Multiple Complications Secondary to L-asparaginase In a Child with Philadelphia-Chromosome-Positive Acute Lymphoblastic Leukemia: Case Report with Review of Literature

Shyam Srinivasan1, Vikramjit Kanwar1, Soumitra Saha2, Raghavendra Gulabrao Mali3, Tanveer Ahmed Shaikh1, Renu Yadav1, Anubha Jain1

1 Department of Pediatric Oncology, Homi Bhabha Cancer Hospital, Homi Bhabha National Institute, Varanasi, Uttar Pradesh, India
2 Department of Pediatric Surgery, Homi Bhabha Cancer Hospital, Homi Bhabha National Institute, Varanasi, Uttar Pradesh, India
3 Department of Radiodiagnosis, Homi Bhabha Cancer Hospital, Homi Bhabha National Institute, Varanasi, Uttar Pradesh, India

Address for correspondence Shyam Srinivasan, DM, Department of Pediatric Oncology, Homi Bhabha Cancer Hospital, Varanasi, Uttar Pradesh 221010, India (e-mail: srinivas.shyam@gmail.com).


Abstract

Keywords
► Philadelphia-chromosome-positive acute lymphoblastic leukemia
► acute pancreatitis
► ventricular thrombus
► gastric perforation
► L-asparaginase

Even though L-asparaginase remains an essential drug for the treatment of childhood acute lymphoblastic leukemia (ALL), its use is associated with several unique toxicities. In this case report, we discuss a young boy with ALL who developed multiple complications simultaneously, including pancreatitis, gastrointestinal perforation, and left ventricular thrombus secondary to L-asparaginase during induction chemotherapy. Patient received immediate surgical intervention for the perforation and was commenced on anticoagulation therapy for the thrombus but eventually expired. This report highlights the importance of being aware of toxicities secondary to the use of L-asparaginase. Multiple complications secondary to L-asparaginase have been rarely reported previously and can be fatal.

Introduction

L-asparaginase has become an integral part in the management of childhood acute lymphoblastic leukemia (ALL) and failure to receive its intended course has been associated with poor outcome.1,2 However, L-asparaginase is also associated with a number of unique toxicities, some of which can have life threatening consequences.3 Here we present a patient with Philadelphia-Chromosome-positive Acute Lymphoblastic Leukemia (Ph+ ALL) who experienced two rare complications during induction therapy: gastric perforation and a left ventricular thrombus which led to his demise.

Case Report

An 8-year-old male presented with on and off fever, bruising over shin and chest and easy fatigability for 2 weeks. A complete blood count showed a total leukocyte count (TLC) of 153 × 10⁹/L with a differential count of 60% lymphocytes, 3% neutrophils, 0.1% eosinophils, and 27% blasts in the peripheral blood. A bone marrow examination was done, flow cytometric...
analysis along with FISH study which was positive for t(9;22), confirmed the diagnosis of B-lineage Ph⁺ ALL. A real-time quantitative polymerase chain reaction (RT-PCR) was suggestive of p190 BCR/ABL fusion transcript. Cerebrospinal fluid analysis was uninvolved for disease. He was treated as per the modified COG AALL1131 protocol. Induction chemotherapy consisted of prednisolone (60 mg/m²/day; 1–28 days), vincristine (1.5 mg/m²/d; days 1, 8, 15, and 22), native Escherichia coli L-asparaginase (10,000 U/m²/d; days 1, 4, 7, 10, 13, 16, 19, and 22) daunorubicin (30 mg/m²/d; days 1 and 15), intrathecal methotrexate (12 mg; days 1, 8, and 30) along with daily imatinib (340 mg/m²/once daily) from day 10. Chemotherapy was administered through peripheral intravenous lines on an outpatient basis. Treatment was uneventful up to day 29 of induction when he presented with abdominal pain and fever. On examination, heart rate was 86/min, blood pressure was 100/70 mm Hg and respiration was 22/min. Abdomen was mildly distended, diffusely tender, and bowel sounds were present. He was started on intravenous fluids, intravenous antibiotics (cefoperazone-sulbactam and amikacin), and analgesics for abdominal pain. The complete blood count showed a hemoglobin of 5 g/dL, platelet of 49 × 10⁹/L, and TLC of 0.42 × 10⁹/L with an absolute neutrophil count of 0.1 × 10⁹/L. Blood tests showed an elevated lipase (1,164 U/L), elevated D-dimer (3,700 ng/mL), with a normal serum sodium (137 mEq/L) and potassium (4.2 mEq/L) and no organism was isolated from blood culture. In view of the above symptoms in a neutropenic child, computerized tomography (CT) scan of the abdomen with contrast was performed on the day of admission which revealed a bulky mass in the left ventricle (LV) of the heart which an incidental finding on CT scan was a well-de...
our patient was a child who had undergone a major gastric surgery, he was commenced on subcutaneous LMWH and since he was severely neutropenic it was decided to defer any cardiac surgery until the time of count recovery.

Our patient did not have any past history of thrombotic episodes or family history of thrombophilia, but the co-occurrence of these unusual complications made us strongly suspect a underlying prothrombotic condition exacerbated by L-asparaginase therapy. The prevalence of genetic prothrombotic abnormalities amongst children with ALL varies around the world, and we do not pre-emptively screen for thrombophilia given that such testing is expensive, and not easily available. The Dutch Children’s Oncology Group has debated the benefit of more aggressive screening and LMWH

Fig. 1 (A) CT abdomen showing left ventricular thrombus (arrow head) and pneumoperitoneum (‘’) (B) with gastric perforation (arrow). (C) 2D-echocardiography confirming the presence of left ventricular thrombus (outlined circle). (D) Intraoperative findings showing perforation of greater curvature of stomach (arrow head) (E) impending perforation of jejunum (double arrow).
prophylaxis during induction for those found to have thrombophilia. The role of genetic predisposition for pancreatitis is less clear but recent genome-wide association studies have found different candidate single-nucleotide polymorphisms associated with pancreatitis in patients with ALL. We could not rule out a pre-existing cardiac thrombus as a baseline 2D-echo was unavailable. Also, thrombotic events and gastric perforation during ALL therapy are often considered to be multifactorial rather than secondary to a single drug. But, the occurrence of several unique toxicities which are often shown to be associated with L-asparaginase, all occurring simultaneously in a patient would be the highlight of this case report.

Conclusion

Though L-asparaginase is an essential drug for the management of childhood ALL, it does possess a unique toxicity profile. Unfortunately, our patient simultaneously experienced several toxicities, including pancreatitis, LV thrombus, and gastrointestinal perforation leading to his demise. Lack of familiarity of the toxicity profile of this drug can make L-asparaginase a difficult drug to use. Being vigilant for these unusual toxicities especially during induction chemotherapy is essential for optimal patient care.

Source of Support
None.

Declaration of Patient Consent
The authors certify that they have obtained all appropriate patient consent forms.

Conflict of interest
None declared.

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