Available Online at http://www.journalajst.com

ASIAN JOURNAL OF SCIENCE AND TECHNOLOGY

ISSN: 0976-3376

Asian Journal of Science and Technology
Vol. 08, Issue, 10, pp.6211-6214, October, 2017

REVIEW ARTICLE

PATHOPHYSIOLOGY OF METASTATIC TUMORS OF ORAL CAVITY: A REVIEW

[*1]Dr. Shivani Singh and [2]Dr. Raghvendra Narayan

[1]Senior Lecturer, Dept of Oral and Maxillofacial Pathology, M.M.College Of Dental Sciences and Research, Mullana(Ambala), Haryana, India – 133207
[2]Associate professor, Dept of paediatrics, M.M Institue of Medical Sciences and Research, Mullana(Ambala), Haryana, India – 133207

ARTICLE INFO

Article History:
Received 19th July, 2017
Received in revised form
26th August, 2017
Accepted 04th September, 2017
Published online 17th October, 2017

Key words:
Metastasis, Oral cavity,
Carcinoma, Primary tumor,
Sarcoma.

ABSTRACT

Carcinoma is a complex disease where basic physiological processes of the body become unregulated, such as cell division, apoptosis and cell migration. "Metastasis is defined as the transfer of the cancer cells from one organ or part to another site, not directly connected with it". Metastasis of a carcinoma basically leads to the morbidity and eventual mortality. Metastatic tumor show similar histology with the primary malignancy and are separated by an amount of intervening healthy tissue. Carcinomas (83%) when compared to sarcomas (17%), are more commonly occurring oral metastatic tumor. Metastasis to the oral cavity is usually less common accounting almost 1% of all the oral malignant tumors. It may involve oral soft tissues and the jaw bones. Oral metastases may be the first sign of the metastatic spread in 25% of cases where as in 23% cases it is the first indication of an undiscovered malignancy at a distant site. Many tumors of internal organs such as liver, kidney, lung or gastric, sometimes may not have severe sign & symptoms in its earliest stage and so, oral metastasis may expose the primary tumor site. Therefore, oral lesions and manifestations may suspect the possibility of metastasis from distant sites and this mandate the necessary investigations for early diagnosis, treatment and better prognosis of the patient.

Copyright©2017, Dr. Shivani Singh and Dr. Raghvendra Narayan. *This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.*

INTRODUCTION

Carcinoma is a complex disease where basic processes are unregulated, such as cell division, apoptosis and cell migration (Hirshberg, 2008). "Metastasis is defined as the transfer of the cancer cells from one organ or part to another site, not directly connected with it" (Sands, 2004). Morbidity and eventual mortality are caused by the metastasis of carcinoma (Hirshberg, 2008). A metastatic tumor exhibits similar histology with the primary malignant tumor. They are found to be separated by an amount of intervening healthy tissue. Carcinomas (83%) are more commonly occurring oral metastatic tumor than sarcomas (17%) (Sands, 2004). Metastasis to the oral cavity is usually less common, accounting approximately 1% of all the oral malignant tumors. Oral soft tissues and the jaw bones is the metastatic target. Oral metastases are the first sign of the metastatic spread in 25% of cases. It is the first indication of an undiscovered malignancy at a distant site in 23% cases. Many tumors of internal organs such as liver, kidney or lung sometimes may not exhibit severe sign & symptoms in their earliest stage and so, oral metastasis may expose the primary tumor site (Rai, 2011). Therefore, oral lesions and their manifestations may suspect the possibility of metastasis from distant sites and this mandate the necessary investigations for early diagnosis, treatment and better prognosis. Metastasis of various cancers to distant organs is a regulated, site –specific process rather than a random event. This non-random process was first explained by *Paget* in his 'seed and soil hypothesis', according to which, the metastatic seed grows preferentially in an organ environment that provides a suitable' soil'. There is interaction between specific receptors on the surface of disseminating tumour cells and the target organ endothelium, for the organ-specific metastasis. In many malignancies the stromal – derived factor 1 (SDF-1/CXCL12)- CXCR4 signalling pathway promotes metastatic cells invasion. The chemokine receptors CXCR4 and CCR7, expressed in primary breast cancers and metastasis but not in normal mammary ductal cells.

Their ligands CXCL12 (SDF-1) and CCL21 respectively are expressed at major sites of metastasis such as lung and lymph nodes. Recently, a breast cancer surface protein, metadherin,

Corresponding author: **Dr. Shivani Singh**
Senior Lecturer, Dept of Oral and Maxillofacial Pathology, M.M. College Of Dental Sciences and Research, Mullana (Ambala), Haryana, India – 133207

is identified which interact with the vasculature of the lung, act as a functional player in lung – specific metastasis of breast cancer cells (Hirshberg, 2008). The discovery of an oral metastatic tumor is usually associated with a terminal disease with poor overall prognosis (Sands, 2004). The aim here is to provide an overall familiarity with metastasis of malignancies with the oral region as the metastatic target and their early diagnosis and treatment plan to improve morbidity and mortality of the patients, which will further improve their survival and quality of life. The metastatic process is a sequential process, which include progression of the primary tumour to invasive carcinoma & dissemination of cancer cells through the lymphatic or blood vessels. Circulating cancer cells endure and settle in the microvasculature of the target organ and extravasate through the vessel wall. Infiltrated cells might progress towards overt metastasis with or without a prevailing period of dormancy. These are supported by functions of the cancer cells themselves or of the tumour microenvironment. Cancer cells must acquire characters which allow them to endure in new environments; hence a successful metastatic colony depends on the ability of cancer cells to be fit into different microenvironments at each step in the metastatic cascade including: the primary tumor, systemic circulation and the final metastatic target (Hirshberg, 2016).

Metastasis to Oral Cavity

As the oral region is not a preferred site for metastatic migration, cancers in this location are usually the results of secondary spread from other primary lesions, especially from the lungs. *Batson OV (1940)* proposed the valveless vertebral venous plexus as a mechanism for bypassing filtration through lungs. According to which, increase in intrathoracic pressure directs blood flow into this system from the caval and azygous venous system which accounts for the increased distribution of axial skeleton and head and neck metastasis (Batson, 1940). The pathogenesis of the metastatic process in the jaw bones is not clear. The jaw bones, especially in the old age, are poor in active marrow, usually found in the posterior part of the mandible. However, remnants of haematopoetic marrow can be detected in edentulous mandibles and in cases of focal osteoporotic bone marrow defects (Hirshberg, 2016). The type of interaction between the bone microenvironment and tumor cells can potentially give rise to osteolytic or osteoblastic metastasis. Osteolytic bone metastases are characteristic for most malignancies. Approximately, 90% of jawbone metastases present as osteolytic lesion. About 5% of the reported cases of metastases to the jaw bones, may not be showing any radiographic change. Osteoblastic bone metastases are rare, eg. Prostate cancer presenting as a osteoblastic lesion radiographically (Hirshberg, 2008). The mandible is most common affected jaw bone with a ratio of 2:1 than the oral soft tissues. Within the oral soft tissues, the attached gingiva (54%) is most commonly affected site. The major primary malignancies manifesting oral metastases are lung, liver and prostate for men where as breast, female genital organs, kidney and colorectum for women. The primary site differs according to their colonization in oral mucosa. In men, the lung is the most common primary malignancy affecting both the jaw bones (22%) and oral mucosa (31.3%) followed by the prostate gland within the jaw bones (11%) and kidney in the oral soft tissues (14%). In women, breast is the most common primary malignancy affecting both the jaw bones and soft tissues (41% and 24.3% respectively), followed by the adrenal and female genital organs within the jaw bones (7.7%) and female genital organs in the soft tissues (14.8%). When the jaw bones are affected, most patients present with swelling, pain and parasthesia, developed within a short period of time (Hirshberg, 2008). Post-extraction site is also a peculiar site for metastasis (Hirshberg, 1995). Hirshberg A, Leibovich P, Horowitz I and Buchner A (1993) reported 55 cases in which tooth extraction preceded the discovery of the metastases. In many of these cases, the metastatic tumor was assumed to be present in the area before extraction. However, in few cases, metastasis probably developed after extraction (Hirshberg, 1997). Attached gingiva is the most common site for the metastatic colonization within the oral soft tissues. The proliferating blood capillaries possess fragmented basement membrane, so are leaky, and are more penetrable by tumor cells than mature vessels. Inflammation leads to the attraction of metastatic cells towards the attached gingiva. Chronic inflammation has been associated to various steps involved in tumorigenesis, including cellular transformation, survival, promotion, proliferation, invasion, angiogenesis as well as metastasis (Hirshberg, 2008; Hirshberg, 2016 and Batson, 1940). Initial presentation of the gingival metastasis; clinically resemble a hyperplastic or reactive lesion, such as pyogenic granuloma, peripheral giant cell granuloma or fibrous epulis (Hirshberg, 2008). Other than the jaw bone and oral soft tissues, major salivary glands are also considered to be a relatively common site for metastasis. The incidence varies between 3-25% of all epithelial malignancies involving the salivary glands, with parotid gland being the most commonly affected, followed by submandibular gland with a much lower incidence. The most important malignant tumors which metastasize to the parotid gland usually originate from neighbouring structures with cutaneous squamous cell carcinomas and melanomas being the most common. In the submandibular gland, majority metastatic tumors originate from distant organs, usually below the clavicles. The difference may be associated with the rich lymphatic plexus found within the parotid gland and absence of lymphnodes within the submandibular gland (Hirshberg, 1995). Various pathogenetic mechanisms have been proposed for the metastasis to the oral cavity, which include epithelial – mesenchymal interaction, angiogenesis and tumor dormancy, apotosis inhibition, metastasis to bone and lymphatic spread.

Epithelial-Mesenchymal Transition

Carcinoma cells show diminished intercellular adhesiveness, as compared to normal epithelia, expressed by loss of E-cadherin-mediated adhesions as they transform into malignancy (Cavallaro, 2004). Followed by detachment from the neighbouring cells, tumor cells breach the basal lamina barrier for the invasion into the adjacent tissues. At this stage, cells progressively acquire mesenchymal characters by expressing mesenchymal molecules (including vimentin and N-cadherin), characterized by elongated cell morphology with established cell-polarity, a process called epithelial to mesenchymal transition (EMT) (Thiery, 2003). The EMT is characterized by complex mechanism of molecular changes resulting the motile property of cancer cell, involving dynamic cytological changes, cell matrix interactions, proteolysis in local environment, actin-myosin contractions and focal contact disassembly (Thompson, 2005). Stromal cells are also associated with modulation of cancer cell motility by secreting growth factors and proteases, supporting the survival and

proliferation of cancer cells in a paracrine fashion (Bhowmik, 2005).

Angiogenesis And Tumor Dormancy

Tumor overgrowth and progression depends upon formation of new blood vessels (angiogenesis) (Christofori, 2004). Folkmam J and Kalluri R (2004) (Folkman, 2004), established that tumor beyond the size of 1 -2 mm is dependent on angiogenesis for tumor growth, survival and metastasis. Increased microvessel density, along with the presence of inflammation, promote tumor cells intravasation and their dispersion through the blood stream. Increased tumor vascularisation i.e Increased microvessel density and expression of pro-angiogenic factors by tumor are usually associated with advanced tumor stage and poor prognosis in various cancers (Reinmuth, 2003). Pugh CW and Ratcliff PJ (2003) (Pugh, 2003), reported hypoxia as a major regulator of angiogenesis, the transcriptional response to oxygen deprivation is largely mediated by hypoxia inducible factor 1(HIF1). A variety of other genes are also associated with various steps of angiogenesis, include nitric oxide synthases, growth factors such as VEGF, angiopoietin, fibroblasts growth factors and their various receptors and genes involved in matrix metabolism, including MMPs, plasminogen activator receptors and inhibitors, and collagen prolyl hydroxylase.

A recent model of tumor angiogenesis proposed that this process involves recruitment of budding vessels from existing blood vessels and incorporation of progenitors of endothelial cell into the growing vascular bed.[16] These fenestrated, leaky new vasculature pathologically assist the entry of tumor cells into the circulation. The pace of malignant cell detachment generally increases with tumor size, on the other hand, dispersion can occur in the early stages of tumorigenesis also, to the point that some metastasis have no known primary source. Hence, angiogenesis has been associated with dual effect on tumor growth, Perfusion supplies needed nutrients and oxygen to the tumor and newly formed endothelial cells stimulate the growth of adjacent tumor cells by secreting growth factors - insulin like growth factors (IGFs), Platelet derived growth factor (PDGF) and granulocyte – macrophage colony stimulting factors. This way angiogenesis is required for continued tumor growth as well as for access to the vasculature leading to metastasis (Kumar, 2005) Tumor cells may also undergo a period of dormancy followed by a rapid growth period during relapse. Most human malignant tumors may arise in the absence of angiogenic activity and stay in a microscopic dormant state for a period of months to years. After surgery or other forms of therapy, local or metastatic recurrences may occur. The reason could be attributed to the switch to the angiogenic phenotype in an otherwise microscopic dormant tumors (Naumov, 2006). *Marches R,* Scheurmann R and Uhr J (2006) (Marches, 2006), reported that dormant cells can continue by completely withdrawing from the cell cycle or by continuing to slowly cycle and die at an equivalent rate.

Apoptosis Inhibition

The metastatic process is also known to be a highly inefficient process, indicating only a small proportion of metastatic cancer cells can successfully colonize at distant sites. Some recent experimental observations have supported the hypothesis that the induction of apoptosis is a defend system to avoid metastasis. Apoptosis may be involved in all the stages of metastatic cascade.[1] It has been reported recently, that highly metastatic cancer cells possess a higher resistance to the programmed cell death when compared to their poorly metastatic counterparts.[19] Apoptosis is inhibited as early as the cancer cell is detached from the ECM in the primary site (anoikis). ECM- dependent inhibition of apoptosis is mediated by the integrin-activated signaling pathway, modulating the activity of apoptosis regulatory genes such as members of the Bcl2 family or the caspases. Tumor cells respond to mechanical stress in the circulation by producing free radicals and nitric oxide (NO) which promote apoptosis (Zieglar, 1998). Another important gene i.e p53 tumour suppressor gene act as a stress sensor, also drives the cell towards apoptosis (Schuler, 2015).

Metastases to Bone

Analyses of tumors that metastasize to bone are the best example of mutual cellular and molecular alterations occuring in the cancer cells and their stroma during site-specific metastasis. Bone homeostasis is maintained by a balance between osteoclasts and osteoblasts. Cancer cells metastasizing to bone perpetually sieze these preserved physiological mechanisms. Prostate cancer cells usually secrete osteoblast-promoting factors such as BMPs (Bone morphogenetic proteins), Wnt-family, endothelium-1 and PDGF (Platelet derived growth factors); whereas osteolytic breast cancer cells prevent to these pathways by secreting soluble inhibitors like osteoclast-inducing factors such as PTHrp (parathormone related protein), IL-8, IL-11.[1] Logothetis CJ and Lin SH (2005) reported that in addition to these, there is also a disruption of homeostatic RANK-RANKL loop between osteoclasts and osteoblasts. Metastatic prostate carcinomas secrete high amount of the RANKL inhibitor osteoprotegerin, there by suppressing osteoclastic reactions during metastasis. On the contrary, osteolytic cancer cells secrete proteases that break RANKL into more active form, activating the osteoclasts (Lynch, 2005). As, the bone is a rich source of matrix-embedded growth factors such as IGF(interstitial growth factors) and TGF-ß (transforming growth factors), are released upon osteolysis and act upon the invading tumor cells to promote the stimulation of osteoclast-promoting factors (Hirshberg, 2008).

Lymphatic Spread

Lymphatics act as the most common pathway for the early dispersion of carcinomas. Sarcomas may also use this route. Tumors do not contain functional lymphatic vessels located at the tumor margins are apparently sufficient for the lymphatic spread of tumor cells. The stress on lymphatic spread for carcinomas and hematogenous spread for sarcomas is misleading, as there are several interconnections between the vascular and the lymphatic systems. Usually the pattern of lymph node involvement follows the natural routes of lymphatic drainage. Carcinomas arising in upper outer quadrants, spread first to axillary lymph nodes e.g breast carcinoma. Cancers of inner quadrants drain to the nodes along the internal mammary arteries and further supraclavicular and infraclavicular nodes become involved. Carcinomas of lung metastasize first to the perihilar tracheobronhial and

mediastinal nodes. Sometimes local lymph nodes may be bypassed, known as skip metastasis, due to venous –lymphatic anastomoses, inflammation or radiation. In many cases, the regional nodes may also serve as effective barriers for further dissemination of the tumor. The tumor cells, after arrest within a node, may be destroyed by a tumor-specific immune response. Drainage of tumor cell debris or tumor antigens, or both, also induces reactive changes within nodes. Hence, enlargement of nodes may be caused by the spread and growth of cancer cells or reactive hyperplasia. Therefore, nodal enlargement in proximity to a cancer does not always mean dissemination of the primary lesion (Kumar, 2005).

Conclusion

Sometimes most of the tumors of internal organs like liver, kidney or lung may not have severe signs and symptoms in its earliest stages, and so go unnoticed for long periods. Some of these malignancies may metastasize to the oral cavity, leading to the secondary tumor, through further investigation and thus exposing the primary site. Thus, there is a need for a thorough knowledge of metastasis from primary to oral cavity as secondary. Since most of the metastasis occur in advanced stages and the exposure of the primary site of the tumor finally may help to initiate the immediate treatment to increase the survival of the patient and to improve their life expectancy.

REFERENCES

Batson, O.V. 1940. The function of the vertebral veins and their role in the spread of metastases. *Ann Surg.,*112:138-149.

Bhowmik, N.A., Moses, H.L. 2005. Tumour-stroma interactions. *Curr Opin Gen Dev.,* 15:97-101.

Cavallaro, U., Christofori, G. 2004. Cell adhesion and signaling by cadherins and Ig-CAMS in Cancer. Nat Rev Cancer, 4:118-32.

Christofori, G. 2006. New signals from the invasive front. Nature., 441:444-50.

Folkman, J., Kalluri, R. 2004. Cancer without disease. Nature., 427(6977):787.

Hirshberg, A. 2016. Metastatic Neoplasms to the Oral Cavity. emedicine.medscape.com/article/1079102-overview.

Hirshberg, A., Buchner, A. 1995. Metastatic Tumours to the Oral Region. An Overview. *Oral Oncol Eur J Cancer* 31B(6):355-360.

Hirshberg, A., Leibovich, P., Horowitz, I., Buchner, A. 1993. Metatatic tumors to post-extraction site. *J Oral Maxillofacial Surg*., 51:1334-7.

Hirshberg, A., Shaipro, A.S., Kaplan, I. 2008. Metastatic tumours to the oral cavity- pathogenesis and analysis of 673 cases. *Oral Oncol.,* 44:743-52.

Kumar, Abbas, Fausto. Robbin's and Cotran's Pathologic basis of disease. seventh edition, Elsevier Saunders, Philadelphia 2005

Logothetis, C.J., Lin, S.H. 2005. Osteoblats in prostate cancer metastasis to bone. *Nat Rev Cancer*., 5:21-8.

Lynch, C.C., Hikosaka, A., Acuff, H.B. 2005. MMP-7 promotes prostate cancer- induced osteolysis via the solubilization of RANKL. *Cancer Cell.,* 7:485-96.

Marches, R., Scheurmann, R., Uhr, J. 2006. Cancer dormancy from mice to man. *Cell Cycle.,* 5:1772-8.

Naumov, G.N., Bender, E., Zurakowski, D., Kang, S.Y., Sampson, D., Flynn, E. 2006. A model of human tumor dormancy: an angiogenic switch from nonangiogenic phenotype. *J Natl Cancer Inst*., 98:316-25.

Pugh, C.W., Ratcliffe, P.J. 2003. Regulation of angiogenesis by hypoxia : role of the HIF system. *Nat Med.,* 9:677-84.

Raffi, S., Lyden, D., Benezra, R. 2002. Vascular and haematopoietic stem cells:novel targets for antiangiogenesis therapy. *Nat Rev Cancer*., 2:826-35.

Rai, H., A.C. R. 2011. Oral Metastasis – A Reason To Expose The Primary Site – A Short Review. *Internet J Pathol.,* 12(1): 1-4.

Reinmuth, N., Parikh, A.A., Ahmad, S.A. 2003. Biology of angiogenesis in tumours of the gastrointestinal tract. *Microsc Res Tech.,* 60:199-207.

Sands, T.M., Pynn, B.R. 2004. A Review of Oral Metastatic Disease. *Oral Health Journal.,* 5:1-6.

Schuler, M., Green, D.R. 2005. Transcription, apoptosis and p53: catch-22. Trends Genet., 21:182-7.

Thiery, J.P. 2002. Epithelial–mesenchymal transitions in tumour progression. *Nat Rev Cancer.,* 2:442-54.

Thompson, E.W., Newgreen, D.F. 2005. Carcinoma invasion and metastasis: a role for epithelial-mesenchymal transition ? Cancer Res., 65:5991-5.

Zieglar, T., Silacci, P., Harrison, V.J., Hayoz, D. 1998. Nitric oxide synthase expression in endothelial cells exposed to mechanical forces. *Hypertension.,* 32:351-5.

****