Hypercalcemic Encephalopathy as the Initial Presentation of Primary Hyperparathyroidism in the Elderly

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Abstract

Primary hyperparathyroidism (pHPT) refers to the parathyroid gland's unregulated excess parathyroid hormone production, leading to calcium metabolism impairment. Parathyroid adenomas are the leading cause of pHPT, which the sestamibi scintigraphy can detect with 95% sensitivity. While pHPT has diverse presentations, osteoporosis and asymptomatic vertebral fractures are the most common. Here we present a case of a 70-year-old female with worsening delirium secondary to pHPT, which the sestamibi scan did not pick up.

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Introduction

Primary hyperparathyroidism (pHPT) is a disorder of impaired calcium metabolism brought on by the parathyroid glands' excessive, unregulated production of parathyroid hormone (1). It is the most common cause of hypercalcemia, affecting up to 7 people out of every 1000, and mainly affects middle-aged women (2). It affects females more frequently than males (3). Primary hyperparathyroidism, which typically occurs from parathyroid adenomas, may present with normocalcemia or hypercalcemia. Our report discusses a 70-year-old female presenting with delirium after a fall. Investigations revealed hypercalcemia, hypophosphatemia, elevated parathyroid hormone (PTH) levels, and a right hip joint hairline fracture. We made a clinical and biochemical diagnosis of primary hyperparathyroidism, despite the Sestamibi scan showing no technetium-99m uptake.

Case Presentation

A 70-year-old hypertensive female presented to the ER with gradually worsening consciousness that began a week ago. Her past history was significant for a fall three weeks ago that left her bedridden.

Examination findings

On examination, the patient appeared dehydrated, malnourished, and cachectic. Her vitals were as follows: Blood pressure: 160/90mmhg, Pulse: 80/min, Temperature: 100°C, Oxygen saturation: 86% on room air. She had thoracic scoliosis with a Cobb angle of 15 degrees. Chest auscultation revealed basal coarse crackles. She was exquisitely tender in her epigastrium with no bowel sounds. Neurological examination revealed hyperreflexia. A sensory or motor examination could not be performed as the patient could not follow commands.

Investigations

Hb: 11.1 g/dl, Corrected calcium level: 15.2 mg/dl, Phosphorus: 2.5 mg/dl, PTH level: 261.5 pg/ml, repeat intact PTH (48 hours later) : 907.3 pg/ml, Serum lipase: 1206 U/L, Serum creatinine 1.7 mg/dl, Blood urea: 77 mg/dl. ALT, ALP, Total Bilirubin, Vit D level, T3 and T4 levels were normal.

In addition, urine analysis revealed gram-positive cocci and candida and serum protein electrophoresis showed no monoclonal bands.

Imaging

Chest X-ray (Figure 1) revealed severe kyphotic spine and bilateral basal patchy consolidations.

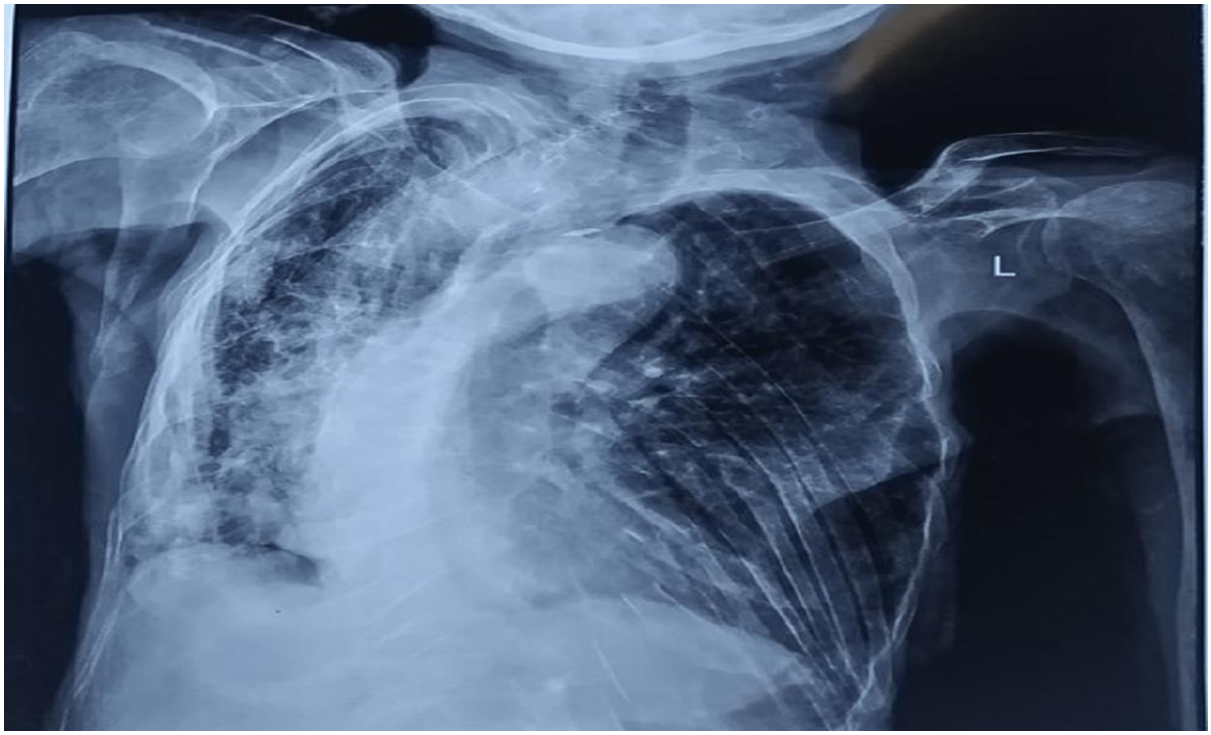

Figure 1: Chest X-Ray

A hip joint X-ray (Figure 2) showed a right-side hip hairline fracture, which is common with falls at this age.

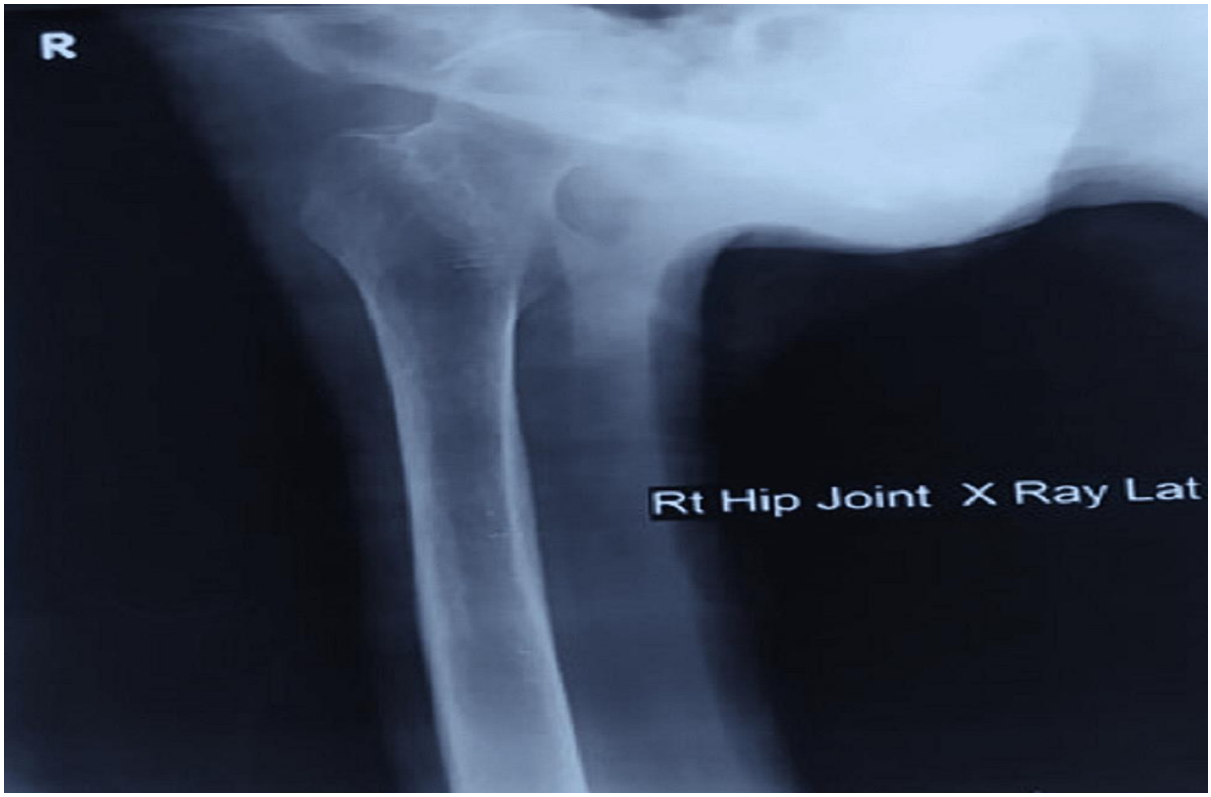

Figure 2: X-Ray of right hip joint

Ultrasound abdomen and pelvis showed a normal-sized liver with heterogeneous echogenicity, mild abdominopelvic ascites, excessive bilateral gut gasses, extensive increased renal parenchymal echogenicity with loss of corticomedullary differentiation CMD, distended gallbladder with an increased wall thickness of 4mm and sludge and proximal common bile duct (CBD) of 5.1mm with the minimal amount of sludge. Echocardiography was normal, with an ejection fraction of 52%.

X-ray skull (Figure 3) revealed a salt and pepper appearance (characteristic of hyperparathyroidism).

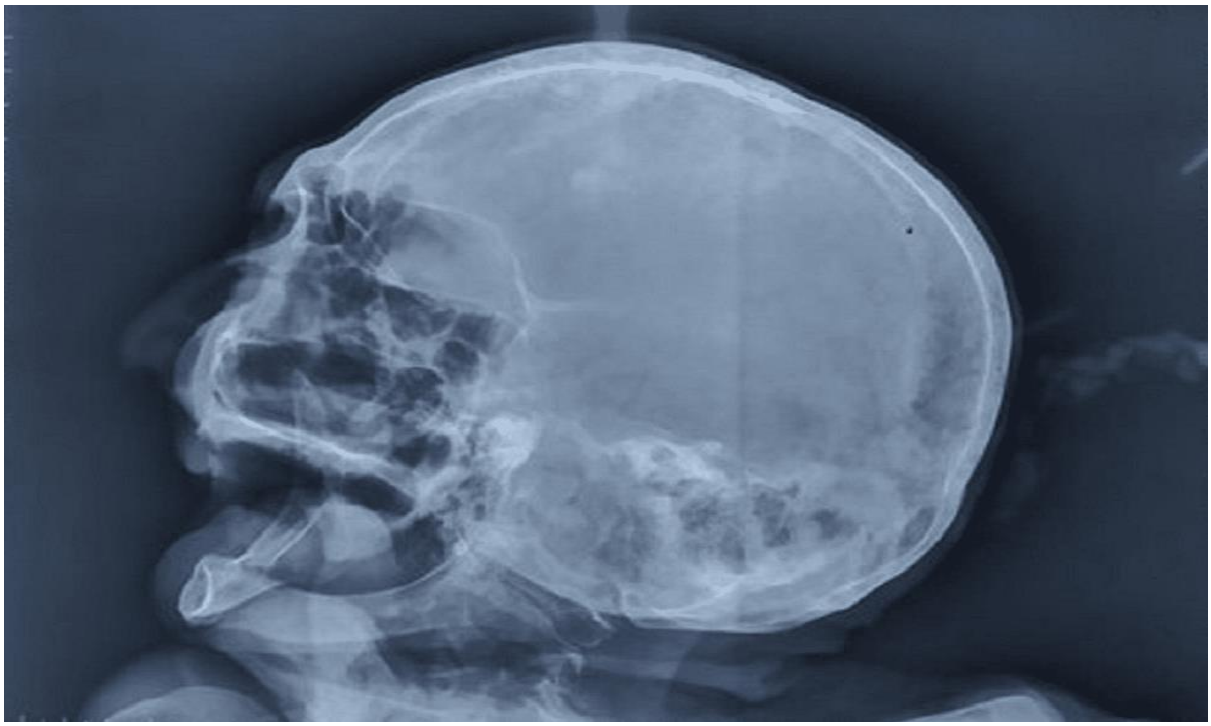

Figure 3: X-Ray Skull

A whole-body bone scan (Figure 4) showed a scoliotic thoracic spine and diffusely increased tracer uptake by the skeleton

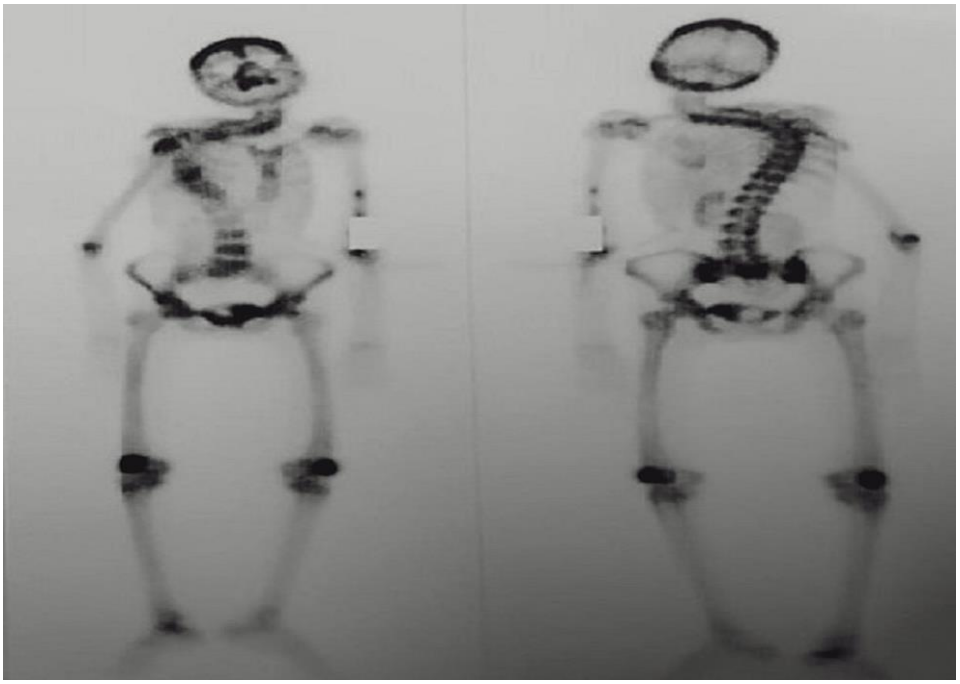

Figure 4: Bone Scan

. Sestamibi scan (Figure 5) showed no uptake of technetium-99m by the parathyroid gland.

Figure 5: Sestamibi Scan

Initial management and diagnosis

Our initial presumptive diagnosis was pneumonia (or urinary tract infection with sepsis) so we started the patient on 5 liters of oxygen via facemask and broad-spectrum antibiotics. The empiric antibiotics cleared her chest and urinary infection, but the altered sensorium persisted. In addition, we began the patient on 6 L/day fluids for her acute pancreatitis and hypercalcemia. However, these measures were only partially able to lower her serum calcium; thus, intravenous bisphosphonate (pamidronate 60 mg) was administered via a slow infusion along with steroids and loop diuretics. These drastically improved her serum calcium levels, and as a result, her sensorium improved.

Since the laboratory investigations showed hypophosphatemia with severe hypercalcemia and elevated iPTH coupled with suggestive radiological findings, we revised our working diagnosis to primary hyperparathyroidism (pHPT). A markedly increased repeat iPTH rendered PTH-independent causes of hypercalcemia, such as malignancies or granulomatous disease, unlikely. Negative findings on the brain, chest and abdominal CT scan with negative electrophoresis results further supported this. To identify the cause of pHPT in this patient, we sought a sestamibi scan, but it showed no scintigraphic evidence of parathyroid adenoma or hyperplasia. Given the high probability of a primary hyperparathyroidism diagnosis, we arranged an MRI neck, but it could not be carried out due to her kyphoscoliosis. As a result, we discharged the patient after normalization of calcium levels and referred her to the otorhinolaryngological team and general surgical unit for further management.

The inherent risks of any surgical procedure due to the compromised respiratory function versus the deteriorating conscious status due to persistent hypercalcemia and the high risk of subsequent pathological fractures meant that the patient withdrew consent for surgery. She later requested discharge against medical advice. Communication with her relatives revealed her demise about one week after her discharge. No autopsy was performed, and histological confirmation of the suspected diagnosis could not be made.

Discussion

Primary hyperparathyroidism (pHPT) is a condition of impaired calcium metabolism caused by high, unregulated parathyroid hormone production by the parathyroid glands (1). Up to 20% of pHPT patients may appear with normal or slightly elevated serum PTH levels in the presence of exceedingly high serum calcium values (2). It is the leading cause of hypercalcemia (affecting up to 7 per 1000 persons), primarily affecting middle-aged women (2). Presenters' typical age range is 25-51 years, with a 7:3 female to male predominance (3) Only 2% of people over 55 years are affected (4). PTAs (parathyroid adenomas) are typically small, weighing less than 1 g and measuring less than 2 cm. The average parathyroid gland size is comparable to that of a rice grain (about 3-5 millimeters in diameter and 30 - 60 mg in weight). Parathyroid hormone levels do not affect the actual gland sizes (volumes) (5).

Primary hyperparathyroidism is mostly asymptomatic but can involve multiple organs (6). The vast majority (>80%) of patients in the USA and Western Europe currently exhibit no symptoms and only a slight elevation of serum calcium and parathyroid hormone (PTH) (1). Contrarily, studies conducted in India, Thailand, and China over the

past five to ten years have found that most patients continue to exhibit renal and bone involvement per the classical pHPT description (7).

In a study on 457 Chinese individuals with pHPT, bone pain (74.8%), urolithiasis (25.5%), fatigue (17.5%), and pathological fracture (13.1%), among other symptoms were noted(7). However, in Western countries, less than 5% of pHPT patients have visible bone disease (8). In about 15% of pHPT patients, the lumbar spine exhibits osteopenia, and some patients may also have osteoporosis. Persistent hypercalcemia and elevated serum intact parathyroid hormone levels are among the initial lab results. Compared to patients with benign PHPT, who have serum PTH values within two times the reference range (1), patients with malignant pHPT have serum PTH concentrations 5-10 times the upper limit of normal (9).

Patients with parathyroid carcinoma typically present with hypercalcemic crisis (>3.5 mmol/L) (9) as opposed to parathyroid adenoma or hyperplasia patients, whose serum calcium levels are usually no more than 0.25 mmol/L above the upper limit of normal (1). When the urinary calcium to creatine ratio is greater than 0.01 , 24-hour urinary calcium levels are typically also elevated. In addition, a perceived correlation between preoperative calcium or PTH levels and the enlarged glands' size is insufficient for identifying the pathologic parathyroid gland(s) in primary hyperparathyroidism (10).

A study to determine how age and gender affect PTH dynamics in healthy subjects concluded that there were no changes to the Cai/iPTH set-point. Thus, uncertainty persists regarding the biological significance of these modest increases in integrated iPTH levels observed during dynamic testing in older, healthy men and women (11). The most frequent cause of primary hyperparathyroidism is an adenoma of the parathyroid gland, which affects 80% of patients, followed by hyperplasia in 15% of cases and carcinoma in 1-5% (12).

Once primary hyperparathyroidism has been confirmed biochemically, the next step is to evaluate bone mineral density at three key locations (the lumbar vertebrae, hip, and forearm) in order to select the best course of treatment, which may involve either surgically removing the gland or conservative management. Since parathyroid adenomas are the most frequent cause of primary hyperparathyroidism, radiological tests are performed to localize any tumors, such as an ultrasound of the neck and technetium-99m sestamibi SPECT-CT (most accurate) (13). Sestamibi scans are 91% sensitive for detecting parathyroid gland adenomas weighing more than 500 g and more than 80% sensitive for detecting those weighing less than 500 g (14). The effectiveness of 99mTc-sestamibi imaging is strongly correlated with the size of the adenoma, with false-negative results being associated with gland weights between 600 and 800 mg (15).

Sestamibi scans are less likely to pinpoint upper-position and smaller-volume parathyroid adenomas. In patients with small adenomas, multiglandular disease, superior adenomas, or preoperative normocalcemia, sestamibi parathyroid imaging is less accurate for detecting abnormal parathyroid tissue (16). According to recent literature, Sestamibi scintigraphy has shown a high sensitivity, in the range of 95%, in patients with the single-gland disease (17). However, preoperative sestamibi scintigraphy frequently fails to detect the abnormal parathyroid gland(s) in patients with double adenomas, 4-gland parathyroid hyperplasia, thyroid nodules, and thyroiditis.

Even though sestamibi scintigraphy is very accurate in patients with single-gland disease and healthy thyroid glands, a small but significant proportion of patients with negative preoperative sestamibi study results ultimately turn out to have a single adenoma as the source of their HPT. Recent research has looked into possible reasons why some patients with the known single-gland disease receive false-negative (FN) sestamibi scintigraphy results. For example, a higher incidence of FN scans has been linked to smaller-volume parathyroid adenomas with a low proportion of oxyphil cells (18).

In our case, the age of the presentation was well over the common age of disease onset. Although hypercalcemia was found incidentally in our patient, she did not remain asymptomatic and rather presented with acute pancreatitis, neurological findings of delirium, and constipation. In our case, clinical presentation and labs consistently favored primary hyperparathyroidism, but the sestamibi scan could not reveal any evidence of the glands' abnormality. This finding, coupled with the patient's age and unique presenting symptoms, make our case unique, which can open new avenues for future researchers to work on. In particular, the reasons for negative sestamibi scans in elderly

females, such as structural atrophy of the glands with maintained functional ability, are an exciting area of exploration. Also, physicians must be cautious and not exclude primary hyperparathyroidism as a cause in older patients with a negative sestamibi scan.

Conclusions

To conclude, we present a case of primary hyperparathyroidism, which is unique given the patients' age, presentation, and a negative sestamibi scan. It adds to the available knowledge of primary hyperparathyroidism and opens a new phase for research in this field.

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