Ameloblastoma and its Malignant Transformation: Treatment Ladder, Related Syndromes and Controversies

Anshuman Kumar[1], Aviral Verma[2], Apala Baduni[3], Navneet Kaur[4]

ABSTRACT

Odontogenic Tumour is a term that encompasses a wide spectrum of lesions ranging from malignant and benign neoplasms, all arising from odontogenic apparatus. Distinction among the tumours may, in part depend on the embryologic stage of initiation and the histologic and gross appearance of the lesion at the age of clinical discovery. Ameloblastomas are known to occur at unusual locations, metastasize, or transform into malignant neoplasms. They may show various biologic behaviours, ranging from cystic expansion to more aggressive infiltration of adjacent tissue. Ameloblastomas have a wide variation in clinical presentation, histology and prognosis, and they are also known for late recurrences, significant local morbidity and systemic spread. Though many advances are being made in the diagnosis and management of this tumour, there always has existed an air of debate and controversy on the very nature and management of this tumour. Various authors have different viewpoints regarding the nature of this tumour due to its myriad presentations. Newer treatment modalities have been tried over the years to prevent recurrence, reduce morbidity and facilitate adequate rehabilitation in patients affected with ameloblastoma.

Keywords: Ameloblastoma, Ameloblastoma Malignant Transformation, Treatment Ladder

INTRODUCTION

As used by most investigators, malignant/metastasizing ameloblastoma is defined as the ameloblastoma that metastasises provided the metastatic lesion must closely resemble the original lesion in the jaws histologically and also be cytologically benign[1]

WHO[2] in 2005 defined metastasizing ameloblastoma as an ameloblastoma that metastasizes in spite of a benign histologic appearance. Metastasizing ameloblastoma shows similar features as ameloblastomas that do not metastasize. Therefore, it is clinical behaviour and not histology that gives the diagnosis of metastasizing ameloblastoma. Confusion may also arise through the use of the term atypical ameloblastoma to denote lesions with fatal outcome for various reasons, either metastasis, histological atypia or relentless local spread.

In early reviews by Small and Waldron[1], metastatic deposits were reported to have occurred in over 30 cases. On further review by Carr and Halpenin – 1968[2], many of them were found to be either cases of misdiagnosis or ones where the metastatic lesion was unproven.

A few cases where metastatic ameloblastoma has been accepted, a feature of a long standing disease that has been operated upon a number of times over the course of years, and finally presenting with metastatic deposits in the lungs has been reported (Vorzimer and Perla - 1932; Schweiter and Banfield - 1943).[2-4]

The literature dealing with metastatic ameloblastoma was reviewed by Lee et al (1959).[5] An arguable discussion of demonstrable lung lesions occurring as a result of aspiration implantation were found in patients with a history of previous surgery and the fact that metastases are usually found in sites where aspirated foreign bodies are usually found. However, metastases have also been noted in other sites, such as cervical and mediastinal lymph nodes, bone and liver, and other viscera considered by some as result of haematogenous spread.[6]

Ameloblastic carcinoma

WHO[1] defines it as primary odontogenic malignancy that combines the cytological atypia with the histological features of ameloblastoma even in the absence of metastases. Ameloblastic Carcinoma is defined as that type of ameloblastoma in which the tumour has behaved in malignant fashion with no resemblance to the primary odontogenic tumour but to a less well differentiated carcinoma nd there has been obvious histological malignant transformation of the epithelial component.

While the WHO[2] publication (Pindborg -1971) classifies odontogenic carcinoma into:

- Malignant ameloblastoma,
- Primary intra-osseous carcinoma and
- Other carcinoma arising from odontogenic epithelium.

Elzay (1982)[7] had liberalised the concept and classified primary intra-osseous carcinoma into:

- Those arising de novo.
- Those arising from odontogenic cysts
- Those arising from ameloblastoma (malignant ameloblastoma and ameloblastic carcinoma)

MANAGEMENT

Radical resection of the primary is done in all cases, and in the present days, radiotherapy has been used to treat some cases of metastatic ameloblastoma though there is very little evidence of its usefulness and more of its side effects. In a case report by Amzerin et al[7], in a patient who had multiple recurrences, combination chemotherapy was given using doxorubicin 50 mg/m^2 and cisplatin 100 mg/m^2. The assessment of response to chemotherapy was made after two cycles. The pain disappeared, and tomography showed local stabilization and partial response

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of the lung lesions (30%). With maintainence of response after six cycles of chemotherapy.

Definitions and classifications of ameloblastic carcinomas have changed over the years, there have been various classifications, the latest by Slootweg and Muller emphasizing histogenesis of the tumor leading to the new WHO classification in 2005.[8]

Less than 60 cases of ameloblastic carcinoma have been reported. Most cases have been reported in China and the reason is not clear.[9]

AMELOBLASTOMA IN UNUSUAL LOCATIONS

Occurrence of ameloblastomas in unusual locations has been documented in literature. These include the sinonsal cavity, nasal septum, infratemporal fossa, frontal sinuses, ethmoid sinuses etc. But these are thought to be local extensions or local spread of a maxillary primary tumour. Most of the cases were reported as recurrences of a previously treated tumour in a neighbouring region, and very few were primary tumours of the region.

Auluck, Shetty, Desai and Mupparapu[10] have reported a case of recurrent ameloblastoma in the infratemporal fossa, as an extension from the mandibular body.

AC Coombs[11] described a case of a maxillary ameloblastoma with an unusual initial presentation of nasal obstruction and with recurrence after radical surgery in the frontal and ethmoid sinuses.

SYNDROMES RELATED TO AMELOBLASTOMA

Reports by Schultz[12] and Ponti[13] et al indicate association of NBCCS to ameloblastoma, although it is not common. It was earlier mentioned in the minor criteria but no longer present in the criteria for diagnosis of NBCCS.

Gardner syndrome[14], also known as familial colorectal polyposis, an autosomal dominant form of polyposis, characterized by the presence of multiple polyps in the colon together with tumors outside the colon which includes epidermoid cysts, fibromas, osteomas of the skull, thyroid cancer, and sebaceous cysts, as well as the occurrence of desmoid tumors in approximately 15% of affected individuals.

Patel and Rees[14] reported a case of unicystic ameloblastoma associated with Gardner's syndrome.

RECENT TRENDS IN MANAGEMENT OF AMELOBLASTOMA

With the newly emerging diagnostic techniques and treatment modalities, management of ameloblastoma and its forms has met few advances in the recent times.

The osteomucoperiosteal flap[15]

Yih described the osteomucoperiosteal flap and modified by Khare and Kumar[15] (Figure 1).

Reports of aggressive ameloblastomas and ameloblastic carcinomas receiving radiation therapy are scarce and mostly from the pre-3 D and cobalt era. Radiotherapy has only been given as adjuvant therapy in only a few cases within the past 20 years. Radiation doses between 41Gy and 54 Gy have been comparatively conservative or not been reported leading to local relapse in half of the cases.[16]

In cases with incomplete resections or nodal metastases, there is no evidence for radiotherapy as a potentially definitive

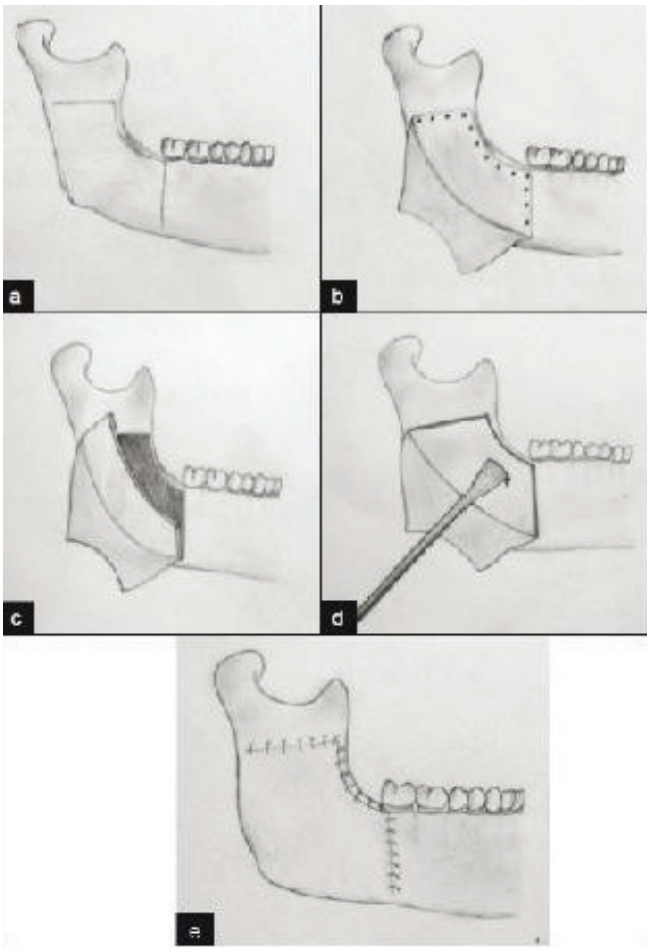

Figure-1: (a) Incision; (b) mucosal flap with osteoperiosteal incision; (c) reflected osteoperiosteal flap by fracturing the inferior osseous portion of the flap; (d) placement of the osteoperiosteal flap into the cavity after removal of the tumor; (e) closure of the mucosal flap

treatment modality yet. Aggressive treatment recommending surgical wide excision with 2-3 cm margins, counterbalances a high tendency of local relapse, therefore, RT was given in a high-precision technique as carbon ion therapy. For intensity-modulated radiation therapy the integral dose to the irradiated volume is substantially lower. Also, increased biological effectiveness of carbon ion beams has been shown to be beneficial in other radioresistant tumors. Carbon ion therapy in active beam application with raster-scanned particle beams is able to produce extremely steep gradients hence delivering high doses to the tumor while sparing normal surrounding tissues[16]

Jensen et al[16] described a case showing fast complete remissions of extensive ameloblastic carcinomas using carbon ion therapy at substantial doses accompanied by very mild treatment-related side effects (mild erythema, xerostomia and mucositis) and no major radiation-related toxicity; hence the patient could be spared extensive, mutilating and potentially incomplete surgical procedures. Therefore radiotherapy with carbon ions can be considered in the definitive treatment of these rare tumors. Higher radiation doses between 66 and 72 Gy in close margin/positive-margin resections as reported by Philip et al[17] lead to local control for the duration of available follow-up (0.8 - 3.3 years) in the reported 3 cases. This is the first case of ameloblastic carcinoma being treated with carbon ion therapy and resulted so far in an excellent post therapeutic outcome

(Figure 1-3). Therefore radiotherapy with carbon ions can be considered in the definitive treatment of these rare tumors.

CONTROVERSIES IN THE MANAGEMENT OF AMELOBLASTOMA

Ameloblastoma is considered the most unexplainable of odontogenic tumors, because of its contradictory clinical and histological features, if its benign histological aspect and its invasive and destructive clinical behaviour are considered, besides the reported capacity of establishing pulmonary metastases, a possible, though infrequent, occurrence. The statement that the treatment of ameloblastoma is controversial has been repeated so often that it has become a basic tenet within our profession. The long-standing controversy has been between curettage, often referred to as the conservative approach, and more extensive surgery such as marginal or segmental resection and hemimandibulectomy. A related topic is the feasibility of sparing the inferior border of the mandible - that is, using marginal rather than segmental resection. To a lesser extent, there has been some controversy about the various forms of cautery, including electrocautery and cryotherapy, as supplemental treatment, especially following curettage. Finally, one modality that has to be considered controversial in that it has recently received support from certain oncology centres, is radiotherapy[18], despite its usually having been condemned as ineffective and even dangerous.

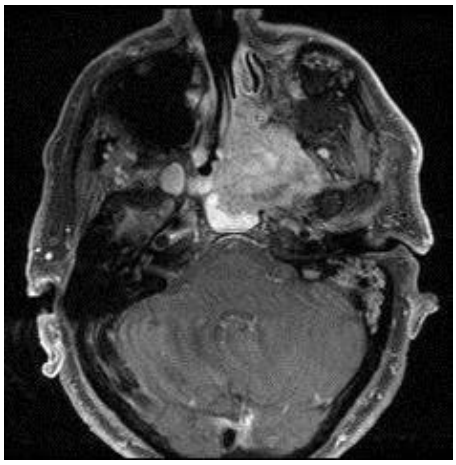

Figure-2: Preoperative MRI showing extensive left maxillary ameloblastic carcinoma[17]

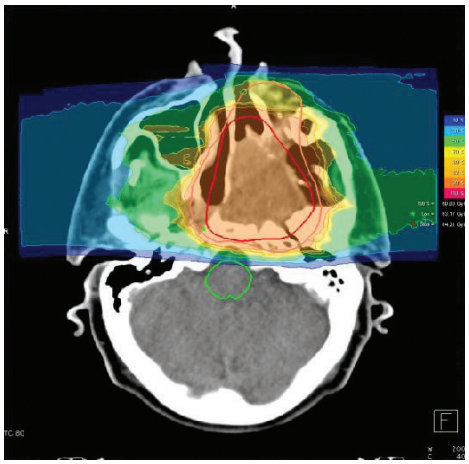

Figure-3: Carbon ion dose distribution corresponding to 60 Gy[17]

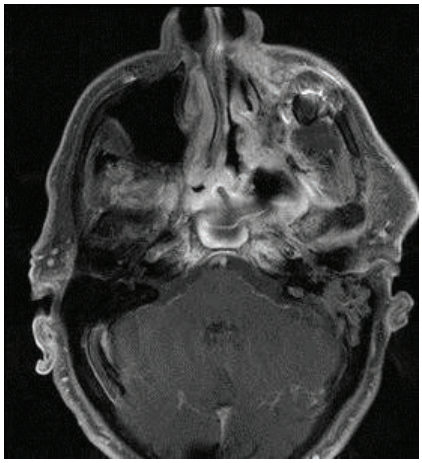

Figure-4: Post therapy MRI showing considerable remission[17]

Some basic queries need to be addressed while evaluating the literature concerning the results of various forms of treatment.[6] Is the diagnosis correct? Often it is difficult to be certain. Tumours that would not now be considered as ameloblastomas have been reported as such in the older literature and even in modern series that include patients treated years ago. Furthermore, it is important that the tissue sections have been examined by a pathologist experienced in odontogenic tumours. Are the details of the treatment sufficiently clear to allow proper evaluation? How extensive is the lesion? The question of using curettage is only meaningful for relatively small lesions. More extensive surgery is usually used for larger tumours, which are obviously less controlled than smaller ones. Were the follow up examinations adequate? Patients with ameloblastoma should be followed up for at least 10 years because recurrences often become apparent many years after surgery. However, follow up periods as short as 6 months and 2 years are found in literature. Moreover, the examinations must be thorough and include radiography.

CURETTAGE VERSUS EXTENSIVE SURGERY

The figures for marginal and segmental resections are complicated by the fact that they are used for more extensive lesions than is curettage. Moreover, resection is used for retreatment of recurrent cases which were previously treated by curettage. It follows that curettage is not a reliable method of eradicating a typical intraosseous ameloblastoma. Consequently, controversy arises as to whether curettage should ever be employed in the treatment of ameloblastoma. The answer is yes, depending upon the circumstances.

In the first place, curettage should never be used in the posterior maxilla, as this region lacks the dense cortical plate that is an effective barrier to the spread of the tumour in mandible. In the posterior maxilla, the tumour can easily spread and invade the cranium via the foramina leading from the pterygomaxillary fossa.

The situation in the body of the mandible is different. Here, a small tumour can be treated with enucleation/curettage, provided the surgeon is fully aware of the high risk of recurrence and will be able to follow the patient adequately for 10 years or more. Moreover, the patient must be fully informed of the risk.

The patient's medical condition and age are two factors that may suggest the use of curettage. It is justified in elderly people, with

a small confined tumour, who are unfit to undergo extensive surgery. It is also justified in younger patients with relatively less extensive tumours who want an intact functional mandible before undergoing a second surgery in case of recurrence. But in both these cases, follow up is vital.

FEASIBILITY OF MAINTAINING THE INFERIOR BORDER OF MANDIBLE

One choice in the treatment of ameloblastoma is whether to perform a resection with continuity defect or without a continuity defect. This decision largely depends on the size of the lesion. If the cortical plate has been greatly thinned out, it increases the risk of pathological fracture and therefore should be included in the resection. Ameloblastomas do not invade the haversian system of compact bone, instead, they just cause pressure resorption.

CONTROVERSIES REGARDING USE OF RADIOTHERAPY, CARNOY'S SOLUTION AND CRYOTHERAPY.

Though for decades radiotherapy has not been suggested as a treatment modality for ameloblastomas, some controversy has arisen in the recent past due to a few case reports claiming effective treatment by radiotherapy.[6] Carnoy's solution is an effective chemical cauterizing agent. Stoelinga and Bronkhorst[6] have used this modality after enucleation and have reported no recurrences. But the follow up period was only 2-2.5 years, which is inadequate. The use of Carnoy's solution seems to be harmless and may have the potential to reduce recurrences, but effectiveness is still under study.

In the previous reports by Atkinson et al[19] that shows cure using irradiation, the follow up periods were insufficient and the patients were also treated with surgery. Therefore the role of radiation is still very questionable and controversial, given its adverse effects.

CONCLUSION

Due to its varied characteristics, presentation and histopathological types, ameloblastoma has always presented a challenge to clinicians with regards to nomenclature, classification and management. What makes this tumour different from other benign tumours is its close behaviour to malignant neoplasms like basal cell carcinoma, with regards to its spread. Diagnostic modalities and treatment options have evolved over the years, presenting various differences of opinion on its management and prevention of recurrence. Effective treatment, though available, still leaves behind the question of whether the lesion would recur or not, as many lesions have recurred after what is considered an "ideal disease free interval". Patients diagnosed with ameloblastoma must be treated following a proper protocol meticulously, and more importantly, follow up is necessary to manage episodes of recurrence and prevention of further morbidity. More advances with regards to controlling the tumour characteristics on a molecular level, are expected in the future. Though many advances have been made in diagnosis and management, the nature of this tumour still remains to be a subject of debate.

REFERENCES

1. Ademola A.O. Ameloblastoma – clinical features and management of 315 cases. J Craniomaxillofac Surg 1993.
2. Rajendran R. Cysts and tumours of odontogenic origin. In Textbook of oral pathology, Elsevier, 2006.
3. RB Lucas. Pathology of Tumours of Oral Tissues. 4th edition. 1984.
4. Ellis E III. Surgical management of oral pathologic lesions. In Contemporary Oral and Maxillofacial Surgery. Elsevier, 1992.
5. Cherrick H M. Odontogenic tumors of the jaw. In Oral and Maxillofacial Surgery, Daniel M. Laskin. 2nd Ed., AITBS, New Delhi. 2009;2:628-643.
6. DG. Gardner. Controversies in the nomenclature, diagnosis and treatment of ameloblastoma – In Controversies in Oral and Maxillofacial Surgery. P Worthington, JR Evans. 1994.
7. Amzerin et al. Metastatic ameloblastoma responding to combination chemotherapy: case report and review of the literature. Journal of Medical Case Reports. 2011;5:491.
8. Philipsen, Reichart, Slootweg, Slater. Neoplasms and tumour-like lesions arising from the odontogenic apparatus and maxillofacial skeleton: In World Health Organization Classification of Tumours. IARC Press. Lyon, 2005.
9. Lu Y, Xuan M, Takata T, Wang C, He Z, Zhou Z, Mock D, Nikai H. Odontogenic tumors. A demographic study of 759 cases in a Chinese population. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1988;86:707-714.
10. Auluck.A, Shetty S, Desai R, Mupparapu M. Recurrent ameloblastoma of the infratemporal fossa: diagnostic implications and a review of the literature. Dentomaxillofacial Radiology. 2007;36:416-419.
11. Coombs A C. Ameloblastoma of the frontal sinuses: a rare site for recurrence. J. surg. case rep. 2011 (1).
12. Schultz SM, Twickler DM, Wheeler DE, Hogan TD. Ameloblastoma associated with basal cell nevus (Gorlin) syndrome: CT findings. J Comput Assist Tomogr. 1987;11:901-4.
13. Ponti G, Pastorino L, Pollio A, Nasti S, Pellacani G, Mignogna MD, Tomasi A, Del Forno C, Longo C, Bianchi-Scarrà G, Ficarra G, Seidenari S. Ameloblastoma: a neglected criterion for nevoid basal cell carcinoma (Gorlin) syndrome. Fam Cancer. 2012;11:411-8.
14. Patel H, Rees RT. Unicystic ameloblastoma presenting in Gardner's syndrome: a case report. Br Dent J. 2005,25;198:747-8.
15. Khare, Kumar. Application of osteomucoperiosteal flap in large unicystic ameloblastoma to promote early bone healing: An alternative to primary bone grafting. Contemp Clin Dent. 2011;2:283–286.
16. Schulz-Ertner D, Karger C P, Feuerhake A, Nikoghosyan A, Coombs SE, Jäkel O, Edler L, Scholz M, Debus J: Effectiveness of carbon ion radiotherapy in the treatment of skull-base chordomas. Int J Radiat Oncol Biol Phys. 2007; 68:449-457.
17. Philip M, Morris C G, Werning JW, Mendenhall WM: Radiotherapy in the treatment of ameloblastic carcinoma. J HK Coll Radiol. 2005;8:157-161.
18. Pechalova PF,. Bakardjiev AG, Beltcheva AB. Jaw cysts at children and adolescence: A single-center retrospective study of 152 cases in southern Bulgaria. Med Oral Patol Oral Cir Bucal. 2011;16:e767-71.
19. Thrall DE. Orthovoltage radiotherapy of acanthomatous epulides in 39 dogs. J Am Vet Med Assoc. 1984;184:826-9.

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