A Novel MECOM Variant Associated with Congenital Amegakaryocytic Thrombocytopenia and Radioulnar Synostosis

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To the Editor

Congenital radioulnar synostosis (RUS) is a rare developmental anomaly of proximal fusion of the radius and ulna, resulting in limited pronation and supination of the forearm. It may accompany other abnormalities in the skeleton, kidney, heart and aneuploidy syndromes[1,2]. A subset of patients with RUS present with bone marrow failure (BMF) syndromes, characterized by amegakaryocytic thrombocytopenia (RUSAT), progressing to myelodysplasia and pancytopenia[2,3]. The hematological manifestations are quite variable, with some presenting with severe BMF in childhood, while others are mild and may not present until adulthood.

Heterozygous germline variants in the homeobox A11 (HOXA11) gene were the first to be associated with RUS and designated RUSAT1[4], but lately, several families have been described with variants in the MDS1 and EVI1 complex (MECOM) locus, and referred to as RUSAT2[2,5,6]. Many of these variants appear *de novo* , while others follow an autosomal dominant inheritance. We, hereby, report the case of a Kuwaiti patient who presented with congenital amegakaryocytic thrombocytopenia (CAMT) in the neonatal period and later noticed to have RUS. Whole exome sequencing revealed a novel MECOM variant.

A.A. is a male Kuwaiti, the first child of consanguineous parents and was first seen at the age of 36 days, following antenatal ultrasound diagnosis of bilateral hydronephrosis and right renal cyst. He was a product of induced vaginal delivery with a birth weight of 2.3 kg. After delivery, he was kept under observation in the neonatal intensive care unit. His CBC showed isolated thrombocytopenia (Plt 34 x10^9/L). He received several platelet transfusions, as well as IVIG twice. Postnatal abdominal ultrasound showed multicystic right kidney, in addition to bilateral hydronephrosis. The mother had no history of thrombocytopenia during pregnancy and there was no other pertinent family history.

Physical examination at presentation showed 2 café-au-lait spots, one on the back, measuring 1x2 cm and another over the left leg, that was less than 0.6 cm. There were no obvious dysmorphic features and other systems were unremarkable. CBC showed WBC 11.2 x10^9/L Hb 10.4 g/dL, MCV 83fl, Plt 49 x10^9/L, ANC 1.8 x10^9/L. Renal function tests were normal. Blood film showed no abnormal cells; there was true thrombocytopenia with giant forms. Antiplatelet antibody was negative. Abdominal ultrasound at age 1 month showed complete replacement of the right kidney by cystic changes with left moderate hydronephrosis. Skeletal survey was reportedly normal.

Bone marrow biopsy showed normal distribution of granulocytic and erythroid precursors, with severe suppression of megakaryocytosis, consistent with a bone marrow failure syndrome. Chromosomal breakage study was normal. The patient was diagnosed with right undescended testis, as well as right inguinal hernia that were operated at age 1 year and 10 months. At the age 2 and a half years, A.A. was noticed to have limited bilateral arm movement supination and pronation. The mother volunteered that she has a similar defect. X-rays confirmed that the child had bilateral radioulnar synostosis. Whole exome sequencing showed that the patient is heterozygous for a previously-unreported MECOM gene, c.2282A>G mutation. Unfortunately, the parents have not been screened for these mutations.

The patient has been under follow up for 4 years, his platelet count has been stable, ranging between 40-50 $x10^9$/L, with no bleeding tendency. In spite of his limited arm rotation, he currently functions normally in his daily activities, however, his hand writing skills and ability to engage in sports are yet to be observed since he is still pre-school age. Platelet transfusion is reserved only for severe bleeding, which he has not had. Bone marrow transplant may be considered in future if his bone marrow failure worsens and/or his marrow shows dysplastic changes.

Dokal et al[3] were the first to report an association between RUS and late-onset BMF, while Thompson et al described its association with CAMT and linked it to the *c.872delA* ,*p.Asn291Thrfs3* variant of the *HOXA11*gene[4,7]. More recently, several germline mutations in the *MECOM* locus have been reported and appear to be the more common cause of RUSAT. Indeed, no other cases of *HOXA11* mutations linked to RUSAT have been described since the initial report. Niihori et al[8] reported the first 3 heterozygous *MECOM*mutations in 3 sporadic patients. These variants and those subsequently reported by Walne et al[2] are in a highly conserved cluster within 10 amino acids (aa750-760) and impact on either the highly conserved Cys2His2 zinc finger motif (zinc finger 8, aa733-755) or the adjacent linker motif (aa756-760). It has been shown that removal of the 8^{th} zinc finger causes granulopoiesis arrest while mutations and deletions in other parts of the complex, outside the 8^{th} and 9^{th} fingers, are associated with hematological disorders without RUS[9].

MECOM codes for a zinc finger transcription factor with important roles in normal development and oncogenesis and is involved in the regulation of embryonic development and hematopoietic stem-cell renewal. Hence the phenotype in individuals with these mutations is very variable ranging from BMF to different skeletal, cardiac, renal malformations, B cell deficiency and sensorineural deafness.

Our patient showed a previously unreported variant in the region of the 8^{th} zinc finger of the MECOM locus. This c.2282A>G missense variant results in the tyrosine to cysteine substitution at codon 761 (p.Tyr761Cys). The amino acid is in the Zinc finger, C2H2 and Zinc finger, C2H2-like protein domains and is highly evolutionarily conserved. Unfortunately, the parents were not screened for the mutation, however, the mother shows RUS, with normal blood counts. This is consistent with the marked variability in the clinical phenotype. The father is also physically and hematologically normal.

Apart from thrombocytopenia, our patient also had renal abnormalities – hydronephrosis and multicystic kidney disease. The natural history of his condition is that he may develop pancytopenia and/or myelodysplasia in the future. He is under close follow up and will be considered for bone marrow transplantation if his condition worsens. In the meantime, he remains hypomegakaryocytic with a platelet count at 30 – 50 x 10^9/l while other blood cellular elements are normal. His renal function and hearing are being monitored, but still remain normal.

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