Metastatic Bone Disease: A Pathophysiologic Overview

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Summary:

Bone is a common site for metastasis of malignant tumours occurring elsewhere in the body. High blood flow in the red marrow and favorable bone-marrow microenvironment help metastatic tumour cells survive, proliferate and infiltrate the bone matrix. The cancer cells produce and secrete a number of osteoclastogenic and osteoblast stimulating factors which recruit and activate osteoclasts and osteoblasts respectively at the metastatic foci. Osteoclasts together with proteolytic enzymes released by tumour cells cause resorption and destruction of bone. On the other hand, stimulated osteoblasts lay down new bone in response to factors released by tumour cells. Degradation products of this bone turnover and tumour-derived proteins are important bio-markers of metastatic bone disease, measures of which also reflect disease prognosis and treatment efficacy. Specific tumour-bone interactions occurring in metastatic bone disease are targets of new strategies of anti-metastasis therapy.

Key words: Metastatic bone disease, bone-marrow microenvironment, osteoclastic bone resorption, osteoblastic metastasis.

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Introduction:

Malignant tumour arising in an organ other than bone and subsequently spreading to bone is termed as metastatic bone disease (MBD)[1]. Bone is the third most common organ involved by metastases, the first two being lung and liver[2,3,4]. On the other hand, metastases constitute the most common group of skeletal malignancies. Cancers of thyroid gland, breasts, lungs, prostate and kidneys account for 75-80% or more of skeletal metastases in adults[4,5,6]. Tumours that less commonly metastasize to bone are cancers of urinary bladder, colon and other parts of the gastrointestinal tract[2,6,8]. In children, metastases to bone originate mostly from neuroblastoma, Wilm's tumour, rhabdomyosarcoma, Ewing sarcoma and teratocarcinoma[4,6]. Soft tissue sarcomas in adults rarely metastasize to skeletal system[5]. Melanoma, lymphoma, and virtually any cancer can metastasize to bone[4,5,7,8,9,10,11].

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Bone metastasis:

Bone is a common site for metastasis owing to the high blood flow in the red marrow[12,13]. Mineralized bone matrix is a rich storehouse of growth factors, such as insulin-like growth factor, transforming growth factor-â, bone morphogenetic proteins and others[12,13,15]. Adhesion molecules present on metastatic tumour cells bind them to stromal cells of the bone-marrow. The tumour cells secrete angiogenic factors and bone resorbing factors which stimulate their proliferation and make their access into the resorbing bone matrix. Growth factors released by the resorbing bone matrix provide a fertile soil for further growth of metastatic tumour cells[13,14,15,16].

Types of bone metastases:

Bone metastases are typically characterized as osteolytic or bone destroying, osteoblastic or sclerotic or bone forming, and mixed, according to the radiographic and pathologic appearance of the lesion[4,5,6,12,13,15]. Osteolytic bone metastases are presumed to be caused by release of osteoclastogenic factors in the bone microenvironment by the metastatic tumour cells [15,16,17]. Osteoblastic lesions are the result of release of factors from the tumour cells that stimulate proliferation, differentiation and activation of osteoblasts leading to bone production [18,19]. Osteolysis is the commonest pattern of bone metastasis which also accompanies the osteoblastic lesions[6,12,14,19].

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Distribution of bone metastases:

Axial skeleton is the most common site affected by metastases. It comprises the spine, ribs, pelvic bones, skull and sternum. Femur and upper end of humerus are the highest

in frequency among long bones[1,2,4,5,6,20]. These bony sites contain areas of marrow that demonstrate high levels of red blood cell production, responsible for carriage of oxygen

to the tissues[1,6]. Vertebral metastases are most frequently found in the lumbar spine, followed by thoracic, cervical and sacral portions. Spread of tumour cells occurs through Batson's plexus to the basivertebral veins; as a result, posterior part of the vertebral body near the entry of the vessels is involved first. In long bones, metaphyses are involved, sometimes with bilateral distribution. Small bones and intervertebral discs rarely have metastases[6].

The bone marrow microenvironment— tumour-host cell interaction:

Once tumour cells from a distant primary colonize bone, their growth and inhabitation are helped by local cells of bone and bone-marrow[12,13,21]. Though cancer cells in advanced metastasis can destroy or lay down bone matrix directly, the effects are mostly mediated by the local cells. Among the host cells, osteoblasts, osteoclasts, endothelial cells, platelets and mesenchymal stem cells play key role in growth and survival of the metastatic tumour cells[12,14,22,23]. Cancer cells produce and secrete both osteolytic and osteoblastic factors. Transforming growth factors (TGF-á and â), parathormone related protein or peptide (PTHrP), interleukins (IL-6,8,11), prostaglandins and powerful osteoclast cytokines such as tumour necrosis factor and interleukin1 are produced by metastatic tumour cells. TGF- á is a potent stimulator of osteoclast formation and osteoclastic bone resorption. TGF- â can stimulate both osteoblast and osteoclast activities, with the later predominating in most tumours[6,14,24,25]. PTHrP is probably the most prominent cause of bone destruction in metastasis. It is responsible for humoral hypercalcemia in malignancy. It induces production of RANKL (receptor activator of nuclear factor kappa B ligand) by osteoblasts. In healthy bone, a normal level of RANKL activity is maintained that regulates normal bone remodelling. In cancer-induced bone disease, RANKL promotes differentiation, activation and survival of osteoclasts leading to bone resorption. This resorption releases factors from bone matrix (particularly TGF-â), which in turn change the phenotype of the tumour cells, further increasing the PTHrP production. Thus a vicious osteolytic cycle between the bone and the tumour cells is established[6,12,13,14,26,27,28,29].

On the other hand, osteoblastic metastases are mediated by stimulation of osteoblasts by cytokines released from tumour cells, either directly, or via release of factors from osseous stroma. Prostatic cancer cells produce osteoblast stimulating factor, bone morphogenetic proteins (MBPs), urokinase-type plasminogen activator and basic fibroblastic growth factor[6,30,31]. Breast cancer cells produce TGF-â and endothelin-1[6,12,46].

All these stimulate osteoblasts which produce collagen, osteocalcin and alkaline phosphatase. As a result new bone is laid down. In some of the breast cancers metastasizing to bone, new bone formation occurs as a physiological attempt to bone repair following bone destruction[6,12].

Changes in bone in metastasis:

Carried by systemic circulation, metastatic tumour cells colonize bone in areas of active marrow. They are attached to endothelial cells and bone matrix proteins like laminin and

fibronectin, probably mediated by adhesion protein integrins. The tumour cells proliferate, form nests or cell mass and replace marrow material. They destroy and invade bone by secreting proteolytic enzymes including matrix metalloproteinases. However, they more predominantly grow in osteolytic defects produced by activated osteoclasts[6,12,14,30]. Radiologically, well-defined, often expansile or moth-eaten lucent or lytic lesions (geographic bone destruction) are usually documented, sometimes with periosteal reactions[1,4,5,6,32,33,34]. The lesions may be solitary or multiple. Histologically tumour nests are seen filling the resorption lacunae or pits, often populated by osteoclasts[6,12,14,26,27]. In primarily osteoblastic type metastasis, new bone is laid down on trabecular bone surfaces or in the marrow cavity as primitive woven bone. There may also be periosteal bone formation which can mimic osteosarcoma. The new bone is usually poorly mineralized, and in about 50% of cases of

metastatic prostate cancer, evidence of osteomalacia is seen[6,12,35,36,37]. However, bone formation can be so extensive as to make the skeleton appear uniformly dense[6,35,37]. Mixed osteolytic- osteoblastic changes are common in many, particularly in metastatic breast carcinomas. Reactive immature woven bone is present in about 40% of all bone metastases, irrespective of the primary site of the tumour. It is often associated with capillary and fibroblast proliferation as well as with infiltration of inflammatory cells and macrophages[6,38].

Markers of metastatic bone disease:

Biochemical markers of bone turnover in metastatic bone disease can be detected in patient's blood and/or urine.These markers are usually proteins or peptides released by tumour or bone cells, or degradation products of cellular activities[12,39].

Markers of bone resorption are measured both in serum and urine. These include fragments of bone collagen, enzymes of osteoclasts e.g. tartrate-resistant acid phosphatase (TRAP) and cathepsin K, and factors that regulate osteoclast recruitment and activity e.g. receptor activator of nuclear factor kappa B (RANK), RANK ligand (RANKL) and its decoy receptor osteoprotegerin. Fragments of bone collagen are hydroxyproline, collagen cross-linking amino acids e.g. pyridinoline and deoxypyridinoline, and cross-link containing fragments of collagen e.g. N-telopeptide and C-telopeptide of collagen type 1 (NTx and CTx respectively)[39,40,41].

Markers of bone formation are measured in serum. These include total and bone alkaline phosphatase, osteocalcin, procollagen type 1 propeptides from amino- and carboxy-terminal ends of synthesizing collagen (called P1NP and P1CP respectively). The later propeptides are cleaved from the ends of procollagen molecule, released in circulation and reflect the amount of newly synthesized collagen[39,40,41].

The markers of bone turnover are excellent indices of disease activity in metastatic bone disease. They have both diagnostic and prognostic value. Moreover, efficacy of treatment can be established by normalization of the test results. Immunoassays selectively measure NTx and CTx in serum and urine. Serum CTx level is found highly sensitive and serum P1NP highly specific for predicting bone metastasis. Bone alkaline phosphatase is an ideal biomarker of bone turnover. Urinary pyridinoline and deoxypyridinoline are also relatively selective bone markers. Urinary hydroxyproline, however, lacks specificity of bone resorption as hydroxyproline is common to almost all forms of collagen[39,40,41,42].

Targeting pathophysiology in therapy of MBD:

Treatment of metastatic bone disease (MBD) is primarily palliative. Aims of treatment in MBD are relief of pain, hypercalcemia and other symptoms, local tumour control, skeletal stabilization and restoration of function. Treatment modalities include chemotherapy, hormone therapy, immunotherapy, radiation, surgery and bone marrow transplantion. Often a multi-modality approach is deployed[12,43,44].

Treatment strategies are being developed targeting specific tumour-bone interactions. An important target is osteoclastic bone resorption. The bisphosphonates group of drugs are readily taken up by osteoclasts, cause a loss of their resorptive capacity, and more importantly, induce their apoptosis[12,14,45]. Diminished osteoclastic bone resorption in turn causes a loss of growth factors from bone matrix resulting in reduced stimulation to the tumour cells. Bisphosphonates may also be taken up directly by the tumour cells causing their death[14]. A modified recombinant version of osteoprotegerin inhibits osteoclast formation, activity and survival. It has decreased osteolytic destruction and tumour burden in bone in animal model. Prevention of bone resorption effectively reduces bone pain[14].

Other targets of therapy are mostly under clinical trial which include PTHrP neutralizing antibody, inhibitor of gene promoter for PTHrP transcription in tumour cells, drugs against RANKL, TGF-â, Cathepsin K and integrins[14,44]. Inhibitors of PTHrP transcription were tested in animal models with humoral hypercalcemia of malignancy and found effective in reducing osteoclastic bone resorption. These agents also make a less favorable environment in bone for tumour growth[14]. Adjuvant anti-resorptive therapy can prevent bone loss due to sex steroid ablation induced by chemotherapy itself in prostate and breast cancers[14]. The drug tested to date that targets osteoblastic bone metastasis is endothelin A receptor antagonist. In a mouse model with breast cancer cell lines, it has dramatically reduced bone metastasis and tumour burden[14,46].

Conclusion:

About two-thirds of the patients with cancer develop bone metastasis[47]. Bone metastasis adds greatly to the

patient morbidity, specially when osteolytic in nature. Reduction in morbidity is an important part of palliation. Understanding of pathogenesis of bone metastasis is essential to target specific tumour-bone interactive processes in anti-metastasis therapy. This short review focuses on key pathogenetic processes occurring in bone metastasis and their role in targeted therapy. Biomarkers of bone resorption or formation are indicators of treatment efficacy and important predictors of prognosis.

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