PATHOPHYSIOLOGY OF BONE METASTSIS AND ITS IMPLICATIONS- A REVIEW

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ABSTRACT:. In tumors with a propensity to spread to bone a significant proportion of patients who present with cancer that appears to be localized will eventually develop incurable metastatic disease. Bone metastases are common in many advanced cancers and are an avoidable yet, annoying source of skeletal morbidity. The bone mineral matrix contains numerous growth factors that are released during normal bone remodeling, providing a fertile microenvironment for tumor cell colonization and proliferation. Tumor cells then release a variety of growth factors that promote bone resorption and increase the risk of skeletal complications. Metastasis of tumor cells to bone requires a complex cascade of events involving detachment from the primary tumor site, invasion of the vasculature, migration and adherence to distant capillaries of the bone, extravasation, and proliferation. Metastatic bone lesions are classified as **osteolytic** or **osteoblastic,** based on their radiographic appearance. Bone is the third most common site of metastatic disease .Carcinomas are much more likely to metastasize to bone than sarcomas. Routine use of whole body PET/CT in restaging HNSCC can therefore, facilitate early detection of occult bone metastases and this detection often influences therapeutic decision making.

KEYWORDS: Metastses,Osteolysis,Osteoblastic bone formation,proteolytic enzymes,CAMs

INTRODUCTION

Metastatic tumors in bone are cancers that started in another location and spread to the bones. More than 90% of all these metastatic lesions in bone are caused by a small number of primary tumors, from various tissues including breast, lung, kidney, prostate, and thyroid. As the population ages, both the number of patients with cancer and the number of them at risk for bone metastasis are expected to increase, challenging medical professionals. Recent advances in our understanding of the process of bone metastasis and trials of therapies to treat and prevent metastasis are improving our ability to more effectively treat bone cancer.[1]

Distant metastasis from Head and Neck Squamous Cell Carcinomas (HNSCC) usually represents incurable disease. Bone metastasis from HNSCC is generally thought to be a late event that occurs in the setting of other widespread metastases. However, while the lung is clearly the most common site of distant spread, bone metastasis from HNSCC occurs frequently enough to be a significant clinical entity that can cause severe local morbidity at the metastatic site. Previous studies showed bone to be the second most common site of distant spread, with reported frequencies ranging from 17% to 31% of sites involved. For HNSCC, bone metastases traditionally have only come to attention through pain symptoms, pathologic fractures, or abnormal laboratory test results, all of which are insensitive for early lesions. Because of the low frequency of bone metastases and the high percentage of equivocal findings, bone scintigraphy is not routinely performed for staging HNSCC. Screening for distant metastases at sites other than the lungs is also usually not recommended for HNSCC. Routine use of whole body FDG-PET/CT in restaging HNSCC however, can facilitate early detection of occult bone metastases and this detection would then definitely influence therapeutic decision making.[2]

Bone is the third most common site of metastatic disease. Carcinomas are much more likely to metastasize to bone than sarcomas. The axial skeleton is seeded more than the appendicular skeleton, partly due to the persistence of red bone marrow in the former. The ribs, pelvis and spine are normally the first bones involved and distal bones are rarely affected. Metastases are established when a single tumor cell or a clump of cells gain access to the blood stream, reach the bone marrow through blood vessels in Haversian canals, extravasate, multiply and neovascularize. Batson's vertebral venous plexus allows cells to enter the vertebral circulation without first passing through the lungs. The sluggish blood flow in this plexus is more conducive to tumor survival, and accounts for the high rate of prostate cancer metastasis to the spine.[3]

Bone metastasis is common in cancer patients, most likely because of the favorable microenvironment of the bone matrix and its ample blood supply. Metastasis of tumor cells to bone requires a complex cascade of events involving detachment from the primary tumor site, invasion of the vasculature, migration and adherence to distant capillaries of the bone, extravasation, and proliferation[4]. Once tumor cells have invaded the bone matrix, they produce growth factors that can directly or indirectly stimulate osteoclasts to degrade the bone. As a result, growth factors that can stimulate tumor cell growth are released from bone, thus establishing a vicious cycle of bone destruction and local tumor growth.[4]

Metastatic bone lesions are classified as **osteolytic, osteoblastic or mixed** based on their radiographic appearance[3]. Osteolytic lesions are the result of increased osteoclast activity accompanied by a concomitant decrease in osteoblastic activity, leading to an abnormally high rate of bone resorption. Lytic bone metastases must be greater than 1 cm and should have destroyed 30-50% of the bone density in order to be seen by x-ray. The osteolytic lesions are most common where the destructive processes outstrip the laying down of new bone. New treatments with medicines that may block bone lysis by tumor cells are currently in clinical trials.

Osteoblastic lesions are characterized by increased bone formation around tumor cell deposits, but they are also combined with unbalanced osteolytic activity and marked increases in bone turnover, as evidenced by increased markers of bone resorption in the serum and urine of those patients . Microscopically, most lesions are mixed. [3] Both types of bone lesions result in significant local bone loss and potential vertebral collapse. Typically, multiple myeloma is associated with osteolytic lesions, prostate cancer is associated with osteoblastic lesions, and breast cancer is associated with mixed lesions [4]

Pathophysiology of Bone Metastases

Bone normally undergoes continual remodeling in response to mechanical stress via the dynamic and orchestrated interactions of osteoclasts and osteoblasts alternately resorbing and repairing bone, respectively, and the mineralized bone matrix contains numerous growth factors that are released during this process. Bone remodeling begins with the activation of osteoclasts by local events, including the release of interleukin-1 (IL-1), leading to bone resorption and the release of other growth factors. These factors, including transforming growth factor-beta (TGF-β) and insulin-like growth factor II (IGF-II),which increase the proliferation and differentiation of osteoblasts, and subsequently form new bone at the site of resorption, thus maintaining bone integrity and strengthening the bone .

The skeleton is the most common site of metastasis in many advanced cancers, and metastasis of tumor cells to the bone matrix involves a complex cascade of events. Bone metastasis begins when primary tumor cells detach from their place of origin by forming new blood vessels and invading the vasculature. These tumor cells then form aggregates and eventually adhere to the vascular endothelial cells of distant capillaries of the bone. Subsequently, the cells escape the circulation, invade the marrow stroma, and eventually adhere to the endosteal surface of the bone (ie, at the interface of bone and marrow) and proliferate.In addition to the numerous growth factors present in the mineralized bone matrix, the bone marrow consists of hematopoietic stem cells, stromal cells, and immune cells that release a number of cytokines and growth factors[5]. This fertile microenvironment promotes the growth of tumor cells that have migrated to bone. Once tumor cells have colonized in the bone matrix, they secrete a plethora of soluble growth factors that stimulate the activity of osteoclasts and/or osteoblasts and disrupt normal bone remodeling . The activation of osteoclasts and bone resorption causes further release of bone-derived growth factors that enhance survival and proliferation of the tumor cells. As a result, the normal homeostasis of the bone is disrupted and excess bone resorption ensues.

Factors in the metastatic process

Tumor cells from certain cancers form metastatic colonies in the bone more readily than do tumor cells from other types of cancer, indicating that they express a phenotype that aids in the metastatic process. A variety of factors have been implicated in the metastatic process, include- proteolytic enzymes, cell adhesion molecules (CAMs), and growth factors.

Proteolytic enzymes are necessary for tumor cells to detach from their primary site, invade the surrounding soft tissue, enter and exit the vasculature, and degrade the bone matrix. Matrix metalloproteinases (MMPs) have been implicated in bone resorption and tumor progression[5]. In human myeloma cells, MMP-9 is constitutively expressed, and coculture of these cells with bone marrow stromal cells increases MMP activity. CAMs, such as integrins, play a critical role in tumor invasion, metastasis, and proliferation . Loss of CAMs at the primary site facilitates the detachment of cancer cells from the primary tumor. Similarly, increased expression of CAMs at the site of metastasis may be necessary for cells to arrest and attach a step essential for osteoclast-mediated bone resorption [5]. Studies have demonstrated that expression of integrin αv β3 in tumor cells increases tumor cell invasion and the development of osteolytic lesions in nude mice. Furthermore, antagonists of integrin αv β3 inhibit bone resorption and tumor angiogenesis, and a recent study demonstrated that ablation of integrin αvβ3 expression in mice by a germline-targeted disruption of the β3 integrin subunit resulted in inhibition of osteolytic bone metastases after inoculation with the B16 murine melanoma cell line. Growth factors like HGF, laminin, fibronectin, collagen-iv can stimulate chemotaxis

of malignant cells and thereby influence tumor cell motility. This is because they govern :

1. Tumor cell detachment(degranulation of E-cadherin,β catenin decreases cell cohesion)
2. Tumor cell motility
3. Interaction with ECM(INTEGRINS allow vessel passage and local invasion with MMPs andUPAs)
4. Interaction with endothelium,platelets,fibrin(for arrest of tumor cells).

Steps of metastasis:

Osteolysis: an important first step

Preclinical evidence strongly suggests that induction of osteolysis is an important first step in the formation of bone metastases. Tumor cells secrete parathyroid hormonerelated protein (PTHrP) and IL-6, which are powerful mediators of osteoclast activation **(Fig.2)**. PTHrP is expressed in human breast cancer cells in vivo, and higher levels of expression are associated with sites of bone metastases, compared with soft-tissue metastases or primary tumor sites. Mice inoculated with a human breast cancer cell line expressing high levels of PTHrP develop predominantly osteolytic bone metastases.

Interestingly, PTHrP has also been described in prostate cancer cells, in both primary tumors and bone metastases, indicating that bone metastases from prostate cancer also have an osteolytic component]. PTHrP, parathyroid hormone (PTH), IL-1, IL-6, and IL-11 participate in osteolysis by stimulating the production of receptor activator of nuclear factor-kB ligand (RANKL) by osteoblasts and stromal cells . RANKL binds to its receptor (RANK) on osteoclast progenitors, leading to the differentiation of the progenitors into mature osteoclasts and initiation of bone resorption. Evidence for the involvement of RANKL in bone resorption is demonstrated by studies showing that osteoclastogenesis, bone degradation, and tumor growth in the bone are prevented by expression of osteoprotegerin (OPG), a protein that blocks the interaction of RANKL and RANK.[6,7]

Osteoblastic lesions: Second Step

Osteoblastic lesions are the result of the production of soluble paracrine factors by the tumor cell that stimulate bone formation by increasing osteoblast activity. They include TGF-β, bone morphogenetic proteins (BMPs), and endothelin-1. Members of the TGF-β family, particularly isoforms 1 and 2, stimulate new bone formation in vivo. Bone morphogenetic proteins are members of the extended TGF-β superfamily synthesized by bone cells and have been shown to stimulate osteoblast differentiation and induce new bone formation in vivo . Furthermore, various BMPs are expressed in a number of cancer cell lines. Endothelin-1 (a growth factor that stimulates osteoblasts in culture) is significantly elevated in the circulation of patients with cancer and bone metastases and is secreted by many cancer cell lines . Additional factors secreted by cancer cells, including IGFs and fibroblast growth factors (FGFs), may also increase bone formation.[1,9] Along with increased bone formation, osteoblastic lesions are also associated with the stimulation of bone resorption evidence of which, is provided by significant increases in biochemical markers of bone resorption. In a recent study of patients with various cancers, urinary levels of the bone resorption marker , N-telopeptide and serum levels of bone-specific alkaline phosphatase, a bone formation marker, were significantly higher in patients with osteoblastic lesions than in patients with osteolytic or mixed lesions.

Furthermore, the levels of these bone markers were significantly correlated with the number of skeletal sites involved in the metastases. However, even though osteoblastic lesions are associated with increases in both osteolysis and bone formation, the sites of bone resorption and bone deposition are uncoupled, meaning that the excessive new bone is deposited away from the sites of bone resorption, resulting in reduced bone strength and an increased risk for fractures and vertebral collapse.[8,9]

Jaw Metastasis and Its Origin In both Genders:

Men	Women
Lung-22%	Breast- 42%
Prostrate-12%	Colorectum- 8%
Kidney-10%	Kidney- 6%
Bone- 9%	Bone- 6%
Adrenalglands-9%	Thyroid- 6%
Liver-7%	Rare tumors- 23%
Testis-7%	

Metstasis commonly occurs to the posterior part of the mandible Hoemopoietic cellularity of the bones is classified according to the criteria of Higuchi into FIVE categories:

- complete red marrow
- incomplete red marrow
- intermediate marrow
- incomplete fatty marrow
- complete fatty marrow

The jaw bones with significantly active marrow are a preferred site for metastatic deposits in the skeleton due to local slowing of blood flow and significant amount of active marrow as found in the posterior area of the mandible so, jaw metastasis commonly occurs here . The difference in the density of vascularity and endothelial characteristics between red and yellow marrow are responsible for the difference in the frequency of tumor deposits in them. The spread of metstatic deposits commonly occurs through the Batson's plexus (vertebral vein system) which extends from skull to sacrum and it is

a common thoroughfare for the spread of thoracic, abdominal and pelvic tumors to HEAD and NECK region, where infiltration through the lungs is bypassed.[10]

Symptoms

Bone metastases are a major clinical concern that can cause severe pain, bone fractures, spinal cord compression, hypercalcemia, anemia, spinal instability, decreased mobility, and rapid degradation in the quality of life for patients. Patients have described the pain as a dull ache that grows worse over time, with intermittent periods of sharp, jagging bone pain. Even under controlled pain management, these periods of breakthrough pain can occur rapidly, without warning, and several times a day.[4,11]

Pain, pathological fractures and hypercalcemia are the major sources of morbidity with bone metastasis. Pain is the most common symptom found in 70% of patients with bone metastases. Pain is caused by stretching of the periosteum by the tumor as well as nerve stimulation in the endosteum.[4] When jaw is involved it may cause- swelling, pain, pathological fracture, masticatory difficulties, loosening of teeth and trismus with or without Numb Chin Syndrome

Diagnosis

Diagnosis and Monitoring of Metastases can be done with :

- Radiographs(IOPA,OPG,Chest)
- Bone scans
- MRI,CT,PET,Ultrasound

. It is difficult to distinguish between metastases and benign lesions such as Paget's disease or osteoporosis on plain film. On bone scan, radiolabeled bisphosphonates are taken up by in areas of bone formation but not by the tumor cells. CT scan is more specific than bone scan and can distinguish between osteolytic and osteoblastic lesions. MRI is the most sensitive method of detection bone metastases because cells can be spotted before local bone reaction has occurred.[10]

Clinical Analysis as for some primary cancers, such as lung and ovarian cancers, which begin to shed tumor cells that form metastases elsewhere in the body before the primary cancer is large enough to be detected by standard diagnostic techniques. Marker molecules that are given off by micrometastases circulating in the bloodstream can now be detected. Biopsy coupled with Immunoenzyme labeling, Immuno histochemistry and Electron microscopy. Tumor markers' analysis because the blood levels of tumor markers can be used to evaluate the recurrence or spread of cancer and the patient's response to treatment. Cytology- Cytomorphometric DNA analysis,which can be used to distinguish metastatic tumors from multicentric tumors.

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