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Tumor Lysis Syndrome (TLS) following intrathecal chemotherapy in a child with acute myelogenous leukemia (AML)

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A B S T R A C T

Tumor Lysis Syndrome (TLS) is a well-known complication of induction therapy for hematologic malignancies. It is characterized by rapid breakdown of malignant white blood cells (WBCs) leading to metabolic derangements and serious morbidity if left untreated. Most commonly, TLS is triggered by systemic chemotherapy, however, there have been case reports of TLS following intrathecal (IT) chemotherapy, all in patients with acute lymphoblastic leukemia (ALL)/lymphoma. Here, we report the first case of a patient with acute myelogenous leukemia (AML) who developed TLS following a single dose of IT cytosine arabinoside (Ara-C).

1. Introduction

Tumor Lysis Syndrome (TLS) is an oncologic emergency that occurs when malignant white blood cells (WBCs) undergo rapid lysis spontaneously and in response to anti-neoplastic therapy, releasing intracellular metabolites into circulation. TLS is characterized by hyperkalemia, hyperphosphatemia, hypocalcemia, and hyperuricemia which can lead to life-threatening complications including dysrhythmias, seizures, and renal failure [1,2]. The greatest risk for TLS occurs in patients with newly diagnosed hematologic malignancies at the time of initiation of systemic chemotherapy. While rare, TLS may be triggered by the initial dose of intrathecal (IT) chemotherapy administered at the time of the diagnostic lumbar puncture. There have been four case reports of TLS with IT chemotherapy, all in patients with acute lymphoblastic leukemia (ALL)/lymphoma [3–6]. Here, we report the first case of a patient with acute myelogenous leukemia (AML) who developed TLS after a single dose of IT cytosine arabinoside (Ara-C).

2. Case

A 16 month old previously healthy male presented to his pediatrician with a one week history of fever, pallor, and irritability. A complete blood count (CBC) showed pancytopenia. He was referred to pediatric oncology and, on exam, had pallor and hepatosplenomegaly. Laboratory evaluation showed pancytopenia with hemoglobin 7.9 g/dl, white blood cell (WBC) 3.2 K/ul with absolute neutrophil count (ANC) of 140, and platelets 120 K/ul. His complete metabolic panel was normal except for an LDH of 555 IU/uL. Bone marrow aspirate and biopsy revealed acute monocytic leukemia (AML) with 50% monoblasts by flow cytometry (CD11c+, CD33+, CD64+, HLA-DR+, CD4+, CD38+). Cytogenetics/FISH showed *MLL* (*KMT2A*) gene rearrangement characterized by t(9;11)(p22;q23) and a subclone with Trisomy 8. Repeat electrolytes prior to the lumbar puncture showed a normal uric acid of 3.8 mg/dL. Lumbar puncture showed central nervous system involvement with 60 WBCs and 85% monoblasts. Intrathecal Ara-(C) 30 mg was administered at the time of the diagnostic lumbar puncture. After completion of mediport insertion, about 3 h after IT Ara-C administration, the patient spiked a fever to 40.3 C and developed respiratory distress with desaturations, requiring re-intubation. Arterial blood gas showed respiratory acidosis and hyperkalemia with potassium level of 7.4 g/dL. He was treated by the anesthesia team with dantrolene for a concern of malignant hyperthermia and with calcium, glucose, and bicarbonate to correct metabolic derangements. Chest x-ray showed enlarged cardiac silhouette and small bilateral pleural effusions. Echocardiogram showed a large pericardial effusion with right atrial and ventricular collapse. He underwent pericardiocentesis revealing a malignant effusion with presence of monoblasts. Seven hours after intrathecal chemotherapy administration, laboratory evaluation revealed a serum potassium of 6.6 meq/L, calcium 7.7 mg/dL, phosphorus 8.6 mg/dL, uric acid 11.7 mg/dL, LDH 1078 IU/L, BUN 28 mg/dL, and Cr 0.4 mg/L. Intravenous fluid hydration was continued and allopurinol was initiated. Six hours later, the uric acid rose to 14 mg/dL and LDH to 1835 IU/L but the potassium level improved to 5.0 mg/dL. Rasburicase 2 mg/kg intravenous was administered with normalization of the uric acid level. The Cr peaked at 0.7 mg/L (2x baseline) but then trended back down to normal. MRI brain was unremarkable. The patient proceeded with systemic chemotherapy for AML and achieved remission at completion of induction I. During induction II, lower

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extremity motor deficits were noted and an MRI spine showed enhancing epidural soft tissue in the canal from T5 to T7, compatible with tumor, minimal epidural soft tissue in the canal from T7 to L4, and cord signal abnormality with mild enhancement from T5 toT7, possibly representing tumor involvement of the cord. A biopsy of the epidural mass showed necrotic tissue and flow cytometry and cytogenetics/FISH were negative for AML. The patient completed intensified therapy for high risk disease while engaging in physical rehabilitation for lower extremity paresis. Six weeks after completion of therapy, he presented with altered mental status and was diagnosed with AML relapse involving bulky CNS chloromatous disease and bone marrow positive for *MLL* gene rearrangement by FISH (flow cytometry negative). He is currently undergoing therapy for relapsed disease.

3. Discussion

Here we report the first case, to our knowledge, of a patient with newly diagnosed AML who developed TLS following a single dose of IT chemotherapy. Within a few hours of IT chemotherapy administration, our patient developed high fever and hyperkalemia, evidence of Ara-C activity and early onset of TLS. Although there was concern at the time for malignant hyperthermia in the setting of general anesthesia, it became apparent that the symptoms were related to the effects of systemic absorption of IT Ara-C.

AML affects about 10,000 children (ages 0–21 years) worldwide annually with an incidence of 5–7 cases per million people per year [7]. CNS involvement is observed in 10–30% of children with AML. Some studies have suggested that children with AML who have CNS involvement at diagnosis have worse outcomes than those who do not [8,9]. For this reason, the standard of care in pediatrics is to perform a diagnostic lumbar puncture at initial diagnosis and administer intrathecal Ara-C empirically. If the child is found to be CNS positive, intrathecal therapy is intensified with more frequent dosing, while if the CNS is negative, prophylactic intrathecal chemotherapy dosing is continued. Ara-C is a purine analog that is incorporated in DNA and acts by inhibition of DNA polymerase, resulting in decreased DNA synthesis and repair. It is converted intracellularly into the active moiety cytarabine 5′-triphosphate (ara-CTP) which competitively inhibits binding of the physiologic substrate deoxy-cytidine triphosphate to DNA polymerase. Ara-C crosses the blood-brain barrier with CSF levels of 40–50% of plasma level and has a half-life of 7–20 min. Ara-C is rapidly metabolized by the liver by the enzyme, cytidine deaminase, and is excreted in the urine. This enzyme is not present in the CNS, resulting in a longer half-life in the CSF of 2–6 h. When administered IT, most of the Ara-C diffuses into systemic circulation where it is rapidly metabolized and causes minimal systemic effects in most cases [6,10,11]. However, factors such as type of malignancy, CNS involvement, and tumor burden may increase the risk of systemic effects.

In a TLS risk classification model, Cairo, et al. stratified patients with AML as low, intermediate, or high risk based on presenting WBC count and LDH, but noted that additional risk factors include kidney involvement at diagnosis and extent of disease. For patients with Burkitt or lymphoblastic lymphoma, advanced stage disease was classified as an independent qualifier for high risk of TLS [12]. Our patient with newly diagnosed AML had a presenting WBC count < 25 K/ul, but LDH > 2xULN, stratifying him as intermediate risk. However, the extent of his extramedullary disease, not entirely evident at initial diagnosis but ultimately revealed, including malignant pericardial effusion, pleural effusions (likely malignant), bilateral nephromegaly, hepatosplenomegaly, and bulky CNS chloromatous disease increased his risk. While standard TLS precautions were taken with hydration (limited due to pericardial and pleural effusions) and allopurinol, knowledge of extent of extramedullary disease prior to anesthesia may have prevented his unexpected respiratory decompensation and led to higher alert for TLS with earlier initiation of allopurinol and prompter administration of rasburicase with the onset of hyperuricemia.

There have been 4 reported cases of TLS occurring as a complication of IT chemotherapy, all in patients with ALL/lymphoma. Three of the cases were in patients with positive CNS disease and included a 44 year old man with B lymphoblastic lymphoma who received IT methotrexate, an 18 year old girl with relapsed B ALL who received triple IT chemotherapy with methotrexate, cytarabine, and hydrocortisone, and a 17 year old boy with B lymphoblastic lymphoma who received IT methotrexate [3–5]. The fourth case was in a 13 year old boy with T lymphoblastic lymphoma without CNS involvement who developed severe TLS and concurrent shrinkage of his mediastinal mass after IT cytarabine [6]. Our patient, the first to be described in this clinical setting with AML, had CNS involvement of disease in common with the 1st 3 cases and an LDH > 2xULN with extramedullary involvement in common with the 4th case. Given these parallels, it would be prudent to monitor closely for TLS in patients whose CSF is positive for malignant cells on the diagnostic lumbar puncture and, for patients with AML, to consider an MRI of the brain and spine if the CSF is positive.

In summary, we present the first case of a patient with AML who developed TLS after a single dose of IT chemotherapy, with the purpose of increasing awareness of the risk of this serious complication. An upfront comprehensive evaluation of extent of disease can help risk stratify patients for early TLS. Therefore, clinicians should consider non-invasive imaging (including chest xray, echocardiogram, and abdominal ultrasound) prior to diagnostic LP with IT chemotherapy to evaluate risk of TLS along with the presenting WBC count, LDH, CNS status. Awareness of risk, close surveillance of labs, and prophylactic measures can spare patients serious morbidity and mortality.

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