Virchows Arch (1997) 430:501–507

CASE REPORT

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Ameloblastoma of the mandible metastasizing to the orbit with malignant transformation

A histopathological and immunohistochemical study

Received: 10 June 1996 / Accepted: 8 January 1997

Abstract We report here a case of ameloblastoma of the mandible with multiple local recurrences and metastasis to the orbit. The patient was a 63-year-old Japanese woman with visual disturbance of her right eye. Diagnostic imaging revealed a mass occupying the right orbital apex with partial intracranial involvement. She had been surgically treated for mandibular ameloblastoma 27 years previously, and the tumour had recurred three times in the past 5 years. The orbital tumour and recurrent ameloblastomas were investigated histopathologically and immunohistochemically. The tumour changed in morphology as it recurred, from follicular ameloblastoma without atypia to apparent malignant tumours disclosing undifferentiated or squamoid features. On immunohistochemical analysis, staining for cytokeratin was positive in the squamoid cells but not in the undifferentiated cells. Both histopathologically and immunohistochemically, the orbital tumour was almost identical to the undifferentiated recurrent tumour. The orbital tumour was distinct from the primary site or sites of recurrence of ameloblastoma, and we concluded that the mandibular ameloblastoma underwent malignant transformation with multiple recurrences and finally metastasized to the orbit.

Key words Ameloblastoma · Metastasis · Orbit · Malignant transformation

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Introduction

Ameloblastoma is a rare tumour that stems from dental embryonic remnants in the mandible or maxilla. Although it is considered to be the most common odontogenic epithelial neoplasm, it accounts for only 1% of all tumours and cysts developing in the jaw [2]. The incidence is the same in the two sexes, and the average age at the time of diagnosis is approximately 33 years [9]. In both behaviour and structure, ameloblastoma can resemble basal cell carcinoma of the skin; although it may be locally invasive and tends to recur at a high rate, it rarely metastasizes [10]. Eliasson et al. [5] reported the characteristics, including long duration of tumour, extensive local disease, frequent surgical procedures or radiation therapy, and mandibular focus of primary ameloblastoma, that are associated with metastasis.

We present a case of ameloblastoma originating in the mandible with multiple local recurrences and metastasis to the orbit without evidence of other systemic metastasis. Histopathologically, the tumour changed from typical follicular ameloblastoma to an undifferentiated or squamoid tumours with high-grade atypia as it recurred. We discuss the histopathological and immunohistochemical findings of this tumour in multiple recurrences and malignant transformation.

Clinical history

A 63-year-old Japanese woman presented to her ophthalmologist on 10 January 1994 with a chief complaint of visual disturbance of her right eye that had begun suddenly and had progressively worsened over about 3 weeks. Her corrected visual acuity of the right eye was 0.15. One week later, right visual acuity had decreased to 0.04, and a large central scotoma was observed in the right eye. On 19 January she was referred to the Department of Ophthalmology, Kochi Medical School Hospital, Japan, with suspected right retrobulbar disease. Ophthalmological examination revealed markedly decreased visual function: visual acuity on the right side was 0.01, and the level of critical fusion frequency in the right eye was about 10 Hz. Her pupils were anisocoric (right > left), and the swinging flashlight test was positive in the right side, but ocular movement was not limited and exophthalmos was not observed.

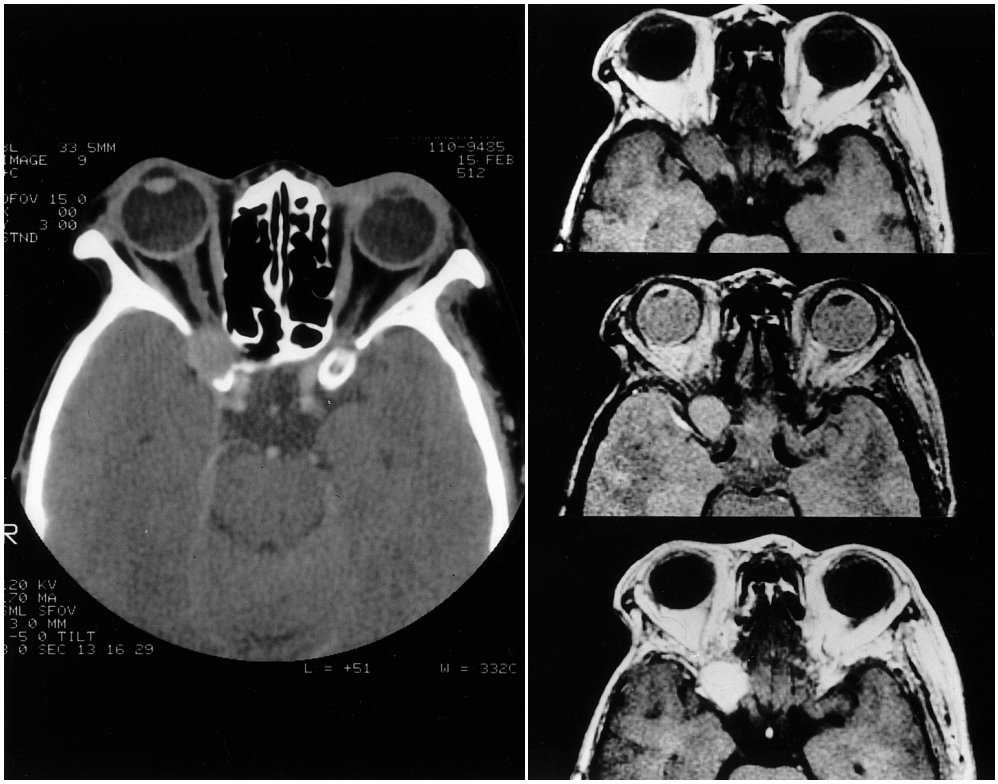


Fig. 1 CT scan (*left*) and MRI (*right*) scan showing a tumour in the right orbital apex with intracranial extension. (MRI: top, T1-weighted imaging; middle, T2- weighted imaging; bottom, enhanced imaging)

Her past medical history was significant for the resection of an ameloblastoma in the right side of the mandible at the age of 36 years in 1967. (The surgery had been performed in another institute, and no records were available to us.) In November 1989, the patient noticed a swelling of the right lower gingiva and visited the Department of Oral Surgery, Kochi Medical School Hospital. Clinical examination revealed a multicystic, radiolucent lesion in the right side of the mandible, indicating local recurrence of ameloblastoma. One month later, surgical resection and curettage of the tumour (intralesional curettage) were performed. Since a series of follow-up radiographs revealed a bone-absorbent shadow in the right mandibular ramus in 1992, partial resection of the right mandible (extralesional tumour resection) was performed. Histopathologically a focus of invasive tumour was present at the margin of the surrounding tissue. In February 1993, a recurrent lesion in the extramandibular tissue was resected with tumour-free margins. In addition, local radiation therapy [2 Gy per session × 5 sessions per week × 3 weeks (15 sessions), 29 Gy in total] and systemic chemotherapy (5-fluorouracil, 2,000 mg in total) were given postoperatively.

Because of her past medical history, it was suspected that the patient's visual signs and symptoms might be caused by invasion or metastasis of ameloblastoma. Diagnostic imaging with computed tomography (CT) and magnetic resonance imaging (MRI) scans revealed a space-occupying lesion in the right orbital apex invading the intracranial space (Fig. 1). Another mass was found in the right frontal parasagittal region on MRI. On 10 March 1994, total resection of the orbital tumour and the frontal parasagittal tumour was performed by a neurosurgical team at Kochi Medical School Hospital. In the 6-month period since surgery, the patient's right visual acuity has been limited to light perception and her right optic disc has remained atrophic, but there has been no evidence of metastasis to other sites.

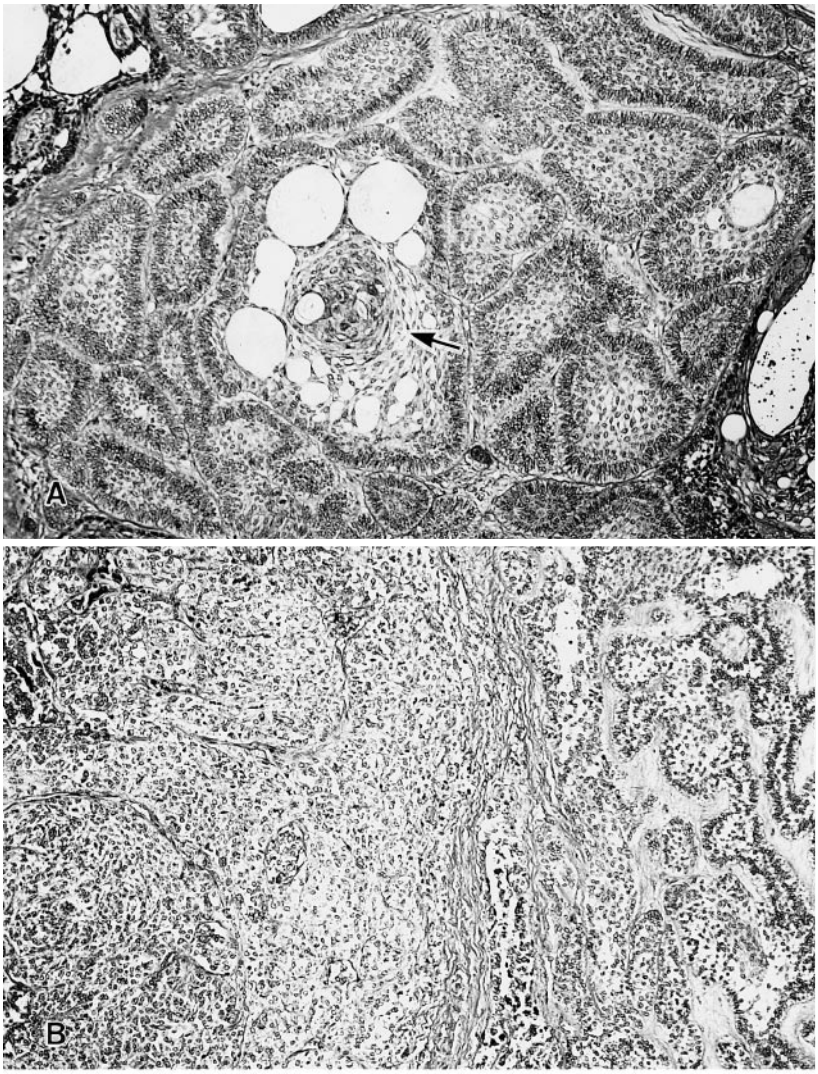
Materials and methods

Both orbital and parasagittal tumours were studied histopathologically and immunohistochemically, and three recurrent ameloblastomas were also reviewed. Tissues and sections of primary ameloblastoma resected in 1967 were not available for this study.

All tumour tissues were fixed in 10% buffered formalin, processed routinely, and embedded in paraffin. Sections 4 μm thick were cut and mounted on poly-*l*-lysine-coated slides. One section from each tumour was stained with haematoxylin and eosin (HE), and the others were used for immunohistochemical study by the streptoavidin–biotin–peroxidase complex method (DAKO SAB-PO kit, Kyoto, Japan) with a panel of monoclonal anti-cytokeratin antibodies: CK7 (OV-TL 12/30, DAKO, 1:400: specificity for cytokeratin #7), MA902 (35β H11, ENZO, New York, N.Y., 1:5,000: specificity for cytokeratin #8), MA903 (34β E12, ENZO, 1:2,000: specificity for cytokeratin #1, 5, 10, and 11), and MA904 (34β B4, ENZO, 1:400, specificity for cytokeratin #1), monoclonal anti-human epithelial membrane antigen (EMA, E29, DAKO, 1:30), and monoclonal anti-vimentin (V9, DAKO, 1:50). Sections immunostained with antibodies against CK7, MA902, MA903, and MA904 were pretreated with pronase (0.1%, 37°C, 20 min).

Pathological findings

The tumour in the first recurrence of ameloblastoma resected in 1989 was composed of epithelial islands consisting of loosely connected angular cells resembling stellate reticulum surrounded by a layer of cuboidal cells with distinct peripheral nuclear palisading resembling internal dental epithelium (Fig. 2A). These features were those of follicular-type ameloblastoma, and focal squamous metaplasia was also observed. There was no cellular atypia, and we found no histopathological features suggestive of malignancy. Immunohistochemically, the tumour cells were positive for MA902 and MA903, but not for CK7 (Fig. 3A, B).



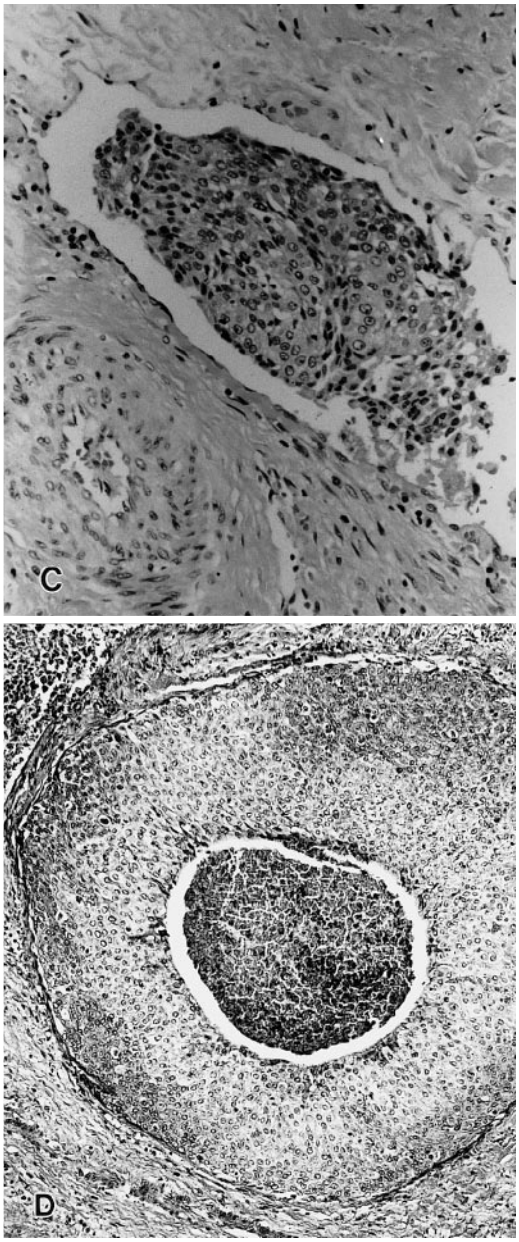


Fig. 2 **A** The first recurrent tumour in the mandible was a follicular ameloblastoma with a focal acanthomatous focus (*arrow*). HE, x85. **B** The second was composed of the regions of follicular ameloblastoma (*right*) and undifferentiated epithelial tumour with high-grade atypia (*left*). HE, x85. **C** Vascular invasion of undifferentiated cells in the second recurrent tumour. HE, x170. **D** The third recurrent tumour, disclosing a poorly differentiated squamoid histological pattern. HE, x85

At the second recurrence in 1992, the tumour, which extended into the soft tissue around the mandible, exhibited the histological patterns of both follicular ameloblastoma and undifferentiated epithelial tumour (Fig. 2B). The former had features almost identical to those of the tumour resected at the first recurrence (Fig. 3C, D), except for minimal immunopositivity for CK7. The two were clearly distinct from each other in histopathological features: the undifferentiated epithelial part of the tumour was highly cellular, exhibited much more cellular atypia and mitotic figures, included focal vascular invasion (Fig. 2C), and was negative on immunostaining with all three anti-cytokeratin antibodies, except for occasional single tumour cells with positivity for MA903 (Fig. 3C, D).

Figure 2D shows the tumour in the third recurrence in 1993. Almost all portions were squamoid, with obvious cellular atypia and relatively low mitotic activity. Immunohistochemically, MA902, MA903 and CK7 were all positive, with stronger and wider staining with MA903 and CK7 than in the previous follicular ameloblastomas.

The orbital tumour resembled the undifferentiated regions in the second recurrent tumour (Fig. 4A, B). It tended to form vague nests, but there were no features of typical ameloblastoma. Immunohistochemically, the cells were negative for MA902, MA903, and CK7. The simultaneously resected frontal parasagittal tumour was a typical meningothelial meningioma (Simpson grade II; Fig. 4C, D) showing diffuse positivity for EMA and vimentin and negativity for CK7, MA902, MA903, or MA904, and was thought to be unrelated to the amelo-

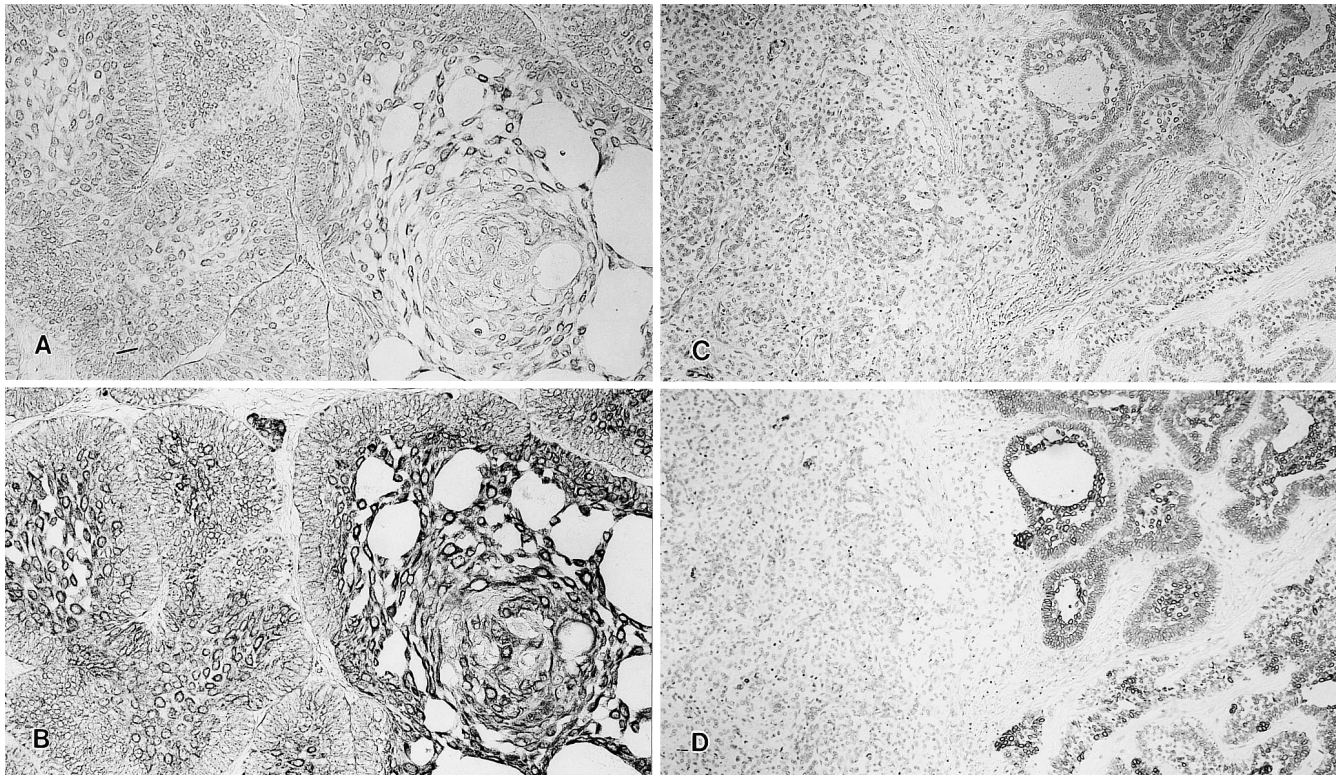


Fig. 3 A, B The first recurrent tumour, showing positivity for **A** MA902 and **B** MA903. SAB, x170. **C, D** The second recurrent tumour, showing positivity for **C** MA902 and **D** MA903 in the regions of follicular ameloblastoma (*right*), but no positive immunohistochemical staining in most cells of the undifferentiated regions (*left*). SAB, x85

blastoma. The tumour cells in the lesions, including the first, second and third recurrences and the orbital lesion, were negative for MA904, EMA and vimentin. Table 1 shows the result of the immunohistochemical profiles of the consecutive resected tumours in this patient.

Discussion

The first recurrence of this tumour exhibited typical features of follicular ameloblastoma. It is therefore reasonable to postulate that the primary mandibular tumour was a follicular ameloblastoma, although we were unable to examine it. Multiple local recurrences of that tumour occurred over several years, and metastasis finally appeared in the orbit without any other metastatic lesion.

Approximately 80% of all ameloblastomas occur in the mandible, and the remaining 20% occur in the maxilla [19]. Ameloblastomas originating in the maxilla occasionally extend through the maxillary sinus to the orbit and may affect the bone of the orbital floor and produce upward displacement of the globe and proptosis [4, 25]. However, to our knowledge no case of ameloblastoma in the mandible metastasizing initially to the orbit has been described. Our detailed clinical examination and CT scan and MRI diagnostic imaging studies revealed that the orbital tumour never came in contact with the mandibular or surrounding lesions. Furthermore, the operative impression was of a solitary intraorbital and intracranial tumour. It is therefore most likely that the orbital tumour was a distant metastatic deposit, rather than the result of continuous invasion from the site of recurrence.

The lung is the most frequent site of metastasis of ameloblastoma [22]. There have been a few reports of local invasion to the orbital floor and orbit as described above, but apparent metastasis to the orbital space has not been previously reported. The orbital tumour in this case was undifferentiated and resembled the foci in the second recurrence in both histopathological and immunohistochemical findings. Vascular invasion was noted at the second recurrence. We concluded that the undifferentiated portion of the second recurrent tumour had metastasized to the orbit and considered that conventional follicular ameloblastoma had undergone transformation to tumours with apparently malignant features.

Cytokeratin is one of the five classes of intermediate filaments and forms the intermediate filaments of epithelial cells. It is collectively a family 20 (so far) biochemically and antigenically different polypeptides, which range in molecular weight from 40 to 67 kDa [14–16]. Tumours derived from epithelial tissues have been shown to express specific cytokeratins [8, 14, 17], because the expression pattern of cytokeratins in tumour cells is determined by cell origin and differentiation pathway. In ameloblastoma and ameloblastic carcinoma, Vigneswaran et al. [24] reported that the major cytokeratins of tu-

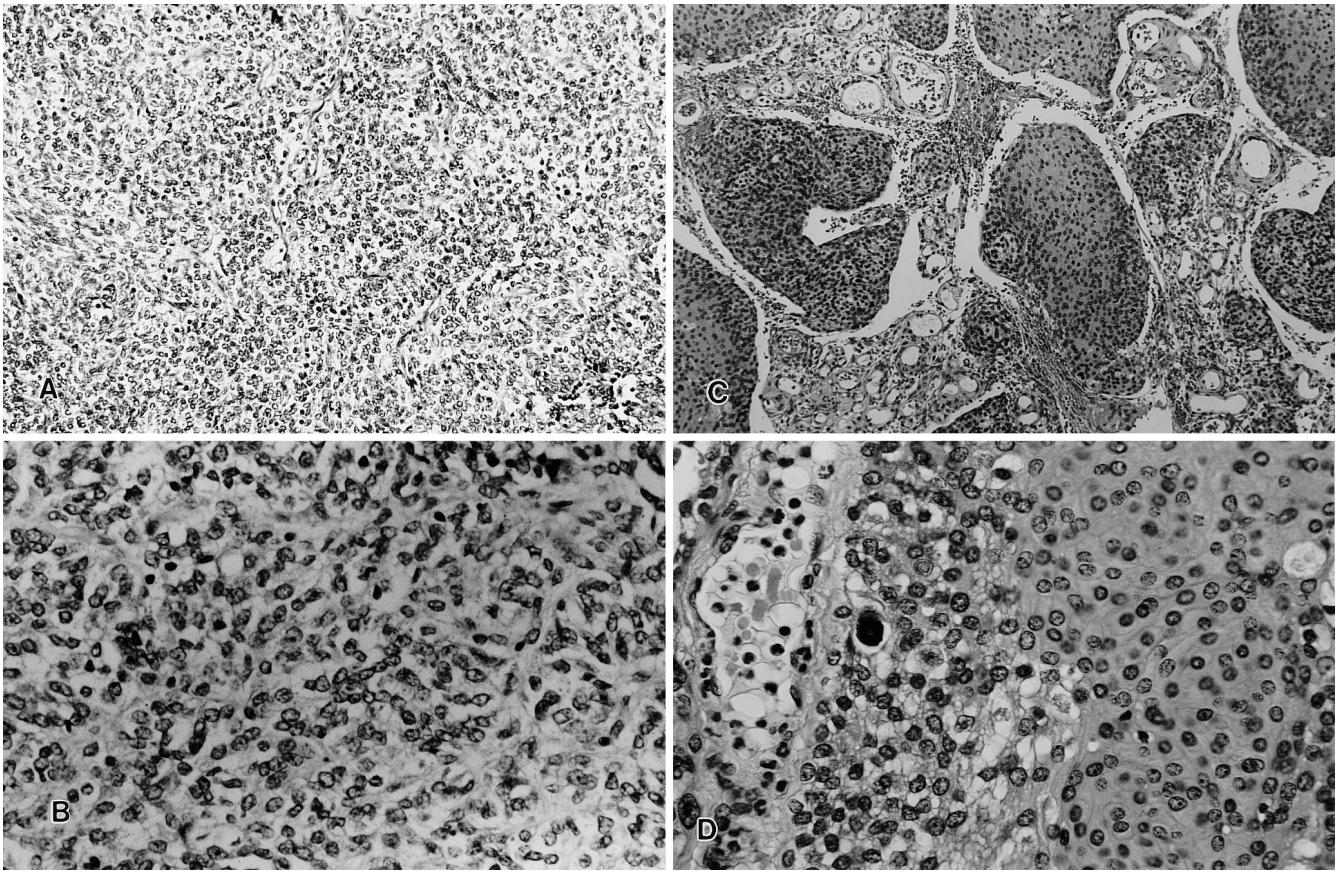


Fig. 4 A, B The orbital tumour, showing a nest-like arrangement of undifferentiated cells. High cellularity with apparent cellular atypia was present. No features of ameloblastoma were present. HE, **A** x75, **B** x250. **C, D** The parasagittal tumour, with islands of meningothelial cells with epithelial features. The tumour cells had uniform, small, round and oval nuclei and abundant cytoplasm. There was no nuclear pleomorphism or mitotic activity. A small calcified (psammoma) body was present. HE, **C** x75, **D** x280

mour cells were cytokeratins 5 and 14 with co-expression of cytokeratins 8, 18 and 19 in ameloblastoma, but ameloblastic carcinoma cells were reactive only for cytokeratin 5/14 and failed to synthesize cytokeratins 8/18 and 19. In our case, the first recurrence showed the presence of high-molecular-weight cytokeratins (5, 10, 11) with co-existence of low-molecular-weight cytokeratin (8). As the morphology changed from follicular ameloblastoma to that of a malignant tumour with the squamoid or undifferentiated features, the pattern of expression of cytokeratins changed. In the squamoid part, the staining for low- and high-molecular-weight cytokeratins (CK7, MA902 and MA903) was positive; however, almost all tumour cells in the undifferentiated part were negative for these cytokeratins. The lack of cytokeratin 1 (MA904), which is typical of keratinizing stratified squamous epithelium, and the presence of cytokeratins 7 and 8 (CK7 and MA902), which are specific for simple epithelium, may reflect the different pathway of tumour differentiation. The lack of cytokeratins in the orbital tumour was reminiscent of the undifferentiated part of the second recurrent tumour. From the expression of cytokeratins, this ameloblastoma has undergone two different morphological transformations.

The parasagittal tumour was thought before surgery to be possibly a metastasis rather than a primary tumour of the central nervous system. However, the tumour cells

Table 1 Immunohistochemical Profiles of the tumours in this case

	First recurrence[a]	Second recurrence[b] A	Second recurrence[b] B	Third recurrence[c]	Orbital tumour	Parasagittal tumour
CK7	–	±	–	+	–	–
MA902	+	+	–	+	–	–
MA903	+	+	±~–	++	–	–
MA904	–	–	–	–	–	–
EMA	–	–	–	–	–	+
Vimentin	–	–	–	–	–	+

[a] Follicular ameloblastoma
[b] Part follicular ameloblastoma (*A*), part undifferentiated tumour (*B*)
[c] Squamoid tumour

differed from the ameloblastoma cells and had a different immunohistochemical profile from those of the orbital tumour. The parasagittal tumour cells were diffusely positive for EMA and vimentin, but negative for the cytokeratins such as CK7, MA902, MA903, and MA904. These results are consistent with those of meningioma [1, 13, 21]. Some meningiomas show positivity for some kinds of cytokeratin [1, 13, 18], but the expression of EMA and vimentin is the most characteristic feature [1, 21]. Reports of EMA and vimentin in ameloblastoma or ameloblastic carcinoma are rare, and Gandy et al. [7] reported EMA and vimentin to be negative in two cases of ameloblastic carcinoma. All consecutive lesions in our case except for the parasagittal tumour also showed negativity for EMA and vimentin.

Malignant features are present in about 2% of cases of ameloblastoma [9], but the classification of ameloblastoma with malignant potential has been controversial. Malignant ameloblastoma was formerly defined in the World Health Organization (WHO) classification as "a neoplasm in which the features of an ameloblastoma are shown by the primary growth in the jaws and by any metastatic growth" [20]. According to this criterion, the diagnosis of malignant ameloblastoma requires the presence of distant metastasis, and both primary and metastatic tumours should retain a benign appearance. However, ameloblastomas with malignant histopathological features with or without metastasis do occur. For this reason, some investigators have proposed the term ameloblastic carcinoma for such tumours, including those transformed from benign-appearing ameloblastomas, as in the present case. In 1982, Elzay proposed classifying primary jaw intraosseous carcinomas as follows: type 1, arising from odontogenic cyst; type 2, arising from ameloblastoma, (A) well-differentiated (malignant ameloblastoma), (B) poorly differentiated (ameloblastic carcinoma); type 3: arising de novo, (A) nonkeratinizing, (B) keratinizing [6]. In addition, Slootweg and Müller [23] attempted to re-subclassify and expanded Elzay's classification by including those ameloblastic carcinomas arising de novo or in association with ameloblastoma or odontogenic cysts. Corio et al. [3] and Lee et al. [12] also used this term in their study. In other words, the ameloblastic carcinoma is an ameloblastoma that has histopathological evidence of malignancy in the primary and/or recurrent tumour, regardless of whether it has metastasized. According to this view, the tumour in our case should be classified as ameloblastic carcinoma. In the new WHO classification of 1992, however, malignant ameloblastoma was re-defined as "a neoplasm in which the pattern of an ameloblastoma and cytological features of malignancy are shown by the primary growth in the jaws and/or by any metastatic growth. Tumours meeting these criteria may arise as a result of malignant change in a pre-existing ameloblastoma, or possibly as a primary malignant ameloblastoma not preceded by an ordinary ameloblastoma" [11]. Our tumour also satisfies these criteria.

Ameloblastoma is a slow-growing tumour, but the effects of multiple recurrence and malignant transformation can be devastating. Early en bloc surgical resection is the treatment of choice for avoiding recurrence. This case illustrates the importance of close monitoring of patients for local and distant disease. Since it is quite possible that other sites of metastasis, including the lungs and lymph nodes, may appear, careful follow-up is needed in this case.

Acknowledgements The authors thank Masahiro Kurisaka, MD, Department of Neurosurgery, Kochi Medical School, for providing the operative findings.

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