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Adenoid Ameloblastoma with Dentinoid

A systematic review

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Abstract

Ameloblastoma and adenomatoid odontogenic tumors are the most common odontogenic neoplasms. However, hybrid variant of the two lesions, Adenoid Ameloblastoma with dentinoid is extremely rare. The lesion comprises of characteristic histopathological features of Ameloblastoma and Adenomatoid odontogenic tumor and also shares certain clinical characteristics with either of the entities. Adenoid Ameloblastoma with dentinoid may be considered at the more aggressive end of spectrum of benign odontogenic neoplasms. Owing to the frequent tendency of lesion 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 WHO classification. The present systematic review aims at collectively presenting the demographic, clinical, radiographic and histopathological features, treatment performed along with its outcome for all the cases of Adenoid Ameloblastoma with dentinoid reported in scientific literature till date.

Keywords: Hybrid Odontogenic Tumor; Adenomatoid Odontogenic Tumor; Adenoameloblastoma; dentinoameloblastoma; Immunohistochemistry

The 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)

Introduction

The process of odontogenesis involves complex molecular interactions. Disruptions in these interactions could result in a distinct spectrum of neoplasms, unique to the jaws, that are collectively termed odontogenic tumors (OTs) [1]. 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 [2,3]. Owing to their development from various components of the tooth forming apparatus, OTs may present a considerable histopathological diversity.

Two or more distinct tumor entities may co-exist within the same lesion; these have been reported as hybrid tumors. These have been defined by Ide et al. as lesions showing the combined histopathological characteristics of two or more previously recognized tumors and/or cysts of different categories [4]. These tumors have not been included in the 2017 WHO classification system of odontogenic neoplasms owing to the inadequate number of reported cases [5].

One such variant of the hybrid odontogenic tumor may exhibit the histological features of both ameloblastoma (AM) and adenomatoid odontogenic tumor (AOT). This hybrid odontogenic tumor was first reported by Slabbert et al. in 1992 as dentinoameloblastoma [6]. The diagnostic term adenoid ameloblastoma with dentinoid (AAD) was first reported by the Armed Forces Institute of Pathology (AFIP) in 1994 by Brannon et al. [7]. Over a period, various terminologies have been associated with the lesions, such as atypical plexiform ameloblastoma with dentinoid [8], ameloblastoma with features of dentinoid [9], hybrid ameloblastoma and adenomatoid odontogenic tumor [10,11], AOT originating within an unicystic ameloblastoma [12] and atypical adenoid ameloblastoma [13]. Owing to the paucity of reported cases of the lesions, the data available regarding their pathogenesis, clinical behavior, diagnosis, and prognostication are limited.

The present systematic review aimed to collectively present the demographic details, clinical features, histopathological patterns, molecular markers, treatment performed along, and the

outcomes of all the cases of AAD 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.

Methods

Case reports and case series of AAD were retrieved by a systematic search of the databases: Medline (Ovid), PubMed, PubMed Central, Web of Science Citation Index Expanded (SCIEXPANDED), Google Scholar with the keywords “Adenoid” OR “Adenomatoid” AND “Ameloblastoma” AND “Dentinoid”. An additional search was performed using keywords “Hybrid” AND “Odontogenic” AND “Tumors”, and the retrieved literature was scanned to identify any cases reported with a name differing 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 colocalized within the same primary lesion site and exhibiting the histopathological characteristics of both AM and AOT, available in English language, were included in this review. On the other hand, lesions with uncertain diagnostic criteria, unclear histopathological characteristics, not exhibiting the features of both the entities 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 as enlisted in Table 1. With respect to the AM component, any of the histoapathological variants of Solid/Conventional AM as well as Unicystic Ameloblastoma (UAM), Peripheral AM and Metastatic AM were considered as eligible for inclusion.

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

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 presence of clear cells within the tumor 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, have also been included and discussed in this study. Also, 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 according to the 4th Edition of WHO Classification of Head and Neck Tumors (2017) [5]. 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. The authors of the included studies were divided into two groups that independently screened the cases and extracted and input the data into the meta-analysis sheets (MS Office Excel, 2016, Microsoft Redmond Campus, Redmond, WA, USA) to eliminate the risk of bias in quality assessment**.**

Results and Discussion

A total of 29 reported cases of AAD could be extracted from 18 publications available in English. The comprehensive findings after a detailed review of all the cases are collectively summarized in Table 2 and Table 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 [6]. The small number of reported cases are reflective of the rarity of AAD. Perhaps, many 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 4/45 cases of AM were re-assessed and re-classified as AAD in a retrospective study by Loyola et al. [13]. Therefore, the actual number of cases might be much greater than those reported in the literature. With increasing case reports on the tumors 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 to 2020. Thus, it can be expected more cases of AAD would be reported in the coming years.

The mean age of the patients presenting the lesion was 38.97 ± 27.43 (range: 15–82) years. The maximum number of cases occurred in the fourth decade (n = 10), followed by the second and fifth decades (n = 5 each, respectively) of life, and the least number of cases were reported in the seventh or above decade [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 [26]. Unlike AOT, which is more common in females, AM does not exhibit sex predilection [27]. In the case of AAD, the reported cases comprised 16 males and 13 females, yielding a ratio of nearly 1:1. The absence of sex 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) than the left side (n = 6). Half of the lesions occurring on the left side (n = 6) were in the maxillary jaw. Considering the less frequency of lesions in the maxilla, it could 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). About 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 [26]. 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 3 cases. Paresthesia and numbness were elicited in 4 cases, with all the lesions inevitably involving the mandibular posterior region. Pain, paresthesia, and numbness are also associated with AM lesions, albeit

uncommonly, and could be attributed to the tumor mass impinging on the peripheral nerves or secondary infection [28].

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. (2015) reported only two cases presented a poorly defined radiolucent lesion, which occurred in the maxillary jaw involving the nasal fossa, nasal and paranasal sinuses, and the orbit [13]. In cases of large AM or AOT, similar involvement of nasal and maxillary sinuses with poorly defined lesions has been reported [27]. The slow-growing, painless clinical course of the lesion, and thin and porous maxillary bone might be the factors for presentation of lesions as extensive, poorly defined radiolucency [29].

Multilocularity was observed in only 2/8 cases reported by Adorno-Farias et al. (2018) [24]. It is observed in the radiographic images of AM, wherein the tumor exhibits the septae of bone extending into the radiolucent tumor mass [30]. 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 [10,11,17].

Furthermore, the histopathology of the AM component of the tumor revealed that 9 cases had a predominant plexiform pattern of ameloblast-like cell proliferation, 9 cases exhibited a follicular pattern, and 9 cases comprised a mixture of both patterns. The follicular and plexiform histopathological patterns in isolated and mixed forms are similar in cases of AM [31], which was similar to our findings. Only two cases had UAM associated with AOT, suggesting that most AADs are associated with solid/muticystic AM.

Desmoplastic changes are infrequently noted in ameloblastoma owing to the loss of expression of Notch receptors representing an early stage of cell differentiation [32,33]. This phenomenon is observed in AAD cases, wherein only one case reported by Salahinejad et al. presented features of desmoplastic AM [20]. 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 center of the follicles [34]. 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 [20].

Squamous metaplasia occurring within the central stellate reticulum-like cells of AM follicles is an occasional histological finding termed “acanthomatous ameloblastoma” [27]. Squamous metaplasia was observed in all of the eight cases reported by Adorno-Farias et al. in 2018 (n = 8). Of these, seven lesions occurred in the mandibular jaw, while the clinical details of 1 case were missing [24]. 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 [35].

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 [36]. The term “adenomatoid” is derived from “adḗn” meaning gland and “-oma” meaning swelling or tumor. 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 [26]. 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 [37]. Duct-like structures were detected in the histopathological images of 19/29 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 [19]. Herein, Rosette-like structures were noted in only a few cases (n = 6), and 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-mineralized tissue, which is collagenous in nature and intimately associated with odontogenic epithelium [38]. The earliest interpretation of the eosinophilic material in AAD as dentinoid was proposed by Slabbert et al. in 1992 [6]. 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 negative 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 [17]. Since collagen and bone are also primarily constituted of collagen fibers, the dentinoid material is controversially considered as bone globules or cementum [26,27].

The formation of dentinoid material in epithelial tumors 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 tumors [39]. 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 some tumors [23]. The lesions represent different directions for tumor differentiation, depending on the initial inductive stimulus, the degree of odontogenesis prior to the stimulus, and the variation in the metaplastic process [40]. 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 [41]. 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. Also, the adenoid or duct-like structure might be present in AMCA. However, the enamel organ-like structures or buds are not observed in odontogenic carcinoma with dentinoid [42]. Cellular atypia and abnormal mitosis were described in only one case of AAD reported by Khalele et al. [21]. Supposedly, 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 emphasizing the cellular morphologies rather than the glandular component might have been missed, which poses as a limitation to the present review strategy.

Besides 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 [8]. Yamazaki et al. found certain areas of amyloid-based extracellular material indicated by positive Congo Red staining [11]. Adorno-Farias et al. demonstrated pseudoducts with PAS-positive material [24]. Loyola et al. [13] stated that although basophilic mucoid material may be observed within the duct-like spaces, secretory component was not detected. 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 mucoid nature [25].

Nine cases of AAD consisted of clear cells in a varied proportion of the tumor cell population. Clear cells may be noted in tumors 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 [43]. The clear cell changes could be attributed to tumor progression or secondary to clonal expansion [44]. 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 [45].

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 [46,47]. The presence of variable dysplastic material along with ghost cells reflects varied productive or inductive potentiality resulting from prosoplasia of the odontogenic epithelium [48]. The ghost cells are common in other odontogenic tumors, such as calcifying epithelial odontogenic tumor (CEOT), and should be differentiated from AAD as they do not comprise the adenoid areas.

Regarding the origin of cells in a tumor and subsequent diagnosis, various biomolecules are identified by immunohistochemistry (IHC) [49]. The odontogenic tumors, especially odontogenic epithelial cells, are associated with various biomarkers owing to complex genetic and epigenetic factors involved in their differentiation [50]. The expression of IHC markers assessed in the reported cases of AAD has been summarized in **Table 4**. The most commonly employed markers for IHC differentiation of epithelial cells are 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 characterized by a specific pattern of polypeptides [51].

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 [52]. Strong immunopositive staining for CK14 was observed in many central and peripheral cells of tumor islands and the adenoid structures and surrounding cells in 6/8 cases reported by Adorno-Farias et al. [24]. The negative expression of CK14 suggests the regions of advanced amelogenesis with the loss of cellular secretory activity, indicating the protective stage of amelogenesis [52].

Strong and diffuse positive immunostaining for CK19 staining was observed in 12/15 cases of AAD. CK19 is homogenously 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 [11,13,24]. It has been hypothesized that CK19 characterizes ameloblasts and preameloblasts with complete differentiation. The negative immunoexpression of the molecule implied that stimuli could not activate the final differentiation process in these tumoral cells [52].

CK7 has been identified in the epithelial cells of Hertwig's epithelial root sheath and also weakly in the stellate reticulum cells and dental lamina near the enamel organ [53]. The strong expression in odontogenic cysts and tumors, such as Glandular odontogenic cyst and CEOT, confirmed their origin from Hertwig's epithelial root sheath cells. However, it is not expressed in tumors, such as ameloblastoma, which develop from the enamel organ [54]. All the eight cases of AAD in the series reported by Adorno-Farias et al. were IHC-negative for CK7 [24].

Although CK8/18 is present in the simple epithelium, such as ductal cells, its positive expression has been demonstrated in cases involving dysplastic epithelia, such as leukoplakia and oral squamous cell carcinoma [55]. The study by Wato et al. on the expression of cytokeratins in the variants of AM identified it as a component in plexiform ameloblastoma [56]. The weakly positive staining of CK8/18 has also been reported previously in the

epithelial cells of the ductal component in AOT [57]. Furthermore, CK8/18 was found to be focally positive in 3/5 cases of AAD reported by Loyola et al. [13]. Similarly, CK17 involved in carcinomas of stratified squamous epithelia constitutes a component of CKs in AM [56,58]. Also, CK17 expression in AAD was detected only in one case by Yamazaki et al. [11], wherein it was focally positive in cells containing the AM, but not the AOT component.

The expression of Calretinin, a 29-kDa calcium-binding protein, has been demonstrated in AM but not in the other types of odontogenic cysts [59]. Although the underlying biological mechanism is not yet known. Calretinin acts as a mediator of intracellular calcium ion signaling, i.e., a secondary messenger intervening in cellular proliferation and differentiation [60]. 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 [61,62]. In corroboration with these findings, the IHC expression of Calretinin was investigated in all AAD cases (n = 4); subsequently, focal but intense positive immunoexpression, limited to the cells in the AM component of the tumor, 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 analyzed and evaluated to assess the proliferative activity in a lesion [63]. The fraction of Ki-67-positive tumor cells, commonly known as Ki-67 labeling index, determines the fraction of a given cell population in the active growth phase and is often correlated with the aggressiveness of any lesion [64]. Ki-67 expression was variable in AAD cases, wherein it was borderline to low in the majority of the reported cases (n = 10) [11,20-25]. However, the mean value of proliferative index as assessed by Ki-67 positive cells (72.4 $\pm$ 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 [13].

p53 is also a routinely employed proliferative marker for malignancy and acts as a regulatory checkpoint in the cell cycle [65]. Normal cellular levels of wild-type p53 protein are low [66], and the half-life is short [67]. Mutant p53 products have a retarded degradation and elevated stability that contributes to their nuclear accumulation [68]. Thus, mutant p53 proteins are detected by IHC, rendering positive nuclear-staining signals, and have been frequently

associated with malignant tumors. p53 expression was low to negative in all the cases (n = 8) reported by Adorno-Farias et al. [24]; 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. [21], 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.

IMP3 (IGF-2 mRNA binding protein 3) is a post-transcriptional regulatory factor involved in embryonic development, and its aberrant expression has been associated with oncogenesis [69]. IMP3 was not expressed in any of the cases (n = 8) reported by Adorno-Farias et al. [24], which ruled out the carcinomatous nature of the lesion. 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 > 50% of cases of AAD that included post-surgical follow-up of the patients (n = 10); of 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 [13]. Another reason for the aggressive nature and recurrence of AAD suggested by Khalele et al. was the inherent aggressive biological potential of the lesion, as indicated by strong immunoexpression of p53 protein [21].

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 (RANKL) along with increased mobility of neoplastic cells due to loss of Syndecan-1 [70]. 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 [70]. 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 9 years of treatment [9]. The maximum number of recurrences in a single case of AAD was reported by Loyola et al., wherein the lesion had recurred nine times [13]. Thus, it can be estimated that AAD has a recurrence rate of ≥ 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, the majority of the recurrences were due to the underdiagnosis of the lesion as AOT and subsequent conservative treatment, which resulted in recurrence. 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 [13].

Multiple recurrences of the lesion after wide excision suggested that the lesion be treated aggressively [8,9,13,16]. All the cases treated with surgical resection had no evidence of recurrence for a variable follow-up period from 6 months to 9 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 [13]. 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 [13]. 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 [22].

Conclusion

AAD is a rare hybrid odontogenic tumor with less than 30 cases reported to date. The lesion occurs at any age and commonly presents as an asymptomatic swelling in the mandible. Histopathologically, the lesion might be different 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 many 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 tumor to rule out such hybrid tumors.

Although molecular studies suggested 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 extended 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 WHO Classification of Head and Neck Tumors. 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 tumors. This would provide clarity to the surgeons and pathologists regarding the diagnosis, management, and prognosis of the entity. Also, future research on the genetic aspects of the tumor could elucidate the pathogenesis of AAD.

Authors' Contribution

The conception and definition of title was done by SS, TC, MS and YA. Initial literature review and basic search strategy was devised by SS and TC. Modifications to the strategy were done by MS, AS and AG. All the authors contributed to performing the search and collecting data from the eligible articles. Data analysis and interpretation was done by SS, TC, MA and YA. SS, TC and AS drafted the manuscript, while critical revision of the manuscript was done by MS and AG. Approval of the final version of manuscript to be published was obtained from all the authors.

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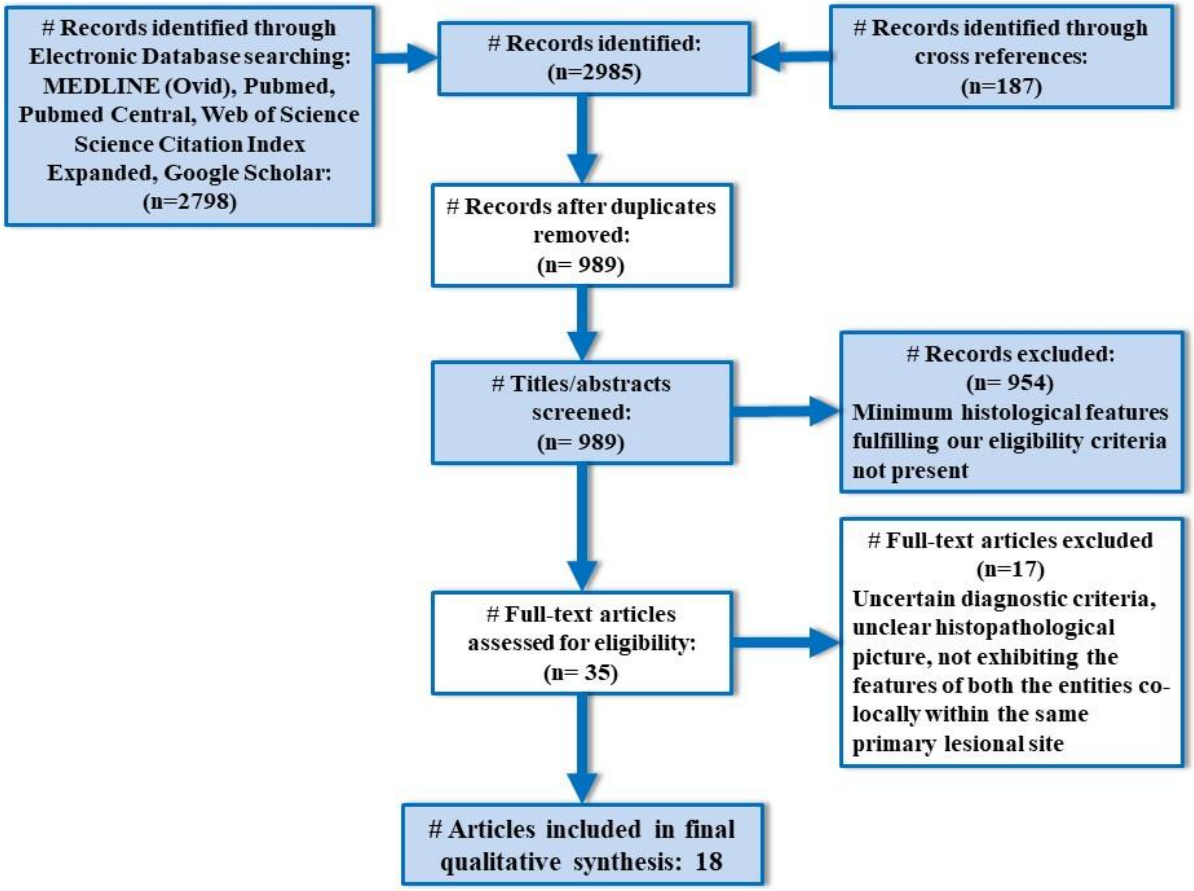

Figure 1: PRISMA Flow Chart indicating selection process of articles for final qualitative synthesis in the present systematic review

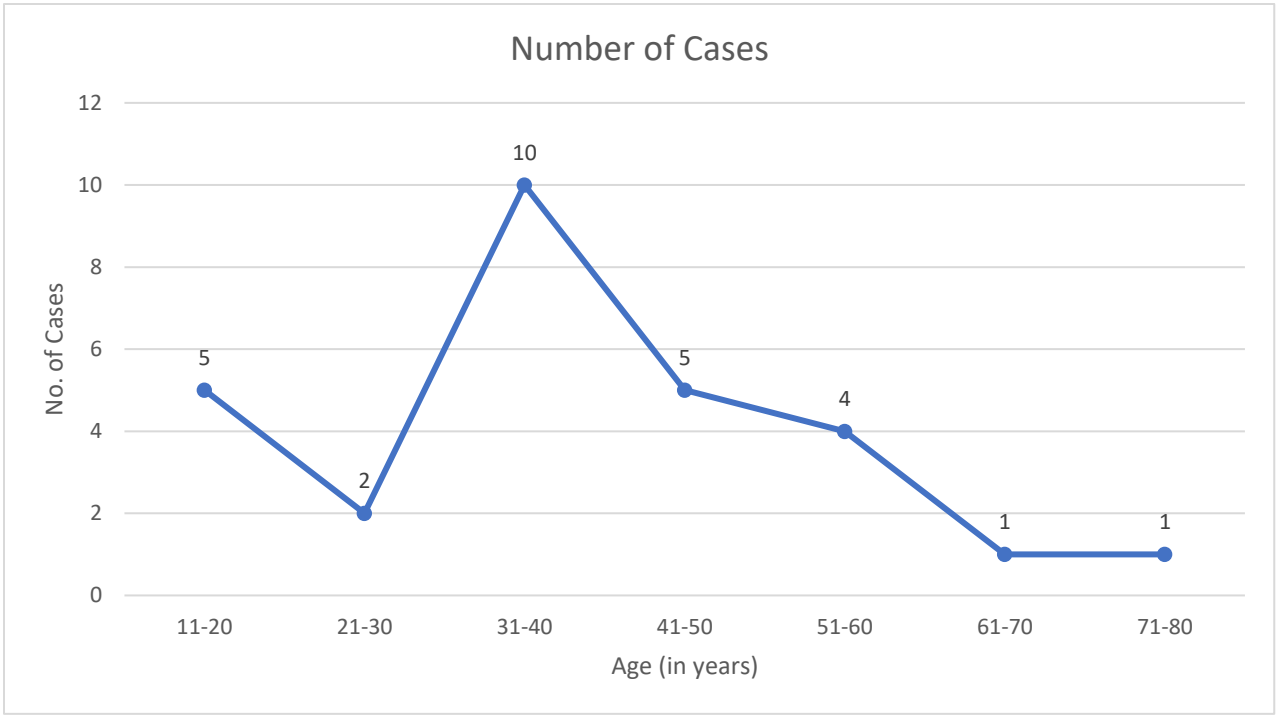

Figure 2: Line diagram exhibiting number of reported cases of AAD belonging to various age groups

649 **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 vacuolization (Gorlin-Vickers Criteria) [14]
AOT 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

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652 **Table 2:** Summarized Parameters of Cases of Adenoid Ameloblastoma with Dentinoid

Author	Year	Age (yrs)	Sex	Duration	Arch	Side	Symptoms	Radiographic features	Histopathological Features	Special Stains / IHC	Final Diagnosis	Treatment [with number of recurrences]	Follow-up with NED
Slabbert et al	1992	24	M	N/P	Mn	L	Swelling	UL RL	AM-F, AM-P, AOT-S, DM	Van Gieson + Masson's trichrome + Congo red – Alcian blue –	Dentinoameloblastoma	WE	N/P
Mastumoto et al	2001	19	M	1 mo	Mn	R	Swelling	WD UL RL	AM-P, AOT-S, AOT-D, DM	Mucicarmine + Alcian blue +	Atypical Plexiform AM with Dentinoid	Marsupialization + Enucleation (1 Rec after 2 yr) WE	2.5 yr
Evans et al	2004	39	M	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 et al	2006	64	F	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 et al	2007	40	M	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
Moridani et al	2008	19	F	2 mo	Mx	R	Swelling	WD UL RL	AM-P, AOT-S, AOT-D, DM	N/P	AAD	Excision	N/P
Ide et al	2009	44	M	N/P	Mx	CM	N/P	WD UL RL	AM-P, AOT-S, AOT-D, AOT4, DM	Calretinin +	AAD	En Excision (3 recs over a 11-year period) Partial maxillectomy	8 yr
Sonone et al	2011	35	F	1 year	Mn	R	Swelling + Numbness	WD UL RL with RO foci	AM-P, AOT-S, AOT-D, AOT-R, DM, GC	Van Gieson + Congo red –	AAD	SR	6 mo
Saxena et al	2012	45	M	2 wk	Mx	L	Swelling	Diffuse RL	AM-P, AM4 AOT-D, AOT-S, DM	N/P	AAD	WE (3 recs) SR	N/P
Yamazaki et al	2014	31	F	N/P	Mn	R	None	WD UL RL with sclerotic area in distal portion	AM-F, AM-P, AOT-S, AOT-D, DM, CC	CK19 ++ CK17 + Calretinin + Ki-67 + Congo red +	Hybrid AM and AOT	SR	36 mo
Loyola et al	2015	55	M	5 mo	Mn	L	Swelling	N/P	AM-F, AM-P, AOT-S, AOT-D, DM	CK19: ++ Ki-67 ++ CK 8/18 –	AAD	1 rec SR	108 mo

		24	F	6 mo	Mx	L	Swelling	WD UL RL		None	Adenoid AM (hybrid/mixed odontogenic tumour)	WE	6 mo
		31	M	1 mo	Mn	R	Swelling	WD RL		None	Adenoid Granular cell AM with Dentinoid	Hemimandibulectomy	18 mo
		40	M	N/P	Mn	CM	Swelling, numbness, parasthesia	WD UL RL.		Calretinin ++ p53 ++	Atypical Adenoid AM	Hemimandibulectomy	14 mo
		16	F	2 mo	Mn	R	Swelling	UL RL		None	AAD	WE	12 mo
Kumar et al	2015	55	M	3 mo	Mn	R	Swelling, pain, paresthesia	WD UL RL	AM-P, AOT-S, AOT-D, AOT-R, DM, GC	CK 19 +	AAD	SR	36 mo
Salahinejad et al	2016	34	F	43 mo	Mx	R	Swelling	PD RL	AM-F, AM-P, AOT-D, DM	CK19 ++ Ki-67 ++ CK 8/18 +	AAD	9 recs SR	19 mo
Khalele et al	2016	33	F	48 mo	Mx	R	Swelling + pain	N/P	AM-F, AM-P, AOT-S, AOT-D, AOT-R, DM	CK19 ++ Ki-67 ++ CK 8/18 –	AAD	5 Recs SR + Radiotherapy+ Neck Dissection	N/P
Sathyanarayan et al	2017	51	M	72 mo	Mx	CM	Swelling + pain	PD RL	UAM, AOT-S, AOT-D, AOT-R, DM	CK19 ++ Ki-67 ++ CK 8/18 +	AAD	5 Recs SR	76 mo
Rai et al	2017	47	M	18 mo	Mx	CM	Swelling	N/P	AM-F, AOT-S, AOT-D, DM	CK19 ++ Ki-67 ++ CK 8/18 +	AAD	2 Recs SR + Radiotherapy+ Neck Dissection	52 mo
Adorno-Farias et al	2018	15	F	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	M	12 mo	Mn	L	Swelling + pain	WD ML RL	AM-F, AOT-S, AOT-D, DM, CC	CK7 - CK14 – CK19 ++ IMP3 - Ki-67 + p53: -		SR	N/P
		46	F	N/P	Mn	N/P	N/P	UL RL		CK7 – CK14 ++ CK19 ++ IMP3 – Ki-67 + p53: -		SR	N/P
		34	F	N/P	Mn		Swelling	UL RL		CK7 – CK14 ++ CK19 – IMP3 – Ki-67 + p53 -		SR	N/P

		N/P	F	N/P	N/P		N/P	UL RL		CK7 - CK14: ++ CK19: ++ IMP3 - Ki-67 + p53 -		SR	N/P
		15	M	12 mo	Mn		Swelling	UL RL	AM-F, AOT-S, AOT-D, DM, CC	CK7 – CK14 ++ CK19 + IMP3 - Ki-67 + p53 -		SR	N/P
		82	M	36 mo	Mn		Swelling	ML RL	AM-F, AOT-D, DM, CC, GC	CK7 – CK14 ++ CK19 - IMP3 - Ki-67 + p53 -		SR	N/P
		46	M	N/P	N/P		N/P	UL RL	AM-F, AOT-D, DM, CC	CK7 – CK14 ++ CK19 – IMP3 – Ki-67 + p53 -		SR	N/P
Arruda et al	2020	51	F	N/P	Mx	L	None	WD UL RL	AM-P, AOT-S, AOT-D, DM	Alcian blue PAS ++ Ki-67: +	AAD	1 Rec SR	108 mo

Not provided – N/P; Mandible – Mn; Maxilla – Mx; Crossing Midline – CM; Well-defined – WD; Poorly defined – PD; Unilocular – UL; Multilocular – ML; Radiolucency – RL; Radiopaque – RO; Wide excision – WE; Surgical Resection – SR; Recurrence – Rec

Table 3: Summarization of various parameters observed following review of case reports and case series of adenoid ameloblastoma with dentinoid

Age	***Lowest*** *15 years*			***Highest*** *82 years*			***Mean*** *38.97*	
Sex	**Males** n=16			**Females** n=13				
Arch	**Mandible** = 18			**Maxilla** = 9				
	Left n=3	CM n=4	Right n=6	Left n=3	CM n=3	Right n=3	Side not provided n=7	
Symptoms	**Asymptomatic swelling** n=16			**Pain** n=3			**Paresthesia/Numbness** n=4	

Radiographic	**Well defined unilocular radiolucency** n=20	**Well-defined multilocular radiolucency** n=2	**Poorly defined radiolucency** n=2	**Radiolucent lesion with Radiopaque foci** n=3
Features of AM component	**Follicular** n=9	**Plexiform** n=9	**Mixed** n=9	**Unicystic Ameloblastoma** n=2
Changes in AM component	**Desmoplastic** n=1	**Granular cells** n=1		**Squamous metaplasia** n=8
Features of AOT component	**Duct-like structures** n=19	**Sheets/ whorls of cells** n=18		**Rosette-like structures** n=6
Other histological features	**Clear cells** n=9	**Ghost cells** n=4		
Recurrences	**Cases reporting recurrences** n=12	**Maximum number of recurrences in a single case** n=9		**Followup details not provided** n=13

Table 4: Summarization of immunohistohemical markers in reported cases of adenoid ameloblastoma with dentinoid

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

IMP3	**Positive** n=0	**Negative** n=8	**8**

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