Hypercalcemia Secondary to Immune Reconstitution Inflammatory Syndrome in an HIV-Infected Individual With Mycobacterium avium Complex

Sanjana S. Awasty 1, Sabih Jafri 1, Saima Manzoor 2, Abid Yaqub 3

1. Division of Internal Medicine, University of Cincinnati Medical Center, Cincinnati, USA 2. Division of Endocrinology, Diabetes and Metabolism, University of Cincinnati Medical Center, Cincinnati, USA 3. Division of Endocrinology, Diabetes and Metabolism, University of Cincinnati, College of Medicine, Cincinnati, USA

Abstract

Immune reconstitution inflammatory syndrome (IRIS) is an uncommon cause of hypercalcemia in HIV-infected patients recently started on highly active antiretroviral therapy (HAART). It is hypothesized that increased granulomatous formation due to IRIS leads to an overproduction of calcitriol. High levels of calcitriol, then, can lead to significant hypercalcemia. We present the case of a 63-year-old male with HIV off HAART presented to the emergency room for confusion, frequent falls, and cough. His CD-4 count was noted to be below 35 cells/µL (255-2,496). Over the course of the hospitalization, the patient was found to have disseminated Mycobacterium avium complex (MAC) infection and was initiated on HAART. Initiation of HAART was followed by an increase in calcium up to 14.1 mg/dL. The hypercalcemia did not respond to either Calcitonin or Pamidronate. Consideration was then given to IRIS in the setting of MAC infection leading to increased granulomatous formation. Calcium levels normalized within three days of therapy after initiation of prednisone for the treatment of IRIS. It is thought that an increase in CD-4 counts leads to the recovery of an immune response. This can lead to granulomatous inflammation. An increase in granuloma formation can cause hypercalcemia due to overproduction of calcitriol via increased 1α-hydroxylase activity from macrophages. Our case report describes IRIS-mediated hypercalcemia in an HIV-infected individual with MAC infection. This unusual cause of severe hypercalcemia should be considered in differential diagnoses for immunocompromised patients in the appropriate setting. Prompt treatment of IRIS with glucocorticoids can lead to the resolution of hypercalcemia.

Introduction

Severe hypercalcemia (>14 mg/dL) typically necessitates investigation for underlying malignancy, though it is important to also complete a thorough evaluation to rule out other causes of hypercalcemia. The commonest cause of hypercalcemia presenting in an outpatient setting is primary hyperparathyroidism whereas malignancy-related hypercalcemia is the most prevalent cause of significant symptomatic hypercalcemia in the hospitalized setting [1]. One unusual etiology of hypercalcemia is immune reconstitution inflammatory syndrome (IRIS). IRIS describes the phenomenon of paradoxical clinical deterioration observed in patients who are started on therapy for systemic disease. It typically occurs in HIV-infected individuals who are started on highly active antiretroviral therapy (HAART) [2] though it has also been seen in patients being treated for Mycobacterium tuberculosis [3]. Interestingly, the syndrome occurs despite expected decreases in HIV viral load and increases in CD4 counts after initiation of therapy. Two types of IRIS have been noted in the literature. "Paradoxical IRIS" refers to the worsening of a pre-existing infection while "unmasking IRIS" describes the initial revelation of a previously unknown pre-existing infection. It typically occurs within 60 days of starting antiretroviral therapy [4]. It has been hypothesized that IRIS-mediated granulomatous formation can cause hypercalcemia due to overproduction of calcitriol via an increase in 1α-hydroxylase activity [5]. Below, we present a case of IRIS-mediated hypercalcemia in the setting of Mycobacterium avium complex (MAC) infection.

Case Presentation

A 63-year-old male with a past medical history significant for dementia and HIV presented to the emergency room with confusion, frequent falls, and productive cough. He was found on the floor by his mother on the day of the presentation. On arrival to the emergency room, he was found to be tachycardic with a heart rate of 109, blood pressure of 133/89, and respiratory rate of 26, saturating 98% on room air. His physical exam was significant for a 5 cm x 5 cm area of ecchymoses over the right parietal scalp and chest wall tenderness to palpation. He was alert and oriented to place, time, and self and was moving all of his extremities

How to cite this article

Awasty S S, Jafri S, Manzoor S, et al. (September 21, 2021) Hypercalcemia Secondary to Immune Reconstitution Inflammatory Syndrome in an HIV-Infected Individual With Mycobacterium avium Complex. Cureus 13(9): e18174. DOI 10.7759/cureus.18174
spontaneously without overt abnormal neurological findings. He stated that he was diagnosed with HIV in 2014. His HIV risk factors included sexual encounters with multiple female and male partners. He took efavirenz-emtricitabine-tenofovir from 2014 to 2015 but then self-discontinued the therapy as he had to travel for work. He was not able to provide additional information about his HIV. He was found to be anemic with a hemoglobin of 8.5 g/dL (13.2-17.1) and had an elevated serum creatinine kinase of 856 µ/L (30-223). During workup, the patient was noted to have a CD-4 count of <35 cells/µL (255-2496), viral load of 658,000 copies/mL (undetectable), and corrected calcium of 11 mg/dL (8.6-10.3).

Infectious disease was consulted for productive cough with abnormal CT imaging findings in the setting of a new diagnosis of AIDS (given CD-4 count <200 cells/µL). Sputum cultures were obtained on day 4 and day 6 of hospitalization which grew Mycobacterium avium. He was started on HAART therapy with bictegravir, emtricitabine, tenofovir, and alafenamide regimen on day 8. He was noted to suddenly increase to 14.1 mg/dL. Further testing revealed a TSH of 1.18 IU/mL (0.45-4.12), PTH 4.0 pg/mL (12-88), and a 25-hydroxy vitamin D level of 115 pg/mL (19.9-79.3). On day 33, he was initiated on prednisone 60 mg to treat IRIS and was noted to have normalized corrected calcium of 8.8 mg/dL by day 36. The prednisone was initiated at 60 mg for five days then tapered to 40 mg for five days, 20 mg for five days, followed by 10 mg for five days. HAART was reinitiated on day 37 after resolution of hypercalcemia and calcium levels remained stable thereafter.

**FIGURE 1: Corrected calcium levels during hospitalization.**

- Day 28 calcitonin given.
- Day 30 pamidronate given.
- Day 31 HAART stopped.
- Day 33 prednisone 60 mg initiated.
- Day 37 HAART reinitiated.

**HAART** - highly active antiretroviral therapy

**Discussion**

Hypercalcemia is a relatively common problem encountered in clinical practice. Our case highlights an unusual cause of hypercalcemia: granuloma-induced hypercalcemia in the setting of IRIS. There are no universally accepted diagnostic criteria for IRIS though it generally includes the presence of a low CD-4 count, initiation of HAART, and presentation of symptoms suggesting an inflammatory state. The exact mechanism of IRIS is unknown though it has been postulated that the increase in CD-4 counts leads to recovery of immune response to specific antigens which may lead to IRIS [2,6]. This, in turn, can lead to granulomatous inflammation [2]. An increase in granuloma formation can cause hypercalcemia due to overproduction of calcitriol via increased 1α-hydroxylase activity from macrophages [5]. This observation has been noted in isolated case reports in HIV-infected individuals with a variety of infectious and noninfectious processes including mycobacterium [5,7-10], cryptococcal [11], and lymphoma [12].
Interestingly, this presentation did not occur until initial treatment with HAART therapy leading to new granulomatous inflammation (Figure 2). The high serum calcitriol level further supported the idea that hypercalcemia was related to a granulomatous process due to increased conversion of 25-hydroxy Vitamin D to the active form of 1, 25-dihydroxy vitamin D [13]. Treatment of IRIS is challenging as there is sparse evidence-based data on effective treatments. Meintjes et al. demonstrated, in a randomized control trial, that a four-week trial of prednisone (1.5 mg/kg/day for two weeks then 0.75 mg/kg/day for two weeks) reduced the need for hospitalization, decreased serum inflammatory marker levels, and improved quality of life [14]. Unfortunately, to the best of our knowledge, there are no established guidelines on the management of hypercalcemia in the setting of IRIS due to the rare nature of the condition, difficulty in diagnosis of IRIS, and lack of published data regarding effective treatment options. Some case reports, though, have suggested that initiation of high-dose prednisone along with treatment for an underlying infection as well as continuing antiretroviral therapy are sufficient to manage severe hypercalcemia [15]. This management regimen is further supported by this case report as there was a noted plateauing of the serum calcium levels after initiation of prednisone in the setting of treatment for MAC. Furthermore, calcium levels remained stable on day 53, 23 days after pamidronate was given and outside its’ duration of action lending itself to the notion that treatment of IRIS was essential in the treatment of this patient’s hypercalcemia.

There is no consensus about the optimal timing of initiating antiretroviral therapy after treatment of an opportunistic infection (OI) though most guidelines recommend beginning therapy within two weeks of treatment for an OI [16].

Conclusions

IRIS-mediated hypercalcemia is a rare adverse event that is observed after starting antiretroviral therapy. Management includes the initiation of high-dose prednisone and treatment of any known opportunistic infections. Given the variety of infections patients with untreated HIV may have that also present with granulomas such as histoplasmosis, candidiasis, Pneumocystis carinii pneumonia, etc., consideration should be given to IRIS-mediated hypercalcemia in those with the recent initiation of HAART therapy.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

Acknowledgements

Dr. Sanjana Awasty and Dr. Sabih Jafri are co-first authors of this report.

References
1. Shepard MM, Smith JW 3rd: Hypercalcemia. Am J Med Sci. 2007, 334:381-5. 10.1097/MAJ.0b013e31812f4947
2. Shelburne SA 3rd, Hamill RJ, Rodriguez-Barradas MC, et al.: Immune reconstitution inflammatory syndrome: emergence of a unique syndrome during highly active antiretroviral therapy. Medicine (Baltimore). 2002, 81:213-27. 10.1097/00005559-200205000-00005
3. Cheng VC, Ho PL, Lee RA, et al.: Clinical spectrum of paradoxical deterioration during antituberculosis therapy in non–HIV-infected patients. Eur J Clin Microbiol Infect Dis. 2002, 21:803-9. 10.1007/s10096-002-0821-2
4. Shelburne SA, Vinnegarula F, Darcourt J, Graviss EA, Giordano TP, White AC Jr, Hamill RJ: Incidence and risk factors for immune reconstitution inflammatory syndrome during highly active antiretroviral therapy. AIDS. 2005, 19:599-406. 10.1097/01.aids.0000161769.06158.8a
5. Monkawa T, Yoshida T, Hayaishi M, Saruta T: Identification of 25-hydroxyvitamin D3 1alpha-hydroxylase gene expression in macrophages. Kidney Int. 2000, 58:559-68. 10.1046/j.1523-1755.2000.00202.x
6. Murdoch DM, Venter WD, Van Rie A, Feldman C: Immune reconstitution inflammatory syndrome (IRIS): review of common infectious manifestations and treatment options. AIDS Res Ther. 2007, 4:9. 10.1186/1742-6405-4-9
7. Ayoudi, H, Alkalali E: Mycobacterium avium-intracellulare and the unpredictable course of hypercalcemia in an AIDS patient. J Hospital Med. 2017, 12:Abstract 408.
8. Curtiss JS II: 36 year old female w/ hypercalcemia secondary to immune reconstitution inflammatory syndrome. Int J STD AIDS. 2006, 17:349-50. 10.1258/095646206776790169
9. Ferrand RA, Elgalib A, Newsholme W, Childerhouse A, Edwards SG, Miller RF: Hypercalcaemia complicating immune reconstitution in an HIV-infected patient with disseminated tuberculosis. Int J STD AIDS. 2006, 17:349-50. 10.1258/095646206776790169
10. Tsao YT, Wu YC, Yang CS, Lin YT: Immune reconstitution associated hypercalcemia. Am J Emerg Med. 2009, 27:e29.e1-3. 10.1016/j.ajem.2008.08.052
11. Bansal N, Shah R, Patel A, Vaidya G, Pantangi P, Mansochna D: Hypercalcemia as a primary manifestation of cryptococcal immune reconstitution syndrome—a rare presentation. Am J Emerg Med. 2015, 33:598.e3-4. 10.1016/j.ajem.2014.08.065
12. Kim SJ, Peluso MJ, Wang Y, Bikel D, Shohack D, Kim S: Rapid onset of hypercalcemia from high-grade lymphoma in the setting of HIV-related immune reconstitution inflammatory syndrome. Bone Rep. 2019, 10:100194. 10.1016/j.bonr.2018.100194
13. Lemann J Jr, Gray RW: Calcitriol, calcium, and granulomatous disease. N Engl J Med. 1984, 311:1115-7. 10.1056/NEJM1984102531111710
14. Meintjes G, Wilkinson RJ, Morroni C, et al.: Randomized placebo-controlled trial of prednison for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. AIDS. 2010, 24:2381-90. 10.1097/QAD.0b013e32833d868
15. Tsao YT, Wu CC, Chu P: Immune reconstitution syndrome-induced hypercalcemic crisis. Am J Emerg Med. 2011, 29:244.e3-6. 10.1016/j.ajem.2010.05.013
16. Kaplan JE, Benson C, Holmes KK, Brooks JT, Pau A, Masur H: Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR Recomm Rep. 2009, 58:1-207; quiz CE1-4.