ATRA INDUCED HYPERCALCEMIA IN A CASE OF ACUTE PROMYELOCYTIC LEUKEMIA

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OBJECTIVES: All Trans Retinoic Acid (ATRA) has been the backbone of all standard treatment protocols for Acute ProMyelocytic Leukemia (APML). Herein, we report a case of ATRA induced hypercalcemia in interaction with fluconazole.

METHODS: A boy with APML was put on standard chemotherapy with ATRA based induction. Due to severe cytopenia, he was on started on antifungal prophylaxis with Fluconazole. Within a week, he presented with severe backache, bone and flank pains. Imaging of the lumbar spine, USG pelvis was unremarkable but we incidentally found serum calcium levels 14.2 mg/dL. Urine calcium: creatinine ratio, vitamin D, phosphorous and Alkaline phosphatase were all normal. Parathyroid hormone was 3.1 pg/ml which precluded the possibility of primary hyperparathyroidism or ectopic PTH secretion as a cause of the hypercalcemia.

RESULTS: We withheld ATRA and treated with hyperhydration, diuresis and Pamidronic acid, and the levels gradually normalized in a week. 2 more episodes of hypercalcemia post 5th day of starting ATRA occurred within the next 2 cycles even at reduced dose of ATRA. Both times he was treated successfully with pamidronic acid.

Post intensive chemotherapy, antifungal prophylaxis was stopped and though he is on maintenance chemotherapy with ATRA he has not developed further hypercalcemia, suggesting that hypercalcemia may have resulted from interaction of ATRA with fluconazole.

CONCLUSION: ATRA metabolism involves liver cytochrome P450 subtypes 2C9 and 3A4. Azoles are inhibitors of these enzymes causing increased plasma concentration of ATRA thereby potentiating the effect of ATRA on calcium metabolism. ATRA also enhances osteoclastic activity leading to bone mineral resorption just like PTH and downregulates IL-6 receptors causing increased IL-6 levels resulting bone resorption and hypercalcemia. Care should be taken when prescribing azole based antifungals with ATRA.