Multi-organ extraosseous 99mTc-HMDP uptake in a case of metastatic melanoma

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Summary

99mTc-diphosphonates are a class of radiopharmaceuticals, used for bone scintigraphy, able to highlight all lesions characterised by altered osteogenesis. We report the case of a 47-year-old male with an end-stage melanoma, presenting a multi-organ extraosseous activity.

Patient underwent whole body scintigraphy using a dual head γ-camera, equipped with LEHR collimators. Images were obtained at 3 hours from i.v. injection of 700 MBq of 99mTc-HMDP. Radiochemical purity was 98.2%. The scan showed a decreased skeletal and urinary activity, as well as an intense extraosseous activity in the lungs (especially in the right one), in the stomach, in the liver and a bit lesser in the spleen. Unknown skeletal metastases were also identified. At the time of bone scan, the patient had hypercalcemia and an oliguric acute kidney injury caused by sepsis. Moreover, ultrasound and chest radiography showed the presence of hepatic metastases and radiographic signs of pneumonia in the right lung, respectively.

Soft tissues calcifications can be classified in two groups: metastatic calcifications, where calcium sediments in normal tissues, and dystrophic calcifications, where this deposit occurs only in previously injured organs. Metastatic calcifications mainly occur in patients with end-stage cancers. Indeed, the patient had high levels of calcium, but not a secondary hyperparathyroidism, so other causes must be researched. It’s common knowledge that a high level of calcium can be found in 10 to 20% of cases with advanced cancer. Indeed, the patient had bone metastases and malignant hypercalcemia. The 99mTc-HMDP uptake was different in the two lungs, with a greater intensity in the right one. This pattern is probably due to two causes: hypercalcemia (linked to the end-stage cancer), that explains the bilateral lungs uptake, and an injured tissue, for example in presence of an infection, that generates a greater uptake in the right lung. The increased uptake of 99mTc-HMDP in other patient’s organs was probably due to some of mechanisms already involved in pulmonary calcifications. Moreover hepatic image showed a patchy activity, with some areas of more evident calcifications, probably due to the presence of malignant metastases.

Malignant hypercalcemia depends on several causes, like the osteoclastic bone resorption and the secretion of parathyroid hormone related protein (PTHrP), and may be associated with extra-skeletal images at bone scintigraphy. A previous oxidant injury can contribute to more intense calcifications in the involved tissues.

KEY WORDS: bone scintigraphy; metastatic calcification; melanoma; malignant hypercalcemia; renal failure.

Introduction

99mTc-diphosphonates are a class of radiopharmaceuticals used for bone scintigraphy, being able to highlight all the lesions that produce an altered osteogenesis. They are obtained from commercial suppliers and require a reconstitution with sodium pertechnetate 99mTc in solution. After intravenous injection, the bone uptake depends on calcium density, but also on other important factors, such as patient hydration, Ca/P ratio, perfusion, and bone homeostasis that includes above all the osteoblastic/osteoclastic activity ratio (1). The urinary apparatus is usually visualized, but in other cases extra-skeletal images can be linked with an abnormality of 99mTc-diphosphonates excretory route or with an increased uptake in pathologically altered tissues or organs (2). This kind of images could be noticed in breast glands, in blood vessel calcifications, in postsurgical scars and in thyroid cartilage. Moreover, appearing of calcifications in soft tissues could be due to dystrophic calcifications, calcified metastases, pulmonary calcifications in hyperparathyroidism, myositis ossificans (3). In particular, 99mTc-hydroxymethylene diphosphonate (HMDP) belongs to the class diphosphonates, is a derivative of methylene diphosphonate but, different from it, offers im-
proved physicochemical and biological characteristics (4). It is currently in use from the 80’s. HMDP kit (Osteocis, Iba molecular) has been used in our Nuclear Medicine Unit, at the Hospital of Biella (BI), Italy. Each vial contains 3.0 mg of sodium oxononate (HMDP). 0.45 mg of stannous chloride, 0.75 mg of ascorbic acid and 10.0 mg sodium chloride, in sterile and pyrogen-free environment. 2 to 10 ml of sterile and pyrogen-free sodium pertechnetate 99mTc is introduced in the vial, with a radioactivity range from 0.74 to maximum 11.1 GBq. After 2 minutes of shaking and 15 minutes resting at room temperature, the solution obtained has to be a clear and colorless, with a value of pH from 5.0 to 7.0. Quality control is performed by chromatography on paper. Radiochemical purity has to be more than 95% and the percentage of total hydrolysed 99mTc plus free 99mTc less than 5%. The activity administered by single intravenous injection is between 300 and 700 MBq in a 50-70 Kg adult. Other activities may be justifiable. Intravenously administrated 99mTc-HMDP is quickly distributed in the extracellular space, skeletal uptake beginning almost immediately. Urinary clearance removes about 30% of administered activity in 1 hour, 48% in 2 hours and 60% in 6 hours. Skeletal phase images should be performed not earlier than 2 hours after injection. Hydration of patient before scanning is required and it is important to reach a better urinary wash-out and improve the contrast. If not, a chronic kidney disease can involve in a decreasing accumulation of 99mTc-HMDP in the skeleton and in its altered biodistribution.

Palmer et al. reported that 99mTc-HMDP is a colloidal preparation which may contain particles up to 280 nm in size and that the labeled colloid may aggregate in vitro in presence of calcium salts; these products may be cleared by a reticuloendothelial system like liver or lungs (5, 6). This can be a possible explanation for liver or lungs uptake. We present here the case of a patient in which extraosseous activity has been detected by whole body scintigraphy in lungs, stomach, liver and spleen, probably due both to metastatic calcifications linked with hypercalcemia and to tissue injury.

Case report

We performed a whole body bone scan in a 47-years-old male, presenting an important back pain morphine-treated and positive for skeletal metastases in T5, T6, T7, T8 and in the IX right rib at a recent thoracic column CT. His history has started 6 years before, with the removal of a melanoma in the right shoulder blade (Breslow thickness 1.5 mm, Clark level III); subsequently he underwent surgical excision of the nodule. Hystopathological analysis revealed metastases in 2 lymph nodes on 31, and pulmonary and diaphragmatic metastases of melanoma (stage IV, M1b); molecular analysis revealed the presence of V600E BRAF mutation in the lymph nodes (substitution at the second position of codon 600 (GTG>GAG), which results in an amino acid change from valine (V) to glutamic acid (E) (p.V600E)). After 3 months, hospitalization was necessary since he began to feel an acute back pain and showed a general deterioration of health, so requiring necessarily a morphine treatment.

Whole body scintigraphy was performed on patient using a dual head γ-camera (Millennium VG Varicam), equipped with a high-resolution parallel-hole low-energy collimator. Images were obtained after almost 3 hours from i.v. injection of 700 MBq of Tc99m, HMDP (Osteocis, Iba molecular). Radiochemical purity was 98.2%. These images showed a decreased skeletal and urinary activity, as well as an intense extraosseous activity in both lungs (especially in the right one), in stomach, in liver and a bit lesser in spleen. Moreover, bone scan detected unknown skeletal metastases in right pubis and left femur (Figure 1). Ultrasound and chest radiograph also showed hepatic metastases of liver segments S4, S6, S7 and a diffuse opacification of the right lung only, respectively (Figure 2, left panel).

At the time of bone scintigraphy, patient had hypercalcemia (7.4 mEq/l) and an oliguric acute kidney injury probably caused by sepsis; the day before, blood test revealed high values of creatinine (5.26 mg/dl, with glomerular filtration rate of 11.99 ml/min), white blood cells (13400 x mmm), neutrophil lymphocyte (9058 x mmm) and c reactive protein (31.7 mg/dl). The patient, already subjected to antibiotic therapy, subsequently underwent an hemodialysis treatment; he died ten days later cause of multi-organ dysfunction linked to terminal stage cancer.

Discussion

A number of pathologic conditions predisposes to soft tissue calcification. The organs most commonly affected by ectopic calcifications are stomach, kidneys, lungs, heart and blood vessels, but the lungs seem particularly susceptible to this complication. Pulmonary calcification occurs with a number of systemic and pulmonary conditions that are mainly classifiable in metastatic calcification by benign and malignant causes, in which calcium deposits in normal tissues, and dystrophic calcification, in which calcium deposits in previously injured lungs (7, 8).

Metastatic calcification occurs mainly in patients on hemodialysis for chronic renal insufficiency, as a result of hyperparathyroidism and acidosis in the interdialytic interval; in addition, the reduced glomerular filtration causes hyperphosphatemia and, consequently, an increased calcium-phosphate product (9). Metastatic calcifications are influenced by serum calcium, phosphate concentration, alkaline phosphatase activity and local pH. When conditions promoting calcium release from bone occur, Ca3(PO4)2 and CaCO3 salts are transported in soluble form, primarily as CaHPO4 and then precipitate as Ca3(PO4)2 and CaCO3 in tissues with favorable environment like an alkaline pH (8, 10). In fact organs more susceptible to metastatic calcification secret free hydrogen ions creating an alkaline environment (8, 10, 11). Moreover, pH of the blood in the lungs is more alkalotic than other tissues due to CO2 taking out and presents a apex-base gradient. Lingman et al. described the case of a man with chronic renal failure presenting a 6 month history of progressive dyspnea in which high resolution CT of the chest showed multiple nodules in the upper
and middle zones (12). A predisposing role in ectopic calcification is played from alkaline phosphatase that operates at an alkaline pH promoting calcium-phosphate products. It is present in almost all tissues but those more represented are bone and liver. On the other hand, a high concentration of alkaline phosphatase is not sufficient by itself to generate soft tissue calcification (8).

Differently from metastatic calcification, dystrophic calcification requires injured tissue, even in the absence of increased serum calcium levels (9). Cotran et al. suggest that cell necrosis caused by oxidant injury and inflammation is accompanied by degradation of phospholipids into fatty acids and, subsequently, by binding of calcium to the fatty acids. It is the “initial phase” of dystrophic calcification, then followed by a “propagation phase” resulting in an increase of the initial nidi (8, 13).

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Figure 1 - Bone scintigraphy: images show a decreased skeletal and urinary activity and an intense extraosseous activity in both lungs (especially in the right one), in stomach, in liver and in spleen. Moreover, bone metastases are poorly visualized in T6, T7, right pubis and ischiopubic ramus, and in the left femur.

Figure 2 - Chest radiography. Left picture: chest radiography (one day after bone scintigraphy) detected opacification suggesting a pneumonia in the top-middle of the right lung. Right picture: chest radiography (four days later) shows diffuse opacification of the right lung.
Our patient had high level of calcemia (7.4 mEq/l). Chest radiography one day after bone scintigraphy detected opacification suggesting a pneumonia in the top-middle of the right lung, then evolved in a diffuse opacification four days later; however, the left lung showed normal findings (Figure 2, right panel). It is known that standard chest radiography has a less sensitivity for the identification of parenchymal calcifications (8, 9). 99mTc-HMDP uptake was different in the two lungs, with a greater intensity in the right one. This scintigraphic pattern is probably due to different causes: a) a hypercalcemia linked to the end-stage cancer and an acute renal insufficiency, that explain a bilateral lung uptake, and b) the presence of injured tissue such as infected or inflamed lung tissue, that explains a greater uptake in the right lung.

About hypercalcemia, metastatic calcification mainly occurs in patients with chronic renal failure accompanied by secondary hyperparathyroidism, however in our case other causes must be searched. It is common knowledge that a high level of calcemia can be found in 10 to 20% of cases with advanced cancer, causing an oncologic emergency (14). In particular, the most commonly involved diseases are myeloma and renal, breast, or squamous cell tumors of any site, particularly lung, but any tumor can cause it. There are four forms of malignant hypercalcemia: a) osteolytic hypercalcemia, that depends on osteoclastic bone resorption; b) humoral hypercalcemia, caused by systemic secretion of parathyroid hormone (PTH) – related protein (PTHrP); c) hypercalcemia found in some lymphomas, that secrete the active forma of vitamin D; d) hypercalcemia caused by ectopic secretion of authentic PTH, that is a rare form (15). Attia et al. founded a 4.9% of incidence of hypercalcemia in 1146 consecutive patients treated for metastatic melanoma at the Surgery Branch of the National Cancer Institute between January 1, 1988 and March 31, 2000. They also reported the case of a patient with stage IV malignant melanoma, without evidence of bone metastases, presenting severe hypercalcemia associated with elevated PTH-rP levels. Immunohistochemistry showed strong expression of PTH-rP in biopsy of the patient’s subcutaneous masses (16).

Our patient had bone metastases and PTH-rP serum concentration was not detected, but we can hypothesize it could have played a role; hypercalcemia, evident since 15 days before bone scanning (6.7 mEq/l) without renal insufficiency (creatinine 1.1 mg/dl), was probably increased by an acute renal failure. On the other hand, an impaired renal insufficiency is a prerequisite for having calcium-phosphate product (9, 17, 18). This important factor has been found in our patient and, probably, has contributed to justify the presence of calcifications in different organs (Figure 3).

The increased uptake of 99mTc-hydroxymethylene diphos-
phonate in other patient’s organs, particularly in stomach, liver and spleen, was probably linked to some of the mechanisms already involved in pulmonary calcification, such as the elevate value of the calcium and the alkalosis. Moreover, hepatic image showed a patchy activity with some areas presenting more intense calcifications. These areas could in part reflect the presence of malignant metastases.

Conclusions

In patients with an end-stage melanoma and renal failure, undergoing bone scanning, it is possible to observe an extraosseous 99mTc-diphosphonates activity in several organs and tissues. This could depend on malignant causes likely related to both osteolytic hypercalcemia by osteoclastic bone resorption and humoral hypercalcemia by systemic secretion of PTH-rP. Previous oxidant injury and inflammation can contribute to a more intense calcification in the involved tissues.

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References