SP-20

Metastasizing Ameloblastoma

Dr.Sudha Jimson, MDS[3], Dr. SUDAKSHINA MUKHERJEE[2*], Dr. Jayasri Krupaa,MDS[1], Dr.N.Anitha,MDS[1]

[1]Department of Oral Pathology and Microbiology, Sree Balaji Dental College and Hospital, Bharath Institute of Higher Education and Research, Pallikaranai, Chennai.

[2]Post Graduate Student, Department of Oral Pathology and Microbiology, Sree Balaji Dental College And Hospital, Bharath Institute of Higher Education and Research, Pallikaranai, Chennai.

[3]Professor and Head, Department of Oral Pathology and Microbiology, Sree Balaji Dental College and Hospital, Bharath Institute of Higher Education and Research, Pallikaranai, Chennai.

Abstract: Ameloblastoma is a benign odontogenic tumour which is locally aggressive and has a high recurrence rate. Though it is the most common odontogenic tumour, the incidence of its metastasis is low and once the metastases occur, which are uncommon, lungs represent the most common site involved. Malignant ameloblastomas are different from ameloblastic carcinomas. Malignant ameloblastomas are tumours considered metastatic despite the appearance of well-differentiated or benign histology, while ameloblastic carcinomas are histologically malignant in both primary and metastatic sites.

Keywords: Malignant ameloblastomas, Metastasizing ameloblastomas, metastasis.

1. INTRODUCTION

Ameloblastoma is a locally invasive neoplasm originated from odontogenic epithelium. The tumor is composed of proliferating odontogenic epithelium which is of enamel organ-type tissue that did not undergo differentiation to the point of hard tissue formation. Characteristically, the tumor lacks enamel and dentin. It has been postulated that the epithelium of origin is derived from one of the following sources-

a) Epithelial lining of odontogenic cyst
b) Dental lamina or enamel organ.
c) Basal cells of surface epithelium
d) Disturbances of developing enamel organ
e) Heterotopic epithelium of other parts of body.

Ameloblastoma is a benign odontogenic tumour which undergoes malignant transformation to ameloblastic carcinoma. However, seldom it metastasizes without undergoing cytological malignant changes, an entity denoted as Metastasizing Ameloblastoma (MA). The term metastasizing ameloblastoma is used to describe a tumour that shows histologic features of classic ameloblastoma in the gingiva or jaw and has metastatic deposits elsewhere. Histologically it is a benign conventional ameloblastoma that metastasizes to different sites and both primary and secondary lesions have histological features of benign ameloblastoma.[1]

2. CLINICAL FEATURES AND METASTASIS

Typically, the primary ameloblastoma arises in mandible of a young adult with average range of presentation being 20-30 years. Metastases are uncommon, which is why metastatic ameloblastoma is considered benign (in addition to the benign features on histology) and generally may manifest after an interval ranging from 10 to 12 years [2]. The metastatic nodules if develops mostly found in lungs (80%), cervical lymph nodes (15%) or extra gnathic bones. Typically, the pulmonary metastasis is multifocal and involve both lungs. The median survival after discovery of metastatic lesion is about two years. Innocuous 'lung granulomas' that are seen on routine chest radiographs of a patient with ameloblastoma can prove to be silent metastasis and it was noted that most patients had multiple recurrences of jaw ameloblastoma. The multiple recurrences could result either from an intrinsically more aggressive tumour, i.e., one that is more proliferative or more infiltrative or from surgery associated tumour "spillage" into adjacent tissue or tumour embolization into lymphatic or blood vessels [3,4]. The pulmonary metastasis can be due to aspiration of tumour fragments during multiple surgical procedures, for recurrent ameloblastoma though it is debatable. The intravascular spread through tumour emboli disseminated by way of blood or lymphatic vessels is more convincing. [3] Because of lack of morphological criteria of malignancy, the biological behaviour of ameloblastomas cannot be predicted. It is difficult to decide about the factors that can be important in the delayed induction of metastasis. It is hypothesized that ameloblastomas possess an inherent low-grade malignancy which is stimulated by multiple recurrences. It is also suspected that the metastatic tumour cells have a slow growth rate, resulting in late clinical manifestation of metastases.

3. PROPOSED MECHANISM FOR METASTASIS OF METASTASIZING AMELOBLASTOMA

When trying to hypothesize the metastatic cascade associated with MA, it was found that benign and malignant tumour follows the same pathway till the blood vessels. However, MA exhibits surprisingly a different behaviour by intravasating into the blood vessels and metastasize. Primary tumour cells of MA manifest EMT by a method called "cadherin switch" by switching E-cadherins to N-cadherins. Now, surge in N cadherins results in two processes – Firstly, cytoskeleton rearrangement occur via

"Rho induced stress fibers", and secondly, by formation of invadopodia through activation of RAC1.[5] Tumor cells increase Src activity by interacting with transmembrane receptors (epidermal growth factor receptor, platelet-derived growth factor receptor, and fibroblast growth factor receptor) which engages with receptor tyrosine kinase intracellularly and integrins extracellularly result in increase in Src activity.[6,7]Activation of Src leads to phosphorylation and activation of mitogen-activated protein kinase which is responsible for regulation of cytoskeleton invadopodia formation and increases in MMP (MMP2, MMP9) activity for migration (single cell migration [SCI] or collective cell migration [CCI]) and invasion of tumour cells.[7,8] At the endothelial lining, tumour cells will take two ways to enter into the vessels. One way is transcellular and another is paracellular intravasation. The entry of tumor cells through the endothelial cells via cell junctions occurs under the influence of various cytokines such as EGF1, TNF1 alpha, and protease-activated receptor 1 (PAR1). Finally, it results in distant metastasis. [8]

4. MOLECULAR MARKERS

Application of various immunohistochemical (IHC) markers have been made to discover the unrevealed aspect of metastasis in MA. The markers which could help in determining their implications in the invasive process of MA, and lacks cytodifferentiation of odontogenic epithelial cells are as follows- Among the important studied markers given in the literature most recognized one is RAS. RAS is a signal transduction protein which regulates malignant transformation and is the most commonly mutated gene in human tumors (about 85% of total) including oral squamous cell carcinoma (OSCC) (5%–50%). Mutational detection of kRAS has clinical importance in prognosis and treatment of various malignancies.[11] Kumamoto et al. carried out an IHC study on kRas, kRaf, and MEK ERK1 and found peripheral and central cells of MA to be moderately positive (++) for these markers on DNA sequencing; The study revealed that out of two MAs, only one exhibited point mutation of kRas which provided with the idea that kRas has an important role in neoplastic transformation of odontogenic epithelium.[9] Kumamoto et al. carried out a study on SHH, PTCH, SMO, and GLI in MA and found that SHH and PTCH were strongly positive (++). MA showed GLI and SMO expression in neoplastic cells as well as stromal cells. GL11 showed strong reactivity in neoplastic cells as compared to stromal cells. High immunoreactivity for p63 in epithelial odontogenic tumours has been found in peripheral neoplastic cells than in central neoplastic cells. Increased expression of p63 and p53 was found which suggested that they have a role in proliferation of odontogenic epithelium. Raised expression of isoform denotes their role in oncogenesis and neoplastic transformation of odontogenic epithelium.[10] (TNF) alpha acts as an endogenous tumour promoter in carcinogenesis process. TNF accelerates the epithelial– mesenchymal transition (EMT) and was linked to the acquisition of an invasive phenotype. [11-13] It has been found that TNF-alpha was positive in neighbouring cells adjacent to the basement membrane. TRAIL was manifested in most peripheral columnar or cuboidal cells and in few central polyhedral cells.[14.] Kumamoto and Ooya studied and showed positive activity of NF-k in all peripheral cells of MA, suggesting its role in oncogenesis and tumor progression.[14] =Other markers are described in a chart form as follows

STUDY	POSITIVE MARKERS	NEGATIVE MARKERS
Kumamoto et al., 2005[14]	β catenin, APC (++)	
Kumamoto et al., 2005[14] Fujita et al., 2006	Cytochrome, APAF1 (++), Caspase-9 (++), AIF (++) B), APC (++)	
	Neoplastic cells - BMP-2 (+), BMP-4 (+/++), BMP-7 (++/+++), BMPRs (++/+++), CBFA1 (++) Stromal cells - BMP-2 (+), BMP-4 (+), BMP-7(+), BMPR'S (+/++), CBFA1 (+)	Nestin
H Kumamoto et al., 2006[21]	MTI-MMP (++), RECK (++), EMMPRIN (++)	
H Kumamoto et al., 2007[22]	pAkt (+/++), P13k (+/++), PTEN (+/++)	
Kumamoto 2007[22]	P-P38MAPK (+,-), p-ERK5 (+)	p-JNK
H Kumamoto et al., 2008[23]	Neoplastic cells - Bid (++), Bim (++), Bad (++) (peripheral) Stromal cells - Bid (+/++), Bad (+)	
Kumamoto et al., 2010[23]	CD133 (+), Bmi-1 (++), ABCG2 (++)	
Kazuma Noguchi et al., 2013[21]	Ki 67 +++	
Rui B et al., 2015[21]	Stellate cells - CK10/13 (+), Spindle cells - p63 (+)	

5. FUTURE PROSPECTS OF METASTASIZING AMELOBLASTOMA

It was found that MA is a confusing lesion bearing a few malignant characteristics. At clinical level, it is very difficult to assess its malignant potential. So careful assessment should be done to diagnose this pathology and give necessary therapy.
Following are some future prospects which should be taken into account

5.1 Role Of Histopathological Malignant Features

The underlying cytodifferentiating character and highlighted metastatic character are two significance/vital intrinsic dispositions of MA. The Notch pathway was shown to be important for cytological differentiation or acquisition of tissue-specific

characteristics in neoplastic cells of odontogenic neoplasms. Notch 1 signalling is activated in the neoplastic epithelium. It was found that activated Notch 1 results in the translocation of Notch to the nucleus and causes cycle arrest; however, Notch1 signalling is related to the acquisition of morphological characteristics in tumorigenesis.[15]

5.2 Tumour Microenvironment

TM consists of stromal myofibroblasts. Stromal myofibroblasts are capable of invading cells and promoting cancer cell invasion.[16]They can also secrete various cytokines (IL-8 and VEGF) and chemokines (e.g., CXCL12). They mainly communicate with cancer cells through a cyclic peptide known as the CXCL12 in order to control cancer cell migration[17]. These tumours myofibroblasts then form invading channels through ECM from which carcinoma cell pass through by maintain their epithelial characteristics [5].

5.3 Difference Between Ameloblastoma And Metastasizing Ameloblastoma

Histopathologically, it is hard to differentiate between MA and non-MA. Studies on MA revealed that certain markers can be linked to its pathophysiology [18,19,20,21]. A study revealed that the altered expression of p-p38 MAPK and p-ERK5 proteins could be involved in the development of neoplastic epithelium [22].

5.4 Role Of Epithelial–Mesenchymal Transition

Various studies have revealed that certain markers in MA have a significant role in the development of metastatic ameloblastoma [23,24]. Findings related to EMT suggest that further studies should be conducted on the role of EMT genes like Snail, Slug, SIP1, and Twist in the disease. It has been hypothesized that these regulators might play a role in odontogenic tumors either acting alone or in concert of EMT [25,26].

6. CONCLUSION

Usually, any malignant tumor cells bear dysplastic morphologic features and mutational molecular characteristics which results in distant metastasis. However, in MA, instead of having benign morphologic features, it surprisingly metastasizes. It will be beneficial to obtain meaningful differentiating features in non-MA and MA for future aspects.

7. REFERENCES

1. Sivapathasundaram. Shafer's Textbook of Oral Pathology, 9th edition, 2020.
2. Gilijamse M, Leemans CR, Winters HA, Schulten EA, van der Waal I: Metastasizing ameloblastoma. Int J Oral Maxillofac Surg 2007, 36(5):462-464.
3. Kunze E, Donath K, Luhr HG, Engelhardt W, De Vivie R. Biology of metastasizing ameloblastoma. Pathol Res Pract 1985;180:526-35.
4. Laughlin EH. Metastasizing ameloblastoma. Cancer 1989;64:776-80.
5. van Zijl F, Krupitza G, Mikulits W. Initial steps of metastasis: Cell invasion and endothelial transmigration. Mutat Res 2011;728:23-34
6. Deep G, Agarwal R. Antimetastatic efficacy of silibinin: Molecular mechanisms and therapeutic potential against cancer. Cancer Metastasis Rev 2010;29:447-63.
7. Fury MG, Baxi S, Shen R, Kelly KW, Lipson BL, Carlson D, et al. Phase II study of saracatinib (AZD0530) for patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC). Anticancer Res 2011;31:249-53.
8. Reymond N, d'Água BB, Ridley AJ. Crossing the endothelial barrier during metastasis. Nat Rev Cancer 2013;13:858-70.
9. Kumamoto H, Takahashi N, Ooya K. K-Ras gene status and expression of Ras/mitogen-activated protein kinase (MAPK) signaling molecules in ameloblastomas. J Oral Pathol Med 2004;33:360-7.
10. Kumamoto H, Ohki K, Ooya K. Expression of p63 and p73 in ameloblastomas. J Oral Pathol Med 2005;34:220-6.
11. Bates RC, DeLeo MJ 3rd, Mercurio AM. The epithelial-mesenchymal transition of colon carcinoma involves expression of IL-8 and CXCR-1-mediated chemotaxis. Exp Cell Res 2004;299:315-24.
12. Bates RC, Mercurio AM. Tumor necrosis factor-alpha stimulates the epithelial-to-mesenchymal transition of human colonic organoids. Mol Biol Cell 2003;14:1790-800.
13. Chuang MJ, Sun KH, Tang SJ, Deng MW, Wu YH, Sung JS, et al. Tumor-derived tumor necrosis factor-alpha promotes progression and epithelial-mesenchymal transition in renal cell carcinoma cells. Cancer Sci 2008;99:905-13.
14. Kumamoto H, Ooya K. Expression of tumor necrosis factor alpha, TNF-related apoptosis-inducing ligand, and their associated molecules in ameloblastomas. J Oral Pathol Med 2005;34:287-94.
15. Takamine K, Ueda Y, Nakano K, Ochiai T, Sugita Y, Kubo K, et al. Notch as a possible cell differentiation factor in pleomorphic adenomas. Int J Med Sci 2015;12:759-63
16. Massague J. TGFbeta in cancer. Cell 2008;134: 215–230
17. Joyce JA, Pollard JW. Microenvironmental regulation of metastasis. Nat Rev Cancer 2009;9:239-52.
18. Kumamoto H, Takahashi N, Ooya K. K-Ras gene status and expression of Ras/mitogen-activated protein kinase (MAPK) signaling molecules in ameloblastomas. J Oral Pathol Med 2004;33:360-7.
19. Kumamoto H, Ohki K, Ooya K. Expression of sonic hedgehog (SHH) signaling molecules in ameloblastomas. J Oral Pathol Med 2004;33:185-90

20. Kumamoto H, Ohki K, Ooya K. Expression of p63 and p73 in ameloblastomas. J Oral Pathol Med 2005;34:220-6.
21. Kumamoto H, Ooya K. Immunohistochemical detection of MT1-MMP, RECK, and EMMPRIN in ameloblastic tumors. J Oral Pathol Med 2006;35:345-51.
22. Kumamoto H, Ooya K. Immunohistochemical detection of phosphorylated JNK, p38 MAPK, and ERK5 in ameloblastic tumors. J Oral Pathol Med 2007;36:543-9.
23. Kumamoto H, Ooya K. Expression of bone morphogenetic proteins and their associated molecules in ameloblastomas and adenomatoid odontogenic tumors. Oral Dis 2006;12:163-70.
24. Kumamoto H, Ooya K. Immunohistochemical detection of phosphorylated Akt, PI3K, and PTEN in ameloblastic tumors. Oral Dis 2007;13:461-7.
25. Hajra KM, Chen DY, Fearon ER. The SLUG zinc-finger protein represses E-cadherin in breast cancer. Cancer Res 2002;62:1613-8.
26. Bolós V, Peinado H, Pérez-Moreno MA, Fraga MF, Esteller M, Cano A, et al. The transcription factor slug represses E-cadherin expression and induces epithelial to mesenchymal transitions: A comparison with snail and E47 repressors. J Cell Sci 2003;116:499-511.