

**Granular cell ameloblastoma: Case report of a particular ameloblastoma histologically  
resembling oncocytoma**

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3 A Short running title: Particular granular cell ameloblastoma

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## 1   **Abstract**

2   Granular cell ameloblastoma is classified as a histological subtype of solid/multicystic  
3   ameloblastoma. Usual granular cell ameloblastoma is histologically characterized by granular  
4   changes of stellate-like cells located in the inner portion of the epithelial follicles. Here we  
5   report a case of another type of granular cell ameloblastoma, showing predominant  
6   anastomosing double-stranded trabeculae of granular cells. This type of granular cell  
7   ameloblastoma is extremely rare, and World Health Organization classification does not  
8   contain the entity. We tentatively termed it “anastomosing granular cell ameloblastoma” in  
9   this report. The present case suggested the importance of differential diagnosis because the  
10   histology of “anastomosing granular cell ameloblastoma” resembled that of salivary gland  
11   oncocytoma rather than that of usual granular cell ameloblastoma. The trabeculae observed in  
12   our case continued to the peripheral cells of a small amount of epithelial sheets of plexiform  
13   ameloblastoma, and the tumor cells were positive for CK19, which is regarded as an  
14   immunohistochemical marker of odontogenic epithelium. Similar to usual granular cell  
15   ameloblastoma, the tumor cells had CD68-positive granules. For the precise diagnosis of this  
16   condition, immunohistochemistry using CK19 and CD68 as well as detailed histological  
17   observation are recommended.

1 **Keywords**

2 Granular cell ameloblastoma; Oncocytoma; CK19; CD68

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## 1    **Introduction**

2        Ameloblastoma is a common benign odontogenic tumor that preferentially affects the  
3    mandible. The current World Health Organization (WHO) classification of odontogenic  
4    tumors divides ameloblastoma into four types: solid/multicystic, extraosseous/peripheral,  
5    desmoplastic, and unicystic types. Granular cell ameloblastoma is one of the histological  
6    patterns comprised in the solid/multicystic type of ameloblastoma. Histologically, the  
7    neoplastic follicles of ameloblastoma mimic the enamel organ of the dental germ. The  
8    parenchymal central cells, which resemble stellate reticulum, sometimes show various  
9    morphological changes. The WHO classification defines ameloblastoma accompanying  
10   granular changes of the central cells as granular ameloblastoma<sup>1</sup>. In addition, Robinson and  
11   Vincent described that the granular cell pattern centrally includes eosinophilic cytoplasmic  
12   granules within the follicular epithelial islands, or within the columnar and cuboidal cells of  
13   the follicular or plexiform variants in the AFIP atlas of tumor pathology<sup>2</sup>. The latter type of  
14   granular cell ameloblastoma is not mentioned in the WHO classification, and includes a  
15   peculiar type composed of predominant anastomosing strand arrangements of eosinophilic  
16   granular cells<sup>3,4</sup>. This rare granular cell ameloblastoma resembles salivary gland tumors such  
17   as oncocytoma<sup>4</sup>. We encountered the peculiar granular cell ameloblastoma in a 50-year-old

1 Japanese female. We report the case and discuss the differential diagnosis from salivary gland

2 oncocytoma.

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## Clinical Summary

A 50-year-old female was referred to Nagasaki University Hospital because of an X-ray radiolucent area in the right mandibular bone detected at a dental clinic. She had no clinical symptoms and her facial appearance was symmetric. A clinical oral examination revealed a solid mass covered with intact mucosa in the right oral floor.

Five years before the present visit, she was treated for a radicular cyst of the left second incisor of the maxilla at our department. The panoramic X-ray image acquired at that time revealed a well-circumscribed radiolucent lesion around the apex of the roots of the lower right first and second molars, as well as a radicular cyst of the maxilla (Figure 1a). The size of the radiolucent area of the mandible was  $18 \times 11$  mm. However, the lesion was overlooked at that time because of the absence of clinical symptoms and was not treated.

The panoramic X-ray image acquired at the present visit again revealed a well-circumscribed radiolucent lesion located in the same region (Figure 1b). The size of the lesion was  $24 \times 15$  mm. Computed tomography (CT) showed a well-circumscribed multilocular lesion with a mass of 30 mm in diameter that extended to the inferior border and lingual side of the mandible, as well as resorption of the interior cortical bone (Figure 2a, 2b). Root resorption was not observed. Although slight swelling of the mandibular lymph nodes

was present, malignancy was not suspected. Magnetic resonance imaging (MRI) yielded observations that were similar to those of CT (Figure 3a, 3b). The apparent diffusion coefficient (ADC) was low and the time–intensity curve (TIC) exhibited a rapid increase and gradual decrease pattern. Based on the clinical and imaging findings, the lesion was suspected of a benign tumor, such as ameloblastoma. But there was no definite evidence to determine whether intraosseous or peripheral ameloblastoma. Thus benign salivary gland tumor and fibrous tumor with bone resorption were not ruled out. We established a pathological diagnosis of granular cell ameloblastoma from a biopsy specimen. The tumor was surgically removed under general anesthesia. Eight months after surgery, no recurrence was detected at the follow-up. A panoramic X-ray image showed uneventful wound healing.



## Pathological Findings

A biopsy specimen showed a demarcated tumor with a fibrous capsule. The tumor was composed of predominant anastomosing cords and small islands of epithelial cells in the fibrous stroma. Intracapsular invasion of the tumor cells were not detected (Figure 4a). Most of the tumor cells had an abundant cytoplasm that was filled with eosinophilic granules and lopsided round nuclei without atypia. Most strands exhibited adhesion of two granular cell rows at the nuclear side of the cells, and the extensive cytoplasm faced the stroma. In addition, in the small islands, a broad cytoplasm was conspicuous at the periphery (Figure 4b). The granules observed in the plump neoplastic cells were stained with periodic acid-Schiff (PAS) reaction (Figure 4c). Although ductal structures were not detected, for the differential diagnosis between odontogenic tumors and salivary gland tumors, such as oncocytoma, immunohistochemistry using antibodies against cytokeratin AE1/AE3, CK19, EMA, S100 protein, vimentin, CD68, and MIB-1 was performed. The immunohistochemical study revealed positive reactivity for cytokeratin AE1/AE3 and CK19 (Figure 4d), and most granular cells contained CD68-positive granules (Figure 4e). The tumor cells were devoid of a reaction for EMA, S100 protein, and vimentin. The MIB-1 labeling index was <1%. CK19 is regarded as a good marker of odontogenic epithelium<sup>5,6</sup>, and double-stranded anastomosing

1 cords is one of the structural components of plexiform ameloblastoma<sup>7</sup>. Therefore the tumor  
2 was suspected of a type of ameloblastoma, though it histologically resembled salivary gland  
3 oncocytoma. Oncocytoma frequently exhibits positive immunoreactivity for EMA<sup>8</sup>, and  
4 negative for CD68<sup>9,10</sup>. We established a pathological diagnosis of granular cell ameloblastoma,  
5 based on the biopsy specimen. The present tumor showed predominant anastomosing pattern  
6 composed of granular cells. Usual granular cell ameloblastoma is characterized by granular  
7 change of inner stellate-like cells in the epithelial follicles according to WHO classification.  
8 To underline the histological specificity, we tentatively term the present tumor “anastomosing  
9 granular cell ameloblastoma” in this manuscript.

10 The resected tumor, which was easily extirpated from the surrounding tissue, was elastic  
11 and hard, and the cut surface exhibited a demarcated whitish yellow solid tumor with a  
12 lobular structure (Figure 5a).

13 Histologically, the surgical specimen showed a well encapsulated tumor, and the tumor is  
14 subdivided into lobules. Collagen-poor stroma with a myxoid appearance was also found in  
15 the lobules (Figure 5b). In addition to the findings of the biopsy, small areas of usual  
16 plexiform ameloblastoma that were connected with epithelial cords were observed. But no  
17 granular change were not detected in the inner stellate-like cells of the sheets of the plexiform

1 ameloblastoma (Figure 5c). This finding confirmed the pathological diagnosis of  
2 “anastomosing granular cell ameloblastoma”.

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## Discussion

Granular cell ameloblastoma accounts for approximately 3.5%–5% of all ameloblastoma<sup>11-13</sup>. Hartman reported that the average age of the patients at the first visit was 40.7 years and that there was no difference between genders in his 20 cases<sup>11</sup>. The WHO classification of odontogenic tumors mentions that granular ameloblastomas are characterized by granular cells located within the center of the follicles<sup>1</sup>. Most previous studies and case reports of granular ameloblastoma dealt with this common type. In addition, AFIP described another type of granular cell ameloblastoma that exhibits a granular appearance within the columnar and cuboidal cells of the follicular or plexiform variants. In this category, a peculiar granular cell ameloblastoma, showing histologically anastomosing double-stranded trabeculae composed of eosinophilic granular cells, is described in the AFIP atlas<sup>2</sup>. The present case exhibited the resemblance to histological features of the anomalous granular cell ameloblastoma. However, the final histopathological diagnosis of “anastomosing granular cell ameloblastoma” is difficult because its histological features resemble those of salivary gland oncocytoma.

Although it is easy to distinguish central ameloblastoma from salivary gland tumor from the anatomical location of the tumors, differential diagnosis between peripheral

1 “anastomosing granular cell ameloblastoma” and oncocytoma is needed. We made differential  
2 diagnosis from oncocytoma because the present case had no conclusive evidence to determine  
3 whether the present tumor was intraosseous or extraosseous. Oncocytoma possess a  
4 well-defined capsule and comprise solid or trabecular arrangements of large oncocytic cells.  
5 These cells have an ample granular acidophilic cytoplasm and small oval or round nuclei<sup>14</sup>.  
6 However, the strands of oncocytoma are not arranged in an ordinary fashion, such as those of  
7 double-stranded trabeculae in “anastomosing granular cell ameloblastoma”. Yamamoto et al.<sup>3</sup>  
8 and Oza and Agrawal<sup>4</sup> diagnosed their cases as being suggestive of oncocytoma based on  
9 biopsy specimen, but confirmed the final correct diagnosis using surgical specimens or  
10 extensive sampling, including follicular type ameloblastoma or usual granular cell  
11 ameloblastoma. In the present case, the positive immunoreactivity for CK19 strongly  
12 suggested that the tumor was derived from the odontogenic epithelium. The surgical specimen  
13 exhibited a small amount of sheets of plexiform ameloblastoma connecting anastomosing  
14 cords. We excluded oncocytoma from the differential diagnosis of these conditions because  
15 oncocytoma is frequently positive for EMA<sup>8</sup> and negative for CD68, because cytoplasmic  
16 granules of oncocyte are considered to be mitochondria<sup>9,10</sup>.

Usual type of granular cell ameloblastoma displays granular changes in the inner portion of the follicular nests, and several immunohistochemical and ultrastructural studies implied that these granules are lysozomal granules<sup>2,15,16</sup>. The present case showed immunolocalization of CD68 in the granular cells, which implied that the present tumor was categorized as one type of granular cell ameloblastoma. Although usual granular cell ameloblastoma and “anastomosing granular cell ameloblastoma” comprise granular cells, their histological structures evidently differ. We noticed a continuity between each layer of the double-stranded cords and peripheral cells of the epithelial sheets of plexiform ameloblastoma. Plexiform ameloblastoma consists long, anastomosing cords or larger sheets of odontogenic epithelium. The cords or sheets of epithelium are bounded by columnar or cuboidal surrounding more loosely arranged epithelial cells<sup>7</sup>. Most plexiform pattern includes anastomosing cords and sheets, and they are connecting each other like a network. Ameloblastoma constructed of almost predominant double-stranded anastomosing cords is very rare. This type of ameloblastoma accompanying granular change is rarely encountered. We considered that the strand consisting of two rows of granular cells was prepared from peripheral cells in the process of the diminishing and disappearance of the central cells of the epithelial follicles or

1 sheets. It is assumed that “anastomosing granular cell ameloblastoma” is configured through  
2 the increase of the cytoplasmic lysozomal granules in the columnar cells of the cords.

3 To establish a differential diagnosis and a final diagnosis of this condition, detailed  
4 histological observation of the trabecular structure and the assessment of the continuity to the  
5 follicular or plexiform ameloblastoma are recommended. In addition, immunohistochemical  
6 examination using CK19 and CD68 is useful.

1 **Disclosure statement:** None Declared

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## Figure legends

### Figure 1

Time course of panoramic X-ray images. Changes in the X-ray radiolucent area of the right mandibular bone are shown: **(a)** five years before surgery and **(b)** just before surgery.

### Figure 2

CT images. CT findings showed a well-circumscribed multilocular lesion with a mass of 30 mm in diameter located at the inferior border and lingual side of the mandible, as well as resorption of the interior cortical bone. **(a)** Axial image. **(b)** Coronal image.

### Figure 3

T2-weighted MRI. The lesion was emphasized by T2-weighted imaging. **(a)** Axial image and **(b)** coronal image.

### Figure 4

Histology of the biopsy specimen. **(a)** The tumor with a fibrous capsule (asterisk) was

composed predominantly of anastomosing epithelial cords and small nests accompanied by fibrous stroma (hematoxylin and eosin, 5×). **(b)** The trabeculae showed a double-stranded structure. Two rows of eosinophilic granular cells bordered each other at the nuclear side (hematoxylin and eosin, 20×). **(c)** The granular cells were filled with PAS-positive granules. No nuclear atypia was seen (40×). **(d)** Immunohistochemical staining showed CK19 localization at the cell surface and cytoplasm (20×). **(e)** Tumor cells had granular expression of CD68 in the cytoplasm (40×).

#### Figure 5

Pathological findings of the removed tumor. **(a)** Cut surface of the surgical material showed a demarcated whitish yellow tumor. A lobulated structure was noticed. **(b)** The tumor comprised anastomosing cords that were lobulated. Myxoid stroma was found within the lobules (hematoxylin and eosin, 2.5×). **(c)** Double-stranded trabeculae continued to peripheral cells of the sheets of plexiform ameloblastoma (hematoxylin and eosin, 20×). Granular change was not observed in the stellate-like cells in the epithelial sheets (Hematoxylin and eosin, 10x).

Fig. 1 Matsushita et al.

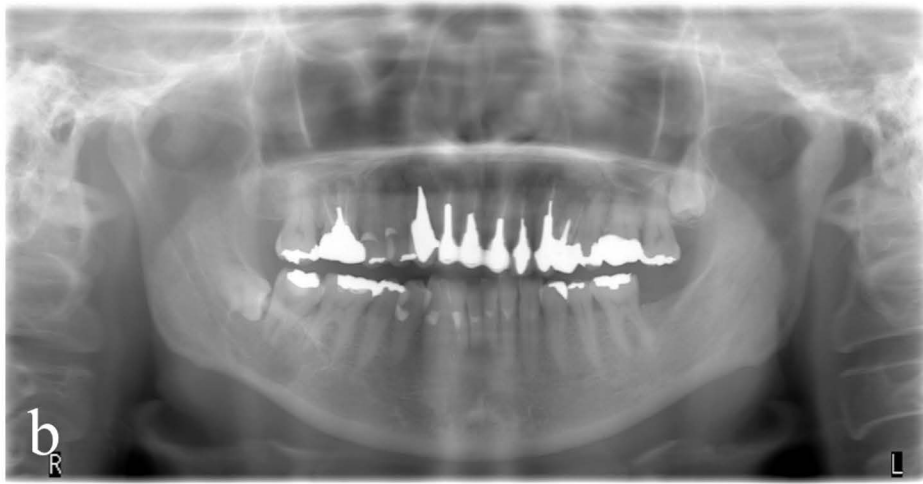


Fig. 2 Matsushita et al.

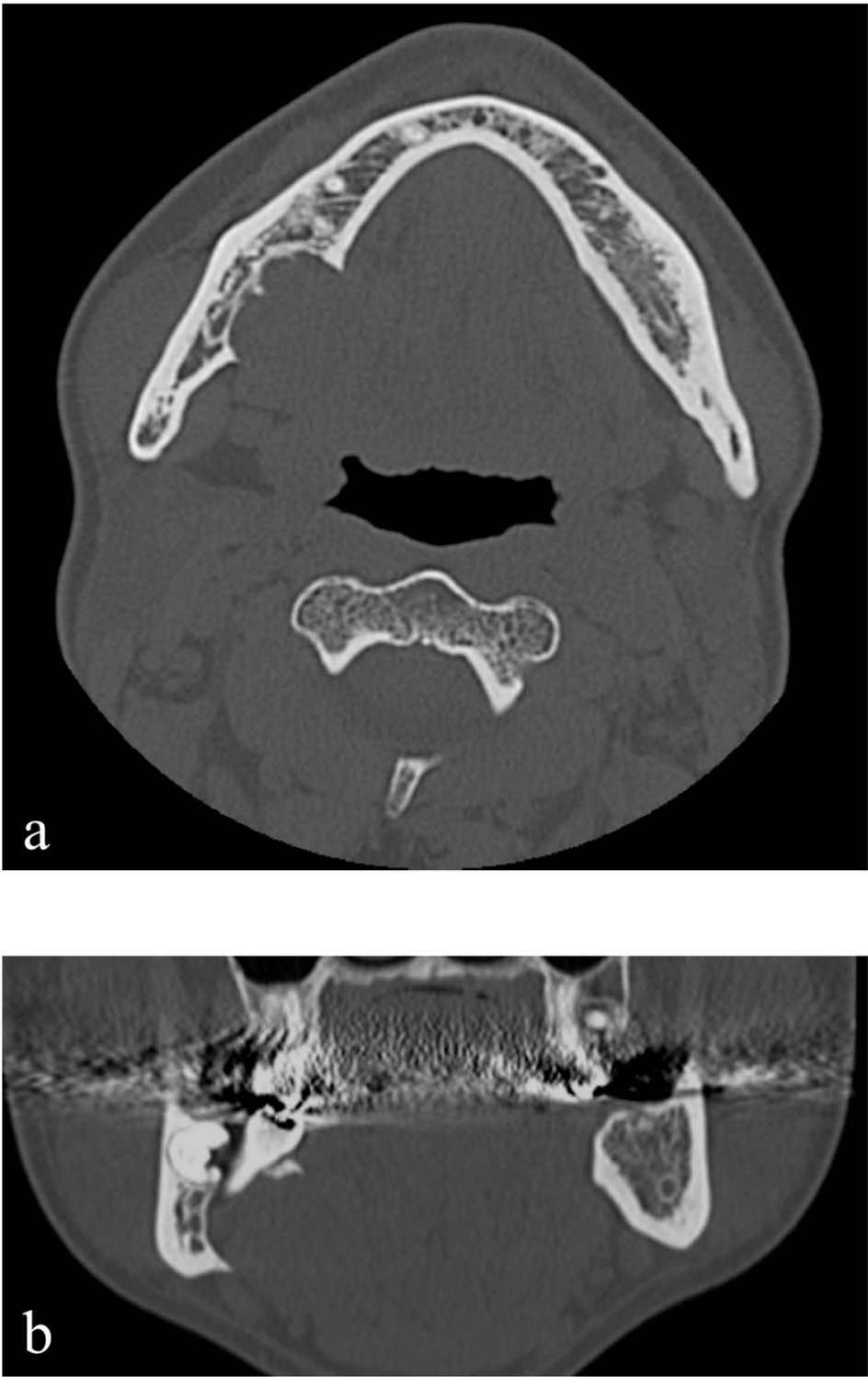


Fig. 3 Matsushita et al.

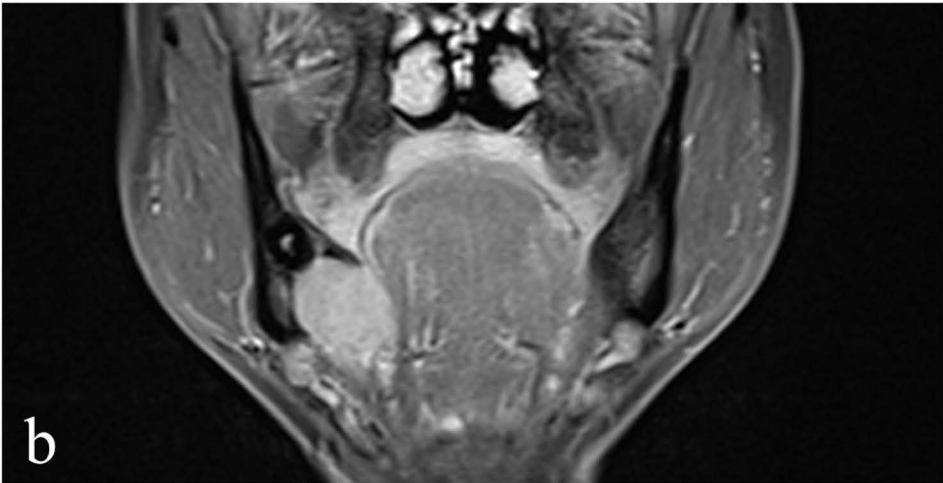
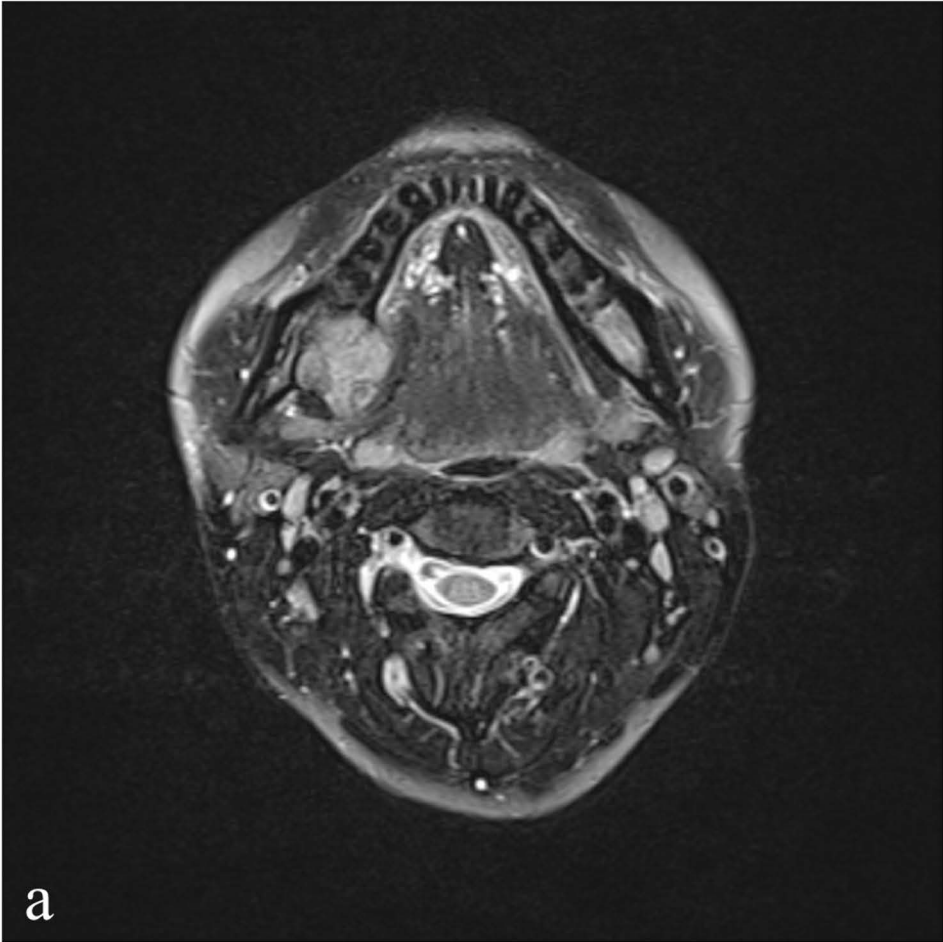




Fig. 4 Matsushita et al.

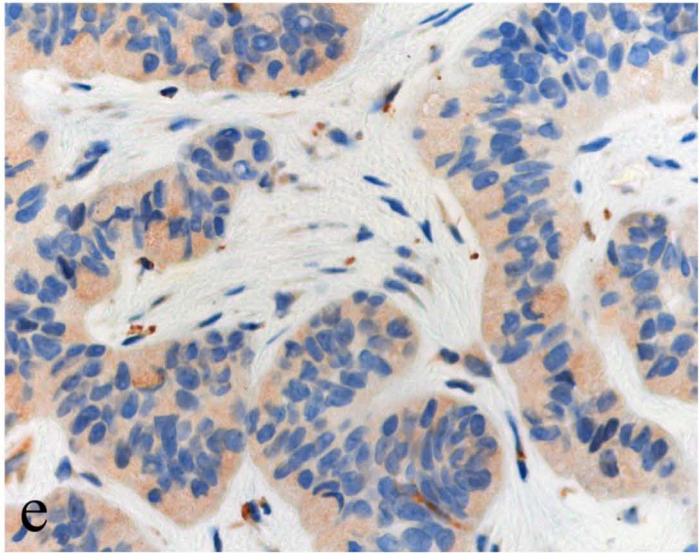
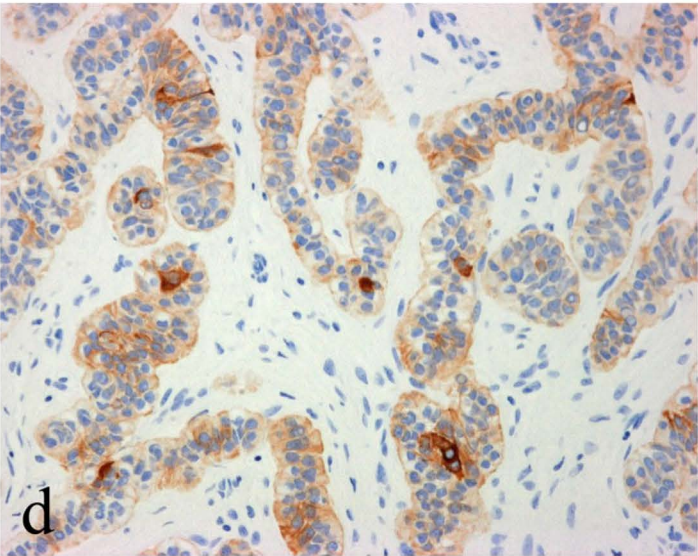
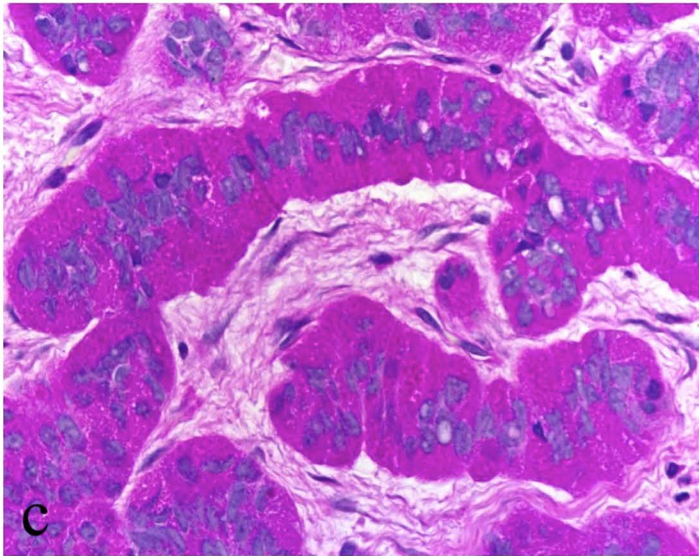
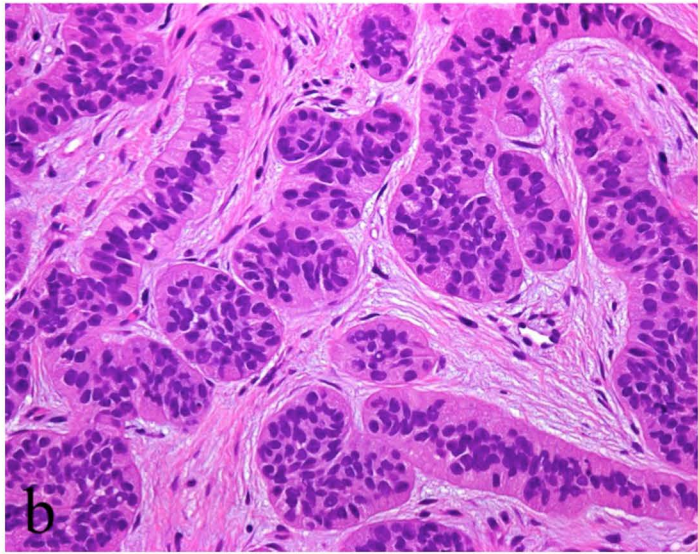
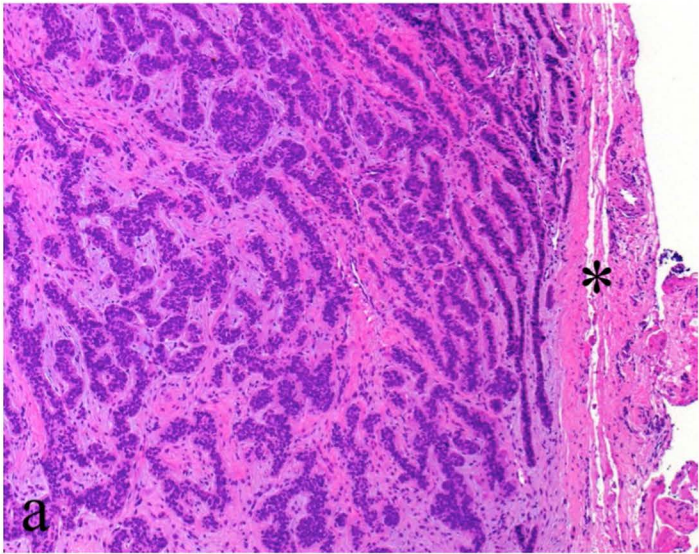




Fig. 5 Matsushita et al.

