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Amegakaryocytic Thrombocytopenia with Radio-Ulnar Synostosis (ATRUS): A Case Report

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Authors' contributions

This work was carried out in collaboration among all authors. Author SB designed the case report and wrote the first draft of the manuscript. Authors PK, IS and RK managed the literature searches. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

The association of bone marrow failure and skeletal defects is well known. However, the genetic basis for most of these syndromes remains unclear. We describe here a syndrome of *congenital amegakaryocytic thrombocytopenia (CAMT)* with skeletal abnormality. This case report summarizes the clinical presentation of an infant with anemia and thrombocytopenia in which the basic work up has led to the diagnosis of ATRUS.

Keywords: Amegakaryocytic thrombocytopenia; CAMT; ATRUS syndrome; radio-ulnar synostosis.

1. INTRODUCTION

CAMT presents in infancy with isolated thrombocytopenia caused by reduced or absence of megakaryocytes in bone marrow with preservation of granulopoietic and erythroid lineages initially, which subsequently culminates in aplastic anemia in majority of cases, in the first

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few years of life [1]. Physical malformations are usually not present; therefore, the diagnosis needs exclusion of other acquired and inherited causes. CAMT is a distinct genetic entity, autosomal recessive in inheritance. Mutations in several other genes have been described in a number of inherited thrombocytopenias that must be considered in the differential diagnosis, among which *amegakaryocytic thrombocytopenia with radio-ulnar synostosis (ATRUS)*, also known as *radioulnar synostosis with amegakaryocytic thrombocytopenia (RUSAT)* is inherited as an autosomal dominant entity. This is an extremely rare entity which has been occasionally reported in literature, so far [2].

2. CLINICAL PRESENTATION

A 4-month-old male child, born to non-consanguineous parents, presented with lethargy, irritability, difficulty in feeding, progressive pallor, bluish spots over tongue and legs for 15 days without any history of fever, hematemesis, melena, jaundice, seizure or altered sensorium. There was no history of similar illness prior to this or in the family. He was the 4th child of the family. Developmental history was normal. On examination there was severe pallor along with multiple petechial spots all over body. There was no visible congenital anomaly, no café-au-lait spot, no lymphadenopathy or hepatosplenomegaly. Other system examinations were normal. He didn't have any family history of hematological or skeletal disorder. The mother had unbooked and uneventful normal vaginal delivery at primary health centre and both mother and child were discharged after 24 hours of delivery. No blood test was done for child. She neither had radiation exposure nor took any teratogenic drug during pregnancy.

He was found to have severe anemia with a hemoglobin of 2 gm%, platelet count of <10,000 but with normal total and differential leucocyte count. Initially he received symptomatic treatment along with red cell and platelet transfusions. Bone marrow study was suggestive of hypoplastic marrow. Cytogenetics was 46XY. Further work up for EBV, CMV and Parvo virus infection was also negative. Vitamin-B-12 level was low. Chromosomal breakage study with Mitomycin-C was normal. Then X-rays of upper limbs were done to look for any congenital anomaly and revealed bilateral proximal radio-ulnar joint synostosis [Fig. 1]. He was discharged on Vitamin B12 supplements with an advise to monitor his CBC weekly, look for any bleeding manifestations and to attend emergency/OPD.The child ultimately succumbed to the disease within one month of presentation at home.

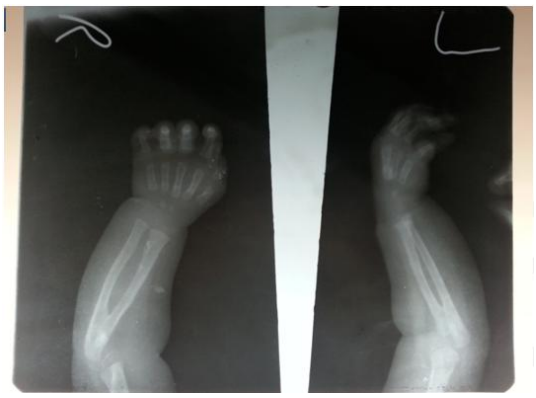

Fig. 1. Forearm radiographs showing proximal fusion of the radius and ulna bilaterallly

3. DISCUSSION

The association of bone marrow failure and skeletal defects are frequent, however, the genetic basis for most of these syndromes is unclear. We described here a syndrome of amegakaryocytic thrombocytopenia associated with radio-ulnar synostosis. Though Vitamin-B-12 was low, it couldn't explain the bone marrow hypoplasia. By the way the clinical features of this syndrome appear to be distinct from other similar conditions, including Fanconi's anaemia (FA) and thrombocytopenia- absent radii (TAR) [3].

Up to 50% of cases of FA are associated with malformations of hands or thumbs. Forearm anomalies specifically identified in FA includes absent, dysplastic or hypoplastic radii. TAR syndrome typically presents with radial aplasia or hypoplasia [4]. Thrombocytopenia is apparent early in life but is generally transient. Absent or dysplasia of the ulnae can accompany TAR, as well as subtle malformations of the fingers. In Diamond Blackfan Anaemia (DBA), 10% of patients may have thumb or upper arm anomalies [5].

Patients with ATRUS usually presents at birth with severe thrombocytopenia and absent marrow megakaryocytes, proximal radioulnar synostosis and other skeletal anomalies such as

clinodactyly, shallow acetabulae and sensorineural hearing loss [6,7]. This does not happen in our patient as he was physically normal and no blood test was done post birth. His blood test and other tests were first done at 4 months of age when he started having oral bleeds and pallor. Bleeding complications are usually proportional to the degree of thrombocytopenia. Subsequent development of hypoplastic anemia and pancytopenia that occurs in several individuals suggests that the defect is not limited to megakaryocytic progenitors.

Homeobox genes encode regulatory proteins, are critical to bone morphogenesis as well as hematopoietic differentiation and proliferation [8-10]. HOXA11 is endogenously expressed in very early hematopoietic precursor cells and involved in regulation of megakaryocytic differentiation [11]. Cases with proximal radio-ulnar synostosis and inherited bone marrow failure syndrome usually have HOXA11 gene (7p15) mutation (RUSAT1). Some cases without the characteristic HOXA11 mutation have also been reported; may be due to MECOM gene (3q26.2) mutation (RUSAT2) [12]. In our patient further genetic evaluation was not done.

This is an extremely rare entity as even less than ten cases have been reported so far. Many varied presentations have been reported with similar condition. Our case had presented in early infancy with anemia and thrombocytopenia at the onset. Dokal et al reported two families of adult onset bone marrow failure with radio-ulnar synostosis [13].

Platelet transfusions are effective as initial symptomatic management. The associated development of aplastic anemia suggests that the defect is at the level of the hematopoietic stem cells. The only definitive treatment is hematopoietic stem cell transplantation [14].

4. CONCLUSION

Establishing the diagnosis in case of inherited bone marrow failure syndrome may be obvious by many external manifestations whereas any abnormality of internal organs including skeletal system may also be a clue. So a high index of suspicion and work up accordingly may help a clinician to reach a proper diagnosis.

CONSENT

Informed consent was taken from the parents.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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