CLINICAL PROBLEM-SOLVING

An Element Out of Place

David E. Velasquez, M.D.,[1] Andrew Allbee, M.D., Ph.D.,[2] J. Carl Pallais, M.D.,[1] Katherine H. Walker, M.D.,[1] and Bruce D. Levy, M.D.[1]

In this Journal *feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information by sharing relevant background and reasoning with the reader (regular type). The authors' commentary follows.*

A 55-year-old woman with hypertension, type 2 diabetes, fibromyalgia, and psoriatic arthritis presented to the emergency department with a 10-day history of nausea, lightheadedness, and abdominal pain, starting 1 day after she had returned from a 3-week trip to Puerto Rico. Two days before her presentation, slurred speech, unsteady gait, and confusion had developed. During the preceding week, she had also had generalized weakness, constipation, polyuria, polydipsia, and palpitations. She reported chronic pain in both knees. She reported no fevers, chills, cough, chest pain, shortness of breath, dysuria, diarrhea, or rash.

Author affiliations are listed at the end of the article. Katherine H. Walker can be contacted at khwalker@bwh.harvard.edu or at the Department of Medicine, Brigham and Women's Hospital, 75 Francis St., Boston MA 02115.

N Engl J Med 2026;395:1849-56.
DOI: 10.1056/NEJMcps2606356
Copyright © 2026 Massachusetts Medical Society.

The gastrointestinal and neurologic symptoms suggest metabolic derangements such as hyponatremia, hypernatremia, uremia, hypercalcemia, or dysglycemia. Hyperglycemia, hypercalcemia, or uremia could explain her polyuria and polydipsia. Diabetes increases susceptibility to infection, and recent travel broadens her infectious exposures (e.g., Zika virus, strongyloides, and leptospira). Nausea, constipation, and abdominal pain raise the possibility of intestinal obstruction or ileus.

Her previous surgeries included below-the-knee amputation of the right leg for infected nonhealing diabetic ulcers 8 months earlier, as well as cholecystectomy and total laparoscopic hysterectomy with bilateral salpingo-oophorectomy more than 10 years earlier. Her family history included diabetes in maternal and paternal relatives and breast cancer in two paternal aunts. Her medications included ixekizumab (an interleukin-17A inhibitor) for psoriatic arthritis, duloxetine, gabapentin, empagliflozin, and insulin degludec. She said that she did not use supplements, tobacco, alcohol, or other drugs. She reported up-to-date vaccinations and no allergies. She and her husband had lived in suburban Massachusetts for 35 years, previously residing in Puerto Rico. She had worked at a transitional housing facility for women until her amputation. She reported no hiking or freshwater swimming.

Further history reveals several factors that increase suspicion for possible infection causing her symptoms; her vascular complications suggest that she may have longstanding poor diabetic control. Ixekizumab increases her risk of fungal infection, and her use of a sodium–glucose cotransporter 2 (SGLT2) inhibitor (empagliflozin) increases the risk of genitourinary infection. The family history increases the possibility of cancer, and her personal history of psoriatic arthritis increases the likelihood of other autoimmune diseases. Gabapentin may cause neurologic symptoms, particularly if acute kidney injury is present.

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society.
Downloaded from nejm.org by heydar dolati on November 6, 2026.

The patient was afebrile. Her blood pressure was 178/81 mm Hg, heart rate 90 beats per minute, and oxygen saturation 99% while she was breathing ambient air. She appeared to be well-nourished. Mucous membranes were dry. No scleral icterus was observed. Cervical lymphadenopathy was absent, and the thyroid examination was normal. Cardiopulmonary and abdominal examinations were normal. The right lower-leg stump was well-healed and nontender; peripheral edema was absent. She had chin and neck hirsutism, mild scalp alopecia, and no rashes, jaundice, or subcutaneous masses. She was somnolent but opened her eyes when spoken to. Despite inattention, she was oriented to self, place, and time. She had no focal neurologic deficits, asterixis, or tremor. Her most recent mammogram (1 year earlier) and colonoscopy (11 years earlier) had been normal.

Physical examination findings are consistent with dehydration and encephalopathy. Diabetic ketoacidosis could explain the patient's abdominal pain, polyuria, dehydration, and encephalopathy; SGLT2 inhibitor use confers a predisposition to euglycemic ketoacidosis during illness or reduced oral intake. The unremarkable cardiopulmonary and abdominal examinations make acute infection or intestinal obstruction unlikely. Age-appropriate cancer screening should resume after stabilization of her acute condition.

The sodium level was 135 mmol per liter, chloride level 95 mmol per liter, and creatinine level 3.94 mg per deciliter (350 μmol per liter; estimated glomerular filtration rate [eGFR], 13 ml per minute per 1.73 m^2 of body-surface area), blood urea nitrogen level 75 mg per deciliter (27.0 mmol per liter), and glucose level 173 mg per deciliter (9.6 mmol per liter). Potassium, bicarbonate, and magnesium levels were normal. The calcium level was 18.9 mg per deciliter (4.72 mmol per liter; normal range, 8.8 to 10.7 mg per deciliter [2.20 to 2.68 mmol per liter]), and the phosphorus level was 5.1 mg per deciliter (1.65 mmol per liter; normal range, 2.4 to 4.3 mg per deciliter [0.80 to 1.40 mmol per liter]). These laboratory values, including a previous creatinine level (0.92 mg per deciliter [80 μmol per liter]), had been normal 6 weeks earlier. The lactate dehydrogenase level was normal. Liver-enzyme and liver-function tests were normal except for an alkaline phosphatase level of 152 U per liter (normal range, 35 to 130). The glycated hemoglobin level was 7.0%. The hematocrit was 31% (which was similar to the previous value); the white-cell count, differential, and platelet count were normal. The mean corpuscular volume and hemoglobin and mean corpuscular hemoglobin concentrations were uninterpretable owing to red-cell agglutination. The lactate level was normal. Chest radiography did not show pulmonary or bony abnormalities. Renal ultrasonography was unremarkable. The patient received 2 liters of lactated Ringer's solution.

Severe hypercalcemia with acute kidney injury explains the neurologic, abdominal, and constitutional symptoms. Urgent calcium-lowering therapy should be initiated alongside diagnostic evaluation. The severity of hypercalcemia, in the context of recently normal calcium levels, makes primary hyperparathyroidism unlikely, given that primary hyperparathyroidism typically increases calcium levels over a period of months to years and rarely to the level seen here. Although excessive ingestion of absorbable alkali, such as calcium carbonate, can rapidly elevate calcium and creatinine levels (milk-alkali syndrome), the absence of supplement use or metabolic alkalosis argues against this diagnosis. Although an elevated serum phosphorus level might otherwise support a diagnosis of calcitriol-mediated or osteolytic hypercalcemia over parathyroid hormone (PTH) or PTH-related peptide (PTHrP)–mediated hypercalcemia, the diagnostic usefulness of hyperphosphatemia is diminished in the context of renal dysfunction.

Cancer is the most likely cause of her severe hypercalcemia. The triad of hypercalcemia, renal dysfunction, and anemia suggests multiple myeloma. However, alkaline phosphatase levels are usually normal in myeloma-associated bone disease, given that osteoblastic activity is suppressed despite osteolytic lesions. In contrast, the increased alkaline phosphatase level arouses concern for bone metastases or PTHrP-mediated hypercalcemia. Fractionated alkaline phosphatase testing could rule out hepatic or intestinal sources.

Anemia and red-cell agglutination imply cold agglutinin disease, which is typically caused by infections (e.g., by *Mycoplasma pneumoniae* or Epstein–Barr virus), autoimmune disorders, or cancers associated with paraproteinemia. Although

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society.
Downloaded from nejm.org by heydar dolati on November 6, 2026.

the findings strongly suggest cancer-associated hypercalcemia, PTH, PTHrP, and vitamin D levels can clarify the cause of the hypercalcemia.

The ionized calcium level was 9.1 mg per deciliter (2.28 mmol per liter; normal range, 4.5 to 5.3 mg per deciliter [1.12 to 1.32 mmol per liter]). The PTH level was 9 pg per milliliter (normal range, 15 to 65).

The suppressed PTH confirms that the hypercalcemia is PTH-independent, which narrows the differential diagnosis to cancer-associated hypercalcemia or vitamin D–mediated causes (either exogenous or unregulated activation in granulomatous disorders or cancer, most commonly lymphoma). Other rare causes of PTH-independent hypercalcemia (e.g., hyperthyroidism and adrenal insufficiency) are unlikely given the severity of the hypercalcemia.

The 1,25 dihydroxyvitamin D and 25-hydroxyvitamin D levels were below detection in each assay: 8 pg per milliliter (normal range, 18 to 78) and 9 ng per milliliter (20 nmol per liter; normal range, 20 to 50 ng per milliliter [50 to 125 nmol per liter]), respectively. Thyrotropin and morning cortisol levels were normal. A random urinary calcium level was 29.6 mg per deciliter (7.40 mmol per liter), with a urinary creatinine level of 114.2 mg per deciliter (10,095 μmol per liter), for a ratio of 0.26 (normal value, <0.22); the microalbumin level was 157 mg per deciliter (normal value, <2). Urinalysis revealed a normal pH, specific gravity of 1.014 (normal range, 1.003 to 1.035), 3+ glucose, 2+ protein, 1+ blood, and 1+ leukocyte esterase. Urinary sediment revealed 3+ bacteria, with 26 white cells per high-power field (normal range, 0 to 9), 7 red cells per high-power field (normal range, 0 to 2), 75 hyaline casts per low-power field (normal value, 0, 1, or 2), and 6 granular casts per low-power field (normal value, 0). A urine culture grew more than 100,000 colony-forming units of mixed flora per milliliter.

The patient received continuous normal saline with intravenous furosemide in order to reach a urine-output level of 150 ml of urine per hour with euvolemia, one dose (120 mg) of denosumab administered subcutaneously, and calcitonin (4 U per kilogram of body weight) administered subcutaneously every 12 hours for four doses. Acute kidney injury precluded bisphosphonate use.

Cancer is the most common cause of hypercalcemia in hospitalized patients; the hypercalcemia is usually due to PTHrP secretion from tumors, osteolytic bone destruction, or less commonly, dysregulated vitamin D activation in lymphomas or leukemias. Urine studies in this patient show glycosuria, which is expected with empagliflozin therapy, and proteinuria that is likely to be consistent with diabetic nephropathy; the presence of casts indicates superimposed tubular injury. Although hypercalcemia can cause volume depletion, granular casts suggest acute tubular necrosis rather than prerenal azotemia. Impaired renal calcium excretion from reduced glomerular filtration and tubular injury exacerbates the hypercalcemia. PTHrP measurement, serum and urine electrophoresis, and imaging are warranted to evaluate for cancer.

Treatment with calcitonin and denosumab, in addition to intravenous saline, is appropriate given the severity of the hypercalcemia. Isotonic saline and furosemide promote urinary calcium excretion and maintain euvolemia during renal dysfunction. Calcitonin acts rapidly (within 4 to 6 hours), but tachyphylaxis limits its efficacy to approximately 48 hours. Denosumab, a receptor activator of the nuclear factor κB ligand (RANKL) inhibitor, provides sustained suppression of osteoclast-mediated bone resorption, with onset of action typically occurring in 2 to 4 days.

The PTHrP level was 3.5 pmol per liter (normal value, ≤4.2). Protein electrophoresis revealed no monoclonal spike in urine; a faint serum spike was not quantifiable. The kappa free light-chain level was 116.2 mg per liter (normal range, 3.3 to 19.4), with a lambda free light-chain level of 61.0 mg per liter (normal range, 5.7 to 26.3), and a kappa-to-lambda ratio of 1.90 (normal range, 0.26 to 1.65). The urinary β_2-microglobulin level was 12.7 μg per milliliter (1076 nmol per liter; normal range, 1.21 to 2.70 μg per milliliter [102 to 230 nmol per liter]). A cold agglutinin titer was 512 (normal value, <64).

Normal PTHrP levels rule out humoral hypercalcemia of malignancy, a subtype of cancer-associated hypercalcemia. Although multiple myeloma remains possible given the elevated β_2-microglobulin and serum free light-chain levels, both elevations may reflect impaired renal clearance. Despite

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society.
Downloaded from nejm.org by heydar dolati on November 6, 2026.

abnormal light-chain levels, the minimally elevated kappa-to-lambda ratio without a corresponding electrophoresis spike argues against classic secretory myeloma. However, nonsecretory myeloma remains possible.

Computed tomography (CT) of the chest revealed punctate lytic lesions of the ribs, sternum, scapula, and spine, without evidence of lung cancer, lymphadenopathy, or pathologic fractures (Fig. 1). CT of the abdomen and pelvis revealed multiple hypoattenuating lesions in the liver, an indeterminate right adrenal nodule, and lytic lesions throughout the axial and appendicular skeleton. CT imaging of the head showed lytic lesions involving the calvarium and skull base without intracranial disease (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Positron-emission tomography–CT confirmed the presence of ^{18}F-fluorodeoxyglucose (FDG)–avid lesions in bone, the liver, and the right adrenal gland (Fig. 2). No primary tumor was identified.

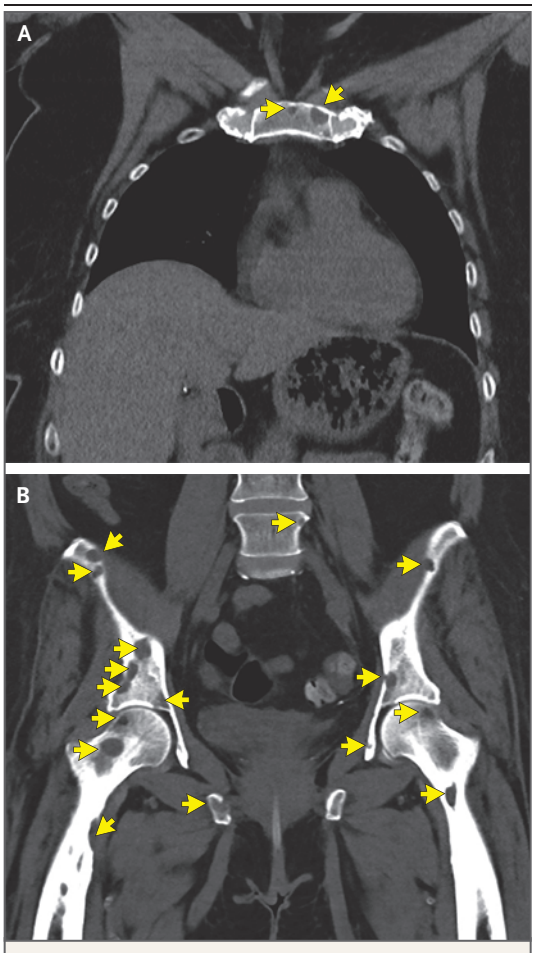


Figure 1. Computed Tomographic (CT) Imaging of the Torso and Pelvis.

CT imaging (coronal view) showed lytic lesions in the superior manubrium (Panel A, arrows), ribs (lesions not shown), and spine, femur, and pelvic bones (Panel B, arrows).

FDG-avid hepatic and adrenal lesions, elevated alkaline phosphatase activity, and an elevated cold agglutinin titer suggest lymphoma over myeloma, even in the absence of lymphadenopathy. Cold agglutinins are associated with lymphoid cancers but are not characteristic of myeloma. Primary bone lymphomas can cause diffuse lytic bone disease and severe hypercalcemia, closely mimicking myeloma. Core-tissue biopsy is essential to differentiate between these entities.

CT-guided core biopsy of the right iliac crest revealed diffuse large B-cell lymphoma (DLBCL), not otherwise specified (Fig. 3). Intravenous saline and furosemide were tapered as the calcium level decreased to normal, and symptoms resolved by hospital day 5. The patient started receiving oral ergocalciferol at a dose of 50,000 U weekly for vitamin D deficiency. Transient hypocalcemia developed, which led to the use of intravenous calcium gluconate, oral calcium citrate supplementation, and oral calcitriol. Renal function remained impaired, with a creatinine level of 1.9 mg per deciliter (170 μmol per liter) and an eGFR of 31 ml per minute per 1.73 m^2. Testing for cryoglobulins, anti–phospholipase A2 receptor antibodies, antinuclear antibodies, and antineutrophil cytoplasmic antibodies was negative, and complement levels were normal. A kidney-biopsy sample showed diffuse nodular diabetic glomerulosclerosis and dense infiltration of the interstitial space by malignant B cells (Fig. 4).

The patient received a total of 4 units of red cells for anemia. Bone marrow biopsy was unremarkable. Chemotherapy with rituximab, cyclophosphamide, doxorubicin, prednisone, and polatuzumab (pola-R-CHP) was initiated, and the patient had no complications from the treatment. She was discharged home after 3 weeks. After six cycles of chemotherapy with curative intent, her creatinine level normalized to 1.1 mg per deciliter (100 μmol per liter). At 6 months of follow-up, calcium levels remained normal.

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society.
Downloaded from nejm.org by heydar dolati on November 6, 2026.

COMMENTARY

This patient presented with constitutional, abdominal, and neurologic signs and symptoms of severe hypercalcemia. Low levels of vitamin D and PTH aroused suspicion for a malignant cause, with imaging revealing diffuse lytic bone lesions and biopsy confirming DLBCL in bone and kidney.

Hypercalcemia occurs in 2 to 30% of patients with cancer.[1,2] Severe hypercalcemia — as indicated by a total serum calcium level exceeding 14 mg per deciliter (3.50 mmol per liter) — represents a medical emergency. Severe hypercalcemia typically manifests with cognitive and renal dysfunction and may be associated with life-threatening cardiac arrhythmias.[1] Expert guidelines recommend prompt management, including isotonic fluid repletion to promote calciuresis and loop diuretics to prevent volume overload in patients with cardiac or renal dysfunction.[1] Calcitonin is recommended early for patients with severe hypercalcemia; it inhibits bone resorption and promotes renal calcium excretion, rapidly reducing serum calcium levels within 4 to 6 hours after administration, but tachyphylaxis limits efficacy to approximately 2 days.[2-4] Intravenous bisphosphonate therapy or denosumab provides longer-term suppression of bone resorption and sustained calcium reduction[3,5] and is recommended for moderate-to-severe or symptomatic cancer-associated hypercalcemia. Denosumab is preferred over bisphosphonates in patients with advanced renal dysfunction (e.g., eGFR, <35 ml per minute per 1.73 m^2) in order to avoid worsening kidney injury.[1] Transient hypocalcemia is common after denosumab or bisphosphonate

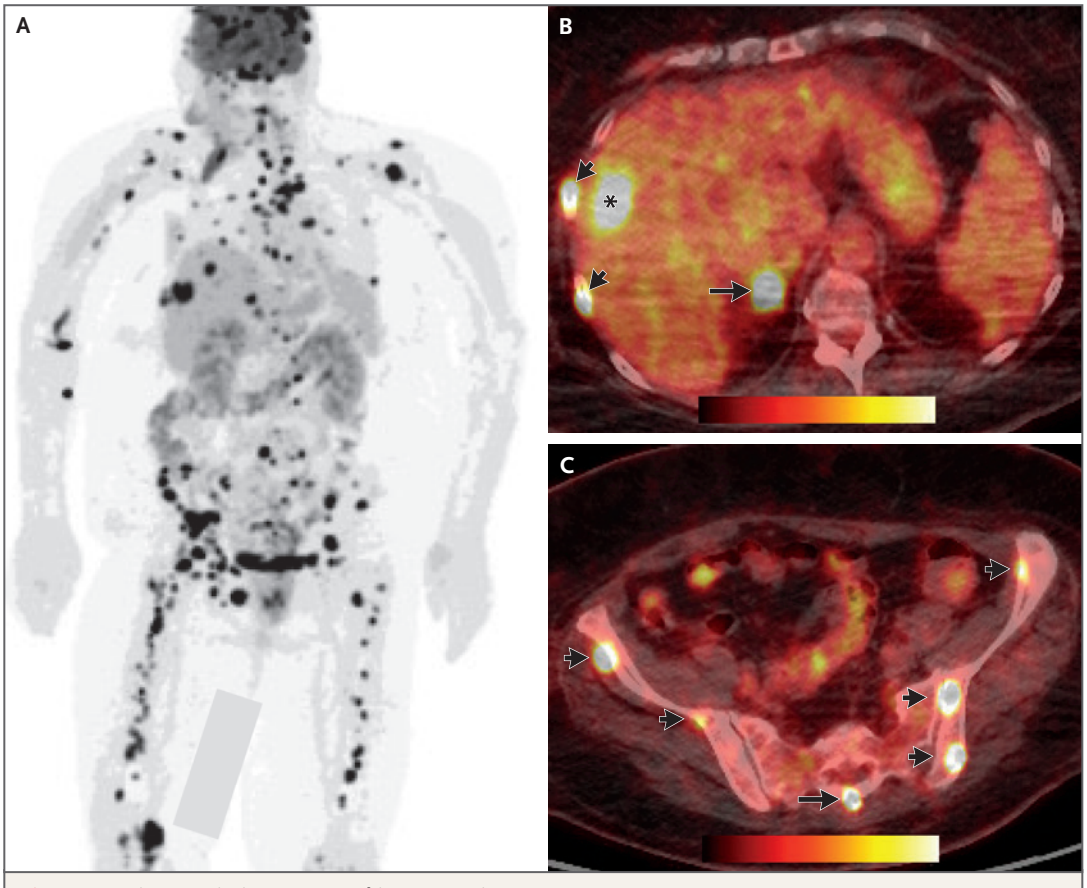


Figure 2. Positron-Emission Tomographic–CT Imaging.

A full-body coronal view from positron-emission tomographic–CT imaging showed numerous ^{18}F-fluorodeoxyglucose–avid lesions (shown in black) in the axial and appendicular skeleton (Panel A). Axial views showed lesions in the adrenal gland (Panel B, long arrow), liver (Panel B, asterisk), ribs (Panel B, short arrows), sacrum (Panel C, long arrow), and ilium (Panel C, short arrows).

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society.
Downloaded from nejm.org by heydar dolati on November 6, 2026.

treatment, reflecting effective suppression of osteoclastic activity; electrolyte monitoring and correction are indicated after treatment, particularly in patients with concurrent vitamin D deficiency and renal impairment.[1,2] In patients with refractory hypercalcemia and renal failure limiting adequate calciuresis or euvolemia, hemodialysis with a low-calcium dialysate can rapidly reduce the serum calcium level.[2] Effective long-term management requires identifying and treating the underlying cause of the hypercalcemia.

Cancer-associated hypercalcemia is attributed to PTHrP secretion or osteolytic metastases in most cases and, rarely, to ectopic vitamin D activation, although the prevalence of each mechanism varies with tumor prevalence.[2,6] Hematologic cancers are an underrecognized but important contributor to cancer-associated hypercalcemia.[2] Although DLBCL classically manifests with lymphadenopathy and constitutional symptoms, one retrospective study involving 250 patients reported that 18% had hypercalcemia at the time of the lymphoma diagnosis.[7] Mechanistically,

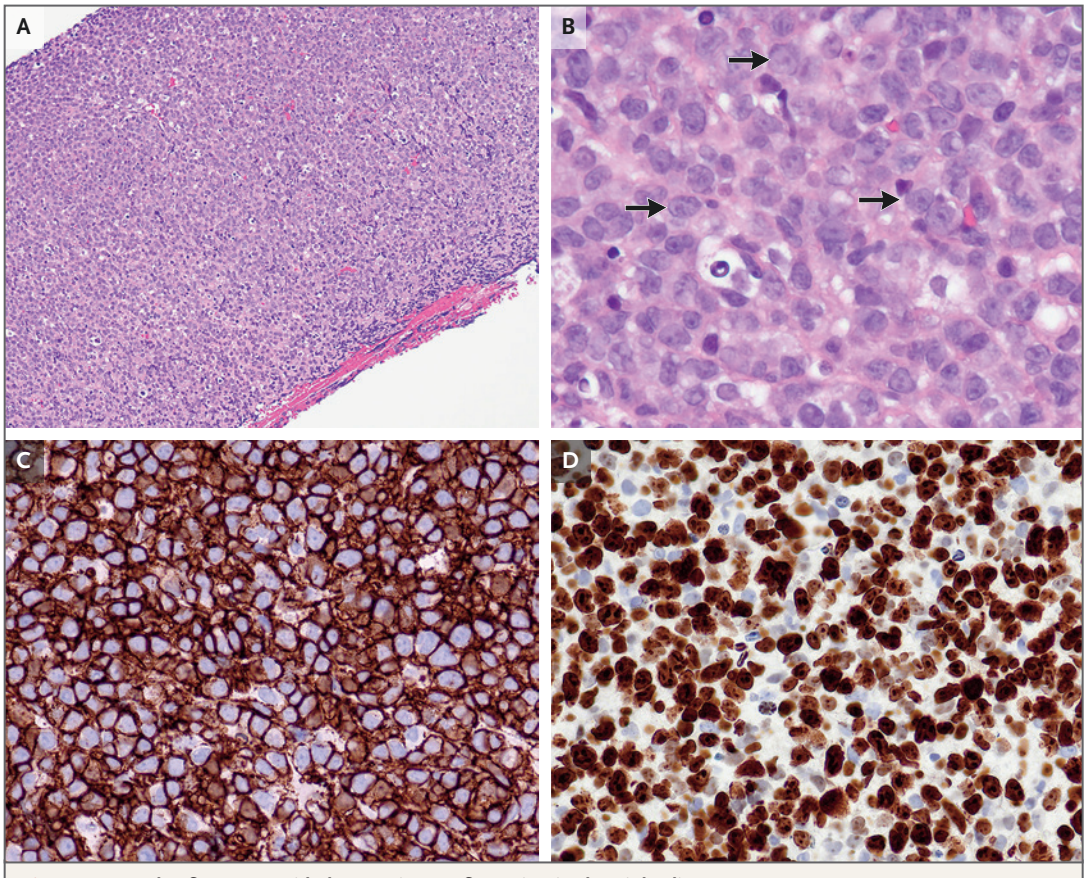


Figure 3. Samples from CT-Guided Core Biopsy of a Lesion in the Right Iliac Crest.

Hematoxylin and eosin staining showed a diffuse infiltrate of large atypical lymphoid cells (Panel A) with ovoid-to-irregular nuclei, vesicular chromatin, and prominent nucleoli (Panel B; arrows point to example atypical lymphoid cells). Panel B shows magnification at six times that in Panel A. Immunohistochemical staining showed that the lymphoid cells were diffusely positive for the B-cell marker CD20 (Panel C). The percentage of cells staining for Ki-67, a marker of proliferation, was markedly increased (>90% of cells) (Panel D), a finding consistent with an aggressive cancer. Panels C and D both show magnification at four times that in Panel A. Additional immunohistochemical markers (not shown) stained the atypical cells diffusely positive for paired box 5 (PAX5), multiple myeloma oncogene 1 (MUM1), B-cell lymphoma 6 (BCL6), and B-cell lymphoma 2 (BCL2). A subset of cells (30 to 40%) stained positive for myelocytomatosis proto-oncogene (MYC). The cells stained negative for CD3, CD5, CD10, CD34, terminal deoxynucleotidyl transferase (TdT), CD138, Epstein–Barr virus–encoded RNAs detected by in situ hybridization, cyclin D1, and CD30. Fluorescence in situ hybridization (not shown) did not detect an *MYC* gene rearrangement.

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society.
Downloaded from nejm.org by heydar dolati on November 6, 2026.

DLBCL-associated hypercalcemia may result from osteolysis, unregulated calcitriol activation, PTHrP production, or mixed causes.[6,8,9] In a single-center retrospective review involving patients with non-Hodgkin lymphoma and hypercalcemia, calcitriol and PTHrP levels were normal in the majority of patients in whom these were measured.[9] The sample size was small (17 patients), but these findings highlight the presumed role of osteolysis and other cytokine-mediated mechanisms in many cases of lymphoma-associated hypercalcemia,[9] as was the cause here. A retrospective study involving 302 patients with lymphoma showed that hypercalcemia at diagnosis was associated with lower overall survival; however, after adjustment for prognostic components, this association was not significant, which suggests that disease stage and tumor biologic factors — rather than hypercalcemia — explained the worse outcomes.[10]

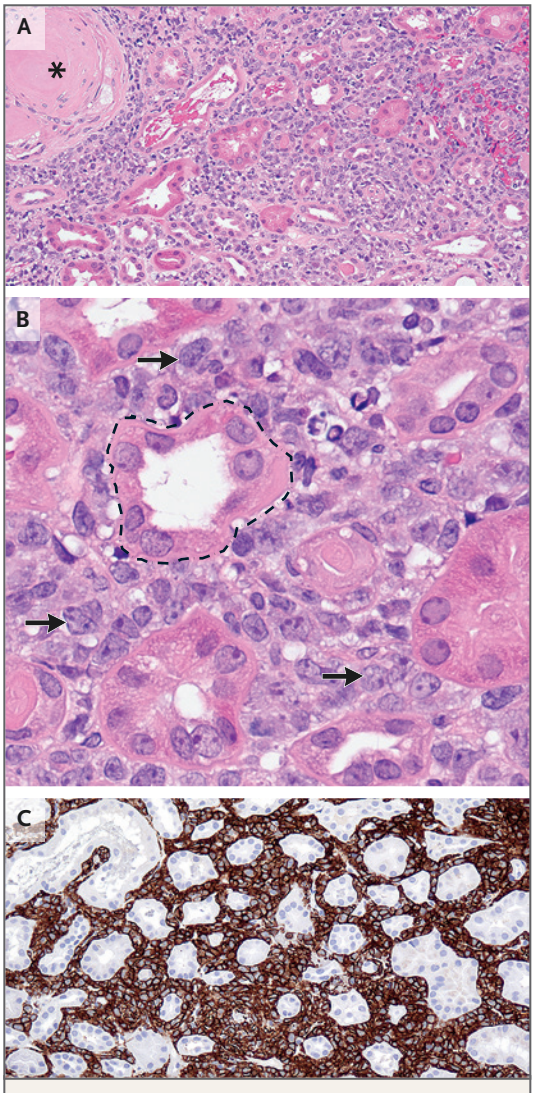


Figure 4. Kidney-Biopsy Sample.

Hematoxylin and eosin staining of a kidney-biopsy sample showed global glomerulosclerosis (Panel A, asterisk) and an interstitial atypical lymphoid infiltrate. The cells infiltrating between the tubules were identical to those seen in the previous bone biopsy with ovoid to irregular nuclei, vesicular chromatin, and prominent nucleoli (Panel B; arrows point to example neoplastic cells, and the dashed line marks an example tubule). Panel B shows magnification at four times that in Panel A. Immunohistochemical staining indicated lymphoid cells diffusely positive for CD20 (Panel C); positive for BCL6, BCL2, and MUM1 (not shown); and negative for CD10 (not shown). Panel C shows magnification at two times that in Panel A.

A diagnosis of DLBCL requires histopathological evidence of a diffuse population of large, atypical B cells effacing tissue architecture and the ruling out of morphologic mimics, including poorly differentiated carcinoma, melanoma, lymphoblastic lymphoma, and other mature B-cell lymphomas (e.g., Burkitt lymphoma). Diagnosis relies on morphologic, immunohistochemical, and cytogenetic evaluation.[11]

Although DLBCL commonly manifests with nodal disease, a large retrospective cohort study showed that one third of cases are confined to extranodal sites, such as bone, liver, kidney, and adrenal gland, at presentation.[12] Lymphoma should therefore remain a diagnostic consideration for hypercalcemia even in the absence of lymphadenopathy or lymphocytosis.

First-line treatment of DLBCL is guided by disease stage, risk category, and CD20 expression on malignant cells.[11] Standard therapy combines an anthracycline-based backbone (cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP]) with rituximab (R), an anti-CD20 monoclonal antibody that targets precursor and mature B cells for cell- and complement-mediated cytotoxicity.[11] Polatuzumab vedotin — an antibody–drug conjugate targeting malignant B cells by means of CD79b — may be substituted for vincristine, according to current clinical guidelines,[13] as was done for this patient. In a randomized trial involving 879 previously untreated patients with intermediate- or high-risk disease, including patients with extranodal DLBCL, the substitution of polatuzumab vedotin for vincristine led to significantly improved 2-year

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society.
Downloaded from nejm.org by heydar dolati on November 6, 2026.

progression-free survival as compared with standard R-CHOP with vincristine (76.7% vs. 70.2%), with 2-year overall survival being similar in the two groups (88.7% and 88.6%, respectively) and a similar safety profile.[14] Consolidative or palliative radiation therapy is used in selected patients with limited-stage, bulky, or symptomatic disease.[11] Molecular data are expected to further refine management, with recent advances in integrative genomic analysis producing multiple molecular-based lymphoma classifiers predicting prognosis and guiding targeted therapy.[15]

This case underscores the roles of hydration (with furosemide), calcitonin, and denosumab in treating cancer-associated severe hypercalcemia in patients with renal dysfunction, as well as the need to treat the underlying cancer for durable correction. Although lymphoma-associated hypercalcemia has classically been attributed to calcitriol excess, this case serves as a reminder that osteolysis and other cytokine-mediated mechanisms may predominate in many cases.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Drs. Suhas Gondi, Gustavo Mercier, and Reid Merryman for review of an earlier version of the manuscript.

AUTHOR INFORMATION

[1]Department of Medicine, Brigham and Women's Hospital, Boston; [2]Department of Pathology, Brigham and Women's Hospital, Boston.

REFERENCES

1. El-Hajj Fuleihan G, Clines GA, Hu MI, et al. Treatment of hypercalcemia of malignancy in adults: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2023;108:507-28.

2. Guise TA, Wysolmerski JJ. Cancer-associated hypercalcemia. N Engl J Med 2022;386:1443-51.

3. Seisa MO, Nayfeh T, Hasan B, et al. A systematic review supporting the Endocrine Society Clinical Practice Guideline on the treatment of hypercalcemia of malignancy in adults. J Clin Endocrinol Metab 2023;108:585-91.

4. Stone MD, Marshall DH, Hosking DJ, Garcia-Himmelstine C, White DA, Worth HG. Comparison of low-dose intramuscular and intravenous salcatonin in the treatment of primary hyperparathyroidism. Bone 1992;13:265-71.

5. Khan AA, Gurnani PK, Peksa GD, Whittier WL, DeMott JM. Bisphosphonate versus bisphosphonate and calcitonin for the treatment of moderate to severe hypercalcemia of malignancy. Ann Pharmacother 2021;55:277-85.

6. Stewart AF. Hypercalcemia associated with cancer. N Engl J Med 2005;352:373-9.

7. Abadi U, Peled L, Gurion R, et al. Prevalence and clinical significance of hypercalcemia at diagnosis in diffuse large B-cell lymphoma. Leuk Lymphoma 2019;60:2922-6.

8. Shibata H, Abe M, Hiura K, et al. Malignant B-lymphoid cells with bone lesions express receptor activator of nuclear factor-kappaB ligand and vascular endothelial growth factor to enhance osteoclastogenesis. Clin Cancer Res 2005;11:6109-15.

9. Shallis RM, Rome RS, Reagan JL. Mechanisms of hypercalcemia in non-Hodgkin lymphoma and associated outcomes: a retrospective review. Clin Lymphoma Myeloma Leuk 2018;18(2):e123-e129.

10. Gauchy A-C, Kanagaratnam L, Quinquenel A, et al. Hypercalcemia at diagnosis of diffuse large B-cell lymphoma is not uncommon and is associated with high-risk features and a short diagnosis-to-treatment interval. Hematol Oncol 2020;38:326-33.

11. Tilly H, Gomes da Silva M, Vitolo U, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;26:Suppl 5:v116-v125.

12. Gupta V, Singh V, Bajwa R, et al. Site-specific survival of extra nodal diffuse large B-cell lymphoma and comparison with gastrointestinal diffuse large B-cell lymphoma. J Hematol 2022;11:45-54.

13. National Comprehensive Cancer Network (NCCN). NCCN guidelines — B-cell lymphomas, version 3. 2026:77 (https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1480).

14. Tilly H, Morschhauser F, Sehn LH, et al. Polatuzumab vedotin in previously untreated diffuse large B-cell lymphoma. N Engl J Med 2022;386:351-63.

15. Chapuy B, Wood T, Stewart C, et al. DLBclass: a probabilistic molecular classifier to guide clinical investigation and practice in diffuse large B-cell lymphoma. Blood 2025;145:2041-55.

Copyright © 2026 Massachusetts Medical Society.

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society.
Downloaded from nejm.org by heydar dolati on November 6, 2026.