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REVIEW

MRI and PET of bone marrow in lymphoproliferative diseases

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Abstract

In lymphoproliferative diseases, bone marrow involvement (BMI) is an essential parameter influencing staging, prognosis and treatment. In addition to pathological analysis of blind bone marrow biopsy, MRI and PET can help to (a) estimate initial BMI and assess the stage of disease, (b) indicate prognosis and (c) assess response to treatment. Regarding diagnosis, the MR patterns of focal and diffuse BMI will be reviewed, and compared to the MR appearance of normal marrow. The technique and the results of dynamic contrast-enhanced (DCE) MRI regarding normal and tumoral marrow will be detailed. An approach of the perfusion parameters of normal and tumoral marrow will thus be presented. The changes of MR patterns linked to BMI will be described after treatment and correlated to the response to treatment of patients with lymphoma and myeloma. Although ^{18}F-FDG–PET has been extensively studied in the management of lymphoma, few studies have examined its value for assessing BMI. ^{18}F-FDG–PET seems to be accurate for this purpose in patients with lymphoma and myeloma. The limitations of MR imaging and ^{18}F-FDG–PET will be detailed. In conclusion, MRI and PET imaging including the functional approach of perfusion by DCE-MR imaging and glucose uptake by ^{18}F-FDG–PET can contribute to the management of patients with lymphoproliferative diseases by its ability to analyse BMI.

Keywords: *Magnetic resonance imaging; bone marrow; lymphoproliferative disorders; positron emission tomography.*

Introduction

Lymphoproliferative diseases encompass a spectrum of malignancies including lymphomas (Hodgkin's disease (HD) and non-Hodgkin lymphomas (NHL)) and plasma cell disorders such as myelomas and solitary plasmocytomas. All these malignant cell proliferations originate histologically from lymphocytes but differ by the degree of cell differentiation. Lymphoma cells are mostly of B lymphocyte origin, and myeloma cells derive from B lymphocytes, differentiated into plasmocytes. They also differ in terms of organ involvement and clinical course. Bone marrow involvement (BMI) and bone lesions represent the main clinical presentation of myeloma while lymph node involvement is the main presentation of lymphomas. In these lymphoid diseases, it is essential to assess whether BMI is present, whether it is focal or diffuse and also the bulk of the marrow involvement by the tumor. Assessment of BMI and the response to treatment of the marrow regions involved is needed for the choice of treatments, particularly in patients with myeloma. Functional imaging of bone marrow, namely bone marrow MRI and PET, plays an increasing role in this.

BMI in lymphoma

In the new WHO classification, HD has been thoroughly defined, and includes both mixed cellularity and nodular

sclerosis subtypes. The latter is most common in developed countries[1]. The pathological classification of NHL is more complex. The WHO classification is now widely accepted[1]. The so-called low-grade NHL, mostly follicular and marginal zone lymphomas, have a prolonged clinical course but cure is not usually achieved unless the disease is strictly localised. By contrast, aggressive lymphoma, mostly diffuse large B-cell, mantle cell, and peripheral T-cell lymphomas are often rapidly progressive diseases characterised by high proliferation rates. Treatment of aggressive NHL with combined chemotherapies results in long-term cure in a large proportion of patients. Before treatment, five factors have been shown to be independently significant for predicting outcome in patients with aggressive NHL: age ($\leq$60 years vs. $>$60 years), tumor stage (Ann Arbor stage I or II vs. stage III or IV), number of extranodal sites of disease ($<$1 vs. $>$1), performance status (0 or 1 vs. $\geq$2), and serum lacticodehydrogenase level (normal vs. raised level). These five factors are used to design a model to predict an individual patient's risk of death: the international progressive index[2]. For advanced HD, seven adverse factors, also including Ann Arbor stages III or IV, have been identified[3]. A bulky mass, larger than 10 cm in diameter, may also confer an increased risk of disease progression.

For HD and NHL, BMI affects the tumor stage and the prognosis, as it is a criterion for Ann Arbor stage IV. Blind bone marrow biopsy from the iliac crest represents the established method to detect BMI. BMI is frequent in so-called low-grade NHL whereas it occurs in about 20% of aggressive NHL, and less than 20% in HD[4]. The accuracy of a marrow biopsy is confined to the sampled site, and focal involvement elsewhere can be missed. Biopsies may falsely underestimate or overestimate marrow tumor burden because lymphomatous BMI is often heterogeneous: performing posterior iliac crest biopsies bilaterally has increased the diagnostic yield in both HD and NHL[4].

BMI in myeloma

Proliferation of monoclonal immunoglobulin-secreting plasmocytes most often occurs in the bone marrow. A monoclonal protein is generally detected in the blood and/or urine. A clinical staging system to provide prognosis and guide treatment was developed by Salmon and Durie based on indirect assessment of tumor mass by blood and urine parameters, and also the presence of osteolysis on conventional radiographs. This staging system helps distinguish patients with stage I, low-tumor-burden disease, who do not usually require treatment until one tumoral lesion is demonstrated. Discovery of at least two unequivocal lytic bone lesions indicates stage III myeloma for which treatment is indicated.

Estimate of tumor burden is usually based on the Salmon and Durie staging system. Bone marrow biopsies or aspirates may underestimate or overestimate BMI because myelomatous BMI is often heterogeneous. However, conventional radiographs used in the Salmon and Durie staging system underestimate myelomatous focal lesions particularly of the axial skeleton[5]. In patients with myeloma, the presence of diffuse osteolysis may be due either to diffuse BMI or osteoporotic changes.

MRI of BMI

The design of imaging sequences and the choice of anatomical regions investigated will depend on the role assigned to MRI for a given patient. In addition to bone marrow biopsy, MRI can help to (a) estimate initial BMI and assess the stage of disease, (b) indicate prognosis and (c) assess response to treatment.

Imaging sequences

T1-weighted spin echo (SE) sequences will assess fat distribution within the bone marrow, which will be compared to the normal age-related distribution of fatty marrow. T2-weighted SE sequences must be combined with selective fat suppression for increased detection of focal lesions. Nullation of the fat signal can also be obtained with short TI inversion-recovery (STIR) sequences. Visual comparison of T1 and fat-suppressed T2 bone marrow signal intensity will detect focal BMI, and will sometimes suspect diffuse BMI. For these latter purposes, gradient echo sequences are not usually performed because the bone marrow signal intensity will be highly dependent on the chosen echo time. Gadolinium (Gd) contrast injection is not useful in detecting focal BMI but can estimate bone marrow perfusion. In order to perform a dynamic study of the bone marrow enhancement during 2–3 min, a 1-s T1-weighted turbo fast low-angle shot (FLASH) sequence is repeated 30 times or more after Gd bolus injection in our institution[6]. Parameters of bone marrow perfusion can then be evaluated from enhancement time curves[7].

Pre-treatment MRI

MR before treatment assesses focal and diffuse BMI. The pattern of BMI includes[6–8]:

- decreased T1 signal intensity due to decreased fat content;
- increased T2 signal intensity due to increased number of tumor cells;
- increased perfusion (particularly high slope), high level of maximum enhancement, and pronounced washout;
- soft tissue involvement and particularly epidural mass.

Post-treatment MRI

In responding patients, MR findings after treatment include[7–10]:

- increased T1 signal intensity of involved regions;
- decreased T2 signal intensity;
- decreased perfusion of involved region;
- decreased volume of the soft tissue involvement, when initially present.

MR limitations

The MR pattern of focal BMI is not specific. The MR pattern of diffuse BMI can be seen in non-neoplastic marrow disorders, particularly when marrow hyperplasia is present, i.e. in patients receiving granulocyte-colony stimulating factors or patients with chronic anemia.

MRI sometimes remains normal in patients with biopsy-proved BMI. When the ratio of fat and non-fat cells in the bone marrow is not altered or only slightly altered, the T1 and T2 signal intensity of the bone marrow remains normal. Similarly, the perfusion can be found to be normal when bone marrow neovascularisation is not increased or only slightly increased[7].

The distribution of fat and non-fat marrow predominantly depends on ageing in normal subjects. On T1-weighted images, the detection of focal lesions can be difficult in the case of a heterogeneous marrow distribution, which can frequently be seen in normal subjects[8]. In such cases, fat-suppressed T2 or STIR images will be helpful to demonstrate focal lesions with high T2 signal intensity and generally well demarcated contours.

At the beginning of diffuse tumor infiltration, tumor cells arrange themselves so as not to displace the bone marrow fat cells, the amount of which remains normal. Then diffuse replacement of normal marrow with tumor cells triggers a decrease of marrow T1 signal intensity. The marrow T1 signal intensity can be homogeneously decreased, but diffuse involvement can also be characterised by a heterogeneous decrease in T1 signal intensity, due to the presence of multiple tiny areas of marrow replacement, known as the variegated or 'salt-and-pepper' pattern[8]. The differentiation of diffuse tumor involvement from the variable patterns of normal bone marrow is difficult and uncertain. The frequency of a normal MR bone marrow pattern on SE T1- and T2-weighted images is high in patients with early stages of BMI by lymphoproliferative diseases, and reaches 24% in stage III multiple myeloma[11,12]. The inter-observer reproducibility in determining diffuse involvement based on T1-weighted images is poor[8]. Different MR techniques have hence been proposed to increase the capabilities of MR imaging to detect and quantify bone marrow diffuse involvement, including chemical-shift imaging, bulk T1 relaxation time measurement, and H^1 spectroscopy[7,8]. All these methods consist of obtaining a fat content or a water/fat fraction measurement. These quantitative measurements can overcome the inter-observer variability in visual analysis of SE images. However, due to the large spectrum of normal-appearing bone marrow, it is not surprising that these quantitative measurements do not increase the capability of MR imaging to detect diffuse marrow involvement. Recent studies have shown that plasma cells isolated from the bone marrow of patients with myeloma had angiogenic potential[13]. It has also been shown that the progression of plasma cell tumors is correlated with an increase of bone marrow vascularisation[13]. Similarly, other lymproliferative diseases such as B-NHL are also capable of inducing angiogenesis[14]. Dynamic contrast-enhanced (DCE) MR imaging can quantify the increased perfusion of the bone marrow in cases of diffuse BMI. When BMI increases, maximum enhancement, slope and washout markedly increase[7]. Decreased contrast enhancement after treatment can be seen in patients with a good response to treatment[7].

Normal MRI in patients with BMI can be seen particularly in patients with early stages of lymphoproliferative disease, such as low-grade NHL and stage I multiple myeloma[8,11].

The distribution of BMI parallels that of hematopoietic marrow including the spine and the pelvic girdle. The limited field of view of MR imaging does not allow the study of the entire bone marrow. However, new MR systems with several coils connected can allow whole spine and pelvic girdle examination for the measurement of the tumor mass.

PET of BMI

Increased glycolysis, a biochemical feature of malignant cells, explains ^{18}F-FDG uptake by lymphomatous masses in PET. ^{18}F-FDG–PET is an effective method of staging lymphoproliferative diseases. It is more sensitive in detecting extra-nodal disease including BMI than CT[15]. The uptake of ^{18}F-FDG appears to correlate with both the histological grade and the proliferation rate of malignant cells[16]. However, few studies have assessed the value of ^{18}F-FDG–PET in patients with BMI.

In lymphoma, ^{18}F-FDG–PET can identify BMI with an accuracy which could be at least as high as iliac crest biopsy[17]. In myeloma, ^{18}F-FDG–PET proved to be highly accurate in detecting focal and diffuse BMI[18].

^{18}F-FDG–PET allows whole-body imaging. However, ^{18}F-FDG–PET shares common limitations with MRI. The uptake of ^{18}F-FDG is not specific in focal or diffuse BMI. Uptake can be observed when marrow hyperplasia is present in patients receiving granulocyte-colony stimulating factors during treatment. Previous involved sites may appear as cold regions within hyperplastic bone

marrow with high FDG uptake. No uptake can be seen in patients with biopsy-proven BMI such as low-grade NHL. Accurate quantitative measurements of the uptake of ^{18}F-FDG are still difficult to obtain in routine clinical practice. Morphologic assessment of the tumor volume or anatomical delineation of BMI, such as soft tissue involvement, is not the scope of this functional imaging technique.

Staging, prognosis and response to treatment

Staging

All patients with newly diagnosed lymphoproliferative disease and where there is clinical suspicion of spine lesion must have MR examination in order to detect vertebral, epidural or paraspinal involvement. ^{18}F-FDG–PET contributes to the initial staging and follow-up (response to treatment) of patients with high-grade NHL and HD. In patients with multiple myeloma, it has been definitely established that more marrow lesions and more patients with BMI are detected with MRI than with conventional radiographs. Detection of focal lesions (by imaging) is part of the Salmon and Durie staging system used to assess the tumor mass and treatment: patients with stage I do not receive treatment unless more aggressive disease is demonstrated at imaging or follow-up.

Response to treatment

During treatment, MRI/PET follow-up studies may demonstrate no change, decreased tumor volume, decreased enhancement and T1/T2 signal changes, or decreased ^{18}F-FDG uptake. The MRI/PET changes reflect the bone marrow response to treatment.

Prognosis

Asymptomatic patients with stage I myeloma in whom relevant marrow abnormalities are detected by MRI have a shorter time lag before the onset of more aggressive disease than those with a normal MRI[11]. The risk of developing vertebral fractures in stage III patients during treatment increases with the extension of BMI at the initial MRI[12].

References

[1] Harris NL, Jaffe ES, Diebold J *et al*. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the clinical advisory committee meeting. J Clin Oncol 1999; 17: 3835–49.

[2] Shipp MA *et al*. The International non-Hodgkin's lymphoma prognostic factors projet. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 1993; 329: 987–94.

[3] Hasenclever D, Diehl V. The International Prognostic Factors Project on Advanced Hodgkin's Disease. A prognostic score for advanced Hodgkin's disease. N Engl J Med 1998; 339: 1506–14.

[4] Juneja SK, Wolff MM, Cooper IA. Value of bilateral bone marrow biopsy specimens in non-Hodgkin's lymphoma. J Clin Pathol 1990; 43: 630–2.

[5] Lecouvet FE, Malghem J, Michaux L, Maldague B, Ferrant A, Michaux J-L, Vande Berg BC. Skeletal survey in advanced multiple myeloma: radiographic versus MR imaging survey. Br J Haematol 1999; 106: 35–9.

[6] Rahmouni A, Divine M, Mathieu D *et al*. Detection of multiple myeloma involving the spine: efficacy of fat-suppression and contrast-enhanced MR imaging. AJR 1993; 160: 1049–52.

[7] Rahmouni A, Montazel J-L, Divine M *et al*. Dynamic Gadolinium-enhanced MR imaging of bone marrow with diffuse tumor infiltration in patients with lymphoproliferative diseases. Radiology 2003 (in press).

[8] Vande Berg BC, Lecouvet FE, Michaux L, Ferrant A, Maldague B, Malghem J. Magnetic resonance imaging of the bone marrow in hematological malignancies. Eur Radiol 1998; 87: 1335–44.

[9] Rahmouni A, Divine M, Mathieu D *et al*. MR appearance of multiple myeloma of the spine before and after treatment. AJR 1993; 160: 1053–7.

[10] Moulopoulos LA, Dimopoulos MA, Alexanian R *et al*. Multiple myeloma: MR patterns of response to treatment. Radiology 1994; 193: 441–6.

[11] Vande Berg BC, Lecouvet FE, Michaux L *et al*. Stage I multiple myeloma: value of MR imaging of the bone marrow in the determination of prognosis. Radiology 1996; 201: 243–6.

[12] Lecouvet FE, Vande Berg BC, Michaux L *et al*. Stage III multiple myeloma: clinical and prognostic value of spinal bone marrow MR imaging. Radiology 1998; 209: 653–60.

[13] Vacca A, Ribatti D, Presta M *et al*. Bone marrow neovascularization, plasma cell angiogenic potential, and matrix metalloproteinase-2 secretion parallel progression of human multiple myeloma. Blood 1999; 93: 3064–73.

[14] Vacca A, Ribatti D, Roncali L, Dammacco F. Angiogenesis in B cell lymphoproliferative diseases. Biological and clinical studies. Leuk Lymphoma 1995; 20: 27–38.

[15] Moog F, Bangerter M, Diederichs CG, Guhlmann A, Merkle E, Frickhofen N, Reske SN. Extranodal malignant lymphoma: detection with FDG PET versus CT. Radiology 1998; 206: 475–81.

[16] Lapela M, Leskinen S, Minn HRI. Increased glucose metabolism in untreated non-Hodgkin's lymphoma: a study with positron emission tomography and fluorine-18-fluorodeoxyglucose. Blood 1995; 86: 3522–7.

[17] Carr R, Barrington SF, O'Doherty MJ, Saunders CA, van der Walt J, Timothy AR. Detection of lymphoma in bone marrow by whole-body positron emission tomography. Blood 1998; 91: 3340–6.

[18] Schirrmeister H, Bommer M, Buck AK *et al*. Initial results in the assessment of multiple myeloma using 18F-FDG PET. Eur J Nucl Med Mol Imaging 2002; 29: 361–6.