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Case Report

A Rare Case of KMT2A Gene Mutation with Tall Stature and Acute Myeloid Leukemia

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Abstract

Lysine methyltransferase 2A (KMT2A) gene mutation is an extremely rare mutation of chromosome 11. It is usually associated with Wiedemann–Steiner syndrome or acute myeloblastic leukemia and commonly inherited as an autosomal dominant trait. The KMT2A gene-encoded lysine methyltransferase plays an essential role in regulating gene expression during early development and hematopoiesis. Clinical features of Weidemann–Steiner syndrome are variable and include facial dysmorphism (thick eyebrows, flat nasal bridge, and hypertelorism), intellectual disability, short stature, hypertrichosis cubiti, and hypotonia. Phenotypically, Wiedemann–Steiner syndrome is similar to Cornelia de Lange syndrome. However, genetic mutation of the KMT2A gene helps to differentiate the two conditions. Here, we present a 15-year-old boy, second born to a non-consanguineously married couple, who presented with facial dysmorphism (thick arched eyebrows, thick lips, low set ears, and flat nasal bridge), tall stature, global developmental delay, attention deficit hyperactive disease, and bleeding manifestations. Clinical and laboratory evaluation was suggestive of leukemia. Genetic testing revealed KMT2A gene mutation.

Key words: Acute myeloid leukemia, Facial dysmorphism, Lysine methyltransferase 2A gene mutation, Mixed lineage leukemia, Wiedemann–Steiner syndrome

INTRODUCTION

Lysine methyltransferase 2A (KMT2A) gene or mixed lineage leukemia (MLL) gene is a protein coding gene. This gene is important in regulating gene expression during early development and hematopoiesis. It regulates the expression of multiple genes including the homeobox (HOX) gene. Recurrent translocations in leukemia usually involve MLL. They can be either acute lymphoblastic leukemia or acute myeloblastic leukemia (AML). Such leukemias involving the MLL have unique clinical and biological characteristics with poor prognosis.

KMT2A gene mutation is also associated with many syndromes and most frequently encountered is the Wiedemann–Steiner syndrome. This was first reported in the year 1989 by Wiedemann Steiner *et al.* as an Autosomal Dominant condition. It's commonly referred to as the "hairy elbow syndrome" due to the presence of hypertrichosis cubiti, but this was not found in all the cases.[1,2] The clinical features of this condition are vivid with no gender predilection. The commonly seen phenotypic variants are – hypertelorism, flat nasal bridge, long philtrum, thick-arched eyebrows, short stature, hypertrichosis cubiti, developmental disorders like-intellectual disability (ID), learning disabilities, attention deficit hyperactive disease (ADHD), and autism spectrum disorders. These neurodevelopmental manifestations can range in severity from mild disease to profound delays.

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CASE REPORT

A 15-year-old boy, 2nd born to a non-consanguineously married couple, born at term gestation with history of perinatal depression requiring newborn intensive care unit care for 4–5 days with global developmental delay, ID, and ADHD was brought with complaints of spontaneous bleeding from

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the gums and skin. On examination, he was found to have facial dysmorphism [Figure 1a] in the form of-thick arched eyebrows, thick lips, depressed nasal bridge, hypertelorism, low set ears with microtia, and an absent external acoustic canal of the left ear [Figure 1b]. He had tall stature with height of 181cm (>97th centile on the combined WHO and IAP growth charts) [Figure 2], but clinical signs for marfanoid habitus was negative, i.e., Wrist sign and Thumb sign [Figure 3]. He was pale and had petechiae over the extremities. Hence, considering the possibility of leukemia, he was evaluated. Complete hemogram showed leukocytosis (16,610 cells/cu mm). Peripheral blood smear showed lymphocytosis (42%) with 6% blast cells and thrombocytopenia (15,000 cells/cu mm). Bone marrow aspiration and biopsy were suggestive of Acute Myeloid Leukemia with basophilia.

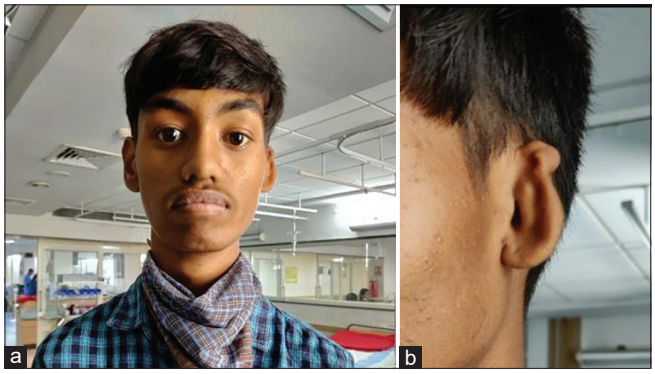

Figure 1: (a) Depicting the facial dysmorphism, and (b) depicting left ear microtia with absent external acoustic canal

Figure 2: This figure depicts the tall stature seen in our case

Karyotyping revealed: 47, XY, + mar [4]/47, XY, t (?: q23.3), mar [15]/46, XY [1].

Fluorescent *in situ* hybridization revealed: KMT2A (MLL) translocation: t (v; 11) (?; q23) [Figure 4].

The next-generation sequencing panel revealed national rental affordability scheme (NRAS) and STAG 2 gene mutations. Hence, a diagnosis of AML with MLL and NRAS/STAG-2 mutation was made. Phenotypically, this boy exhibited features of Wiedemann–Steiner Syndrome, but tall stature was an exception. He was initially treated with induction chemotherapy with Daunorubicin and cytarabine – 3+7 cycles at the end of which he had minimal residual disease (MRD), that is, MLL analysis of 1%, which was treated with high dose cytarabine. Following this regimen, he was free of MRD and bone marrow transplant (BMT) was done with a full HLA matched sibling. Despite the poor prognosis associated with KMT2A gene mutation and AML, the child is currently doing well after BMT.

DISCUSSION

Wiedemann–Steiner syndrome (WDSTS) associated with KMT2A gene mutation is an exceptionally rare autosomal dominant syndrome with a prevalence of <1 in 1,000,000.[3]

In 2012, Jones *et al.*[4] identified the haploinsufficiency of the gene KMT2A (MLL) as the genetic cause of WDSTS. Whole-exome sequencing was performed in six patients with a suggestive phenotype (hypertrichosis cubiti, short stature, ID, and facial features consistent with the patients reported by Wiedemann and Steiner) and detected de novo loss-of-function mutations in five of the six patients. KMT2A encodes a DNA-binding protein that methylates a lysine residue on histone H3 lysine K4 (H3K4). It consists of 37 exons, but a major transcript of 14982 bp produces a 3969 amino acids protein from 36 of the 37 exons. The

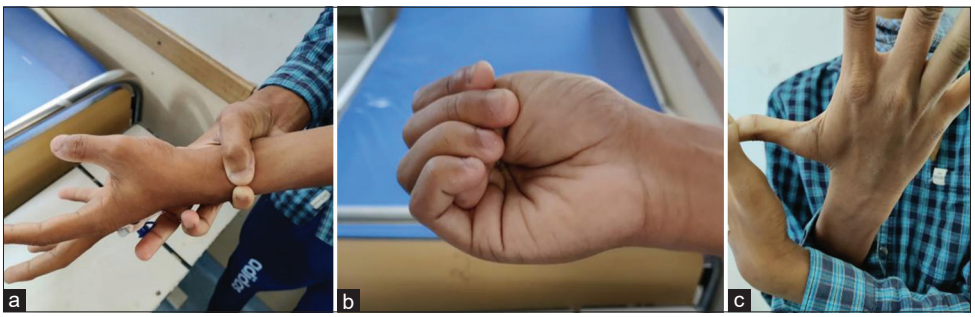

Figure 3: (a-c) Negative clinical signs of marfanoid habitus

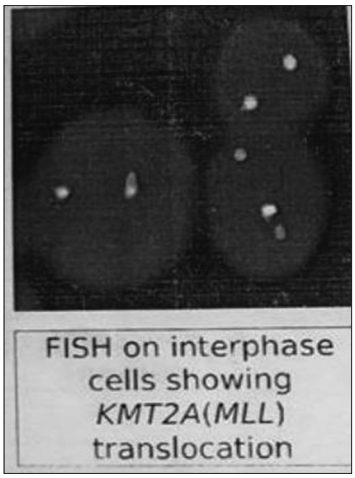

Figure 4: Fluorescent *in situ* hybridization showing mixed lineage leukemia translocation

protein contains several functional domains, including the SET domain, responsible for its H3K4 methyltransferase activity.[5] As discussed above, histone methyltransferases act as "writers." KMT2A, indeed, positively regulates the expression of many target genes, including genes belonging to the HOX complex and other genes involved in embryonic development.[6-8] Studies on mice also demonstrated that KMT2A is highly expressed in adult hippocampal neurons and is critical for synaptic plasticity, cognition, complex behaviors, and long-term memory.[9,10] Other members of the family of H3K4 methyltransferases are associated with other chromatinopathies, ex-KMT2D and KMT2B are associated with Kabuki syndrome and Kleefstra syndrome, respectively.

A French study[2] of 33 cases of Weidemann–Steiner syndrome observed a broad phenotypic spectrum with regard to ID (mild to severe), the facies (typical or not of WSS) and associated malformations (bone, cerebral, renal, cardiac, and ophthalmological anomalies). Hypertrichosis cubiti that was supposed to be pathognomonic in the literature was found only in 61% of their cases. This is the largest series of WSS cases yet described to date. A majority of patients exhibited suggestive features, but others were less characteristic, only identified by molecular diagnosis. The prevalence of WSS was higher than expected in patients with ID, suggesting that KMT2A is a major gene in ID.

In a study of Wiedemann–Steiner syndrome in monozygotic twins,[11] they identified a *de novo* mutation in KMT2A associated with psychomotor developmental delay, facial dysmorphism, short stature, hypertrichosis cubiti, and small kidneys. This finding in monozygotic twins gave specificity to the WSS. The article says that the description of more cases of WSS is needed for further delineation of this condition. Small kidneys with normal function have not been described in this condition in the medical literature before.

In our study, the child showed tall stature in association with KMT2A gene mutation which is a rare manifestation and was similar to a case reported in a study conducted by Lee *et al.*[5] This was a study conducted on two unrelated individuals who were diagnosed as atypical Wiedemann–Steiner syndrome, in which one of the children was found to have tall stature.

CONCLUSION

KMT2A gene mutation being rare has vivid phenotypical presentation. In our case, the boy has exhibited tall stature. Leukemia caused due to KMT2A gene mutation is usually associated with poor prognosis. The child is currently doing well and is on follow-up.

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