DOI: http://doi.org/10.4038/jmj.v28i1.39

Review article
Metastatic disease of skeleton

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Bone metastasis is a catastrophic complication for most patients with cancer and can cause significant morbidity to a patient. It stands 3rd most common site secondary to liver and lungs. Prostate and breast are more common to cause bone metastasis. They can be osteolytic, osteoblastic or a combination of both. Vertebrae are commonly involved (50-70%). Proximal femur, ribs, sternum, pelvis, and skull are other common sites. Only 10% of patients get symptoms. Pain, pathological fractures, spinal cord compression syndromes and hypercalcaemia are common presentations. Precise mechanism of metastasis is not understood. Establishment of skeletal metastasis involves interactions between the tumor cell and the cellular elements in the bone microenvironment. Majority of patients need non operative conservative treatment. Principles of treatment include control of local symptoms; maintain function and mobility and prevention of pathological fractures.

Introduction

Metastasis is a common event in a malignancy. Skeleton is the third commonest site other than lungs, and liver[1]. Bone microenvironment provides a fertile soil for the growth of many tumors. In view of bone tumours, metastatic tumours are commoner than primary bone tumours. With improvements of investigations and treatment modalities, incidences of metastatic bone tumours have risen.

Epidemiology

Certain cancers have high chance of getting bone metastasis (osteotrophic), particularly breast and prostate. 70 % of breast and prostate cancers have shown skeletal metastasis in their autopsy studies[1]. Other cancers include thyroid (40%), renal (35%), bronchus, melanoma, etc[1,2]. Hematologic malignancies also frequently involve the skeleton. The most obvious of these is myeloma which almost always causes osteolytic lesions[6]. Bowel, bladder, rectal carcinoma has a lower risk of incidence.

Skeletal metastasis can be osteolytic, osteoblastic or combination of both. Breast carcinoma causes osteolytic lesions whereas prostate causes commonly osteoblastic lesions[5]. Certain lymphomas cause mixed lesions. These are commonly occurring in either middle aged or old patients. 75% of patients reported are over 50 years[1].

Site of metastasis

Parts of skeleton that have abundant red marrow are more liable to metastatic deposits. They are commonly multifocal. Vertebrae are commonly involved (50-70%). Proximal femur, ribs, sternum, pelvis, and skull are other common sites. Anterior portion of vertebral body is commonly involved followed by pedicle or lamina.

A major determinant of the site of skeletal metastasis is blood flow; because, prostate carcinoma frequently metastasizes to the vertebral column, the access occurs through the vertebral venous plexus (Batson's plexus). Batson's plexus is a low-pressure, high-volume system of vertebral veins, which can communicate with the intercostal veins, and runs up the spine. This plexus has extensive intercommunications with other venous systems such as the pulmonary, caval, and portal systems.

Presentation

90 % of patients have no symptoms[1]. Commonest symptom is intractable dull pain and it occurs due to stretching of overlying periosteum, through nerve stimulation of endosteum, or due to pathological fractures. Vertebral fractures can be associated with neurological symptoms such as sensory motor weakness nerve compression syndromes or cauda equina syndrome (altered bladder bowel dysfunction and saddle anesthesia). Hypercalcemia occurs in 10% of patients with skeletal metastasis particularly in osteolytic lesions. It is commonly seen in breast carcinoma (30% of cases)[6]. They present with fatiguability, ureteric stones, pancreatitis, depression, anorexia,or vomiting.

Molecular basis of tumour origin

Exact biological mechanism is not completely understood, but there is a complex interaction between tumour cells and normal host cells that initiate the cycle of bone destruction and tumour growth. Bone is a living tissue. It has abundant rich blood supply and good source of oxygen and nutrients, providing a good fertile microenvironment for proliferation of tumour cells. They interact with bone stroma by releasing biological factors whose ligands are expressed in bone cells and stroma.

They can be osteolytic, osteoblastic or a combination of both. Here, normal balance between bone formation and bone resorption is disrupted. Certain

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biological factors expressed by tumour cells such as Parathyroid hormone related peptide (PTHrP), Transforming growth factor β (TGF β), interleukin[11,6]cause enhanced bone resorption (osteolytic lesions)[1,2]. Other examples are calcitonin receptors, osteopontin, tumour necrosis factor α, prostaglandins, and receptor activator of nuclear factor- Ƙ etc[1,3]. Osteoblastic lesions are produced by enhanced bone formation with reduced bone resorption. TGF β,osteoprotegerin (OPG), bone morphogenetic protein (BMP), Insulin growth factors stimulate differentiation and activity of osteoblasts[1,4]. Mixed lesions are as a result of combination of both factors.

Therefore, tumour cells secrete factors that stimulate osteoclasts causing bone resorption and in turn releases growth factors (GF) from bone matrix and stimulate tumour growth as it happens as a vicious cycle. TGF β plays a role in promoting osteolytic bone lesions by inducing tumour production of PTHrP, a known stimulator of osteoclastic bone resorption in breast carcinoma. So blockade of TGF β signaling in tumour cells or by neutralization of PTHrP has a therapeutic effect of controlling tumour growth. Tumour cells interact with osteoblasts or stromal cells to induce osteoclast formation by increasing RANKL expression. Receptor activator of nuclear factor- Ƙ ligand (RANKL), a member of tumour necrosis factor family expressed by tumour cells binds with RANK, a receptor expressed on osteoclasts and stimulate osteolysis.

Management

Majority of patients need non operative conservative treatment. Principles of treatment include control of local symptoms; maintain function and mobility and prevention of pathological fractures. Adequate analgesics are required to reduce intractable bone pain. Chemotherapy is useful for certain type of metastasis especially breast carcinoma (tamoxifen). Bisphosphonates cause increased osteoclast apoptosis, therefore reducing lytic activity of bone metastasis. It also has effect of anti-tumour activity and prevents bone metastasis. Endocrine treatment is useful in hormone sensitive tumours especially breast and prostate carcinoma[1,2].

Immunotherapy is still under investigation, but in future antibodies for PTHrP can be used to reduce osteoclast bone metastasis. Radiotherapy is commonly used as a palliative measure to reduce local pain; but it is a short term control. Further, Radio-immunotherapy is a new concept where antibody labelled with radio nucleotide is used to deliver radiotherapy to tumour cells. Surgery for bone metastasis is used for limited indications such as to prevent pathological fractures, to attempt curative excision if it is a small deposit, and to prevent or relieve neurological compromise. Surgical reconstruction and endoprostheses are now available. New interventional radiological techniques have been developed such as embolization of vascular metastasis, percutaneous injections to bone lesions.

Summary

Bone metastasis is a catastrophic complication for most patients with cancer and can cause significant morbidity to a patient. Careful investigation and multidisciplinary management can improve survival and decrease morbidity.

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