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Hypercalcemia in the setting of HTLV-1 infection and a normal PTHrP level

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Summary

Human T-cell lymphotropic virus-1 (HTLV-1) causes adult T-cell leukemia and lymphoma (ATLL) and is a rare but important cause of hypercalcemia. A 53-year-old male with HTLV-1-associated myelopathy presented with acute on chronic bilateral lower extremity weakness and numbness. Initial blood work revealed hypercalcemia with corrected calcium of 16.2 mg/dL (8.5–11.5) with normal levels of phosphorus and alkaline phosphatase. Workup for hypercalcemia revealed parathyroid hormone (PTH) of 14 pg/mL (10–65), 25 hydroxy vitamin D at 19.6 ng/mL (30–100), 1,25 dihydroxy vitamin D at 6.7 pg/mL (19.9–79.3), thyroid-stimulating hormone of 1.265 μIU/mL (0.5–5), undetectable PTH-related protein (PTHrP) and lactate dehydrogenase of 433 U/L (100–220). The urine calcium creatinine ratio was 0.388. Reverse transcriptase PCR was positive for HTLV-1 and negative for HTLV-2. Peripheral blood flow cytometry and lymph node biopsy confirmed ATLL. He received treatment with fluids, calcitonin and denosumab after which serum calcium levels fell (nadir: 7.7 mg/dL) and then normalized. Humoral hypercalcemia in this setting is mediated by receptor activator of nuclear factor-kappa B ligand (RANKL), PTHrP and other cytokines. PTHrP levels depend on levels of the TAX gene product, cell type and lymphocyte-specific factors. Thus, a low level, like in our patient, does not rule out HTLV-1 infection/ATLL as the cause of hypercalcemia. Hypercalcemia is known to be responsive to monoclonal antibodies against RANKL given the compound's role in mediating hypercalcemia in these cases.

Learning points:

- Human T-cell lymphotropic virus-1 infection and adult T-cell leukemia and lymphoma are associated with high rates of hypercalcemia and hypercalcemic crises.
- Hypercalcemia in these cases is mediated by osteoclastic bone resorption carried out by several agents including receptor activator of nuclear factor-kappa B ligand, parathyroid hormone-related protein (PTHrP), macrophage inflammatory protein 1 alpha, interleukins, etc. A normal PTHRrP does not rule out humoral hypercalcemia of malignancy in this setting, as indicated by this case.
- Hypercalcemia in such settings is highly responsive to monoclonal antibodies against RANKL given the role the ligand plays in resorptive hypercalcemia.

Background

Human T-cell lymphotropic virus-1 (HTLV-1) is a retrovirus, largely endemic to some parts of the world including South Africa, Japan and the Caribbean (1, 2, 3). While most infected individuals are asymptomatic, they could present with a wide array of clinical manifestations including myelopathy, arthritis, uveitis, virulent Strongyloides infections and adult T-cell leukemia and lymphoma (ATLL) (1, 2). HTLV-1 infections and ATLL are also rare but important causes of hypercalcemia and hypercalcemic crises (1, 2).

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Case presentation

A 53-year-old male with past history of HTLV-1 infection-associated myelopathy/tropical spastic paraparesis (HAM/TSP) and deep vein thromboses on anticoagulation presented with acute on chronic bilateral lower extremity weakness and numbness. In addition, he reported constipation and polyuria of recent onset. No saddle anesthesia or other neurologic deficits were endorsed. No fever or infectious symptoms were reported. Review of systems was otherwise negative. The patient did not use any supplements and reported no change in medications consumed. No history of using bone-active drugs was present.

Investigations

Spinal cord compression was ruled out with imaging. Initial investigations revealed metabolic abnormalities including hypoalbuminemia (serum albumin: 2 g/dL), hypercalcemia (corrected serum calcium: 16.2 mg/dL) with serum phosphorus of 2.7 mg/dL (2.5–4.5) and alkaline phosphatase of 126 mg/dL (20–140). Prerenal acute kidney injury was noted with BUN of 57 mg/dL and serum creatinine of 3.52 mg/dL (prior baseline: 1 mg/dL) with pH 7.37, HCO_3 of 22.

Workup for hypercalcemia revealed parathyroid hormone (PTH) level of 14 pg/mL (10-65), low level of 25 hydroxy vitamin D at 19.6 ng/mL (30–100) and 1,25 dihydroxy vitamin D level low at 6.7 pg/mL (19.9–79.3). Patient was euthyroid with thyroid-stimulating hormone (TSH) measured at 1.265 µIU/mL. The urine calcium creatinine ratio was calculated to be 0.388, indicating hypercalciuria. The PTH-related protein (PTHrP) level returned low at <2 pmol/L. Lactate dehydrogenase (LDH) was found elevated at 433 U/L (100–220). Levels of metabolites measured are tabulated (Table 1). No monoclonal proteins were detected on serum electrophoresis. Smudge cells and atypical lymphocytes were detected on peripheral smear and mild nonspecific generalized lymphadenopathy with marked splenomegaly was found on imaging. Flow cytometry was then done, revealing an atypical CD4+ helper T-cell population at 7.8% of the total, positive for markers including CD3, CD4, CD5 and CD45. Reverse transcriptase PCR returned positive for HTLV-1 and negative for HTLV-2. Clonal T-cell receptor gene rearrangements were found, suggesting a likely monoclonal or oligoclonal T-cell population. Lymph node biopsy revealed ATLL.

Treatment

He was initiated on i.v. fluid repletion and treated with calcitonin (4 units/kg) for 48 h. Upon lack of normalization of calcium levels, the patient was given 1 dose of 120 mg of denosumab subcutaneously and started on vitamin D supplementation to avoid hypocalcemia resulting from its use.

Outcome and follow-up

The patient developed mild hypocalcemia (corrected serum calcium nadir of 7.7 mg/dL) which was managed using supplements of calcium and calcitriol then changed to cholecalciferol, on which he was discharged. He remained normocalcemic for about 5 weeks following discharge, after which he developed another episode of hypercalcemia, treated similarly given prior response to denosumab. The patient was started on chemotherapy for ATLL but unfortunately passed away from complications of the neoplasm 3 months after this presentation.

Discussion

This case, in a patient with a history of HTLV-1 infection and associated spastic paraparesis, demonstrates an interesting instance leading up to the detection of an underlying

Table 1 Serum levels of metabolites.

Serum metabolite measured	Level prior to treatment	Level after treatment
Corrected serum calcium (albumin 2 g/dL), mg/dL	16.2	7.7–>8.5
Phosphorous, mg/dL	2.7	2.4
Alkaline phosphatase, mg/dL	126	117
Parathyroid hormone, pg/mL	14	Not measured
25 hydroxy vitamin D, ng/mL	19.6	Not measured
1,25 dihydroxy vitamin D, pg/mL	6.7	Not measured
Thyroid-stimulating hormone, µIU/mL	1.265	Not measured
PTHrP, pmol/mL	<2	Not measured
Lactate dehydrogenase, U/mL	433	Not measured
Urine calcium creatinine ratio	0.388	Not measured

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malignancy causing hypercalcemia. A normal level of TSH, 25 hydroxy vitamin D, 1,25 dihydroxy vitamin D and PTH would lead to further workup for underlying malignancies, in all instances with an elevated PTHrP level. However, our case reveals that even with a low or normal value of PTHrP, for reasons explained later, this workup must be carried out, especially in patients with risk factors for malignancies and no other evident causes of hypercalcemia.

HTLV-1 virus is the only retrovirus other than the human immunodeficiency virus with the ability to cause infections in human beings (3). It is transmitted by parenteral, sexual and transplacental routes. It is endemic to certain parts of the world including Japan, certain Caribbean and African countries (2, 4).

While most individuals (>90%) infected with HTLV-1 remain asymptomatic, it can cause syndromes such as HAM/TSP, uveitis, arthritis, myositis and dermatitis, (4) as well as ATLL, with a cumulative lifetime risk of around 4–7% (5). HTLV-1 infection, whether in asymptomatic carriers, individuals with sequelae of infection, or individuals with ATLL, increases the risk of hypercalcemia (1, 2, 4). Individuals with ATLL have some of the highest reported incidences of hypercalcemia among hematologic malignancies, with 50–70% of patients developing at least 1 episode of hypercalcemia (1, 2). It is mostly seen in patients with the acute variant of ATLL rather than the lymphomatous, chronic, or smoldering variants (1, 4). Hypercalcemic crises, defined as serum calcium level greater than 14 mg/dL, oliguria and altered mental status have been often described in this patient population (2, 3, 4). When present, it is said to be an independent predictor of lower overall survival, usually less than 6 months, and is a poor prognostic factor, as seen in our patient (4).

Hypercalcemia is caused primarily by increased bone resorption. It is mediated by multiple compounds with the largest role being played by receptor activator of nuclear factor-kappa B ligand (RANKL), followed by PTHrP, macrophage inflammatory protein 1 alpha, gp 46, interleukins and TNF among others (1, 2, 3, 4). Calcitriol too has been reported to cause hypercalcemia in this subset of patients (5). Very rarely, patients with ATLL have ectopic production of PTH causing hypercalcemia (5).

RANKL is a surface protein that is part of the TNF superfamily, found on osteoblasts, which binds to the RANK receptor found on the surface of osteoclast precursors (6). It mediates their conversion to mature osteoclasts, engaging in bone resorption (6). The nuclear transactivation of X (TAX) gene product in HTLV-1-infected cells increases RANKL expression. Shu *et al*. found an increased expression of RANKL and decreased expression of an antagonist compound called osteoprotegerin (OPG) in cell lines infected with HTLV-1 (5). They also found that differentiation of bone marrow mononuclear cells into osteoclasts increased dramatically upon infection with HTLV-1 and that this process was inhibited by the addition of OPG and RANKL inhibitors (5). A viral surface protein named gp46-197 is also known to block the action of OPG by competing for the same antigenic sites through molecular mimicry (2). Mice treated with gp46-197 exhibited decreased bone growth and hypercalcemia, which could be reversed using OPG (2).

PTHrP may be produced by HTLV-1-infected cells; Nosaka *et al*. also found an increased expression of PTHrP mRNA in infected cells (2). Further, it was found that the amount of PTHrP produced was directly proportional to the burden of infected cells with the level of the compound being 20–50 times higher in ATLL when compared to HAM/TSP (2, 7). PTHrP binds to the receptor for PTH by virtue of its structural similarity with PTH. It then results in bone resorption, renal tubular reabsorption of calcium and upregulation of other inflammatory mediators including RANKL, which in turn cause hypercalcemia (8). PTHrP expression is variable in individuals with HTLV infection and ATLL, with some studies indicating that it may be related to variable levels of the TAX gene product causing transactivation of the PTHrP gene promoter (2, 5, 7). Other studies indicate that PTHrP expression is independent of TAX and that PTHrP expression may be dependent on cell type and require lymphocyte-specific factors for its production (9). Furthermore, levels of PTHrP in the serum do not always correlate with the presence of hypercalcemia in patients with ATLL, suggesting that other factors may be involved in its pathogenesis (2). Our patient had low levels of PTHrP among mediators of hypercalcemia. However, this does not rule out HTLV infection or ATLL as the cause of hypercalcemia.

Factors that were found to determine the degree of hypercalcemia included the extent of bone marrow invasion by tumor cells and RANKL expression (2).

It has also been found that growth factors released from osteolytic bone stimulate tumor cell proliferation, establishing a vicious bidirectional cycle involving tumor and bone cells (5).

Guidelines for therapy for hypercalcemia in this setting are similar to those in other malignancies (6). The i.v. fluid repletion is of prime importance. Routine use of loop diuretics is not recommended unless a patient develops fluid overload. Calcitonin can be used in doses of

4 or 8 U/kg q6–12 h for 48 h if patients respond to initial doses. However, a fall in serum calcium with this therapy is often transient due to tachyphylaxis as a result of the downregulation of calcitonin receptors on osteoclasts (6). Bisphosphonates or denosumab are the definitive agents to treat hypercalcemia of malignancy (6).

Given the role that RANKL plays in hypercalcemia in patients with HTLV-1 infection and other malignancies, it has been postulated that MABs against RANKL may work marginally better than bisphosphonates in the treatment of hypercalcemia, while also lending themselves to be used in the setting of compromised renal function (6, 10). Serious side effect profiles are similar between the two groups. Availability, cost-effectiveness, ease of administration and minor side effect profiles vary, necessitating individually tailored treatment in patients (6, 10). Patients may develop hypocalcemia as a consequence of the use of denosumab with nadir seen in 7 days. Hypomagnesemia, low vitamin D levels, renal dysfunction, malabsorption and prior parathyroidectomy are risk factors for the above (6).

To summarize, HTLV-1 infection, in the absence or presence of clinical manifestations, increases the risk of hypercalcemia, especially in the setting of ATLL. Investigations may not reveal elevated levels of commonly tested mediators like PTHrP or 1,25 dihydroxy vitamin D levels, but this does not rule out the infection or neoplasm as the cause of the hypercalcemia. Management of hypercalcemia is in keeping with guidelines for the management of other causes of hypercalcemia but may be better responsive to monoclonal antibodies against RANKL.

Declaration of interest
The author declares that there is no conflict of interest could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
Written informed consent for the publication of their clinical details were obtained from the patient.

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