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Research article

Multifaceted profile of PTH excess-related secondary osteoporosis: customized therapy and rehabilitation approach

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Abstract: Many causes of secondary osteoporosis have been identified; endocrine types (such as those linked to male hypogonadism, Cushing's syndrome, acromegaly, thyrotoxicosis, primary hyperparathyroidism, etc.) represent one of the most challenging ailments since a personalized approach of the endocrine disease is simultaneous required. We aimed to introduce the case of a senior lady who was diagnosed with secondary osteoporosis that was associated with primary hyperparathyroidism and a conservative approach was decided, from anti-osteoporosis drug and calcium lowering agents to the physical rehabilitation and lifestyle recommendations. She also presented double unilateral adrenal incidentaloma and a pituitary incidentaloma as well as a suspected ovarian cyst that she further declined to investigate. Mitigating the non-surgical management in primary hyperparathyroidism showcase (in addition to the zoledronic acid for both osteoporosis and hypercalcemia) a complex program of rehabilitation that included a diet intervention in terms of an adequate hydration and a personalized nutrition for kidney stones primary and secondary prevention, mild physical exercise, avoidance of calcium supplements and keeping a daily chole-calciferol replacement.

Keywords: osteoporosis, rehabilitation, health, fracture, hypercalcemia, zolendronate, fracture, hyperparathyroidism

1. Introduction

Many causes of secondary osteoporosis have been studied; endocrine types (such as those linked to male hypogonadism, Cushing's syndrome, acromegaly,

thyrotoxicosis, primary hyperparathyroidism, etc.) represent one of the most challenging ailments since a personalized approach of the endocrine disease is simultaneous required [1-3]. Parathormone (PTH) excess coming from an endocrine parathyroid tumor causes low bone mineral density (BMD), damaged trabecular bone score (TBS), and increased osteoporotic (low-trauma or spontaneous) fracture risk in addition to a multidisciplinary panel of complications such as those related to the digestive, cardiovascular, dermatologic, renal, and neurologic status [4-6]. Multifaceted intervention in terms of rehabilitation targets all these potential complications [7-9].

Objective

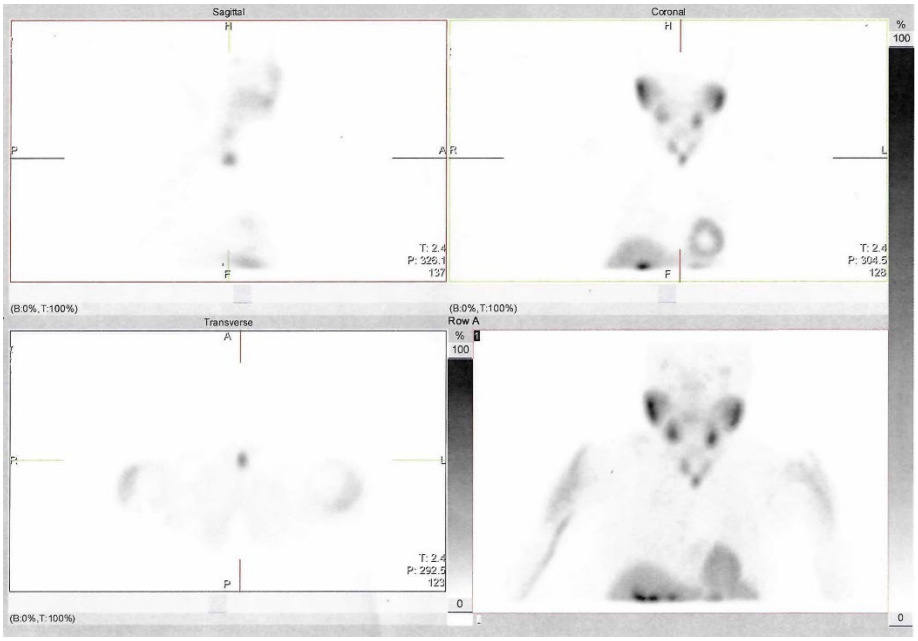
We aimed to introduce the case of a senior lady who was diagnosed with secondary osteoporosis that was associated with primary hyperparathyroidism and a conservative approach was decided, from anti-osteoporosis drug and calcium lowering agents to the physical rehabilitation and lifestyle recommendations.

2. Results: a clinical vignette

2.1 Admission: recent history of hypercalcemia

An 80-year-old non-smoker female was admitted for nausea, epigastralgy and anorexia. After clinical examination, corneal edema with complete loss of vision of the left eye was detected. She had a blood pressure of 160/80 mmHg, heart rate of 68 bpm and a body mass index of 26.19 kg/m^2. She entered menopause at the age of 44 and did not receive any hormone replacement therapy. Her personal medical history included grade 3 arterial hypertension, ischemic heart disease and nephrolithiasis. Over the past 8 months, she had elevated levels of total serum calcium, ionized calcium and parathormone on multiple blood assessments, in association with a high serum creatinine and urea, but did not receive any medical therapy (primary health care settings). Prior to the current admission, parathyroid 99m-Techentium (99m-Tc) sestamibi scintigraphy was performed and an area with increased late uptake was described, suggestive for a parathyroid tumor located posterior, medial and inferior to the left thyroid lobe. (Figure 1)

Figure 1. 99m-Tc sestamibi parathyroid scintigraphy showing an area with increased late uptake suggestive for a parathyroid tumor that was located posterior, medial and inferior to the left thyroid lobe.



Biochemical evaluation revealed a slightly elevated serum urea of 54 mg/dL (normal: 15-50), however with normal serum creatinine of 1 mg/dL (normal: 0.5-1.1), mild hyperglycemia of 103 mg/dL (normal: 70-100) and mild normochromic normocytic anemia. (Table 1)

Table 1. Biochemical assays of an 80-year-old patient with left inferior parathyroid adenoma

Parameter	Patient's value	Normal range	Units
Alanine aminotransferase (ALT)	20	0-35	U/L
Aspartate aminotransferase (AST)	24	14-36	U/L
Total cholesterol	201	0-200	mg/dL
Triglycerides	163	50-200	mg/dL
Fasting glycaemia	103	70-100	mg/dL
Glycated hemoglobin A1c (HbA1c)	5.88	4.8-5.9	%
Serum creatinine	1.01	0.5-1.1	mg/dL
Serum urea	54	15-50	mg/dL
Sodium	139	137-145	mmol/L
Potassium	4.2	3.5-5.2	mmol/L
Magnesium	2	1.6-2.4	mg/dL
Hemoglobin	11.9	12-15.5	g/dL
Hematocrit	34.9	36-48	%
Mean corpuscular volume (MCV)	85.3	83-96	fL
Mean corpuscular hemoglobin (MCH)	29.1	27-34	pg

2.2 Endocrine panel

Endocrine panel showed normal thyroid function, with thyroid stimulating hormone (TSH) of 1.7 μUI/mL (normal: 0.35-4.94), free levothyroxine (FT4) of 13.5 pmol/L (normal: 9-19) and negative thyroid antibodies TPOAb (anti-thyroperoxidase antibodies), TgAb (anti-thyroglobulin antibodies) and TRAb (anti-TSH receptor antibodies). In addition, blood endocrine assays such as plasma metanephrines and normetanephrines, serum serotonin, neuronal specific enolase and carcinoembryonic antigen were also within normal range, while chromogranin A was elevated. (Table 2)

Table 2. Endocrine and humoral panel of a female patient with persistently elevated serum calcium levels

Parameter	Patient's value	Normal range	Units
TSH	1.7	0.35-4.94	μU/mL
FT4	13.5	9-19	pmol/L
TPOAb	0	0-5.61	UI/mL
TgAb	13.2	0-115	UI/mL
TRAb	0.8	0-1.75	UI/L
Calcitonin	2.75	1-4.8	pg/mL
Plasma metanephrines	24	0-100	pg/mL
Plasma normetanephrines	81.1	0-216	pg/mL
Serum serotonin	93.1	20-206	ng/mL
Chromogranin A	608.8	20-100	ng/mL
Neuronal specific enolase	6	0-18.3	μg/L
Carcinoembryonic antigen (CEA)	0.8	0-3	ng/mL
Cancer antigen 125 (CA 125)	11.6	<35	U/mL

2.3 Bone status & mineral metabolism

Bone status assessment confirmed a high total serum calcium of 11.9 mg/dL (normal: 8.5-10.2) and ionized calcium of 5.54 mg/dL (normal: 3.9-4.9), low serum phosphorus of 2.4 mg/dL (normal: 2.5-4.5) with markedly elevated parathormone (PTH) of 147.8 pg/mL (normal: 15-65) and low-normal 25-hydroxyvitamin D (25-OHD) of 20.7 ng/mL (normal: 20-100). Bone formation markers (blood) osteocalcin, alkaline phosphatase and P1NP, as well as bone resorption marker serum CrossLaps were all normal. (Table 3)

Table 3. Bone evaluation of an elderly female with complicated primary hyperparathyroidism

Parameter	Patient's value	Normal range	Units
Total serum calcium	11.9	8.5-10.2	mg/dL
Ionized calcium	5.5	3.9-4.9	mg/dL
Total proteins	6.8	6.5-8.7	g/dL
Serum phosphorus	2.4	2.5-4.5	mg/dL
PTH	147.4	15-65	pg/mL
25-OHD	20.7	20-100	ng/mL
Osteocalcin	21.7	15-46	ng/mL
Alkaline phosphatase	63	38-105	U/L
P1NP	30.8	20.25-76.31	ng/mL
CrossLaps	0.7	0.33-0.782	ng/mL

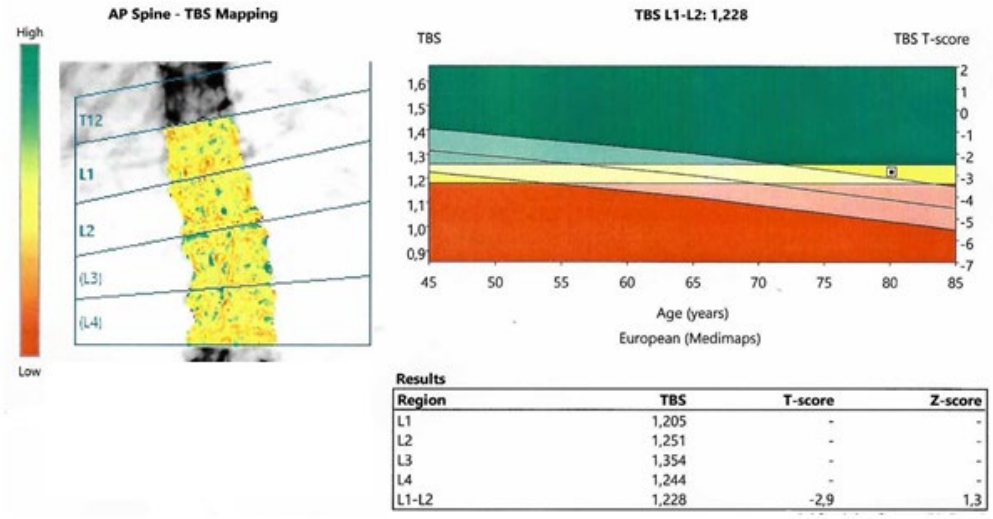
Dual-Energy X-ray Absorptiometry (DXA) evaluation confirmed osteoporosis, with a L1-L2 BMD of 0.751 g/sqcm, T-score of -3.5 SD, Z-score of -1.7 SD, femoral neck BMD og 0.573 g/sqcm, T-score of -3.4 SD, Z-score of -1.5 SD, total hip BMD of 0.623 g/sqcm, T-score of -3.1 SD, Z-score of -1.3 SD and non-dominant third distal radius BMD of 0.610 g/sqcm, T-score of -3.0 SD, Z-score of -0.3 SD. (Table 4)

Table 4. DXA showing osteoporosis in a senior lady (GE Lunar Prodigy device)

Region	Bone Mineral Density (g/cm²)	T-score (SD)	Z-score (SD)
Lumbar spine L1-L2	0.751	-3.5	-1.7
Femoral neck	0.573	-3.4	-1.5
Total hip	0.623	-3.1	-1.3
1/3 distal radius	0.610	-3.0	-0.3

Bone microarchitecture was also partially degraded, with a Trabecular bone score (TBS) of 1.228. (Figure 2)

Figure 2. TBS assessment based on central DXA at lumbar spine

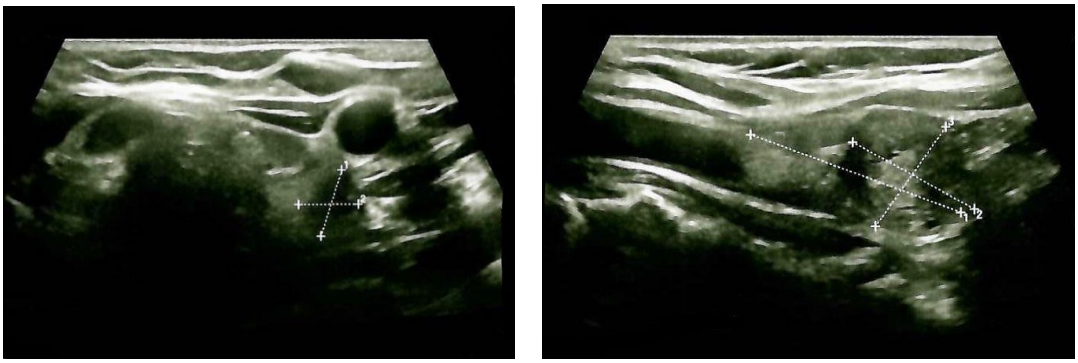


2.4 Other key imagery findings

Anterior neck ultrasound showed multinodular goiter. (Figure 3)

Figure 3. Neck ultrasound: (A) hypoechoic, inhomogeneous nodule of 1.00 by 0.83 by 0.76 cm located posterior and inferior to the left thyroid lobe; (B) hypoechoic nodule with necrosis areas in the lower half of the right thyroid lobe, of 1.80 by 1.60 by 1.43 cm (longitudinal plane)

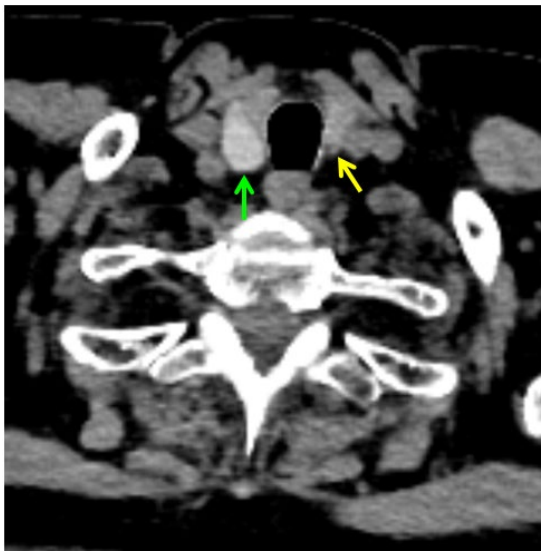
(A) (B)



Contrast-enhanced computed tomography (CT) of the cervical region confirmed the presence of a left latero-cervical, para-tracheal, enhanced nodule,

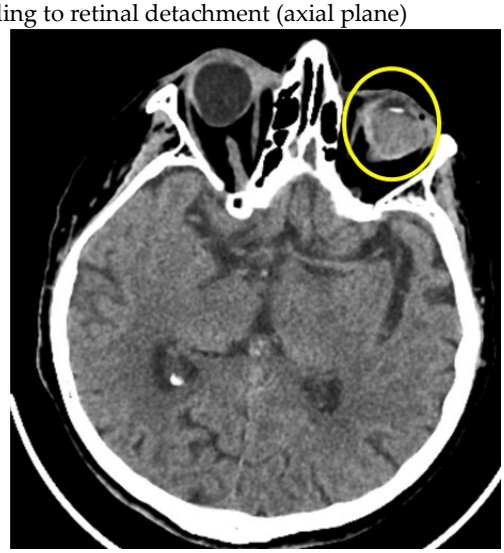
lenticularly shaped, in close contact with the posterior and inferior part of the left thyroid lobe, of 0.70 by 0.74 by 1.10 cm suggestive for a left inferior parathyroid adenoma. A thyroid nodule of 1.19 by 2.04 cm was also found, displaying spontaneous hyper-density and mild enhancement, located in the posterior and inferior part of the right thyroid lobe, in close contact with the right internal jugular vein and the right lateral wall of the trachea, but keeping a cleavage plane from these structures. (Figure 4)

Figure 4. Contrast-enhanced CT of the cervical region: left latero-cervical, paratracheal, enhanced nodule, lenticularly shaped, in close contact with the posterior and inferior part of the left thyroid lobe, of 0.70 by 0.74 by 1.10 cm (yellow arrow); thyroid nodule of 1.19 by 2.04 cm with spontaneous hyper-density and mild enhancement, in the posterior and inferior part of the right thyroid lobe, in close contact with the right internal jugular vein and the right lateral wall of the trachea, but keeping a cleavage plane from these structures (green arrow) (axial plane)



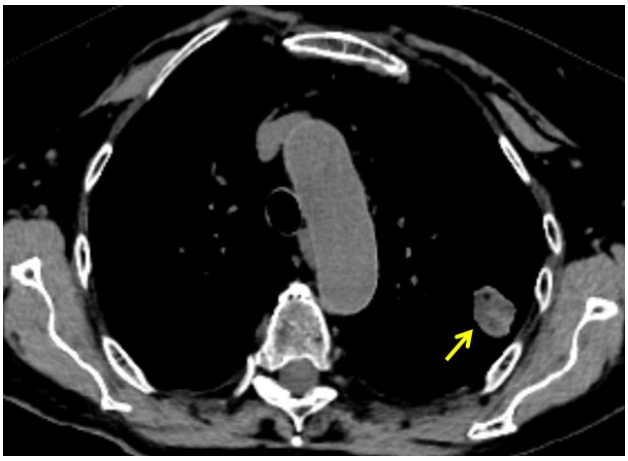
Head CT showed a heterogeneous, minimally asymmetric pituitary gland with a micro-nodule of 0.47 by 0.31 cm located in the caudal part of the sella and the left eye containing hyper-dense fluid corresponding to retinal detachment. (Figure 5)

Figure 5. Contrast-enhanced head CT: the left eye containing hyper-dense fluid corresponding to retinal detachment (axial plane)



Thorax CT scan showed the presence of a pulmonary mass in the apical-posterior segment of the left upper lobe, dense, heterogeneous, mildly enhanced, with lobulated contour, of 1.96 by 2.38 by 2.43 cm. (Figure 6)

Figure 6. Thorax CT scan: apical-posterior segment of the left upper pulmonary lobe with a dense, heterogeneous mass (yellow arrow) with lobulated contour, of 1.96 by 2.38 by 2.43 cm (axial plane)

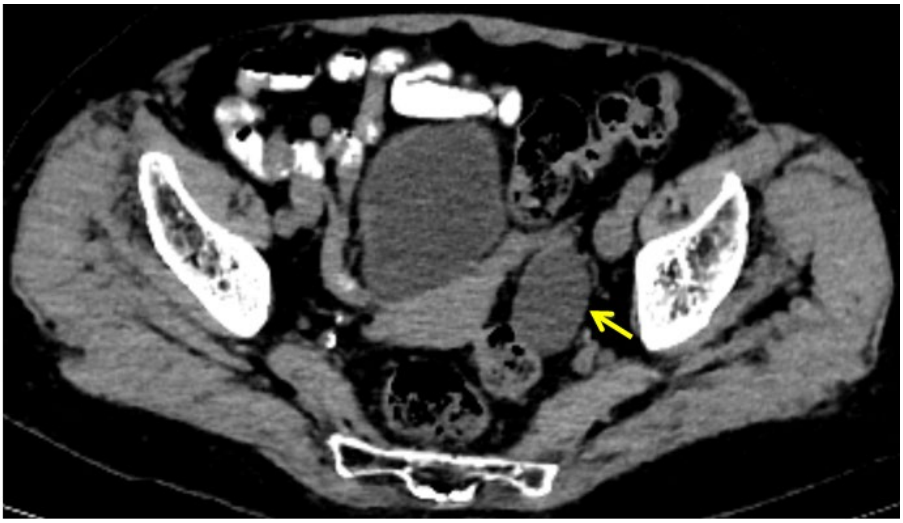


Abdominal CT evaluation disclosed the presence of left renal microlithiasis and 2 right adrenal masses with negative density in the body of 1.23 by 2.82 cm and in the lateral limb of 1.83 by 1.13 cm, respectively; the left adrenal gland was hyperplastic (two right adrenal incidentalomas). Pelvic CT revealed the presence of a cystic, encapsulated mass in the left ovary, of 2.80 by 3.90 cm. (Figure 7)

Figure 7. (A) Abdominal CT scan showing renal microlithiasis; (B) pelvic CT scan showing the left ovary with a cystic mass of 2.80 by 3.90 cm (axial plane)

(A)

(B)

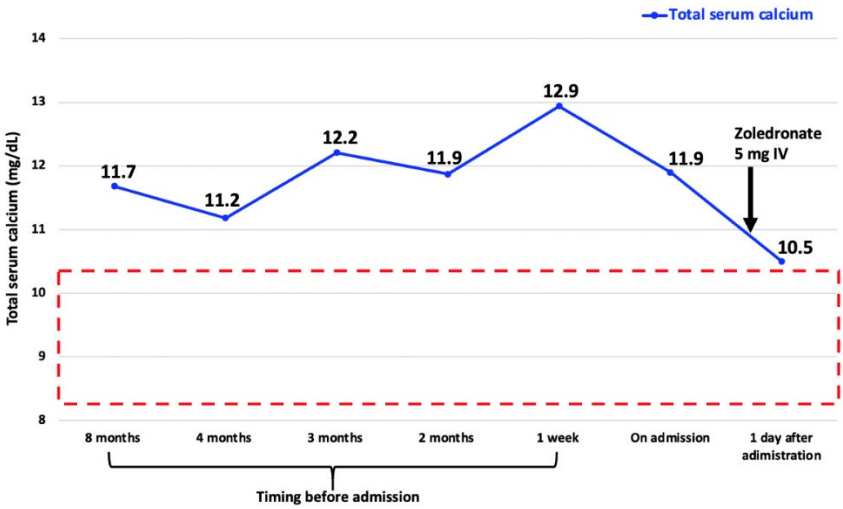


2.5 Management

Hence, a diagnosis of primary hyperparathyroidism (most probably, a single gland disease) was established. Taking into consideration the co-morbidities and the patient' option, a conservative approach was decided. Additionally, she showed two adrenal incidentalomas and the specific hormonal assays confirmed they were non-secretor. She declined further investigations of the pulmonary mass as well as of the ovarian cyst. She also associated a pituitary micro-incidentaloma and the specific endocrine assays confirmed a non-functioning status.

Hence, a double targeted medication was offered for both PTH-associated hypercalcemia and osteoporosis. Zoledronate (intravenously 5 mg per year) was administered and followed by a decrease in total serum calcium to 10.50 mg/dL and ionized calcium to 4.65 mg/dL. (Figure 8)

Figure 8. Total serum calcium levels evolution before admission and after 5 mg of zoledronate administration amid the diagnosis of primary hyperparathyroidism-related hypercalcemia



Further multidisciplinary surveillance is mandatory. Notably, interventional strategy was backed up by a rehabilitation program in terms of

having an adjusted regime of physical exercise, lifestyle intervention, including diet, for osteoporosis, hypercalcemia, and kidney stones.

3 Discussion

Here, we present a vignette of a senior lady confirmed with age-related and PTH-associated bone loss according to the central DXA scan. While parathyroidectomy is expected to offer the best prognostic with concern to the overall health, including the skeleton profile, a decision of conservative management was taken at this point in accordance to the subject' preference and general health status [10-12]. Under these circumstances, a potent bisphosphonate such as zoledronic acid was appreciated as the adequate regime to counteracting hypercalcemia, but, also, to functioning as agent against osteoporosis in an otherwise poorly compliant patient [13-15].

As lifestyle intervention, vitamin D supplements and avoidance of calcium supplements were added. Also, maintaining a good oral hydration as daily life basis is essential in patients with endocrine tumor-related hypercalcemia [16-18]. Generally, hypercalcemia represents a common finding in real-life setting according to the different screening protocols that vary across distinct centers and regions, but nowadays hypercalcemia is mostly asymptomatic at first diagnosis (which was not this case), but it may complicate as a life-threatening emergency, particularly, in older individuals with a poor hydration status or co-presence of a certain renal damage [19-20]. The most common cause of increased serum calcium level is primary hyperparathyroidism followed by the hypercalcemia of malignancy as found in different cancers of distinct origins such as breast, pulmonary, etc. [21-23]. Of note, the female subject showed a suspected ovarian cyst that she further declined to investigate, but it should be taken into account in the overall prognosis.

Additionally, the rehabilitation plan included specific recommendations according to the stones (urinary) analysis, as primary and secondary prevention in this instance. Yet, the true reduction rate of the kidney stones in primary hyperparathyroidism is less likely feasible unless the removal of the parathyroid tumor and correction of the hypercalcemia, that may be done via cinacalcet in certain patients, too (mostly, in non-surgery candidates or as bridge to parathyroidectomy, unless the presence of renal/tertiary hyperparathyroidism) [24-26].

On the other hand, a physical exercise program was initiated to prevent fractures and sarcopenia (mild physical and balance fitness as well as brisk walking) which are regarded as adequate amid clinical circumstances as seen here [27-29]. On final note, we need to pay attention to two other endocrine ailments that have been confirmed across imagery scans, namely, two types of incidentalomas at pituitary and adrenal glands. None of them was suspected for a malignancy, but long standing surveillance is mandatory [30,31]. Neither they showed a hormonal excess, but, generally, mild cortisol autonomous production (coming from the adrenal incidentaloma), respectively, prolactin excess (from the hypophyseal microadenoma) might cause bone loss and increased long term fracture risk [32-36].

As prior specified, a compliant patient that should adhere to the non-surgical recommendations represents the key factor to address the issue of complicated PTH and calcium excess on long-term surveillance [37,38]. Another factor that should be taken into consideration with regard to the overall management stands for the patient' age and associated life expectancy that does not actually contra-indicate a parathyroidectomy according to the current guidelines and current surgical procedures that allow a low rate of post-operatory complications following endocrine surgery of any type, including for a parathyroid

tumor, as seen in other diseases with seniors as surgery candidates [39-41]. Thyroid and parathyroid removal of the eutopic glands seems safe nowadays, if the procedure is performed by an experienced surgeon, regardless of one individual' age [42,43]. Yet, the overall disease burden that comes with long-term elevated PTH and calcium as well as other unrelated co-morbidities might impair the rate of surgery success [44,45]. Notably, the recent COVID-19 pandemic and even early post-COVID-19 era involved a larger number of endocrine patients who were potentially surgery candidates to delay their procedures or to experience novel medical and surgical entities that impaired the overall outcome, while on the other hand, the access to medication and rehabilitation programs was affected, as well [46-50].

4 Methods

The patient agreed for the anonymous presentation of her data with regard to the endocrine and imagery panel. The Ethical approval was obtained to collect the data across a retrospective analysis. Demographic features as well as medical records of the subjects had been accessed. Also, the biochemistry, and hormonal profile was provided in terms of thyroid, parathyroid and bone health assessments. Fracture risk was evaluated by using a central DXA device (GE Lunar Prodigy).

5 Conclusion

Mitigating the non-surgical management in primary hyperparathyroidism showcase (in addition to the zoledronic acid for both osteoporosis and hypercalcemia) a complex program of rehabilitation that included a diet intervention in terms of an adequate hydration and a personalized nutrition for kidney stones primary and secondary prevention, mild physical exercise, avoidance of calcium supplements and keeping a daily cholecalciferol replacement.

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