Ref: Ro Med J. 2019;66(4)
DOI: 10.37897/RMJ.2019.4.23

TERTIARY HYPERPARATHYROIDISM – LOCATION DILEMMA

Lecturer Mara Carsote[1,2], MD, PhD, Assist. Prof. Simona Elena Albu[1,3], MD, PhD, Assist. Prof. Florica Sandru[1,4], MD, PhD, Lecturer Mihai Cristian Dumitrascu[1,3], MD, PhD, Andrei Goldstein[2], MD, Lecturer Ana Valea[5,6], MD, PhD

[1] "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[2] "C.I. Parhon" National Institute of Endocrinology, Bucharest, Romania
[3] Emergency University Hospital, Bucharest, Romania
[4] Elias Emergency University Hospital, Bucharest, Romania
[5] Clinical County Hospital, Cluj-Napoca, Romania
[6] "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania

ABSTRACT

Renal failure is associated with numerous complications including cardiovascular, dermatological, neurological, surgical and endocrine. Hypovitaminosis D induces secondary hyperparathyroidism and long term effects are represented by autonomous stimulation of the parathyroid glands (tertiary hyperparathyroidism). Fail of PTH (parathyroid hormone) levels control through vitamin D replacement makes necessary a surgical intervention because of the risk of chronic complications in addition to the general morbidities caused by chronic kidney disease including osteoporosis. Our aim is to present a case of an adult woman with a very long history of renal failure complicated with tertiary hyperparathyroidism and osteoporosis. The clue of the case is the difficult localisation of PTH source after total parathyroidectomy was previously done in order to remove it and timing of re-intervention. There is a challenge to adequately locate the parathyroid remnants after a prior glands removal and a skilled surgeon is still the best "tool". However, the risk of surgery in a cases with multiple complications is very high so it is preferable a pre-operatory localisation. The neck ultrasound is the most accessible tool offering a good accuracy if there is no mediastinal localisation and also the combination with parathyroid scintigram increases the rate of detection.

Keywords: parathormone, hyperparathyroidism, renal failure

Abbreviations
BMD = bone mineral density
DXA = Dual-Energy X-Ray Absorptiometry
PTH = parathormone
SD = standard deviation

INTRODUCTION

Renal failure is associated with numerous complications including cardiovascular, dermatological, neurological, gastrointestinal, surgical and endocrine (1,2). The lack of renal function causes a deficiency of parathormone (PTH) action at the level of kidney cortex thus the activation of vitamin D which normally goes through hydroxylation as final step does not take place anymore (3,4). Hypovitaminosis D induces secondary hyperparathyroidism and long term effects are represented by autonomous stimulation of the parathyroid glands (tertiary hyperparathyroidism) (3-7). Vitamin D supplements of active type fail to success and parathyroid surgery remains a feasible option (5-7). Even small remnants of the parathyroid glands either eutopic or ectopic may be intensely active due to chronic stimulation and they might produce large amounts of PTH which are not correlated with the

Corresponding author:
Assist. Prof. Florica Sandru
E-mail: florysandru@yahoo.com

anatomical size of the adenoma (8). Fail of PTH levels control through vitamin D replacement makes necessary another surgical intervention because of the risk of chronic complications in addition to the general morbidities caused by chronic kidney disease including osteoporosis (9,10). As useful tools for the practitioners in order to evaluate to bone status we mention the bone turnover markers, the levels of bone hormones like PTH as well as central DXA (Dual-Energy X-Ray Absorptiometry) (11-13).

AIM

Our aim is to present a case of an adult woman with a very long history of renal failure complicated with tertiary hyperparathyroidism and osteoporosis. The clue of the case is the difficult localisation of PTH source after total parathyroidectomy was previously done in order to remove it.

MATERIAL AND METHOD

This is a case report. Hormonal and imaging data are introduced.

CASE REPORT

This is 63-year old Caucasian female diagnosed with chronic kidney disease more than 15 years ago. She is under haemodialysis soon after the diagnosis was established. She spontaneously went through menopause by the age of 48 years. For the last decade she was also confirmed with osteoporosis and she was treated with oral bisphosphonates. Also she had the four parathyroid glands removed a few years after starting haemodialysis. She continued with vitamin D of different regimes in the mean time. She associates chronic ischemic cardiac disease, atrial fibrillation, and high blood pressure under adequate therapy.

Two years ago the patient's assessment indicated a bone mineral density (BMD) improvement with a relative control of blood mineral metabolism: a PTH level of 480 pg/ml (normal: 16-65 pg/ml) and a 25-hydroxivitamin D of 34 ng/ml (normal: 30-100 ng/ml), and alkaline phosphatase of 412 U/l (normal: 40- 180 U/l). At that point she continued with 1 μg of active vitamin D and drug holiday was decided for risendronate. No visualisation of the parathyroid remnants was possible though anterior cervical ultrasound, cervical and mediastinal computed tomography, parathyroid scintigram.

The next year PTH dramatically increased to 1912 pg/ml (normal: 15-65 pg/ml) as well as bone turnover markers: CrossLaps (for resorption) of 5.4 ng/ml (normal: 0.33-0.782 ng/ml), osteocalcin (for formation) of 300 ng/ml (normal: 15-46 ng/ml). DXA showed a L2-4 lumbar BMD of 0.877 g/sqcm, T-score of -2.7 SD (a -2.3 SD was registered one year before) and Z-score of -1.6 SD; femoral neck BMD of 0.812 g/sqcm, T-score of -1.6 SD, Z-score of -.0.5 SD, total hip BMD of 0.825 g/sqcm, T-score of -1.4 SD, Z-score of -0.6 SD; third distal left radius BMD of 0.418 g/sqcm, T-score of -4.1 SD, Z-score of -3.1 SD. The doses of vitamin D were increased and risendronate was re-started. No location of the parathyroid glands was done by ultrasound or computed tomography.

Currently, one year later, PTH levels are still high of 1931 pg/ml (normal: 15-65 pg/ml), CrossLapss had a small decrease to 4.7 ng/ml (normal: 0.33-0.782 ng/ml) while osteocalcin had the same values; a total serum calcium of 10.3 mg/dl (normal: 8.5-10.2 mg/dl), and phosphorus of 7.1 mg/dl (normal: 2.3-4.7 mg/dl) was assessed. BMD improved to each central site: L2-4 lumbar BMD of 0.933 g/sqcm, T-score of -2.2 SD and Z-score of -0.8 SD; femoral neck BMD of 0.874 g/sqcm, T-score of -1.2 SD, Z-score of 0.2 SD, total hip BMD of 0.885 g/sqcm, T-score of -1 SD, Z-score of 0.1 SD; third distal left radius BMD of 0.432 g/sqcm, T-score of -4 SD, Z-score of -2.9 SD. Parathyroid scintigram Tc99 identified a left inferior parathyroid adenoma superior to sternum area for the first since the tertiary hyperparathyroidism relapsed after first parathyroid surgery (Figure 1). The lesion of 1 cm (centimetre) was also confirmed at anterior cervical ultrasound at the same level and then surgically removed with a lowering of PTH levels (Figure 2).

DISCUSSION

There a challenge to adequately locate the parathyroid remnants after a prior glands removal and a skilled surgeon is still the best "tool" (14). However, the risk of surgery in a cases with multiple complications as here is very high so it is preferable a pre-operatory localisation. That is why the surgery was postponed in this situation. The neck ultrasound continues to be the most accessible tool offering a good accuracy if there is no mediastinal localisation (15). One study on 810 patients showed that eutopic parathyroids with abnormal pattern are more likely to be inferior as this was the case (16). Yet in cases with renal failure and persistent hyper-

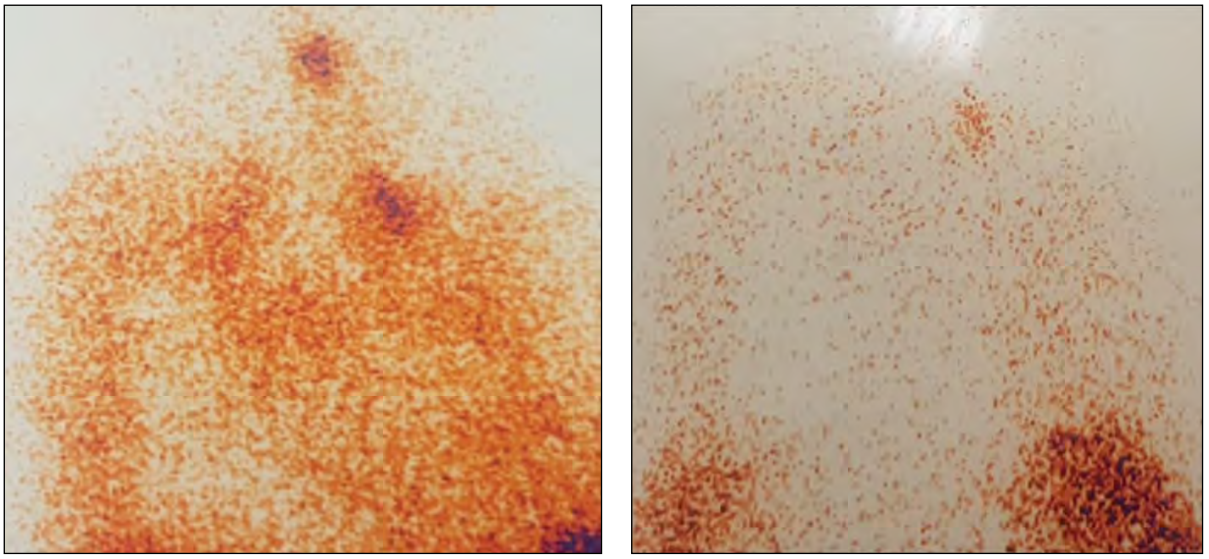

FIGURE 1. *Parathyroid scintigram Tc99 (Technetium) identified a left inferior parathyroid adenoma superior to sternum area (different timing)*

FIGURE 2. *Cervical ultrasound identifies a parathyroid adenoma causing tertiary hyperparathyroidism*

parathyroidism the re-intervention decision is delicate and a close selection needs to be done (17). In this particular situation the values of PTH are extremely high as seen here in addition to increased bone turnover profile reaching levels that are completely different to usual cases of primary hyperparathyroidism or primary osteoporosis (18,19). Moreover, even the patient had extremely high PTH serum calcium levels were controlled through haemodialysis (20).

CONCLUSION

The reoperation of a patient with tertiary hyperparathyroidism and a long standing history of parathyroidectomy are based on a rigorous selection and the pre-operatory location of the parathyroid adenoma is crucial even challenging.

REFERENCES

1. Mikhail A, Brown C, Williams JA, Mathrani V, Shrivastava R, Evans J, Isaac H, Bhandari S. Renal association clinical practice guideline on Anaemia of Chronic Kidney Disease. *BMC Nephrol.* 2017 Nov 30; 18(1):345.
2. Stevens PE, Levin A; Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. *Ann Intern Med.* 2013 Jun 4; 158(11):825-30.
3. Jean G, Souberbielle JC, Chazot C. Vitamin D in Chronic Kidney Disease and Dialysis Patients. *Nutrients.* 2017 Mar 25;9(4).
4. Machado HKAG, Martins CSW, Jorgetti V, Elias RM, Moysés RMA. Chronic kidney disease is a main confounding factor for 25-vitamin D measurement. *J Bras Nefrol.* 2019 Sep 26. pii: S0101-28002019005030101.
5. Valea A, Botezan O, Turturea R, Carsote M, Rusu C. Surgery for primary hyperparathyroidism diagnosed as acute renal failure. *Journal of Surgical Sciences.* 2018;5(2):108-112.
6. Gheorghisan-Galateanu AA, Carsote M, Valea A, Nica AE, Ghemigian A. Renal hyperparathyrodisim after total parathyroidectomy. *Journal of Surgical Sciences.* 2016;3(2):103-106.
7. Chandran M, Wong J. Secondary and Tertiary Hyperparathyroidism in Chronic Kidney Disease: An Endocrine and Renal Perspective. Indian *J Endocrinol Metab*. 2019 Jul-Aug; 23(4):391-399.
8. Golingan H, Samuels SK, Camacho P, Dadhania DM, Pedraza-Taborda FE, Randolph G, Parangi S, Bimston DN, Harrell RM. Management of hyperparathyroidism in kidney transplantation

candidates: a need for consensus. *Endocr Pract.* 2019 Nov 4. doi: 10.4158/EP-2019-0392.
9. Poiana C, Radoi V, Carsote M, Bilezekian J. New Clues that May Link Osteoporosis to the Circulating Lipid Profile. *Bone Research* 2013; 1(3):260-266.
10. Hruska KA, Sugatani T, Agapova O, Fang Y. The chronic kidney disease - Mineral bone disorder (CKD-MBD): Advances in pathophysiology. *Bone.* 2017 Jul;100:80-86.
11. Albulescu DM, Carsote M, Ghemigian A, Popescu M, Predescu AM, Tuculina MJ, Bugala AS, Bataiosu M, Marinescu RI, Dascalu IT, Stan M, Cumpata CN, Bechir ES. Circulating 25-hydroxycholecalciferool in relationship to Central Dual-Energy X-Ray Absorptiometry Assesses. A clinical study. *Rev.Chim.* (Bucharest). 2018;69(12):3683-3687.
12. Radu L, Carsote M, Gheorghisan-Galateanu AA, Preda SA, Calborean V, Stanescu R, Gheorman V, Albulescu DM. Blood Parathyrin and Mineral Metabolism Dynamics. A clinical analyze. *Rev. Chim.* (Bucharest). 2018;69(10):2754-2758.
13. Kanis JA, Cooper C, Rizzoli R, Reginster JY; Scientific Advisory Board of the European Society for Clinical and Economic Aspects of Osteoporosis (ESCEO) and the Committees of Scientific Advisors and National Societies of the International Osteoporosis Foundation (IOF). European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int.* 2019 Jan; 30(1):3-44.
14. Dordea M, Moore U, Batty J, Lennard TWJ, Aspinall SR. Correlation of surgeon-performed parathyroid ultrasound with the Perrier classification and gland weight. *Langenbecks Arch Surg.* 2018 Nov; 403(7):897-903.
15. Stern S, Tzelnick S, Mizrachi A, Cohen M, Shpitzer T, Bachar G. Accuracy of Neck Ultrasonography in Predicting the Size and Location of Parathyroid Adenomas. *Otolaryngol Head Neck Surg.* 2018 Dec; 159(6):968-972.
16. LoPinto M, Rubio GA, Khan ZF, Vaghaiwalla TM, Farra JC, Lew JI. Location of abnormal parathyroid glands: Lessons from 810 parathyroidectomies. *J Surg Res.* 2017 Jan; 207:22-26.
17. McIntyre CJ, Allen JL, Constantinides VA, Jackson JE, Tolley NS, Palazzo FF. Patterns of disease in patients at a tertiary referral centre requiring reoperative parathyroidectomy. *Ann R Coll Surg Engl.* 2015 Nov; 97(8):598-602.
18. Carsote M, Preda SA, Mitroi M, Camen A, Radu L. Serum Osteocalcin, P1NP, Alkaline Phosphase, and CrossLaps in Humans: the relationship with body mass index. *Rev. Chim.* (Bucharest). 2019; 70(5):1615-1618.
19. Bechir ES, Carsote M, Tuculina MJ, Bataiosu M, Dascalu IT, Raescu M, Rica R, Daguci C, Daguci L, Predescu A, Andrei OC, Mercut R, Cumpata CN. Biochemical Analysis of Mineral Metabolism and Central Bone Mineral Density in 157 Adult Women. *Rev. Chim.* (Bucharest). 2018; 69(12):3565-3568
20. Jamal SA, Miller PD. Secondary and tertiary hyperparathyroidism. *J Clin Densitom.* 2013 Jan-Mar; 16(1):64-8.