (2014)	31	Female	N/P	Mn	Right	None	WD UL RL with sclerotic area in distal portion	AM-F, AM-P, AOT-S, AOT-D, DM, CC CK17 + Calretinin + Ki-67 + Congo red +	CK19 ++	Hybrid AM and AOT	SR	36 mo
Loyola <i>et al.</i> <sup>13</sup> (2015)	55	Male	5 mo	Mn	Left	Swelling	N/P	AM-F, AM-P, AOT-S, AOT-D, DM	CK19: ++ Ki-67 ++ CK8/18 –	AAD	1 rec; SR	108 mo
	24	Female	6 mo	Mx	Left	Swelling	WD UL RL		None	Adenoid AM (hybrid/ mixed odontogenic tumour)	WE	6 mo

N/P = not provided; Mn = mandible; Mx = maxilla; CM = crossing midline; WD = well-defined; PD = poorly defined; UL = unilocular; ML = multilocular; RL = radiolucency; RO = radiopaque; WE = wide excision; SR = surgical resection; Rec = recurrence.

Table 2 (cont'd.): Summarised parameters of cases of adenoid ameloblastoma with dentinoid

Author and year of publication	Age in years	Gender	Duration	Arch	Side	Symptom	Radiographic feature	Histopathological feature	Special stains/IHC	Final diagnosis	Treatment (with number of recurrences)	Follow-up with NED
Loyola <i>et al.</i> <sup>13</sup> (2015)	31	Male	1 mo	Mn	Right	Swelling	WD RL	AM-F, AM-P, AOT-S, AOT-D, DM	None	Adenoid granular cell AM with dentinoid	Hemimandibulectomy	18 mo
Kumar <i>et al.</i> <sup>19</sup> (2013)	40	Male	N/P	Mn	CM	Swelling, numbness, parasthesia	WD UL RL	AM-F, AM-P, AOT-S, AOT-D, DM	Calretinin ++ p53 ++	Atypical adenoid AM	Hemimandibulectomy	14 mo
	16	Female	2 mo	Mn	Right	Swelling	UL RL	AM-P, AOT-S, AOT-D, AOT-R, DM, GC	None	AAD	WE	12 mo
Salehinejad <i>et al.</i> <sup>20</sup> (2016)	55	Male	3 mo	Mn	Right	Swelling, pain, paresthesia	WD UL RL	AM-P, AOT-S, AOT-D, AOT-R, DM, GC	CK19 +	AAD	SR	36 mo
	34	Female	43 mo	Mx	Right	Swelling	PD RL	AM-F, AM-P, AOT-D, DM	CK19 ++ Ki-67 ++ CK8/18 +	AAD	9 recs; SR	19 mo
Khalele <i>et al.</i> <sup>21</sup> (2016)	33	Female	48 mo	Mx	Right	Swelling + pain	N/P	AM-F, AM-P, AOT-S, AOT-D, AOT-R, DM	CK19 ++ Ki-67 ++ CK8/18 -	AAD	5 recs; SR + radiotherapy + neck dissection	N/P
	51	Male	72 mo	Mx	CM	Swelling + pain	PD RL	UAM, AOT-S, AOT-D, AOT-R, DM	CK19 ++ Ki-67 ++ CK8/18 +	AAD	5 recs; SR	76 mo
Rai <i>et al.</i> <sup>23</sup> (2017)	47	Male	18 mo	Mx	CM	Swelling	N/P	AM-F, AOT-S, AOT-D, DM	CK19 ++ Ki-67 ++ CK8/18 +	AAD	2 recs; SR + radiotherapy + neck dissection	52 mo
Adorno-Farias <i>et al.</i> <sup>24</sup> (2018)	15	Female	12 mo	Mn	N/P	Swelling	UL RL	AM-F, AOT-S, AOT-D, DM	CK7 - CK14 - CK19 + IMP3 - Ki-67 + p53 -	AM with adenoid features	SR	N/P
	37	Male	12 mo	Mn	Left	Swelling + pain	WD ML RL	AM-F, AOT-S, AOT-D, DM, CC	CK7 - CK14 - CK19 ++ IMP3 - Ki-67 + p53 -	AM with adenoid features	SR	N/P
	46	Female	N/P	Mn	N/P	N/P	UL RL		CK7 - CK14 - CK19 ++ IMP3 - Ki-67 + p53 -		SR	N/P

N/P = not provided; Mn = mandible; Mx = maxilla; CM = crossing midline; WD = well-defined; PD = poorly defined; UL = unilocular; ML = multilocular; AM = ameloblastoma; RL = radiolucency; RO = radiopaque; WE = wide excision; SR = surgical resection; Rec = recurrence.

Table 2 (cont'd.): Summarised parameters of cases of adenoid ameloblastoma with dentinoid

Author and year of publication	Age in years	Gender	Duration	Arch	Side	Symptom	Radiographic feature	Histopathological feature	Special stains/IHC	Final diagnosis	Treatment (with number of recurrences)	Follow-up with NED
Adorno-Farias <i>et al.</i> <sup>24</sup> (2018)	34	Female	N/P	Min	N/P	Swelling	UL RL	AM-E, AOT-S, AOT-D, DM, CC	CK7 – CK14 – CK19 + IMP3 – Ki-67 + p53 – CK7 – CK14 – CK19 ++ IMP3 – Ki-67 + p53 – CK7 – CK14 – CK19 ++ IMP3 – Ki-67 +	AM with adenoid features	SR	N/P
	N/P	Female	N/P	N/P	N/P	N/P	UL RL				SR	N/P
	15	Male	12 mo	Mn		Swelling	UL RL	AM-E, AOT-S, AOT-D, DM, CC	CK7 – CK14 ++ CK19 ++ IMP3 – Ki-67 + p53 – CK7 – CK14 ++ CK19 ++ IMP3 – Ki-67 + p53 – CK7 – CK14 ++ CK19 ++		SR	N/P
	82	Male	36 mo	Mn		Swelling	ML RL	AM-E, AOT-D, DM, CC, GC	CK7 – CK14 ++ CK19 ++ IMP3 – Ki-67 + p53 – CK7 – CK14 ++ CK19 ++ IMP3 – Ki-67 + p53 –		SR	N/P
	46	Male	N/P	N/P		N/P	UL RL	AM-E, AOT-D, DM, CC	CK7 – CK14 ++ CK19 + IMP3 – Ki-67 + p53 – Alcian blue		SR	N/P
Arruda <i>et al.</i> <sup>25</sup> (2020)	51	Female	N/P	Mx	Left	None	WD UL RL	AM-P, AOT-S, AOT-D, DM		AAD	1 rec; SR	108 mo

N/P = not provided; Mn = mandible; Mx = maxilla; CM = crossing midline; WD = well-defined; PD = poorly defined; UL = unilocular; ML = multilocular; RL = radiolucency; RO = radiopaque; WE = wide excision; SR = surgical resection; Rec = recurrence.

**Table 3:** Summary of various parameters observed following review of case reports and case series of adenoid ameloblastoma with dentinoid (N = 29)

Parameters	n
<b>Age in years</b>	
Lowest	15
Highest	82
Mean ± SD	38.97 ± 27.43
<b>Gender</b>	
Males	16
Females	13
<b>Mandible</b>	<b>18</b>
Left	3
CM	4
Right	6
<b>Maxilla</b>	<b>9</b>
Left	3
CM	3
Right	3
<b>Mandible and maxilla (side not provided)</b>	<b>7</b>
<b>Symptoms</b>	
Asymptomatic swelling	16
Pain	3
Paresthesia/numbness	4
<b>Radiographic</b>	
Well defined unilocular radiolucency	20
Well-defined multilocular radiolucency	2
Poorly defined radiolucency	2
Radiolucent lesion with radiopaque foci	3
<b>Features of AM component</b>	
Follicular	9
Plexiform	9
Mixed	9
Unicystic ameloblastoma	2
<b>Changes in AM component</b>	
Desmoplastic	1
Granular cells	1
Squamous metaplasia	8
<b>Features of AOT component</b>	
Duct-like structures	19
Sheets/whorls of cells	18
Rosette-like structures	6
<b>Other histological features</b>	
Clear cells	9
Ghost cells	4
<b>Recurrences</b>	
Cases reporting recurrences	12
Maximum number of recurrences in a single case	9
Follow-up details not provided	13

SD = standard deviation; CM = centre; AM = ameloblastoma; AOT = adenomatoid odontogenic tumour.

presence of clear cells within the tumour islands in the AOT component of the lesion and ghost cells within the odontogenic epithelial nests/islands in the AOT component or within ameloblastomatous epithelium were also included and discussed in this review. Moreover, the desmoplastic changes, which may occur in the stromal component of AM, are now regarded as a histopathological variant of AM rather than a distinct entity.<sup>5</sup> However, these additional features are not considered as definitive criteria for the lesion, but rather represent varying stages of odontogenic cell differentiation in the lesion.

#### DATA EXTRACTION

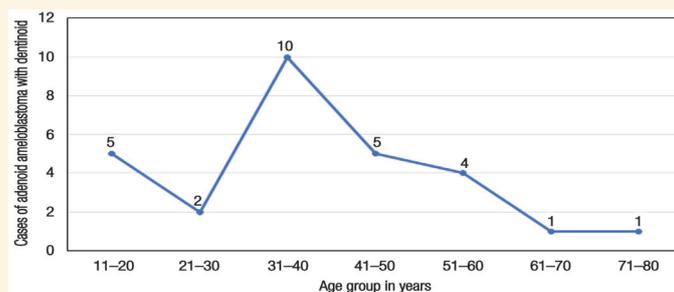
Data on the demographic, clinical, radiographic and histopathological features and molecular markers were assessed. The treatment performed and their outcomes in all the reported cases were elicited. In order to minimise the risk of bias in quality assessment, the authors were divided into two groups that independently screened the cases and extracted the data from the included articles. The data was entered into meta-analysis sheets (MS Office Excel, 2016; Microsoft Redmond Campus, Redmond, WA, USA).

### Results and Discussion

A total of 29 reported cases of AAD were extracted from 18 publications available in English. The comprehensive findings following a detailed review of all the cases are collectively summarised [Tables 2 and 3].

The first case of AAD was reported by Slabbert *et al.* in 1992, and till date, only 29 cases of AAD have been reported.<sup>6</sup> The low number of reported cases are reflective of the rarity of AAD. It is possible that several cases of AAD might be overlooked by pathologists as AM or AOT, depending on the predominance of either entity in the microscopic examination. This possibility is supported by the fact that 4 out of 45 cases of AM were re-assessed and re-classified as AAD in a retrospective study conducted by Loyola *et al.*<sup>13</sup> Therefore, the actual number of cases might be much higher than those reported in the literature. With increasing case reports on the tumours and subsequent increase in the awareness amongst pathologists, hybrid lesions, such as AAD, are identified accurately, which is in-line with the fact that more than half of the cases of AAD (n = 19) were reported during the years 2015–2020. Thus, more cases of AAD may be expected to be reported in the following years.

The mean age of the patients presenting the lesion was 38.97 ± 27.43 (range: 15–82) years. The maximum



**Figure 2:** Number of reported cases of adenoid ameloblastoma with dentinoid belonging to various age groups.

number of cases occurred in the fourth decade ( $n = 10$ ), followed by the second and fifth decades ( $n = 5$  each) of life, and the least number of cases were reported in the seventh decade or above [Figure 2]. The pattern of age distribution of the lesion was identical to that of AM and relatively less similar to AOT, which tends to occur in first or second decade.<sup>26</sup> Unlike AOT, which is more common in females, AM does not exhibit gender predilection.<sup>27</sup> In the case of AAD, the reported cases comprised of 16 males and 13 females, yielding a ratio of nearly 1:1. The absence of gender predilection in AAD was also similar to that observed in AM.

The cases of AAD occurred twice more frequently in the mandible ( $n = 18$ ) compared to maxilla ( $n = 9$ ), with a slight predilection for the right ( $n = 9$ ) compared to the left side ( $n = 6$ ). Considering the lower frequency of lesions in the maxilla, it may be deduced that a high percentage of lesions occurring on the left side were in the maxilla (3/6 maxillary AAD), whereas AAD occurring in the mandible exhibited a predilection for the right side (6/9 cases).

In seven instances, the lesion involved the entire arch on both sides crossing the midline, indicating the aggressive potential of the lesion. Interestingly, the tendency of the lesion to infiltrate both sides was equal in both the jaws, encompassing the entire mandible ( $n = 4$ ) or maxillary jaw along with maxillary sinus and orbital floor ( $n = 3$ ). Approximately two-third of AOTs have been reported to occur in the maxillary jaw with a predilection for the left side, while AM frequently tends to occur in the posterior region of the mandibular jaw with a slight predilection for the right side.<sup>26</sup> Thus, the pattern of occurrence of AAD in the jaws is similar to AOT in the maxilla and AM in the mandible.

Similar to the clinical presentation of both AOT and AM, most of the patients presented an asymptomatic swelling ( $n = 16$ ), which was accompanied by pain in only three cases. Paraesthesia and numbness were elicited in four cases, with all the lesions inevitably involving the mandibular posterior region. Pain, paraesthesia and numbness are also

associated with AM lesions, albeit uncommonly, and could be attributed to the tumour mass impinging on the peripheral nerves or secondary infection.<sup>28</sup>

The radiographic evaluation revealed that the lesion presented as a well-defined unilocular radiolucency ( $n = 20$ ), which was similar to that commonly noted in AOT. Loyola *et al.* reported only two cases, which presented a poorly defined radiolucent lesion occurring in the maxillary jaw involving the nasal fossa, nasal and paranasal sinuses, as well as the orbit.<sup>13</sup> In cases of large AM or AOT, similar involvement of nasal and maxillary sinuses with poorly defined lesions has been reported.<sup>27</sup> The slow, painless clinical course of the lesion as well as the thin and porous maxillary bone might be the factors that lead to lesions' extensive, poorly defined radiolucency.<sup>29</sup>

Multilocularity was observed in only 2 out of 8 cases reported by Adorno-Farias *et al.*<sup>24</sup> It is observed in the radiographic images of AM, wherein the tumour exhibits the septae of bone extending into the radiolucent tumour mass.<sup>30</sup> In three cases, radiopaque foci were also displayed within the unilocular radiolucency in the mandible. In all these cases, ghost cells and dystrophic calcifications were noted on the histopathologic examination for focal radiopacities.<sup>10,11,17</sup>

Furthermore, the histopathology of the AM component of the tumour revealed that nine cases had a predominant plexiform pattern of ameloblast-like cell proliferation, nine cases exhibited a follicular pattern, and another nine cases comprised a mixture of both patterns. The follicular and plexiform histopathological patterns in isolated and mixed forms are similar in cases of AM, which was similar to the current findings.<sup>31</sup> Only two cases had UAM associated with AOT, suggesting that most AADs are associated with solid/multicystic AM.

Desmoplastic changes are infrequently noted in ameloblastoma owing to the loss of expression of notch receptors representing an early stage of cell differentiation.<sup>32,33</sup> This phenomenon is observed

in AAD cases, wherein only one case, reported by Salehinejad *et al.*, presented features of desmoplastic AM.<sup>20</sup> In addition to the desmoplastic changes in the stroma, the lesion also comprised of large amounts of granular cells. Granular cell ameloblastoma is a rare subtype of ameloblastoma, in which granular cells are located in the centre of the follicles.<sup>34</sup> Thus, only one case of granular cells occurring centrally within the ameloblastic follicles and desmoplastic changes within the connective tissue stroma in AAD has yet been reported.<sup>20</sup>

Squamous metaplasia occurring within the central stellate reticulum-like cells of AM follicles is an occasional histological finding termed 'acanthomatous ameloblastoma'.<sup>27</sup> Squamous metaplasia was observed in all the eight cases reported by Adorno-Farias *et al.* Amongst them, seven lesions occurred in the mandibular jaw, whereas the clinical details of one case were unreported.<sup>24</sup> The current findings were in accordance with the inference of Bansal *et al.*, which stated that the occurrence of squamous metaplasia is common in AM cases occurring in the mandible than maxilla.<sup>35</sup>

The other component associated with AM in the case of AAD is that of AOT. The biological mechanism underlying this mixture is yet to be elucidated. The transformation from one lesion to another seems to be a possible pathogenic mechanism.<sup>36</sup> The term 'adenomatoid' is derived from 'adén', which means gland, and '-oma', which means swelling or tumour. The peculiar feature of AOT that led to the derivation of the term is the presence of duct-like structures lined by cuboidal or columnar epithelial cells.<sup>26</sup> Previous studies on the retention of extracellular matrix molecules in the duct-like structures of AOT suggested a key role of Osteonectin in the formation and maintenance of duct-like architecture.<sup>37</sup> Duct-like structures were detected in the histopathological images of 19 out of 29 reported AAD cases in this study.

In addition to these duct-like structures, areas comprising the odontogenic epithelial cells proliferating in the form of sheets, cords, trabeculae and whorls are also observed in AOT in 18 cases. Another characteristic feature noted in AOT is the formation of nests or rosette-like structures by odontogenic epithelial cells.<sup>19</sup> Herein, rosette-like structures were noted in only a few cases (n = 6); thus, their presence was not considered a definite criterion for the diagnosis of AAD.

An associated extracellular homogenous dentinoid material of varying amounts is invariably present in addition to the AM and AOT components in AAD. Dentinoid is defined as a non-mineralised

tissue, which is collagenous in nature and intimately associated with odontogenic epithelium.<sup>38</sup> The earliest interpretation of the eosinophilic material in AAD as dentinoid was proposed by Slabbert *et al.* in 1992.<sup>6</sup> The study found that the material was positively stained for collagen via Van Gieson and Mason's trichrome staining, negatively for amyloid staining by Congo Red and negatively for keratin by formic acid Alcian blue stain. The interpretation of the collagenous nature of dentinoid in AAD was further supported by Sonone *et al.* via positive Van Gieson staining and negative Congo Red staining.<sup>17</sup> Since collagen and bone are also primarily constituted of collagen fibres, the dentinoid material is controversially considered as bone globules or cementum.<sup>26,27</sup>

The formation of dentinoid material in epithelial tumours is a result of a metaplastic process rather than epithelial-ectomesenchymal interaction. This phenomenon could be attributed to the gene products usually present in normal ectomesenchymal cells and the ameloblast-like cells of mixed odontogenic tumours.<sup>39</sup> The outcome was the conversion of epithelial cells by subsequent interaction and co-expression of the mesenchymal phenotype. Thus, the neoplastic epithelial cells committed to ameloblastic differentiation could produce extracellular material of variable composition in a few tumours.<sup>23</sup> The lesions represent various directions for tumour differentiation, based on the initial inductive stimulus, the degree of odontogenesis prior to the stimulus and the variation in the metaplastic process.<sup>40</sup> The clinicopathological significance and prognostic value of the dentinoid material in AAD have not yet been determined and warrants further study.

The formation of dentinoid material has also been described in some malignant odontogenic neoplasms, such as primary intraosseous odontogenic carcinoma and odontogenic carcinoma.<sup>41</sup> The presence of cellular atypia in concomitance with other signs of malignancy in AAD may render ameloblastic carcinoma (AMCA) or odontogenic carcinoma as an appropriate diagnosis. Furthermore, the adenoid or duct-like structure might also be present in AMCA. However, the enamel organ-like structures or buds are not observed in odontogenic carcinoma with dentinoid.<sup>42</sup> Cellular atypia and abnormal mitosis were described in only one case of AAD reported by Khalele and Al-Shiaty.<sup>21</sup> Presumably, the possibility of AAD with features of malignancy to be diagnosed as AMCA further adds to the challenge of acknowledging the exact frequency of reported cases of AAD. The case reports of these malignant neoplasms with dentinoid emphasising the cellular morphologies rather than the glandular

**Table 4:** Summary of immunohistochemical markers in reported cases of adenoid ameloblastoma with dentinoid (N = 29)

Marker	Expression		Total
	Positive	Negative	
CK14	6	8	14
CK19	12	3	15
CK7	0	8	8
CK8/18	3	2	5
CK17	1	0	1
Calretinin	4	0	4
Ki-67	(Low) 10	(High) 5	15
P53	(High) 1	(Low to negative) 8	9
IMP3	0	8	8

component might have been missed, which pose as a limitation to the present review strategy.

Along with dentinoid, other types of extracellular materials have been identified in various studies. Matsumoto *et al.* reported that some of the cystic or duct-like spaces in AAD were positive for Alcian blue and Mucicarmine staining.<sup>8</sup> Yamazaki *et al.* found certain areas of amyloid-based extracellular material indicated by positive Congo Red staining.<sup>11</sup> Adorno-Farias *et al.* demonstrated pseudoducts with PAS-positive material.<sup>24</sup> Loyola *et al.* stated that although basophilic mucoïd material may be observed within the duct-like spaces, secretory component was not detected.<sup>13</sup> In the most recent case of AAD reported by Arruda *et al.*, Alcian blue staining revealed a significant amount of basophilic material and scarce PAS-positive eosinophilic material in duct-like spaces, indicating its mucoïd nature.<sup>25</sup>

Nine cases of AAD consisted of clear cells in a varied proportion of the tumour cell population. Clear cells may be noted in tumours of the head and neck and could be a resultant product due to artifacts of fixation, lack of cell organelles and intracellular accumulation of various substances, such as glycogen, mucin, lipids, tonofilaments and immature zymogen granules.<sup>43</sup> The clear cell changes could be attributed to tumour progression or secondary to clonal expansion.<sup>44</sup> Furthermore, the population of neoplastic cells comprising the OTs is derived from the dental lamina, which appears to be clear in routine HE-stained sections due to the abundance of glycogen content.<sup>45</sup>

Ghost cells were detected in four reported cases of AAD. The exact nature of ghost cells remains controversial; however, these cells might be the product of abortive enamel matrix or aberrant keratin formation.<sup>46,47</sup> The presence of variable dysplastic material along with ghost cells reflects varied

productive or inductive potentiality resulting from prosoplasia of the odontogenic epithelium.<sup>48</sup> The ghost cells are common in other odontogenic tumours, such as calcifying epithelial odontogenic tumour (CEOT), and should be differentiated from AAD as they do not comprise the adenoid areas.

Regarding the origin of cells in a tumour and subsequent diagnosis, various biomolecules are identified by immunohistochemistry (IHC).<sup>49</sup> The odontogenic tumours, particularly odontogenic epithelial cells, are associated with various biomarkers owing to complex genetic and epigenetic factors involved in their differentiation.<sup>50</sup> The expression of IHC markers assessed in the reported cases of AAD has been summarised [Table 4]. The most employed markers for IHC differentiation of epithelial cells are known as cytokeratins (CKs). CKs comprise a group of at least 20 polypeptides constituting specific intermediate filaments of epithelial cells. The various epithelia or carcinoma associated with these CKs are characterised by a specific pattern of polypeptides.<sup>51</sup>

CK14 has been identified as the primary, intermediate filament of odontogenic epithelium, present in the dental lamina, reduced enamel epithelium, duct-like structures of AOT, and in almost all the cells of the enamel organ associated with the secretory activity of the odontogenic epithelial cells.<sup>52</sup> Strong immunopositive staining for CK14 was observed in several central and peripheral cells of tumour islands and the adenoid structures and surrounding cells in 6 out of 8 cases, as reported by Adorno-Farias *et al.*<sup>24</sup> The negative expression of CK14 suggests the regions of advanced amelogenesis with the loss of cellular secretory activity, indicating the protective stage of amelogenesis.<sup>52</sup>

Strong and diffuse positive immunostaining for CK19 staining was observed in 12 out of 15 cases of AAD. CK19 is homogeneously expressed in the stellate reticulum-like cells, peripheral preameloblast-like cells, areas of squamous metaplasia, some cells of the adenoid structures and areas with whorled appearance.<sup>11,13,24</sup> It has been hypothesised that CK19 characterises ameloblasts and preameloblasts with complete differentiation. The negative immunopositive expression of the molecule implied that stimuli could not activate the final differentiation process in these tumoral cells.<sup>52</sup>

CK7 has been identified in the epithelial cells of Hertwig's epithelial root sheath and weakly in the stellate reticulum cells and dental lamina near the enamel organ.<sup>53</sup> The strong expression in odontogenic cysts and tumours, such as glandular odontogenic cyst and CEOT, confirmed their origin from Hertwig's epithelial root sheath cells. However, it is not expressed

in tumours, such as ameloblastoma, which develop from the enamel organ.<sup>54</sup> All the eight cases of AAD in the series reported by Adorno-Farias *et al.* were found to be IHC-negative for CK7.<sup>24</sup>

Although CK8/18 is present in the simple epithelium, such as ductal cells, its positive expression has been demonstrated in cases involving dysplastic epithelia, including leukoplakia and oral squamous cell carcinoma.<sup>55</sup> The study by Wato *et al.* on the expression of cytokeratins in the variants of AM identified it as a component in plexiform ameloblastoma.<sup>56</sup> The weakly positive staining of CK8/18 has also been reported previously in the epithelial cells of the ductal component in AOT.<sup>57</sup> Furthermore, CK8/18 was found to be focally positive in 3 out of 5 cases of AAD reported by Loyola *et al.*<sup>13</sup> Similarly, CK17 involved in carcinomas of stratified squamous epithelia constitutes a component of CKs in AM.<sup>56,58</sup> Moreover, CK17 expression in AAD was detected only in one case by Yamazaki *et al.*, wherein it was focally positive in cells containing the AM, but not the AOT component.<sup>11</sup>

The expression of calretinin, a 29-kDa calcium-binding protein, has been demonstrated in AM but not in the other types of odontogenic cysts.<sup>59</sup> Although the underlying biological mechanism is not yet known, calretinin acts as a mediator of intracellular calcium ion signalling, i.e. a secondary messenger intervening in cellular proliferation and differentiation.<sup>60</sup> It is also considered as a specific IHC marker for neoplastic ameloblastic epithelium, which is expressed only in AM and in odontogenic keratocyst but not in AOT.<sup>61,62</sup> In corroboration with these findings, the IHC expression of calretinin was investigated in all AAD cases (n = 4); subsequently, focal but intense positive immunorexpression, limited to the cells in the AM component of the tumour, was noted.

In addition to the biomolecules that aid in identifying the origin or type of cells in question, specific markers indicate the proliferative activity of the cells. The expression of the human Ki-67 protein is analysed and evaluated to assess the proliferative activity in a lesion.<sup>63</sup> The fraction of Ki-67-positive tumour cells, commonly known as Ki-67 labelling index, determines the fraction of a given cell population in the active growth phase and is often correlated with the aggressiveness of any lesion.<sup>64</sup> Ki-67 expression was variable in AAD cases, wherein it was borderline to low in the majority of the reported cases (n = 10).<sup>11,20–25</sup> However, the mean value of proliferative index as assessed by Ki-67 positive cells (72.4 ± 24.9 positive cells per high-power field) in the five cases of AAD reported by Loyola *et al.* was found to be higher than AOT and AM and was closer to that observed in AMCA. They inferred that the higher

Ki-67 indices in AAD were reflective of its inherent aggressive biological nature.<sup>13</sup>

p53 is also a routinely employed proliferative marker for malignancy and acts as a regulatory checkpoint in the cell cycle.<sup>65</sup> Normal cellular levels of wild-type p53 protein are low, and their half-life is short.<sup>66,67</sup> Mutant p53 products have a retarded degradation and elevated stability that contributes to their nuclear accumulation.<sup>68</sup> Thus, mutant p53 proteins are detected by IHC, rendering positive nuclear-staining signals, and have been frequently associated with malignant tumours. p53 expression was low to negative in all the cases (n = 8) reported by Adorno-Farias *et al.*<sup>24</sup> The study also concluded that the lesion could be differentiated from AMCA, since the latter has a high p53 expression. However, in the case reported by Khalele *et al.*, the lesion exhibited a strong positive expression for p53, indicating a high proliferation potential of AAD, and thus a prolonged interval of follow-up is essential in such cases.<sup>21</sup>

IGF-2 mRNA binding protein 3 (IMP3) is a post-transcriptional regulatory factor involved in embryonic development, and its aberrant expression has been associated with oncogenesis.<sup>69</sup> IMP3 was not expressed in any of the cases (n = 8) reported by Adorno-Farias *et al.*, which ruled out the carcinomatous nature of the lesion.<sup>24</sup> Overall, AAD could be deemed less aggressive than AMCA because of negative staining for p53, IMP3 and low expression of Ki-67 in most cases.

The primary purpose of employing an IHC panel inclusive of proliferative markers is to correctly identify the nature of the lesion and subsequently determine the prognosis of the lesion. Once the prognosis of the lesion is determined, the surgeon can confidently decide the treatment plan. Despite low proliferative indices on IHC analysis, multiple recurrences of the lesion were reported in more than 50% of cases of AAD, including post-surgical follow-up of the patients (n = 10). Amongst these, seven cases showed occurrence in the maxilla. The reason for recurrence in most of the maxillary AADs has been suggested as the inability to achieve a complete excision with adequate margin in maxilla, owing to porous structures with high vascularity within which the lesion infiltration makes removal of all the neoplastic cells rather challenging.<sup>13</sup> Another reason for the aggressive nature and recurrence of AAD suggested by Khalele and Al-Shiati was the inherent aggressive biological potential of the lesion, as indicated by strong immunorexpression of p53 protein.<sup>21</sup>

The tendency to aggressively invade the local structures in AM has been attributed to the degradation of extracellular matrix, resulting from an increase in matrix metalloproteinases and receptor activator of

nuclear factor-kappa B ligand along with increased mobility of neoplastic cells due to loss of syndecan-1.<sup>70</sup> On the other hand, AOT is clinically well-contained. The lack of direct contact of neoplastic epithelium with the adjacent bone tissue and induction of reactive bone formation by Osteonectin have been suggested as factors responsible for limited destruction in AOT.<sup>70</sup> Thus, additional studies are essential to establish a correlation between the expression of these molecular markers and the prognosis of the lesion in AAD.

In only seven cases, there was no evidence of disease on post-surgical follow-up. However, the follow-up period was 1–3 years in most of the cases, while AAD is known to recur even after nine years of treatment.<sup>9</sup> The maximum number of recurrences in a single case of AAD was reported by Loyola *et al.*, wherein the lesion had recurred nine times.<sup>13</sup> Thus, it can be estimated that AAD has a recurrence rate of  $\geq 75\%$ , although the precise rate could not be determined owing to the lack of post-treatment follow-up in almost 33% (n = 12) of reported cases and the paucity of the available literature of the lesion. Moreover, most of the recurrences were due to the underdiagnosis of the lesion as AOT and subsequent conservative treatment. The reason for the tendency of AAD to be misdiagnosed could be attributed to the predominance of AOT-like areas in the histopathological image, which might overshadow the AM areas, thereby leading to a benign diagnosis and conservative treatment.<sup>13</sup>

Multiple recurrences of the lesion following wide excision suggested the lesion should be treated aggressively.<sup>8,9,13,16</sup> All the cases treated with surgical resection had no evidence of recurrence for a variable follow-up period from six months to nine years. Also, the recurrences after the surgical resection of the lesion in the absence of disease until the time of the report except in one case wherein the patient had another recurrence.<sup>13</sup> Thus, surgical resection could be deemed appropriate treatment for AAD cases, while in cases involving maxillary sinus and floor of the orbit or those recurring even after excision, radiotherapy with radical neck dissection may be preferred.<sup>13</sup> In the case of AAD with UAM component, simple wide excision of the lesion was sufficient with no evidence of disease after a one-year follow-up, although evaluation of outcomes with prolonged follow-up period in more such cases is warranted.<sup>22</sup>

## Conclusion

AAD is a rare hybrid odontogenic tumour with less than 30 cases reported to date. The lesion may occur

at any age and commonly presents as an asymptomatic swelling in the mandible. Histopathologically, the lesion might vary due to follicular, plexiform, or mixed AM or UAM in conjunction with whorls of epithelial islands, duct-like structures, and infrequently, rosette-like structures of AOT along with a dentinoid component. Other features, such as granular cells, clear cells, ghost cells and desmoplasia, are seldom noted in AAD.

Furthermore, the lesion is frequently misdiagnosed as AM or AOT, and the individual entities composing the lesions owing to the abundance of either component in an incisional biopsy overshadows the other component. This leads to underdiagnosis of the lesion as AOT in several instances, and subsequent conservative treatment results in recurrence. Thus, it is imperative to identify the features of each component in the histopathological specimens of the odontogenic tumour to rule out such hybrid tumours.

Although molecular studies suggest that the lesion is relatively benign compared to AMCA, its aggressive clinical involvement cannot be overlooked as it has been reported to involve both sides of the jaws and extend to paranasal sinuses and orbital floor. Multiple recurrences following wide excision of the lesion indicated that the lesion should be treated aggressively, placing it at the aggressive end of the spectrum of benign odontogenic lesions. Therefore, an accurate diagnosis of the lesion to determine the treatment plan and the subsequent prognosis is imperative.

With the increasing number of cases reported in the last decade, AAD may be included as a distinct odontogenic neoplasm in the future. Consequently, a large number of AAD cases could be reported in the forthcoming future owing to an increase in the available literature on hybrid odontogenic tumours. This would provide clarity to the surgeons and pathologists regarding the diagnosis, management and prognosis of the entity. Moreover, future research on the genetic aspects of the tumour could elucidate the pathogenesis of AAD.

## AUTHORS' CONTRIBUTION

SS, TC, MS and YA conceptualised and defined the work. SS and TC conducted the initial literature review and devised the basic search strategy. MS, AS and AG modified the search strategy. All the authors contributed to performing the search and collecting data from the eligible articles. SS, TC, MA and YA analysed and interpreted the data. SS, TC and AS drafted the manuscript, while critical revision of the

manuscript was done by MS and AG. All authors approved the final version of the manuscript.

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