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Managing childhood acute lymphoblastic leukemia in a child with Emery-Dreifuss muscular dystrophy

Aishvarya Diptivilasa[1], Nita Radhakrishnan[2], Shruti Verma[3]

[1]Junior Resident, [2]Associate Professor, [3]IAP Fellow, Department of Pediatric Hematology Oncology, Post Graduate Institute of Child Health, Noida, Uttar Pradesh, India

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ABSTRACT

Genetics is increasingly being integrated into clinical oncology practice. It is necessary for risk stratification of disease, for prognostication, for recognition of underlying predisposition, and for recognition of potential toxicity and predicting outcomes. The prevalence of genetic syndromes, their clinical significance, effect on cancer, and its treatment have been defined in recent times. In this present work, we describe the challenges we faced while managing a child with acute lymphoblastic leukemia with an underlying rare muscular dystrophy. The details were recorded from case files and prospectively collected data. Dose modification of certain chemotherapeutic drugs was planned to reduce toxicity in the child. The child responded to treatment and is currently in remission. The recognition of genetic entity and their potential interactions with treatment received for cancer is vital to plan the treatment.

Key words: Cancer; Muscular dystrophy; Cancer genetics

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INTRODUCTION

With the advent of genomics, germline mutations are being increasingly described in children who present with malignancies.[1] Identification of underlying genetic mutations is important for the child's treatment and has implications for surveillance for the child and families and prenatal diagnosis to prevent future births. There are published guidelines that guide a clinician who is faced with the prospect of managing these patients. In other genetic disorders, however, the published literature is sparse. We describe the experience of managing a child with muscular dystrophy and acute lymphoblastic leukemia (ALL).

CASE REPORT

A 15-year-old male, the second child of non-consanguineous parents, presented to us with features of poor appetite, fatigue, and pallor. He was pale with no bleeding or hepatosplenomegaly on examination. He was found to have bilateral elbow flexion contractures and an equinus deformity of both feet. On probing, there was a history of difficulty walking since the age of 4 with limping. He was evaluated then and was found to have bilateral proximal muscle weakness, calf hypertrophy, and mild winging of scapulae. There was no relevant family history and no symptoms of any underlying cardiac abnormality. He underwent evaluation for this at the primary treatment

Address for Correspondence:
Nita Radhakrishnan, Associate Professor, Department of Pediatric Hematology Oncology, Post Graduate Institute of Child Health, Noida, Uttar Pradesh, India. **Mobile:** +91-9999041524. **E-mail:** nitaradhakrishnan@yahoo.com

center; creatinine phosphokinase was mildly elevated, and genetic testing for dystrophin gene was negative. He underwent Z tendon lengthening surgery with Z-plasty and posterior capsule release for both ankles at the age of 10 years. On evaluation at our center, complete blood count showed Hb of 6.6 g/dL, white blood cells count of 3490 cells/micL, and platelet count of 103,000/micL with 70% lymphoblasts in peripheral smear. Bone marrow study and flow cytometry confirmed B lineage acute lymphoblastic leukemia. There was no evidence of common molecular/cytogenetic abnormalities on multiplex PCR or karyotyping. Neurological and genetic evaluation was taken for any guidance on the use of chemotherapy in the setting of muscular dystrophy. 2D-ECHO showed normal cardiac function. In the absence of a clear genetic diagnosis at this point, no specific guidelines were possible. The possible difficulties anticipated were worsening of neuromuscular status upon addition of steroids and vincristine, anthracycline-induced cardiac complications, and unusual toxicity to any usual chemotherapeutic or antimicrobial agent. After discussion with the multidisciplinary team and the family, he was started on BFM-2009 induction with the omission of all doses of vincristine. Never conduction studies done before the onset of chemotherapy were indicative of limb-girdle myopathy. He tolerated protocols 1A and 1B of induction and was in MRD-negative remission on day 78. He did encounter Grade 4 neutropenia with mucositis after the first cycle of high-dose methotrexate given at 5 g/m^2 with leucovorin rescue. He is continued on further cycles with dose reduction of methotrexate and is in maintenance therapy. His muscular dystrophy is stable and has not progressed further during the past 18 months of treatment for ALL.

Next generation sequencing done revealed a novel heterozygous mutation c.794_796del (p.Lys265del) in exon 4 of Lamin A and C (LMNA) gene that was consistent with the phenotype described and suggestive of Emery-Dreifuss muscular dystrophy (EDMD). 65% of probands with autosomal-dominant LMNA mutation have been reported as *de novo* without any family history.

DISCUSSION

EDMD is a slowly progressive chronic disorder with a triad of joint contractures and cardiac abnormalities such as cardiomyopathies and skeletal myopathies. EDMD manifests as type 1 where patients present from skeletal muscle involvement initially and type 2 where cardiac involvement occurs early in life.[2] Autosomal dominant and recessive EDMD results from mutations in LMNA gene which helps make proteins LMNA. Skeletal manifestations include contractures in elbow, neck, and ankle joints as is noted in our case with symmetrical weakness of biceps, triceps, or peroneal muscles. A debilitating symptom that has been described is syncope and sudden cardiac death following arrhythmias which include atrial fibrillation or flutter, ventricular, or supraventricular arrhythmias or conduction defects. Modest elevation of CPK is usually noted as was seen in our case.[3]

In view of no literature on managing leukemias in the setting of this genetic disease, the following difficulties were anticipated. First, the worsening of underlying neuromuscular and cardiac status was expected on exposure to common chemotherapeutic agents with potential for this toxicity. Proximal myopathy due to the use of prednisolone and sensory, motor and autonomic neuropathy due to vincristine have been reported in apparently healthy children. Exaggerated neuropathy in patients with previously undiagnosed neuropathy such as Charcot Marie tooth disease has also been reported. Agents that trigger malignant hyperthermia such as succinylcholine and volatile anesthetic drugs were avoided as per recommendations. A close cardiological follow-up with monthly echocardiogram and electrocardiogram is being done to diagnose arrhythmias early. The child was also advised to report palpitations, syncope, or exertional intolerance which could herald cardiac involvement. During the febrile neutropenic period, a close watch on dyselectrolytemias with correction of the same was done to prevent any cardiac conduction abnormalities. Second, a worsening of underlying lung capacity due to neuromuscular weakness and precipitation of respiratory failure or hypostatic pneumonia was anticipated during induction as well as during the febrile neutropenic period. The child was advised preventive breathing exercises including spirometry with emphasis on early mobilization during periods of sickness. Finally, idiosyncratic reactions to chemotherapeutic agents following altered pharmacokinetics have been reported in many genetic disorders. We did encounter Grade 4 toxicity to methotrexate which was unusual as it is a commonly used agent in our clinical practice. The case is being reported for the unusual combination and the absence of any guidance on how to manage it in the reported literature.

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Work attributed to:
Post Graduate Institute of Child Health, Noida, Uttar Pradesh, India.

Orcid ID:
Dr. Nita Radhakrishnan - https://orcid.org/0000-0002-7941-5641

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