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■ CASE REPORT

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When Mild Is Not Benign: Subtle Hypercalcemia and Confusion Unmasking a Destructive Femoral Lesion in End-Stage Renal Disease

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ABSTRACT

Background: Hypercalcemia of malignancy is an important metabolic complication of cancer that may produce neurologic manifestations and is associated with poor prognosis. Diagnosis and management can be particularly challenging in elderly patients with end-stage renal disease (ESRD), in whom abnormalities of calcium and parathyroid hormone homeostasis may complicate interpretation.

Case Presentation: An 86-year-old man with ESRD and prostate cancer in remission presented with acute confusion, worsening left hip pain, and abnormal laboratory findings. Nephrology evaluation found a creatinine of 5.9 mg/dL and calcium of 10.8 mg/dL. Hospital studies showed anemia secondary to ESRD, elevated serum calcium at 10.8 mg/dL, ionized calcium at 1.50 mmol/L, intact parathyroid hormone (PTH) at 26.3 pg/mL, elevated parathyroid hormone-related peptide (PTHrP) at 3.0 pmol/L, and a normal PSA of 1.3 ng/mL. Radiographs and CT demonstrated a large destructive lytic lesion involving the left lesser trochanter and proximal femoral shaft, highly suspicious for malignancy of uncertain primary origin. Bone scintigraphy subsequently demonstrated intense tracer uptake spanning approximately 13 cm of the left proximal femur, further supporting an active osseous process. Despite medical management, the patient's hypercalcemia persisted, and his encephalopathy worsened. After multidisciplinary discussions, the family opted for comfort care.

Discussion: Malignancy-associated hypercalcemia may result from PTHrP secretion or osteolytic bone destruction, while ESRD can complicate the interpretation and management of calcium abnormalities. This case highlights that even mild total hypercalcemia, particularly when accompanied by elevated ionized calcium, new confusion, and progressive focal bone pain, should prompt consideration of an underlying destructive osseous process.

Keywords: Hypercalcemia; End-stage renal disease; PTHrP; Destructive bone lesion; Lytic bone lesion; Malignancy; Prostate cancer; Palliative care.

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1. Introduction

Hypercalcemia is a common metabolic complication of malignancy, occurring in about 20-30% of cancer patients [1,2]. Hypercalcemia of malignancy causes significant morbidity and often signals advanced disease and limited survival [2-4]. Mortality can exceed 50% within three months, especially in the elderly and those with bone metastases [5-7]. Malignancy-associated hypercalcemia is usually multifactorial. It often involves PTHrP secretion, osteolytic bone metastases, ectopic vitamin D production, or, rarely, ectopic PTH secretion [1,2]. Osteolytic metastases in large bones, such as the femur, can release substantial calcium due to osteoclast activation [8,9]. ESRD patients are especially vulnerable [10]. ESRD is the last stage of chronic kidney disease (CKD), defined by a glomerular filtration rate (GFR) under 15 mL/min/1.73 m^2 and often treated with dialysis or transplantation [10,11].

Altered mineral metabolism, secondary hyperparathyroidism, and impaired vitamin D metabolism make the diagnosis and interpretation of hypercalcemia more challenging in patients with ESRD [11,12]. Furthermore, conventional treatments for hypercalcemia, including intravenous hydration and bisphosphonate therapy, may be limited by advanced renal dysfunction or concomitant cardiac disease [13,14].

Bone metastases in the femur carry a high risk of pathologic fracture and severe morbidity, especially in older adults [15,16]. Large lytic lesions can remain clinically silent until late in the disease, when pain, immobility, or hypercalcemia develop [17].

This case highlights how a seemingly mild elevation in total calcium (10.8 mg/dL), accompanied by subtle neurologic symptoms (confusion) and focal bone pain in an elderly patient with end-stage renal disease, may signal an underlying destructive osseous malignancy. A destructive proximal femoral lesion is highly suspicious for malignancy of uncertain primary origin. Hypercalcemia is a potential contributor and an important diagnostic clue to underlying cancer, especially in an older patient with ESRD.

2. Case Presentation

An 86-year-old man with a history of myocardial infarction, hypertension, hypothyroidism, ESRD not on chronic hemodialysis, and prostate cancer in remission presented to the emergency department after abnormal outpatient laboratory results (especially calcium) and worsening confusion. The family reported progressive cognitive decline over two weeks. Symptoms included disorientation, lethargy, and decreased oral intake. During this time, the patient developed persistent left hip pain that worsened with movement, limiting ambulation. There was no trauma or recent fall.

The patient was afebrile and hemodynamically stable at presentation. He appeared fatigued and was intermittently confused. Neurological examination showed no focal deficits, but attention and orientation were impaired. The left proximal femur was tender, and hip motion was limited by pain. Initial laboratory and endocrine findings are summarized in Table 1.

Table 1. Initial Laboratory and Endocrine Findings

Laboratory Test	Patient Value	Reference Range (Normal)
Serum Calcium	10.8 mg/dL	8.6–10.2 mg/dL
Ionized Calcium	1.50 mmol/L	1.12–1.32 mmol/L
Creatinine	5.9 mg/dL	0.6–1.3 mg/dL
Hemoglobin	9.6 g/dL	13.5–17.5 g/dL (male)
Phosphate	4.7 mg/dL	2.5–4.5 mg/dL
Albumin	3.4 g/dL	3.5–5.0 g/dL
Intact PTH	26.3 pg/mL	10–65 pg/mL
PTHrP	3.0 pmol/L	0–2.0 pmol/L
PSA	1.3 ng/mL	0–4 ng/mL

Serum protein electrophoresis and immunofixation showed no monoclonal gammopathy, and the vitamin D level was 36 ng/mL. Radiography of the left femur demonstrated a large destructive lytic lesion involving the proximal femoral shaft with cortical thinning (Figures 1 and 2), raising concern for an underlying malignancy of uncertain origin. CT further demonstrated approximately 13 cm of osseous destruction with surrounding soft-tissue involvement. Bone scintigraphy demonstrated intense tracer uptake involving the left proximal femur (Figure 3), consistent with a metabolically active osseous lesion. Further MRI evaluation was not pursued.

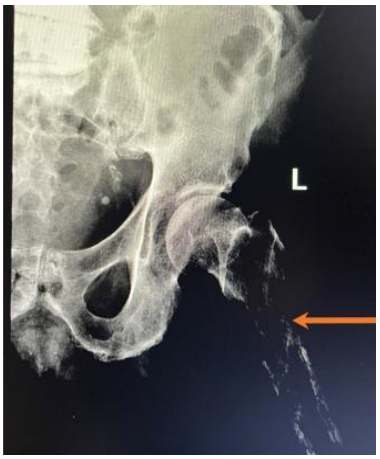

Figure 1. Radiograph of the left femur showing permeative destruction of the left lesser trochanter and the proximal femoral shaft.

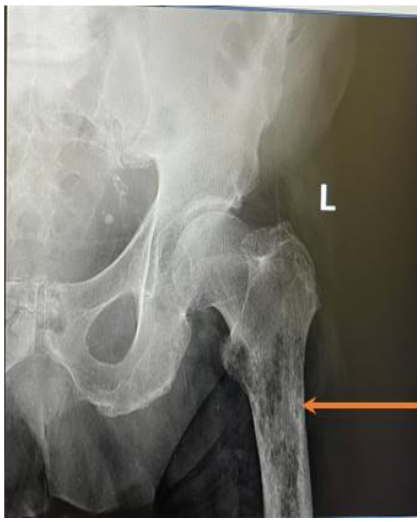

Figure 2. Radiograph of the left femur (second view) showing permeative destruction of the left lesser trochanter and the proximal femoral shaft.

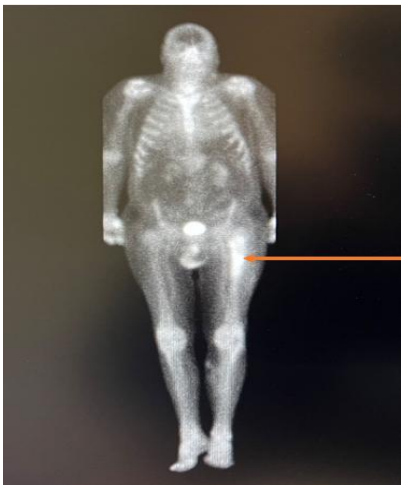

Figure 3. Whole-body nuclear medicine bone scan. An area of markedly increased tracer uptake is present along the left proximal femur, spanning approximately 13 cm.

Orthopedic surgery was consulted for possible intervention; however, the patient's advanced age and comorbidities limited surgical options. For hypercalcemia, he received salmon calcitonin 4 units/kg subcutaneously every 12 hours for two days, pamidronate 60 mg intravenously once, and approximately 2 L of intravenous crystalloid administered cautiously at 60 mL/h because of his advanced renal dysfunction. Despite treatment, serum calcium remained approximately 10.5–10.7 mg/dL, while his mental status fluctuated and oral intake progressively declined. On hospital day 4, following multidisciplinary discussions, the family elected comfort-focused care and declined further invasive evaluation to establish the etiology of the destructive bone lesion. He was discharged home with hospice care and died several days later.

3. Discussion

Neurologic manifestations of hypercalcemia are variable and may include fatigue, impaired concentration, confusion, delirium, and, in severe cases, marked alteration in consciousness [18]. Importantly, symptom severity does not always parallel the absolute serum calcium concentration and may be influenced by the rapidity of calcium elevation, patient age, and underlying comorbidities [19]. In this patient, the total calcium elevation was relatively mild at 10.8 mg/dL; however, the ionized calcium was clearly elevated at 1.50 mmol/L. Although hypercalcemia cannot be established as the sole cause of his encephalopathy, its presence alongside new confusion, progressive focal bone pain, an inappropriately normal PTH level, elevated PTHrP, and a large destructive femoral lesion raised substantial concern for an underlying malignancy-associated process [20].

Malignancy-associated hypercalcemia most commonly results from PTHrP secretion, osteolytic bone destruction, excess calcitriol production, or, rarely, ectopic PTH secretion [1,21]. Tumor-mediated activation of osteoclasts through cytokine- and RANKL-dependent pathways can promote bone resorption, calcium release, and skeletal destruction [22]. Hypercalcemia of malignancy is associated with advanced disease and poor survival [23,24,30].

Other common clinical features can be general (dehydration, polyuria, polydipsia), gastrointestinal (e.g., nausea, vomiting, constipation, anorexia), or neurologic (e.g., fatigue, delirium, myopathy) [1]. The rapidity of onset is more likely to correlate with symptom severity than the degree of hypercalcemia [1]. The syndrome typically results from one of four major mechanisms: (1) PTH-related peptide secretion (humoral hypercalcemia of malignancy); (2) osteolytic bone metastases; (3) excess calcitriol production; and (4) ectopic parathyroid hormone secretion [2].

Patients with ESRD present unique challenges when evaluating hypercalcemia because advanced kidney disease alters calcium-phosphate homeostasis, vitamin D metabolism, and PTH regulation [25]. These abnormalities may complicate interpretation of modest elevations in serum calcium. In this patient, the intact PTH level of 26.3 pg/mL was within the laboratory reference range but was inappropriately normal in the setting of hypercalcemia, supporting consideration of a PTH-independent process. The concomitant elevation in PTHrP further increased concern for an underlying malignancy [20,26].

An inappropriately normal PTH level in the presence of hypercalcemia should prompt consideration of PTH-independent etiologies, including malignancy [1,26,27]. The femur is a recognized site of skeletal metastasis, and large lytic lesions can compromise cortical integrity and increase the risk of pathologic fracture [8,28]. Progressive focal bone pain should therefore prompt evaluation for an underlying osseous process [29]. In elderly patients, progressive bone pain should prompt evaluation for malignancy, particularly when accompanied by metabolic abnormalities such as hypercalcemia [1,30].

Management of hypercalcemia depends on its severity, underlying mechanism, symptoms, and comorbidities. Intravenous isotonic fluid administration promotes renal calcium excretion but must be used cautiously in patients with ESRD because of the risk of volume overload [13,14]. Calcitonin provides a relatively rapid but short-lived reduction in serum calcium, whereas bisphosphonates such as pamidronate inhibit osteoclast-mediated bone resorption; bisphosphonate use requires particular caution

in severe renal dysfunction [14,31,32]. Denosumab, a monoclonal antibody targeting RANKL, has demonstrated efficacy in hypercalcemia of malignancy, including bisphosphonate-refractory disease [33]. In severe or refractory hypercalcemia, hemodialysis with a low-calcium dialysate may be considered when clinically appropriate [34]. Studies demonstrate median survival ranging from weeks to a few months, depending on the underlying malignancy and disease burden [24]. For patients who do not wish to pursue further investigation or treatment, early involvement of palliative care teams is recommended to address symptom control, decision-making, and quality of life [35]. Hospice and palliative care services play a crucial role in ensuring comfort during the final stages of life [35].

4. Conclusion

This case demonstrates that even mild hypercalcemia accompanied by new confusion and progressive focal bone pain may provide an important clue to an underlying destructive osseous process in an elderly patient with ESRD. Although the total calcium elevation was modest at 10.8 mg/dL, the elevated ionized calcium, inappropriately normal PTH, elevated PTHrP, and large destructive femoral lesion raised substantial concern for malignancy. The normal PSA and negative serum protein electrophoresis and immunofixation further emphasized the diagnostic uncertainty regarding the primary origin of the lesion. Because histopathologic confirmation was not pursued following transition to comfort-focused care, the underlying malignancy could not be definitively established.

5. Limitations

The principal limitation of this case is the absence of histopathologic confirmation of the destructive femoral lesion. Because the patient experienced progressive clinical decline and his family elected comfort-focused care, further invasive diagnostic evaluation was not pursued. Consequently, the primary origin of the suspected malignancy and the precise contribution of malignancy to the patient's hypercalcemia could not be definitively established.

6. Contributors

The authors wrote and edited the manuscript. The authors approved the final version of the manuscript and are responsible for all aspects of this study.

7. Patient Consent

Written informed consent was obtained from the patient or the patient's legally authorized representative for publication of this case report and accompanying images.

8. Competing Interests

The authors declare no competing interests.

9. Funding

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10. References

1. Anastasopoulou C, Mewawalla P. Malignancy-related hypercalcemia. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026.

2. Mirrakhimov AE. Hypercalcemia of malignancy: an update on pathogenesis and management. North Am J Med Sci. 2015;7(11):483-493. PubMed | CrossRef

3. Rouf R, Bhuiyan AKMMR, Alam A, et al. Prevalence and associated factors of hypercalcemia of malignancy among advanced cancer patients attending a palliative care unit of a tertiary care hospital in Bangladesh. Cancer Rep (Hoboken). 2025;8(3):e70157. CrossRef

4. Feldenzer KL, Sarno J. Hypercalcemia of malignancy. J Adv Pract Oncol. 2018;9(5):496-504.

5. Hu MI. Hypercalcemia of malignancy. Endocrinol Metab Clin North Am. 2021;50(4):721-728. PubMed | CrossRef

6. Globus O, Sagie S, Lavine N, et al. Early death after a diagnosis of metastatic solid cancer: raising awareness and identifying risk factors from the SEER database. PLoS One. 2023;18(9):e0281561. CrossRef

7. Singh VA, Haseeb A, Alkubaisi AA. Incidence and outcome of bone metastatic disease at University Malaya Medical Centre. Singapore Med J. 2014;55(10):539-546. PMC | CrossRef

8. Jayarangaiah A, Kemp AK, Theetha Kariyanna P. Bone metastasis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026.

9. Schmid-Alliana A, Schmid-Antomarchi H, Al-Sahlanee R, et al. Understanding the progression of bone metastases to identify novel therapeutic targets. Int J Mol Sci. 2018;19(1):148. PubMed | CrossRef

10. Nolin TD. Altered nonrenal drug clearance in ESRD. Curr Opin Nephrol Hypertens. 2008;17(6):555-559. PubMed | CrossRef

11. Rout P, Aslam A. End-stage renal disease. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026.

12. Saliba W, El-Haddad B. Secondary hyperparathyroidism: pathophysiology and treatment. J Am Board Fam Med. 2009;22(5):574-581. PubMed | CrossRef

13. McDonald D, Drake MT, Crowley RK. Treatment of hypercalcaemia of malignancy in adults. Clin Med (Lond). 2023;23(5):503-507. PubMed | CrossRef

14. Sternlicht H, Glezerman IG. Hypercalcemia of malignancy and new treatment options. Ther Clin Risk Manag. 2015;11:1779-1788. . PubMed | CrossRef

15. Macedo F, Ladeira K, Pinho F, et al. Bone metastases: an overview. Oncol Rev. 2017;11(1):321. PubMed | CrossRef

16. Poirier JL, Wurtz LD, Collier CD. Increased number of medical comorbidities associated with increased risk of presenting with pathological femur fracture in metastatic bone disease. Iowa Orthop J. 2023;43(1):87-93. PubMed

17. Dao A, McDonald MM, Savage PB, et al. Preventing osteolytic lesions and osteomyelitis in multiple myeloma. J Bone Oncol. 2022;37:100460. PubMed | CrossRef

18. Sadiq NM, Anastasopoulou C, Patel G, et al. Hypercalcemia. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026.

19. Aresta C, Passeri E, Corbetta S. Symptomatic hypercalcemia in patients with primary hyperparathyroidism is associated with severity of disease, polypharmacy, and comorbidity. Int J Endocrinol. 2019;2019:7617254. PubMed | CrossRef

20. Nessa L, Enabi J, Gonuguntla S, et al. Uncovering hypercalcemia of malignancy following parathyroidectomy for hyperparathyroidism. JCEM Case Rep. 2024;2(12):luae203. PubMed | CrossRef

21. Ganesh M, Baim S. Hypercalcemia of malignancy in a case of peripheral nerve sheath tumor: elucidating the roles of simultaneous mechanisms. AACE Clin Case Rep. 2020;6(3):e135-e140. PubMed | CrossRef

22. Russo S, Scotto di Carlo F, Gianfrancesco F. The osteoclast traces the route to bone tumors and metastases. Front Cell Dev Biol. 2022;10:886305. PubMed | CrossRef

23. Seccareccia D. Cancer-related hypercalcemia. Can Fam Physician. 2010;56(3):244-e92. PMC

24. Ashfaq S, Shafiq W, Siddiqi AI, et al. Survival outcomes in malignancy-related hypercalcemia: a tertiary care single-center experience. J Cancer Allied Spec. 2024;10(2):675. PMC | CrossRef

25. Drüeke TB. Hyperparathyroidism in chronic kidney disease. In: Feingold KR, Adler RA, Ahmed SF, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com; 2025.

26. Pellicciotti F, Giusti A, Gelli MC, et al. Challenges in the differential diagnosis of hypercalcemia: a case of hypercalcemia with normal PTH level. World J Clin Oncol. 2012;3(1):7-11. CrossRef

27. Chengalpet Jaishankar B, Kibria SM, Sudarshanan A, et al. A case of hypercalcaemia with suppressed parathyroid hormone in a middle-aged female: diagnostic challenge and association with hyperthyroidism. Cureus. 2024;16(10):e72020. PubMed | CrossRef

28. Nguyễn MV, Carlier C, Nich C, et al. Fracture risk of long bone metastases: a review of current and new decision-making tools for prophylactic surgery. Cancers (Basel). 2021;13(15):3662. CrossRef

29. Zajączkowska R, Kocot-Kępska M, Leppert W, et al. Bone pain in cancer patients: mechanisms and current treatment. Int J Mol Sci. 2019;20(23):6047. PubMed | CrossRef

30. Gupta S, Rastogi A, Singh P, et al. Treatment outcomes and survival in hypercalcemia of malignancy: a grave metabolic emergency. Cureus. 2023;15(3):e35783. PubMed | CrossRef

31. Flanagan AM, Chambers TJ. Inhibition of bone resorption by bisphosphonates: interactions between bisphosphonates, osteoclasts, and bone. Calcif Tissue Int. 1991;49(6):407-415. PubMed | CrossRef

32. Norman SJ, Reeves DJ, Saum LM. Use of pamidronate for hypercalcemia of malignancy in renal dysfunction. J Pharm Pract. 2021;34(4):553-557. PubMed | CrossRef

33. Thosani S, Hu MI. Denosumab: A new agent in the management of hypercalcemia of malignancy. Future Oncol. 2015;11(21):2865-2871. PubMed | CrossRef

34. Loh HH, Mohd Noor N. The use of hemodialysis in refractory hypercalcemia secondary to parathyroid carcinoma. Case Rep Crit Care. 2014;2014:140906. PMC | CrossRef

35. Masters JL, Josh PW, Kirkpatrick AJ, et al. Providing clarity: communicating the benefits of palliative care beyond end-of-life support. Palliat Care Soc Pract. 2024;18:26323524241263109. PMC | CrossRef