ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 9, Issue, 05, pp.50362-50366, May, 2017

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

METASTATIC TUMOURS TO THE JAW AND ORAL CAVITY – A BRIEF REVIEW

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ARTICLE INFO

Article History:
Received 09th February, 2017
Received in revised form
30th March, 2017
Accepted 16th April, 2017
Published online 23rd May, 2017

Key words:

Tumour,
Metastasis,
Cancer,
Oral cavity.

ABSTRACT

Metastasis is a complex biological course that begins with detachment of tumour cells from the primary tumour, spreading into distant tissues invading through the lymphovascular structures followed by their survival in the circulation. The prime reason for morbidity and mortality in any type of cancer is due to metastasis that occurs as a result of adaptation of genetically unstable cancer cells. Metastasis is very uncommon to the jaw bones and oral cavity. The reason for this review is to through light on awareness of the clinical presentation of metastatic tumours which are variable which may lead to erroneous diagnosis or may create diagnostic dilemma.

Citation: Shristi Nadar and Don, 2017. "Metastatic Tumours to the Jaw and Oral Cavity – a brief review", *International Journal of Current Research*, 9, (05), 50362-50366.

INTRODUCTION

Cancer cells are formed due to mutation of a single cell with a malignant phenotype. The properties of malignant tumours include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angio-genesis, and activating invasion and metastasis, in addition to reprogramming of energy metabolism and evading immune destruction (Hanahan, 2011). The deadly aspect of cancer cells is their ability to metastasise from one site to another. When the area of cancer cells at the originating site become clinically detectable, it is called primary tumour. Some cancer cells also acquire the ability to penetrate and infiltrate surrounding normal tissues in the local area, forming a new tumour. This process of formation of a newly formed tumour in the adjacent site is called metastasis. Tumour cells may also spread to near the primary tumour. For metastasize to occur, a cancer cell must break away from its tumour, invade either the circulatory or lymph system, which then carry it to a new location and establish itself in a new site. Most tumours and other neoplasms can metastasize, although in varying degree.

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Metastatic tumors (MT) to the oral region are uncommon, comprising only 1-3% of all malignant oral neoplasms. Metastatic lesions may occur in the oral soft tissues, in the jawbones or in both osseous and soft tissues (Meyer, 1965; Nishimura, 1982). It is the process of metastasis that results in morbidity and eventual mortality (Bodner, 2006). The most common primary sources of metastatic tumors to the oral region are the breast, lung, kidney, bone, prostate and colon (D' Silva, 2006). Because of their rarity, metastatic tumours to the oral region are challenging to diagnose. Therefore, they should be considered in the differential diagnosis of inflammatory and reactive lesions that are common to the oral region (Hirshberg, 1995). In some cases, the oral lesion is the first and only symptom of malignant disease of a primary which might be growing silently elsewhere in the body (Clausen; Meyer, 1965; McDaniel, 1971). The jaws and mouth are uncommon sites for metastatic dissemination with only about 1 % of oral malignancies attributed to metastases (Servato *et al*., 2013). Nevertheless, the incidence of metastatic tumors to the jaws is probably higher than suggested (Hirshberg , 1995; Hirshberg, 1994; Metastatic tumours to the oral cavity, 2010; Allon, 2014).

EPIDEMIOLOGY

Metastatic tumours to the oro facial region are uncommon and account for approximately 1-1.5% of all malignant oral tumours (van der Waal, 2003). Metastatic tumours to the jaw bones are more frequently reported than those in the oral mucosa (Bodner, 2003). Mostly metastatic tumours are seen in patients aged between 40-70years. A study showed an equivalent sex distribution for metastatic jaw disease, though women exhibited more metastases then men at 31 to 41 years of age and men exhibited a significantly greater incidence of metastases than women 71 to 80 years of age (Nisha, 19667). The nature of primary tumour and the site of metastases within the oral cavity differ between the sexes (Rajappa *et al*., 2005). The most common sources of metastatic tumours to the oral region are primary cancers from the lung, breast, kidney and bone. The breast is the most common primary site for tumours that metastasize to the jaw bones, whereas the lung is the most common source for cancers that metastasize to the oral soft tissues (Hirshberg, 2008).

The origin of metastasis to the oral mucosa in women is as follows.

- Breast – 24%
- Genital organs – 14.8%
- Kidney – 12%
- Lung – 9.4%
- Bone – 9.4%
- Skin – 6.8%
- Colorectum – 6.8%
- Rare tumours – 16.8%

The origin of metastasis to the jawbone in women is as follows.

- Breast – 36.6%
- Genital organs – 9.5%
- Kidney – 8.5%
- Colorectum – 7.1%
- Bone – 6.7%
- Adrenal gland – 5.8%
- Thyroid – 5.4%
- Rare tumours – 20.4%

The origin of metastasis to the oral mucosa in men is as follows:

- Lung - 31%
- Kidney -14%
- Skin -12%
- Liver - 75%
- Colorectum – 5.2%
- Bone – 5.2%
- Testis – 4.5%
- Esophagus – 4.5%
- Stomach – 3.7%
- Rare tumours -12.4%

The origin of metastases to the jaw bone in men is as follows:

- Lung- 25%
- Kidney – 10.8%
- Liver – 8.6%
- Prostate – 7.5%
- Bone – 7.5%
- Adrenal gland – 5.3%
- Colorectum – 4.7%
- Testis – 4.4%
- Esophagus – 3.6%
- Stomach – 2.5%
- Bladder – 2.5%
- Rare tumours – 17.6%

PATHOGENESIS

There are several discrete, complex and interrelated steps in the process of cancer metastasis (19-21). Though clinical observations say that carcinomas spread through lymphatics and sarcomas through hematogenous route, this concept is not valid anymore due to the presence of numeros venolymphatic anastomoses (22)

TUMOR HETEROGENEITY

Cancers, in order to survive and metastasize, have to evolve and become heterogeneous. Nowell had proposed that the acquired and accumulating mutations within the tumor, together with selection pressures would result in the adaptation of the tumor cells, making them heterogeneous and plastic, in order to develop strategies to survive a hostile environment and use these resources to grow and proliferate (Gupta, 2006). Evidence now says, this contribution toward the plasticity of the tumor cells could also be via epigenetic mechanisms (Feinberg, 2006). There are two general models of heterogeneity of cancer cells. They are: (Meyer, 1965) Clonal evolution model that Nowell had proposed (Nishimura, 1982) Cancer stem cell model that states that cancer cells have only limited proliferative potential. It is a small subset of population called cancer stem cells (CSC) that consistently proliferate and give rise to new tumors. Proponents of this hypothesis say that certain properties of stem cells make them quintessential to accumulate the genetic or epigenetic changes needed for tumorogenesis. It is this small population that have the different properties of cancers like drug resistance, invasion and metastasis 12-14.

ANGIOGENESIS

Once the tumor cells, irrespective of their origin, have become defiant to the host's immune/regulatory mechanisms, the growth and metastatic spread of the cancer cells depends on a rich vascular supply. Cancer cells can stimulate neo-angiogenesis, during which new vessels sprout from previously existing capillaries, or, in some cases can stimulate vasculogenesis, in which endothelial cells arise from the bone marrow. Tumor angiogenesis is basically a four-step process.

- The basement membrane in tissues is injured locally.
- There is immediate destruction and hypoxia.
- Endothelial cells activated by angiogenic factors migrate.
- Endothelial cells proliferate and stabilize.
- Angiogenic factors continue to influence the angiogenicprocess.

Data derived from examinations of human lung cancer, brain metastases indicate that tumor cell division takes place within 75 μm of the nearest blood vessel, whereas tumor cells residing beyond 150 μm from a vessel undergo programmed cell death (Gupta, 2006). This process is stimulated as and when tumor cells need nutrients and oxygen. This is achieved by inducing an imbalance between the angiogenic stimulators and inhibitors, i.e an increase in the angiogenic inducers and a decrease in the inhibitors. Several inducers and inhibitors have been identified. Some important angiogenic inducers are—vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), angiogenin, transforming growthfactor (TGF)-α, TGF-β, tumor necrosis factor (TNF)-α, platelet-derived endothelial growth factor, granulocyte colony-stimulating factor, placental growth factor and interleukin 8. There are many naturally occurring proteins that can inhibit angiogenesis—angiostatin, endostatin, interferon, platelet factor 4, thorombospondin, prolactin 16 kd fragment, and tissue inhibitor of metalloproteinase 1, 2 and 3 (Gupta, 2006; Nishida *et al*., 2006; Hanahan *et al*., 2011)

APOPTOSIS INHIBITION

Metastasis is a highly inefficient process, where very few cells successfully metastasize. The induction of apoptosis is a prophylactic measure to avoid metastasis. There is sufficient evidence in literature to apprise us about the anti- apoptotic measures of tumour cells. This is significant due to the fact that circulating cancer cells have to pass through several stressful steps, including survival in the bloodstream, arrest in the capillary bed and resumption of proliferation in distant organs (Wu, 2011)

ROLE OF miRNAS

MicroRNAs (miRNAs) are a group of endogenous, non-coding, 18 to 24 nucleotide length single-strand RNA molecules. miRNAs play crucial roles in regulating fundamental cellular biological processes such as cell cycle, differentiation and apoptosis. Many recent molecular studies of head and neck cancer and OSCC specifically have revealed the deregulation of miRNAs. The recent explosion of new literature pertaining to miRNAs have shown that miRNA expression profiles could explain the pathogenesis, metastasis and chemoresistance of cancers. miRNAs involved in metastasis could be prognostic markers and therapeutic targets in metastatic tumours. Liu *et al*, using microarray analysis, identified that reduced levels of miR 138 and 222 enhanced the metastatic potential of tongue squamous cell carcinoma. Chang *et al* observed that increased expression of miR 211 was associated with advanced nodal metastasis and vascular invasion of oral squamous cell carcinoma. Lajer *et al* and Liu *et al*, have demonstrated the inhibiton of, factor inhibiting-hypoxia inducible factor (FIH) by increased expression of miRNA 31 thereby indirectly promoting metastasis. Besides, miRNAs are also implicated in maintaining the stemness of stem cells which may become oncogenic if, over or under expressed. Various other miRNAs implicated in metastasis aremiRNAs 27a, 29a, 30d, 143, 145,328 (Gorenchtein *et al*., 2012; Schoof, 2012; Kumar, 2013)

METASTASIS

Metastatic lesions to the oral region are rare as they are not a favoured target. They are more often a secondary spread from other metastatic lesions. It was proposed by Batson that the valveless vertebral plexus could be the rationalebehind metastasis to the head and neck region. Studies state that the metastatic process could be a site-specific event more than being a random event. What, then, could be the driving force behind primaries of various organs metastasizing to the oral cavity? Jaw bones with active marrow attract cancer cells. Metastasis to the jaw bones usually manifests in older adults. However, remnants of hematopoietic active marrow detected in the posterior region of the mandible may be the reason. Also, chronic inflammation and the rich network of capillaries in the gingiva may play an important role in attracting tumor cells. The proliferating capillaries with their fragmented basement membranes, make them vulnerable to the penetration of metastasizing cancer cells (Schoof, 2012; Kumar *et al*., 2013)

CLINICAL PRESENTATION

AGE AND SEX

Metastatic tumour in oral region occurs mostly in patients of age 40-70 years. A study showed an equivalent sex distribution for metastatic jaw disease, though women exhibited more metastases than men at 31 to 41 years of age and men exhibited a significantly greater incidence of metastases than women 71 to 80 years of age (Nisha, 1672). This is most likely is a reflection of the fact that primary breast carcinoma occurs at an early age in women, whereas prostate and lung carcinomas occurs later in life in men (Jemal *et al*., 2004).

SITE

Metastatic tumours to the oral region are uncommon and accounts approximately 1-3% of all malignant oral tumour (Wu *et al*., 2011). Metastatic tumours to oral cavity may involve jaw bones or oral soft tissues. Mandibular lesions are more common accounting about 83.5% and mostly involve the posterior part of the mandible. Mandibular predilection was more prominent in females than in males (Nisha, 1672). In dentulous patients, 80% of metastatic tumours to oral soft tissues occur in attached gingiva whereas in edentulous patients, they are equally distributed between the tongue and alveolar mucosa (Rajendran and Sivapathasundaram, 2013). Metastatic tumours to jaws may extend to overlying soft tissues, appearing to be dental and periodontal infection. Alternatively, metastasis may occur directly in soft tissues, usually gingiva (Neville, 2002).

CLINICAL APPEARANCE

An exophytic, ulcerated lesion is the most common clinical presentation of metastatic lesions in the oral soft tissues. Early lesions, mainly those located in the gingiva may resemble a hyperplastic or reactive lesion, such as pyogenic granuloma, peripheral giant cell granuloma or fibrous epulis (Hirshberg *et al*., 2008). With the progression of the disease, oral metastatic lesions, especially those located in the soft tissues, may cause progressive discomfort, pain, bleeding, superinfection, dysphagia, interference with mastication, and disfigurement (Allon *et al*., 2014). Metastatic tumors show variable presentation. Tongue and gingiva are common sites of metastatic tumours. Gingival metastatic tumours in their early stages resemble hyperplastic reactive lesions.

They also show polypoid exophytic growth. In the tongue it could be a submucosal mass or may present as an ulcer. In the edentulous patients, metastatic lesions are spread between the tongue and alveolar mucosa.

RADIOGRAPHICAL FEATURES

Metastatic tumors do not possess a pathognomonic radiographic appearance (Adebayo, 2001). Radiographic findings in metastatic tumors to the jaw may range from the absence of any manifestation to a lytic or opaque lesion with ill-defined margins. The radiographic appearance of lesions has been attributed to a disruption of balance between osteoclastic and osteoblastic activity that occurs during normal bone turnover. (Goltzman, 2001) Tumour type may affect the radiographic appearance of the lesion, prostatic carcinoma metastases are classically osteoblastic while metastatic breast or renal carcinoma may be osteolytic, osteoblastic or mixed. The entire mandible may also have a motheaten appearance (Lossos, 1992; Ogutcen, 2002). The cortical bone of adjacent structures such as the mandibular canal, maxillary sinus and nasal floor is resorbed. Extension through the cortical plate of the jaws may stimulate a spiculated periosteal reaction (Gaver *et al*., 2002)

HISTOPATHOLOGY

The diagnosis of metastatic tumors in the oral region is difficult due to their rare occurrence. Jaw lesions more commonly present with a known or previously treated primary. An intraoral incisional biopsy and histopathologic examination is the means to confirm and identify a malignant tumor and potentially it's metastatic origin. The pathologist may not provide an exact diagnosis, since metastatic lesion does not represent a single disease and histological appearance is variable. If any history of a previous tumor exists; the microscopic findings of the metastatic lesion should be compared with that of the primary tumor. Usually a distinction of a metastatic tumor from a primary malignancy can be made.

In some cases, special staining, immune histochemical procedure, and electron microscopy may be performed to identify the nature of primary tumor (Clausen; Aniceto1990; Krishna, 2010) Once a metastatic tumor is suspected an appropriate referral for an oncologic work up is required. Advanced imaging, scintigraphy and regional investigations based on the suspected source should be done to find out or confirm the origin and identify any other areas of secondary spread.

Metastatic breast carcinomas typically are positive for cytokeratin 7, but negative for cytokeratin 20, thyroid transcription factor-1(TTF1) and Prostate specific antigen (PSA) (Rajappa, 2005) In contrast, metastatic colorectal carcinomas are typically CK20 positive, but CK7, TTF1 and PSA negative (Hirshberg, 2008; Gupta, 2006; Langley, 2007). A metastatic lesion that stains positively for CK7 and TTK1 likely would be from a lung carcinoma (Langley, 2007). Metastatic prostate carcinoma would be positive for PSA (Morgan-Parkes, 1995) but negative for other three markers.

TREATMENT AND PROGNOSIS

The treatment and prognosis is primarily based on the site of origin and the degree of metastatic spread (Aniceto *et al*., 1990) Unfortunately, the identification of a metastatic tumor usually represents a poor overall prognosis. The time from the appearance of the metastasis to death is several months. If the primary tumor was successfully treated and the patient's medical condition permits, the metastatic lesion should be aggressively treated. Whereas if the primary tumour is recurrent then conservative management of the jaw is done. Management may involve surgical resection, radiation, chemotherapy or a combination of these techniques. This goal of palliative treatment is to reduce the patient's pain and preserve oral function. This may involve reducing the size of the tumor through radiotherapy, chemotherapy or local surgical excision (Krishna, 2010) Oral metastases usually are evidence of a widespread disease and indicate a grave prognosis.

Conclusion

The diagnosis of a metastatic lesion in the oral region is challenging, both to the clinician and to the pathologist. The prognosis of metastatic lesions to the oral cavity is very poor, combination chemotherapy to alleviate the symptoms is the only preferred therapeutic modality (Beena *et al*., 2011) Hence, careful clinical and histopathological assessement lead to definitive diagnosis of the metastatic lesion and its origin.

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