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Case report

METASTATIC EXTRAOSSEOUS ACCUMULATION OF 99MTC-MDP IN A PATIENT WITH GIANT CELL TUMOR OF THE HUMERUS – A CASE REPORT

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Abstract

Introduction: Proposed mechanisms for extraosseous 99mTc - MDP uptake are extracellular fluid expansion, enhanced regional vascularity and permeability, and elevated tissue calcium concentration. It can be due to nonmalignant causes, such as parathyroid adenoma, vitamin D intoxication or Paget disease or can be of malignant origin. Malignant conditions are sometimes associated with a life-threatening hypercalcemia and metastatic calcifications.

Case report: We report a case of a 50-year-old female complaining of back pain and pain in the right leg. CT and MRI scan of the thorax showed a soft tissue mass at the level of the proximal metadiaphysis of the left humerus, with osteolysis of the bone, as well as a penetration of the cortex in multiple spots. Giant cell tumor of the humerus was confirmed by core biopsy. Bone scan showed increased uptake of the tracer in facial bones and mandibula, in the head of the left humerus, both iliac bones and the right acetabulum. Also, extraosseous accumulation of the tracer was found in both lungs, in the heart, and in the stomach, consistent with metastatic calcifications. The patient was diagnosed with a multicentric giant cell tumor, and was treated with monoclonal antibody therapy with Denosumab for two months. Six months later, she passed away. There are many differential diagnoses regarding extraooseous tracer uptake on bone scintigraphy. Careful work-up is necessary because the treatment planning might be completely different once the etiology is elucidated.

Keywords: bone scan, giant cell tumor, extraosseous uptake, metastatic calcification

Introduction

Bone scan performed with 99mTc-MDP (bone seeking agent) is accumulated by both chemical adsorption onto the surface of the hydroxyapatite in the bone and incorporation into the crystalline structure of the hydroxyapatite. Sometimes extraosseous Tc-99m MDP uptake may appear, which is presumably linked with mechanisms such as extracellular fluid expansion, enhanced regional vascularity and permeability, and elevated tissue calcium concentration[1]. It can be due to non-malignant causes, such as parathyroid adenoma, vitamin D intoxication or Paget disease or it can be of malignant origin[2,3]. Malignant conditions are sometimes associated with a life-threatening hypercalcemia and metastatic calcification.

Case report

We report a case of a 50-year-old female, complaining of a back pain and pain in the right leg. She was treated with analgetics, opioids and CoX-2 inhibitors.

Computed tomography (CT) scan of the thorax showed a soft tissue mass at the level of the proximal metadiaphysis of the left humerus, with osteolysis of the bone, as well as a penetration of the cortex in multiple spots, especially on the medial contour. The tumefaction was relatively well-limited from the environment, so that the proximal epiphysis of the left humerus was intact (Figure 1). Multiple osteolytic changes were seen along the body of the left scapula and glenoid processus. Core biopsy was performed and a diagnosis of a giant cell tumor (GCT) of the left humerus was made. Furthermore, CT of the abdomen revealed oval osteolytic tumor formations bilaterally and diffuse at both iliac wings, more commonly to the right, as well as to the corpus and the acetabulum posteriorly. Bilateral hip arthrosis and similar osteolytic changes were also observed on the head of the right femur. Several smaller osteolytic changes were seen on the left femur.

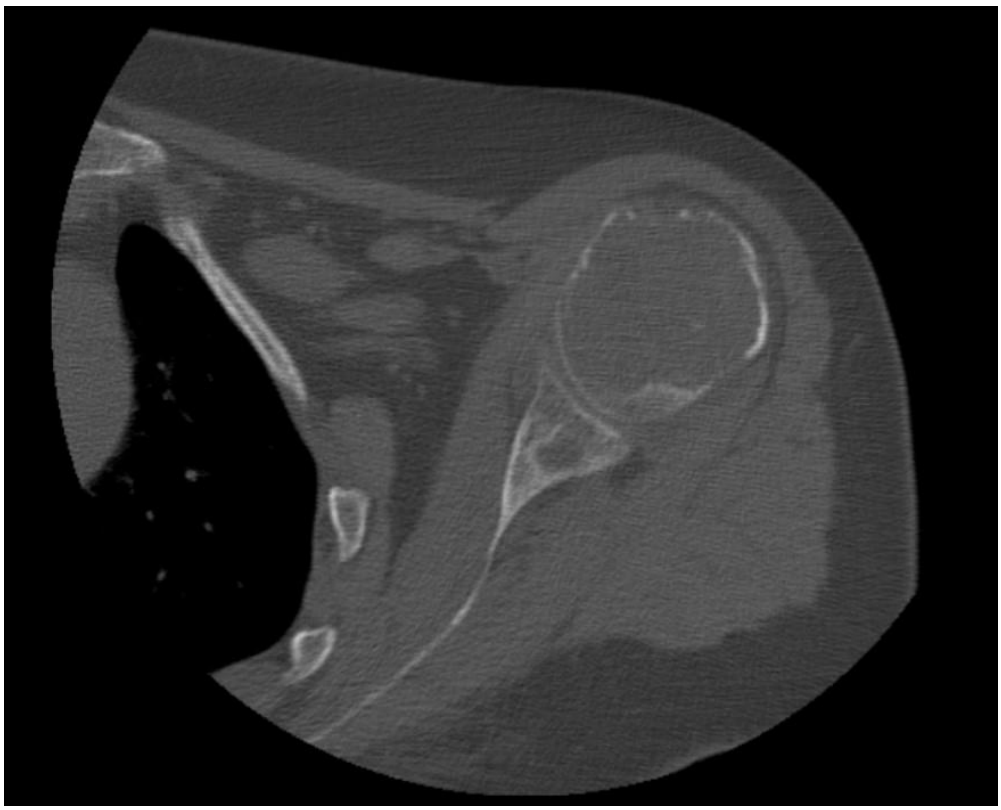

Fig. 1. CT scan of the left humerus

MRI of the left shoulder revealed that at the level of the proximal metaphysis, the neck with diaphyseal and epiphyseal propagation, presented bone expansion of the left humerus with a more accentuated diaphyseal eccentric medial extension where septation was also observed, compared to the CT examination. Cortical thinning presented with clear interrupted cortical continuities, but no evidence of paraosseous breakthrough of the soft tissue substrate. The change had a solid cystic component, with more pronounced cystic changes in the projection of the major and minor tubercle, and after the application of contrast, there was signal enhancement in the soft tissue part. Similar changes were observed in the scapula, with more pronounced cystic components towards the glenoid (Figure 2).

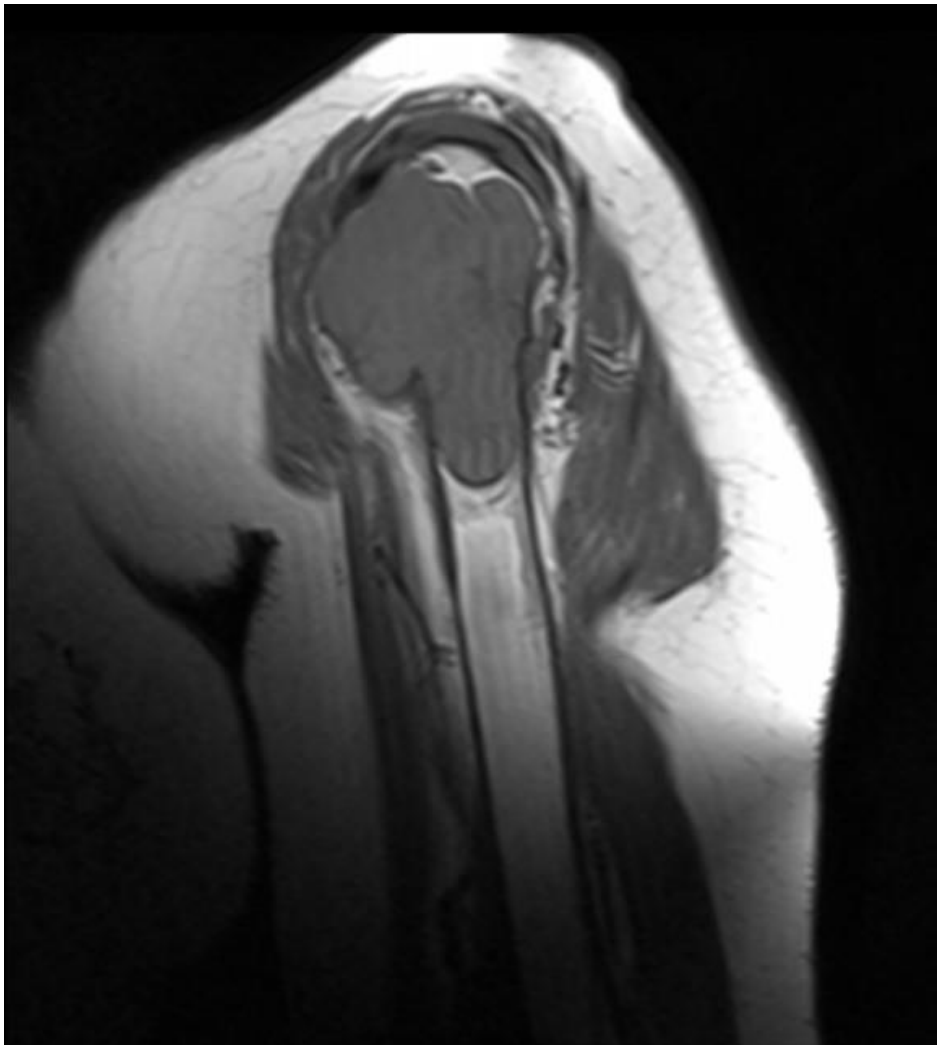

Fig. 2. MRI of the left humerus

The next two months the patient was treated with monoclonal antibody therapy with Denosumab of 120 mg (Amp. XGEVA). After six months, she complained of cough, and lung CT scan was performed revealing modified architectonics of the parenchyma with the presence of diffuse subpleural nodular densities with surrounding ground glass bilateral opacification. Atelectatic segments were present in both upper lobes. CT of the left humerus confirmed the same abnormal morphology and structure as seen on the previous CT image.

The patient was hospitalized at the University Clinic for Orthopedic Surgery because she complained of a very strong pain in the right hip and in the left knee, several weeks after treatment with Denosumab. Her health condition was becoming worse, and she was transferred to the Intensive care unit, with a diagnosis of "metachronous multicentric giant cell tumor of the bone". With a diagnosis of multifocal osteolysis, the patient was referred to our department for a bone scan. The whole body scan (WBS), performed two hours after application of 740 MBq 99mTc-MDP, showed increased tracer uptake in the facial bones and mandibula, in the head of the left humerus, both iliac bones, the right acetabulum as well as extraosseal accumulation of the tracer in both lungs, in the heart and in the stomach (Figure 3).

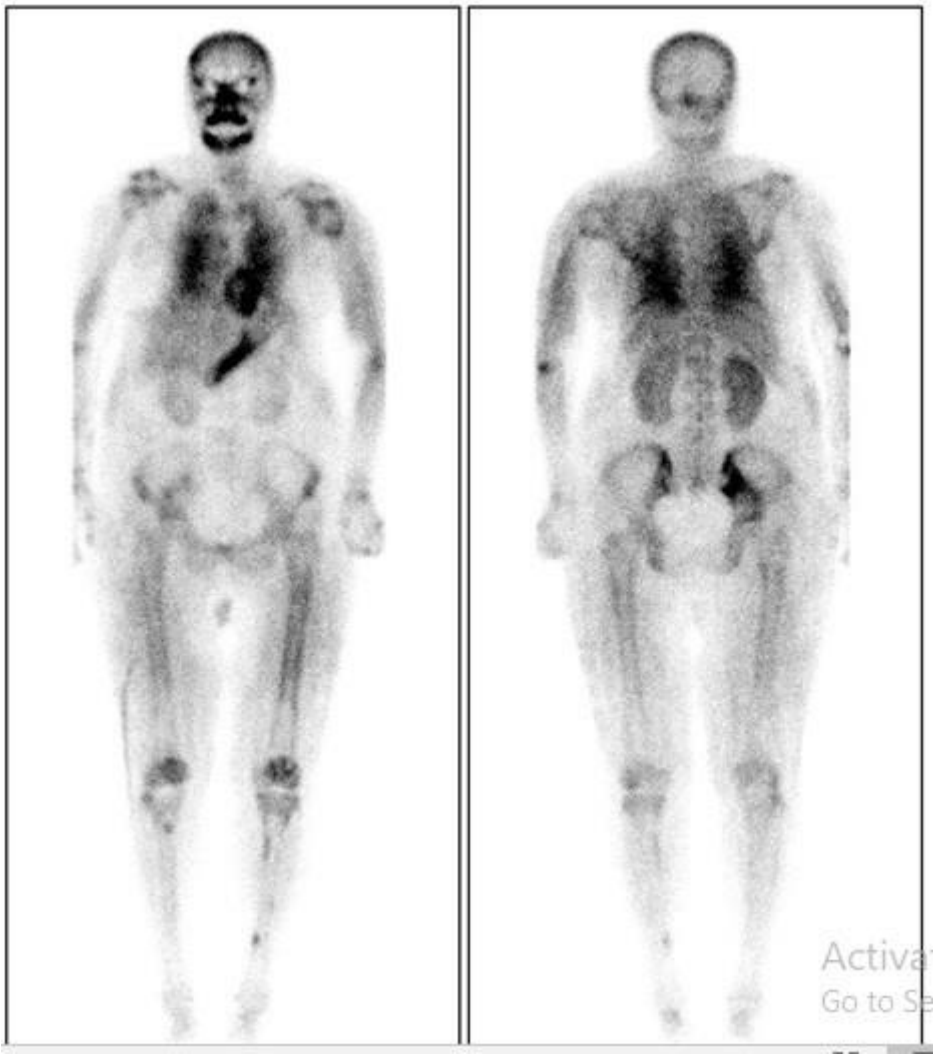

Fig. 3. Whole body scan with 99mTc-MDP

Laboratory findings were as following: CRP=37.72 (<6mg/L), Ca=4,85 (normal, 2.1-2.6 mmol/l), K=2.46 (normal, 3.8-5.5 mmol/L), Na=137.93 (normal, 137-145mmol/L), AP=175.43 (normal, 36-126U/L), CK 394.52 (normal, 24-173 U/L), D-dimer=6684 (normal, 0-500 ngr/mL).

One day following the bone scan, due to cardio-respiratory insufficiency the patient passed away.

Discussion

Extraosseous localization of 99mTc-MDP, although not a common finding, can sometimes be seen on a bone scan because of artifacts as normal or as abnormal finding related to neoplastic processes[4]. There are three major types of extraosseous calcification: dystrophic, metastatic and heterotopic[5]. Heterotopic calcification represents a process that goes along with active extra- and intracellular metabolic processes. Intracellular calcification is based on the mitochondria function as the main regulator of calcium concentration - "lime-catcher". On the other hand, the extracellular calcification is coordinated by the matrix vesicles in the extracellular spaces. Special type of heterotopic calcifications are: tumor-associated hypercalcemia, drug-induced hypercalcemia, tumor calcinosis, primary and tertiary hyperparathyroidism, intratumoral calcifications, calcifications of organs, etc[6].

Dystrophic calcification results from accumulation of amorphous calcium densities in the mitochondrial matrix and formation of vacuoles from necrotic cells[7]. Metastatic

calcification was first described by Virchow in 1855. The underlying mechanism of 99mTc-MDP neoplastic uptake has been related to necrosis and/or abnormal calcification in the soft tissue, developing secondary to calcium metabolism abnormality. Hypercalcemia can occur secondary to chronic renal failure, hyperparathyroidism, hypervitaminosis D, sarcoidosis, amyloidosis, myeloma, malignant hypercalcemia of lymphomas and metastatic neoplasms[8,9]. Metastatic calcification is a deposition of calcium salts in otherwise normal tissue, because of the release of parathyroid related peptide in malignant tissues and free hydrogen ions secreted by the lungs, kidneys and stomach, leading to precipitation of ionized calcium mainly in the alkaline pH environment of these organs[10-12].

Our case presents metastatic calcification from GCT of the proximal humerus, inoperable case since it has metastasized in the iliac bones, detected by CT of the pelvic region and confirmed with our bone scan. Although the calvaria and mandibula accumulation raised the suspicion of metabolic bone scan, PTH concentration was not evaluated because the patient died the other day.

Typically, most of the GCT are seen in patients aged between 20 to 50 years, with a peak prevalence in the third decade of life [1`]. Commonly GCT occurs in the distal femur, proximal tibia and distal radius, with rare involvement of the proximal humerus with only 4%. The epiphysis of long bones in skeletally mature patients is the commonest location of GCT[14,15]. These tumors are benign, but rarely they can metastasize mainly in the lungs. The bone scan as a widely used and available diagnostic procedure may help to detect multiple foci, if multicentric disease is clinically suspected. In our patient, bone scan detected uptake in both lungs, in the stomach and heart. Increased gastric uptake always with diffuse lung uptake indicate hypercalcemia[16].

Since no lung metastasis were detected on the CT scan of the thorax, we made the conclusion of metastatic calcification. This type of extraosseous uptakes of 99mTc-MDP may be seen in other malignancies as reported in the literature. Frequently, hypercalcemia due to increased bone resorption with associated renal disturbances occurs in myeloma and occasionally in patients with T-cell lymphomas, Hodgkin's disease, or B-cell lymphomas[17] .

99mTc-MDP activity in both lungs, stomach as well as the kidneys was presented in a case of a 37-year-old woman with indolent variety of a non-Hodgkin's lymphoma. Bone marrow biopsy showed normocellular reactive bone marrow with no lymphomatous infiltration[18].

A young 25-year-old patient was diagnosed with diffuse large B-cell non-Hodgkin's lymphoma and bone marrow biopsy revealed metastatic infiltration as well. His bone scan revealed extraosseous tracer uptake involving different segments of both lungs, diffuse uptake in the stomach and homogenously enhanced uptake in the rest of the skeleton[19].

Yasir Majeed with his colleagues reported two different cases of female patients with breast cancer showing 99mTc-MDP uptake in the lungs, with no correlation on the SPECT/CT findings regarding any anatomical abnormalities[20].

99mTc-MDP uptake was higher in low- or poorly differentiated soft tissue tumors as well as in epithelial malignant tumors and blastomas, compared to mesenchymal tumors and germ cell tumors, as reported by Liu *et al.*[21]. Bone scan revealed other foci of increased osteoblastic activity in the pelvic region and together with the extraosseous uptakes of 99mTc-MDP represented the advanced stage of the disease.

Our patient was inoperable and a therapy with monoclonal antibody Denosumab was prescribed. This therapy with Denosumab (amp. XGEVA) was first approved by the FDA for use in June, 2013. Denosumab is a fully humanized monoclonal antibody to RANK ligand (RANKL). By inhibiting the osteoclastic activity, the osteoclast-induced bone destruction is reduced[22]. It is the first and only therapeutic modality in patients with advanced, unresectable, progressive GCT of bone that are inoperable, and in cases where surgical

treatment would increase morbidity. It acts by reducing the volume of the tumor and reducing the rate of relapses[23,24].

PubMed literature search for metastatic pulmonary calcification showed 858 results, while metastatic pulmonary calcification detected by bone scan only 24 results, mainly in patients with hyperparathyroidism, multiple myeloma and lymphoma. Metachronous GCT of the humerus showed only 4 results in PubMed. To the best of our knowledge, no case with metachronous GCT and metastatic pulmonary calcification has yet been published. There are many differential diagnoses regarding the extraooseous tracer uptake on bone scintigraphy and careful work-up is necessary for the treatment planning that can be completely different once the etiology is elucidated.

Conflict of interest statement. None declared.

References

1. Okamoto Y. Accumulation of technetium-99m methylene diphosphonate. Conditions affecting adsorption to hydroxyapatite. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1995; 80(1): 115-119. doi: 10.1016/s1079-2104(95)80027-1.
2. Xu YH, Song HJ, Qiu ZL, Luo QY. Multiple extraosseous accumulation of 99mTc-MDP in acute lymphocytic leukemia and reference to literature. *Hell J Nucl Med* 2010; 13: 273-276. PMID: 21193884.
3. Hwang GJ, Lee JD, Park CY, Lim SK. Reversible extraskeletal uptake of bone scanning in primary hyperparathyroidism. *J Nucl Med* 1996; 37: 469-471. PMID: 8772648. quiz 154-6. PMID: 12968045.
4. Elgazzar A.H. Diagnosis of Soft Tissue Calcification. In: Orthopedic Nuclear Medicine. Springer, Berlin, Heidelberg 2004.
5. Seifert G. Heterotope (extraossäre) Verkalkung (Kalzinose). Atiologie, Pathogenese und klinische Bedeutung [Heterotopic (extraosseous) calcification (calcinosis). Etiology, pathogenesis and clinical importance]. *Pathologe* 1997; 18(6): 430-438. doi: 10.1007/s002920050238.
6. Duvvuri B, Lood C. Mitochondrial Calcification. *Immunometabolism* 2021; 3(1): e210008. doi: 10.20900/immunometab20210008.
7. Wale DJ, Wong KK, Savas H, Kandathil A, Piert M, Brown RK. Extraosseous findings on bone scintigraphy using fusion SPECT/CT and correlative imaging. *AJR Am J Roentgenol* 2015; 205(1): 160-172. doi: 10.2214/AJR.14.13914.
8. Majeed Y, Riaz S, Hassan A. Appearances of soft tissue calcification on Tc99m MDP bone scan. *J Pak Med Assoc* 2019; 69(4): 600. PMID: 31000873.
9. Kempter H, Hagner G, Savaser AN, Huben H, Minguillon C. Metastatic pulmonary calcification in a patient with multiple myeloma nonsecretory. *Respiration* 1986; 49: 77-80. doi: 10.1159/000194863.
10. Meyer MA, Mc Claughry P. Reversible Tc-99m diphosphonate uptake in gastric tissue related hypercalcemia associated with malignancy: A comparative study using FDG PET whole body imaging. *Clin Nucl Med* 1995; 20(9): 767-769. doi: 10.1097/00003072-199509000-00002.
11. Yasuo M, Tanabe T, Komatsu Y, Tsushima K, Kubo K, Takahashi K, *et al*. Progressive pulmonary calcification after successful renal transplantation. *Intern Med* 2008; 47(3): 161-164. doi: 10.2169/internalmedicine.47.0442
12. Ghostine B, Sebaaly A, Ghanem I. Multifocal metachronous giant cell tumor: case report and review of the literature. *Case Rep Med* 2014; 2014: 678035. doi: 10.1155/2014/678035.

13. Turcotte RE, Wunder JS, Isler MH, Bell RS, Schachar N, Masri BA, *et al*. Giant cell tumor of long bone: A Canadian sarcoma group study. *Clin Orthop Relat Res* 2002; 397: 248-258. doi: 10.1097/00003086-200204000-00029.
14. Akaike G, Ueno T, Matsumoto S, Motoi N, Matsueda K. Rapidly growing giant cell tumor of bone in a skeletally immature girl. *Skeletal Radiol* (2016); 45(4): 567-573. doi: 10.1007/s00256-015-2276-4.
15. Ignac Fogelman, Susan Clarke, Gary Cook, Gopinath Gnanasegaran. Atlas of Clinical Nuclear Medicine, Third Edition.Copyright year 2014. ISBN 9781841846538.
16. Mundy GR, Guise TA. Hypercalcemia of malignancy. *Am J Med* 1997; 103(2): 134-145. doi: 10.1016/s0002-9343(97)80047-2.
17. Palaniswamy SS, Padma S, Harish V, Rai JK. Hypercalcemia with extraosseous MDP uptake in a bone scan as initial presentation in a case of cutaneous T-cell lymphoma. Journal of Cancer Research and Therapeutics 2011; 7(1): 72-74. doi: 10.4103/0973-1482.80474.
18. Zaman M, Riffat Hussain R, Sajjad Z, Mansoor Naqvi M, Khan K, Khan G, *et al*. Concomitant gastric and lung uptake of 99mTc - MDP on bone scan in a patient with diffuse large B-cell Non-Hodgkin's lymphoma. *Pakistan Journal of Radiology* 2010; 20(4): 171-173. https:// ecommons.aku.edu/pakistan_fhs_mc_radiol.
19. Majeed Y, Riaz S, Hassan A. Appearances of soft tissue calcification on Tc99m MDP bone scan. *J Pak Med Assoc* 2019; 69(4): 600. PMID: 31000873.
20. Liu S, Xie J, Yu F, Cai H, Wu F, Zheng H, Ma C, *et al*. 99mTc-Methylene Diphosphonate Uptake in Soft Tissue Tumors on Bone Scintigraphy Differs Between Pediatric and Adult Patients and Is Correlated with Tumor Differentiation. *Cancer Manag Res* 2020; 12:2449-2457. doi: 10.2147/CMAR.S241636.
21. Chawla S, Henshaw R, Seeger L, Choy E, Blay JY, Ferrari S, *et al*. Safety and efficacy of denosumab for adults and skeletally mature adolescents with giant cell tumour of bone: interim analysis of an open-label, parallel-group, phase 2 study. *Lancet Oncol* 2013; 14(9): 901-908. doi: 10.1016/S1470-2045(13)70277-8.
22. Borkowska A, Goryń T, Pieńkowski A, Wągrodzki M, Jagiełło-Wieczorek E, Rogala P, *et al*. Denosumab treatment of inoperable or locally advanced giant cell tumor of bone. *Oncol Lett* 2016; 12(6): 4312-4318. doi: 10.3892/ol.2016.5246.
23. Thomas D, Henshaw R, Skubitz K, Chawla S, Staddon A, Blay JY, *et al*. Denosumab in patients with giant-cell tumour of bone: an open-label, phase 2 study. *Lancet Oncol* 2010; 11(3): 275-280. doi: 10.1016/S1470-2045(10)70010-3.