MANAGEMENT OF HYPERPARATHYROIDISM: A CLINICAL CASE

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Abstract: *Hyperparathyroidism is characterized by overproduction of parathormone, its serum levels being regulated through negative feedback, by calcium and vitamin D levels, which act through their receptors. Currently, there are large variations in symptoms, so more information regarding the disease and determining calcium levels as screening test helps identifying hyperparathyroidism in asymptomatic patients. Surgery has proven to be an effective method of treatment, resulting in a reduction in the lithic effects that parathormone in excess has on bone density. Combined imaging of 99m Technetium sestamibi scintigraphy and SPECT/CT is the most sensitive method in detecting the location of the affected gland.*

INTRODUCTION

The major role of parathormone (PTH) is to regulate the ionized calcium levels by acting on three target organs: bone, kidney and gastric mucosa. The effect of PTH on intestinal calcium absorption results from increased renal production of the intestinal metabolite of vitamin D, 1,25-dihydroxyvitamin D. With its integrated effects on the three target organs, PTH acts to increase calcium flow in the extracellular fluid and thereby defend against hypocalcaemia.(1)

Localization studies continue to be essential in the management of patients with hyperparathyroidism. The most successful procedures are 99m Technetium sestamibi scintigraphy, single photon emission computed tomography (SPECT), computed tomography (CT), magnetic resonance imaging (MRI) and ultrasound. Parathyroid scintigraphy can be associated with SPECT and CT, obtaining striated sections, indicating the distribution of the radiopharmaceutical in parathyroid glands. Moreover, adding SPECT and CT offers increased sensitivity and specificity to the scintigraphic examination. Used in combination, they are successful in at least 80% of cases(1)

Diagnostic management of hyperparathyroidism should include: evaluation of 25-hydroxyvitamin D levels, 24-hour urine, serum creatinine or creatinine clearance, osteodensitometry by dual energy x-ray absorptiometry (DEXA), PTH levels, phosphatemia and calcemia.(2)

The treatment of primary hyperparathyroidism (HPTP) is different from the treatment of the secondary form: if in HPTP parathyroidectomy is the only curative treatment and is generally accepted that any patient with HPTP to be guided to surgery, mainly due to long-term effects on bone mass and renal complications, in secondary hyperparathyroidism surgical treatment should be considered only when medical treatment cannot control hyperparathyroidism.(4) Parathiroidectomy should be performed in all patients with HPTP symptoms (2), but it also should be considered in most asymptomatic patients.

Severe osteoporosis, once identified, requires an assessment of its etiology, primarily a parathyroid pathology, hyperparathyroidism being the most common cause.

The purpose of our work is to demonstrate the importance of complete endocrine evaluation of any case of severe osteoporosis.

CASE REPORT

A 71-year-old female patient from Sibiu is admitted at the Clinical County Emergency Hospital of Sibiu, in the Endocrinology Department, presenting the following symptoms: sore throat, choking, fatigue, chest pain, dizziness, dry cough and polyarthralgia.

From her medical family history, we mention maternal parents and grandparents with cardiovascular pathology (hypertension and stroke) and a sister with type 2 diabetes and stroke.

The patient has been known for 20 years with hypertension on treatment, post-total hysterectomy for uterine fibroids, osteoporosis with vertebral compression and rheumatoid arthritis. At the indication of the rheumatologist and physiotherapist, she received antiresorptive treatment during 10 years, with alendronate sodium trihydrate and colecalciferol (Fosavance), then ibandronic acid (Bonviva), until 2015 when Bonviva treatment was discontinued and replaced with Alpha D3, then cholecalciferol (Vigantoletten), with improved clinical evolution in osteodensitometry parameters.

Table no. 1. Osteodensitometry testing: T-score

Year	Lumbar spine (SD)	Hip (SD)
2007	-4	-2,4
2011	-4	-2,5
2012	-3,2	-1,6
2013	-3,8	-1,3
2014	-3,5	-1,7
2015	-3,2	-1,4
2016	-3,2	-2,1
2017	-3,3	-1,8

In September 2012, the patient consulted an endocrinologist at the recommendation of the cardiologist, having high blood pressure (220/110 mmHg), augmented by emotional lability, predominantly in the evening accompanied

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by vertigo, lumbar pain (predominantly on the right side) and paresthesia of the extremities.

Laboratory data revealed normal thyroid function. In the thyroid ultrasound, there is an asymmetric thyroid gland with a regular border, diffuse hypertrophy, with granular structure, with Doppler signal; in both thyroid lobes, there are several transonic nodules, with diminished Doppler signal in the right side of thyroid isthmus, of 5/3mm and 6/3 mm, and thus the diagnosis of microcystic goitre is established.

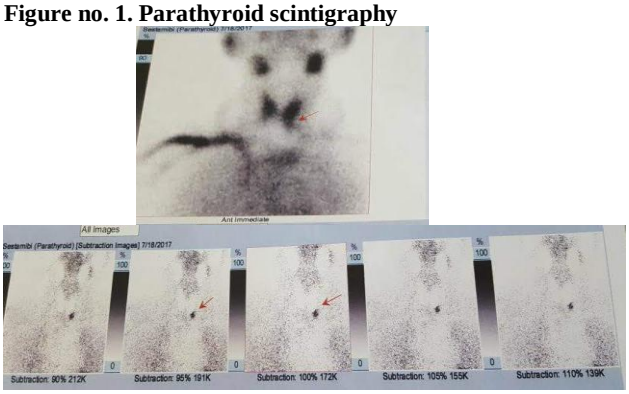
On endocrinologist's recommendation, the patient is guided for further investigations to exclude an adrenal pathology, with plasma renin, metanephrines, normetanephrines and serum aldosterone within normal reference range.

In October 2015, laboratory data revealed increased PTH levels (192 pg/mL), insufficient levels of 25-hydroxyvitamin D3 (37.94 nmol / L), normal serum calcium levels, thyrotropin (TSH) and free thyroxine (FT4) levels within normal reference range; thyroid ultrasound revealed a micronodular goitre, with nodules with a maximum diameter of 7 mm. The diagnosis of vitamin D deficiency with secondary hyperparathyroidism and euthyroid micronodular goitre was established, thus it was recommended to discontinue Bonviva therapy and replace it with Alpha D3 10 mcg/day. At subsequent 3 months reevaluations on Alpha D3 therapy, PTH is maintained increased (153.69 pg/mL), with calcemia and calciuria within normal limits.

The patient still had high values for blood pressure (180/100 mmHg) with antihypertensive treatment with angiotensin converting enzyme inhibitors and diuretics. PTH maintains the same elevated values, with normal calcemia and in September 2016, calciuria levels were of 336 mg/24 h, osteodensitometry revealed a T-score of -3.2 standard deviations (SD) at lumbar spine as presented in table no. 1 and Alpha D3 was replaced by Vigantoletten 1000 IU/day.

In March 2017, thyroid ultrasound revealed the same aspect and parathyroids were not visualized; the patient presented the same symptomatology and was guided to perform a parathyroid scintigraphy with Technetium sestamibi. It revealed an area with increased uptake of the radiotracer in the left inferior parathyroid lobe as presented in figure no. 1. Together with hormonal evaluation, the diagnosis of left inferior parathyroid adenoma with HPTP and vitamin D deficiency was established. At the time, the patient also had asymptomatic renal microlithiasis.

Figure no. 1. Parathyroid scintigraphy



The recommendation for surgery with parathyroid adenoma excision was refused by the patient.

In April 2018, the patient is admitted at the Endocrinology Department for the same symptoms listed above and for endocrinological reevaluation. During the admission, PTH levels were maintained at 90.61pg/mL, with high levels of total serum calcium (10.25 mg), alkaline phosphatase, TSH and FT4 were within normal limits. Evaluation of osteoporosis parameters was done, which releaved insufficient levels of 25-hydroxyvitamin D (29.5ng / mL) and normal levels of beta crosslaps and osteocalcin. Another new element in this case was the absence of renal microlithiasis and thyroid nodules, excluded by abdominal and thyroid ultrasounds. At cervical ultrasound parathyroids were not visualized.

The patient is guided to the Nuclear Medicine Unit of the Clinical County Emergency Hospital of Cluj, to repeat the parathyroid scintigraphy in order to make the right decision on the treatment needed in this case.

DISCUSSIONS

Primary hyperparathyroidism is commonly found in clinical endocrinology practices around the world. An update of current diagnostic information, clinical features and management of this disease (5) is important for a more accurate management of the treatment.

In the clinical case presented, the differential diagnosis between primary and secondary hyperparathyroidism is under discussion. Secondary hyperparathyroidism, diagnosed initially, was supported by increased PTH levels, normal calcemia, parathyroid ultrasound, which at that time denied the presence of parathyroid hyperplasia or adenoma, and decreased levels of 25-hydroxyvitamin D.

Subsequently, the detection of the parathyroid adenoma classifies this clinical case in the form of primary hyperparathyroidism, although the levels of 25-hydroxyvitamin D remain low. The particularity of this case is the presence of complications of hyperparathyroidism, as the onset of severe osteoporosis and subsequently hypertension resistant to medical treatment, showing the importance of endocrinological assessment of these cases.

Given the value of PTH, calcemia, 25-hydroxyvitamin D, osteodensitometry and symptomatology present at the time the scintigraphy was performed, which raises the suspicion of a parathyroid adenoma, the question is whether or not the patient has a surgical indication.

According to the current guidelines, surgery for parathyroid adenomas is indicated depending on certain parameters listed in table no. 2 below.

Table no. 2. Indications of parathyroidectomy of primary hyperparathyroidism

Parameters	Value
Age	< 50 years
Calcaemia	>1mg/dL (0,25mmol/L) above reference range
Bone	T-score <−2.5 (any localization) or significant reduction in BMD Fracture or osteitis fibrosa
Renal	CrCl<60 ml/min Urinary calcium levels >400mg/24 h Symptomatic or life-threatening hypercalcemia Nephrolithiasis or nephrocalcinosis

The diagnosis of a possible multiple endocrine neoplasia (MEN) was taken into consideration. Due to the suggestive onset of symptoms (hypertension resistant to medical treatment) for an adrenal pathology, specific laboratory analyzes were performed, such as plasma renin, metanephrines, normetanephrines, serum aldosterone, which all were within normal reference range, and calcitonin was also used as a diagnostic marker in the case of medullary thyroid cancer, but it was negative in two determinations performed, thus denying the diagnosis of MEN.

A randomized, double-blind, placebo-controlled, randomized trial included postmenopausal women aged 45-60 years with a T-score in the lumbar spine (LS) <-1.0 and > -2, 5 and baseline T score> -2.5 in the entire hip and without previous osteoporotic fractures or any trauma, followed the efficacy and safety of oral ibandronate (150 mg) in the postmenopausal women with a decreased bone mass.(12)

The subjects received 150 mg of monthly ibandronate administered by mouth and also placebo, and increased bone mineral density (BMD) was achieved after 1 year on ibandronate therapy compared with subjects receiving placebo. For one year, 88.2% of the participants treated with ibandronate achieved an increased bone mineral density compared to those receiving placebo (38.6%).(12)

Our patient has been treated with bisphosphonates for about 10 years due to the low BMD and radiological changes detected by the rheumatologist, and a slight increase in BMD has been observed and the risk of fractures has been reduced.

Tc-99m sestamibi scintigraphy is currently the golden standard for the localization of ectopic parathyroid tissue in primary hyperparathyroidism.(8) The presence of extraparathyroid lesions in Tc-99m sestamibi scintigraphy can lead to diagnostic traps. (8) Brown tumours, also called osteoclastomas, are rare neoplastic lesions which appear in the evolution of primary or secondary hyperparathyroidism.(9) In a patient with long-standing hyperparathyroidism, the absorption of brown tumours in the Tc-99m sestamibi scintigraphy may mimic a parathyroid carcinoma with bone metastases.(8) Thus, performing a scintigraphy is important for establishing a clearer etiology of the case presented above.

CONCLUSIONS

In the diagnosis of any form of hyperparathyroidism, biochemical and hormonal investigations correlated with imaging techniques are important in order to establish a diagnosis as accurate as possible, in order to have a correct management of the case, that will provide a better understanding of the patient's health and a higher quality of life.

Primary hyperparathyroidism may increase patient morbidity and mortality if untreated correctly and on time. Although surgery is the only curative therapy, there has been much progress in the diagnosis and surgical management of primary hyperparathyroidism over recent decades.

The case presented demonstrates that the complete hormonal investigation of any case of severe osteoporosis is important, identifying a possible parathyroid etiology. Patients with hypertension and severe osteoporosis should be investigated to exclude a possible HPTP secondary to a parathyroid adenoma.

Bisphosphonates are effective not only in maintaining bone mineral density, but also in the balance of calcium levels in HPTP cases.

REFERENCES

1. Shoback DM, Schafer AL, Bikle DD. Metabolic Bone Disease. In Gardner DG, Shoback D. Greenspan's Basic and Clinical Endocrinology, 10th ed. McGraw-Hill; 2017. p. 244-245.
2. Wilhelm SM, Wang TS, Ruan DT, et al. The American Association of Endocrine Surgeons Guidelines for Definitive Management of Primary Hyperparathyroidism. JAMA Surg. 2016;151(10):959-968.
3. Grigorie D. Parathyroid glands. In Poiana C, Fica S. Endocrinology for medical students and resident doctors. Bucharest: Carol Davila Publishing; 2015. p. 176-177.
4. Ghervan C. Parathyroid glands. In Duncea I, Ghervan C, Georgescu C, Valea A, Lencu C, Ilie I. Endocrinology, 2nd ed. Cluj Napoca: Iuliu Hatieganu Medical Publishing; 2011. p. 147-148.
5. Bilezikian JP, Brandi ML, Eastell R, Silverberg SJ, Udelsman R, Marcocci C et al. Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism: Summary Statement from the Fourth International Workshop. J Clin Endocrinol Metab. 2014 Oct;99(10): 3561-3569.
6. Georgescu C. Practical endocrinology. Cluj Napoca: Iuliu Hatieganu Medical Publishing; 2013. p. 111.
7. Potts JT, Juppner H. In Jameson JL. Harrison's Endocrinology. Bucharest: ALL publishing; 2014. p. 416-418.
8. Dias D, Simões-Pereira J, Leite V. Tc-99m sestamibi scintigraphy and primary hyperparathyroidism: uptake beyond parathyroid glands. BMJ; 2018.
9. Sonmez E, Tezcaner T, Coven I, Terzi A. Brown Tumor of the Thoracic Spine: First Manifestation of Primary Hyperparathyroidism. J Korean Neurosurg Soc. 2015 Oct;58(4):389-392.
10. Madkhali T, Alhefdhi A, Chen H, Elfenbein D. Primary hyperparathyroidism. Ulus Cerrahi Derg. 2016;32(1):58-66.
11. Adler RA, El-Hajj Fuleihan G, Bauer DC, Camacho PM, Clarke BL, Clines GA. Managing Osteoporosis in Patients on Long-Term Bisphosphonate Treatment: Report of a Task Force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2016;31:16.
12. McClung MR, Bolognese MA, Sedarati F, Recker RR, Miller PD. Bone.2009 Efficacy and safety of monthly oral ibandronate in the prevention of postmenopausal bone loss. Bone. 2009 Mar;44(3):418-22.