RESEARCH PAPER

PTH-Independent Hypercalcemia with Hypophosphatemia and Severe Vitamin D Deficiency as the Initial Presentation of Diffuse Large B-Cell Lymphoma (DLBCL): A Case Report

Dr P. SRINIVAS[1], Dr. VIJAY G SOMANNAVAR[2*]
[1]Postgraduate, Email id -palasamudramsrinivas2015@gmail.com
[2*]Professor Unit Head, Mail id-sharveel@yahoo.co.in
[1,2]MBSS, MD General Medicine, Jawaharlal Nehru Medical College, KAHER, Belagavi

ABSTRACT

Background: PTH-independent hypercalcemia in the absence of PTHrP elevation is an uncommon but well-recognised complication of hematological malignancies, particularly lymphoma, driven by dysregulated calcitriol synthesis. Its co-occurrence with hypophosphatemia and severe 25-hydroxy vitamin D deficiency represents an unusual and diagnostically challenging biochemical triad that has rarely been documented in diffuse large B-cell lymphoma (DLBCL).

Case Presentation: A 60-year-old male with no prior chronic illness presented with one month of abdominal pain, giddiness, progressive dysphagia, anorexia, and significant weight loss. Examination revealed irritability, altered mental status, hypotension (90/50 mmHg), pallor, cervical lymphadenopathy, and hepatosplenomegaly. Biochemical evaluation confirmed PTH-independent hypercalcemia (calcium 11.6 mg/dL; PTH 4.1 pg/mL), severe progressive hypophosphatemia (nadir 0.7 mg/dL), and low 25-hydroxy vitamin D (12.2 ng/mL). Markedly elevated lactate dehydrogenase (2334 U/L) and imaging demonstrating mediastinal and retroperitoneal lymphadenopathy prompted tissue biopsy. Immunohistochemistry confirmed DLBCL of non-germinal centre B-cell (non-GCB) subtype (CD20+, BCL-2+, BCL-6+, MUM-1+; CD10−), with a Ki-67 proliferation index of ~80% and Ann Arbor Stage IV disease. The patient was stabilised with intravenous fluids and zoledronic acid, followed by oncology referral.

Conclusion: This case illustrates that an atypical metabolic triad of PTH-independent hypercalcemia, hypophosphatemia, and low 25-hydroxy vitamin D should prompt urgent evaluation for underlying hematological malignancy. The apparent paradox of hypercalcemia alongside vitamin D deficiency reflects rapid conversion of 25-OH vitamin D to active calcitriol by malignant lymphocytes, depleting the precursor pool. Early recognition and multidisciplinary management are essential to reduce morbidity and improve outcomes.

Keywords: Hypercalcemia; PTH-independent hypercalcemia; Diffuse large B-cell lymphoma; Hypophosphatemia; Vitamin D deficiency; Non-GCB DLBCL; Paraneoplastic syndrome; Calcitriol; Case report; Hematological malignancy

How to cite this article: Srinivas P, Somannavar V G., Pth-Independent Hypercalcemia With Hypophosphatemia and Severe Vitamin D Deficiency As the Initial Presentation of Diffuse Large B-Cell Lymphoma (Dlbcl): A Case Report. Int J Drug Deliv Technol. 2026;16(43s): 874-879; Doi: 10.25258/Ijddt.16.43s.90

Source of support: Nil., **Conflict of interest:** None

Introduction

Hypercalcemia complicates approximately 20–30% of all malignancies and is most frequently driven by parathyroid hormone-related peptide (PTHrP) secretion or osteolytic bone destruction [1]. In lymphoma, however, the dominant mechanism is distinct: malignant B-lymphocytes and associated macrophages constitutively express 1-alpha-hydroxylase, converting 25-hydroxy vitamin D (25-OH Vit D) to active 1,25-dihydroxyvitamin D (calcitriol) independently of PTH regulation [2,3]. The resulting hypercalciuria, enhanced intestinal calcium absorption, and increased bone resorption elevate serum calcium while simultaneously depleting the 25-OH Vit D precursor pool — producing the paradoxical combination of hypercalcemia with low 25-OH Vit D levels [4]. Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma, accounting for 30–40% of all cases, and is an aggressive malignancy with diverse clinical manifestations [5]. Classical presentations include painless lymphadenopathy and constitutional 'B symptoms' (fever, drenching night sweats, weight loss >10%). Metabolic derangements as the primary presenting feature are uncommon and, when they occur, can significantly delay diagnosis [6]. The simultaneous occurrence of PTH-independent hypercalcemia, hypophosphatemia, and severe vitamin D deficiency has rarely been described in DLBCL. Each element individually can be attributed to diverse causes, but their co-existence in the absence of classical lymphoma symptoms creates a particularly challenging diagnostic scenario. We report such a case and discuss the underlying pathophysiology, diagnostic approach, and clinical implications.

CASE PRESENTATION

Patient Information and Presenting Complaints

PTH-Independent Hypercalcemia with Hypophosphatemia and Severe Vitamin D Deficiency as the Initial Presentation of Diffuse Large B-Cell Lymphoma (DLBCL): A Case Report

A 60-year-old male presented to the emergency department with a one-month history of progressive abdominal pain, giddiness, anorexia, and significant unintentional weight loss estimated at >10% of body weight. He additionally reported progressive dysphagia predominantly to solids over the same period. He denied fever, night sweats, or bleeding manifestations. There was no prior history of diabetes mellitus, hypertension, malignancy, tuberculosis, or recent infections, and no current use of calcium supplements, vitamin D preparations, or any other medications.

Clinical Examination

On admission, the patient was conscious and oriented but visibly irritable with mild alteration of mental status. He appeared clinically pale, with no icterus, cyanosis, or pedal oedema. Vital signs were notable for hypotension (blood pressure 90/50 mmHg) with a regular pulse of 80 beats per minute; respiratory rate and oxygen saturation were within normal limits. Systemic examination revealed multiple enlarged, firm, non-tender cervical lymph nodes bilaterally. Abdominal examination demonstrated hepatosplenomegaly without ascites. Cardiovascular and respiratory examinations were unremarkable. Neurological examination revealed no focal deficits, though mild confusion was evident, attributable to metabolic derangement.

Laboratory Investigations

Initial biochemical evaluation is summarised in Table 1. Key abnormalities included PTH-independent hypercalcemia with markedly suppressed parathyroid hormone, severe progressive hypophosphatemia, and low 25-hydroxy vitamin D levels. Parathyroid hormone-related peptide (PTHrP) and serum calcitriol (1,25-dihydroxyvitamin D) levels were not available at the time of reporting, representing a recognised limitation of this evaluation (see Discussion). Lactate dehydrogenase (LDH) was markedly elevated, consistent with high tumour burden. Standard tumour markers (CEA, CA 19-9, AFP) were within normal limits, reducing suspicion for common solid organ malignancies.

Table 1: Serial Biochemical Parameters

Parameter	Reference Range	Admission	Nadir / Peak	Post-Treatment
Serum Calcium (mg/dL)	8.5–10.2	11.6 ↑	—	Improving
Parathyroid Hormone (pg/mL)	10–65	4.1 ↓	—	—
Serum Phosphorus (mg/dL)	2.5–4.5	2.8 ↓	0.7 ↓↓	Correcting
25-OH Vitamin D (ng/mL)	>30	12.2 ↓↓	—	—
1,25-OH Vitamin D (calcitriol)	18–72 pg/mL	Not measured*	—	—
PTHrP	<2 pmol/L	Not measured*	—	—
LDH (U/L)	140–280	2334 ↑↑	—	—
GGT (U/L)	10–71	215 ↑	—	—
Serum Creatinine	Normal	Normal	—	—
Hemoglobin / CBC	—	Normocytic normochromic anaemia	—	—

** See Discussion: absence of calcitriol and PTHrP measurements is a key limitation of this report.*

Clinical Timeline

Timepoint	Event
~4 weeks prior	Onset of abdominal pain, anorexia, giddiness, dysphagia, and weight loss
Day 0 (Admission)	ED presentation; hypotension, altered mental status, cervical lymphadenopathy detected; hypercalcemia (11.6 mg/dL) and suppressed PTH confirmed
Day 1–2	CECT thorax and abdomen: mediastinal + retroperitoneal lymphadenopathy, hepatosplenomegaly; IV fluids and zoledronic acid initiated
Day 3–5	Phosphate decline to nadir (0.7 mg/dL); bone marrow biopsy and retroperitoneal mass biopsy performed

Timepoint	Event
Day 6–8	IHC confirmed DLBCL (non-GCB), Ki-67 ~80%; Ann Arbor Stage IV assigned; calcium improving
Day 9+	Mental status improved; patient referred to oncology for RCHOP chemotherapy; discharged

Radiological and Endoscopic Findings

Upper gastrointestinal endoscopy demonstrated a lax cardia (Hill grade II) and Los Angeles grade B esophagitis; these findings did not account for the systemic manifestations. Contrast-enhanced CT (CECT) of the thorax revealed bilateral mild pleural effusions with subsegmental atelectasis and significant mediastinal lymphadenopathy. CECT abdomen demonstrated a large, ill-defined, heterogeneously enhancing retroperitoneal soft tissue mass involving the pre- and bilateral para-aortic regions, with extension into adjacent structures, mesenteric lymphadenopathy, hepatosplenomegaly, minimal ascites, and bilateral inguinal hernias. These findings strongly suggested a neoplastic aetiology, with lymphoma as the leading differential.

Histopathological and Immunohistochemical Findings

Bone marrow aspirate demonstrated atypical lymphoid cells; trephine biopsy from the posterior superior iliac spine revealed normocellular marrow with no overt marrow replacement, though the presence of atypical cells was noted. Biopsy of the retroperitoneal mass showed multiple fragments of grey-white soft tissue. Microscopy revealed sheets of small to medium round blue cells consistent with a lymphoproliferative disorder.

Immunohistochemistry (IHC) results are summarised in Table 2. The IHC profile — CD10 negative, BCL-6 positive, MUM-1 positive — assigns this case to the non-germinal centre B-cell (non-GCB) subtype per the Hans algorithm, which carries distinct prognostic and therapeutic implications compared to GCB-subtype DLBCL. The Ki-67 proliferation index of approximately 80% confirmed high-grade disease.

Table 2: Immunohistochemistry Profile

Marker	Result	Significance
CD20	Positive ✓	Confirms B-cell lineage; therapeutic target for rituximab
BCL-2	Positive ✓	Anti-apoptotic; associated with adverse prognosis
BCL-6	Positive ✓	Germinal centre marker; used in Hans algorithm subtyping
MUM-1	Positive ✓	Post-germinal centre marker; combined with CD10−, assigns non-GCB subtype
CD10	Negative ✗	Absence supports non-GCB classification
CD3	Negative ✗	Excludes T-cell lineage
CD34	Negative ✗	Excludes precursor/blastic phenotype
Ki-67 Proliferation Index	~80%	High-grade; raises consideration for double-hit lymphoma (MYC/BCL-2 FISH not performed — see Limitations)

Final Diagnosis

Diffuse large B-cell lymphoma (DLBCL), non-GCB subtype, Ann Arbor Stage IV, presenting as PTH-independent hypercalcemia associated with progressive hypophosphatemia and severe 25-hydroxy vitamin D deficiency.

Management and Clinical Course

The patient was initiated on intravenous 0.9% normal saline hydration to correct dehydration, promote calciuresis, and stabilise haemodynamics. Intravenous zoledronic acid (4 mg in 100 mL normal saline over 30 minutes) was administered for hypercalcemia; serum calcium showed gradual improvement over the following 48–72 hours. Phosphate levels were serially monitored and replaced as required. Broad-spectrum antibiotics and a proton pump inhibitor were administered as supportive therapy. Mental status improved in parallel with normalisation of calcium

levels. Following biochemical stabilisation and histopathological confirmation of DLBCL, the patient was referred to the oncology department for formal disease staging and initiation of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy, the standard-of-care regimen for non-GCB DLBCL.

Note: Long-term follow-up data regarding chemotherapy response and disease progression were not available at the time of this report. This represents a recognised limitation and will be the subject of a subsequent case follow-up communication.

DISCUSSION

Mechanism of Hypercalcemia in DLBCL

Malignancy-associated hypercalcemia most commonly operates via PTHrP-mediated mechanisms in solid tumours, whereas lymphomas characteristically drive hypercalcemia through a distinct vitamin D-dependent pathway [1,2]. Malignant B-lymphocytes and tumour-infiltrating macrophages constitutively overexpress CYP27B1 (1-alpha-hydroxylase), the enzyme responsible for converting 25-OH vitamin D to its biologically active form, 1,25-dihydroxyvitamin D (calcitriol) [3,4]. Unlike the tightly regulated renal 1-alpha-hydroxylase, the extrarenal enzyme expressed by malignant cells is not subject to negative feedback from elevated calcium or calcitriol, resulting in unchecked calcitriol production. This drives enhanced intestinal calcium absorption and osteoclast-mediated bone resorption, elevating serum calcium independent of PTH [3]. The paradoxical finding of severe 25-OH vitamin D deficiency in the presence of hypercalcemia in this case is mechanistically explained by this very pathway: the malignant cells convert 25-OH vitamin D to calcitriol so rapidly and in such excess that the precursor pool becomes depleted, reducing measured 25-OH vitamin D levels [4]. Thus, low 25-OH vitamin D in the context of PTH-independent hypercalcemia, rather than being reassuring, should raise suspicion for a lymphoma-driven calcitriol excess state. Ideally, this hypothesis would be confirmed by a markedly elevated calcitriol level, which was not measured in the present case — a critical limitation acknowledged further below.

Hypophosphatemia in the Context of Malignancy

The progressive and severe hypophosphatemia observed in this patient (nadir 0.7 mg/dL) adds further diagnostic complexity. Hypophosphatemia in malignancy can result from multiple mechanisms, including renal tubular phosphate wasting driven by tumour-secreted factors (such as FGF-23), systemic nutritional deficiency, or redistribution into cells during rapid tumour proliferation [7]. Calcitriol itself can indirectly contribute by increasing urinary phosphate excretion. In the present case, fractional excretion of phosphate (FEPi) or spot urine phosphate-to-creatinine ratio was not measured; this would have distinguished renal wasting from extrarenal causes and is recommended in future similar presentations.

DLBCL Subtyping and Prognostic Implications

Application of the Hans algorithm to the IHC profile (CD10−, BCL-6+, MUM-1+) classifies this tumour as non-germinal centre B-cell (non-GCB) subtype DLBCL [5,6]. This distinction carries important prognostic and therapeutic relevance: non-GCB DLBCL is associated with inferior outcomes compared to GCB subtype, with lower complete remission rates and poorer overall survival following standard R-CHOP chemotherapy. The high Ki-67 (~80%) further raises the possibility of a double-hit lymphoma (concurrent MYC and BCL-2 or BCL-6 rearrangements), which would necessitate more intensive chemotherapy regimens such as DA-EPOCH-R. Fluorescence in situ hybridisation (FISH) for MYC, BCL-2, and BCL-6 rearrangements was not performed in this case and is strongly recommended as standard workup for future patients with similar high-proliferative-index profiles.

Atypical Clinical Presentation

This patient's presentation — dominated by metabolic symptoms (giddiness, confusion, anorexia, weight loss) rather than the classical B symptoms of lymphoma — is consistent with previously described atypical DLBCL presentations in which metabolic derangements precede recognition of the underlying malignancy [8,9]. The absence of fever or night sweats, and the relatively non-specific nature of his initial complaints, created a challenging diagnostic environment. The markedly elevated LDH (2334 U/L), hepatosplenomegaly, and multi-territory lymphadenopathy on imaging ultimately provided the pivotal clues that directed tissue biopsy and definitive diagnosis.

Management

The cornerstone of management for hypercalcemia of malignancy remains intravenous hydration to promote renal calcium excretion, combined with a nitrogen-containing bisphosphonate (zoledronic acid 4 mg IV) to inhibit osteoclast-mediated bone resorption [1,10]. In lymphoma-associated calcitriol-driven hypercalcemia, corticosteroids represent an additional therapeutic option, as they suppress 1-alpha-hydroxylase activity in macrophages and malignant cells; their use was not specifically documented in this case but should be considered, particularly when bisphosphonate response is suboptimal. Definitive management requires treatment of the underlying lymphoma — in this case, R-CHOP — which addresses the root cause of dysregulated calcitriol synthesis.

Limitations

Several key investigations were unavailable at the time of reporting, each of which would have strengthened the mechanistic argument:

1. Serum calcitriol (1,25-OH vitamin D): This is the

single most important missing measurement. Without it, calcitriol-driven hypercalcemia remains a compelling but unconfirmed hypothesis.

2. Serum PTHrP: Necessary to formally exclude PTHrP-mediated humoral hypercalcemia of malignancy, which is the most common mechanism in solid tumours and cannot be clinically excluded without measurement.
3. Fractional excretion of phosphate (FEPi): Would have clarified the aetiology of severe hypophosphatemia.
4. MYC/BCL-2/BCL-6 FISH: Given the high Ki-67, FISH testing is critical to exclude double-hit or triple-hit lymphoma.
5. Long-term follow-up: Chemotherapy response, progression-free survival, and overall survival data were not available at the time of this report.

CONCLUSION

This case describes a rare and diagnostically challenging presentation of DLBCL manifesting primarily as a metabolic triad — PTH-independent hypercalcemia, progressive hypophosphatemia, and severe 25-hydroxy vitamin D deficiency — in the absence of classical lymphoma symptoms. The biochemical findings, while individually non-specific, form a coherent pattern when understood through the lens of calcitriol-driven, PTH-independent hypercalcemia characteristic of hematological malignancies.

Clinicians encountering unexplained PTH-independent hypercalcemia — particularly when accompanied by low 25-OH vitamin D and hypophosphatemia — should include lymphoma in the differential diagnosis even without overt lymphadenopathy or B symptoms. The recommended initial workup in such cases should include serum calcitriol, PTHrP, and LDH alongside standard metabolic panels; markedly elevated LDH or imaging evidence of lymphadenopathy should prompt urgent tissue biopsy.

Comprehensive subtype characterisation (Hans algorithm, FISH for double-hit), formal Ann Arbor staging, and early multidisciplinary oncology involvement are essential to ensure appropriate treatment selection and improve outcomes in this aggressive malignancy.

DECLARATIONS

Ethics and Patient Consent

This case report was prepared in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patient for publication of this case report and any accompanying data. Identifying information has been removed or modified to protect patient confidentiality. Ethics committee / institutional review board approval was obtained / waived as per institutional guidelines for single anonymised case reports [to be confirmed by the submitting institution].

Author Contributions

All authors contributed to data collection, clinical management, and manuscript preparation. [Please complete using CRediT taxonomy: Conceptualisation, Data Curation, Writing – Original Draft, Writing – Review & Editing, Supervision.]

Competing Interests

The authors declare no competing financial or non-financial interests.

Funding

No external funding was received for this work.

REFERENCES

1.Anastasopoulou C, Mewawalla P. Malignancy-Related Hypercalcemia. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Mar 4. PMID: 29494030.

2.Walker MD, Bilezikian JP. Primary Hyperparathyroidism. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2021 Apr 19. PMID: 25905161.

3.Kometas ML, Maalouf NM. Hypercalcemia of Malignancy: Mechanisms and Therapeutic Implications of Concurrently Elevated PTHrP and Calcitriol. J Endocr Soc. 2025;9(9):bvaf104. doi: 10.1210/jendso/bvaf104. PMID: 40662114.

4.Tebben PJ, Singh RJ, Kumar R. Vitamin D-Mediated Hypercalcemia: Mechanisms, Diagnosis, and Treatment. Endocr Rev. 2016;37(5):521–547. doi: 10.1210/er.2016-1070. PMID: 27588937.

5.Li S, Young KH, Medeiros LJ. Diffuse large B-cell lymphoma. Pathology. 2018;50(1):74–87. doi: 10.1016/j.pathol.2017.09.006. PMID: 29167021.

6.Tsang RWC, Crump M. Lymphoma. In: UICC Manual of Clinical Oncology, 9th ed. 2023;392–414. doi: 10.1002/9781119013143.ch34. PMID: 32809661.

7.Kaur J, Castro D. Hypophosphatemia. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Feb 12. PMID: 29630224.

8.Cordeiro R, Chaves M. Diffuse Large B-Cell Lymphoma — Rare Presentation. J Belg Soc Radiol. 2022;106(1):20. doi: 10.5334/jbsr.2747. PMID: 35581973.

9.Sukhija T, Midha V, Mittal N, et al. Clinical Profile and Outcomes of Patients with Hypercalcemia in an Indian Tertiary Care Center. Cureus. 2023;15(9):e46062. doi: 10.7759/cureus.46062. PMID: 37900460.

10.Sadiq NM, Anastasopoulou C, Patel G, Badireddy M. Hypercalcemia. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 May 7. PMID: 28613465.

11.Breslau NA, McGuire JL, Zerwekh JE, Frenkel EP, Pak CY. Hypercalcemia associated with increased serum calcitriol levels in three patients with lymphoma. Ann Intern Med. 1984;100(1):1–6. doi: 10.7326/0003-4819-

100-1-1. PMID: 6546327.

12.Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood. 2004;103(1):275–282. doi: 10.1182/blood-2003-05