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Case Report

Rapid onset of hypercalcemia from high-grade lymphoma in the setting of HIV-related immune reconstitution inflammatory syndrome

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ABSTRACT

Hypercalcemia in HIV patients has been previously reported, but 1,25-$(OH)_2$ vitamin D-mediated hypercalcemia, due to increased activity of extrarenal 1-alpha hydroxylase, is rarely described with HIV-related infections or malignancies. We describe a case of 1,25-$(OH)_2$ vitamin D-mediated hypercalcemia in a patient presenting with progressive cognitive decline and weakness. Initial evaluation revealed a new diagnosis of HIV, for which he was started on antiretroviral therapy (ART). He was also noted to have mild asymptomatic hypocalcemia, likely from his acute illness and malnutrition, which was not further investigated at the time. While the patient's mental status initially improved with ART, he became progressively delirious and was found to be hypercalcemic approximately 4 weeks after the initiation of ART. Possible etiologies for hypercalcemia were vigorously evaluated, including granulomatous disease, infection, and malignancy, in the setting of suspected immune reconstitution inflammatory syndrome (IRIS), due to recent initiation of ART. Infectious workup was unrevealing, but computed tomography (CT) of the chest, abdomen, and pelvis revealed new extensive diffuse lymphadenopathy and hepatomegaly, not present on admission studies. Cytology and flow cytometry of a liver biopsy specimen revealed CD10 positive high-grade B-cell lymphoma. Chemotherapy was not pursued due to poor performance status. Over the next week, spontaneous tumor lysis developed, and the patient expired. Postmortem, his 1,25-$(OH)_2$ vitamin D level returned as markedly elevated. Immunohistochemical staining of his liver biopsy tissue showed strong expression of CYP27B1.

1,25-$(OH)_2$ vitamin D-mediated hypercalcemia is uncommon in a patient with newly diagnosed HIV and, in this case, was likely due to IRIS unmasking an underlying high-grade lymphoma and restoration of immune function (including T-cells and cytokine production). This case emphasizes the importance of including aggressive lymphomas, capable of progressing over days to weeks, in the evaluation of hypercalcemia in HIV patients at risk for developing IRIS and the rapid dynamic changes in mineral homeostasis that can occur with such an aggressive tumor in an immunocompromised host.

1. Introduction

Hypercalcemia is uncommon, occurring in 0.2 to 4% of the general population, and is most often due to hypercalcemia of malignancy or primary hyperparathyroidism (Tebben et al., 2016). Hypercalcemia in HIV-infected patients has been previously described, although 1,25-$(OH)_2$ vitamin D-mediated hypercalcemia, due to HIV-related infections or malignancies, is distinctly unusual. HIV-infected patients may present with 1,25-$(OH)_2$ vitamin D-mediated hypercalcemia in association with immune reconstitution inflammatory syndrome (IRIS) (Murdoch et al., 2007). IRIS is defined as the paradoxical clinical worsening of a preexisting condition or the unmasking of a new condition, after the initiation of antiretroviral therapy (ART), and is attributed to the recovery of the immune system, with both positive and negative outcomes for the host (French, 2009). Prior case reports describe 1,25-$(OH)_2$ vitamin D-mediated hypercalcemia in IRIS-associated infections caused by *Mycobacterium tuberculosis* and *Mycobacterium avium* complex (MAC) (Tsao et al., 2009; Tsao et al., 2012). Hypercalcemia from IRIS-

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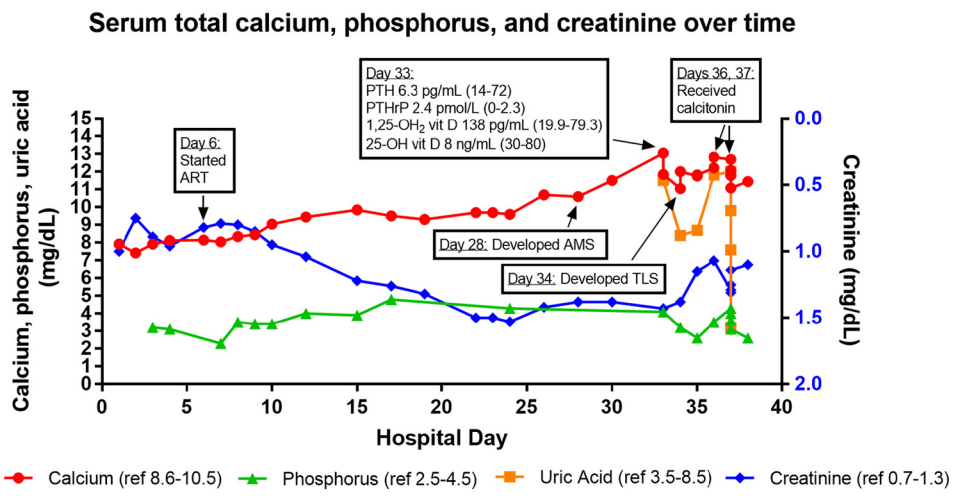

Fig. 1. Serum total calcium (mg/dL), phosphorus (mg/dL), uric acid (mg/dL), and creatinine (mg/dL) (upper panel) and CD4 cell count (cells/mL), CD4 percentage, and viral load (copies/mL) (lower panel) during the patient's 38 days of hospitalization.
For reference, CD4 cell counts were 46 cells/ml and 43 cells/ml on days 2 and 33, respectively (ref 420–1250). CD4% were 3% and 7% on days 2 and 33, respectively (ref 28–59). Viral loads were 4,002,666 copies/mL, 24,132 copies/mL, and 1317 copies/mL on days 3, 15, and 33, respectively.
Abbreviations: ART, antiretroviral therapy; PTH, parathyroid hormone; PTHrP, PTH-related protein; AMS, altered mental status; TLS, tumor lysis syndrome; VL, viral load.

related non-infectious conditions such as lymphoma, however, have not, to our knowledge, been reported.

Recent studies suggest that patients with HIV have an increased incidence of presenting with non-Hodgkin or Hodgkin lymphoma during the first 3 to 6 months following the initiation of ART (Lanoy et al., 2011; Jaffe et al., 2011; Yanik et al., 2013). In fact, 12% of patients studied in a large HIV-associated lymphoma cohort had presentations compatible with lymphoma in the setting of unmasking lymphoma IRIS, defined as lymphoma diagnosed within 6 months after ART initiation with a ≥0.5 log reduction in HIV RNA (Gopal et al., 2014). We describe a case of 1,25-$(OH)_2$ vitamin D-mediated hypercalcemia due to rapidly progressive lymphoma within 4 weeks of ART initiation in a patient with newly diagnosed HIV, whose viral load demonstrated a 3-log reduction during that time period. Furthermore, this patient's presentation was remarkable in that the rapid onset of spontaneous tumor lysis, due to the high-grade lymphoma, negated the initially symptomatic moderate hypercalcemia.

2. Materials and methods

For immunohistochemistry, sections were deparaffinized and rehydrated. Endogenous peroxidase was blocked with 3% hydrogen peroxide. Goat CYP27B1 antibody (1:50) or rabbit PTHrP antibody (1:100) was applied to paraffin-embedded liver sections (1:50, overnight, 4C) and was detected with biotinylated anti-goat secondary antibody, followed by ABD peroxidase reagent (all antibodies were from Santa Cruz Biotechnology, Inc., Santa Cruz, CA). 1-alpha hydroxylase expression was visualized by diaminobenzidine substrate and hematoxylin counterstaining. Skin sections were used as positive (goat CYP27B1 antibody, 1:50) and negative (normal goat serum) controls, respectively. Deidentified normal liver biopsy sections were obtained as controls for these studies from the University of California, San Francisco (UCSF) Department of Gastroenterology through a protocol approved by the UCSF Institutional Review Board. Normal skin biopsy sections were obtained from the Department of Pathology and Laboratory Medicine at the San Francisco Veterans Affairs Health Care System.

3. Case report

A 64-year-old man with a history of schizophrenia presented to a local free clinic shortly after relocating from Turkmenistan to San Francisco. His daughter reported that he had developed a productive cough, slowed speech, mild confusion, generalized weakness, anorexia and a 45-pound weight loss over the prior 5 months. While he was previously employed as a healthcare worker and independent in his activities of daily living (ADLs), he had become gradually dependent on others for assistance with ADLs and was now wheelchair-bound. A few months prior to presentation, he was evaluated by a physician in Turkmenistan to rule out a cerebrovascular accident and was diagnosed with prior hepatitis B infection by core antibody positivity, as well as a "nonspecific encephalopathy". In the clinic, the patient was found to be hypotensive (systolic blood pressure 70 mmHg) and tachycardic [pulse 110 beats per minute (bpm)], and he was sent to the Zuckerberg San Francisco General Hospital Emergency Department for further evaluation of progressive cognitive and physical decline.

In the Emergency Department, the patient's vital signs included temperature 36.7 °C, blood pressure 88/56 mmHg, heart rate 112 bpm, respirations 20/min, and oxygen saturation 98% without supplemental oxygen. On physical examination, he was ill-appearing and cachectic with temporal wasting and was oriented only to self. He exhibited generalized weakness and was unable to sit up or stand without assistance. Cardiopulmonary exam revealed rales at the left lung base. He had no scleral icterus or oral thrush, and the remainder of his examination revealed normal heart, abdomen, skin, and joints.

Initial laboratory evaluation revealed that the patient was HIV antibody positive. HIV parameters at admission included a CD4 cell count of 46 cells/uL (ref 420–1250), CD4 percentage of 3% (ref 28–59) and HIV viral load > 4 million copies/mL. Complete blood count showed white blood cell count 4.6 k/uL (ref 3.9–11.7), hemoglobin 8.9 g/dL (ref (13.3–17.7), hematocrit 27.2% (ref 39.8–52.2), platelets 113 k/uL (ref 150–400). Chemistry panel was notable for total serum albumin corrected calcium of 7.9 mg/dL (ref 8.6–10.5), with the remainder of the chemistry panel normal, including a serum phosphate of 3.2 mg/dL (ref 2.5–4.5) and serum creatinine of 1.0 mg/dL (ref 0.7–1.3) (Fig. 1). Liver function tests were normal. The patient's initial hypocalcemia was not further evaluated at this time.

Admission imaging included a chest X-ray and CT for evaluation of productive cough, which showed mild bibasilar consolidation. The patient underwent diagnostic evaluation for tuberculosis, which was negative by serial sputum AFB smears, cultures, and Gene Xpert® testing. Broncho-alveolar lavage cultures grew *Pseudomonas aeruginosa*, and he was treated with a 7-day course of levofloxacin.

Head CT was performed to evaluate declining mental status and was negative for acute abnormalities. A subsequent brain magnetic resonance imaging (MRI) revealed patchy areas of T2/FLAIR hyperintensity in the periventricular and right frontal subcortical white matter, as well as confluent white matter hyperintensity in the bilateral occipital lobes, without associated enhancement or diffusion abnormalities. Cerebrospinal fluid (CSF) examination was negative for opportunistic pathogens, including negative cryptococcal antigen testing and John Christopher [JC] virus polymerase chain reaction (PCR). Altered mental status was attributed to HIV encephalopathy. Additional

workup for opportunistic pathogens included negative acid-fast bacilli-specific blood cultures and negative fungal markers. ART with standard therapy doses of tenofovir alafenamide, emtricitabine, and dolutegravir was started on hospital day 6, after CNS opportunistic infections had been excluded. Appropriate prophylaxis for opportunistic infections, including daily fluconazole for *Cryptococcus* prophylaxis, was also initiated. Abdominal CT angiography was performed to assess for cirrhosis and showed normal liver size and contour, without evidence of cirrhosis, but revealed 2 subcentimeter lesions, thought to be benign (LI-RADS classification 2). A psychiatric consultant diagnosed bipolar disorder, rather than schizophrenia, and he was treated with olanzapine. With these interventions, the patient's mental status markedly improved by hospital day 9. He became more oriented, conversant with his family, and cooperative with providers. His albumin-corrected serum total calcium also improved on ART to 9.7 mg/dL (Fig. 1).

The patient remained hospitalized, awaiting discharge to a rehabilitation facility. By hospital day 15, his HIV viral load had decreased to 24,132 copies/mL. On hospital day 28, his mental status worsened, and he became progressively more impulsive, agitated, and delirious. Laboratory testing now demonstrated an elevated albumin-corrected serum total calcium of 13.0 mg/dL, confirmed by elevated ionized calcium of 1.59 mM (ref 1.12–1.32). Lactate dehydrogenase (LDH) level was high at 850 U/L (ref 110–210), and serum creatinine rose to 1.53 mg/dL (ref 0.7–1.3)] (Fig. 1). Plasma intact parathyroid hormone (PTH) was undetectable [< 6.3 pg/mL (ref 14–72)], serum PTH-related protein (PTHrP) was 2.4 pmol/L (ref 0–2.3), serum 25-OH vitamin D was low at 8 ng/mL (ref 30–80), and the serum 1,25-$(OH)_2$ vitamin D level not available at this time later returned as markedly elevated to 138 pg/mL (ref 19.9–79.3) (Fig. 1). Additionally, liver function tests were newly elevated [aspartate aminotransferase (AST) 168 U/L (ref 10–48), alanine aminotransferase (ALT) 171 U/L (ref 10-40), alkaline phosphatase 1093 U/L (ref 56–119), total bilirubin 5.3 mg/dL (ref 0.1–1.1), and direct bilirubin 4.0 mg/dL (ref 0.1–0.3)]. Due to increasing serum creatinine, the patient's hypercalcemia was initially treated with intramuscular calcitonin injections (administered at a dose of 4 units/kg) on hospital days 36 and 37. Possible etiologies of hypercalcemia, including granulomatous disease, infection, and malignancy, were evaluated in the setting of presumed IRIS due to recent initiation of ART. The entire serologic workup for opportunistic infections was repeated and remained negative. HIV parameters were rechecked and showed a CD4 T lymphocyte count of 43 cells/uL, CD4 percentage of 7%, and HIV viral load of 1317 copies/mL.

Renal ultrasound was performed to assess etiologies for acute kidney injury and incidentally revealed 2 large, complex hepatic lesions. CT of the abdomen and pelvis now showed new bilateral pleural effusions and extensive diffuse lymphadenopathy, including a large area of hypoattenuation in the liver, suggestive of an infiltrative process (Fig. 2). Cytology and flow cytometry of a liver biopsy specimen revealed CD10 positive lymphocytes, compatible with a high-grade B-cell lymphoma. Based upon these findings, an unmasking lymphoma IRIS was diagnosed, and the patient was evaluated by oncology consultants. The consensus was that his performance status was too poor to undergo chemotherapy, and his family decided to focus his care on comfort measures only.

During the next week, the patient developed spontaneous tumor lysis syndrome, and corrected serum calcium fell from 13 to 11 mg/dL without any treatment. Serum phosphate rose to 4.3 from 2.6 mg/dL, and serum uric acid and LDH became elevated to 12 mg/dL (ref 3.5–8.5) and 987 U/L (ref 110–210), respectively, and the patient expired shortly thereafter.

To investigate the source of the markedly elevated serum 1,25-$(OH)_2$ vitamin D level, immunostaining of liver tumor sections and other control tissues was performed using a CYP27B1, 1-alpha hydroxylase, antibody, as previously described (Bikle et al., 2018). Positive control was a normal skin biopsy, and negative controls were sections from normal liver biopsies from HIV positive and HIV negative, normocalcemic subjects as described in Materials and Methods. Strong expression of 1-alpha hydroxylase was evident in the lymphocytes of the liver tumor compared to absent staining in normal control liver biopsy (Fig. 3). Additionally, the lymphocytes did not stain for PTHrP. Strongly positive staining of the skin biopsy for 1-alpha hydroxylase was also noted, confirming the specificity of the immunostaining procedures, since this protein is known to be strongly expressed there.

4. Discussion

Hypercalcemia in HIV-infected patients is uncommon, with one study of 66 patients reporting an incidence of only 2.9% (Peter, 1992) with the most common etiologies identified as granulomatous diseases and malignancies. Hypercalcemia associated with high 1,25-$(OH)_2$ vitamin D levels is typically due to the increased and unregulated activity of extrarenal 1-alpha hydroxylases in ectopic sites, resulting in overproduction of 1,25-$(OH)_2$ vitamin D from 25-(OH) vitamin D.

Risk factors for IRIS in this case included nadir CD4 T lymphocyte count < 100 cells/uL and a plasma HIV viral load decrease of 2.5 logs at the time of IRIS, compared with levels before ART initiation (Manabe et al., 2007). A recent study suggested higher odds for developing IRIS with the initiation of contemporary more potent HIV regimens versus older treatments (Perez-Rueda et al., 2017). Conditions associated with IRIS after the initiation of ART can lead to 1,25-$(OH)_2$ vitamin D-

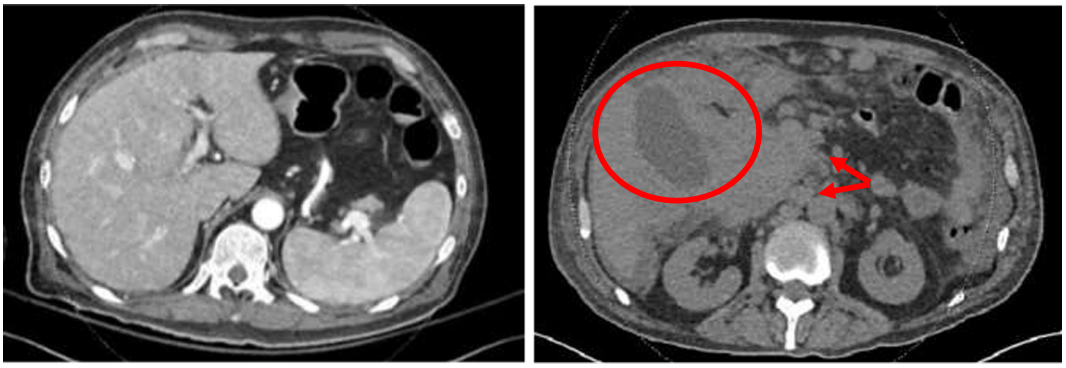

Fig. 2. Abdominal imaging during the patient's hospitalization.
A: CT angiography of the abdomen on admission showed two subcentimeter, low density lesions with no lymphadenopathy.
B: CT of the abdomen and pelvis after 27 days of ART showed new extensive diffuse lymphadenopathy (arrows), including a large area of hypoattenuation in the liver (circled).

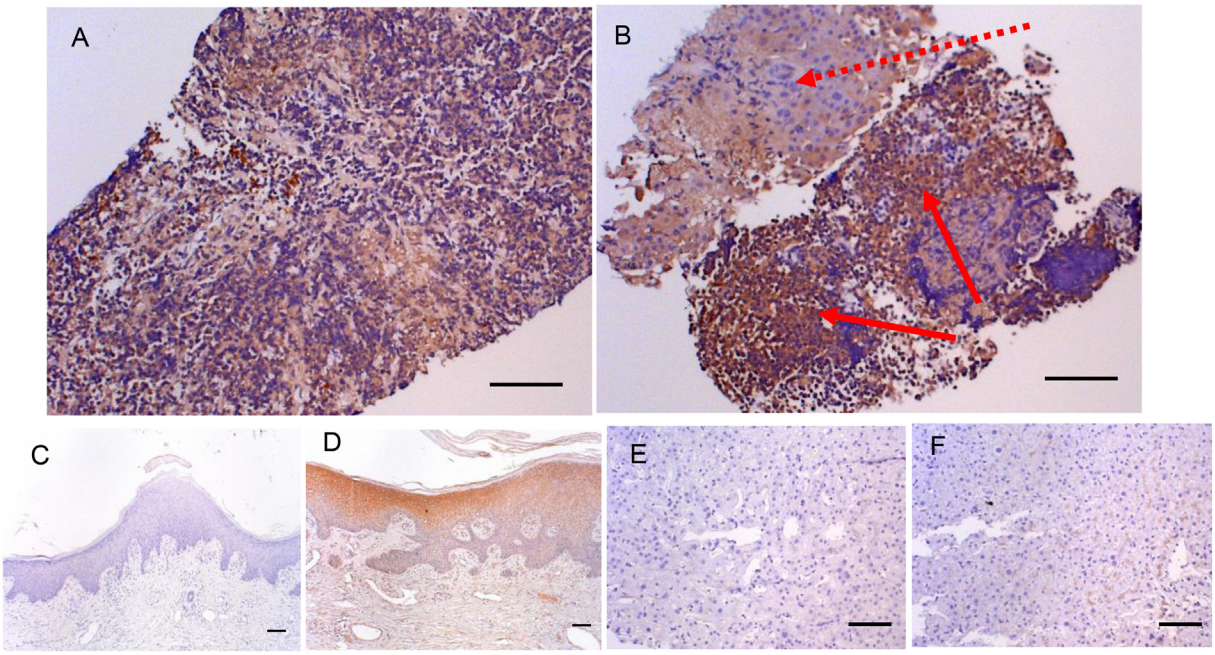

Fig. 3. Immunostaining of sections from the liver tumor biopsy from the patient and from normal liver and skin biopsies from control subjects for detection of Cyp27B1 or 1-alpha hydroxylase were completed as described in Materials and Methods. Bars = 50 μm.
A and B: Sections of the patient's liver tumor showed strong and diffuse staining for 1-alpha hydroxylase (brown) in the lymphocytes (solid arrow), but not in normal hepatocytes (dashed arrow). Magnification is 20×.
C and D: Skin section from a healthy control subject in which the 1-alpha hydroxylase antibody was omitted from the incubation (negative control); skin section from a healthy control subject showing positive (brown) immunostaining for 1-alpha hydroxylase in the epidermis. Magnification is 10×.
E: Section from liver biopsy from a HIV negative, normocalcemic control subject showed absent staining for 1-alpha hydroxylase. Magnification is 10×.
F: Section from liver biopsy from an HIV positive, normocalcemic patient showed absent staining for 1-alpha hydroxylase. Magnification is 10×. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

mediated hypercalcemia and, in most cases, are attributable to opportunistic infections. Case reports have described 1,25-$(OH)_2$ vitamin D-mediated hypercalcemia, associated with mycobacterial infections in HIV-infected patients, (Tsao et al., 2009; Tsao et al., 2012) and non-infectious inflammatory conditions, such as sarcoidosis (Gomez et al., 2000) and autoimmune thyroiditis and Graves disease (Jubault et al., 2000), as well as the presentation of new malignancies.

Lymphomas are known to cause hypercalcemia, occurring in about 13% of non-Hodgkin lymphomas and 5% of Hodgkin lymphomas, due to increased 1,25-$(OH)_2$ vitamin D production in essentially all cases of Hodgkin lymphoma and ~30–40% in non-Hodgkin lymphoma (Tebben et al., 2016). In the remaining 60-70% of cases of non-Hodgkin lymphoma, hypercalcemia is mediated by PTHrP. In an older case series of 15 patients with lymphoma and hypercalcemia, seven of these patients presented with elevated 1,25-$(OH)_2$ vitamin D levels (Adams et al., 1989). The types of lymphoma varied (B-cell, small noncleaved and immunoblastic sarcoma 40%, follicular center cell 27%, Hodgkin 20%, T-cell 13%). This study also included 4 patients with AIDS-associated lymphoma. That series was reported in 1989, a time when highly effective ART was not available and included one patient with HIV-related lymphoma with a high 1,25-$(OH)_2$ vitamin D level (Adams et al., 1989). Further laboratory studies using lymphoma cells cultured from the HIV-infected host showed that these cells had the capacity to metabolize 25-(OH) vitamin D into a compound similar to 1,25-$(OH)_2$ vitamin D by chromatography. Another case report described two patients with Burkitt lymphoma who presented with hypercalcemia and suppressed PTH, although 1,25-$(OH)_2$ vitamin D levels were not reported (Spiegel et al., 1978). Recent studies have shown that patients with HIV infection have an increased incidence of non-Hodgkin and Hodgkin lymphoma during the first 3 to 6 months of ART (Lanoy et al., 2011; Jaffe et al., 2011; Yanik et al., 2013), the time-frame in which our patient presented with his aggressive lymphoma and high tumor burden. In a cohort of 482 patients with HIV-associated lymphoma, approximately 12% of patients studied were found to have a course compatible with IRIS unmasking the presence of a lymphoma, with 9% of those patients (n = 5) having Burkitt lymphoma (Gopal et al., 2014).

This patient initially presented with hypocalcemia, thought to be due to acute illness, malnutrition and possibly vitamin D deficiency; further evaluation was not pursued. He quickly developed hypercalcemia following the initiation of ART, along with rapid interval presentation of high-grade B-cell lymphoma. Initial imaging studies of the brain, chest, abdomen, and pelvis showed no sign of underlying malignancy prior to ART initiation. Thus, lymphoma was thought to be an unmasking phenomenon associated with immune reconstitution in the setting of highly potent ART. We demonstrated strong immunostaining in the lymphocytes of his tumor for 1-alpha hydroxylase, ectopically overexpressed by this B cell lymphoma, whereas staining for PTHrP was absent in these cells. It has been reported that cytokines may stimulate 1,25-$(OH)_2$ vitamin D in B- and T-lymphocytes, with CYP27B1 expression increased when these cells are activated (Bikle et al., 2018). Other studies have shown that macrophages, after activation by cytokines such as interferon-ɣ (IFN-ɣ), stimulate 1-alpha hydroxylase activity in granulomatous diseases (Seymour and Gagel, 1993). B-cell lymphomas have been shown to overexpress 1-alpha hydroxylase and be associated with hypercalcemia. Activated macrophages within the tumor itself are also thought to be involved in the pathogenesis of lymphoma-associated hypercalcemia (Luceri and Haenel, 2013). However, to date, none of these tumors was reported to be associated with HIV-related IRIS. Multiple cytokines, including IFN-ɣ, interleukin-18 (IL-18), and interferon-inducible protein 10 (IP-10 or CXCL-10), have been found to be helpful as biomarkers for IRIS (Sereti et al., 2010), although the time course of cytokine production as reflected in serum levels after the initiation of ART has not been firmly established. Therefore, we postulate that T-cell derived cytokines may

also play a role in activating lymphoma cells and macrophages leading to 1,25-$(OH)_2$ vitamin D-mediated hypercalcemia in patients with lymphoma in the setting of IRIS. We also note that the patient received fluconazole daily starting on hospital day 3 for *Cryptococcus* prophylaxis. Fluconazole is an inhibitor of 1-alpha-hydroxyalase and has been shown to reduce levels 1,25-$(OH)_2$ vitamin D (Sayers et al., 2015), so it is possible that the elevation in the patient's 1,25-$(OH)_2$ vitamin D level may have been even more pronounced had he not been treated with fluconazole.

We report this case because it dramatically unfolded over just 38 days. The patient initially presented with advanced AIDS along with *hypocalcemia*, likely from severe malnutrition and illness. With the initiation of ART inducing IRIS, his serum calcium normalized as he rapidly developed marked tumor burden from a high-grade lymphoma producing 1,25-$(OH)_2$ vitamin D, leading to *hypercalcemia*. This is just one form of hypercalcemia due to malignancy. He had no bone metastases, and PTHrP and PTH levels were not elevated. Spontaneous tumor lysis then ensued, common in rapidly growing lymphomas like his, and serum calcium levels spontaneously decreased. This fall in serum calcium (counteracting the high 1,25-$(OH)_2$ vitamin D levels) was likely driven by rising serum phosphorus levels characteristic of the tumor lysis syndrome. Unfortunately, due to a tenuous functional status, chemotherapy was not initiated because it was felt that he could not tolerate it.

In conclusion, 1,25-$(OH)_2$ vitamin D-mediated hypercalcemia, driven by an increase in extrarenal 1-alpha hydroxylase expression, is uncommon in patients with newly diagnosed advanced HIV. In our patient, 1,25-$(OH)_2$ vitamin D overproduction and hypercalcemia emerged, likely due to the development of IRIS. IRIS, we speculate, unmasked an underlying high-grade lymphoma as immune function (T-cells and cytokine production) was restored. This case emphasizes the importance of considering IRIS in a patient who has recently initiated ART, because granulomatous infections and lymphomas are capable of causing hypercalcemia, and aggressive lymphomas in the setting of IRIS may progress rapidly (in just days) with ART initiation. This sequence can result in marked effects on serum calcium homeostasis with clinical consequences.

Transparency document

The Transparency document associated with this article can be found, in online version.

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