UNIVERSITY OF MEDICINE AND PHARMACY CRAIOVA

DOCTORAL SCHOOL

PHD THESIS

– ABSTRACT –

ROLE OF RADIO-IMAGING EXAMINATION IN DIAGNOSIS AND EVALUATION OF BONE DETERMINATIONS IN MALIGNANT HEMOPATHIES

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I. INTRODUCTION

Bone determinations are common regardless of determinable neoplasia, skeletal involvement occurring in 30-70% of cases of malignancies, breast cancer being the primary cause of bone metastasis in women, in men being determined by prostate neoplasms.

The diagnosis and assessment of bone determinations are essential for optimal treatment of neoplasia. The purpose of radio-imagistic explorations is to identify the neoplastic bone damage as soon as possible to determine the stage of disease, to assess the presence of subsequent complications (including pathological fractures), to monitor response to treatment, and occasionally to guide the bone marrow biopsy for histological confirmation.

Hematologic malignancies as a whole are the fourth most common form of cancer in men and the third most common in women. By the age of 75 years, nearly 1 in 20 people will develop a hematologic malignancy. Neoplastic bone involvement caused by haematological malignancies is the result of hematogenous dissemination or the direct extension of the disease to adjacent soft tissues.

Radio-imagistic exploration plays an important role in staging malignant haemopathies, in monitoring response to treatment, relapse detection and evaluation of complications. Radio-imagistic investigations, in order to assess bone involvement, include conventional radiology, computer tomography exploration and magnetic resonance. Additionally nuclear imaging methods can be used - PET-CT and bone scintigraphy.

Conventional radiology is the imaging method of first choice in detecting bone anomalies in malignant hematopathies. However the radiographic features are nonspecific. Lesions may be solitary, or more frequently, polyostotic. They are primarily osteolytic, but can be sclerotic or mixed.

The advantage of computed tomography (CT) is its good anatomical resolution, soft tissue contrast and detailed morphology. CT is not a routine method in studying bone involvement, but they may be found incidentally, using bone window.

Magnetic resonance imaging (MRI) has a spatial resolution and a good contrast. It is an optimal imagistic method to assess both normal and pathological bone marrow.

II. LEVEL OF KNOWLEDGE

Bone tissue is a connective tissue characterized by stiffness, hardness, perfectly adapted to functions of support and resistance,with a regeneration and repair capacity [8]. Bone substance is presented in two forms - compact bone and cancellous bone [2,4,22,28]. Bone tissue is composed of bone matrix and cellular elements included in this matrix (osteoprogenitor cells, osteoblasts, osteocytes, osteoclasts and lining cells) [2,28]. Biologically, the bone is a plastic organ that is in constant motion, a result of its continual adaptation to different conditions in which is found [11,22,29].

The skeleton is the most frequent localization of determinations in many advanced forms of cancer and the metastasis of tumor cells in the bone matrix involves a complex cascade of events [15].

The objectives of radio-imagistic explorations in bone determination in malignant haemopathies are represented by: detection of tumoral lesions, lesions loco-regional or distant extension, the existence of modifications of the parenchymatous or cavitary organs, the existence of supra and subdiaphragmatic adenopathies, the imagistic staging of the hematological disease in order to establish treatment.

The radio-imagistic exploration plays an important role in staging malignant haemopathies, in monitoring the response to treatment, in detection of relapses and evaluating the complications. However, the role of medical imaging in evaluating the response to treatment is often limited and the sequential quantification of biological markers of the disease are sufficientin assessing the response to chemotherapy.

Malignant haemopathies are a heterogeneous group of diseases that have in common an abnormal proliferation of blood cells comprising lymphoma, leukemia and multiple myeloma.

Multiple myeloma is a neoplastic disease of B lymphocytic line, characterized by proliferation of malignant plasmocytes in the hematopoietic bone marrow [9,13,21,24,26] and represents 10% of haematological malignancies [5,18,23].

Malignant lymphoma includes non-Hodgkin lymphoma and Hodgkin's disease. NHL constitutes a heterogeneous group of neoplasia derived from a single cell type - lymphocytes – that has suffered a mutagenic transformation that gives it a high growth and survival degree compared with other blood cellular components [1,3, 12,14,17,19,30]. Hodgkin's disease is a malignant proliferation of lymphoid tissue whose diagnosis is based on a strict morphopathological criteria: the presence of Reed-Sternberg cells, on the background of a polymorphous lymphoid cellular infiltrate [6,7,10,16,25].

Leukemias are diseases characterized by neoplastic proliferation of hematopoietic tissue with the development into the blood of numerous incompletely differentiated cells and the infiltration by these cells of various organs [20,27].

Any of these three neoplasic haematological entities can determine the emergence of modifications in bone marrow, modifications that can be correctly identified and assessed using radio-imagistic exploration.

III. PERSONAL CONTRIBUTION

1. The objectives of the personal study

The purpose of this paper is to assess the role of radio-imagistic exploration techniques in the diagnosis and assessement of bone determinations in malignant haemopathies. This objective required the study of elementary radio-imagistic modifications, both general and applied to each type of haematological malignancy infiltrating the bone structures.

2. Materials and methods

The paper comprises a retrospective and prospective study, which includes a number of 188 patients admitted and treated between 2010-2014 in Colţea Clinical Hospital, Bucharest.

The prospective study required the elaboration of an examination protocol, depending on the clinical suspicion of bone damage by hematologic neoplasia. Also, there have been instances in which the malignant haemopathy was suspected, due to the radio-imagistic aspect of different bone structures. Subsequently, it was necessary corroborating the radio-imagistic explorations results with the clinico-biological data.

The retrospective study concerns the radio-imagistic assessment of the bone lesions after applying the appropriate treatment to each type of malignant haemopathy.

In this group of 188 cases, multiple myeloma sums 100 subjects with this neoplasia, leukemia include a total of 24 cases, and malignant lymphoma contribute with a total of 64 patients.

Of the 188 cases studied in this paper, the sex distribution showed a slight predominance of females (51.06%) than male. However, the predominance of the female sex is not valid in each group of the studied group, this being met only in cases of multiple myeloma, where a total of 44 patients are men, the remainder being females. In case of lymphoma is observed a predominance of male, with a rate of male / female of 1.3, and the group of cases of leukemia showed a gender equality of patients suffering from this disease.

Distribution by age in the analysed group showed that the highest frequency of occurrence of bone determinations in malignant haemopathies, regardless of the patient's sex, is in the 60-69 age decades (29.78%) and 70-79 decades (26.59%). In these dominant age groups, there was a slightly higher incidence in females compared to males.

3. Radio-imaging examination techniques used for diagnosis and assessment of bone determinations in malignant hemopathies

In the study group, of the 188 cases of malignant hemopathies with bone determinations, 165 were conventionally radiologic explored, computed tomography was used in a number of 103 cases, and magnetic resonance imaging was used in 180 patients.

Computer tomography exploration was used as a first choice of radio-imagistic method in 5.82% cases, mainly in patients with lymphoma, where it was necessary staging the disease or where MRI exploration was not possible.

MRI examinations were performed in 163 patients who were diagnosed with a form of malignant haematological disease, the remaining 19 being subsequently diagnosed as having a form of malignant haemopathy, consecutive to the imagistic suspicion.

4. The analysis of radio-imagistic changes in malignant hemopathies

Hematologic neoplasias may determine in bone tissue a series of morphological changes that guide the examiner to the diagnosis of bone determination.

Through this paper is desired an evaluation of radio-imagistic techniques in the diagnosis and assessment of secondary bone determinations in malignant haemopathies. To this purpose, we examined the basic radio-imagistic changes in the study group:

osteoporosis, osteolysis, osteosclerosis, vertebral fractures and compression, bone marrow edema, space replacement processes, and aseptic necrosis. Each of these modifications had their defining characteristics analyzed: number, shape, size, localization, structure, associated lesions, bone contour modifications.

5. Analysis of radio-imagistic post-treatment modifications in malignant hemopathies

In the study group, out of the 188 patients, during and/ or post-therapy were investigated a total of 81, of which 46 were diagnosed with multiple myeloma, 21 presented lymphoma, and 14 had a form of leukemia. All these patients were investigated by MRI. Because the accuracy of the images obtained by this method is superior to those obtained by conventional radiology and computer tomography, we analyzed post-treatment modifications in these patients through the premise of the results obtained by MRI.

6. Discussion

The analytical study of radio-imagistic modifications, as diagnostic elements of bone determinations in malignant haemopathies, allowed highlighting some of their specificity characteristics in interrelation with the three haematological neoplasic entities: multiple myeloma, lymphoma and leukemia.

The total number of 188 cases includes 100 cases of multiple myeloma (53.19%), 64 patients with lymphoma (30.04%) and 24 cases of subjects with leukemia with bone determinations (16.77%).

Depending on the type of malignant haemopathy and on the diagnostic possibilities and assessment of each radio-imagistic method, we analysed the bone modifications determined by these neoplasia, in terms of their effect on the bone marrow, translated imagistically through the development of osteoporosis, of focal bone lesions, as well as the most frequent complications determined by these

malignant haemopathies. These had the following characteristics analysed: lacalization, dimensions, contours and infiltrative character, where appropriate.

In terms of localization, we found that the lumbar spine segment is the main area of detection of these lesions, regardless of their shape and of the type of determinant malignant haemopathy (48.26%).

Osteoporosis is a constant radiological modification in bone determinations consecutive to malignat haemopathies, its characteristics being still nonspecific, it being differentiated of those determined by postmenopause or senile. It has been detected in a number of 73 out of the total of 100 cases of multiple myeloma (73%), respectively in 33 out of the 64 cases of lymphoma (54.56%), and in case of leukemia, osteoporosis was evidentiated in 11 out of 24 subjects (45.83%).

The presence of focal bone lesions was detected in 83 out of the total of 100 patints with multiple myeloma (83%), and in cases of lymphomas in 42 out of 64 cases (65.62%). Leukemias presented focal bone lesions in a proportion of 62.5%, comprising a number of 15 cases. The investigations revealed four structural models of these focal bone lesions, namely: lytic lesions, osteosclerotic lesions, fatty degenerated lesions, and osteosclerotic rim lesions.

Vertebral fractures were encountered in 21% cases of multiple myeloma, in 21.87% of cases of lymphoma and in 16.66% cases of leukemia. The existence of vertebral compression was detected in 30% of cases of multiple myeloma, the percentage of their detection in cases of lymphoma being 34.37%, and in patients with leukemia evidentiated in a proportion of 20.83%.

Aseptic necrosis proved to be as much as important, due to its determinant clinical implications, as it is uncommon, representing only 1.06% of all malignant neoplasia studied. It was identified in one patient with non-Hodgkin lymphoma and one diagnosed with chronic lymphocytic leukemia. Both patients were under treatment for the primary disease.

Bone marrow edema was evidentiated using MRI in a number of 62 cases of the total of 188 studied cases (34.44%). Bone marrow edema in circumscribed form was encountered in most cases, both in newly diagnosed patients (15 patients), as well as those under treatment.

The presence of space replacement processes denotes the presence of lesion with a highly agressive character and were found in a number of 19 cases from the studied group (10.1%).

VI. FINAL CONCLUSIONS

1. Conventional radiologic explorations constitute the primary stage of diagnostic study in the investigational algorithm of a suspicion of bone determination in malignant haemopathies.
2. The evidentiation of suggestive modifications in bone determination requires further investigation through MRI in order to make a complete characterization of bone marrow modifications.
3. The absence of specific clinical manifestation can not exclude the bone determination diagnosis, therefore radiographic exploration is a necessary investigation.
4. In terms of correct and especially complete investigative techniques to evidentiate radiological modifications considered specific, the conventional radiological examination can guide the diagnosis to bone determinations in malignant haemophaties.
5. Computer tomography is a method with superior accuracy compared to conventional radiography, but insufficient for diagnosis.
6. Computer tomography can make a complete assessment of all lesions in lymphoma, being particularly useful in the accurate staging of neoplasia.
7. Computed tomography is a radiological method that allows accurate diagnosis of both lytic and sclerotic bone determinations, but it cannot differentiate those encountered in malignant haemophaties from other neoplasia.
8. MRI is a sensitive and specific method in detecting bone marrow infitration.
9. To a higher or lesser extent, elementary radio-imagistic modifications studied in this paper, were found with different frequencies in haematological neoplasms – multiple myeloma, lymphoma, leukemia.
10. Osteoporosis is found in any of the three entities of malignant haematophaties, the identification of osteoporotic changes being important when complications exist, such as vetebral fractures.
11. The character of osteoporosis in case of malignant haemopathies is nonspecific, having the same radio-imagistic charateristics and cannor be distinguished from senile or postmenopausal osteoporosis.
12. Bone marrow edema is a frequent modification in malignant haemopathies.
13. Focal bone lesions in haematological neoplasms are frequent, but not mandatory as manifestations of these entities.
14. Space replacement process can be present in haematological neoplasms, as form of bone determinations.
15. Vertebral fractures are a frequent complication in the evolution of malignant haemopathies.
16. Aseptic necrosis ia a realtively rare complication in malignant haemopathies.
17. Post treatment modifications of bone determinations in malignant haemopathies can be most accurately assessed using magnetic resonance exploration.
18. Specific algorithms of diagnosis of bone determinations in malignant haemopathies are characteristic to each neoplasic entity.

18a. In case of suspicion of bone determinations in lymphoma, with suggestive clinical symptoms, the first diagnostic stage is represented by radiographic examination or direct exploration using magnetic resonance.

18b. Evidentiating any radiological sign of bone involvement requires the use of an MRI examination, eventually followed by a bone biopsy in the affected bone segment.

18c. In case of bone determinations in leukemia an MRI exploration is more reliable, followed by a bone biopsy, than radiography – MRI sequence. CT examination is performed when there are contraindications for MRI.

19. Specific algorithms in assessement of bone determinations in malignant haemopathies are distinct according to the diagnosed hematologic neoplasms.

    19a. In multple myeloma as method of first intention conventional radiology can be used, or directly, MRI exploration of symptomatic bone segments.

    19b. CT exploration is required in case of staging lymphoma.Explorarea computer-tomografica este impusa in cazul limfomului pentru stadializare. If on the bone window are identified lesions, further investigations are needed, such as bone radiography or MRI, eventually followed by bone marrow biopsy.

    19c. CT, in leukemia patients with bone determinations is reserved if MRI is contraindicated. For a complete assessement it is recomended MRI investigation.

20. Monitoring algorithm of bone determinations during and after therapy presents also specific features depending on the malignant haemopathies.

    20a. In multiple myeloma radiographies of affected bone segments, or direct MRI investigation are performed, with monitoring depending on the identified aspect through the same type of radio-imagistic exploration.

    20b. Lymphoma patients that are under specific treatment must have a CT examination performed for restaging, followed by MRI analisys of bone marrow.

    20c. Due to the superiority of MRI compared to other methods of diagnosis in leukemia, monitoring bone lesions is being made through this method.

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