Discordant Findings of Skeletal Metastasis Between Tc\textsuperscript{99m} MDP Bone Scans and F\textsuperscript{18} FDG PET/CT Imaging for Advanced Breast and Lung Cancers—Two Case Reports and Literature Review

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Traditionally, Tc\textsuperscript{99m} methyl diphosphate (MDP) bone scintigraphy provides high-sensitivity detection of skeletal metastasis from breast and lung cancers in regular follow-up. Fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT), based on the glucose metabolism of malignant cells, plays a role in describing tumor growth, proliferation of neoplasm and the extent of metastasis. In general, concordant findings of skeletal metastasis are seen on both types of image, especially in cases of breast and lung cancer. However, there were extremely discordant findings of skeletal metastasis between bone scans and F\textsuperscript{18} FDG PET/CT imaging in two cases among 300 consecutive F\textsuperscript{18} FDG PET/CT follow-up exams of patients with malignancies, during the past year, in our center. Both cases, one of breast cancer and one of lung cancer, had negative bone scintigraphic findings, but a diffusely high grade of F\textsuperscript{18} FDG avid marrow infiltration in the axial spine, leading to the diagnosis of stage IV disease in both cases. Owing to variant genetic aberrance of malignance, F\textsuperscript{18} FDG PET/CT reveals direct evidence of diffuse, rapid neoplasm metabolism in the bone marrow of the spine, but not of secondary osteoblastic reactions \textit{in vivo}. F\textsuperscript{18} FDG PET/CT should always be employed in the follow-up of patients with malignancies.

Key Words: F\textsuperscript{18} FDG PET/CT, skeletal metastasis, Tc\textsuperscript{99m} MDP bone scintigraphy

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in up to 70% of patients with advanced breast or prostate cancer [2], and in approximately 15–30% of patients with carcinomas of the lung, colon, stomach, bladder, uterus, rectum, thyroid or kidney. Bone metastases have been characterized as osteolytic, osteoblastic or mixed lesions containing both elements [3]. Most patients with breast cancer have predominantly osteolytic lesions, although at least 15–20% of them have predominantly osteoblastic lesions [4]. Once tumors metastasize to bone, they are usually incurable: only 20% of patients with breast cancer are still alive 5 years after the discovery of bone metastasis [5].

Tc\textsuperscript{99m} methyl diphosphate (MDP) bone scintigraphy, which is a cost-effective and useful tool in widespread disease, is the most commonly used means of detecting bone metastasis and has variable diagnostic sensitivity with comparatively low specificity. However, F\textsuperscript{18} fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) based on the glucose metabolism of malignant cells, may describe tumor growth, proliferation of neoplasm and the extent of metastasis, including distal skeletal involvement. In general, concordant findings of skeletal metastasis are seen on both types of image, especially in those of breast and lung cancers. However, there were extremely discordant findings of skeletal metastasis between bone scans and F\textsuperscript{18} FDG PET/CT in two cases among 300 consecutive F\textsuperscript{18} FDG PET/CT follow-up exams during the past year in our PET center.

**CASE PRESENTATIONS**

**Case 1**
A 51-year-old male patient with chronic cough for more than 3 weeks in February (2006) had received clinic medication to no avail, and was admitted for advanced diagnosis. Tracing his history, only duodenal ulcer and acute appendicitis post appendectomy, 20 years ago, were revealed. He was, however, a heavy smoker and habitually chewed betel nut. Initially, a large soft mass in the right lower lobe (RLL) of the lung was seen on chest X-ray, and thoracic CT suggested lung cancer with mediastinal nodal involvement. Based on imaging, the stage was considered to be IIIb, T3N2Mx. Pathology demonstrated adenocarcinoma, which was determined to be grade II after CT-guided biopsy. Tc\textsuperscript{99m} MDP skeletal scintigraphy revealed only a hot spot in the right anterior sixth rib, heterogeneous lower grade of Tc\textsuperscript{99m} MDP activity in the spine, and extraosseously faint Tc\textsuperscript{99m} MDP activity in the RLL lung mass, as shown in Figure 1. Less convincing evidence of distal bony metastases was found by a bone scan in March. The patient then received his first course of chemotherapy. F\textsuperscript{18} FDG PET/CT was arranged for treatment follow-up due to an uncontrollable lung mass on chest X-ray after 1 month.

Extremely discordant imaging patterns between F\textsuperscript{18} FDG PET/CT and bone scans were seen, as shown in Figure 2. Diffusely extensive spotty high-grade F\textsuperscript{18} FDG avid marrow activity was distributed in the spine, pelvis and proximal long bone, but there was no obvious lytic or sclerotic bony destruction on CT. A higher grade of RLL lung mass with central necrosis and mediastinal nodal activity was also noted, but the patient was free of hepatic metastases. Under F\textsuperscript{18} FDG PET/CT, stage IV disease was diagnosed. Radiotherapy and gefitinib treatment were planned for aggressive control in subsequent months. Another Tc\textsuperscript{99m} MDP bone scan was arranged for July, and a lower grade of Tc\textsuperscript{99m} MDP with heterogeneous pattern in the lumbar spine, bilateral proximal long bones and the old hot spot in the right anterior sixth rib were detected. However, the patient died in late July due to poor hemodynamic function, hepatic failure from severe hepatic metastases and pancytopenia.

**Case 2**
A 53-year-old female with left breast cancer (infiltrative ductal carcinoma with negative immunohistochemistry of ER/PR/Her2neu) had received modified radical mastectomy in October 2003. Chemotherapy and radiation therapy were also arranged. She had her follow-up in the city hospital. Tc\textsuperscript{99m} MDP skeletal scintigraphy was arranged to be administered annually. On serial Tc\textsuperscript{99m} MDP scans, there was a hot spot in the left hemivertebral body of L2 with mildly progressive activity. Therefore, possible degenerative change was considered first, as shown in Figure 3. However, progressive elevation of the tumor marker CA153 to over 130IU/mL was noted. Under an impression of distal metastases, F\textsuperscript{18} FDG PET/CT was arranged. Typically, multiple high-grade F\textsuperscript{18} FDG avid osteolytic bony metastases in the spine, pelvis and proximal long bones were seen, as shown in Figure 4. Magnetic resonance imaging also demonstrated distal bony metastases. Due to severe pathologic fractures,
Discordant findings between F18 FDG PET/CT imaging and bone scan

Figure 1. Two MDP skeletal scintigraphies were performed in early March and July. Visualized activity in both soft tissue and kidneys did not support the diagnosis of the super scan. Initial skeletal imaging in March revealed tiny spot activity in the right anterior aspect of the sixth and fourth ribs, heterogeneous spinal activity and extraosseous tumor activity in the right lower lobe of the lung. The second skeletal imaging in July showed diffusely heterogeneous increased MDP activity in bilateral proximal humerus, femur and sacroiliac joint. Although a progressive change in the MDP scintigraphic pattern was seen, less convincing evidence of typical multiple bony metastases was demonstrated.

Figure 2. FDG PET/CT was performed later in March due to restaging of lung adenocarcinoma. Unfortunately, a large high-grade FDG avid pulmonary mass with central necrosis, conglomerated bilateral mediastinal supraclavicle nodal activity, right pleural effusion and extremely disseminated heterogeneous nest-like high-grade FDG avid neoplasm metastatic foci within the narrow cavity of the spine, pelvis, rib cage and bilateral proximal long bones were seen on FDG PET/CT. Stage IV disease and poor prognosis were indicated. However, no evidence of hepatic metastasis was demonstrated by FDG PET/CT at this time.
Figure 3. Anterior and posterior views of skeletal scintigraphy in: (A) 2005; (B) 2006. Progressively heterogeneous MDP activity in the posterior aspect of L2 (arrow) and faint activity in L3 were seen between serial annual skeletal scintigraphies. However, no overt evidence of abnormal MDP activity in the rest of the skeletal system was noted. Based on one spinal hot lesion and elevation of serum CA153, FDG PET/CT was arranged for further evaluation.

Figure 4. (A) Magnetic resonance imaging (MRI). (B) FDG PET/CT. An L2 pathologic compression fracture (thin arrows) is demonstrated on MRI and FDG PET/CT. Multiple vertebral bony metastases (thick arrows) in the T/L spine and sacrum are also seen on MRI and FDG PET/CT, but are discordant with the findings of serial skeletal scintigraphy. Diagnosis of osteolytic bone metastases is favored.
she received surgical fixation. Final pathology showed bony metastasis of breast cancer (Figure 5).

**DISCUSSION**

High blood flow, certain adhesive molecules of tumors and a large repository of immobilized growth factors, including transforming growth factor-β, insulin-like growth factor I and II, fibroblast growth factors, platelet-derived growth factors, bone morphogenetic proteins and calcium, together, result in bone becoming the preferred site of metastases [3]. These growth factors, which are released and activated during bone resorption, provide a fertile ground in which tumor cells can grow. Stephan Paget first proposed the “seed-and-soil hypothesis” to explain the mechanism of bone metastasis in 1889, and animal models of bone metastasis support this hypothesis [1]. During normal bone turnover, there is a balanced remodeling sequence: osteoclasts resorb bone first and then osteoblasts form bone at the same site. Osteoclasts arise from precursor cells in the monocyte-macrophage lineage [6], and these differentiate into inactive osteoclasts. Expression of receptor activator of nuclear factor-κB ligand (RANKL) and macrophage colony stimulating factor by stroma cells or osteoblasts plays a critical role in the maturation of osteoclasts.

Most osteotropic factors, such as parathyroid hormone, 1,25-dihydroxyvitamin D3 and prostaglandins, induce the formation of osteoclasts by increasing the expression of RANKL on marrow stroma cells and osteoblasts, rather than by acting directly on osteoclast precursors [7,8]. The ratio of RANKL to osteoprotegerin regulates the formation and activity of osteoclasts. Osteoclasts resorb bone by secreting proteases that dissolve the matrix and produce acid that releases bone mineral into the extracellular space under the ruffled border of the plasma membrane of osteoclasts, which faces bone and is the resorbing organelle of the cell. Osteoblasts, the bone-forming cells, arise from mesenchymal stem cells, which form

*Figure 5. Pathology shows: (A) infiltrative ductal carcinoma of the breast; (B, C) malignant bony metastasis from bony fragment after fixation of pathologic fracture. [Figures provided by United City Hospital, Kaohsiung, Taiwan.]*
osteoblasts, adipocytes and muscle cells. CBFA1 (core-binding factor α1) is a critical factor for the differentiation of osteoblasts, and many growth factors can enhance the maturation of these cells. However, the differentiation of osteoblasts is less well understood than that of osteoclasts.

We are familiar with purely osteolytic bone destructive metastasis in multiple myelomas, due to osteolytic dysfunction with unknown etiology. However, overproduction of urokinase-type plasminogen activator (u-PA) by prostate-cancer cells increases bone metastasis [9]. Prostate cancer cells also release prostate-specific antigen and kallikrein, a serine protease, which can cleave parathyroid hormone (PTH)-related peptide, resulting in block of tumor-induced bone resorption [3]. Kallikrein may also activate osteoblast growth factors. Bone metastases from prostate cancer are predominantly osteoblastic, with increased numbers of irregular bone trabeculae [10].

In osteolytic metastases, the destruction of bone is mediated by osteoclasts rather than tumor cells [11,12]. However, the factors responsible for the activation of osteoclasts vary depending on the tumor. Several osteoclastogenic factors have been implicated in the increased activity of osteoclasts, including interleukin-1, interleukin-6, macrophage inflammatory protein 1α and RANKL. In the vicious cycle of osteolytic metastasis, especially in breast cancer, tumor cells secrete PTH-related peptide as the primary stimulator of osteoclastogenesis. In addition, tumor cells produce other factors that increase the formation of osteoclasts, including interleukin-6, prostaglandin E2, tumor necrosis factor and macrophage colony-stimulating factor. These factors increase the expression of receptor activator of RANKL, which acts directly on osteoclast precursors to induce the formation of osteoclasts and bone resorption.

In Case 2, there was progressive Tc\textsuperscript{99m} MDP accumulation in L2, probably related to osteoblastic remodeling after pathologic fracture. However, the other multiple high-grade F\textsuperscript{18} FDG avid osteolytic metastases in the T/L spines and pelvis, observed by magnetic resonance imaging and F\textsuperscript{18} FDG PET/CT, are not consistent with Tc\textsuperscript{99m} MDP skeletal scintigraphy for osteoblastic activity. Distal marrow/bone metastases of solid malignant neoplasms, such as those of breast cancer/lung cancer, have variable patterns of osteoblastic/osteolytic activity. Therefore, monitoring bony metastases should be based on multiple imaging modalities, in addition to Tc\textsuperscript{99m} MDP skeletal scintigraphy (which was the only modality used traditionally).

In Case 1, the patient with lung adenocarcinoma, extremely discordant imaging results were found among the osteoblastic activity detected by Tc\textsuperscript{99m} MDP skeletal scintigraphy, osteolytic activity detected by skeletal CT and marrow activity detected by F\textsuperscript{18} FDG PET. Based on this phenomenon, we considered the case to be one of diffusely high-grade FDG avid neoplasm occupying the marrow, but not evoking an effect on osteocytes. Homogeneously reactive marrow activity post chemotherapy seems less likely. Unfortunately, this finding is consistent with poor prognosis [13], despite shrinkage of tumor size after radiation therapy. F\textsuperscript{18} FDG PET/CT should always be employed to detect marrow/bony metastases in detail, following screening studies using Tc\textsuperscript{99m} MDP skeletal scintigraphy.

REFERENCES

傳統上釘 99m 甲基雙磷酸鹽骨骼造影提供高靈敏度偵測骨轉移，尤其在乳、肺癌的診斷與追蹤。近年來，氟化去氧葡萄糖正子電腦斷層造影根據腫瘤細胞葡萄糖代謝，在腫瘤學上，成為描述腫瘤生長增生及轉移很重要的影像。一般而言，對乳、肺癌骨轉移，甲基雙磷酸鹽骨骼造影與氟化去氧葡萄糖正子電腦斷層造影皆有一致性結果。然而一年間連續三百名正子造影受檢者中，兩名嚴重乳、肺癌患出現兩種造影極度不一致判讀，即甲基雙磷酸鹽骨骼造影呈現無轉移所造成之骨再生活度，但氟化去氧葡萄糖正子電腦斷層造影卻呈現簡易性高糖質吸收骨髓浸潤或蝕骨作用，因此診斷為第四期腫瘤轉移。由於腫瘤是基因變異疾病，同為乳、肺癌仍可呈現不同蛋白質體表現，本文將根據文獻回顧，討論兩種影像差異因素，然而氟化去氧葡萄糖正子電腦斷層造影在腫瘤追蹤是近代非常重要的影像診斷方法。

關鍵詞：氟化去氧葡萄糖正子電腦斷層造影，骨轉移，甲基雙磷酸鹽骨骼造影

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