Acute-onset hypokalemic paralysis with arsenic trioxide therapy in patient with acute promyelocytic leukemia

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Acute myeloid leukemia (AML) is characterized by clonal proliferation of myeloid precursors with a reduced capacity to differentiate into mature cellular components.[1] Acute promyeloctic leukemia (APL; previously called AML-M3), a subtype of AML, is further characterized by a balanced translocation t(15;17)(q24.1;q21.1). It is an interesting model in cancer research because it responds to the differentiation and apoptosis induction therapy using arsenic trioxide (ATO) and all-trans retinoic acid (ATRA).[2]

There have been a number of concerns regarding the short- and long-term toxicities associated with ATO, and hypokalemia is one of the known effects of ATO toxicity.[3] Herein, we report a case of APL in which the patient developed acute onset hypokalemic paralysis while on ATO therapy. As far as we know, there is no other documented case in the literature of ATO-induced hypokalemia, presenting with acute onset paralysis.

Case presentation and summary

A 34-year-old female had presented with complaints of generalized weakness, ecchymotic patches all over her body, and repeated episodes of epistaxis for 10 days. On evaluation, she had anemia (hemaglobin, 7.8 gm/dL; normal,12-15 gm/dL), thrombocytopenia (platelet count, 21 x 10^9/L; normal,150-450 x 10^9/L), leukocytosis (total leukocyte count, 18.15 x 10^9/L; normal, 4.5-11 x 10^9/L), and peripheral blood smear showed 30% promyelocytes (normal, nil). Bone marrow aspirate smears were hypercellular with 32% myeloblasts, CD13- and CD33-positive, and positive for promyelocytic leukemia–retinoic acid receptor-alpha (PML-RARα).

She was diagnosed with APL and was given induction therapy with ATRA and idarabucin. However, developed a severe form of differentiation syndrome after 11 days of therapy and accordingly ATRA was stopped and she was switched to ATO. A bone marrow analysis on day 28 after initiation of ATO showed the patient had attained morphological remission, and she was subsequently given consolidation therapy with 4 cycles (each 25 days) of ATRA (45 mg/m^2 a day) and ATO (0.15 mg/kg a day), which the patient tolerated well. Repeat reverse transcription polymerase chain reaction for PML-RARα, further confirmed molecular remission. The patient began maintenance chemotherapy with ATO (0.15 mg/kg a day for 10 days every month). The other chemotherapy agent was ATRA (45 mg/m^2 a day) in the 4 cycles of consolidation and ATO (0.15 mg/kg a day) alone during 8 cycles of maintenance. Before each cycle of chemotherapy, the patient underwent thorough evaluation with complete blood count, liver function test, renal function test, electrolytes, and electrocardiogram (ECG), all of which were documented to be within normal limits.

On the fourth day of intravenous ATO, as part of the first maintenance chemotherapy cycle, the patient developed acute onset weakness of all four limbs and was not able to get up from a lying position when she woke up in the morning. There was no preceding history of fever, diarrhea, vomiting, or drug abuse. Her bowel and bladder functions were normal. On clinical examination, she was afebrile, pale, and had a pulse rate of 98 beats a minute and blood pressure of 130/84 mmHg. On neurological examination, the patient was awake, conscious, and oriented in time, place, and person, with normal higher mental functions. There was no cranial nerve

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deficit, and motor power in both lower limbs (proximal and distal bilaterally symmetrical muscle weakness) was 2/5 (0, no contraction; 5, normal), and 4/5 in the upper limbs, with a handgrip of 60% of normal strength. She had absent deep tendon jerks and superficial reflexes, bilaterally mute planters, no sensory deficit, no cerebellar signs, and no neck stiffness. Her chest was clear, with no adventitious sounds, and her cardiovascular and abdominal examinations were unremarkable.

Further investigations revealed severe hypokalemia (serum K^+, 2.1 mEq/L), a hemoglobin level of 8.8 gm/dL, a total leukocyte count of 4.8 x 10^9/L, and platelet count of 21.2 x 10^9/L. The patient's serum magnesium levels throughout the period of hospitalization were in the range of 2-2.5 mEq/L, and spot urinary potassium was consistently below 15 mEq/L. Other investigations including serum calcium and sodium level, renal function parameters, liver function tests, and thyroid function profile were within normal limits. Magnetic-resonance imaging of the cervical spine was also normal. The QTc on ECG was 0.41 sec, and there were no U waves. The patient's blood sugar levels were: fasting, 180 mg/dL; post-prandial, 240 mg/dL; and her hemoglobin A1c level was 7.1% (normal targets levels in diabetes, 6.5%-7.5%). She was started on metformin during her hospital stay.

The patient was diagnosed with hypokalemic paralysis. Because she had severe hypokalemia, ATO was withheld for 6 days. She was managed with an intravenous potassium replacement of 40 mEq/L, in 500 ml of normal saline over 2 hours, given every 8 hours for the first 2 days, and then 20 mEq/L intravenous infusion over 1 hour, every 8 hours for the next 2 days, along with serum potassium monitoring every 12 hours. Then oral supplementation with potassium chloride (15 ml, every 8 hours; 15 ml = 20 mEq of potassium) was given for 2 days as her serum potassium levels rose to 3.5 mEq/L. Oral supplementation was stopped on day 6, because her serum potassium level reached 4.5 mEq/L.

The patient improved notably and recovered completely as her serum potassium levels returned to normal. ATO was reintroduced, with daily monitoring of serum potassium, with a view to maintain serum potassium levels within normal limits. The patient tolerated the remaining doses of ATO well, without any subsequent events of hypokalemic paralysis.

Discussion

Hypokalemia is a common adverse effect of ATO therapy, with an overall incidence of 13%-50%, and a grade 3-4 incidence of 5%-14%.[3-7] However, the mechanism of how ATO causes hypokalemia was not documented in any of those studies. The most common association of hypokalemia is in reference to prolongation of the QT interval and ventricular tachyarrhythmias. It has been ascribed to the inhibition of rapid potassium channels, a change that slows ventricular repolarization and predisposes to ventricular instability.[6]

Hypokalemic paralysis is a relatively uncommon but life-threatening clinical syndrome. This syndrome represents a heterogeneous group of disorders characterized by hypokalemia and acute systemic weakness, resulting from either alteration in the transcellular distribution of potassium or actual potassium depletion from renal or extra renal lossess.[7] Most cases are due to familial or primary periodic paralysis, and those sporadic cases associated with other conditions including hyperthyroidism, renal tubular acidosis, and certain endocrinopathies, as well as drugs and gastrointestinal potassium lossess.[8,9] The most prominent clinical features of hypokalemia are neuromuscular, although other systems may also be affected. The cardinal laboratory finding is low serum potassium – less than 3.5 mEq/L during an acute attack – although it is usually much lower, as happened with our patient. Abnormalities in the ECG that can be suggestive of hypokalemia include the flattening and inversion of T waves and the appearance of U waves; however, these abnormalities are not well correlated with the severity of hypokalemia.[8] Our patient did not have any abnormalities in the ECG suggestive of severe hypokalemia, despite having very low levels of serum potassium.

The symptomatology results from the increased ratio between intracellular and extracellular potassium concentrations, which modifies polarization and thereby alters the function of excitable tissue, such as nerves and muscle. Diagnosis of hypokalemic paralysis is considered in any patient presenting with sudden-onset, areflexic pure motor weakness that involves one or more limbs, without alteration in the level of consciousness or sphincter function with laboratory evidence of hypokalemia, as was the case with our patient.

There was no family history or past personal history of similar events for our patient to suggest familial hypokalemic periodic paralysis, or any clinical or biochemical features to suggest thyrotoxic hypokalemic periodic paralysis, which might have predisposed her to hypokalemic paralysis.

Hypokalemia in our patient could not be attributed to decreased potassium intake because the patient was not following any dietary restrictions and was on a balanced diet. As far as the loss of potassium was concerned, there was no history suggestive of any gastrointestinal loss (upper or lower gastrointestinal tract) or renal loss, because the patient was not on diuretics and her spot urinary potassium was consistently below 15 mEq/L, suggestive of appropriate potassium conservation by the kidneys.

After a comprehensive evaluation of the patient, including a detailed history and thorough investigation, no apparent cause of hypokalemia, except therapy with ATO, could be ascertained. Probably the apparent mechanism of

hypokalemia induced by ATO was the transcellular shift of potassium, which was corrected by potassium supplementation along with discontinuation of ATO therapy.

The combination of ATRA and chemotherapy in the treatment of APL has led to improvement in event-free survival and overall survival of the patients.[10] However, as with most chemotherapy schedules, there is significant associated mortality in a minority of patients and significant morbidity in a majority, which further compounds the financial aspects of chemotherapy. For a resource-constrained environment, such as a developing country like India, the emergence of ATO as a single agent, effective in inducing remissions in patients with relapsed and newly diagnosed APL, has given new hope in this scenario.[11]

Conclusion

ATO therapy is safe and effective in APL. Hypokalemic paralysis is one of the rarest of rare manifestations of ATO-induced hypokalemia, which can be effectively managed by potassium supplementation and temporary withholding of ATO. It is, therefore, prudent to follow closely the recommendation to monitor and maintain serum potassium levels above 4 mEq/L during intravenous ATO therapy to prevent ATO-induced hypokalemia and the associated life-threatening complications.[12] With the global consensus on therapeutic doses, schedules of administration, and protocols for constant monitoring and supplementation of electrolytes, the incidence of ATO toxicity has been drastically reduced, and the overall profile of ATO therapy is now remarkably favorable.

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