Role of PET

In Evaluation Of Bone Metastases

Essay

Submitted for the fulfillment of M.Sc. degree
In nuclear medicine

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2008

بسم الله الرحمن الرحيم

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وربُّكَ الأَكْرَم * الّذي عَلَّمَ بالقَلَمِ * عَلَّمَ الإِنْسَانَ مَا لَم يَعْلَم *

صدق الله العظيم

سورة العلق، الآيات 1-5

ABSTRACT

Metastatic bone disease is the most common malignancy of bone, and is the source of significant morbidity in cancer population.

Bone scintigraphy remains the most frequently performed nuclear medicine study and the most cost-effective and available whole-body screening test for the assessment of bone metastases in spite of its low sensitivity for detecting early marrow lesions and purely lytic lesions.

Positron emission tomography (PET) is the gold standard in metabolic imaging and is characterized by high-contrast resolution, whole body tomographic data and the ability to perform absolute quantitation of tracer uptake.

PET may be superior to bone scintigraphy in the detection of metastases because it detects the presence of tumor directly by its increased metabolic activity, rather than indirectly by showing tumor involvement due to increased bone mineral turnover. This has allowed the detection of metastatic marrow lesions earlier than with bone scintigraphy, & is sometimes more accurate in evaluation of the therapeutic response of bone metastases.

Key Words:

PET, FDG, PET/CT, M-CSF, TGF-B, PSA

Acknowledgement

*First and foremost thanks to **Allah**, The most kind, the most merciful, to whom I relate success in achieving any work in my life and who helped me to pass safely through all problems that I thought impossible to overcome.*

*I would like to express my utmost gratitude to **Prof Dr. Khaled El Saban**, for his generous help. He suggested the subject of this work & gave me much of his advice.*

*My sincere thanks and deepest gratitude also go to **Dr. Ahmed Zaher**, I can't find any word to express my grateful appreciation to his generous help, encouragement, support and enormous educational potential.*

Also, I would like to express my deepest thanks to my staff of Nuclear Medicine Department in National Cancer Institute and also to my colleague Dr. Yasser Gaber for his generous help and support.

Last but not least, many thanks to my family and my husband who are always pushing me forward.

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AMDP	*Aminomethlen ediphosphonic acid*
BS	*Bone scan*
CT	*Computed Tomography*
DMAD	*Dimethyl-amino diphonate*
DPD	*Dicarboxypropane diphosphonate*
DTC	*Differentiated Thyroid Carcinoma*
18F	*Flourine 18*
FDG	*Fluorodeoxyglucose*
FDG-6-P	*Fluorodeoxyglucose-6-phosphate*
67Ga	*Gallium -67*
GIT	*Gastro Intestinal Tract*
GLUT	*Glucose transporters*
HD	*Hodgkin's disease*
HEDP	*Hydroxy ethylidene diphosphonate*
123 I ,131 I	*Iodine -123, Iodine -131*
IL-6	*Interleukins 6*
KeV	*Kilo Electron Volts*
M-CSF	*Macrophage colony stimulating factor*
MDP	*Methylene diphosphonate*
MeV	*Million Electron Volt (Megavolt)*
MGUS	*Monoclonal Gammopathy of Undetermined Significance*
MIBG	*Metaiodo benzyl guanidine*

MM	*Multiple Myeloma*
NSCLC	*Non Small cell Lung Carcinoma*
PET	*Positron emission tomography*
PPV	*positive predictive value*
PSA	*Prostate-Specific antigen*
PTHR	*Parathyroid hormone receptor.*
RANKL	*Receptor activator of nuclear factor –KB*
˜˜RCC	*Renal cell carcinoma*
SPECT	*Single Photon Emission Computed Tomography*
SGLT	*Sodium-glucose transporters*
SS	*skeletal scintigraphy*
SUR	*standardized uptake ratio*
SUV	*Standardized uptake value*
^{201}T	*201- Thallium*
^{99m}Tc	*Technetium -99m*
U-PA	*Urokinase –type plasminogen activator*
WBS	*whole-body scan*

BONE METASTASES

Introduction

Metastatic disease to bone is the most common malignancy of bone, and the development of metastatic bone disease is the source of significant morbidity in cancer population.

The skeleton is surpassed only by the lungs and liver for incidence of metastatic diseases. Any bone of the skeleton can be involved however; the axial skeleton is most commonly involved. Involvement of the appendicular skeleton most commonly involves the proximal portion of lower extremities.

At autopsy, 70% of patients who die of cancer have been shown to have skeletal metastases **(Neff JR. et al, 1992).**

Many of the lesions are asymptomatic and too small to be recognized radiographically, the proximal femur was found to be the site of metastatic lesions in 11% of all patients, however, when involved, they are often likely to fracture.

Approximately 40% of all pathological fractures occur in the proximal femur. The risk of pathological fracture is correlated to the extent of the lesion, the type of destruction and the anatomic location.

Lesions in high stress areas as the lesser trochanter are oftenly associated with pathological fracture with highly anaplastic and rapidly growing vascular lesion, which are usually osteolytic.

Presentation of patients with skeletal metastases takes many forms, metastases may be found on routine staging studies including bone scan. They typically become clinically evident as a result of pain and dysfunction.

Spinal metastases may present with pain with or without pathological fracture as well as spinal instability or compression of spinal cord.

Metastases to long bones of the extremities typically present secondary to pain or pathological fracture, **(Neff JR. et al, 1992).**

Pathophysiology of osseous metastases

Both osteolytic and osteoblastic bone metastases can be viewed as part of the dysregulation of bone remodling that occurs with the development of osseous metastases, occasionally both types of metastases occur in association with the same malignancy, such as with breast cancer.

However, breast cancer is associated with primarily osteolytic metastases, contrasting with prostatic cancer that has primarily osteoblastic features **(Mohammed K et al 2003).**

The skeleton is a common site of metastases because of significant access to blood flow and the ability of marrow stromal cells to bind to circulating tumor cells via the presence of adhesion molecule **(Mohla S et al; 2003).**Understanding the metabolic functions involved in the balance of osteoclast and osteoblast activity within the marrow stroma will help support the rational behind newer therapies in the treatment of bone metastases.

Osteoclasts arise from monocyte macrophage lineage and are induced by macrophage colony stimulating factors (M-CSF) and by binding to the receptor activator of nuclear factor –KB (RANKL) ligand present on the surface of osteoblasts and stromal cells **(Mohla S et al ;2003).**

Osteobastic secretion of cytokines such as interleukins 6(IL-6), IL-1, and prostaglandin E_2,also aids in the induction of osteoblastic formation .

Osteoclasts adhere to the surface of the bone via intergrins where they control osseous resorption by protease secretion.

Osteoblasts arise from mesenchymal cells and their differentiation is controlled by several growth factors produced by the stromal cells**,** such as TGF-B and PDGF **(Roodman G et tal;2004).**

Within the bone matrix most metastatic solid tumors secret Parathyroid hormone-related peptide, this binds to the parathyroid hormone receptor (PTHRI) and stimulates osteoblast development.

The activation of (PTHRI) also stimulates expression of RANKL on stromal cells, which has been shown to induce formation of osteoclasts.

Osteoclasts induced resorption of bone results in local increase in calcium concentration, which in turn stimulates tumor growth and parathyroid hormone- related protein production.

Therefore, a significant relationship appears to exist between bone destruction and metastatic tumor growth mediated through cell signaling involving the micro environment.This phenomenon has been viewed as a (vicious cycle) **(Rood man G et al; 2004).**

This vicious cycle may be also seen with prostate cancer, however, the mechanisms related to osteoblastic metastases are less recognized. Paracine factors such as endothelin and PDGF also appear to stimulate osteoblastic metastases and tumor growth **(Brown J and Coleman R et al; 2002).**

In addition , prostate cancer cells secrete both prostate-specific antigen (PSA) and urokinase –type plasminogen activator (U-PA) ,which activate growth factors within the marrow stroma, such as TGF-B and insulin - like growth factors I and II that in turn stimulate osteoblastic activity **(Rood man G et al;2004)**.

Pathogenesis of metastases

Despite the fact that tumors originate from signal cell that lacks normal control mechanisms, tumors consist of vast numbers of cells. Only a limited number of cells may have the genetic potential to metastasize. Although numerous tumor cells gain access to the systemic circulation, only small numbers of cells, probably less that 0.1%, survive the transport **(Folkman J et al; 1995).**

While random sites of metastases can occur, selection of the metastatic site depends on cohesions of molecules specific to endothelium within the arterioles, capillaries and post capillary venules of particular organ. The mechanical aspects of pain, on the other hand are strain related. This pain is aggravated by weight-bearing activities and relieved by rest. This Patten of pain results from the loss of structural integrity **(Healey JH et al; 1993).**

As already stated, for the metastatic tumor to grow within bone there must be a mechanism for bone lyses which is thought to occur secondary to effects on the host Osteoclasts and Osteoblasts, rather than by a direct effect of the tumor cells themselves .Typically, Osteoclasts stimulation out weighs osteoblasts stimulation and a lytic lesion of bone results .

This net bone loss reduces bone strength and stiffness, thereby leading to pain with weight bearing. Pain of this character is less likely to be immediately responsive to medical management.

Increasing mechanical pain may signal impending pathological fracture and warrant protected weight bearing as well as a consideration of prophylactic operation for stabilization.

Many metastatic tumors to bone have no presenting symptoms. These lesions may come to medical attention as an incidental finding on plain

radiographs or, more commonly, by bone scintigraphy in the setting of staging of a known primary tumor.

Another common complication, hypercalcaemia of malignancy, occurs most commonly in squamous cell lung cancer, breast cancer, multiple myeloma and renal cell carcinoma. The historic incidence has ranged from 19.0% to 49.5 **(Plukett T et al; 2000) .**The hypercalcaemia is mediated by one of two mechanisms in metastatic bone disease .Advanced metastatic disease with severe bone destruction at multiple sites is the more frequent cause of this complication. In addition, tumors such as squamous cell carcinoma may secret parathyroid hormone-related protein and produce the equivalent of secondary hyperparathyroidism.

With decrease in activity because of pain, disuse osteolysis can exacerbate the hypercalcemia with mild disease.Patients may develop fatigue, lethargy, nausea, vomiting, anorexia and disorientation. Early initiation of biphosphonate therapy may prevent hypercalcemia. Pathologic fractures may be the first sign of metastatic disease of the skeletal system.

In breast carcinoma, as many as 35% of patients with bone disease experience fracture **(Plukett T et al; 2000).** Breast, lung, renal and thyroid cancer have been the most common cause of pathological fractures, **(Higinbotham N and Marcove R; 1998).** The spine is the most common site of skeletal metastases, so spinal instability and neurological abnormalities are common sequalea of spinal cord compression. If diagnosed late, it may lead to significant morbidity and dramatically impacts the quality of remaining life. Loss of propioception, sphincter control, motor or sensory function reflects spinal cord compression that needs treatment.

Knowledge of the neurological signs of spinal cord compression can prevent these devastating complications.