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Brown tumors mimicking bone and lung metastases: Key role of radionuclide imaging

Tumeurs brunes mimant des métastases osseuses et pulmonaires : rôle clé de l'imagerie isotopique

Hypercalcemia is frequently observed in cancerology and leads to suspecting bone metastases [1]. However, a clinician must not forget a common cause of benign hypercalcemia: hyperparathyroidism [2]. Hyperparathyroidism rarely complicates by brown tumors. These may mimic metastatic lesions leading to an inappropriate therapeutic management [3]. We report the case of a patient followed for breast carcinoma with suspected bone, lung and liver metastasis. She had hypercalcemia and lytic bone lesions motivating a bone scintigraphy to search bone metastases. The bone scan showed focal uptake abnormalities consistent with metastatic lesions. However, further radionuclide investigations confirmed the diagnosis of brown tumors complicating a parathyroid adenoma and mimicking lung and bone metastases.

Case report

Our case is a 53-year-old woman, followed for left breast carcinoma. She had undergone left mastectomy and axillary lymph node dissection. The histopathologic examination showed a 1.3 cm infiltrating ductual carcinoma staged T1N0M0 and SBR2 with positive estrogen receptors. She had anti-estrogen hormonotherapy for 5 years. Three years after the end of this treatment, an abdominal ultrasound examination suspected liver metastases and computed tomography (CT) was indicated. In addition to the liver masses, CT scan showed lytic bone lesions within the 9th dorsal vertebra, the sacrum and both iliac bones evoking bone metastases. A right lung metastasis was suspected on the lung window of the CT scan and on the planar thoracic radiography. The patient also presented hypercalcemia reaching 3 mmol/l suggesting bone metastases and hormonal therapy and bisphosphonates were prescribed. She was referred to our department to undergo a bone scintigraphy. The whole-body scan performed 2 hours after intravenous injection of 666 MBq of ^{99m}Tc-hydroxymethylene diphosphonate (^{99m}Tc-HMDP) showed several foci of moderately increased uptake within both axial and peripheral skeleton (*figure 1*A), which was compatible with secondary bone lesions. Scintigraphy was also characterized by a diffuse skeletal high uptake with prominent calvarium. This aspect, in the context of hypercalcemia, helped us to suspect a metabolic bone disease such as primary hyperparathyroidism (PHPT). The parathyroid hormone (PTH) was assayed and its high level of 227.7 pmol/l (the reference range for the laboratory was 1.6–6 pmol/l) confirmed hyperparathyroidism.

The patient was then referred for parathyroid scintigraphy. Planar images and hybrid single-photon emission computed tomography-computed tomography (SPECT/CT) were performed after intravenous injection of 592 MBq of ^{99m}Tc-sestamibi. The examination was carried out with pin-hole then parallel collimators focused respectively on the neck and the thorax. Planar images showed a large area of pathological uptake of the radiotracer projecting below the lower pole of the right thyroid lobe suggesting an abnormal parathyroid (*figure 2*A) and a posterior right thoracic area of pathological sestamibi uptake (*figure 2*B). The cervico-thoracic SPECT/CT and the fused images, beside confirming and localizing the pathological parathyroid gland, revealed numerous foci of ^{99m}Tc-sestamibi uptake within the rib cage, scapulae and clavicles corresponding to lytic bone lesions. Since similar lytic bone lesions of the spine and pelvis were previously described on the CT scan as bone metastases, all the bone lesions seen on the ^{99m}Tc-HMDP bone scan were, at first, thought to be related to bone metastases and a whole body scan with ^{99m}Tc-sestamibi was not performed. After consulting a second radiologist, the largest lesion which corresponded on the CT scan to a 9 cm lytic mass within the sixth right rib expanding into the pulmonary parenchyma, containing amorphous calcifications and without periosteal reaction or invasion of the adjacent soft tissue suited the diagnosis of brown tumor more than bone metastasis (*figure 2*B). The other thoracic foci also corresponding to lytic lesions of tissular density, with sclerotic borders and without periosteal reaction were also consistent with brown tumors. All these brown tumors mimicked bone metastasis on the bone scintigraphy and the largest one mimicked a lung metastasis on the lung window of the previous CT scan. The patient successfully underwent surgery with removal of a 3 cm lower right parathyroid mass. Histology confirmed a parathyroid adenoma. PTH levels decreased considerably after surgery and the patient presented hypocalcaemia for which she was treated with calcium and vitamin D. At this level it was most probable that the abnormal foci of high uptake on the bone scan would be related to brown tumors. But, with no histological proof, the metastatic origin of some of these foci could not be excluded.

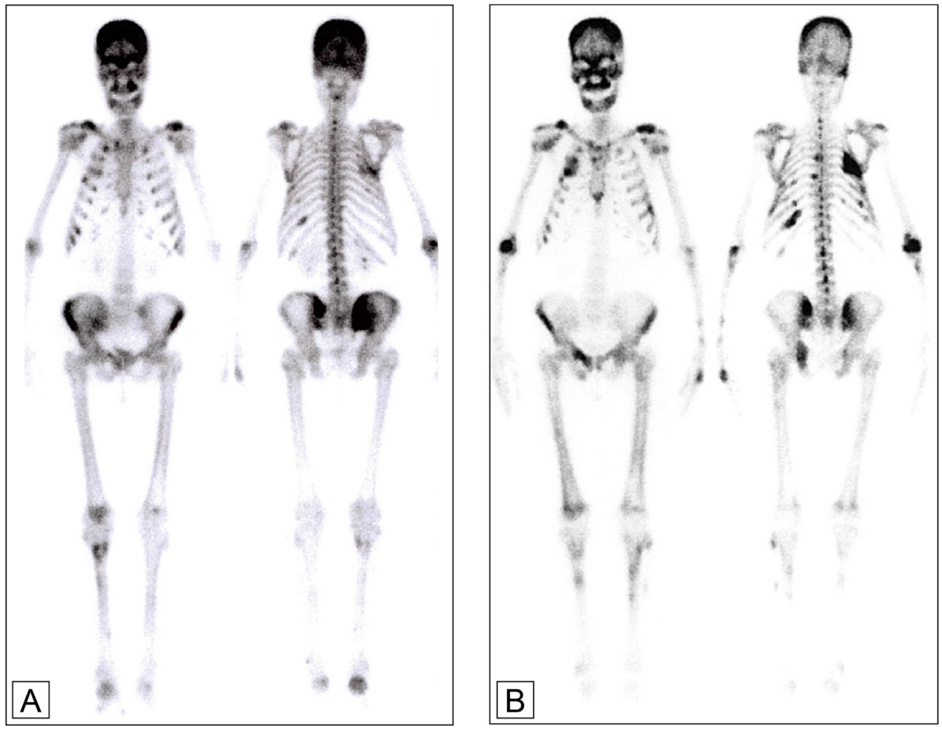

FIGURE 1

A. Whole body bone scan with ^{99m}Tc-HMDP showing a generalized increased uptake throughout the skeleton with prominent calvarium and multiple foci of moderately increased uptake on axial and peripheral skeleton. B. Post-surgical whole body bone scan showing a flare-up of the previously diagnosed and new foci of high uptake within axial and peripheral skeleton related to a hungry bone syndrome, and a slight decrease of the calvarium uptake

Four months after surgery, a second ^{99m}Tc-HMDP whole-body bone scintigraphy under the same conditions showed an intense bone uptake within the previously diagnosed lesions and some new foci (*figure 1*B). These foci were corresponding, on the whole-body SPECT/CT, to the previously suspected brown tumors with marked central calcifications. This aspect was compatible with a "hungry bone syndrome'' and confirmed the diagnosis of brown tumors. Magnetic resonance imaging of the liver diagnosed biliary cysts instead of liver metastases and a biological assay showed a normal level of tumor markers. Thus, the hormonal therapy and bisphosphonates were discontinued.

Discussion

Hypercalcemia is the most common metabolic complication of breast cancer found in 30% to 40% of cases [4] and is often related to local osteolysis by massive bone metastases. It may also result from the presence of factors produced by the tumor cells as PTHrP causing humoral hypercalcemia of malignancy [1,5].

Bone scintigraphy is a very sensitive technique used for the detection of local changes in bone metabolism like metastatic lesions [6] and has an undisputed place in the assessment of the skeletal tumor burden in patients with cancer and hypercalcemia [1]. About 90% of patients with skeletal metastases have multiple lesions, and the number of abnormal foci on the bone scan increases the probability of a metastatic origin. However, because of the large variety of conditions that may be causing an increased bone turnover, the bone scan lacks specificity [6]. PHPT is one of the most frequent causes of benign hypercalcemia [2] and is caused in 85% of cases by a parathyroid adenoma [5]. Studies have shown that the frequency of PHPT is greater in the presence of breast cancer than it is in the general female population (2.88% in breast cancer patients against 0.04%–0.08% in all adult women) [5,7]. Thus, this etiology of hypercalcemia should not be forgotten in a cancer patient even when bone metastases are present or suspected.

Skeletal symptoms are seen in less than 5% of cases of PHPT. Severe skeletal changes, termed osteitis fibrosacystica, are caused by a generalized increase in osteoclastic bone resorption, accompanied by fibrovascular marrow replacement and increased osteoblastic activity. Aggregates of osteoclasts, reactive giant cells and hemorrhagic debris occasionally form a mass known as brown tumor, which represents the terminal stage of bone remodeling [3]. Brown tumors rarely complicate PHPT (in 3% of cases) [8] and may be asymptomatic [9]. Symptoms

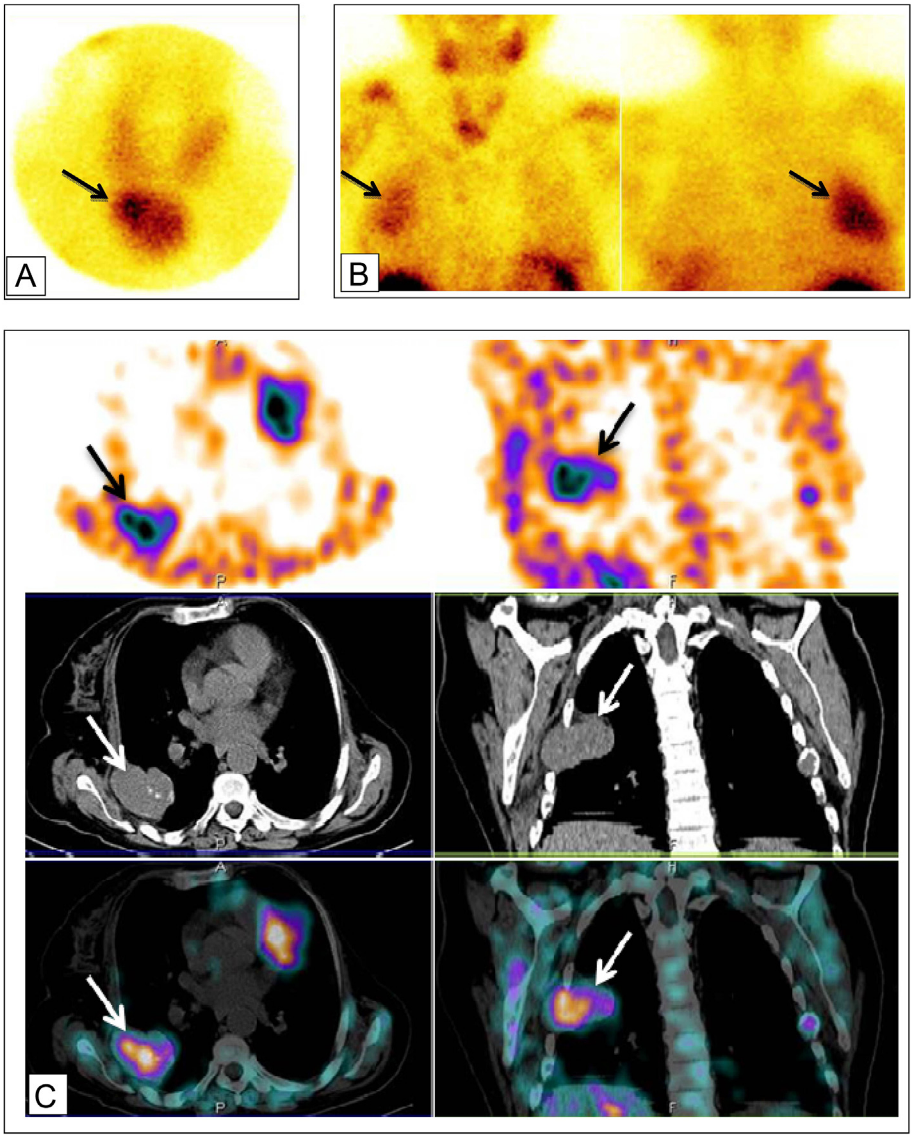

FIGURE 2

A. Parathyroid scintigraphy with ^{99m}Tc-sestamibi showing an area of pathological sestamibi uptake below the lower pole of the right thyroid lobe suggesting a pathological parathyroid gland. B. Anterior and posterior views of a planar thoracic scintigraphy with ^{99m}Tc-sestamibi showing a posterior right thoracic area of pathological sestamibi uptake. C. Cervico-thoracic SPECT/CT with ^{99m}Tc-sestamibi showing sestamibi uptake by a large lytic mass within the sixth right rib, expanding into the pulmonary parenchyma, containing amorphous calcifications and without periosteal reaction or invasion of the adjacent soft tissue

related to brown tumors depend on their size, their site and the nature of the adjacent structures. Bone pain, fractures and neurological deficit were described [10,11]. These lesions and related symptoms usually regress after correction of the hyperparathyroidism [9].

Brown tumors have no specific radiological features and appear as single or most frequently multiple well-defined osteolytic lesions of the axial or appendicular skeleton that can be mistaken for bone malignancies [3,6]. The absence of periosteal reaction or soft tissue invasion suggests their benign nature [11,12]. The appearance of brown tumors is not specific on the bone scan either, where they result in foci of increased uptake which may look like bone metastases [9]. Nevertheless, associated scintigraphic features of metabolic bone disease may suggest PHPT and thus brown tumors. These features consist of a generalized increased uptake throughout the skeleton with prominent calvarium and mandible, beading of the costo-chondral junctions and a "tie" sternum [13]. In our case, this metabolic superscan aspect, despite the presence of multiple high uptake foci suggestive of bone metastases, allowed us to suspect associated PHPT.

Since oxyphil cells are rich in mitochondria which are the site of intracellular sestamibi sequestration, parathyroid scintigraphy with ^{99m}Tc-sestamibi has a good sensitivity for the detection of parathyroid adenomas [14]. A positive scan is correlated to the size of the adenoma and the ionized calcium levels. The procedure may include a hybrid SPECT/CT acquisition, which is useful in localizing the pathological parathyroid gland and identifying ectopic adenomas [9]. This precise location is helpful to perform minimally invasive parathyroidectomy [15]. Sestamibi uptake within brown tumors and bone metastases has also been described [14,16]. In our case, while the ^{99m}Tc-sestamibi scintigraphy visualized the abnormal cervical and thoracic uptake, SPECT/CT allowed us to localize the parathyroid adenoma and the bone lesions. In the context of hyperparathyroidism, the absence of periosteal reaction or soft tissue invasion by these bone lesions was in favor of brown tumors and the diagnosis of bone metastases was revised. Multiple brown tumors without focal uptake of sestamibi were also described and are thought to be related to a lack of mitochondria in these lesions. In such cases, ^{18}F-FDG PET/CT scan might enable the depiction of the brown tumors. The intracellular glucose metabolism of the giant cells macrophages has been suggested to partly explain the increased ^{18}F-FDG uptake [17].

Following a successful surgery, abrupt lowering of serum PTH levels causes a decrease in bone resorption as well as an increase in bone formation and minerals uptake such as calcium resulting in its low serum levels [18]. Hungry bone syndrome is a common complication of the parathyroid surgery present in 13% to 30% of cases and is related to a rapid bone remineralization [3]. This syndrome causes a flare-up of previously faintly visualized or non-visualized lesions on the bone scan, indicating the "hungry bone state" and increased bone formation [18]. This flare-up phenomenon encountered in our case is also in favor of the diagnosis of brown tumors instead of bone metastases. Thus, while there is no histological proof, the comparison of the pre-surgical and post-surgical bone scan lesions, the post-surgical resolution of hypercalcemia and a normal level of tumor markers allowed us to assume that there were only brown tumors and no bone metastases.

Beside rarity, originality of our work lies in the key role that radionuclide imaging procedures had in leading to the diagnosis of hyperparathyroidism, localizing the parathyroid adenoma, diagnosing brown tumors that mimicked bone and lung metastases and finally allowing a more appropriate therapeutic management.

Disclosure of interest: the authors declare that they have no conflicts of interest concerning this article.

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Hela Charfi[1], Manel Nouira[1], Faten Ezzairi[2], Raja Sfar[1], Mohsen Guezguez[1], Habib Essabbah[1]

[1]University hospital Sahloul, department of nuclear medicine, 4054 Sousse, Tunisia
[2]University hospital Farhat-Hached, department of cancerology, Sousse, Tunisia

Correspondence: Hela Charfi, university hospital Sahloul, department of nuclear medicine, 4054, Sousse, Tunisia
helacharfi29@gmail.com

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