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Case report

Mycobacterium avium-intracellulare and the unpredictable course of hypercalcemia in an AIDS patient



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ABSTRACT

A 37-year-old man with AIDS presented with altered mental status four weeks after stopping his medications for *Mycobacterium avium-intracellulare* (MAI). He had low CD4 cell count and severe hypercalcemia. Bone marrow biopsy revealed bone marrow infiltration by granulomas positive for acid-fast bacilli and cultures grew MAI. His hypercalcemia continued to worsen with the initiation of MAI therapy but we were able to treat it successfully with pamidronate and calcitonin.

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Introduction

Hypercalcemia above 14 mg/dL is often attributed to malignancy, but patients with HIV warrant further investigation into opportunistic infections such as *Mycobacterium avium-intracellulare* (MAI). Although previous reports discussed the association between MAI and hypercalcemia, the onset and clinical course of hypercalcemia is not known. We present a case of hypercalcemia with MAI that worsened with the initiation of anti-mycobacterial therapy and a review of the literature of the onset of hypercalcemia in relation with MAI diagnosis and explore potential triggers.

Case presentation

A 37-year-old man with AIDS on highly active antiretroviral therapy (HAART) and chronic therapy for *Mycobacterium avium-intracellulare* (MAI) presented with altered mental status four weeks after stopping his medications. His family reported progressive confusion and weight loss. He did not have any recent history of sick contacts, travel, animal exposure, nor illicit drug use. On physical examination, his temperature was 38.1 °C, blood pressure 130/50, heart rate 118, respiratory rate 16 with O₂ saturation 95% on room temperature. He was somnolent and cachectic.

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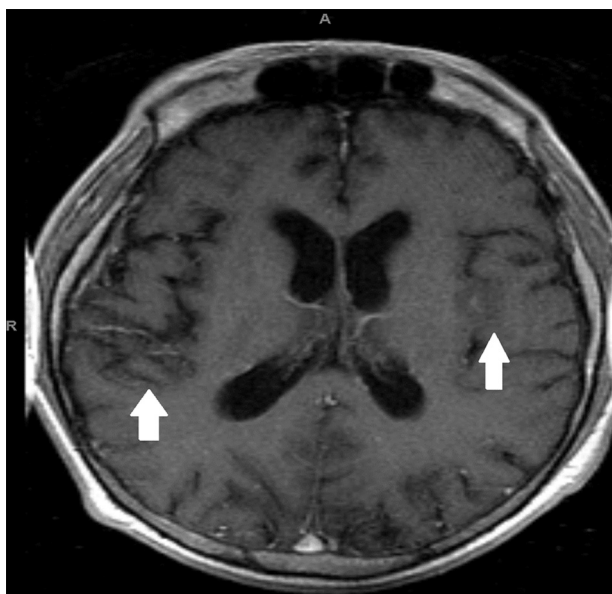


Fig. 1 – Magnetic resonance imaging of the brain showing areas of abnormal parenchymal signal intensity (arrows) involving cortex and subcortical white matter within the frontal lobes, right temporal lobe, and left insula.

Laboratory work-up showed normocytic anemia with a hemoglobin of 8 g/dL, leukopenia 0.9/ μ L, thrombocytopenia 60/ μ L, CD4 count 7/ mm^3 , creatinine 1.4 mg/dL, corrected calcium 12 mg/dL (ref 8.4–10.4 mg/dL), ionized calcium 1.6 mmol/L (ref 1.15–1.27 mmol/L), phosphorus 2 mg/dL (ref 2.3–5.6), and albumin 1.8 g/dL (ref 3.5–5 d/dL). His 25-hydroxycalciferol level was low 9 ng/ml (ref 30–100), PTH was suppressed 6 pg/mL (ref 11–80 pg/mL) and PTH-related peptide was undetectable.

Magnetic resonance imaging (MRI) of the brain showed scattered areas of abnormal parenchymal signal intensity likely from tuberculous meningoencephalitis (Fig. 1). Computed tomography (CT) of the chest, abdomen and pelvis revealed necrotic mesenteric lymph nodes and splenomegaly.

Serum protein electrophoresis and skeletal survey were negative. Bone marrow biopsy revealed bone marrow

infiltration by granulomas positive for acid-fast bacilli and cultures grew MAI. His hypercalcemia was treated with intravenous fluids and he was started on clarithromycin, rifampin and ethambutol for MAI. His serum calcium trended up from 12 mg/dL on admission to 14 mg/dL by hospital day six so he was started on calcitonin and pamidronate with normalization of serum calcium and improvement in the patient's mental status within 24 h.

The patient's calcium levels remained within normal range but his clinical condition deteriorated as he developed severe sepsis, disseminated intravascular coagulation (DIC), and respiratory failure requiring endotracheal intubation and mechanical ventilation secondary to hospital-acquired pneumonia. A follow-up brain CT showed worsening in the size of the lesions secondary to hemorrhage in the setting of DIC. After extubation, he was found to have major cognitive deficits with being oriented only to self. At the time of discharge, his hypercalcemia, sepsis, and DIC have all resolved, however, his cognitive impairment persisted.

Discussion

Between 1981 and 1987, 5.5% of AIDS cases reported to the Centers for Disease Control (CDC) had non-tuberculous mycobacterial infection, with MAI being the culprit in 96% of cases.¹ The incidence of opportunistic infections decreased with the advent of HAART and a more recent study from 1994 to 2007 suggested that the rate of *Mycobacterium avium* complex infection is 2.5 per 1000 person-years in individuals with AIDS.² The mechanism of hypercalcemia in granulomatous disease is thought to be related to vitamin D dysregulation but this does not always correlate with vitamin D metabolite levels.³

A review of the literature yielded only eight cases of MAI-associated hypercalcemia (Table 1). Three of these cases presented with hypercalcemia at the time of diagnosis of MAI³⁻⁵; Tsao et al. described hypercalcemia presenting as part of the spectrum of immune reconstitution inflammatory syndrome (IRIS) against MAI.⁶ Four reports described hypercalcemia in patients who were undergoing treatment for MAI, soon after starting or changing antimicrobial therapy.^{7,8} One patient was diagnosed three weeks after initiating treatment

Table 1 – Previous reports of MAI-associated hypercalcemia.

Study	Timeframe of MAI diagnosis in relation to hypercalcemia	Potential hypercalcemia trigger	Hypercalcemia treatment
Tsao et al. ⁶	At presentation	Starting HAART with subsequent development of IRIS	Steroids
Shrayyef et al. ³	At presentation	Initiation of vitamin D and calcium supplementation three weeks prior	Unknown
Choudhary et al. ⁷	Six months prior	Changes in MAI therapy	Steroids
Playford et al. ⁸			
Case 1	Four months prior	Changes in MAI therapy	Bisphosphonate
Case 2	Four weeks prior	Initiating MAI therapy	Bisphosphonate
Aly et al. ⁴	At presentation	Six months after starting HAART	Bisphosphonate
Newell et al. ¹²	Six months prior	Unknown	Bisphosphonate
Delahunt et al. ⁵	At presentation	Unknown	Bisphosphonate and steroids

for vitamin D deficiency.³ Our patient presented with hypercalcemia at the time of diagnosis, which worsened within days of restarting MAI therapy. In all these cases, no association between the development of hypercalcemia and organ involvement or choice of anti-MAI therapy was observed.

The suggested treatment of hypercalcemia in granulomatous disease is steroids which are thought to downregulate calcitriol synthesis by macrophages.⁹ Given our concern for lymphoma as part of our differential diagnosis, we elected not to use steroids as they cause histopathological alterations on biopsy and delay in making the diagnosis.¹⁰ Our patient was treated with calcitonin and pamidronate. Bisphosphonates can be safely used for the treatment of osteoporosis in HIV patients,¹¹ and Shrayef et al. previously used pamidronate successfully for the treatment of hypercalcemia with MAI.³

It is unknown if there is a genetic predisposition for some individuals with AIDS who are infected with MAI to develop hypercalcemia. Our review of the literature suggests that certain triggers may be implicated such as immune reconstitution after starting HAART, improved host defence mechanism after initiating or incurring change in anti-MAI therapy or dysregulated response to vitamin D treatment.

Conclusions

While hypercalcemia is a known complication of granulomatous disease, clinicians should be aware of the variability in presentation of hypercalcemia with MAI, whether as the first manifestation or a late presenter in the disease course. As we showed in this case, hypercalcemia may worsen within days of initiating anti-mycobacterial therapy. We suggest careful monitoring of serum calcium levels upon diagnosis of MAI infection and after initiation of mycobacterial therapy or vitamin D supplementation. Pamidronate and calcitonin are acceptable treatment alternatives to steroids for hypercalcemia treatment.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Horsburgh CR Jr, Selik RM. The epidemiology of disseminated nontuberculous mycobacterial infection in the acquired immunodeficiency syndrome (AIDS). *Am Rev Respir Dis.* 1989;139:4-7.
2. Buchacz K, Baker RK, Palella FJ Jr, et al. AIDS-defining opportunistic illnesses in US patients, 1994-2007: a cohort study. *AIDS.* 2010;24:1549-59.
3. Shrayyef MZ, DePapp Z, Cave WT, Wittlin SD. Hypercalcemia in two patients with sarcoidosis and *Mycobacterium avium* intracellulare not mediated by elevated vitamin D metabolites. *Am J Med Sci.* 2011;342:336-40.
4. Aly ES, Baig M, Khanna D, Baumann MA. Hypercalcaemia: a clue to *Mycobacterium avium* intracellulare infection in a patient with AIDS. *Int J Clin Pract.* 1999;53:227-8.
5. Delahunty JW, Romeril KE. Hypercalcemia in a patient with the acquired immunodeficiency syndrome and *Mycobacterium avium* intracellulare infection. *J Acquir Immune Defic Syndr.* 1994;7:871-2.
6. Tsao YT, Lee SW, Hsu JC, Ho FM, Wang WJ. Surviving a crisis of HIV-associated immune reconstitution syndrome. *Am J Emerg Med.* 2012;30:1661, e5-1661.e7.
7. Choudhary M, Rose F. Posterior reversible encephalopathic syndrome due to severe hypercalcemia in AIDS. *Scand J Infect Dis.* 2005;37(6-7):524-6.
8. Playford EG, Bansal AS, Looke DF, Whitby M, Hogan PG. Hypercalcaemia and elevated 1,25(OH)(2)D(3) levels associated with disseminated *Mycobacterium avium* infection in AIDS. *J Infect.* 2001;42:157-8.
9. Sandler LM, Winearls CG, Fraher LJ, Clemens TL, Smith R, O'Riordan JL. Studies of the hypercalcaemia of sarcoidosis: effect of steroids and exogenous vitamin D3 on the circulating concentrations of 1,25-dihydroxy vitamin D3. *Q J Med.* 1984;53(Spring):165-80.
10. Kan E, Levi I, Benharroch D. Alterations in the primary diagnosis of lymphomas pretreated with corticosteroid agents. *Leuk Lymphoma.* 2011;52:425-8.
11. Vescini F, Grimaldi F. Bisphosphonates in the treatment of HIV-related osteoporosis. *Endocrine.* 2015;48:358-9.
12. Newell A, Nelson MR. Hypercalcaemia in a patient with AIDS and *Mycobacterium avium* intracellulare infection. *Int J STD AIDS.* 1997;8:405.