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The Incidence of Fractures in Multiple Myeloma and Their Dependence on the Severity of Osteoporosis and the Level of Total Calcium in the Blood Serum

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Abstract Multiple myeloma (MM) osteolysis can affect any bone, but more often it affects those in which the content of the cortical substance is greater than the spongy. Osteoporosis, in general, is characterized by a progressive decrease in bone mass per unit volume, violation of bone microarchitecture, deterioration of the quality indicators of their tissue, resulting in increased bone fragility. Calcium level and mineral density are the indicators most quickly reacting in violation of bone metabolism. The article presents the results of using these data in predicting the occurrence of fractures in MM.

Keywords Multiple myeloma (MM), Osteolysis, Osteoporosis, Calcium, Bone metabolism, Fractures

1. Introduction

Bone tissue damage in multiple myeloma (MM) is a clinical pattern that can be observed in all patients in the advanced stage of the disease. Manifestations of changes in bone tissue in multiple myeloma are osteoporosis, osteolysis, hypercalcemia, pathological fractures, and a combination of these processes [1, 3, 5, 13, 16].

The pathophysiological mechanisms of osteolytic destruction in MM are rather multifaceted and consist not only in the secretion of osteoclast-activating factors by myeloma cells, but also in suppressing the proliferation of osteoblastic cells, which leads to the destruction of the bone matrix without subsequent replacement. Myeloma osteolysis can affect any bone, but more often the lesion occurs in those bones in which the content of the cortical substance is greater than that of the spongy [3, 5]. Osteoporosis, in turn, is characterized by a progressive decrease in bone mass per unit volume, violation of microarchitecture of bones and deterioration in the quality indicators of their tissue, resulting in increased bone fragility [6].

Unlike osteoporosis, which is characterized by a uniform decrease in mineralized osteoid, osteolytic lesion radiologically looks like a “completely empty area”, which indicates the absence of mineralization of the bone defect [1].

Clinically, these forms of bone lesions practically do not differ from each other, but in the aggregate they determine the originality of the clinical picture of MM. So, in 70-90% of patients ossalgia of varying severity [1, 3, 5].

In the early stages of the disease, bone pain, non-intensive and non-permanent, is most often localized in the lumbosacral spine and in the chest. Such non-specific symptoms often provide a basis for the diagnosis of intercostal neuralgia or radiculitis [1, 2, 16].

Sometimes the first symptoms of the disease are sudden sharp pains in the spine or chest that occur as a result of a pathological fracture and indicate far-gone changes in the skeleton that were asymptomatic before.

The most frequently affected are: the spine, especially the lower thoracic and lumbar regions, ribs, skull, pelvis, sternum, and from the large tubular bones - the femur and

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humerus. Spinal fractures occur in 50% of patients with MM, in 30% of cases, fractures have a different location. Spinal cord compression develops in about 10% of cases [3-5].

Until recently, the mechanisms of bone tissue destruction were not fully studied [5, 14]. Most studies suggest that increased bone destruction is associated with tumor infiltration, correlated with tumor size [1, 11, 12, 16].

According to recent studies, an intensive study of the molecular mechanisms of osteoporosis and osteolysis in MM is taking place. The accumulation of clonal malignant cells specific for this disease and their interaction with the stromal elements of the bone marrow leads to the activation and proliferation of osteoclasts, and also stimulates the production of various cytokines and growth factors, including interleukins (IL) 1β, 3, 6, 11, tumor necrosis factor- α (TNF-α), hepatocyte growth factor, as well as a heterogeneous class of lymphokines that increase bone resorption [13-15].

In patients with MM, along with signs of intense bone resorption, expressed in an increase in the number and activity of osteoclasts, proliferation of functionally defective osteoblasts, their apoptotic death and, as a result, incomplete bone formation are noted [1, 5, 13]. In conditions of increased osteoclast activity and in the absence of a compensatory enhancement of recovery processes, osteoblasts are not able to compensate for the loss of bone mass.

2. Main Body

2.1. Purpose of the Study

The purpose of the study was to study of the frequency of bone fractures in multiple myeloma and the determination of the dependence of fractures on the degree of osteoporosis and the level of Ca + in the blood.

2.2. Material and Methods of Investigation

The study was conducted in the Department of stem cell therapy at the Research Institute of Hematology and Blood Transfusion of the Republic of Uzbekistan. A total of 30 patients participated in the study. They are divided into 2 groups: group A - 15 patients with MM who had bone fractures, group B with signs of osteoporosis without bone fractures (control group). Among patients in group A2, there was a fracture of the femoral neck, 2 fracture of humerus, 4 patients of a compression fracture of the lumbar vertebrae, a 5 compression fracture of the thoracic vertebrae and 2 fracture of the ribs.

At the same time, in 11 patients with multiple myeloma accompanied by fractures, autologous hematopoietic stem transplantation (HSCT) was performed (subgroup 1A) and, accordingly, in group A, a subgroup of patients who had fractures but who did not undergo HSCT could be distinguished.

Diagnosis of the disease was carried out according to the standard algorithm for the diagnosis of multiple myeloma. MRI and digital X-rays were used to diagnose bone complications. To predict fractures in MM, it was decided to study bone mineral density using densitometry. The study of bone mineral density (g/cm^2) of the investigated skeletal zones was carried out using an LUNAR Prodigy X-ray axial densitometer from GE (USA) with CORE v software. 8.5 by the method of dual energy X-ray densitometry.

The study of BMD was performed in standard zones of the bones of the axial skeleton. Densitometric measurements were performed on the lumbar spine and proximal femurs (femoral neck). Given that the presence of osteoporosis can be the cause of pathological fractures in patients with MM, the incidence of fractures was determined depending on the presence of osteoporosis. According to the definition of the state of bone tissue according to WHO, T-score = 1 is taken as the norm. From 1 to 2 - osteopenia, 2 and above - osteoporosis.

The level of total and ionized calcium in the blood was also determined. Calcium was determined on a biochemical analyzer using Human reagents.

2.3. Results and Discussion

Hypercalcemia was observed in 13 (80%) observed patients with fractures (group A) (table 1). In patients with fractures of the long tubular bones, the calcium level was high and reached 3.3 mmol/l, with fractures of the ribs and vertebrae, the calcium level was determined at the level of 3.0-3.1 mmol/l. In 2x patients who had multiple compression fractures of the thoracic vertebrae (more than 4x), the calcium level was 3.3-3.4 mmol/l. The level of ionized calcium in these patients was also higher than the norm by 0.6-1.1. Mol/l.

Table 1. The concentration of total calcium serum

Groups					
№	consists of:	n	Calcium concentration	t	p
B	Patients with MM and without fractures	15	1.973 ± 0.015	-21.463	0.000
A	Patients with MM + fractures	15	3.363 ± 0.063*		
A1	Patients with MM + fractures + HSCT	11	3.391 ± 0.081*	-16.684	0.000
A2	Patients with MM & without HSCT + fractures	5	3.300 ± 0.100*	-12.710	0.000

Note: MM- Multiple Myeloma; HSCT - hematopoietic stem cell transplantation; * - Statistical reliability ($p<0.05$) of differences in calcium concentration compared to the value in the group of patients with multiple myeloma and without fractures

When performing densitometry, the T-score did not fall below -1, -1.35 in the studied zones. During osteosynthetic operations in these patients, it was found that osteolytic foci were replaced by a soft-tissue formation of a jelly-like structure with vascularization. When conducting a histological analysis of this structure was determined plasmacytoma. Despite a good T-score, osteolytic lesions of the vertebrae, ribs and sternum were diagnosed by X-ray and magnetic resonance imaging (MRI). MRI scans showed a direct image of the bone marrow, unlike all other methods of radiation diagnosis. Replacing the normal bone marrow with the spongy bone with myeloma tissue resulted in a decrease in the signal intensity by T1VI. This change in signal was an early sign of osteolysis. In 3 patients with a modified T1VI signal within 3 months there was a fracture at the site of the altered signal, including 1 - a fracture of the proximal clavicle, in 2 - a compression fracture of the lumbar vertebrae. Probably, hypercalcemia in group A is associated with enhanced bone resorption by osteoclasts and is most pronounced in patients with massive osteolytic lesions. Patients in this group were subjected to surgical treatment. They underwent osteosynthesis of long bones and stabilization of the vertebrae of the TPF.

In patients of group B, hypercalcemia was not detected, in 2 patients the level of calcium was lower than normal – 1.8 mol/l. These patients also had a low total protein content. When performing densitometry, the T-score is lower than -1.5, -2.35 in the studied zones, but there were no pathological fractures. These patients had moderate ossalgia and did not need surgical treatment.

In group B, no hypercalcemia was detected; in 2 patients, the calcium level was below normal - 1.8 mol/l. An analysis of this case also revealed a low total protein content in these patients. Probably, hypercalcemia in group A is associated with increased bone resorption by osteoclasts and is most pronounced in patients with massive osteolytic lesions.

Patients in this group were subjected to surgical treatment. Osteosynthesis of long bones and stabilization of the vertebrae of the TPF were performed.

During osteosynthetic operations in these patients, it was found that the osteolytic foci were replaced with soft tissue formation of a jelly-like structure with vascularization. On the histological analysis of this structure was determined plasmacytoma. Osteolytic lesions were diagnosed by X-ray and magnetic resonance imaging. The latter method was more informative (87%).

Table 2. The concentration of total calcium in the blood serum of patients with multiple mileoma and bone fractures

	Patients with MM+ fractures		t	p
Calcium concentration in serum of blood	3,363±0,063*	+ HSCT	-0.276	0.785
		3.391 ± 0,081*		
		without HSCT	0.499	0.623
		3.300 ± 0,100*		

Note: MM- Multiple Myeloma; HSCT - hematopoietic stem cell transplantation

A distinctive feature of MRI research is the possibility of obtaining multi-plane images of the spine over a large distance, as well as of the spinal cord, which makes it possible to more accurately diagnose the cause and topic of compression syndrome, which often occurs during MM. This is of great importance for the choice of treatment tactics for patients. MRI scans show a direct image of the bone marrow, unlike all other methods of radiation diagnosis, which reflect only the response of the bone to myeloma.

Replacing a normal bone marrow with a spongy bone with myelomatous tissue leads to a decrease in signal intensity at T1VI. This change in signal is an early sign of MB. In 3 patients with a modified T1VI signal within 3 months a fracture occurred. In 1 patient a fracture of the maximal clavicle, in 2x a compression fracture of the lumbar vertebrae (fig. 1, table 1).

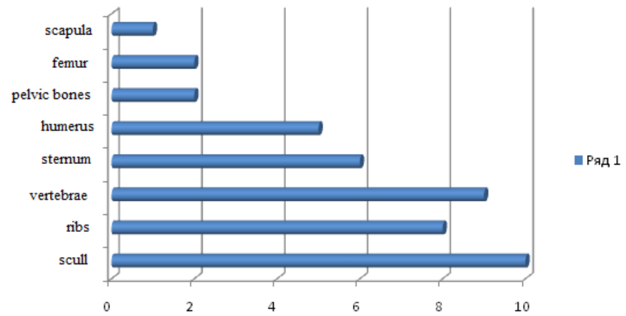

Figure 1. The frequency of bone damage according to x-ray

When using whole-body MRI in the primary diagnosis of patients of groups A and B, it was found that almost all patients with MM have one or another degree of bone damage. Diffuse and diffuse focal bone changes were found in 28 of 30 patients examined (89%). The bones of the skull, then the bones of the spine, ribs, etc., are most often affected.

Table 3. The incidence of fractures and osteoporosis

Lumbar spine	Fractured patients	Patients without fractures
Patients with osteoporosis	4	9
Patients without osteoporosis	11	6

As a result, in patients with MM, the presence of fractures is not associated with the degree of impairment of bone mineral density. Probably there is a dysfunction of the parathyroid glands or an imbalance of the hormones regulating mineral metabolism. In patients with myeloma, it was not generalized osteoporosis that was diagnosed, but lysis of the bone tissue around the area damaged by the tumor, with no signs of regeneration. Osteoporosis can also be iatrogenic, since in the treatment of MM the main place is occupied by GCS in large doses.

Consequently, the occurrence of fractures also depends on the depth of the bone lesion and the cause is not osteoporotic, but osteolytic bone areas, where the solid bone is replaced by the soft tissue component of the tumor.

3. Conclusions

Hypercalcemia is a symptom that determines the degree of bone damage in multiple myeloma: the higher level of total calcium is evidence of osteolytic lesions in the bones. Defined direct dependence of the level of calcium and frequency of fractures.

Impaired bone mineral density (osteoporosis) is not associated with fractures. And it in general is an indicator of dysregulation of mineral metabolism in the bones.

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