Jacek Teodorczyk[1], Wojciech Cytawa[1], Bogna Brockhuis[1], Piotr Lass[1, 2]
[1]Department of Nuclear Medicine, Medical University of Gdańsk, Poland
[2]Department of Molecular Spectroscopy, Institute of Experimental Physics, University of Gdańsk

Advanced, lately diagnosed primary hyperparathyroidism in a patient mistakenly treated for multiple bone metastasis. A case report and review of the literature

Abstract

We report a case of 66-years-old woman mistakenly diagnosed as a metasases' dissemination on a basis of mulitifocal skeleton lesion showed by 99mTc-MDP scanning, high serum calcium level and a vague breast tumour history. Additionally she suffered had humer and femur fractures. Immobilised and diagnosed as a cancer patient, she he was referred to palliative care. In hospice for the first time the suspicion of hyperparathyroidism was raised. When 99mTc-MIBI SPECT/CT scan revealed a parathyroid adenoma, also considering her biochemical parameters, she underwent the surgery. Following this her biochemical parameters normalised. This case illustrates a pitfall, which sometimes happens in this rare disease. A review of literature is provided.

Key worsds: parathyroid, hyperparathyroidism, 99mTc-MIBI, scintigraphy, metastases

Adv. Pall. Med. 2012; 11, 2: 77–82

Introduction

The incidence of primary hyperparathyroidism (PHP) is 42 per 100,000 of population. In a group of women over 60 years of age its incidence is higher and reaches 4 per 1000. In about 80% of cases a single parathyroid adenoma is responsible for clinical symptoms [1], which are as follows: fatigue, musculoskeletal pain, polyuria, nocturia, polydipsia, constipation, heartburn, memory loss, and depression [2]. Late skeletal manifestation of primary, secondary and tertiary hyperparathyroidism are bone focal lesions known as brown tumors [3]. Primary hyperparathyroidism may lead to clinical pitfalls. PHP diagnosis is based on elevated serum calcium level, and parathormone level simultaneously. Increased calcium level in daily practice should raise suspicion of parathyroid hyperactivity. Unfortunately, patients with oncologic anamnesis can mistakenly be treated as patients with metastatic bone disease.

Case report

A 66-years-old woman was referred to Nuclear Medicine Department to perform MIBI-Tc99m scintigraphy with intention to localize the hyperactive parathyroid gland. She was admitted to hospital with high level of parathormone and calcium. The patient's medical history has began in 2003 with a diagnosis of osteopenia detected in routine den-

Address for correspondence: Jacek Teodorczyk, MD
Department of Nuclear Medicine, Medical University of Gdańsk 80–211 Dębinki St. 7 Poland
Tel./fax.: + 48 (58) 349 22 00
e-mail: badklin@gmail.com

Advances in Palliative Medicine 2012, 11, 77–82

sitometry. It was interpreted as a postmenopausal osteoporosis and was treated with calcium administration. Densitometry repeated in 2008 revealed progression of osteopenia. Because of joints' swelling and pain she was referred to rheumatologist who discovered elevated calcium level (3,34 mmol/l) and alkaline phosphatise FALK (233 U/L normal values — 32–104 U/L). She was advised to consult oncologist and gynaecologist. One year later she had a fracture of left humeral neck during routine daily activities. No laboratory tests were conducted in emergency room. She was advised to consult an oncologist. This wrong direction of diagnostic process probably resulted from breast tumor resection in anamnesis, which in fact turned out to be benign. She was mistakenly treated as cancer patient with skeletal localization of metastatic disease — brown tumours were wrongly classified as bone metastases. In 2010 she manifested renal colic episode. JJ-catheter in the left ureter was implanted. In December 2010 she was referred to bone scintigraphy in our department, performed with 99mTc-MDP. It revealed increased multiple focal uptake in left clavicle, left tibia, right scapula suggesting that it might correspond to multiple metastases, however the diffused skull uptake and general impression might suggest the disturbances in calcium–phosphate metabolism (Figure 1).

A few months later patient had another fracture — of right femoral neck. Because of immobilization and classifying the patient as oncologic with multiple bone metastases, she was referred to hospice.

The physician in palliative care unit for the first time raised the suspicion of hyperparathyroidism. He holistically analyzed the patient's history considering all available data, including calcium and phosphate levels, densitometries, bone scintigraphy, clinical symptoms and repeated calcium and phosphate tests, additionally verifying parathormone level. Parathormone turned out to be 1238 pg/ml and calcium was 12.06 mg/dl, which finally confirmed the diagnosis. Ultrasound revealed no focal abnormality corresponding to parathyroid gland. She was then referred to our nuclear medicine department to perform dual-phase MIBI-Tc99m planar scintigraphy with additional, tomographic SPECT-CT imaging. Planar imaging was performed 20 minutes and 120 minutes after injection of 740 MBq of MIBI-Tc99m solution. SPECT-CT study of neck and upper thorax was performed 130 minutes after tracer administration. Planar and SPECT/CT imaging was performed using standard double-head SPECT/CT gamma camera (Symbia T6, Siemens, Erlangen Germany). CT scan was a low-dose, non-contrast study. The scan revealed retention of tracer in delayed phase, which was considered to be hyperactive parathyroid gland. Tomographic and hybrid SPECT/CT imaging allowed to precisely assess the structure and localization of the gland: its size was 51 x 27 x 26 mm and it was localized between trachea and vertebral column, at the level of C6-Th2.

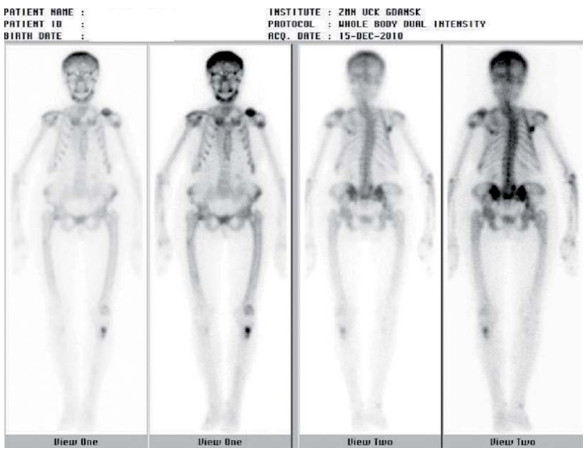

Figure 1. Increased 99mTc-MDP focal uptake in left clavicle, left tibia, right scapula suggesting brown tumors and raised diffuse uptake in skull typical for calcium-phosphate metabolic disturbances

The SPECT/CT also showed high accumulation of MIBI-Tc99 in the brown tumor of left clavicle (Figure 2). In October 2011 she was operated — the removed tumor was parathyroid adenoma. Biochemical parameters were normalized.

Discussion and review of literature

Our patient's history is an unfortunate example of a long and incorrect diagnostics with the happy ending. She was early classified as a cancer patient, despite only a benign breast tumor history, which considerably delayed the final correct diagnosis. High calcium levels were misinterpreted as a consequence of bone metastases. Skeletal pain was interpreted as a sequelae of metastatic or rheumatologic disease and pathological fractures.

Such stories however happen. There are several reports on brown tumors or osteitis fibrosa cystica mimicking bone metastases on 99mTc-MDP or 99mTc-MIBI scintigraphy in the literature [4–22]. False positive results may also happen at PET scanning [23–25]

It should be remembered that brown tumors may also rarely appear in a deep vitamin D deficiency [26].

Brown tumor is a form of osteitis fibrosa cystica (OFC), first described by Engel in 1864 and von Recklinghausen. When OFC usually presents as osteomalacia, brown tumor is its localized form. The pathology involves excessive osteoclast resorption with

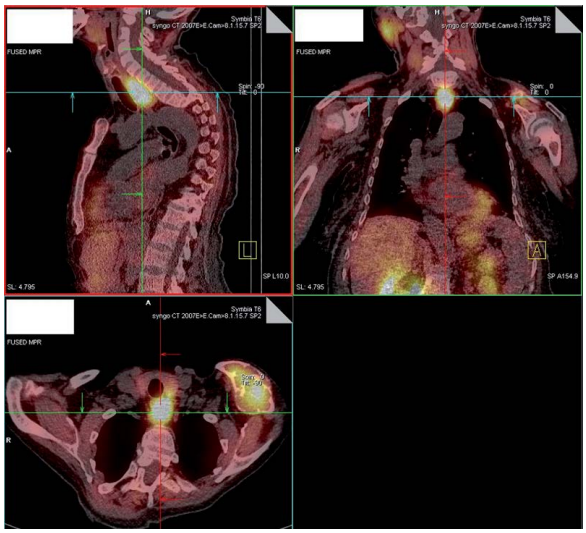

Figure 2. SPECT-CT with 99mTc-MIBI presenting high uptake in primary parathyroid adenoma localized retrotracheally and in brown tumor of left clavicle

destruction of cortical bone, proliferation of fibrotic tissue and formation of fibrous cysts [27]. Brown tumours may be observed in facial bones — particularly the jaws, also in ribs, pelvis, humerus and femur, also in vertebrae. It has nothing common with brown adipose tissue, its brow colour originates from blood-originating hemosiderin. From the orthopaedic point of view, the risk of pathologic fracture is of concern when a brown tumour corrupts over 2/3 of the long bone cortex, especially in the weight bearing area [20, 28]. After the parathyroidectomy usually quite rapid regression of brown tumour follows [29, 30], although the refractory cases may happen [31].

The sources of pitfalls in brown tumours diagnostics are numerous.

First, brown tumours are today fairly rare, because the screening improvements in laboratory medicine since the advent of multichannel analyser enables early diagnosis and treatment of hyperparathyroidism [27, 32, 33]. The widespread of bone densitometry enabled wide screening of those patients and they are referred to surgeon much sooner with a lesser degree of hypercalcemia and greater recognition of osteoporosis [33]. In rare cases the brown tumour may be the first manisfestation of hyperparathyroidism [34]. In Europe today this condition became quite rare. Therefore clinicians sometimes simply forget this possibility.

On histological exam the lesion may mimic a giant cell tumour of bone [35], therefore a bone biopsy may be quite contributing or even decisive [20, 29, 30], but not in all cases.

Radiologically, the multiple osteolytic lesions may be indistinguishable from metastases [36].

This refers also to CT and MRI scanning [17, 30, 37]. On the other hand MRI may be important for determination of hemorrhage, cystic component and indirect estimation of fracture risk in brown tumour [18, 38]. MRI scanning can depict the nature of the tumour: solid, mixed solid, cystic or purely cystic, discontinuity of bone cortex and adjacent soft tissue enhancement, fluid levels [39]. It may be important for progniosis, but little useful in differential diagnosis.

On 99mTc-MDP scanning false positive diagnosis a metastases' dissemination may be not distinguishable from brown tumours as a results of low specificity of bone scanning, visualising any focal bone lesion, including also several other benign conditions like trauma, infections and metabolic bone diseases [7, 11, 13, 14, 16, 21, 40]. Single focus of increased radiotracer's uptake may represent metastasis in about 50% in patient with an established cancer diagnosis. Even in multiple foci up to 35% of rib lesions and 53% of spine lesions may not be of metastatic character [14, 40].

On 99mTc-MIBI scanning radiotracer's accumulation is visible in some [6, 7, 17, 27], but not all brown tumours [8]. The precise mechanism for the increased uptake of 99mTc-MIBI in a brown tumour is not fully elucidated, but probably it is secondary to increased perfusion, metabolism and osteoclastic activity [7, 27]. Some authors argue that parallel multifocal uptake both in99mTc-MDP or 99mTc-MIBI scanning may lead to correct multiple brown tumours diagnosis [19], it should be remembered however that sestamibi uptake may happen in metastases of diverse origin [41]. Also 99mTc-MDP scanning may be positive at negative 99mTc-MIBI findings, when a lytic component is predominant [16].

PET scanning may be contributory, but it was reported to produce false positive results, mimicking mestastases dissemination as well [42–45]. It may detect brown tumour foci with great sensitivity, but it lack parameters SUV including for the differential diagnosis [20]. Sometimes it can elucidate previously false-negative scintigraphic findings [46]. PET also can be useful in staging and restaging of parathyroid carcinoma bone metastases [47].

Summary

Therefore, facing all the diagnostics problems mentioned above the most important is clinical approach. Diagnostic imaging is important for estimating of diseases extent, but little contribut-

ing to differential diagnosis. In such cases, as ours, it may be even misleading. Brown tumour should always be in mind on the clinician's list of differential diagnoses when multiple osteolytic lesions are encountered [20]. Then, the synthetic analysis of clinical, laboratory and radiological data is necessary. Patients with hypercalcaemia and multifocal skeletal lesions should not be treated palliative way just because a cancer in their past medical history. Hyperparathyroidism is curable disease, providing the proper diagnosis is established.

References

1. Łącka K. Molecular aspects of the etiopathogenesis of the parathyroid gland diseases. Endokrynol. Pol. 2005; 56: 327–333.
2. Taubman M.L., Goldfarb M., Lew J.I. Role of SPECT and SPECT/CT in the surgical treatment of primary hyperparathyroidism. Int. J. Mol. Imaging 2011: 141593.
3. Brown T.W., Genant H.K., Hattner R.S. i wsp. Multiple brown tumors in a patient with chronic renal failure and secondary hyperparathyroidism. Am. J. Roentgenol. 1977; 128: 131–134.
4. Bassler T., Wong E.T., Brynes R.K. Osteitis fibrosa cystica simulating metastatic tumor. An almost forgotten relationship. Am. J. Clin. Pathol. 1993; 100: 697–700.
5. Joyce J.M., Idea R.J., Grossman S.J. i wsp. Multiple brown tumors in unsuspected primary hyperparathyroidism mimicking metastatic disease on radiograph and bone scan. Clin. Nucl. Med. 1994; 19: 630.
6. Lu G., Shih W.J., Xiu J.Y. Technetium-99m MIBI uptake in recurrent parathyroid carcinoma and brown tumors. J. Nucl. Med. 1995; 36: 811–813.
7. Pai M., Park C.H., Kim B.S. i wsp. Multiple brown tumors in parathyroid carcinoma mimicking metastatic bone disease. Clin. Nucl. Med. 1997; 22: 691–694.
8. Caglar M., Naldöken S. Multiple brown tumors simulating bone metastases: a case of parathyroid adenoma coexisting with papillary carcinoma of the thyroid. Clin. Nucl. Med. 2000; 25: 772–774.
9. Gupta A., Horratas M.C., Mattari A.R. i wsp. Disseminated brown tumors from hyperparathyroidism masquerading as metastatic cancer: a complication of parathyroid carcinoma. Am. Surg. 2001; 67: 951–955.
10. Ohnishi H., Abe M., Miyagawa M. i wsp. Tl-201, Tc-99m sestamibi, and Tc-99m HMDP uptake in multiple brown tumors. Clin. Nucl. Med. 2003; 28: 601–603.
11. Enia G. A lie which became the truth. G. Ital. Nefrol. 2007; 24: 151–153.
12. Hsieh M.C., Ko J.Z., Eng H.L. Pathologic fracture of the distant femur in osteitis fibrosa cystica simulating metastatic disease. Arch. Orthop. Trauma Surg. 2004; 124: 584–589.
13. Sugden C.J., Laird B.J. Hammers and nails: a report. Palliat. Med. 2004; 18: 734–746.
14. Meydan N., Barutca S., Guney E. i wsp. Brown tumors mimicking bone metastases. J. Natl. Med. Assoc. 2006; 98: 950–953.
15. Pianou N., Housianakou I., Papathanasiou N. i wsp. Brown tumors in the technetium-99m methyldiphosphonate bone scan mimicking metastases of parathyroid carcinoma. Hell. J. Nucl. Med. 2006; 9: 146–148.
16. Zanglis A., Andreopoulos D., Zissimopoulos A. i wsp. Multiple brown tumors with Tc-99m MDP superscan appearance and negative Tc-99m MIBI uptake. Clin. Nucl. Med. 2006; 31: 640–643.
17. Miyakoshi M., Kamoi K., Takano T. i wsp. Multiple brown tumors in primary hyperparathyroidism caused by an adenoma mimicking metastatic bone disease with false positive results on computed tomography and Tc-99m sestamibi imaging: MR findings. Endocr. J. 2007; 54: 205–210.
18. Sahan M.H., Guner S., Guner S.I. Radiological findings in the primary hyperparathyroid case with multiple brown tumors: a case report. Eastern J. Med. 2008; 13: 30–44.
19. Kirk J., Au-Yong I., Ganatra R. Multimodality imaging of a retrosternal parathyroid adenoma with multiple brown tumors. Clin. Nucl. Med. 2009; 34: 555–559.
20. Su A.W., Chen C.F., Huang C.K. i wsp. Primary hyperparathyroidism with brown tumor mimicking metastatic bone malignancy. J. Chin. Med. Assoc. 2010; 73: 177–180.
21. Van Asseldonk E.J., de Sévaux R.G., Flucke U.E. i wsp. Multiple osteolytic bone lesions. Neth. J. Med. 2011; 69: 399.
22. Nunes A., Muhiddin K., Hosking P. i wsp. Neoplasms of the parathyroid glands and brown tumours — a case study. Radiography 2012; 18: 51–54.
23. Van Baardwijk A., de Jong J., FArens A. i wsp. False-positive FDG-PET scan due to brown tumours. Eur. J. Nucl. Med. Mol. Imaging 2006; 33: 393–394.
24. Al-Makhzomi A., Satekge A., Seynaeve P. i wsp. PET/CT positive brown tumour — a potentially misleading finding in the evaluation of a patients for malignant primary tumour and metastases. S.A. J. Radiol. 2007; 11: 103–104.
25. Kemps B., van Ufford H.Q., Creyghton W. i wsp. Brown tumors simulating metastases on FDG PET in a patient with parathyroid carcinoma. Eur. J. Nucl. Med. Mol. Imaging 2008; 35: 850.
26. Arunkumar K.V., Kumar D., Deepa D. Brown tumor in mandible as a first sign of vitamin D deficiency: A rare case report and review. Indian J. Endocrinol. Metab. 2012; 16: 310–315.
27. Rubin M.R., Livolsi V.A., Bandeira F. i wsp. Tc99m-sestamibi uptake in osteitis fibrosa cystica simulating metastatic bone disease. J. Clin. Endocrinol. Metab. 2001; 86: 5138–5141.
28. Khosla S., Melton J. 3rd. Fracture risk in primary hyperparathyroidism. J. Bone Miner. Res. 1991; 6 (supl.): N103–107.
29. Mateo L., Massuet A., Sol M. i wsp. Brown tumor of the cervical spine: a case report and review of the literature. Clin. Rheumatol. 2011; 30: 419–424.
30. Young Mok J., Yeon Kim H., Hsing Chien H. i wsp. A case of primary hyperparathyroidism with rapid regression of a brown tumor after parathyroidectomy. J. Korean Endocr. Soc. 2010; 25: 50–55.
31. Hamouda M., Handous I., Dhia N.B. i wsp. Brown tumors in dialyzed patients with secondary hyperparathyroidism: Report of 16 cases. Hemodial. Int. 2012; doi: 10.1111/j.1542-4758.2012.00695.x. [Epub ahead of print].
32. Younes N.A., Shafagoj Y., Khatib F. i wsp. Laboratory screening for hyperparathyroidism. Clin. Chim. Acta 2005; 353: 1–12.
33. Mazzaglia P.J., Berber E., Kovach A. i wsp. The changing presentation of hyperparathyroidism over 3 decades. Arch. Surg. 2008; 143: 260–266.
34. Chavin H.C., Pisarevsky A.A., Chavín C. i wsp. Brown tumor as the initial manifestation of primary hyperparathyroidism. Medicina (B Aires) 2008; 6: 219–221.

35. Parisien M., Silverberg S.J., Shane E. i wsp. Bone disease in primary hyperparathyroidism. Endocrinol. Metab. Clin. North Am. 1990; 19: 19–34.
36. Teng C.T., Nathan M.H. Primary hyperparathyroidism. Am. J. Roentgenol. Radium Ther. Nucl. Med. 1960; 83: 716–731.
37. Hoshi M., Takami M., Kajikawa M. i wsp. A case of multiple skeletal lesions of brown tumors, mimicking carcinoma metastases. Arch. Orthop. Trauma Surg. 2008; 128: 149–154.
38. Gotway M.B., Leung J.W., Gooding G.A. i wsp. Hyperfunctioning parathyroid tissue: spectrum of appearances on noninvasive imaging. Am. J. Roentgenol. 2002; 179: 495–502.
39. Hong W.S., Sung M.S., Chun K.A. i wsp. Emphasis on the MR imaging findings of brown tumor: a report of five cases. Skeletal. Radiol. 2011; 40: 205–213.
40. Rybak L.D, Rosenthal D.I. Radiological imaging for the diagnosis of bone metastases. Q. Nucl. Med. 2001; 45: 53–64.
41. Buyukdereli G., Ermin T., Kara O. i wsp. Tc-99m MIBI uptake in traumatic vertebral fractures and metastatic vertebral lesions: comparison with Tc-99m MDP. Adv. Ther. 2006; 23: 33–38.
42. Hsu C.H., Liew P.L., Wang W. i wsp. Enhanced FDG uptake in brown tumors mimics multiple skeletal metastases in a patient with primary hyperparathyroidism. Acta Radiol. 2008; 49: 949–950.
43. Hermoye A., Malghem J., Lecouvet F. i wsp. F-18 FDG PET/CT as a noninvasive diagnostic and follow-up tool in brown tumors due to secondary hyperparathyroidism. Clin. Nucl. Med. 2009; 34: 330–332.
44. Le Stanc E., Wattel C., Hameg A. i wsp. FDG PET/CT findings in secondary hyperparathyroidism not mimicking multiple bone metastases. Eur. J. Nucl. Med. Mol. Imaging 2009; 36: 334.
45. Airaghi L., Pisano G., Pulixi E. i wsp. Unusual presentation in a case of primary hyperparathyroidism. J. Res. Med. Sci. 2011; 16: 1078–1081.
46. Santiago Chinchilla A., Ramos Font C., Muros de Fuentes M.A. i wsp. False negative of the scintigraphy with 99mTc-sestamibi in parathyroid carcinoma with associated brown tumours. Contributions of the 18F-FDG-PET/CT. Rev. Esp. Med. Nucl. 2011; 30: 174–179.
47. Evangelista L., Sorgato N., Torresan F. i wsp. FDG-PET/CT and parathyroid carcinoma: Review of literature and illustrative case series. World J. Clin. Oncol. 2011; 2: 348–354.