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Case Report

Ameloblastoma with adenoid features with multiple local recurrences: report of a case with clinicopathologic and immunohistochemical studies

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Abstract: Ameloblastoma with adenoid features is characterized by the formation of cribriform or glandular tubular structures in addition to the conventional ameloblastoma; however, many aspects of the clinical and histologic characteristics are unclear. We report a case of ameloblastoma with adenoid features that occurred in the mandible and had multiple recurrences. The patient was a 54-year-old woman who presented with a chief complaint of painless swelling in the left mandibular molar region. On the first visit, a bone expansion was noted in the lingual alveolar region of the left mandibular molar. Panoramic radiograph and computed tomography revealed a unilocular radiolucent finding extending from the left mandibular first molar to the anterior edge of the left mandibular ramus. A biopsy was performed and the diagnosis was ameloblastoma. Therefore, we performed left mandibular tumor resection. Histopathologic findings showed that tissue corresponding to the conventional ameloblastoma had proliferated, and the tumor nests had a duct-like and cribriform structure. However, no whorl/morula-like structure or dentinoid was observed, leading to a diagnosis of ameloblastoma with adenoid features. Thereafter, the tumor recurred twice, and resection surgery was performed, but both cases showed the same histopathologic findings as the initial surgery. Morphologic features are important to distinguish between ameloblastoma with adenoid features and conventional ameloblastoma. In addition, ameloblastoma with adenoid features has a stronger tendency to recur than conventional ameloblastoma, and surgical resection with a sufficient margin of safety and strict postoperative follow-up are necessary.

Keywords: Ameloblastoma with adenoid features, recurrence, immunohistochemistry, odontogenic tumor, hybrid tumor

Introduction

Odontogenic tumors are derived from tissues that appear during tooth development. Although the majority of cases are benign, ameloblastoma is an epithelial odontogenic tumor in which the cells that make up the tumor parenchyma are derived from the odontogenic epithelial cells of the tooth germ. Ameloblastoma is known to be locally invasive, and to prevent recurrence, it is desirable to perform resection with a safe margin. Among odontogenic tumors, ameloblastoma is reported to occur most frequently, accounting for 41.9-53.1% of all odontogenic tumors [1, 2]. In the 4th edition of the WHO classification for odontogenic tumors, ameloblastoma was divided into four subtypes based on clinical and imaging characteristics: 1) ameloblastoma, 2) ameloblastoma, extraosseous/peripheral type, 3) ameloblastoma, unicystic type, and 4) metastasizing ameloblastoma [3]. Although the majority of ameloblastomas can be classified based on this criterion, some lesions are difficult-to-diagnose and defy this classification. Histopathologically, ameloblastoma with adenoid features produce tissue that corresponds to conventional ameloblastoma, and have cribriform or tubular structures [4]. In addition, deposition of dentinoid material can occur, which is not observed in conventional ameloblastoma [5-10]. Whorled epithelial structures, calcifications [5, 6, 10-12], clusters

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of ghost cells [5, 6, 11, 12], clear cells [5, 6, 10] and focal loss of ameloblastic differentiation [5] can also be found. Given the fact, the 5th edition of the WHO classification for odontogenic tumors added adenoid ameloblastoma to the previous classification [13]. However, few cases have been reported to date, and many details remain unclear, including the clinicopathologic characteristics, appropriate treatment, recurrence rate, and prognosis of ameloblastoma with adenoid features.

In the present study, we experienced an ameloblastoma with adenoid features that occurred in the mandible and had multiple recurrences, and we would like to report an overview of the case, and discuss adenoid ameloblastomas and ameloblastomas with adenoid features that have been reported so far.

Case report

A 54-year-old woman visited our department with a chief complaint of painless swelling in the left mandibular molar region. In 1 year before the initial visit at our department, mobility of the left mandibular second molar was observed, and it was extracted at a nearby dental clinic. Thereafter, there were no problems in that area, but in 4 months before the initial visit, the patient began to notice tenderness in the left submandibular region. The patient was followed up, but swelling of the gingiva corresponding to the left mandibular second molar was observed, and the patient visited a nearby dental clinic. When a panoramic radiograph was taken, a cystic radiolucent area was detected in the left mandibular molar area, and the patient was referred to our department for further investigation and treatment. No special notes were found regarding past medical history or family history. As for the present condition, systemic findings were 174.3 cm in height and 62.1 kg in weight, and the ECOG performance status grade was 0. As for extraoral findings, the facial appearance was bilaterally symmetrical, and no swelling was observed in the left cheek or submandibular region. Furthermore, no evidence of left trigeminal nerve palsy was observed. No trismus was observed, and no obvious abnormal findings were observed in the cervical lymph nodes. As for intraoral findings, bone expansion and fluctuation were palpable in the lingual alveolar area of the left mandibular first molar and left mandibular second molar (**Figure 1A**). The left mandibular first molar had a root canal filling, and no tooth mobility was observed. The periodontal pockets of the left mandibular second premolar and first molar were less than 3 mm. Imaging findings included a unicystic radiolucent finding extending from the mesial root of the left mandibular first molar to the anterior edge of the left mandibular ramus on panoramic radiograph (**Figure 1B**) and plain computed tomography (CT) (**Figure 1C**). The CT number inside the lesion was 15-40 Hounsfield units, which suggested that there was a collection of fluid components. The lingual cortical bone of the left mandibular molar area was expanded by the lesion and partially disappeared. Root resorption was observed in the distal root of the left mandibular first molar adjacent to the lesion. Contact between the lesion and the mandibular canal was observed. Magnetic resonance imaging (MRI) revealed a mass lesion with internal heterogeneity dimensions of 45 × 25 × 37 mm in which fluid components had accumulated in the jawbone in the area corresponding to the left mandibular molar (**Figure 1D**). Based on these findings, the clinical diagnosis was a left mandibular tumor. Therefore, in 5 months after the initial visit at our department, an incisional biopsy was performed (**Figure 2A**). Biopsy findings showed that the capsule of the lesion was thin and difficult to separate from the surrounding bone and periosteum. The fluid inside the lesion was brown and serous. Histologic findings of the biopsy specimen (**Figure 2B**) revealed solid proliferation of tumor cells, and occasional duct-like structures were observed. Eosinophilic hyaline-like stroma was observed in the lumen of the duct-like structure. The morphology of the tumor cells was basal cell-like cells with a high nucleus-cytoplasm ratio and a nearly circular nucleus. A small number of mitotic counts were observed, and the Ki67 labeling index was 3%. The diagnosis on the biopsy specimen was ameloblastoma, but the differential diagnosis included adenomatoid odontogenic tumor (AOT) and salivary gland tumor mainly composed of basaloid cells. In 6 months after the initial visit, left mandibular tumor resection, left segmental mandibulectomy, and reconstruction using a mandibular reconstruction plate and free ilium were performed under general anesthesia (**Figure 3A**, **3B**).

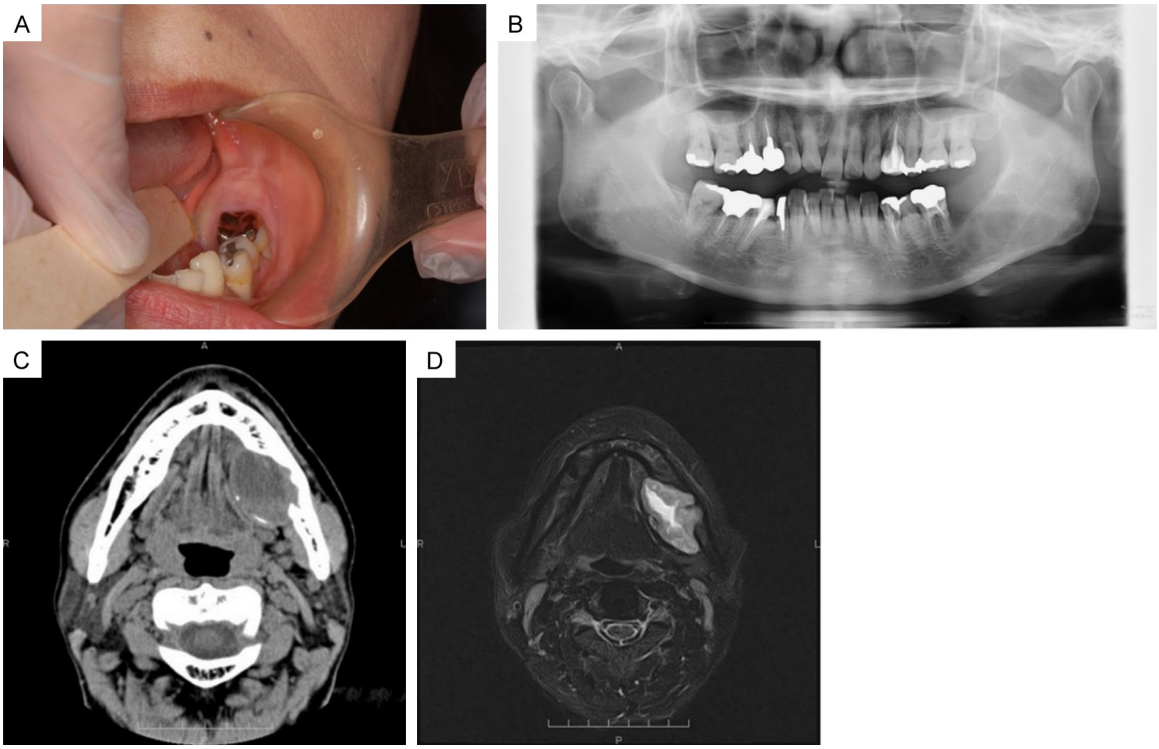

Figure 1. Intraoral findings and panoramic radiograph, computed tomography (CT), and magnetic resonance imaging (MRI) findings at initial visit. A: Bone expansion was found in the lingual alveolar area of the left mandibular first molar to left mandibular second molar. B: Panoramic radiograph finding. A unilocular X-ray image was observed in the mandible from the left mandibular first molar to the left mandibular ramus. C: CT findings. The CT number inside the lesion ranged from 15-40 Hounsfield units, which was thought to be a fluid collection. The lingual cortical bone of the left mandibular molar was expanding and partially disappeared. D: MRI finding. A mass lesion of 45 × 25 × 37 mm in size with a heterogeneous internal fluid collection in the mandible corresponding to a left mandibular molar was observed.

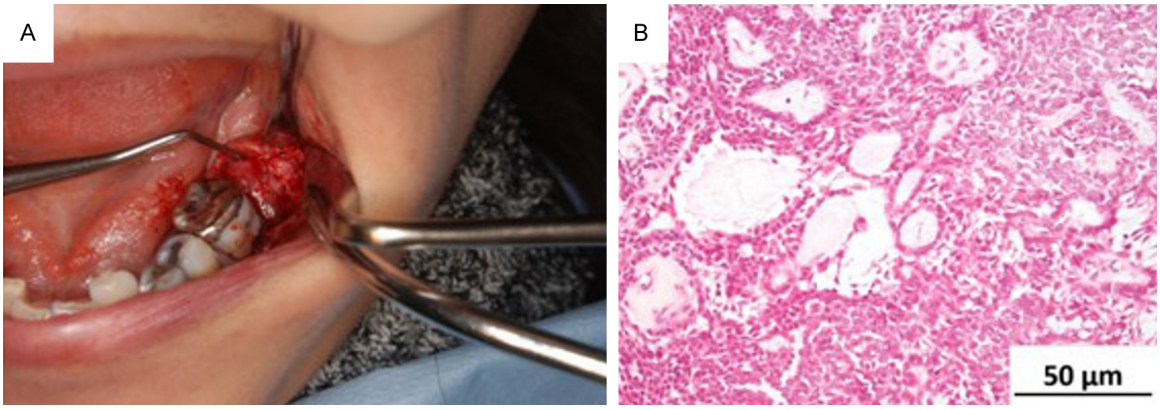

Figure 2. Biopsy findings. A: Findings on incisional biopsy. The capsule of the lesion was thin and difficult to separate from the surrounding bone and periosteum. The lesion was brown and serous. B: Histologic findings of the biopsy specimen. There was solid proliferation of tumor cells and scattered glandular duct-like structures were observed. Eosinophilic hyaline-like stroma was observed in the lumen of the duct-like structures. The morphology of the tumor cells was basal cell-like cells with a high nucleus-cytoplasm ratio and a nearly circular nucleus (Magnification ×200).

Histologic findings revealed that the lesion was multinodular with clear borders. Most of the tumor was composed of basaloid cells with a high nucleus-cytoplasm ratio and exhibited a

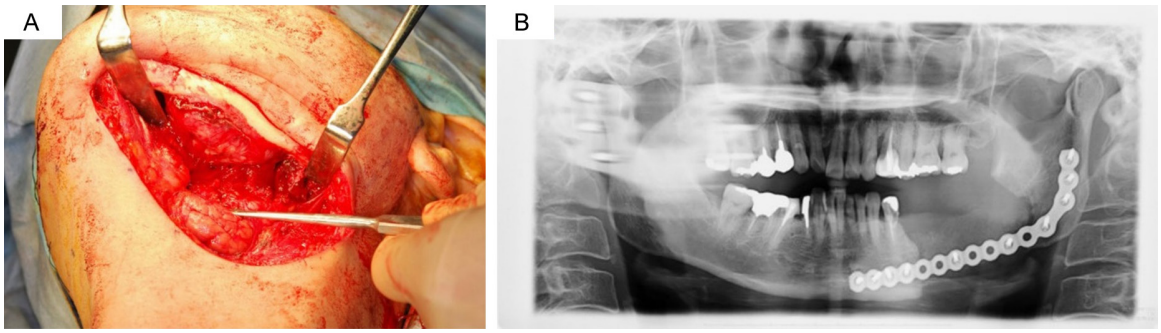

Figure 3. Findings at initial surgery. A: The lesion was exfoliated under the periosteum, and where there was adhesion between the lesion and the periosteum, exfoliation was done between the lesion and the periosteum. The lingual side of the mandible was expanded and partially obliterated by the lesion. B: Postoperative panoramic radiograph findings.

glandular or cribriform structure (**Figure 4A**, **4B**). In addition, some areas showing solid proliferation were also observed (**Figure 4C**, **4D**). A rim of basal cell-like cells was observed at the edge of the tumor nest, and within the tumor nest, there was proliferation of stellate or spindle-shaped cells resembling enamel pulp (**Figure 4D**). Although the cell density was very high, only a few mitotic figures were observed. In addition, nuclear palisading was observed at the margin of the tumor nest. Immunohistochemical staining (**Table 1**) showed that tumor cells were positive for keratin 19 (**Figure 4E**), 34βE12 (**Figure 4F**) and p63 (**Figure 4G**). Ki67 (**Figure 4H**) and p53 were focally positive, but no region with Ki67 labeling index exceeding 10% was observed. On the other hand, CEA, EMA, keratin 7, S-100 protein, and α-SMA were negative. BRAF V600E (**Figure 4I**) was negative, and β-catenin (**Figure 4J**) was positive in the cytoplasm, but no translocation into the nucleus was observed. Thus, this case showed a conventional ameloblastoma-like tissue, glandular tubular structure, and cribriform structure. However, no whorl/morula-like structures and dentinoid were observed. Therefore, the final diagnosis was ameloblastoma with adenoid features.

In 1 year and 6 months after the initial visit, after confirming that there was no evidence of local recurrence 12 months after the surgery, two dental implants were placed in the left mandibular molar region. Thereafter, regular follow-up was performed, but 1 year and 10 months after the initial surgery, mobilization of the dental implant placed in the left mandibular molar region and swelling from the left mandibular lateral incisor to the lingual alveolar region corresponding to the left mandibular first molar were observed, and an elastic soft mass was palpated. The covering mucosa of the same area was normal, and no evidence of lingual nerve paralysis was observed. The patient's facial features were bilaterally symmetrical, and paresthesia with a Numerical Rating Scale of 8/10 was observed in the left lower lip and chin. Panoramic radiograph and contrast-enhanced CT revealed a well-circumscribed multilocular mass that occurred intraosseously from the left mandibular lateral incisor to the left mandibular molar (**Figure 5A**, **5B**). A clinical diagnosis of recurrence of left mandibular ameloblastoma was made, and in 2 years and 4 months after initial visit, an incisional biopsy was performed, resulting in a histologic diagnosis of ameloblastoma. Therefore, in 2 years and 6 months after the initial visit, a left mandibular tumor resection was performed under general anesthesia (**Figure 5C**).

Examination of the excised specimen revealed that the lesion consisted of fibrous tissue and basal cell-like cells, with duct-like or reticular structures and solid proliferation (**Figure 5D**). Although the cell density was very high, there were few mitotic counts. In other words, findings similar to those at the initial surgery were observed, and a diagnosis of recurrent ameloblastoma with adenoid features was made. The surgical margin was negative.

Thereafter, follow-up observation was performed again. However, in 2 years and 8 months after the initial visit, a contrast-enhanced CT scan revealed a multilocular mass lesion with clear borders extending from the posterior part of the left mandibular molar to the left mandib-

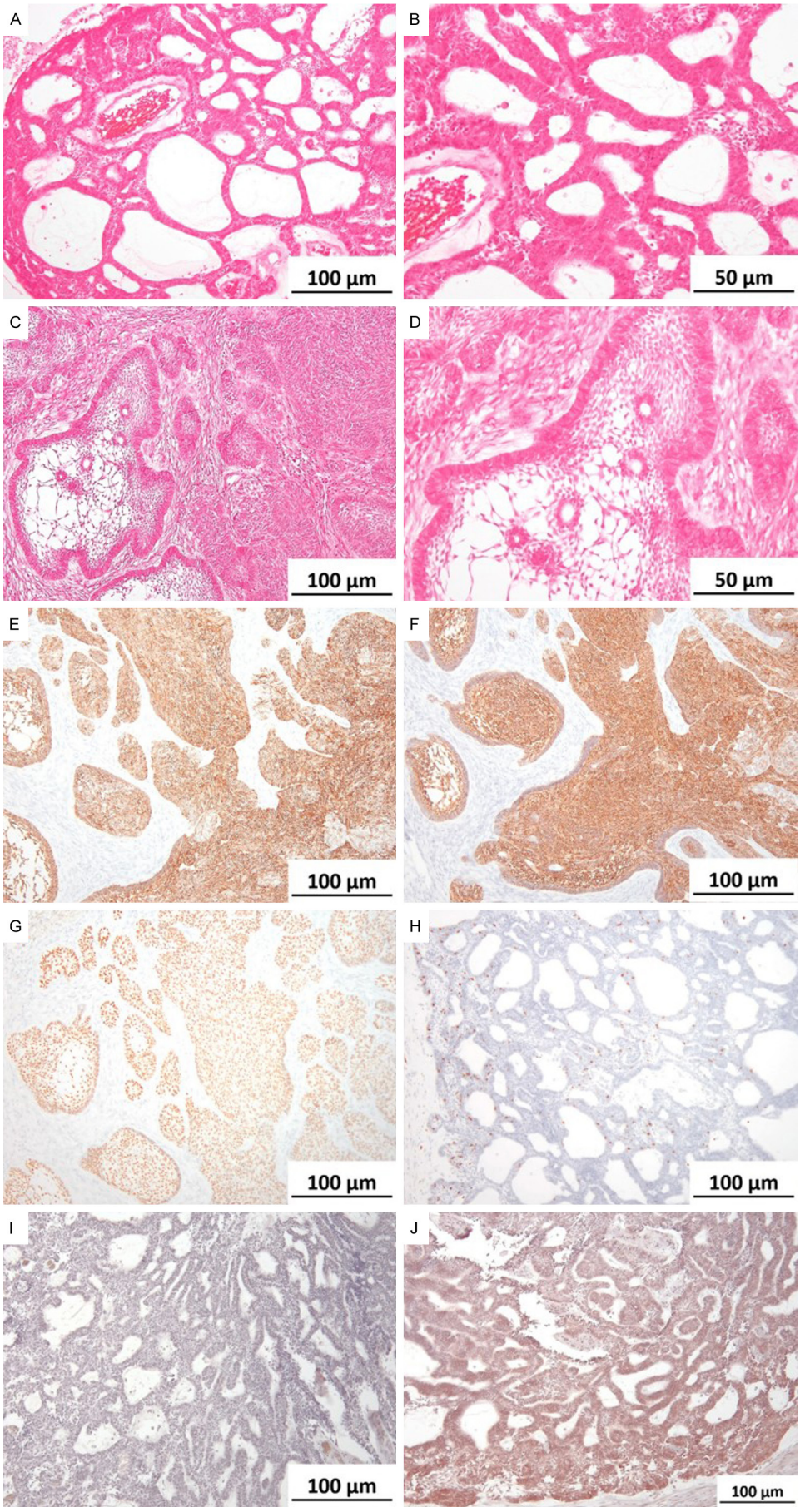
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Figure 4. Histologic findings of resected specimen. Most of the tumor was composed of basal cell-like cells with a high nucleus/cytoplasm ratio and exhibited a glandular or cribriform structure (A: Magnification ×100, B: Magnification ×200). In addition, some areas showing solid proliferation were also observed (C: Magnification ×100, D: Magnification ×200). A rim of basal cell-like cells was observed at the edge of the tumor nest, and within the tumor nest there was proliferation of stellate or spindle-shaped cells resembling enamel pulp (D). Tumor cells were positive for keratin 19 (E), 34βE12 (F), and p63 (G), and Ki67 (H) were focally positive. BRAF V600E (I) was negative, and β-catenin (J) was positive in the cytoplasm, but no translocation into the nucleus was observed (E-J, Magnification ×100).

Table 1. Results of immunohistochemical staining

	Duct-like structure	Solid nest
EMA	-	-
CEA	-	-
CK7	-	-
CK19	+	+
34βE12	+	+
p63	+	+
S-100 protein	-	-
α-SMA	-	-
BRAF V600E	-	-
β-catenin	++ (cytoplasm)	+/-
p53	+/-	+/-
Ki67	5-10%	< 5%

Abbreviations: EMA, epithelial membrane antigen; CEA, carcinoembryonic antigen; CK, cytokeratin; SMA, smooth muscle actin.

ular ramus (**Figure 6A**). In addition, contrast-enhanced MRI revealed a multilocular mass-like structure with relatively clear boundaries on the anterior border of the left mandibular ramus, the medial side of the left masseter muscle, and the floor of the mouth at the lower border of the mandible (**Figure 6B**, **6C**). The lesion at the left masseter muscle had enlarged by compressing the masseter muscle, and there was evidence that it had partially infiltrated the masseter muscle (**Figure 6B**).

Regarding extraoral findings, a spherical, elastic, soft mass was palpated on the left cheek. Intraoral findings showed secondary healing of the previous surgical wound and no depression was observed (**Figure 6D**). In addition, a spherical, elastic, soft mass was palpated at the anterior edge of the left mandibular ramus. Based on these findings, the clinical diagnosis was recurrence of ameloblastoma. An incisional biopsy was performed, and the histologic diagnosis was recurrent ameloblastoma. Therefore, in 2 years and 10 months after the initial visit, we performed left mandibular tumor resection, left segmental manbibulectomy, and reconstruction using a vascularized free scapula flap under general anesthesia (**Figure 7A**, **7B**). Because of the frequent recurrences, the fact that the lesion extended to the lower border of the mandible, and the lesion that invaded the surrounding tissues such as the masseter muscle, we decided to perform a segmental mandibulectomy and extend the excision to include the surrounding soft tissues. The lesion on the anterior edge of the left mandibular ramus was included in the resection side, including the surrounding buccinator muscle, masseter muscle, and medial pterygoid muscle. After confirming the anterior and posterior margins of the tumor, anteriorly, the left mandibular lateral incisor was extracted and osteotomy was performed in the same area, and posteriorly, osteotomy was performed from the mandibular notch toward the angle of the mandible to remove the lesion and the mandibular area as en-block (**Figure 7B**). The inferior alveolar nerve was excised and the lingual nerve was preserved.

The histopathologic findings of the resected specimen this time were similar to previous findings, and the tumor was composed of basal cell-like cells as well as fibrous tissue, with duct-like, reticular structures, and solid proliferation (**Figure 8A**). The cell density was extremely high, and the number of mitotic counts in this specimen was increased compared to previous specimens. The Ki67 labeling index was on average less than 10%, but in some areas where it exceeded 10% (**Figure 8B**). Excision margins were negative. There were no obvious signs of invasion, venous invasion, or lymphatic invasion, and there were no findings conclusively indicating metastasizing ameloblastoma, and the findings were ameloblastoma with adenoid features. During postoperative follow-up, the reconstructed free scapula flap became necrotic 4 weeks after the surgery, so it was reconstructed again using a free

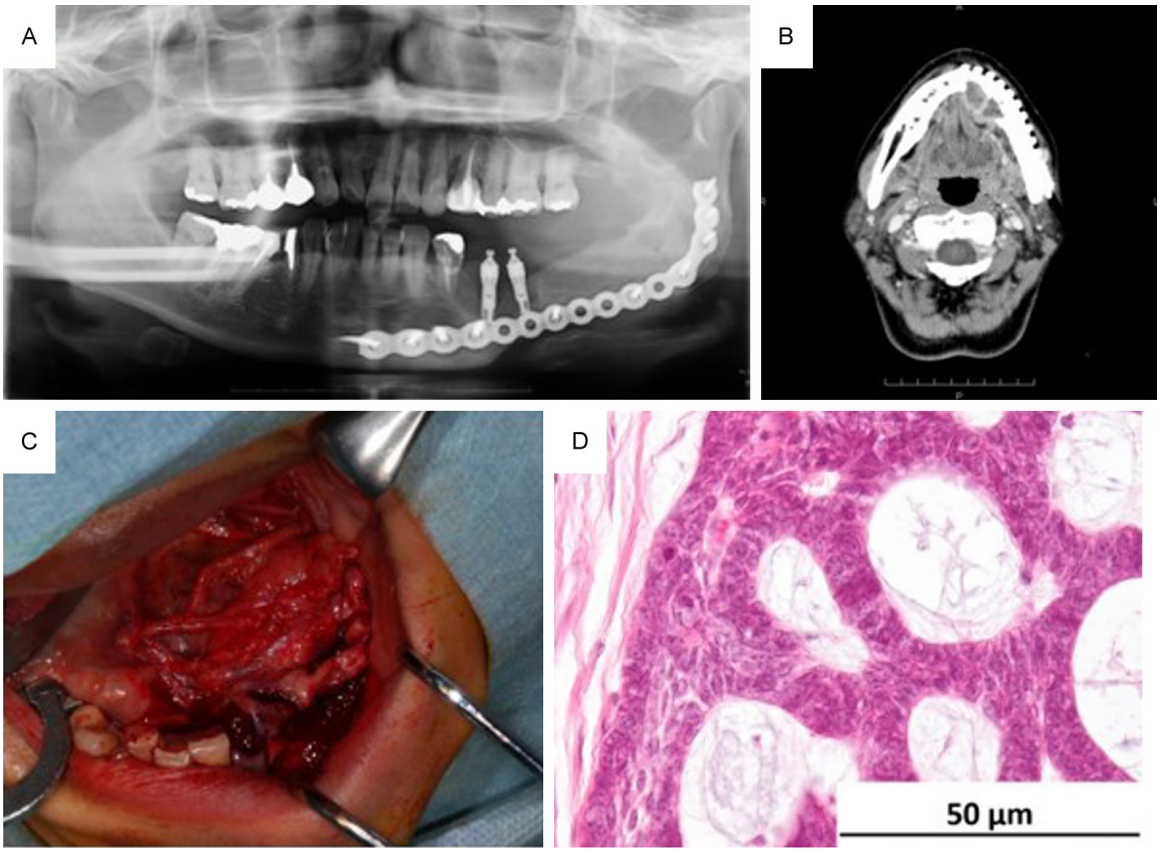

Figure 5. Clinical and pathologic findings at recurrence. (A, B) Panoramic radiograph (A) and contrast-enhanced computed tomography (B) revealed a well-circumscribed multilocular mass that occurred centrally in the mandible from the left mandibular lateral incisor to the left mandibular molar. (C) The lesion was clearly identified by an intraoral approach. (D) The lesions were composed of basal cell-like cells against a background of fibrous tissue, with glandular duct-like or reticular structures and solid proliferation (Magnification ×400).

fibula flap (**Figure 9**). The patient was followed up and there was no recurrence since then.

Discussion

Ameloblastoma with adenoid features is characterized by the formation of a cribriform or glandular tubular structure in addition to the conventional ameloblastoma. Many aspects of the clinical and histopathologic characteristics remain unknown, partly because there are few reported cases. Morais et al. reported a systematic review of previously reported cases of adenoid ameloblastoma [14]. According to their report, the first case of adenoid ameloblastoma was reported by Slabbert et al. in 1992 [15], but only 30 cases have been reported since then until 2022. They reported that the mean age of patients was 40.8 ± 12.4 years (range: 15-70 years), and three patients were under 20 years of age, 10 were between 20 and 49 years of age, and 8 were over 50 years of age. The lowest number of reported cases was one case among people under 18 years of age. Sex was male (19 cases) and female (11 cases), with a slightly higher incidence in males. In terms of favorite sites, the mandible (n=16) was the most affected site compared to the maxilla (n=14), and most tumors involved the posterior region of the mandible. 16 of the 30 adenoid ameloblastoma patients presented with asymptomatic swelling, and only 4 patients had pain. Trigeminal paralysis was observed in 3 of the 30 cases, all of which involved the posterior mandible. Although this case did not meet the diagnostic criteria for adenoid ameloblastoma, this case was also a case of ameloblastoma with adenoid features arising from the left mandibular molar region to the mandibular ramus, and the chief complaint was painless swelling. Swelling was a frequent clinical finding (53.3%) in the ameloblastoma with

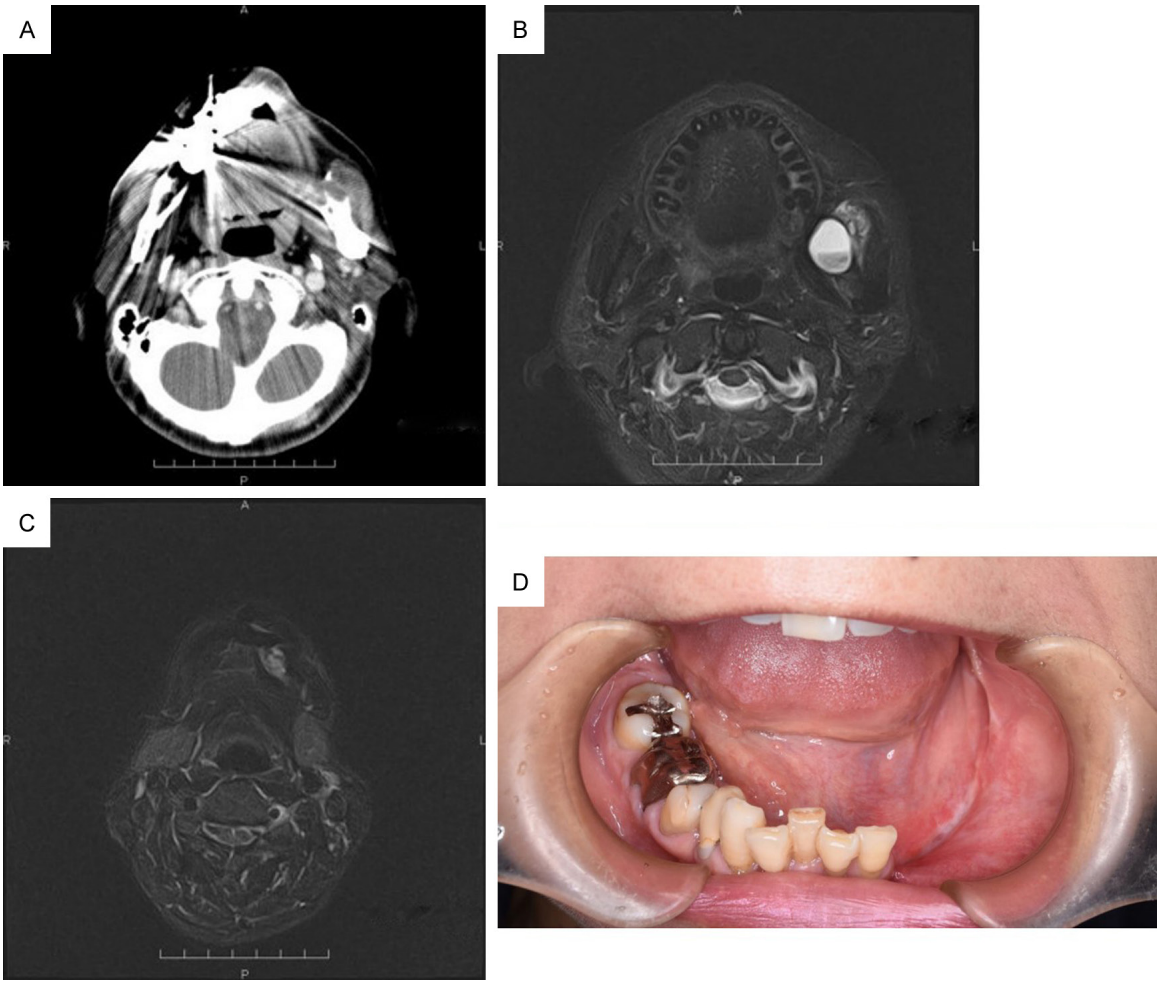

Figure 6. Contrast-enhanced computed tomography (CT), contrast-enhanced magnetic resonance imaging (MRI) findings and intraoral finding at second recurrence. (A-C) Contrast-enhanced CT revealed a multilocular mass lesion with smooth margins from the posterior part of the left mandibular molar to the left mandibular ramus (A). In addition, contrast-enhanced MRI revealed a multilocular mass-like structure with relatively clear boundaries on the anterior border of the left mandibular ramus, the medial side of the left masseter muscle, and the floor of the mouth at the lower border of the mandible (B, C). The lesion in the left masseter muscle had enlarged by compressing the masseter muscle, and there was evidence that it had partially invaded the masseter muscle (B). (D) There were no obvious abnormal findings in the oral cavity.

adenoid features cases included in this systematic review, whereas pain (13.3%) and paresthesia (10%) were less commonly described. Considering all cases, tooth displacement was reported in only 10% of the cases. In addition, 20% of the cases showed cortical bone destruction.

Imaging findings showed unilocular or multilocular translucency, and in a few cases, opacity reflecting the formation of calcifications. In the present case, a multilocular transparent image occurred from the mandibular molar area to the mandibular ramus, but no opaque image was observed.

Differential diagnosis of ameloblastoma with adenoid features are AOT, dentinogenic ghost cell tumor (DGCT), and calcifying odontogenic cyst (COC) [6]. DGCT is a rare locally invasive tumor with ghost cells appearing within ameloblastoma-like nests and induction of dentinoid and osteodentin formation at the connective tissue border. DGCT is similar to ameloblastoma with adenoid features in that they have calcifications, ghost cells and dentinoids in addition to ameloblast-like structures. These two tumors are histologically distinct based on the presence (ameloblastoma with adenoid features) or absence (DGCT) of adenoid morphology. To differentiate ameloblastoma with ade-

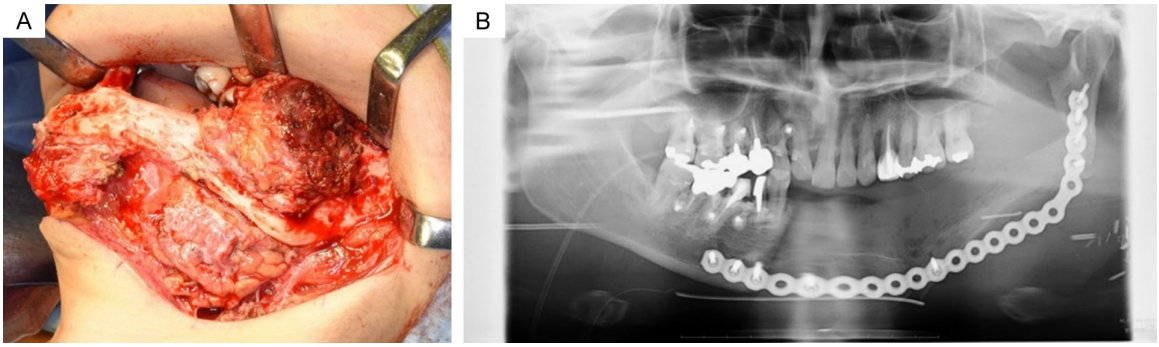

Figure 7. Surgical findings for the second recurrent lesion. A: The lesion on the anterior edge of the left mandibular ramus was clearly defined by including the surrounding buccinator muscle, masseter muscle, and medial pterygoid muscle on the resection side. B: Postoperative panoramic radiographic finding.

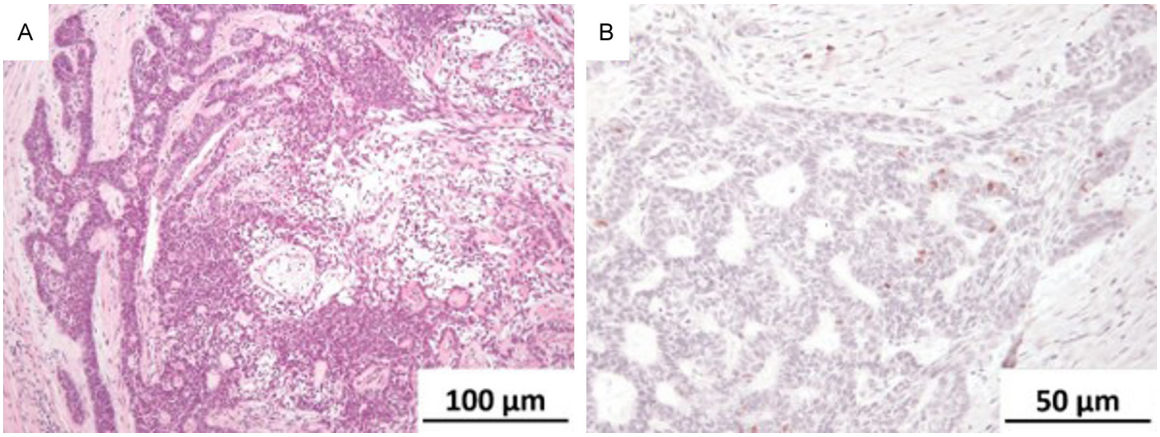

Figure 8. Histologic findings of the second recurrent lesion. A: The tumor was composed of basal cell-like cells against a background of fibrous tissue, with duct-like, reticular structures, and solid proliferation (Magnification ×100). B: The Ki67 labeling index was on average less than 10% (Magnification ×200).

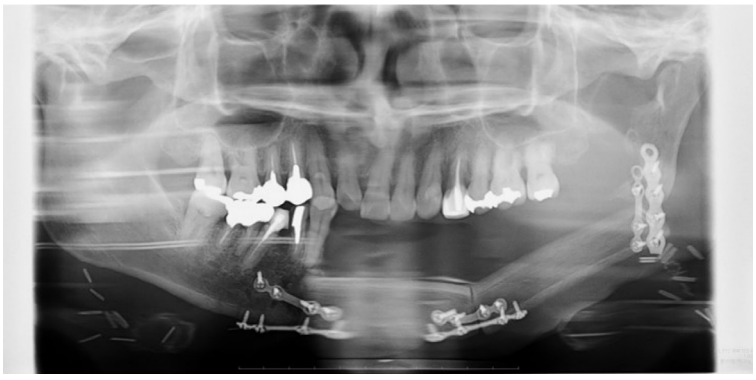

Figure 9. Panoramic radiograph findings after reconstruction with free fibula flap.

noid features from these diseases, the following findings are necessary to diagnose adenoid ameloblastoma: 1) conventional ameloblastoma-like tissue, 2) duct-like structures, 3) whorl-like or morula-like structures, and 4) cribriform structures. In the present case, 1) normal ameloblastoma-like tissue and 2) duct-like structures were observed, but no other findings were observed, so the diagnosis was histologically ameloblastoma with adenoid features. However, adenoid, pseudoglandular, or cribriform structures have been described in several DGCT cases [16, 17]. It has also been reported that dentinoids and ghost cells may or may not be present in ameloblastoma with adenoid features and DGCT, and that epithelial pearls, a histologic finding

required for the diagnosis of ameloblastoma with adenoid features, may also be seen in DGCT [18]. In other words, ameloblastoma with adenoid features and DGCT overlap considerably histologically, and it may be difficult to distinguish between the two based on histological findings alone. Adorno-Farias et al. reported that the finding of dentinoid material is not essential for the diagnosis of ameloblastoma with adenoid features, and that they found dentinoid material in only two of the eight cases of ameloblastoma with adenoid features they reported [4]. Additionally, although the presence of ghost cells in ameloblastoma with adenoid features has been reported in some studies [11, 12], and their presence may indicate a potential for extension and recurrence of this tumor [11], this feature was observed in only one of the eight cases reported by Adorno-Farias et al. [4]. Regarding histopathologic features, Morais et al. reported that 50% of the ameloblastomas with adenoid features cases reviewed showed a plexiform pattern as the predominant morphological pattern, and 36.7% of cases showed the simultaneous presence of plexiform and follicular patterns. They also reported that most of the cases showed histopathologic features such as odontogenic epithelium resembling a stellate reticulum (93.3%) and a cribriform pattern (90%), and duct-like structures and spiral cellular condensations were observed in 100% of cases. Dentinoid material was present in 70% of cases, and different cellular morphologies were also reported, including the presence of ghost cells (23.3%), clear cells (43.4%), spindle cells (16.7%), and multinucleated giant cells (20%) [14]. The histologic criteria for ameloblastoma with adenoid features need to be further investigated by accumulating more cases.

Furthermore, although the histologic diagnosis of ameloblastoma with adenoid features is currently based on morphologic criteria as mentioned above, some immunohistological features of ameloblastoma with adenoid features have also been reported. The odontogenic tumors, particularly odontogenic epithelial cells, are associated with various biomarkers owing to complex genetic and epigenetic factors involved in their differentiation [19]. Keratin is present in all epithelia, stable expression is observed even with tumorigenesis, and it is widely used as an epithelial marker. It has been reported that positive staining for keratin 14 and keratin 19 is observed in the majority of cases of ameloblastoma with adenoid features, showing high expression of each [4]. Keratin 14 is a family of major intermediate filaments of the odontogenic epithelium and is presented 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. It has been reported that many peripheral and central cells in the tumor nest of this tumor show strong immunopositive staining for keratin 14 [4]. In this case, immunohistochemical staining for 34βE12, which has activity against keratins 1, 5, 10, and 14, was performed and positive findings were obtained. Keratin 19 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 [4, 5], and positive findings in the majority of cases of ameloblastoma with adenoid features [5]. In the present case as well, keratin 19 was found to be positive in both duct-like structures and solid nests. Keratin 7 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 [20]. Keratin 7 is positive in odontogenic tumors and cysts such as calcifying epithelial odontogenic tumor and glandular odontogenic cyst, but it is known that it is not expressed in ameloblastoma that arise from enamel organs [21]. Keratin 7 was negative in the present case as well, and it is thought that ameloblastoma with adenoid features would also be slightly positive or negative. The overexpression for CK7 in AdAMs were associated with the diffusing dentinoid materials [18]. Regarding p63, a member of the p53 family and a transcription factor that plays an important role in normal epithelium and tumors, positive findings were observed in both duct-like structures and solid nests in the present case. Immunohistochemically, p63 is known to be positive in the nuclei of basal cells and squamous cell carcinoma cells. It has also been reported that p63 becomes positive in the cytoplasm of breast cancer and some malignant tumors of other organs. Thus, a relationship with prognosis, malignancy, and proliferation ability has been pointed out. It is suggested that the repeated recurrences in this case may

be related to the high expression of p63, and it may be possible to diagnose the tendency for recurrence by determining the immunostaining property of p63. In addition, Adorno-Farias D et al. reported that p53 was negative in all cases of ameloblastoma with adenoid features, and since ameloblastic carcinoma is often p53 positive, the absence of p53 immunopositivity in this tumor will help differentiate it from ameloblastic carcinoma [4].

Recently, BRAF has attracted attention as a molecular target for ameloblastoma and ameloblastic carcinoma. BRAF, an oncogene, is a member of the RAF family that acts on cell proliferation signal transduction pathways and is involved in cell differentiation and proliferation. Among the RAF family, BRAF has the highest frequency of genetic mutations, with more than 30 reported mutation patterns, most of which are mutations in which valine at position 600 is replaced with glutamic acid (V600E). Diniz et al. reported that *BRAF V600E* mutations are found in 82% of ameloblastomas and 38% of ameloblastic carcinomas [22]. However, *BRAF V600E* was negative in this case. The *BRAF V600E* mutation, which is usually identified in ameloblastoma and unicystic ameloblastoma, was reported to be found in only 5.6% of adenoid ameloblastoma cases [18, 23, 24]. The fact that *BRAF V600E* mutation, which is usually seen in ameloblastomas, is rare in ameloblastoma with adenoid features may be a key point in the differential diagnosis, and analysis of a large number of cases is warranted in the future.

The Ki67 labeling index in the present case was low, around 5-10%. Ki67 expression in ameloblastoma with adenoid features varies depending on the report, and the majority of previously reported cases showed borderline to low levels [4, 7, 18, 25-29]. However, the mean value of the proliferation index (72.4 ± 24.9 positive cells per high-power field) evaluated with Ki67-positive cells in five cases of ameloblastoma with adenoid features reported by Loyola et al. was higher than that of AOT and ameloblastoma, and was similar to that observed in ameloblastic carcinoma [5]. In addition, Vered et al. also reported that ameloblastoma with adenoid features usually has a high Ki-67 proliferation index [30], and further accumulation of cases is needed.

Although *CTNNB1* mutations encoding β-catenin are frequently detected in odontogenic cysts and tumors with ghost cells, including COC and DGCT, the majority of enamel epitheliomas lack mutations in this gene. Reflecting this genetic mutation, nuclear translocation of β-catenin is detected in COC by immunostaining [31], which is thought to be useful in differentiating it from ameloblastoma. Regarding the localization of β-catenin in ameloblastoma with adenoid features, Bastos et al. reported that, unlike conventional ameloblastoma, β-catenin migrates into the nucleus, and in some cases (< 50%) *CTNNB1* mutations are observed [23]. It was also reported that *CTNNB1* mutation was found in only 16.7% of ameloblastomas with adenoid features [18, 23, 24]. From a molecular biological perspective, these reports suggest that ameloblastoma with adenoid features and DGCT are not two different tumors, but that both share histologic characteristics of benign odontogenic tumors with alterations in the WNT pathway. Namely, based on the low frequency of CTNNB1 mutations and the similarity of the clinicopathologic findings between ameloblastoma with adenoid features and DGCT, it is possible that ameloblastoma with adenoid features is not an independent disease, but rather one of the same groups of WNT pathway-activated odontogenic tumors as DGCT, and further case collection and investigation is required. However, in the present case, β-catenin was positive in the cytoplasm, but no translocation into the nucleus was observed. It has been demonstrated that nuclear β-catenin is present during tooth development and that canonical WNT activation is associated with dentin formation [32]. The lack of nuclear translocation of β-catenin in the present case may be related to the absence of dentinoids.

In addition, regarding KRAS mutations, which occur in 70% of AOT cases, Bastos VC et al. reported that no cases of KRAS mutations were found in ameloblastoma with adenoid features cases when they were screened [23]. In other words, ameloblastoma with adenoid features and AOT are thought to have different genetic and developmental backgrounds.

Ameloblastoma with adenoid features is reported to be more locally invasive than conventional ameloblastoma and has a greater tendency

to recur [4, 5, 14, 33]. Currently, surgical resection is the first choice for treatment of ameloblastoma with adenoid features, as is usually the case with ameloblastoma. However, in this case, recurrence was observed despite an adequate safety margin during the primary surgery, and several recurrences were observed during reoperation despite resection including surrounding soft tissues and removal of bone in contact with the tumor. Jayasooriya et al. reported that 45.4% of cases had at least one recurrence after tumor resection [33]. Moraris et al. also reported that recurrence was a common finding, observed in 30% of cases [14]. Loyola et al. reported that even with curative treatment for conventional ameloblastoma, tumor recurrence occurs in 15-30% of cases, while in the case of ameloblastoma with adenoid features, the recurrence rate is approximately 75% [5]. Furthermore, Loyola et al. revealed that the recurrence rate of ameloblastoma with adenoid features is higher than that reported for ameloblastoma and metastasizing ameloblastoma [5]. However, this high recurrence rate may be due to the fact that these reports involve a relatively large number of cases of ameloblastoma with adenoid features arising in the maxilla, which makes tumor resection with adequate margins difficult, and the tendency of some previously reported cases of ameloblastoma with adenoid features to recur because they were initially diagnosed as AOT and treated with a simple excisional approach. Even with these considerations, it is necessary to develop a treatment plan keeping in mind that the recurrence rate for cases of ameloblastoma with adenoid features is higher than for conventional ameloblastoma. For this purpose, it is important to accurately identify the extent of the lesion and determine the appropriate extent of resection; and in some cases, extended resection may be necessary.

Conclusion

We described a rare case of ameloblastoma with adenoid features. Morphologic features are important to distinguish between ameloblastoma with adenoid features and conventional ameloblastoma. The following histologic features must be confirmed for diagnosis: pseudoducts, squamous metaplasia, nuclear hyperchromatism, clear cells, whorled aspect of epithelial structures, cribriform growth pattern, proliferation of spindle cells and extracellular eosinophilic material. In addition, ameloblastomas with adenoid features have a greater tendency to recur than normal ameloblastomas, and surgical resection should be performed with an adequate safety margin and strict postoperative follow-up. The clinical and histologic features of ameloblastoma with adenoid features are still unclear, and further accumulation of cases is needed.

Disclosure of conflict of interest

None.

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