Nuclear medicine in myeloma: the state of the science and emerging trends

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Abstract

We present the different imaging modalities in relation to myeloma, ranging from the time tested X-ray radiography to the newer promising methods of fluorine-18 fluorodesoxyglucose-positron emission tomography (^{18}F-FDG-PET) and technetium-99m methoxy isobutyl isonitrite (^{99m}Tc-MIBI) scintigraphy. A small discussion regarding newer methods such as fluoride-18 positron emission tomography (^{18}F-PET), fluorine-18-fluoro-deoxy-L-thymidine positron emission tomography (^{18}F-FLT PET), carbon-11 methionine positron emission tomography (^{11}C-methionine PET) and the tritiated thymidine labeling index is also included. They have different mechanisms of tracer uptake enabling the visualization of the spectrum of the disease manifestations ranging from osteoblastic to osteolytic lesions, and also the study of the metabolic status, proliferative and protein activity, in skeletal and in extra-skeletal sites.

Introduction

Myeloma, more often referred to as 'multiple' myeloma (MM) owing to its involvement of multiple skeletal sites, makes up about 10% of all hematological malignancies [1] and the most common primary malignancy of the bone [2].

The spectrum of myeloma ranges from the innocuous monoclonal gammapathy of unknown significance (MGUS), at the mildest end of the spectrum, followed by smoldering myeloma (SM) which is intermediate between MGUS and full blown MM, to the highly lethal plasma cell leukemia. There are also variants such as solitary plasmacytoma and extra-skeletal plasmacytoma.

The current staging and treatment decisions give a high weightage to skeletal radiography. Skeletal radiography is the current gold-standard against which emerging methods will be compared. However, since the sensitivity for detecting lytic bone lesions by X-ray radiography is rather low, more sensitive methods are applied with an intention to reduce the risk of under-staging disease, and hence the risk of under-treatment. Imaging methods can more accurately stage and classify patients within the myeloma spectrum and hence enable their confident management.

Discussion

The monoclonal gammapathy of unknown significance (MGUS) and smoldering myeloma (SM) are usually detected as incidental findings in blood investigations of older individuals, whereas bone pain, fatigue and renal failure in the elderly would lead to more specific tests for multiple myeloma (MM).

Outside clinical trial protocols, the current standard of care for MGUS and SM includes observation and close follow-up respectively. However, the standard of care for MM includes chemotherapy and bone marrow transplantation [1].

The International Myeloma Working Group in 2002 devised a set of guidelines in classifying patients within the myeloma spectrum. The guidelines state the presence of skeletal lytic lesions on X-ray skeletal survey as one of the criteria for a patient to be classified as symptomatic MM patient. In other words, without end organ damage including bone lesions on X-ray survey, a patient would possibly be classified into MGUS or SM, rather than MM [3].

The X-ray survey's main limitation is that approximately 50% bone destruction must occur before there is any radiographically visible evidence of a bone lesion [4]. This fact implies an inherent risk of under-staging with X-ray radiographic survey, the current gold-standard of imaging in MM. Moreover, radiographic changes are not reliable as indicators of prognosis because they are not easy to quantify. X-ray imaging also cannot pick up lesions confined to the marrow [5].

Computed tomography (CT) scans basically being an augmented form of X-ray imaging also suffer from some of the same disadvantages as X-ray skeletal survey, such as the requirement of significant bone erosion to occur before a lesion can be visualized [6]. The CT scans have the ability to pick up certain lesions such as soft tissue lesions and diffuse osteopenia with better sensitivity compared to the X-ray radiography [6]. The cost and the limitations in the use of CT-scans can make it prohibitive in comparison to X-ray skeletal survey [7].

Magnetic resonance imaging (MRI) can pick up intramedullary lesions before there is any cortical erosion or reactive process. On T1 weighed MRI, marrow lesions appear as areas of reduced signal intensity due to the replacement of fat in the marrow by proliferating plasma cells. Hence, MRI has a good sensitivity for assessment of bone marrow involvement, especially in the spine and pelvis of the bone marrow and provides a good assessment of tumor burden. But the field of view of MRI excludes regions with high amount of red marrow such as the skull, sternum, ribs and long bones which may frequently be infiltrated by malignant plasma cells. So, MRI if used alone would under-stage 10% of MM patients compared to whole body X-ray survey. Moreover, MRI findings are not specific to MM, as MRI does not differentiate disease process from drug induced reactive marrow. There is also an age-dependent variability due to the

fact that younger patients tend to have highly cellular marrow [6, 8-10].

As early as in the 1980s, there were studies evaluating nuclear medicine techniques in MM such as the technetium-99m methyl diphosphonate (^{99m}Tc-MDP) bone scan with a half life of 6h and the critical organ for absorbed radiation dose being the urinary bladder and gallium-67-citrate (^{67}Ga-C) scan with $T_{1/2}$ of 78h and large intestine being the critical organ. Not only were these techniques evaluated for disease detection, but also studied the inter-relationships of scan patterns with disease-activity and prognosis. The ^{67}Ga-C scintigraphy showed a high gallium-to-bone ratio when coupled with a normal or slightly abnormal scan, while ^{99m}Tc-MDP bone scan indicated a fulminant process. Thus, it was suggested that sub-populations of MM patients needed localized radiation to treat these aggressive foci of disease [4, 11].

The ^{99m}Tc-MDP bone scan may show lytic lesions as 'cold lesions' which are vulnerable to be overlooked. The ^{99m}Tc-MDP scan is not preferred for lytic bone lesions as it has half the sensitivity (Fig. 1) of X-ray radiography and also cannot pick up lesions confined to the marrow [4].

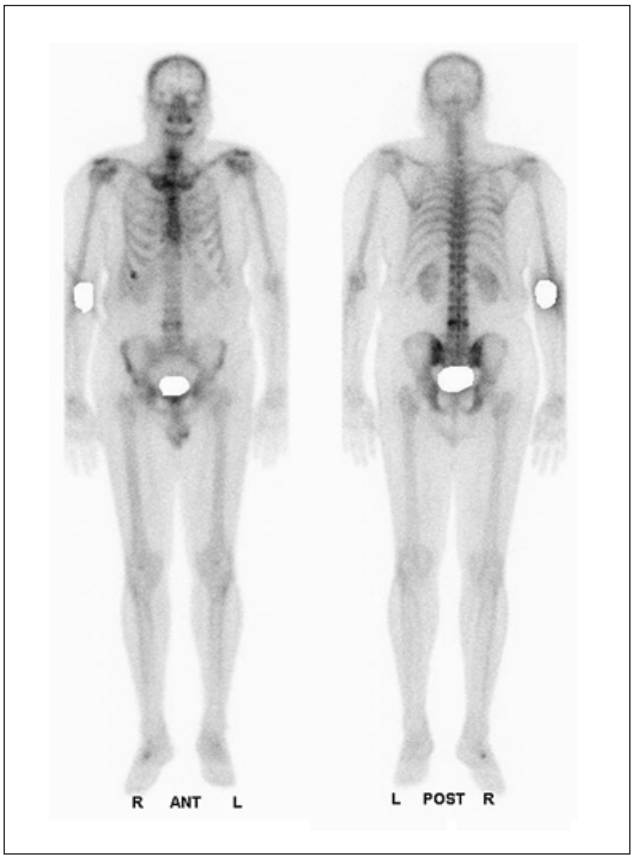

Figure 1. Anterior and posterior whole body ^{99m}Tc-MDP bone scan in a patient with MM demonstrating the lack of visualization of osteolytic lesions. However, an area of increased uptake in the lumbar region (L-4) corresponds to vertebral compression collapse.

Fluorine-18 fluoro desoxyglucose-positron emission tomography (^{18}F-FDG-PET) can investigate both soft tissue and skeletal lesions (Fig. 2). The $T_{1/2}$ of ^{18}F is 110min and whole body effective dose from a standard pet scan is 1.6mSv. Another 2mSv (200mrem) may be due to low dose whole body CT scan performed for every PET/CT study. This procedure is capable of providing functional and morphological involvement and has a greater avidity to lytic lesions due to their higher glycolytic rate and a relative hypoxic environment compared to sclerotic lesions [8, 12, 13].

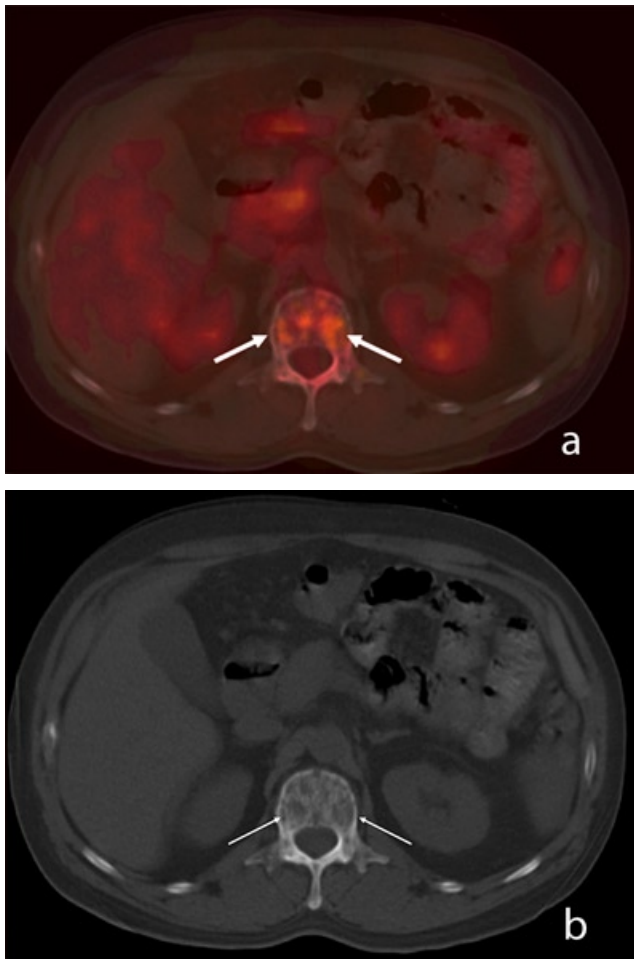

Figure 2. Axial 18F-FDG-PET/CT fusion slice (**a**) showing lytic lesions in the vertebral body with increased avidity. The same lytic lesions visualized on an axial conventional CT scan (**b**).

The ^{18}F-FDG-PET scan is equivalent to MRI in the evaluation of spine and pelvic lesions, superior to MRI in whole body analysis and can provide a more accurate assessment of appendicular skeletal involvement [8]. FDG-PET or MRI when performed in solitary plasmacytomas can upstage a proportion of patients due to the chance they have to detect bone marrow or multiple vertebral involvements [14]. The International Myeloma Foundation's 'Durie-Salmon Plus' staging system which has integrated ^{18}F-FDG-PET and MRI provides an equal relevance to both methods for upstaging a proportion of patients and hence influence their clinical management [15]. In patients with MM, the detection of abnormal uptake on follow-up studies with ^{18}F-FDG-PET after stem cell transplantation confers a poor prognosis [16].

Technetium-99m methyl isobutyl isonitrile (^{99m}Tc-MIBI) is a rapid technique for whole body evaluation, a good alternative to ^{18}F-FDG-PET scan, especially when PET facility is unavailable [8]. The maximum radiation absorbed dose is to the large intestine. The ^{99m}Tc-MIBI scan findings correlate well with disease activity as determined by the biochemical markers such as serum β-2-microglobulin and serum albumin. These markers have been designated by the interna-

tional staging system to be dominant predictive markers [17]. Focal ^{99m}Tc-MIBI uptake with moderate or without or diffuse uptake and in the absence of inflammation or other pathology, rules out MGUS/SM and confers a poorer prognosis [18]. In other words, focal ^{99m}Tc-MIBI uptake is highly indicative of MM. In case of treated patients with MM, the presence of focal or intense diffuse tracer uptake suggests active and advancing disease, whereas a negative scan indicates remission [4].

The sensitivity of ^{99m}Tc MIBI scans is better than that of X-ray, at 77% vs. 45%. Forty percent of patients evaluated with ^{99m}Tc-MIBI at first diagnosis were upstaged because this test has a high sensitivity and also increases the number of detected lesions per patient. Scintigraphy with ^{99m}Tc-MIBI has been recently reported as more specific than conventional X-rays in detecting active focal lesions in MM patients [18, 19].

Since ^{99m}Tc-MIBI is a substrate for the p-glycoprotein (p-gp) efflux pump, its rate of washout from the bone marrow of those patients who are over-expressing these transport proteins increases over time. We know that p-gp is one of the primary mechanisms for multiple drug resistance, even in MM, so, ^{99m}Tc MIBI is feasible for use as an index of p-gp over-expression and as a predictor of response to subsequent chemotherapy [20]. A fast clearance of ^{99m}Tc-MIBI from the bone marrow of MM patients is associated with poor response to chemotherapy, but a slow clearance of tracer does not necessarily predict prompt response to chemotherapy, owing probably to multiple mechanisms of drug resistance [20-22]. Multi-drug resistance is characterized by fast tracer washout, and not by decreased uptake. Hence, when image acquisition is done as early as 10min after ^{99m}Tc-MIBI injection, the diagnostic accuracy of ^{99m}Tc-MIBI scan is not significantly affected by p-gp over-expression and hence multidrug resistant MM patients can also be monitored with confidence [5].

Zoledronic acid is a drug used in the prophylaxis against skeletal-related events in MM patients as well as in metastatic bone disease from other cancers. Zoledronic acid induces jaw necrosis as an adverse effect and this may be seen in up to 15% of MM patients who receive zoledronic acid for about 36 months. While ^{99m}Tc-MDP may be used in the early detection of jaw necrosis in patients of metastatic bone disease from other cancers, in case of MM, the use of ^{99m}Tc-MIBI and ^{18}F-FDG is recommended [23].

A newer method which uses fluoride-18 is fluoride-18 positron emission tomography (^{18}F-PET). It has an uptake mechanism similar to that of ^{99m}Tc-MDP. In the bone extracellular-fluid, the fluoride ions are exchanged with hydroxyl groups in hydroxyapatite crystals of the bone to form fluoroapatite, which is deposited mainly at the bone surface, especially where bone modeling and turnover are at their greatest. Bone uptake of ^{18}F-fluoride is two-fold higher and shows faster blood clearance resulting in better target to background ratio than that of ^{99m}Tc-MDP. This radiopharmaceutical can detect the minimal osteoblastic activity accompanying a lytic lesion, which may not be identifiable on a ^{99m}Tc-MDP bone scan [6, 24, 25]. A study which included 44 patients with various malignancies, of which four had MM showed that ^{18}F-PET/CT is both sensitive and specific for the detection of lytic and sclerotic malignant bone lesions. Lytic lesions in MM demonstrated increased uptake at the margins of the lesions [6].

Fluorine-18-fluoro-deoxy-L-thymidine (^{18}F-FLT) PET is another novel technique designed to analyze the bone marrow component in hematological disorders. Conventional bone marrow biopsy and microscopy would need specific staining procedures to demonstrate the number of abnormal cycling cells. Moreover, bone marrow sampling is an invasive procedure and only a small proportion of the total bone marrow content is investigated, which makes it vulnerable for sampling errors. Fluoro-18-FLT is incorporated into DNA in the place of thymidine and its uptake is hence related to the rate of DNA synthesis which is a surrogate for proliferation rate. Furthermore, ^{18}F-FLT has adequate specificity to detect the uptake by proliferating cells and this confers a great advantage over ^{18}F-FDG-PET which relies on metabolic activity rather than proliferating activity [25]. Eighteen patients of various bone marrow malignancies, including two MM patients, were studied for ^{18}F-FLT uptake assessment and it was shown that in some hematological disorders such as myelodysplatic syndrome and myeloproliferative disorders, marrow ^{18}F-FLT uptake was higher while in MM cases, there was low uptake in the affected areas, due to the activity being predominantly lytic. Other conditions with decreased marrow cell turnover such as myelofibrosis and aplastic anemia also showed decreased uptake of ^{18}F-FLT [25]. So, when used in MM, ^{18}F-FLT may help in differentiating old, inactive lytic lesions from foci of rapidly proliferating MM cells which could be potential targets for local radiation treatment. Also ^{18}F-FLT may show a high marrow uptake comparable to that of myeloproliferative disorders in case of progression of MM to plasma cell leukemia which is the most aggressive extreme of the myeloma spectrum.

Carbon-11-methionine PET is another new method in which this radiolabelled amino acid is rapidly taken up and incorporated into newly synthesized immunoglobulins. This method may provide an estimate of tumor-burden and may help in locating more active medullary and extramedullary aggregates of plasma-cells which are actively synthesizing immunoglobulins. It is suggested that ^{11}C-methionine positive lesions without structural changes of cancellous bone might represent early manifestation of MM in which lytic changes are yet to develop. Extramedullary MM was also detected and localized with high sensitivity with ^{11}C-methionine PET/CT. A lack of metabolic ^{11}C-methionine uptake in CT-proven osteolytic lesions in treated patients may be interpreted as indicative of macroscopically inactive disease. The detection and localization of active MM lesions with ^{11}C-methionine may be helpful in estimating the burden of MM mass and also help in initiation of local radiation therapy [26]. A major drawback of ^{11}C tagged molecules is that ^{11}C is a cyclotron produced radionuclide which has a short half life of only 20min [27].

Tritiated thymidine is used as a labeling index in MM. Normal subjects show a median proportion of 1% cycling cells. With progressive disease, the labeling index increases, suggesting a more proliferative phenotype. Though the labeling index has important prognostic significance as patients with more than 1% bone marrow cells in S phase have worse prognosis, the lack of standardized reproducible methods to measure labeling index has at present limited its use as a prognostic marker [28].

In conclusion, for the diagnosis of MM patients, the ^{99m}Tc-MDP did not prove to be better than the much easier and simpler X-ray survey. However, better imaging modalities

are now used, like ^{99m}Tc MIBI doubling up as an indicator of multiple-drug-resistance and the ^{18}F-FDG-PET proving to be more accurate in disease quantifying and staging. Other newer pet methods using various radiopharmaceuticals have their own spectra of abilities in the diagnostic imaging of MM, such as the fluoride-18-PET having an ability of early detection of lytic and sclerotic lesions, the ^{18}F-FLT PET having the ability to image proliferating cells and ^{11}C-Methionine with the ability to detect areas of higher disease burden, all prior to the manifestation of X-ray changes. We should also mention another nuclear medicine technique using tritiated thymidine for a labeling index which offers prognostic information.

The authors declare that they have no conflicts of interest

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"Happiness is multiplied by division. Wealth is divided by division"

Ph. C. Grammaticos