



Primary Hyperparathyroidism Manifesting with Severe Hypercalcemia in a Nonagenarian Man: Pitfall of Common Imaging Techniques, Localization by ^{18}F -Choline Positron Emission Tomography/Computed Tomography and Successful Management with Calcimimetics

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ABSTRACT

A nonagenarian hypertensive man with chronic kidney disease (CKD) was admitted to the emergency department for gastrointestinal symptoms and worsening symptoms of depression. Severe hypercalcemia (15.3 mg/dL) was found and he was hospitalized. Fluids, loop diuretics and glucocorticoids were administered intravenously, which partially reduced calcium levels over a few days and improved his clinical condition. PTH levels proved increased (306 pg/mL) and 25-OHD levels were reduced; primary hyperparathyroidism (PHPT) was diagnosed. Neck ultrasonography (USG) did not show parathyroid enlargement, nor did $^{99\text{m}}$ Technetium-sestamibi (SESTAMIBI) scintigraphy reveal hyperfunctioning parathyroid glands. By contrast, ^{18}F -choline PET/CT evidenced a nodule located close to the oesophagus, behind the right thyroid lobe, which proved compatible with a hyperfunctioning parathyroid gland. Since the patient declined surgery, and zoledronate was unfit owing to areas of rarefaction of the jaw, the calcimimetic cinacalcet was started; the dosage was progressively titrated up to 120 mg/day with normalisation of calcium levels over time. PTH levels, however, proved erratic and showed an upward trend over the first year of therapy; however its levels partially decreased following increase of vitamin D levels by replacement therapy. Cinacalcet is a useful and safe drug, which can normalise calcium levels and improve the clinical condition, even in very old patients with severe PHPT who decline or are unfit for surgery.

KEYWORDS

primary hyperparathyroidism; hypercalcemia; ^{18}F -Choline PET/CT; cinacalcet

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INTRODUCTION

The incidence of primary hyperparathyroidism (PHPT) increases with age and reaches 95 to 196 per 100,000 in patients aged 70 to 79 years, with a 2-fold higher rate in females (1). Nonetheless, PHPT is overlooked and under-treated in the old population (1, 2).

PHPT generally presents with mild hypercalcemia, which is discovered by routine biochemical screening in over 90% of patients, who are mostly asymptomatic. Occasionally, elderly patients present with pain due to a bone fracture which causes mobility impairment, and thus reduced autonomy. So-called abdominal groans and psychic moans, are rarely the first clue to diagnosing PHPT but should be properly investigated. By contrast, renal involvement (nocturia, polyuria and nephrolithiasis) is not uncommon (3). Finally, a few patients have potentially life-threatening hypercalcemia (3). Neck ultrasonography (USG) and ^{99m}Techne- tium-sestamibi (SESTAMIBI) scintigraphy are the most frequently used morphological and functional imaging techniques to detect pathological parathyroid glands; however, ¹⁸F-choline Positron Emission Tomography (PET)/Computed Tomography (CT) is being increasingly used in difficult/equivocal cases (4). Although parathyroidectomy remains the only definitive cure for PHPT, surgery is rarely advocated in elderly adults, because of concerns about comorbidities (1); in addition, calcimimetics have opened up a new therapeutic era.

Here, we describe the case of a nonagenarian man who complained of multifaceted symptoms and was diagnosed with symptomatic severe hypercalcemia due to PHPT, in whom the usual imaging techniques failed to detect the parathyroid tumour which was successfully located by ¹⁸F-choline PET/CT. The patient, who declined surgery, was successfully managed by means of calcimimetics.

CASE REPORT

A 90-year-old man suffering from nausea, hyporexia, constipation and psychomotor impairment was brought to the emergency department of our hospital. Anamnesis revealed hypertension on therapy with irbesartan plus hydrochlorothiazide, stage 3 chronic kidney disease (CKD), dyslipidemia, and recent-onset depression on polypharmacotherapy (sertraline, trazodone and prazepam). The patient was alert and afebrile but poorly cooperative; his blood pressure was high (160/100 mmHg). Blood tests revealed increased creatinine levels: 1.6 mg/dL (n.v. 0.7–1.2) and severe hypercalcemia: 14.5 mg/dL (n.v. 8.2–10.2), which was equivalent to 15.3 mg/dL when corrected for reduced (3 g/dL, n.v. 4–5.5) albumin levels. Chest X-ray, electrocardiogram (QTc: 410 ms) were normal and arterial blood gas analysis did not show acidosis; abdominal X-ray showed faecal retention without air-fluid levels. Saline infusion was started and 125 mg methylprednisolone was administered intravenously (i.v.). The patient was hospitalized in our Internal Medicine ward; he was alert but slow, and complained of nausea. His albumin-corrected calcium level was 15.5 mg/dL. Saline (2 L/day), methylprednisolone (80 mg/day i.v.), furosemide (40 mg/day i.v.)

and metoclopramide (20 mg/day i.v.) were started, and hydrochlorothiazide (known to reduce calcium excretion) was withdrawn. The following day, calcium was slightly reduced: 14.2 mg/dL; phosphorus levels were reduced: 2.3 mg/dL (n.v. 2.5–4.5), whereas PTH levels proved increased: 306 pg/mL (n.v. 15–65, intact PTH immunoassay); 25-OHD levels were reduced: 11 ng/mL (n.v. ≥ 30), creatinine levels: 1.6 mg/dL (glomerular filtration rate: 45 mL/min) were unchanged, and thyroid function (TSH: 1.8 μ U/mL) was normal.

A diagnosis of PHPT was made. On the second day of therapy, calcium levels were reduced to 13.5 mg/dL, remaining unchanged on the third day; at this time-point, however, a 15% overall reduction in calcium levels from the baseline had led to clinical improvement in the patient's condition. Neck USG showed subcentimetric isoechoic thyroid nodules with peripheral vascularization, and no enlarged parathyroid glands. Abdominal USG did not show kidney stones. Dual ^{99m}Techne- tium pertechnetate/SESTAMIBI subtraction scintigraphy did not reveal hyperfunctioning parathyroid glands also in the delayed 2h-scan. CT of the thorax and mediastinum, without contrast, evidenced a 12 mm ovoid solid formation, of possible parathyroid origin, localized in the right para-oesophageal space (Figure 1 a, b, c). ¹⁸F-choline PET/TC evidenced an oval-shaped 12 mm nodule (SUV: 8.1) located close to the oesophagus, behind the middle third of the right thyroid lobe, which proved compatible with a hyperfunctioning parathyroid gland (Figure 1 d, e). Dual-energy X-ray absorptiometry revealed wrist (T score: -1.9) and lumbar spine (T score: -1.3) osteopenia. The combined intravenous therapies decreased only partially calcium levels: 12.4 mg/dL (day 10, %: -25% vs baseline values). With a view to administering zoledronate i.v. (at a reduced dosage owing to CKD), in order to further reduce calcemia, jaw X-ray was performed; this revealed several areas of bone rarefaction which would have put the patient to high risk of developing osteonecrosis and for which orthognathic surgery was advised. This was declined by the patient and the drug was not therefore administered. Since the patient refused surgery, the calcimimetic cinacalcet 60 mg/day in two split doses was started; after 3 days, calcium levels were unchanged and the patient, who felt well, was discharged; frequent calcium checks were scheduled. Ten days later, since calcium levels were unchanged (12.6 mg/dL) cinacalcet was increased to 90 mg/day; calcium levels proved reduced (11 mg/dL) four weeks later. However, on the following evaluation calcium levels was 11.9 mg/dL and cinacalcet was increased to 120 mg/day in two split doses with steady normalisation of calcium levels (range: 9–10 mg/dL) thereafter, whereas PTH levels were erratic and showed an upward trend during the first 1-year follow-up examination (Figure 2). After the normalisation of calcium levels, cholecalciferol (25,000 IU/month) was started, and the dose was increased (50,000 IU/month) over time with increase in 25-OHD levels: 20 ng/mL. PTH levels partially decreased following the increase in 25-OHD levels (Figure 2). Patient's gastrointestinal symptoms did not relapse, and depression symptoms improved significantly and only sertraline was left in therapy. Long-term clinical and biochemical follow-up was scheduled.

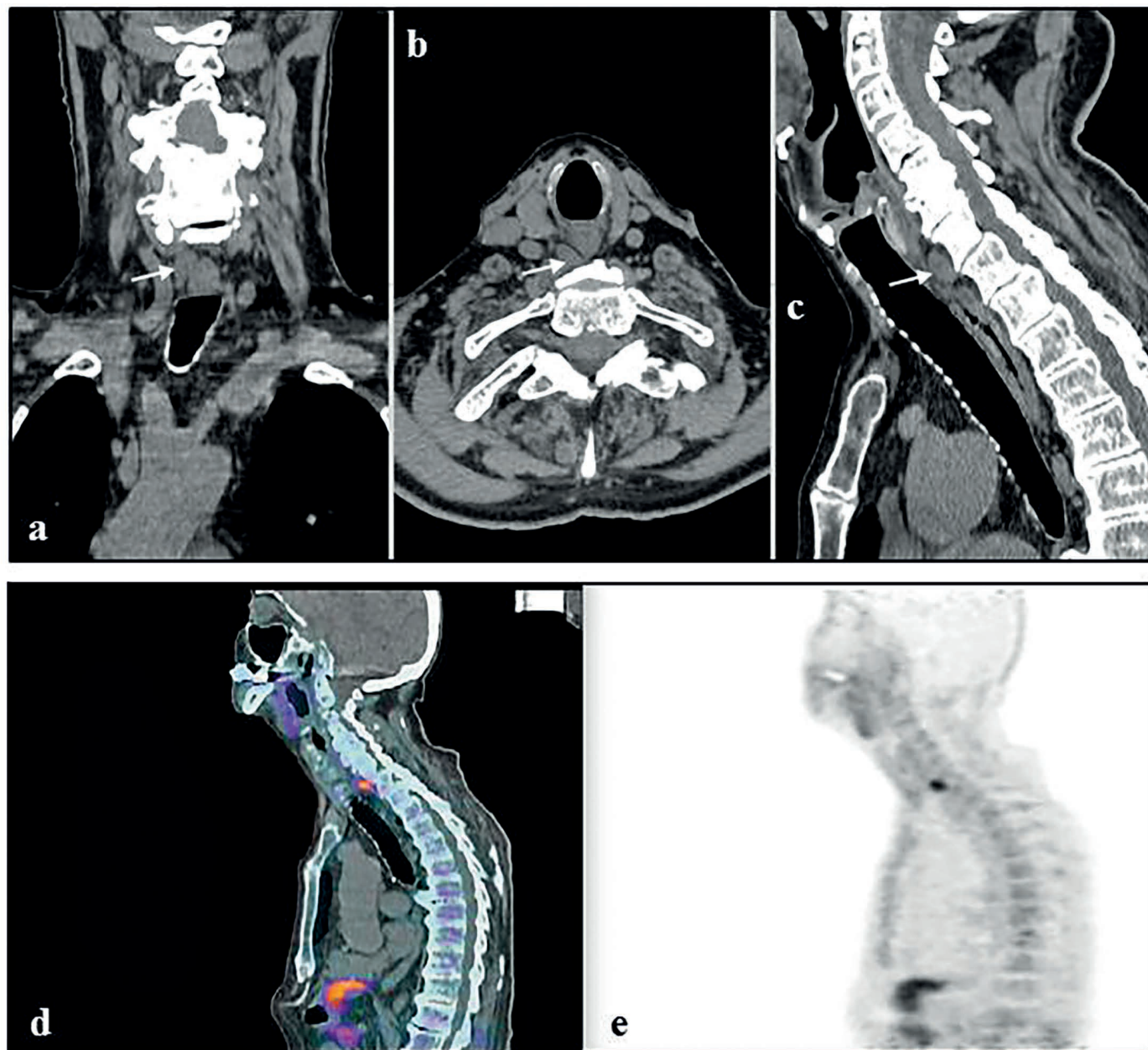


Fig. 1 Computed tomography, without contrast, showed a 12 mm ovoid solid formation (arrow) (a: coronal section, b: transaxial section, c: sagittal section) of possible parathyroid origin, localized in the right para-oesophageal space. Fused ^{18}F -Choline PET/TC (d) and PET (e) showed a high focal uptake (SUV max 8.1) of the tracer by a 12 mm hypodense right para-oesophageal nodule (arrow), which was compatible with a hyperfunctioning parathyroid gland.

DISCUSSION

In the elderly, PHPT is often asymptomatic or displays non-specific symptoms; rarely life-threatening hypercalcemia occurs. In this scenario, polypharmacy can further increase calcium levels (thiazides) or impair bone health (glucocorticoids); vitamin D deficiency may weaken skeleton status. Two of these harmful issues (thiazides and vitamin D deficiency) were present in our patient's clinical history.

In a recent Italian prospective multi-centre study on 604 patients (83% females, mean age: 61 ± 14 years) with mild PHPT (mean PTH levels: 163.0 pg/mL, mean calcium levels 10.9 mg/dL), the authors ascertained that 40.7% patients were "symptomatic", having at least one of the following features: (i) nephrolithiasis, either symptomatic or

asymptomatic (i.e., discovered on USG evaluation) (29.1%); (ii) clinical fragility fractures (11.6%); (iii) symptoms such as nausea, vomiting and constipation (5.6%) (5). Although not specifically designed for elderly patients, this study highlights that symptoms of PHPT, unless overt, must be investigated.

PHPT must be investigated in patients admitted to the emergency department in whom hypercalcemia is ascertained. Unfortunately, the calcium ion is not routinely included in the blood test array in this setting. In a retrospective cross-sectional study performed in an emergency department, Lindner et al. reported that hypercalcemia (mean calcium levels: 10.9 mg/dl) was found in 0.7% of 15,000 patients in whom calcium was assayed. Only 26% of hypercalcemic patients had symptoms that were probably related to hypercalcemia, such as nausea, weakness

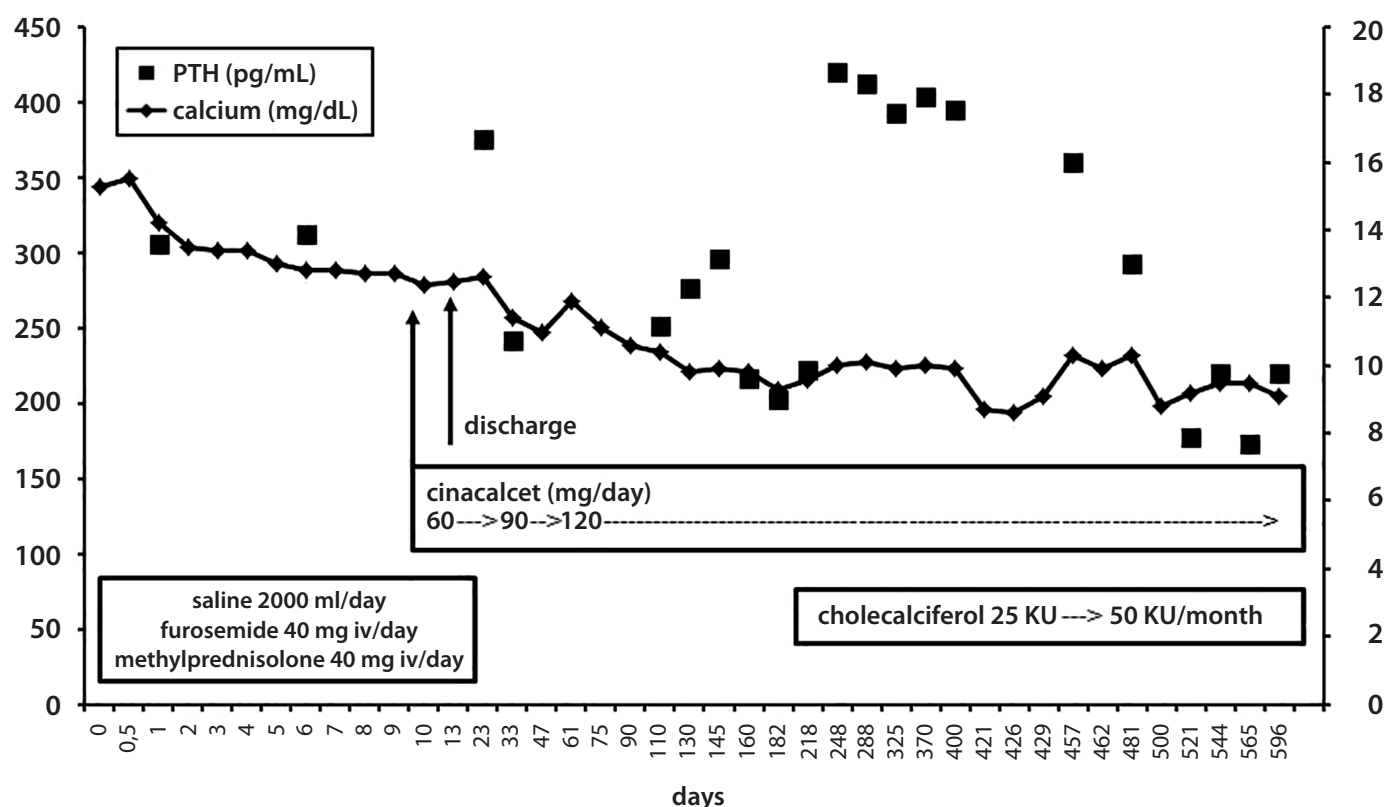


Fig. 2 PTH and albumin-adjusted calcium levels throughout hospitalization and during follow-up in the patient studied.

and disorientation; PHPT was found in only 8% of these patients (6).

Taken together, these studies showed that gastrointestinal symptoms are a common feature of PHPT. In our elderly patient, some of these symptoms (nausea, hyporexia and constipation) were the main reason for his admission to the emergency department, where severe hypercalcemia (subsequently related to PHPT) was ascertained; his symptoms improved following a moderate reduction in calcium levels, and vanished as calcemia normalised over time. Therefore, the so-called abdominal groans, although *per se* non-specific, should prompt an evaluation of the calcium level and, if this is increased, of PTH levels.

Although often deemed unspecific and poorly correlated to calcium levels, neuropsychiatric symptoms, such as depression, may be indicators of hypercalcemia, which is often overlooked.

In our patient, apathy and reduced mental and physical performance, had been ascribed to depression by a neurologist, and specific therapy had been started, with poor benefit. Severe hypercalcemia secondary to PHPT was only subsequently diagnosed and treated. As the patient's calcium levels first decreased and then normalised over time with combined therapies, his depression symptoms greatly improved and specific therapy was reduced.

In our very old hypertensive patient, severe hypercalcemia was managed by combined therapies. First of all saline was infused which expanded the intravascular space, and promoted diuresis and calcium excretion. Loop diuretic (furosemide) was used in order to prevent a potential volume overload with subsequent congestive heart failure induced by saline. Although loop diuretics reduce calcium reabsorption in the loop of Henle, they can para-

doxically increase calcemia by causing volume depletion when used improperly without fluid replacement (7).

In addition, before an etiological diagnosis of hypercalcemia was made, glucocorticoids were used. Once the diagnosis of PHPT was made, the drug was tapered and withdrawn. Glucocorticoids reduce the intestinal absorption of calcium and increase urinary calcium excretion but they have potential complications also in the short-term therapy and are ineffective in PHPT; glucocorticoids still have a significant role in the management of hypercalcemia secondary to granulomatous diseases or haematological malignancies (7).

In our patient, neck USG failed to detect the pathological parathyroid gland, which was subsequently localized behind the trachea by ^{18}F -choline PET/TC. Ectopic gland can be difficult to detect by USG, particularly those in the retro-tracheal region, because of the poor acoustic window due to the tracheal air column (8). MIBI SPECT, which displays tridimensional images, is the functional imaging technique of choice for the localization of parathyroid adenomas. However, it displays misleading imaging results in nearly one third of patients, particularly in presence of small parathyroid adenomas (4). In our case, planar MIBI scintigraphy, also in the delayed 2h-scan, failed to detect the hyperfunctioning parathyroid gland, which was localized by ^{18}F -choline PET/TC close to the oesophagus, behind the middle third of the right thyroid lobe. This imaging technique is based upon the avid uptake of choline, a precursor of the cellular membrane component phosphatidylcholine, by hyperfunctioning parathyroid cells. ^{18}F -choline PET/TC, although it cannot yet be recommended as the first-line approach, is superior to MIBI SPECT/CT, particularly for the localization of small parathyroid adenomas (4).

Parathyroidectomy, the only curative treatment for PHPT, has a high success rate when performed by experienced surgeons. However, elderly patients with PHPT are seldom referred for parathyroidectomy, because they are unfit owing to their associated comorbidities, which may increase the surgical risk (1, 2). Our nonagenarian patient declined surgery and was successfully treated with the calcimimetic cinacalcet. This drug is indicated for the treatment of patients with PHPT who are unfit or decline parathyroidectomy, or in whom hypercalcemia relapses after surgery.

Cinacalcet increases the sensitivity of the calcium-sensing receptor on the parathyroid cells to the inhibitory action of extracellular calcium; hence it reduces PTH secretion and, consequently, serum calcium. However, it has no effect on bone mineral density (9).

In a double-blind, randomized, placebo-controlled study involving 67 subjects (78% females, mean age: 72 years) with moderate PHPT (mean PTH levels: 164.0 pg/mL, calcium levels: 11.7 mg/dL) unfit for parathyroidectomy, and normal 25-OHD levels, Khan et al. found that cinacalcet (median dosage 60 mg/day) normalized calcium levels in 76% of patients, and reduced PTH levels by 24% vs the baseline. Cinacalcet was generally well tolerated, causing only minor side-effects, such as nausea and myalgias (9).

In our patient, cinacalcet was titrated up to 120 mg/day and normalised calcium levels over time with no side-effects, whereas PTH levels proved erratic and showed an upward trend at least during the first year of therapy. This finding is in contrast with the results of the study of Khan et al.; however in our report the PHPT were more severe as featured by higher PTH and calcium levels, and 25-OHD levels were reduced.

The initial increase of PTH levels might be due to several factors which interplayed: vitamin D deficiency secondary to both patient's old age and to stage 3 CKD, decreased PTH metabolism secondary to CKD, and, not least, methodological bias since most but not all PTH samples were assayed in the laboratory of our hospital. In particular, hypovitaminosis D may have worsened the primary hyperparathyroidism by further stimulating PTH synthesis and secretion, resulting in secondary hyperparathyroidism that superimposed on the pre-existing PHPT. However, once plasma vitamin D levels increased by replacement therapy, PTH levels partially decreased.

In summary, PHPT is an often overlooked disease in the elderly, and can present with a wide range of symptoms,

often unspecific, which must be investigated. In this frail population, calcium levels can rarely be life-threatening as ascertained in our patient, and require a timely and proper management. Although parathyroidectomy is the treatment of choice for PHPT whenever possible, calcimimetics are a safe and effective alternative therapeutic tool in this subset of patients, too.

INFORMED CONSENT

Oral Informed consent has been obtained by the patient

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

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