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Case Report

A Rare Complication in a Patient with Acute Promyelocytic Leukemia; ATRA and Posaconazole Associated Hypercalcemia

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ABSTRACT

All-trans retinoic acid (ATRA), a derivative of vitamin A, has dramatically altered the treatment landscape for acute promyelocytic leukemia (APL). APL is characterized by the abnormal maturation of myeloid cells, which become arrested at the promyelocyte stage. ATRA effectively induces these cells to differentiate and undergo apoptosis. While generally well-tolerated, ATRA has been associated with rare adverse effects, including hypercalcemia. This case report underscores the importance of vigilant monitoring for ATRA-related side effects, especially when combined with medications which inhibit cytochrome P450 enzymes. Antifungal prophylaxis is common during leukemia treatment. Here, we present a rare instance of hypercalcemia in a pediatric patient attributed to the concurrent use of posaconazole and ATRA. A 15-year-old girl presented with widespread bruising, abnormal uterine bleeding, and pancytopenia. Subsequent investigations led to an APL diagnosis. Classified as standard-risk APL, she received chemotherapy according to the acute myelogenous leukemia-Berlin-Frankfurt-Münster 2004 protocol. After an ATRA course was started in the third month of maintenance treatment, she applied to the hospital with constitutional symptoms of weakness and fatigue on the third day of treatment. In the biochemical tests of the patient, serum Ca concentration was determined to be 16.5 mg/dL. Parathormone was 64.3 pg/mL and the 25-OH D vitamin level was 22 ng/mL and so were within the normal limits. Complete blood count was within the normal range. Although hypercalcemia is a side effect seen in the combined use of ATRA and azole antifungals, to the best of our knowledge, this is the first report in the literature that it was observed in the pediatric age group due to the simultaneous use of posaconazole and ATRA.

Keywords: All-trans retinoic acid (ATRA), posaconazole, hypercalcemia

Introduction

All-trans retinoic acid (ATRA), a derivative of vitamin A, has dramatically altered the treatment landscape for acute promyelocytic leukemia (APL) (1). APL is characterized by the abnormal maturation of myeloid cells, which become arrested at the promyelocyte stage. ATRA effectively induces these cells to differentiate and undergo apoptosis (2). While generally well-tolerated, ATRA has been associated with rare adverse effects, including hypercalcemia (3). The widespread use of antifungal agents in leukemia treatment often leads to a higher incidence of antifungal-related side effects in this patient population.

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Case Presentation

A 15-year-old girl was diagnosed with APL following investigations which revealed pancytopenia after she presented with symptoms of widespread bruising and abnormal uterine bleeding. Her laboratory tests revealed the following; hemoglobin was 5.5 gr/dL, leukocyte was 1,140/mm^3, thrombocyte was 8,000/mm^3, whereas the bone marrow aspirate showed increased numbers of leukemic promyelocytes (90%) and coagulation tests were consistent with pre-DIC condition. Serum calcium (Ca) concentrations were 9 mg/dL and phosphorus was 3.2 mg/dL. Serum electrolytes and renal function tests were within the normal limits. The bone marrow was hypercellular with 90% leukemic promyelocytes. A chromosome analysis showed 46 XX with translocation (15q+; 17q-) karyotype.

Our patient was considered as being in a standard risk group for APL and she was given acute myelogenous leukemia-Berlin-Frankfurt-Münster 2004 protocol chemotherapy. In this protocol, induction, consolidation, intensification and maintenance chemotherapy courses were applied to the patient sequentially. This protocol includes five types of antineoplastic and antimetabolic drugs (cytarabine, idarubicin, etoposide phosphate, mitoxantrone and thioguanine). ATRA is administered concurrently with cycles of 25 mg/m^2/day in 2 divided doses for 15 days with each 4-week cycle of chemotherapy. ATRA courses were started for the patient, as per the protocol recommendation.

Posaconazole treatment was arranged as 300 milligrams/day prophylaxis, as recommended by the department of pediatric infectious diseases.

Maintenance chemotherapy was planned to be given as 6-thioguanine 40 mg/m^2/day PO and cytarabine 40 mg/m^2 subcutaneously every four weeks for four consecutive days for one year. During maintenance treatment, ATRA was planned to be given 25 mg/m^2/day for fourteen days every three months, starting from the third month.

After the ATRA course was started in the third month of maintenance treatment, she was admitted to the hospital with constitutional symptoms of weakness and fatigue on the third day of treatment. In the biochemical tests of the patient, the serum Ca concentration was 16.5 mg/dL, albumin was 5.1 g/dL, creatinine was 0.9 mg/dL and uric acid was 7.1 mg/dL. Parathormone was found to be 64.3 pg/mL and the 25-OH D vitamin level was found to be 22 ng/mL and so they were within the normal limits. The complete blood count was within the normal range. She was also not using any other medications.

Intravenous hydration and furosemide were started simultaneously. Posaconazole treatment was stopped. After 8 hours, the serum Ca level was measured as 16.2 mg/dL, and corticosteroid was added to the treatment at two doses of 10 mg/m^2/day. After steroid treatment was given in 2 doses with an interval of 12 hours, the serum Ca level was measured as 15 mg/dL. Since the patient's complaints of weakness and fatigue persisted and a significant decrease in her Ca level could not be achieved, 1 mg/kg bisphosphonate (pamidronate) treatment was started. After the first dose of pamidronate treatment, the second dose of pamidronate treatment was given the next day as the control Ca was high at 14 mg/dL. After the second dose, control Ca was measured as being 8 mg/dL. 48 hours after hypercalcemia was detected, both laboratory parameters and the patient's complaints completely resolved. ATRA treatment for 2 weeks was given as planned. Posaconazole was discontinued during subsequent ATRA treatments and hypercalcemia did not recur. Consent was obtained from the patient for publication.

Discussion

ATRA is a cornerstone of APL treatment. Its metabolism, primarily mediated by the cytochrome P450 enzymes CYP2C9 and CYP3A4, can be significantly impacted by azole antifungals. Given their potent inhibitory effects on the cytochrome P450 system, triazole antifungals are commonly used prophylactically in APL patients in order to prevent fungal infections (4).

Invasive aspergillosis is the most common invasive fungal infection among patients with low white blood cell counts. Despite routine antifungal prevention for high-risk hematological cancer patients, breakthrough fungal infections can still occur. Posaconazole has emerged as a valuable option for preventing fungal infections in these vulnerable individuals (5). Prophylaxis with posaconazole was started for our patient, who was at risk for IFI during the period of severe and long-lasting neutropenia.

Although hypercalcemia is a side effect seen in the combined use of ATRA and azole antifungals, to the best of our knowledge, this is the first report in the literature in which it was observed in the pediatric age group due to the simultaneous use of posaconazole and ATRA.

This case highlights the importance of monitoring ATRA's side effects when it is used in combination with drugs inhibiting the cytochrome P450 enzymes.

The exact cause of ATRA-induced hypercalcemia remains uncertain; it is unclear if the parent drug or a metabolite is responsible. Consequently, monitoring ATRA levels might not be helpful in preventing this complication. The proposed mechanisms for ATRA-related hypercalcemia include enhanced bone breakdown by osteoclasts, elevated interleukin-6 stimulating bone resorption, and increased parathyroid hormone-related protein (6-9). Nagasawa and Okawa (3) suggested that ATRA might cause hypercalcemia by increasing PTH-related protein levels.

Sakamoto et al. (10) observed hypercalcemia not only in leukemia patients during initial ATRA treatment, but also in those who had achieved complete remission and were continuing ATRA therapy. This suggests that a genetic predisposition affecting retinoic acid metabolism or its hormone-like actions might be prevalent in the Japanese population (10).

The first treatment of hypercalcemia is to increase the urinary excretion of calcium hydration, via loop diuretics such as furosemide. If there is hypercalcemia due to excess vitamin D, glucocorticoid is effective. Calcitonin reduces osteoclastic resorption in bones, but this effect is short term and transient. Nitrogen-containing bisphosphonates, pamidronate and zoledronic acid, induce osteoclast apoptosis. These are potent inhibitors of bone resorption. Bisphosphonates can rapidly lower serum calcium levels in patients with hypercalcemia from various causes. Its effects last for weeks (11).

Here, a pediatric APL patient with hypercalcemia secondary to ATRA treatment was successfully treated with bisphosphonate. Cordoba et al. (9) found that bisphosphonates such as zoledronic acid can effectively treat hypercalcemia and may be used preventively during subsequent ATRA treatments in order to avoid this complication. Sakamoto et al. (10) reported the successful use of bisphosphonate (pamidronate) in the treatment of hypercalcemia due to ATRA use in an 11-year-old patient diagnosed with APL.

In our patient, we first discontinued posaconazole and then added bisphosphonate (pamidronate) when she had no benefit from the supportive treatment (hydration, forced diuresis) and corticosteroid. We continued ATRA treatment in our patient. No definitive approach has been found in the literature for this side effect, which is not common in the pediatric age group.

Although it is clear that the patients' use of azole group antifungals with ATRA treatment triggers hypercalcemia, there are cases where only ATRA use also causes hypercalcemia (10).

Since there was no clear approach on this issue, we did not discontinue ATRA treatment. During our patient's ATRA cycles, we discontinued azole antifungal prophylaxis and performed close biochemical monitoring. No recurrence of hypercalcemia was observed.

We present this case because it is rare in the pediatric age group, has a variety of approaches, and, to the best of our knowledge, is the first report of hypercalcemia secondary to posaconazole and ATRA treatment in a pediatric APL patient.

Ethics

Informed Consent: Consent was obtained from the patient for publication.

Authorship Contributions

Surgical and Medical Practices: Y.Y., M.D., Concept: Y.Y., Design: Y.Y., A.T.Y., Data Collection and/or Processing: Y.Y., A.T.Y., H.G., Analysis and/or Interpretation: Y.Y., H.G., Literature Search: Y.Y., M.D., Writing: Y.Y.

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References

1. Huang ME, Ye YC, Chen SR, et al. Use of all-trans retinoic acid in the treatment of acute promyelocytic leukemia. Blood. 1988; 72:567-72.
2. Sato A, Imaizumi M, Saito T, et al. Detection of apoptosis in acute promyelocytic leukemia cells in vivo during differentiation-induction with all-trans retinoic acid in combination with chemotherapy. Leuk Res. 1999; 23:827-32.
3. Nagasawa M, Okawa H. All-trans retinoic acid induced hypercalcemia in a patient with acute promyelocytic leukemia: its relation to increased PTH-rP. Int J Hematol. 1994; 59:143-4.
4. Marill J, Cresteil T, Lanotte M, Chabot GG. Identification of human cytochrome P450s involved in the formation of all-trans-retinoic acid principal metabolites. Mol Pharmacol. 2000; 58:1341-8.
5. Mattiuzzi G, Yilmaz M, Kantarjian H, et al. Pharmacokinetics of posaconazole prophylaxis of patients with acute myeloid leukemia. J Infect Chemother. 2015; 21:663-7.
6. Afacan Ozturk HB, Albayrak M, Maral S, et al. Hypercalcemia associated with the interaction between all trans retinoic acid and posaconazole in an acute promyelocytic leukemia case. J Oncol Pharm Pract. 2021; 27:2027-9.
7. Sakakibara M, Ichikawa M, Amano Y, et al. Hypercalcemia associated with all-trans-retinoic acid in the treatment of acute promyelocytic leukemia. Leuk Res. 1993; 17:441-3.

8. Niesvizky R, Siegel DS, Busquets X, et al. Hypercalcaemia and increased serum interleukin-6 levels induced by all-trans retinoic acid in patients with multiple myeloma. Br J Haematol. 1995; 89:217-8.

9. Cordoba R, Ramirez E, Lei SH, et al. Hypercalcemia due to an interaction of all-trans retinoic acid (ATRA) and itraconazole therapy for acute promyelocytic leukemia successfully treated with zoledronic acid. Eur J Clin Pharmacol. 2008; 64:1031-2.

10. Sakamoto O, Yoshinari M, Rikiishi T, et al. Hypercalcemia due to all-trans retinoic acid therapy for acute promyelocytic leukemia: a case report of effective treatment with bisphosphonate. Pediatr Int. 2001; 43:688-90.

11. Lietman SA, Germain-Lee EL, Levine MA. Hypercalcemia in children and adolescents. Curr Opin Pediatr. 2010; 22:508-15.