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A case of false results of osteoscintigraphy in search of bone metastases after endoprosthesis of shoulder and hip joints

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Abstract: *the clinical case demonstrates the erroneous interpretation of the results of a radionuclide study of the locomotor system without taking into account the anamnesis and clinical and laboratory data. To search for bone metastases, osteoscintigraphy is used all over the world, which allows to diagnose them at a preclinical stage of the process, ahead of radiological ones by 4-5 months. Cancer of the mammary and prostate glands, as well as kidney cancer, metastasize to the bones very early. About 50% of cases of these metastases are detected in the absence of clinical manifestations, which prompts regular control osteoscintigraphy regardless of complaints and clinical condition of patients. Research is carried out on gamma cameras, and phosphate compounds labeled with the technetium isotope are used as a radioactive drug. 3 hours after its intravenous injection with an activity of 600 MBq, in normal conditions against the background of uniform distribution in the bones, increased accumulation is noted in the area of the base of the skull, ribs, angles of the shoulder blades, vertebrae, pelvic bones, and meta-epiphyseal sections of tubular bones. The results of the research are evaluated qualitatively and quantitatively. With high-quality, hyperfocuses of the isotopes are visually determined in separate areas of the skeleton. But it is the quantitative analysis that allows us to draw a conclusion about the secondary damage to the skeleton. A difference in the accumulation of the isotope in any part of the skeleton in comparison with an unaffected area above 150% is considered a sign of metastases. It should be noted that phosphates labeled with radioactive technetium sometimes provide a fairly high level of fixation in areas of inflammatory, degenerative-dystrophic or traumatic processes. What we observed in this case. A patient with breast cancer underwent joint endoprosthesis twice: first of the shoulder, and then of the hip joint. The cause was pathological osteoporosis and degenerative-dystrophic changes. On subsequent control osteoscintigrams, there were no foci of increased accumulation of the radiopharmaceutical in the skeleton. But after the second endoprosthesis of the hip joints six months later, hyperfixation of the isotopes in the corresponding joints was detected, on the basis of which the conclusion of their metastatic lesion was made. The patient did not indicate before the study about*

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the recent endoprosthesis. She did not notice any pain syndrome. In order to calm down, she did an osteoscintigraphy after 5 months. The inclusion of the isotopes in the hip joints was significantly reduced and did not exceed the upper limit. Some laboratory parameters such as alkaline phosphatase and ionized calcium are known to be significantly elevated in metastatic bone disease. The patient's content was within normal limits. All this made it possible to remove the preliminary conclusion regarding the secondary damage to the skeleton. And the increased accumulation of radionuclide should be considered a consequence of postoperative intervention. Thus, before passing a verdict on bone metastases, a thorough study of the anamnesis, radiological and clinical laboratory research data is necessary.

Key words: Metastases; Shoulder Joints; Radiopharmaceutical; Breast Cancer; Hip Joints; Endoprosthesis; osteoscintigraphy.

Introduction

It is known that metastases (Mts) to the skeleton in women are most often observed with breast cancer (BC) (up to 85% of all cases of Mts bone damage by malignant tumors), which is associated with intensive blood circulation in the bones and the release of adhesive molecules by tumor cells that form connections with bone marrow cells. BC can cause the following Mts: osteolytic (when the penetration of atypical cells into osteoclasts provokes atrophy of bone tissue, which threatens fractures), osteoblastic (when osteoblasts are affected and atypical cells cause the growth of bone tissue) and mixed (when cells of 2 types are affected simultaneously and there is most common) [1, 2]. Primarily, Mts in breast cancer are found in the spine: in the lumbar region up to 59%, in the thoracic region up to 57% [3, 4]. But quite often Mts are also observed in other parts of the skeleton: in bones of the pelvis and hip joints up to 49%, shoulder joints and ribs up to 30%, femurs up to 24%, skull up to 20%, cervical spine up to 17%, shoulder bones up to 13%, in other areas – 3% [5, 6]. Clinical manifestations often precede radiological methods of diagnosis of Mts, but they are sometimes difficult to recognize, as patients associate them with other causes. There are three main clinical syndromes: 1) pain (with tumor infiltration of nerve endings), 2) pathological bone fractures (characteristic of osteolytic Mts); 3) hypercalcemia (namely ionized calcium – IC) and high level of alkaline phosphatase (AP). Therefore, for the diagnosis of bone Mts, laboratory and functional examination methods are also used, such as determining the level of IC and AP of the blood (increased concentrations of which appear earlier than radiological changes) [7, 8].

Despite the improvement of radiological research methods, osteoscintigraphy (OSG) remains the main and most sensitive method for detecting Mts in the skeleton, which allows detecting minimal remodeling in bone structures [9]. But it is quite difficult to determine their nature, because the increase in fixation of the osteotropic radiopharmaceuticals (RPC) occurs in disorders of various etiologies. For differential diagnosis, additional OSG modes are used, which significantly increases the specificity of the method and allows to distinguish between benign and malignant changes [10, 11]. Such opportunities are provided by the following scintigraphic technologies:

1) SPECT is used to obtain a three-dimensional image of a questionable area;
2) to obtain the exact anatomical localization of a questionable area with hyperfixation of RPC, use a combined study of SPECT with RCT (SPECT/RCT);
3) to obtain the exact anatomical localization of a questionable area with hyperfixation of RPC, a combined study of SPECT with RCT (SPECT/RCT) is used [12, 13].

Phosphate compounds labeled with technetium 99 m (Tc99m), such as methylene diphosphonate, pyrophosphate or poltech, are used as RPC [14, 15]. They make it possible to diagnose Mts at the preclinical stage of development. OSG changes in metastatic skeletal disease precede radiological changes by 4-5 months. Up to 50% of cases of

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bone Mts in breast cancer are initially detected against the background of relative clinical well-being. Therefore, OSG in this pathology is performed regardless of the complaints and clinical condition of the patients.

During the SPECT examination, scanning of the entire skeleton is performed in the front and back projections, and polypositional scintigraphy is performed on planar gamma cameras. On the series of slices, the foci of hyperfixation of RPC are clearly visualized according to the localization of Mts. According to the results of our own research, the sensitivity of OSG in the diagnosis of Mts is about 90%, and SPECT is up to 96%. The latter significantly exceeds planar scintigraphy in terms of the volume of diagnostic information, provides three-dimensional visualization of the distribution of RPC and allows diagnosing Mts of smaller sizes, which increases the efficiency of diagnosis [16]. It should be noted that increased accumulation in the bones of the skeleton can be observed in benign, inflammatory, degenerative-dystrophic processes (arthritis, osteomyelitis, spondylitis), places of fractures and after surgical interventions [17]. In the diagnosis of traumatic injuries of the skeleton, OSG is on average 2.5 times more sensitive than traditional X-ray examination. During computer processing of OSG results, the level of RPC accumulation in selected areas of interest is determined as a percentage, which never exceeds the limit of 150% in the absence of metastatic lesions. Therefore, the anamnesis and clinical picture are very important, in doubtful cases it is necessary to perform scintigraphy with tumoritropic RPC (MIBI-Tc99m) or use other hybrid methods of radiation diagnostics (PET/RCT). All this makes it possible to carry out differential diagnosis of malignant and benign processes earlier than with radiological studies, detect Mts in a timely manner and start treatment (with remote radiation therapy, treatment with Sr89-chloride and other osteotropic RPC). In addition, radionuclide research methods allow obtaining images of the entire skeleton, which is very important in patients with suspicion of multiple Mts. Therefore, it is necessary to start the study of patients with radionuclide methods, and in the case of multiple Mts, additional studies may not be conducted [18, 19, 20, 21].

Aim

To investigate the differential diagnostic value of osteoscintigraphy in the detection of Mts in the skeleton in breast cancer.

Materials and methods

OSG to patient D. 67 years was spent in the radionuclide department of the Kyiv City Clinical Hospital No.18, which is located at the Department of Radiology and Radiation Medicine of the O.O. Bogomolets National Medical University. The diagnosis of lobular infiltrative adenocarcinoma was established in 1997, according to TNM – T2, N0, M0. The research was carried out on the SPECT-1 planar gamma camera, which was developed and manufactured by the Institute of Scintillation Materials of the National Academy of Sciences of Ukraine (Kharkov) (Pic. 1).

Pic. 1. View of the SPECT-1 gamma camera

The SPECT-1 gamma camera provides radionuclide gamma scintigraphy in planar single- and multi-frame static and dynamic visualization modes. It includes a detector made of a scintillation crystal of sodium iodide (NaI), activated by thallium, a light guide and photoelectronic multipliers, as well as a computer system for processing and saving the results of examinations. When a gamma quantum hits a crystal, it transfers its energy to light photons and a flash occurs, which is registered by a matrix of photoelectron multipliers (PEM).

A chemical compound containing phosphate compounds labeled with technetium 99m (Tc99m) was used as a RPC – Poltech MDP Ts-99m from Polatom (Poland) with an activity of 600 MBq (Pic. 2 a, b). Tc99m itself was obtained

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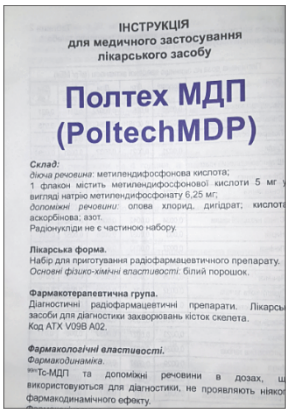

a *– RFC instruction for OSG* ***b*** *– a set for carrying out OSG* ***c*** *– generator Tc-99^m*

Pic. 2. Generator and sets for conducting OSG

using a generator (Pic. 2 c). The Tc99m isotope has a very short half-life – about 6 hours, so the molybdenum-99 generator (its half-life is 66 hours) is installed directly in the places where technetium is used – in radionuclide departments. Disintegrating, molybdenum forms Tc99m, which is in the form of sodium pertechnetate (NaTcO4), which is washed out of the column by elution.

On average, the effective dose for OSG is up to 4,0 mSv, and for patients of this category of AD, the annual permissible dose is 100 mSv. The principle of the method consists in the ability of phosphate compounds (monophosphates, diphosphonates, pyrophosphates) labeled with radionuclide Tc99m to be included in mineral metabolism and accumulate in the organic matrix (collagen) and mineral part (hydroxylapatite) of bone tissue. The distribution of radiophosphates is proportional to blood flow and the intensity of calcium metabolism. The diagnosis of pathological changes in bone tissue is based on the visualization of foci of hyperfixation or, more rarely, defects in the accumulation of labeled osteotropic compounds in the skeleton.

Initially, OSG was performed in Whole Body scanning mode 3 hours after IV injection of RPC according to the research protocol [14]. Registration of diagnostic images on the gamma camera was performed in the front and back projection in the horizontal position of the patient (on her back) for 20-40 minutes. Next, we proceeded to a polypositional examination in the front and back projections (Pic. 3). The main fields of research are: 1) head, shoulder joints, cervical spine; 2) thoracic and lumbar sections of the spine, ribs, shoulder blades and sternum (depending on the projection); 3) pelvic bones and hip joints.

Recording of information on the gamma camera computer was carried out until reaching 600,000 pulses from each field (Even-Sapir E., 2005). In a normal skeleton, 3 hours after intravenous administration, a physiologically uneven distribution of RPC is noted: its maximum accumulation is recorded in the bones formed by spongy bone tissue (vault and base of the skull, facial skeleton, spine, ribs, corners and edges of the shoulder blades, pelvic bones, epiphyses long tubular bones). While in the diaphyses of

Pic. 3. Polyposition study of patient D. during OSG (field 2 in direct projection)

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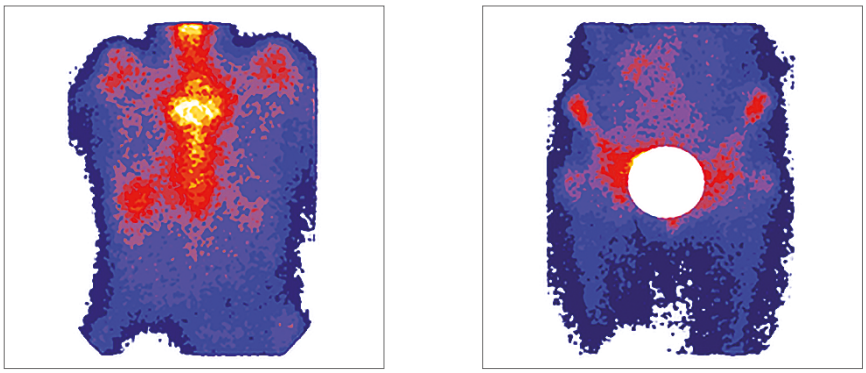
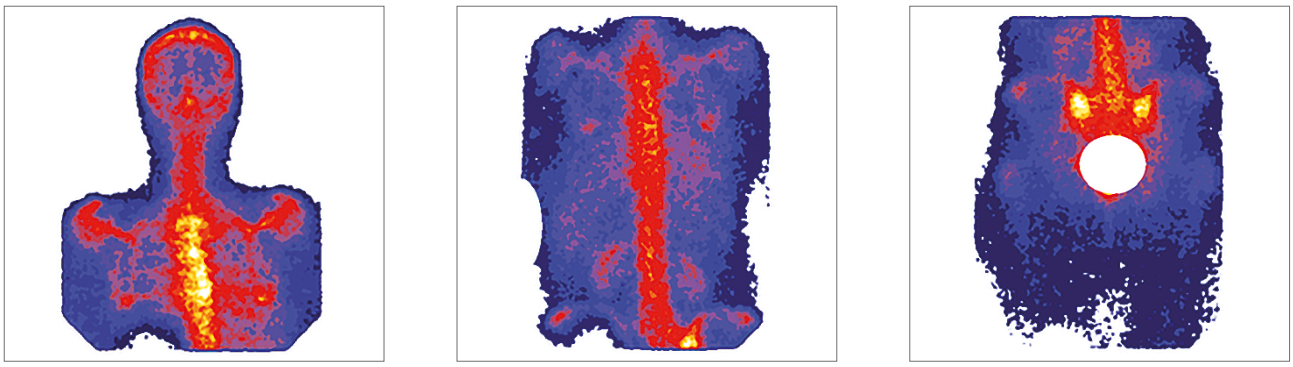


a *– front projections: fields 2, 3*

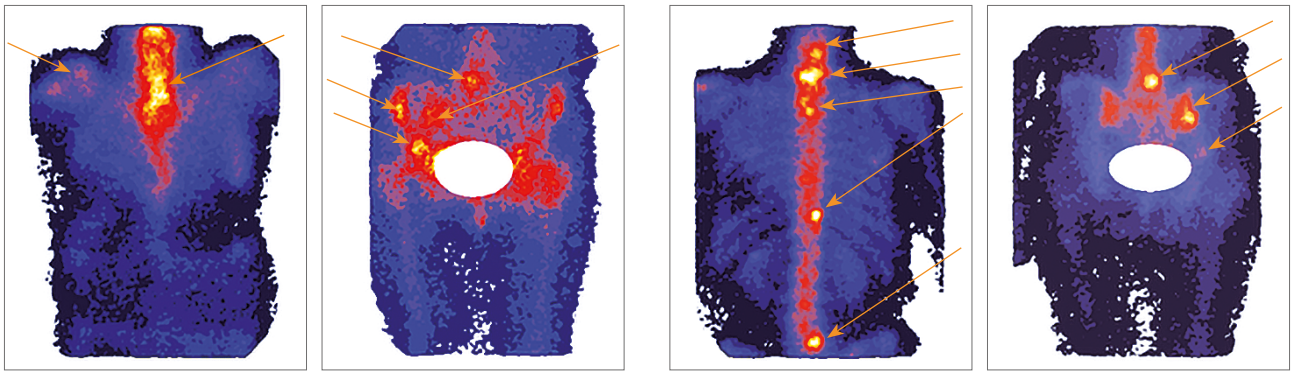


b *– rear projections: fields 1, 2, 3*

Pic. 4. The results of polypositional OSG are normal (data from our own archive)

long tubular bones, the accumulation of RPC is significantly lower. Normally, the kidneys are visualized on osteoscintigrams, as they play a leading role in removing osteotropic RPC from the body. Therefore, before the examination, it is necessary to empty the bladder or shield its area (Pic. 4).

But in addition to the qualitative assessment of OSG results, to confirm the presence of Mts in the bone, a quantitative analysis is required, which is achieved precisely by computer processing of areas of interest. The drug accumulation level of 150% and above is considered a sign of the presence of Mts. This is primarily characteristic of osteoblastic Mts (Pic. 5), for osteolytic indicators are much lower (with rapidly progressing ones, even «cold» foci can be visualized).



a *– front projections: fields 2, 3. Mts in the right shoulder joint, handle of the sternum, L-4, right hip joint, wing of the right iliac bone, right sacroiliac joint*

b *– rear projections: fields 1, 2, 3. Multiple Mts in the spine: C 3, 4, 5, Th1, 2, 3, 4, 12; L4; right hip joint, right sacroiliac joint*

Pic. 5. The results of polypositional OSG with multiple Mts in the skeleton (data from our own archive).

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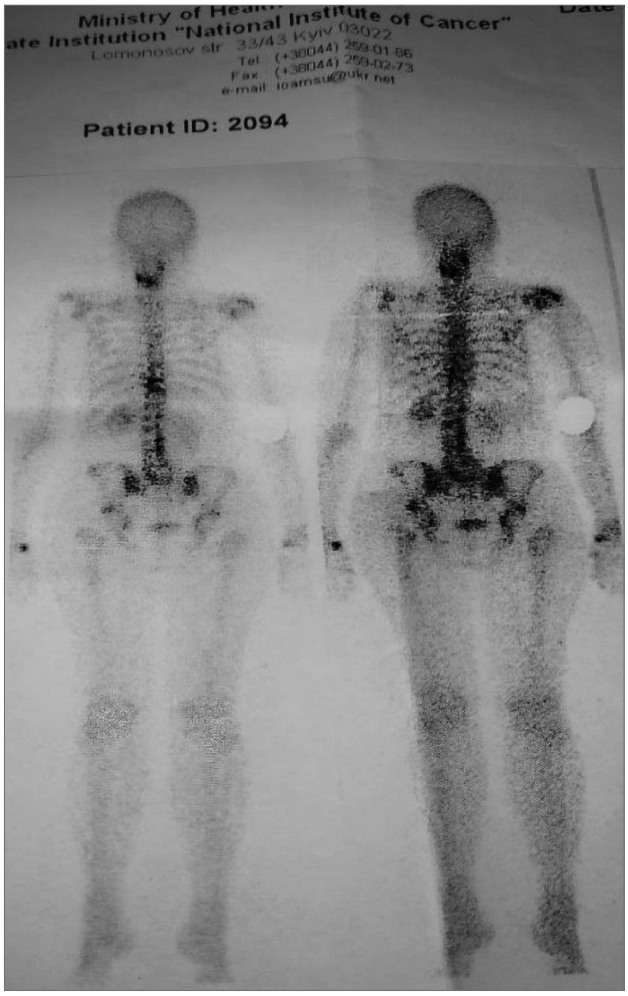
Description of a clinical case

Patient D. The 67-year-old has been suffering from breast cancer since 1997, when a left-sided mastectomy was performed. OSH was performed every 3 years as a preventive examination or when pain syndrome occurs in any part of the skeleton. For ten years, no pathological foci of RFD accumulation in the bones were observed. In 2008, endoprosthesis of the shoulder joints was performed (indications are pathological osteoporosis and degenerative-dystrophic changes). At the next OSG in 2010, in the radiology department of the National Cancer Institute, a slight increase in the accumulation of RFP in these joints was detected (119% in the left and 125% in the right), which did not exceed 150%, and there was no conclusion of Mts damage to the skeleton. Other areas of the skeleton were «clean» (Pic. 6).



Pic. 6. Results of planar OSG of patient D. at the National Cancer Institute in 2010

For 12 years, the patient underwent control radionuclide studies at the National Cancer Institute. Changes in the accumulation of RFP in the skeleton were not observed during this time. Already in 2022, by appointment, she underwent OSG in the radionuclide department of the radiological department of the Kyiv City Clinical Hospital No. 18 due to the lack of the drug in the cancer institute (Pic. 7).

As can be seen on the scintiphoto, areas of hyperfixation of RFD in the skeleton were not detected. This pattern was observed until 2024, when in February, hip replacements were performed for the same reason as shoulder replacements. During a scintigraphic examination of the skeleton in August 2024 in the radiology department of the National Cancer Institute, hyperfixation of RPC in the hip joints was already detected (169% and 167%, respectively) (Pic. 8).

Taking into account the diagnosis of the patient, she was given a conclusion – Mts in the hip joints. In other parts of the skeleton (including in the shoulder joints), hyperfixation of the RPC was not detected. Before the study, the patient forgot to inform about the endoprosthesis of hip joints this year. She did not notice a pain syndrome, therefore, in order to calm down, she turned to the radionuclide department of the radiological department of the Kyiv City Clinical Hospital No. 18 for a control OSG in December 2024 (Pic. 9).

According to the results of OSG in patient D. slight hyperfixation of RPC was found in both hip joints (135% and 133%, respectively). But the percentage of phosphate inclusion did not exceed 150% and had a downward trend compared to the data from 08.2024. Other areas of the skeleton were «clean», without hyperfixation of RPC. Therefore, patient D. the conclusion «Osteoscintigraphic signs of the consequences of endoprosthesis of hip joints» was issued. But for additional confirmation of the absence of secondary bone damage, the patient was offered a blood test for the content of AP and IC.

AP (alkaline phosphatase) is an enzyme responsible for the exchange of proteins and fats, as well as the deposition (deposition) of calcium in bones. It is found in many cells of the body, especially in the liver and biliary tract, where it is

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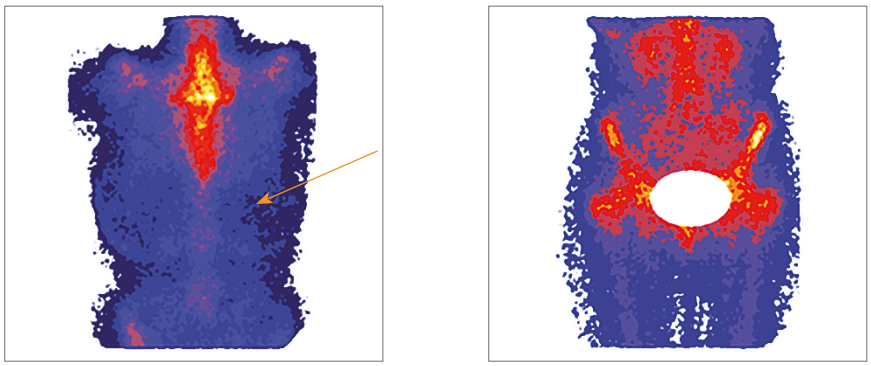
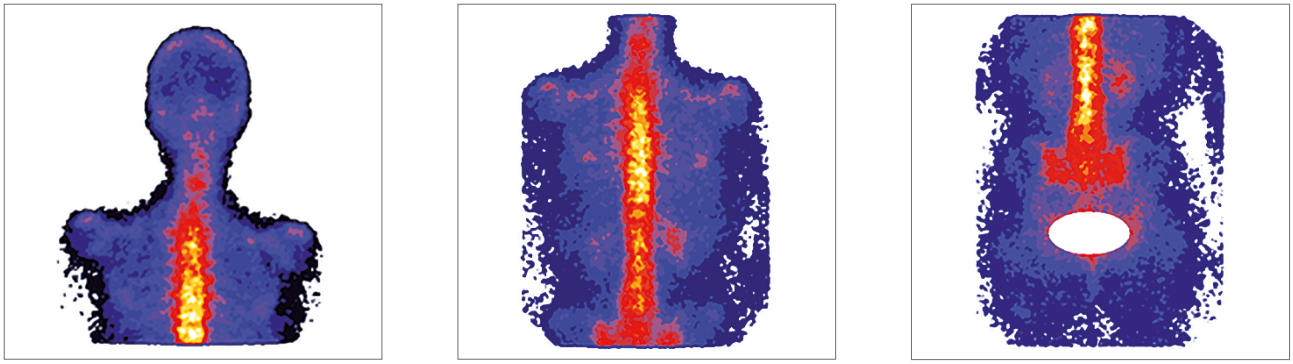


a *– front projections: fields 2, 3, the absence of the left mammary gland is observed (arrow)*



b *– rear projections: fields 1, 2, 3*

Pic. 7. The results of polypositional OSG of patient D. in the radiological department of the Kyiv City Clinical Hospital No. 18 in 2022

involved in important chemical processes. Also, AP is formed in osteoblast bone cells, where it is responsible for the formation, growth and restoration of bones after damage. When these cells are destroyed, it enters the blood. Normally, a certain part of the cells is renewed, so a certain amount of the enzyme is normally present in the blood. When the cells of the organ are destroyed, for example, with Mts in the bones, liver or with hepatitis, a high level of this enzyme is determined in the blood. The greater the scale of destruction, the higher the indicator. It is determined in blood serum in the form of two main fractions (according to the localization of the enzyme) – liver and bone. Bone isoenzyme LF is synthesized and released by osteoblasts in the process of bone formation [10]. The processes of bone formation and destruction are interrelated, in connection with which the level of bone isoenzyme reflects the activity of osteoblasts due to a high process of bone formation or stimulation of osteoblasts due to excessive destruction of bone tissue. To differentiate the origin of AP in Mts in the bones, it is recommended to determine the activity of the bone isozyme [6]. Its increase occurs with bone damage and disease with high activity of osteoblasts. The normal value of this enzyme in postmenopausal women, as in patient D., is in the range of 35-141 units/l. In the presence of Mts in bones, these values can increase 10-15 times. Therefore, in this case, it was appropriate to determine this enzyme. In the patient D. the level of AP was 108 U/L, which did not exceed the upper limit of reference values, which indicated the absence of a secondary malignant process in the bones of the skeleton. And the determined concentration of the enzyme most likely indicated the processes of repair and restoration of cells in the postoperative period.

IC (ionized calcium) is the physiologically active part of blood calcium that is not bound to proteins. Its role in the body is responsibility for the transmission of impulses along nerves, muscle contraction, maintenance of normal heart rhythm, regulation of hormone secretion, cell division, blood clotting, normalization of blood pressure, etc. Free calcium is up to 50% of the total and its level is controlled by

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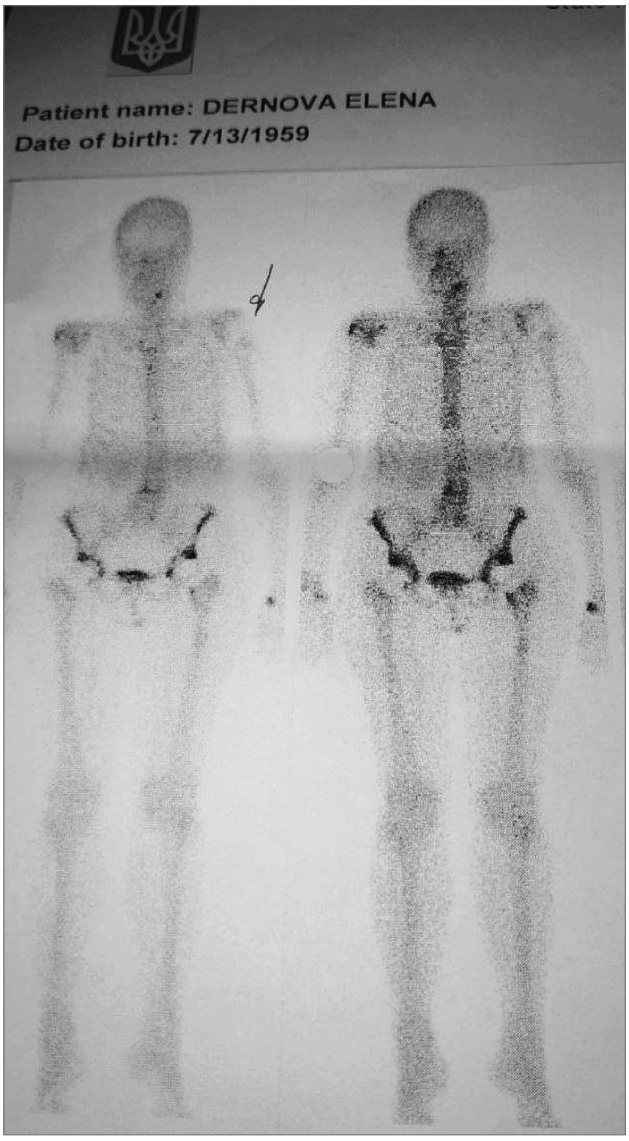

Pic. 8. OSG results in the radiology department of the National Cancer Institute in August 2024

parathyroid hormone, calcitonin, and vitamin D3 (in active form). But calcium also affects the hormonal background. In addition to many pathological processes, its increased level is also observed in oncopathology with metastases in the bones or primary localization of the tumor in the bones. At the same time, hypercalcemia occurs >2.75 mmol/l (up to 90% of cases), with reference values of 1.35-2.55 mmol/l. This is a serious complication of Mts in the bones, which occurs due to the production of large amounts of calcium by osteoclast cells. The level of calcium that enters the blood is several times higher than the kidneys can withstand. This provokes the development of polyuria, and also disrupts the normal functioning of many organs. IC concentration in patient D. was also within the normal range – 1.9 mmol/l, which indicated the absence of a secondary malignant process in the skeleton.

Thus, when performing OSG to detect secondary bone damage by a malignant process, it is always necessary to carefully collect anamnesis, take into account clinical and relevant laboratory data to prevent false conclusions.

Discussion

False-positive interpretation of OSG results for the detection of Mts in the skeleton is primarily related to the primary diagnosis. It is known that breast and prostate cancers, kidney cancer metastasize to bones very early. Therefore, when receiving data of even a small hyperfixation of RPC in any part of the skeleton, they are sometimes interpreted as a secondary lesion. There are appropriate protocols for the management of patients with breast cancer, when, in addition to RCT, a bone scan is prescribed, which is more specific and sensitive, especially for osteoblastic Mts. To make a final verdict in doubtful cases, it is better to use such hybrid studies as SPECT/RCT or PET/RCT. The latest method with fluorodeoxyglucose (18F-FDG) is increasingly used for differential diagnosis, control of treatment, and forecasting of remissions in inflammatory processes in the joints. PET/CT visualizes and quantifies metabolic activity as well as protein expression in vivo and provides a comprehensive, whole-body evaluation, potentially revealing inflammation prior to structural changes in inflammatory joint diseases. It is necessary to approach comprehensively. Pay attention to clinical manifestations, the presence (absence) of pain syndrome, as well as some laboratory indicators characteristic of this oncopathology. And only on the basis of all the results of the study – RCT, OSG and clinical and laboratory data, it is necessary to make a conclusion about the metastatic lesion of the skeleton. Each patient is a separate case, a separate life, and it must always be remembered that a false positive verdict can spoil a person's future life. It should be noted that false negative conclusions also have negative consequences. As a result, timely treatment measures are not carried

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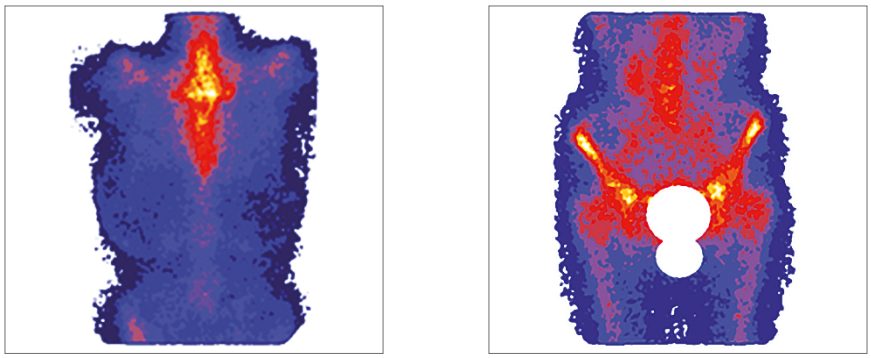
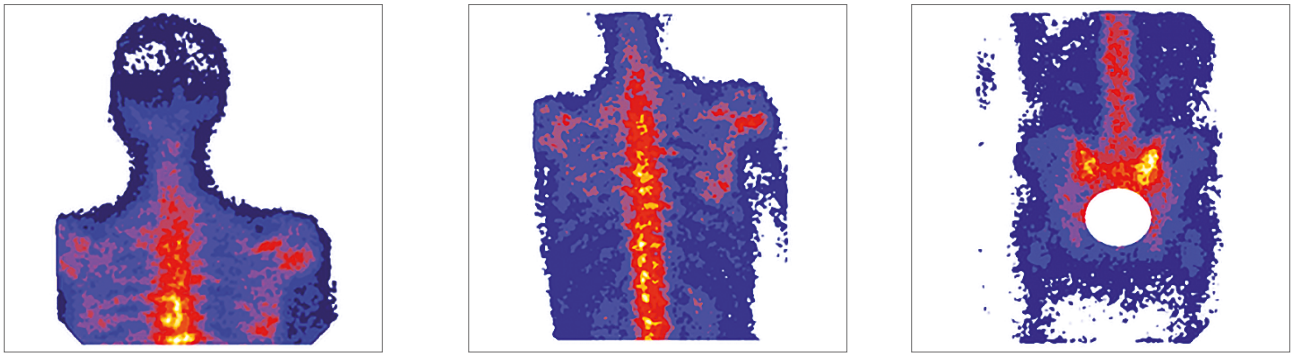


***a** – front projections: fields 2, 3. Slight hyperfixation of the RFD in the hip joints*



***b** – rear projections: fields 1, 2, 3*

Pic. 9. The results of polypositional ultrasound examination of patient D. in the radiological department of the Kyiv City Clinical Hospital No. 18 in December 2024

out, which contributes to the rapid development of the process, deterioration of the quality of life and its shortening. In our case, thanks to repeated radionuclide examination of the skeleton and additional laboratory blood tests for the content of AP and IC, the diagnosis of metastatic lesions of the skeleton in patient D. was removed.

Conclusions

Thus, OSG is a highly sensitive and objective method for differential diagnosis of skeletal lesions of various genesis.

OSG, due to its specificity, detects metastatic lesions of the skeleton with minimal damage, sometimes without clinical manifestations, which allows timely initiation of appropriate treatment.

It may make sense to carry out OSG before endoprosthesis to detect the degree of inclusion of RFP in the corresponding joints for comparison with the postoperative state.

The method of OSG allows differentiation of inflammatory processes in the joints in the postoperative period with metastatic lesions.

Mandatory consideration of OSG results with anamnesis and clinical and laboratory data can prevent both false-positive and false-negative conclusions.

It is necessary to include PET/CT studies in the standard management protocols of patients with endoprosthetics.

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Conflict of interests

This publication does not cause any conflict between the authors, has not been and will not be the subject of commercial interest or remuneration in any form.

Consent to publication

All authors have read the text of the article and gave consent to its publication.

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Випадок помилкових результатів остеосцинтиграфії в пошуках кісткових метастазів після ендопротезування плечових і тазостегнових суглобів

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Анотація: *клінічний випадок демонструє хибність інтерпретації результатів радіонуклідного дослідження опорно-рухової системи без урахування анамнезу та клініко-лабораторних даних. Для пошуку метастазів к кістки в усьому світі використовують остеосцинтиграфію, яка дозволяє діагностувати їх ще на доклінічній стадії розвитку процесу, випереджаючи рентгенологічні на 4-5 місяців. Дуже рано метастазують у кістки рак молочної і передміхурової залоз, а також рак нирки. Біля 50% випадків цих метастазів виявляються при відсутності клінічних проявів, що спонукає регулярно проводити контрольну остеосцинтиграфію незалежно від скарг і клінічного стану хворих. Дослідження проводять на гамма-камерах, а в якості радіоактивного препарату використовують фосфатні сполуки, мічені ізотопом технецію. Через 3 години після його внутрішньовенної ін'єкції активністю 600 МБк в нормі на фоні рівномірного розподілу в кістках відзначається підвищене накопичення в області основи черепа, ребр, кутів лопаток, хребців, кісток тазу, мета-епіфізарних відділах трубчастих кісток. Результати дослідження оцінюються якісно і кількісно. При якісній візуально визначаються гіпервогнища препарату в окремих ділянках скелету. Але саме кількісний аналіз дозволяє зробити висновок щодо вторинного ураження скелету. Різниця накопичення ізотопу в якій-небудь ділянці скелету в порівнянні з неураженою ділянкою вище 150% вважається ознакою метастазів. Слід відзначити, що фосфати, мічені радіоактивним технецієм, іноді дають досить високий рівень фіксації в зонах запальних, дегенеративно-дистрофічних або травматичних процесів. Що ми спостерігали і в даному випадку. Пацієнтці з раком молочної залози двічі було проведено ендопротезування суглобів: спочатку плечових, а потім тазостегнових. Причиною були патологічний остеопороз і дегенеративно-дистрофічні зміни. На подальших контрольних остеосцинтиграмах вогнищ підвищеного накопичення радіофармпрепарату в скелеті не було. Але після другого ендопротезування тазостегнових суглобів через півроку була виявлена гіперфіксація препарату в відповідні суглоби, на підставі чого зроблений висновок метастатичного їх ураження. Пацієнтка не вказувала перед дослідженням про проведене недавнє ендопротезування. Больового синдрому не відмічала.*

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З метою заспокоєння зробила остеосцинтиграфію через 5 місяців. Включення препарату в тазостегнові суглоби значно зменшилося і не перевищувало верхню граничну межу. Відомо, що деякі лабораторні показники, такі як лужна фосфатаза та іонізований кальцій, можуть значно підвищуватися при метастатичному ураженні кісток. У пацієнтки їх вміст був в межах норми. Все це дозволило зняти попереднє заключення щодо вторинного ураження скелету. А підвищене накопичення радіонукліду вважати наслідком післяопераційного втручання. Таким чином, перш ніж виносити вердикт о кісткових метастазах, необхідне ретельне вивчення анамнезу, даних променевого і клініко-лабораторних досліджень.

Ключові слова: метастази, остеосцинтиграфія, плечові суглоби, радіофармпрепарат, рак молочної залози, тазостегнові суглоби, ендопротезування.