PTHrP-Induced Refractory Malignant Hypercalcemia in a Patient With Chronic Lymphocytic Leukemia Responding to Denosumab

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Clinical Practice Points

- Hypercalcemia is a common disorder in patients with solid tumors and to a lesser degree hematologic malignancies such as myeloma and lymphoma.
- Humoral hypercalcemia of malignancy is often difficult to control with standard calcium-lowering therapies and may require advanced therapies such as the RANKL antagonist denosumab.
- It is possible that RANKL antagonists play a direct inhibitory role in the tumorigenesis of chronic lymphocytic leukemia cells via a RANKL receptor–associated pathway.

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Introduction and Case Report

A 35-year-old Hispanic man was diagnosed with chronic lymphocytic leukemia (CLL) after assessment of a large neck mass. Bone marrow biopsy results revealed 20% lymphoma cells in a nodular and interstitial patten in a normocellular marrow. In addition to CD38 and surface kappa-positive and FMC-7 negative cells on flow cytometry, cytogenetics revealed multiple numerical and structural abnormalities on chromosomes 5, 8, 11, and 18 with karyotype 45,XY, add(5)(q35),−8,add(11)(p15), add(18)(p11.2)[6]/46,XY[14]. Fluorescent in-situ hybridization (FISH) CLL panel was negative for *ATM*, *RB1*, *P53*, and trisomy 12. Before the patient received chemotherapy, however, he began to develop symptoms of pain and tingling in his upper extremities consistent with radicular neuropathy. Magnetic resonance imaging and computed tomography of the neck revealed progression of malignancy to invade the cervical spinal canal with root impingement. A lumbar puncture performed at that time resulted in cytology positive for CD38 CLL. He then completed 6 cycles of fludarabine, cyclophosphamide, and rituximab (FCR) with intrathecal methotrexate and experienced a complete response, documented by flow cytometry of the peripheral blood and the cerebrospinal fluid, bone marrow biopsy results, and positron emission tomography/computed tomography 8 months after his initial diagnosis.

Two months after completing FCR, he developed recurrent swelling and pain in his neck and was found to have new left-sided neck lymphadenopathy (level V) that was refractory to 2 cycles of FCR as well as 1 cycle of bendamustine with rituximab. At that point, radiotherapy localized to the neck was provided, which resulted in resolution of his symptoms. Two months later (20 months after initial diagnosis), he presented to with severe right hip pain and was found to have destructive bony lesions of his acetabulum as well as lesions in the left shoulder and right orbit. He was also found to have malignant hypercalcemia, which was effectively treated with hydration and zoledronate during a short hospital stay. Biopsy of the acetabular mass and a bone marrow biopsy performed at that time demonstrated 100% cellularity with a population of variably sized cells that were consistent with persistence of his CLL. No evidence of Richter transformation was noted. Radiotherapy was then initiated to treat his bony lesions and was

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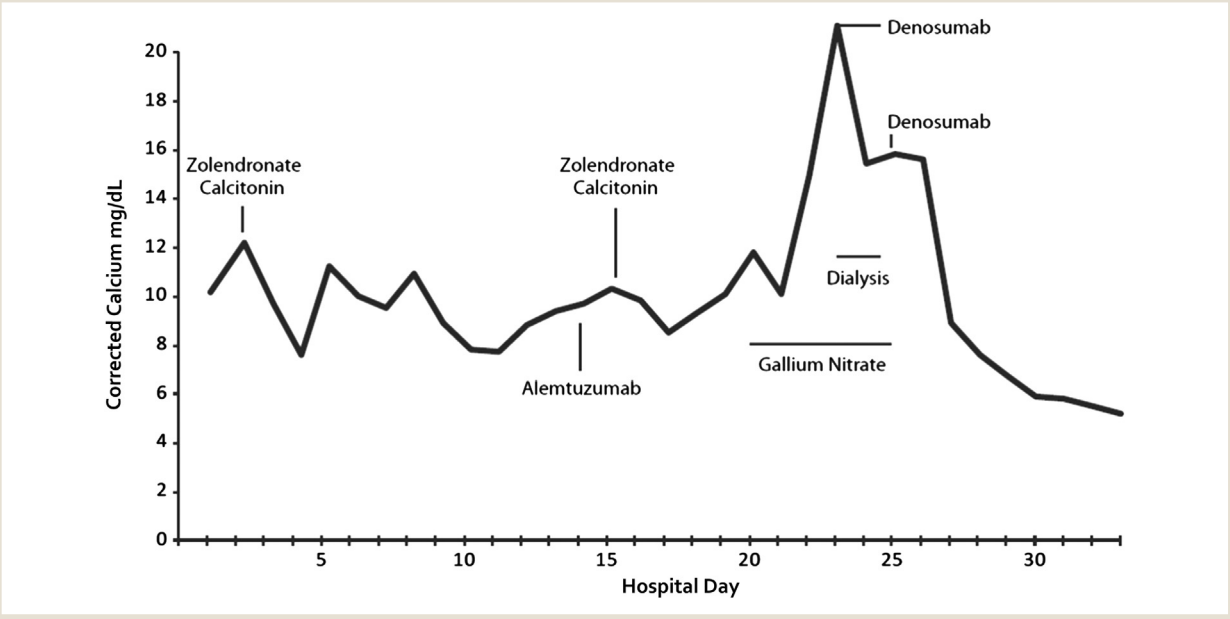
Figure 1 Corrected Serum Calcium Levels From Hospital Days 0 Through 33 and Selected Interventions

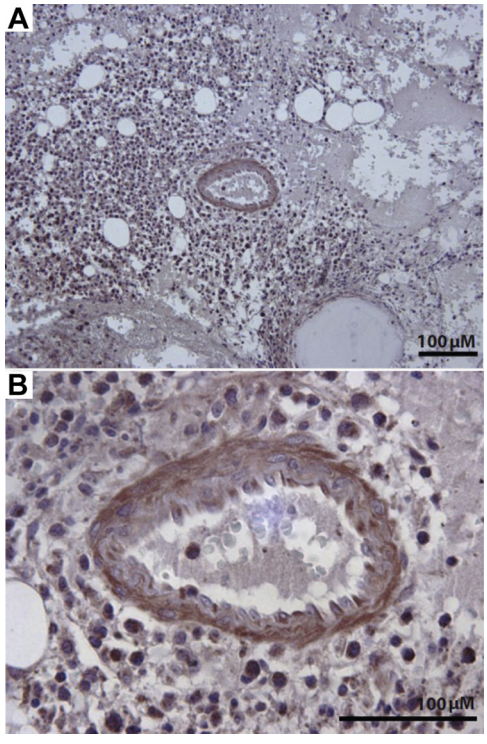


tolerated well. He then underwent 3 weeks of rituximab, ifosfamide, carboplatin, and etoposide salvage therapy with 20% reduction in bone marrow cellularity. Stem cell transplantation was considered for refractory disease but was not performed as a result of poor performance status and lack of a suitable human leukocyte antigen–matched donor. His karyotype at this time was notable for the original changes in chromosomes 5, 8, 11, and 18, and there were 3 to 4 copies of the *MYC* (8q24) gene by FISH without evidence of a *MYC* gene rearrangement.

Thirty days later (22 months after his initial diagnosis), he was admitted again with hypercalcemia and neutropenic fever. During his stay, the hypercalcemia recurred, ranging from 11 to 13 mg/dL on days 1 through 5 (Figure 1). He was provided with intravenous hydration with normal saline, and calcitonin was provided at 4 U/kg every 12 hours. On day 2, he received 4 mg of zoledronate. His calcium normalized, and laboratory studies revealed parathyroid hormone–related protein (PTHrP) elevated at 7.1 pmol/L (normal, < 2 pmol/L), low parathyroid hormone, and low 25 and 1,25-hydroxy vitamin D levels. He remained hospitalized for assessment and treatment of his febrile illness. A bone marrow biopsy on day 14 revealed persistent CLL with 90% CLL in the bone marrow. He initiated alemtuzumab therapy for his refractory CLL, and broad-spectrum antibiotics were continued for his neutropenic fever. Steroid therapy was considered but not administered as a result of concern of worsening infection.

On day 15, his calcium level increased, prompting readministration of zoledronate 4 mg and 8 U/kg of calcitonin every 6 hours. Serum calcium levels stabilized but remained persistently elevated. Mineral metabolism was consulted and recommended gallium nitrate at 200 mg/m^2 for 5 days. Calcium levels improved to 10.8 mg/dL on day 21. On day 23, however, his calcium suddenly rose to 21.3 mg/dL, at which time he underwent emergent dialysis for 2

Figure 2 Immunohistochemistry Staining of Bone Marrow Biopsy Sample Revealing Intense Staining of PTHrP Within Malignant Cells. (A) Original Magnification, ×40. (B) Original Magnification, ×100



Abbreviation: PTHrP = parathyroid hormone–related protein.