CASE REPORT

All-Trans-Retinoic-Acid Unmasking Hypercalcemia of Hyperparathyroidism

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Abstract We present a patient of acute promyelocytic leukaemia managed with all-trans-retinoic-acid and arsenic trioxide who developed hypercalcemia with target organ damage. The patient also was simultaneously discovered to be symptomatic from hyperparathyroidism, which was unmasked after ATRA administration. Patient was successfully managed without any interruption of ATRA therapy and parathyroidectomy. We discuss the mechanisms of ATRA in causing hypercalcemia and its possible role in index case in unmasking hyperparathyroidism. Present case refutes Occam's razor and emphasise that known adverse effects shouldn't withhold clinicians from working up for other common causes for a given condition.

Introduction

Acute promyelocytic leukaemia (APML) is a hematological malignancy, a subtype of acute myeloid leukaemia (AML-M3) presenting with coagulopathy. It has the best prognosis amongst all the acute myeloid leukemias. The introduction of all-trans-retinoic-acid (ATRA) in 1988 changed the course of the disease progression and the outlook of the clinicians towards this leukemia with hardly any mortality secondary to the disease. Despite such good clinical outcomes, side effects secondary to ATRA are not infrequent. Common adverse reactions include differentiation syndrome, headache, bone pains and skin dryness,

whereas extremely rare adverse reactions include pseudo-tumor cerebri, hypercalcemia and erythema nodosum.

We present a case that highlights the rare but important side-effect i.e., ATRA induced hypercalcemia. The patient also was simultaneously discovered to be symptomatic from hyperparathyroidism, which was unmasked after ATRA administration. We underscore the fact that despite ATRA being an established cause of hypercalcemia, patients on ATRA should be evaluated for other routine causes of hypercalcemia. We thus conclude that all patients don't fit into Occam's razor and may follow the Hickam's dictum.

Case Report

A 35 year-old female presented to our centre with complaints of gum bleeds and fever of 7 days duration. She had no history of similar complaints in the past. There was no history of constipation, fatigue, depression, polyuria, polydipsia, dehydration, anorexia, nausea, muscle weakness, and changes in sensorium in the past. She had no history of exposure to chemicals or alternative forms of medication. She was married for 11 years with two children, last child birth 5 years back. She belonged to lower socioeconomic strata. On presentation to our hospital, she was found to have pallor, active oozing from gums and ecchymotic patches over both upper limbs. Systemic examination was unremarkable.

Investigations

On evaluation, she was found to have pancytopenia (Hb-6.3gm/dL, platelet count-17000/μL, total leukocyte count-1300/μL, absolute neutrophil count-550/μL and 66 %

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promyelocytes). Her coagulogram, renal and liver function tests were normal at presentation. At presentation her serum calcium (corrected) was 8.3 mg/dL, phosphate 3.1 mg/dL and alkaline phosphate of 120U/L. Baseline chest X-ray and ultrasound (USG) abdomen were normal. With a clinical possibility of acute promyelocytic leukemia (APML), bone marrow biopsy was done which showed hypercellular marrow spaces with 80 % promyelocytes. Cytochemistry suggested that blasts were MPO positive. RT-PCR study for PML-RAR α transcripts was positive, which confirmed the final diagnosis of APML (intermediate risk).

Treatment Given

She was started on arsenic trioxide (0.15 mg/kg OD) and all-trans-retinoic-acid (ATRA- 45 mg/m² in divided doses) with steroid prophylaxis (Prednisolone @ 1 mg/kg OD). Patient had no evidence of differentiation syndrome during her course of chemotherapy.

Complications During Therapy

Starting from day 5 of ATRA therapy, her electrolyte profile suggested an increasing trend of calcium level (Fig. 1). A peak calcium level of 14.0 mg/dl was on day 7 of starting ATRA. However, the patient was clinically asymptomatic. On day 15 of ATRA, the patient complained of severe, colicky left sided flank pain requiring parenteral analgesic for symptomatic relief. USG showed left lower ureteric stone (1.3 cm) with associated hydroureteronephrosis. The patient also started having high grade remittent fever with microbiological evidence of urosepsis (*Klebsiella sps*) requiring parenteral antibiotics. Percutaneous nephrostomy was done

to decompress the pelvi-calyceal system. With these measures her fever subsided.

For definitive care of ureteric stone, IVP was performed for exact delineation of pelvicalyceal system. It showed non opacified left kidney with faint opacification of upper calyces. In order to evaluate the functional capacity of left kidney a 99mTc renal scan was performed. Results of study showed moderately impaired perfusion and cortical tracer uptake. Pooling of the tracer was noted in the upper calyx and PCS during the initial half of the dynamic study with slow clearance of the tracer through the prominent left ureter by the end of the dynamic study. Cortical tracer retention was noted in the pre-void and post-void images which cleared adequately by 3 h of the study. On the other hand, right kidney showed preserved perfusion and cortical tracer uptake with adequate clearance of the tracer from the end of the dynamic study.

Search for the Cause for Hypercalcemia

Workup for hypercalcemia was done. X-ray of the hand and skull— showed no evidence of long term side effects of hyperparathyroidism in the form of resorption of digits or punched out lesions (Fig. 2a, b). USG neck showed 1 × 1.3 cm of hypoechoic lesion located behind the mid-pole of left lobe of the thyroid. For better localization, 99mTc Sestamibi parathyroid scan was done. Static image at 10 min and 2 h were acquired after intravenous injection of Tc99 m Sestamibi. Early image at 10 min showed increased tracer uptake in the left lobe of thyroid as compared to the right lobe. SPECT/CT localized the increased tracer uptake to well-defined, hypodense lesion (1.7 × 1.1 cm), in the trachea-oesophageal groove and posterior to

Fig. 1 Graph predicting calcium levels during the course of the illness in relation to the ATRA therapy and parathyroidectomy

Fig. 2 **a** Normal X-ray of the digits of the hand, **b** Normal X-ray skull with no features of hyperparathyroidism

the midpole of left lobe of the thyroid with extension towards inferiorly (Fig. 3a, b). Delayed image at 2 h were also taken which showed washout of tracer from the right lobe of the thyroid. Tracer retention was noted in a region in the left lobe of the thyroid. Her serum iPTH and 25-OH vitamin D level were 271.2 pg/mL (normal: 15–65 pg/mL) and 14.70 ng/mL (normal: 11.1–42.9 ng/mL).

Based on the history, clinical examination, and baseline radiology and baseline/serial electrolyte measurements it was inferred that the occurrence of hypercalcemia temporally correlated to unmasking of hyperparathyroidism secondary to ATRA therapy. Other possibilities include hypercalcemia in malignancy, interaction of ATRA with antifungal therapy and co-incidental hyperparathyroidism independent of basic disease course.

ATRA and ATO were continued for her basic disease and she was managed with adequate hydration with oral and intravenous fluids (3 liters/m²/day) and diuretics. After final confirmation of primary hyperparathyroidism, the patient was taken up for left inferior parathyroidectomy. Patient was taken up for percutaneous nephrostomy guided stone removal.

Post-Operative Follow Up

She was monitored for any complications of parathyroidectomy. Starting 12 h postoperatively laboratory features suggested hungry bone syndrome with serum calcium-7.80 mg/dL (8.8–10.2 mg/dL), ionized calcium-0.281Meq/L (0.8–1.2Meq/L), and phosphate-4.12 mg/dL (2.5–4.5 mg/dL). She was treated with intravenous and oral calcium supplementation accordingly. Postoperative serum

iPTH level was normal-37.23 pg/mL (11.1–42.9 ng/mL). Gradually her calcium level normalised and the patient was henceforth continued with oral calcium supplementation to maintain her normal serum calcium levels.

In total, the patient received 40 days of ATO/ATRA. Repeat bone marrow performed showed 1 % blast and 2 % promyelocytes, confirming the disease in remission. Repeat PML-RAR α was negative.

Discussion

ATRA is a physiological metabolite of vitamin A. ATRA's pharmacological effect is through terminal differentiation and apoptosis of leukemic cells. The role of this drug in APL was first described in 1988 [1]. Common reported side effects with ATRA treatment are headache, hypertriglyceridemia, bone pain, liver dysfunction and skin dryness [1]. Apart from these common adverse effects, rarely, ATRA associated hypercalcemia has been reported. Most of the cases have been reported from Asian populace, particularly Japanese ethnicity suggesting a genetic predisposition among this population [2–4]. Multiple mechanisms of hypercalcemia secondary to ATRA therapy have been proposed such as:

1. Direct effect of ATRA leading to enhanced osteoclastic activity leading to bone mineral resorption just like PTH [3].
2. Cytokines like IL-6 may have a positive effect on bone resorption and hypercalcemia. Niesvizky et al. did in vitro study of the effect of ATRA on myeloma cell growth. They found that ATRA down regulated IL-6 receptors,

Fig. 3 Tc99 m Sestamibi showing increased uptake in the left lower inferior parathyroid

thereby increasing the serum IL-6 levels, which positively correlated with serum calcium levels [5].

3. In vitro, as well as in vivo study of bovine parathyroid tissue and healthy individuals respectively by Chertow et al. suggested that vitamin A increases serum parathyroid hormone level and subsequent serum calcium levels via stimulation of lysosomal proteolytic function [6].
4. ATRA has been found to cause hypercalcemia via increasing PTH-rP levels [7].
5. ATRA metabolism involves liver cytochrome P450 subtypes 2C9 and 3A4. Many drugs, especially anti-fungals are inhibitors of these enzymes causing increased plasma concentration of ATRA thereby potentiating the effect of ATRA on calcium metabolism [8, 9].

Regarding the onset of day of hypercalcemia following commencement of ATRA therapy, there have been varied reports ranging 6–63 days [9]. In our case, calcium levels started to rise by day 5 of ATRA therapy.

Our patient did not receive anti-fungal hence likelihood of interference with ATRA metabolism is remote. The other differential in this case was hypercalcemia of malignancy; but hypercalcemia is commonly seen in relation to solid malignancies. Haematological malignancies usually are not so commonly associated with hypercalcemia except in those cases of high tumour overload with high proliferative index. English literature review search suggests that hypercalcemia in association with APML can rarely be seen only in context of ATRA.

Unlike the previously reported cases [1, 3, 7, 9], index case is unique to have primary hyperparathyroidism associated with high iPTH levels. Normal radiology of skull and digits rules out the presence of clinically significant hyperparathyroidism for a long term preceding the diagnosis of APML. ATRA administration in the index case tipped off calcium homeostasis and unmasked the parathyroid adenoma. Amongst various cases in the past, dose adjustment or intermittent withdrawal of ATRA was done to manage hypercalcemia [2, 10]. As our patient's disease was not in remission and we found a treatable cause of hypercalcemia, we decided neither to discontinue nor reduce the dose of ATRA during induction chemotherapy. We initially managed hypercalcemia conservatively and subsequently with surgical parathyroidectomy leading to normalization of calcium levels.

Points to Remember

1. ATRA related hypercalcemia is a rare but important side-effect.
2. ATRA can unmask the dormant hyperparathyroidism.

3. Known and established causes of hypercalcemia like parathyroid adenoma should always be ruled out before labelling any case of hypercalcemia as secondary to drug.

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Compliance with Ethical Standards

Conflict of interest None of the authors have any conflict of interest to mention.

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Informed consent Informed consent was obtained from the participant included in the study.

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