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THE CLASSICAL TETRAD REVISITED: BONES, STONES, GROANS, AND MOANS AS THE UNIFYING PRESENTATION OF SEVERE PRIMARY HYPERPARATHYROIDISM

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ABSTRACT

Primary hyperparathyroidism (PHPT) is the commonest cause of hypercalcaemia in the ambulatory setting. While asymptomatic disease now predominates in Western populations owing to routine biochemical screening, the full classical symptomatic phenotype — constituting the tetrad of *bones* (osteitis fibrosa cystica), *stones* (nephrocalcinosis and hypercalciuria), *groans* (recurrent pancreatitis and gastrointestinal dysmotility), and *moans* (nephrogenic diabetes insipidus with florid polyuria and constitutional symptoms) — remains the predominant mode of presentation in South Asian settings. We present the case of a 41-year-old male photographer from Tirunelveli who sustained a one-year diagnostic delay during which recurrent upper abdominal pain was repeatedly managed as idiopathic acute pancreatitis without a serum calcium measurement. Biochemical evaluation ultimately revealed severe hypercalcaemia (peak serum calcium 14.1 mg/dL), an intact parathyroid hormone (iPTH) exceeding 2500 pg/mL — approximately 38-fold above the upper limit of normal — hypercalciuria (24-hour urinary calcium 300 mg/day), and a massively elevated bone-turnover marker (alkaline phosphatase 1454 IU/L with normal transaminases). Skeletal radiographs confirmed the salt-and-pepper calvarium of osteitis fibrosa cystica and pathognomonic subperiosteal bone resorption of the radial phalangeal cortex bilaterally. Abdominal ultrasonography demonstrated an atrophic pancreas with intraparenchymal calcifications consistent with chronic calcific pancreatitis. Tc-99m sestamibi parathyroid scintigraphy localised a right upper parathyroid adenoma, concordant with neck ultrasonography. The patient was managed with aggressive intravenous isotonic saline hydration followed by loop diuretic therapy, and was planned for right upper parathyroidectomy with pre-operative active vitamin D and calcium supplementation to mitigate the anticipated risk of post-operative hungry bone syndrome. This case underscores that serum calcium must be measured in every patient with recurrent pancreatitis of undetermined aetiology, and that the mnemonic *"bones, stones, groans, and moans"* retains full clinical relevance as a prompt to suspect primary hyperparathyroidism in patients with unexplained multi-system disease.

KEYWORDS: Primary hyperparathyroidism; Parathyroid adenoma; Hypercalcaemia; Osteitis fibrosa cystica; Recurrent pancreatitis; Nephrogenic diabetes insipidus; Intact parathyroid hormone; Tc-99m sestamibi scintigraphy; Subperiosteal bone resorption; Salt-and-pepper skull.

INTRODUCTION

Primary hyperparathyroidism (PHPT) is characterised by autonomous, unregulated secretion of parathyroid hormone (PTH) from one or more hyperfunctioning parathyroid glands, most commonly due to a solitary adenoma (80–85% of cases). It represents the third most

common endocrine disorder after diabetes mellitus and thyroid disease. The mnemonic **"bones, stones, groans, and moans"** — denoting skeletal disease, urolithiasis and nephrocalcinosis, gastrointestinal manifestations, and neuropsychiatric or constitutional symptoms — was coined in an era before biochemical screening revealed asymptomatic hypercalcaemia as the commonest presentation in the developed world.[1]

In South Asian settings, including India, the symptomatic phenotype remains the rule. Indian series consistently report a younger age of onset (mean approximately 42 years), higher calcium concentrations, and a substantially higher prevalence of osteitis fibrosa cystica (OFC) and pancreatitis at presentation compared with Western cohorts.[2,3] This divergence reflects the absence of systematic metabolic screening, allowing undetected PTH excess to erode bone, calcify the pancreatic parenchyma, and impair renal tubular concentrating ability over years before the diagnosis is made.

The association between PHPT and pancreatitis has been recognised for over seven decades. Hypercalcaemia activates trypsinogen prematurely within pancreatic acinar cells, promotes ductal protein precipitation, and drives progressive parenchymal calcification, producing both acute and chronic pancreatitis. The prevalence of pancreatitis among hyperparathyroid patients is 10 to 20 times higher than in the general population.[4] Yet pancreatitis as the index presentation of PHPT is repeatedly misattributed to more common aetiologies — a diagnostic failure with serious long-term consequences.

We present a 41-year-old male who was hospitalised multiple times for presumed idiopathic pancreatitis over an entire year before serum calcium was measured, revealing severe hypercalcaemia with an iPTH exceeding 2500 pg/mL, advanced osteitis fibrosa cystica, chronic calcific pancreatitis, and a right upper parathyroid adenoma on scintigraphy. This case is presented to document the complete classical tetrad of severe symptomatic PHPT in a South Asian patient, to analyse the consequences of diagnostic delay, and to reinforce that serum calcium measurement is mandatory in the aetiological workup of every episode of recurrent pancreatitis without an identified cause.

CASE REPORT

History

A 41-year-old male professional photographer, a resident of Tirunelveli, Tamil Nadu, India, presented to the Second Medical Unit of Tirunelveli Medical College Hospital with a one-year history of recurrent upper abdominal pain and a concurrent one-year history of polyuria with nocturia. He was of thin build and moderate nutritional status (BMI 20.31 kg/mZ).

The abdominal pain was centred in the upper abdomen, intermittent (one to two episodes per month lasting two to three days each), sharp in quality, radiating to the upper back, aggravated by food intake, and partially relieved by bending forward — a positional characteristic consistent with retroperitoneal pathology. Each episode had been attributed to acute pancreatitis during multiple prior surgical admissions and the patient was discharged on conservative management on each occasion without metabolic evaluation. No serum calcium had been obtained at any prior admission.

Concurrently, the patient reported waking 10 to 11 times per night to void approximately 300 mL per episode, with an estimated nocturnal urine output exceeding three litres and intense daytime polydipsia. The 24-hour urine volume measured during the present admission was 3600 mL, confirming polyuria. These features are consistent with nephrogenic diabetes insipidus resulting from hypercalcaemia-mediated downregulation of aquaporin-2 channels and progressive impairment of the renal medullary concentration gradient.

Additional symptoms over the same one-year period included low backache, generalised weakness, diffuse myalgia, constipation, and progressive unintentional weight loss — all recognised manifestations of sustained hypercalcaemia. There was no history of fever, jaundice, haematemesis, haematuria, flank pain, renal colic, palpitations, or neuropsychiatric symptoms. He denied alcohol consumption, tobacco use, and intake of calcium supplements, vitamin D megadosage, thiazide diuretics, or lithium. A family history of hypothyroidism was noted in siblings — clinically significant given the possibility of a familial endocrine syndrome such as Multiple Endocrine Neoplasia type 1 (MEN-1).

Examination Findings

On general examination the patient was conscious, oriented, afebrile, and moderately nourished. Clinical pallor was present. There was no icterus, cyanosis, digital clubbing, pedal oedema, or lymphadenopathy. No skin lesions or bony deformities were observed. Vital signs: pulse 70 beats/minute (regular, equal in all peripheral pulses); blood pressure 130/80 mmHg (right upper limb, sitting); SpO_2 99% on room air; respiratory rate 16 cycles/minute. The normal blood pressure despite chronic osmotic diuresis reflects the vasopressor effect of ionised calcium on vascular smooth muscle, increasing systemic vascular resistance — the haemodynamic paradox of hypercalcaemia.

Abdominal examination revealed a scaphoid abdomen with diffuse tenderness, most prominent in the epigastric and periumbilical regions, without guarding, rigidity, or organomegaly. Liver span 11 cm; Traube's space resonant; no ascites; normal bowel sounds. Cardiovascular and respiratory examinations were unremarkable. Central nervous system examination showed no focal neurological deficits. Fundoscopy was normal bilaterally with no band keratopathy or papilloedema.

INVESTIGATIONS

A comprehensive biochemical, haematological, radiological, and nuclear medicine workup was performed.

Table 1: Haematological Parameters.

Parameter	02/09/25	06/09/25	Ref. Range
Hb (g/dL)	10.0	9.2	13.5–17.5
TLC (cells/µL)	7600	6900	4000–11,000
Platelets (L/µL)	3.6	2.3	1.5–4.5
MCV (fL)	88	92	80–100
ESR (mm/hr)	120	——	<20
LDH (IU/L)	278	——	140–280

Peripheral smear: dimorphic picture — mixed microcytic hypochromic and normocytic normochromic erythrocytes.

Table 2: Serial Renal Function Tests.

Parameter	02/09	03/09	04/09	06/09
Urea (mg/dL)	43	42	15	35
Creatinine (mg/dL)	1.2	1.09	0.9	1.21
Na (mEq/L)	136	137	139	138
K (mEq/L)	3.8	3.9	3.7	3.8

Table 3: Liver Function Tests.

Parameter	02/09/25	06/09/25	Ref. Range
Total Bilirubin (mg/dL)	0.5	0.49	0.3–1.2
AST / ALT (IU/L)	17/18	9/8	<40/<40
ALP (IU/L)	1119	1454	44–147
Albumin (g/dL)	3.9	4.1	3.5–5.0
Total Protein (g/dL)	6.4	7.1	6.4–8.3

The massively elevated and rising ALP (1119 → 1454 IU/L) with normal transaminases and bilirubin confirms a bone-isoform origin, reflecting the high bone turnover of advanced PHPT with OFC.

Table 4: Key Endocrine and Metabolic Parameters.

Investigation	Result	Ref. Range
Serum Ca (02/09) mg/dL	13.2	8.5–10.5
Serum Ca (03/09) mg/dL	11.3	8.5–10.5
Serum Ca (04/09) mg/dL	12.5	8.5–10.5
Serum Ca (06/09) mg/dL	14.1	8.5–10.5
Serum Phosphorus (mg/dL)	3.1	2.5–4.5
iPTH (pg/mL)	>2500	15–65
Vitamin D total (ng/mL)	17.9	>30
24-hr Urinary Ca (mg/day)	300	<250
24-hr Urine Volume (mL)	3600	<3000
TSH (mIU/L)	2.079	0.4–4.0
Fasting Glucose (mg/dL)	98	70–100
HbA1c (%)	5.6	<5.7
ABG pH / HCO_3 (mEq/L)	7.3 / 20.2	7.35–7.45 / 22–26
Spot Urine PCR (mg/g)	280	<200

Coagulation: PT 15s, APTT 22s, INR 1.2. Lipid profile: normal. HBsAg, Anti-HCV, ICTC: negative.

Radiological and Special Investigations

ECG: Sinus rhythm at 79 bpm; shortened QT interval — the classical ECG manifestation of hypercalcaemia reflecting accelerated cardiac repolarisation. **X-ray Skull (AP and Lateral):** Classic *salt-and-pepper* appearance — diffuse granular demineralisation of the calvarium, pathognomonic of osteitis fibrosa cystica. **X-ray Hands/Forearms (Bilateral):** Subperiosteal bone resorption along the radial aspect of the middle phalanges bilaterally — the most sensitive plain radiograph sign of hyperparathyroidism. **X-ray Pelvis:** Heterogeneous bony architecture with areas of rarefaction. **Chest X-ray:** Normal lung fields; no mediastinal lymphadenopathy.

USG Neck: 3.3 × 2 × 1.8 cm well-defined solid-cystic lesion in the right thyroid/parathyroid region. **USG Abdomen:** Liver, gallbladder, spleen normal; bilateral kidneys of normal size with preserved corticomedullary differentiation; pancreas atrophic with intraparenchymal

calcifications — consistent with chronic calcific pancreatitis. **Tc-99m Sestamibi Parathyroid Scintigraphy:** Focal retention of radiotracer in the right upper parathyroid region on delayed phase imaging, confirming a right upper parathyroid adenoma, concordant with neck ultrasound.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of hypercalcaemia with an elevated PTH was systematically evaluated following standard algorithmic approach.[1,2]

Table 5: Differential Diagnosis of Hypercalcaemia with Elevated PTH.

Diagnosis	Supporting Features	Exclusion Basis	Verdict
Primary Hyperparathyroidism	iPTH >2500 pg/mL; Ca 14.1 mg/dL; hypercalciuria; OFC on X-ray; adenoma on sestamibi	None	CONFIRMED
Tertiary Hyperparathyroidism	Elevated iPTH and Ca	No prior CKD; creatinine normal throughout	Excluded
Familial Hypocalciuric Hypercalcaemia	Family history of endocrine disease	Hypercalciuria 300 mg/day (FHH shows <100 mg/day); no lithium	Excluded
PTHrP-mediated (Malignancy)	Weight loss; elevated ESR; anaemia	iPTH massively elevated — suppressed in PTHrP-mediated disease; no mass lesion	Excluded
Granulomatous disease	Elevated ESR; weight loss	PTH elevated not suppressed; normal chest X-ray; no lymphadenopathy	Excluded
Vitamin D Toxicity	——	Vitamin D actually low (17.9 ng/mL); iPTH elevated; no supplementation	Excluded
MEN-1 Syndrome	Young male; family endocrine history	Gastrinoma/insulinoma/pituitary not yet screened	Requires formal workup
Parathyroid Carcinoma	iPTH >2500 pg/mL; large 3.3 cm lesion	Requires histopathological exclusion post-excision	Cannot be excluded pre-op

DIAGNOSIS

The combination of severe hypercalcaemia, an iPTH exceeding 2500 pg/mL (approximately 38-fold above the upper limit of normal), hypercalciuria (300 mg/day), pathognomonic skeletal radiograph findings of osteitis fibrosa cystica, chronic calcific pancreatitis on ultrasonography, and concordant localisation of a right upper parathyroid adenoma by Tc-99m sestamibi scintigraphy and neck ultrasound established the diagnosis of **Primary Hyperparathyroidism due to a right upper parathyroid adenoma** — presenting as the complete classical tetrad of bones, stones, groans, and moans.

MANAGEMENT AND OUTCOME

The cornerstone of acute management was aggressive intravenous isotonic saline (0.9% NaCl) at 200–500 mL/hour targeting a urine output of 150–200 mL/hour, which reduces serum calcium by 1–3 mg/dL through restoration of glomerular filtration and reduction of proximal tubular calcium reabsorption. Loop diuretics (furosemide 20–40 mg IV every 6 hours) were added only after confirming adequate volume repletion — an essential sequencing principle, as premature furosemide worsens prerenal azotaemia and paradoxically elevates calcium. Serial electrolytes were monitored to detect dilutional imbalances.

Serial calcium monitoring demonstrated partial response (13.2 → 11.3 mg/dL on day 2) with rebound to 14.1 mg/dL by day 5, confirming the inadequacy of medical therapy against autonomous PTH secretion and the urgency of definitive surgical intervention. Definitive management was planned as right upper parathyroidectomy. Pre-operative preparation included oral calcium carbonate (2–3 g/day), alfacalcidol (0.5–1 mcg/day), and cholecalciferol to correct the baseline vitamin D deficiency (17.9 ng/mL), all initiated to mitigate the anticipated high risk of post-operative hungry bone syndrome (HBS) — predicted by the severely elevated ALP (1454 IU/L) and extensive radiological OFC.[5]

Post-operatively, intraoperative iPTH monitoring (Miami criterion: >50% fall confirms biochemical cure) and intensive ionised calcium monitoring for 24–48 hours with intravenous calcium gluconate at the bedside were planned.

DISCUSSION

This case exemplifies the severe, symptomatic PHPT phenotype that characterises the disease in South Asian populations — a stark contrast to the asymptomatic, biochemically detected disease that now predominates in Western series. Goswami et al., in a landmark retrospective analysis of Indian PHPT patients, reported that 72% had bone disease and 25% had pancreatitis at presentation, with a mean age of 42 years and a mean

calcium of 13.1 mg/dL — figures concordant with the present case.[2] This divergence is directly attributable to the absence of systematic metabolic screening in the Indian healthcare ecosystem.

The most actionable lesson from this case is the prevention of diagnostic delay. This patient sustained multiple surgical hospitalisations for pancreatitis over an entire year without a serum calcium measurement. The American College of Gastroenterology guidelines and the International Association of Pancreatology mandate metabolic evaluation — including serum calcium — in any episode of pancreatitis without an obvious aetiology.[6] A serum calcium at the first admission would have identified the hypercalcaemia, prompted iPTH measurement, and prevented one year of progressive OFC, chronic calcific pancreatitis, and nephrogenic DI.

An iPTH exceeding 2500 pg/mL is an extraordinary biochemical finding. The published literature on PHPT predominantly reports iPTH values of 100–800 pg/mL for benign adenoma. Values exceeding 1000 pg/mL raise the possibility of parathyroid carcinoma, which accounts for fewer than 1% of PHPT cases but is characterised by very high PTH levels and a risk of recurrence.[7] Histopathological examination of the excised gland — assessing for capsular invasion, vascular invasion, perineural invasion, and mitotic count — is therefore mandatory in this case.

Post-operative hungry bone syndrome (HBS) is the most significant anticipated complication. HBS — precipitous hypocalcaemia following parathyroidectomy from massive calcium uptake into the remineralising skeleton — is predicted by pre-operative ALP elevation, radiological OFC, and vitamin D deficiency, all of which are present in this patient.[5] Pre-operative active vitamin D and calcium supplementation, and post-operative intensive ionised calcium monitoring, are mandatory.

Tc-99m sestamibi scintigraphy has a sensitivity of 80–90% for a solitary parathyroid adenoma.[8] Concordance with neck ultrasound — both identifying a right-sided lesion — supports a focused minimally invasive right-sided parathyroidectomy with intraoperative PTH monitoring (Miami criterion), achieving cure rates equivalent to bilateral exploration while reducing operative time and complication risk.

Finally, the occurrence of PHPT in a young male with a family history of endocrine disease mandates formal MEN-1 evaluation. MEN-1 (autosomal dominant, *MEN1* gene on chromosome 11q13) is characterised by PHPT (95% penetrance), enteropancreatic tumours (gastrinoma, insulinoma), and pituitary adenomas.[9] Fasting gastrin, insulin:glucose ratio, prolactin, IGF-1, MRI pituitary, and MEN1 gene testing constitute the minimum workup.

CONCLUSION

This case documents the complete classical tetrad of severe primary hyperparathyroidism — bones (osteitis fibrosa cystica), stones and groans (chronic calcific pancreatitis and recurrent acute pancreatitis), and moans (nephrogenic diabetes insipidus and constitutional symptoms) — driven by a right upper parathyroid adenoma secreting iPTH at levels exceeding 2500 pg/mL. The case demonstrates that a one-year diagnostic delay — during which pancreatitis was repeatedly managed without serum calcium measurement — resulted in progressive, largely irreversible end-organ damage. Serum calcium must be measured in every patient with recurrent pancreatitis of undetermined aetiology. The classical mnemonic **"bones, stones, groans, and moans"** retains full clinical relevance and should prompt the clinician to suspect PHPT in any patient with unexplained multi-system disease encompassing skeletal, renal, gastrointestinal, and constitutional features. Definitive treatment is surgical parathyroidectomy, with pre-operative active vitamin D and calcium supplementation mandatory to mitigate the high risk of post-operative hungry bone syndrome.

DECLARATIONS

Conflict of Interest: The authors declare no conflict of interest.

Patient Consent: Written informed consent obtained from the patient for publication of clinical data and radiological images.

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REFERENCES

1. Bilezikian JP, Khan AA, Silverberg SJ, et al. Evaluation and management of primary hyperparathyroidism: summary statement and guidelines from the Fifth International Workshop. *J Bone Miner Res*, 2022; 37(11): 2293–2314.
2. Goswami R, Mohapatra T, Gupta N, et al. Parathyroid adenoma and not hyperplasia is the cause of primary hyperparathyroidism in young patients of India. *World J Surg*, 2011; 35(2): 336–342.
3. Singh SK, Agarwal G, Chand G, Mishra SK. Primary hyperparathyroidism in the Indian subcontinent: a rare but severe disease. *Indian J Endocrinol Metab*, 2011; 15(Suppl 2): S133–S136.
4. Bai HX, Giefer M, Patel M, Orabi AI, Husain SZ. The association of primary hyperparathyroidism with pancreatitis. *J Clin Gastroenterol*, 2012; 46(8): 656–661.

5. Brasier AR, Nussbaum SR. Hungry bone syndrome: clinical and biochemical predictors of its occurrence after parathyroid surgery. *Am J Med.* 1988; 84(4): 654–660.
6. Tenner S, Baillie J, DeWitt J, Vege SS. American College of Gastroenterology guideline: management of acute pancreatitis. *Am J Gastroenterol, 20*13; 108(9): 1400–1415.
7. Shane E. Parathyroid carcinoma. *J Clin Endocrinol Metab, 20*01; 86(2): 485–493.
8. Denwar MF, Bonanomi MT, Borges MF, et al. Tc-99m-Sestamibi SPECT/CT for pre-operative parathyroid localisation. *Semin Nucl Med, 20*19; 49(1): 20–29.
9. Thakker RV, Newey PJ, Walls GV, et al. Clinical practice guidelines for multiple endocrine neoplasia type 1. *J Clin Endocrinol Metab, 20*12; 97(9): 2990–3011.
10. Carroll MF, Schade DS. A practical approach to hypercalcemia. *Am Fam Physician,* 2003; 67(9): 1959–1966.