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Myelofibrosis and Vitamin D Deficient Rickets- A Rare Association

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Myelofibrosis is a rare hematological condition in infancy. We report a case of a 6-month-old infant who was diagnosed to have myelofibrosis due to Vitamin D deficient rickets. This rare association of myelofibrosis and rickets is discussed here with a review of relevant literature.

Key words: *Infant, Myelofibrosis, Vitamin D deficient rickets.*

Myelofibrosis is an uncommon hematological condition characterized by progressive fibrous tissue replacement of the bone marrow. Fewer than 100 cases of pediatric myelofibrosis have been reported worldwide(1) and in young children it may be primary or secondary. One of the rare causes for secondary myelofibrosis is vitamin D deficient rickets(2). We report a 6-month-old male infant, who was diagnosed to have myelofibrosis due to vitamin D deficient rickets and succumbed to the same.

Case Report

A 6-month-old, exclusively breast fed male infant, born after a full term normal

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delivery to parents of non consanguineous marriage was hospitalized for seizures with fever. His birth weight was 2.5 kg and his developmental milestones were appropriate for age. He weighed 6.5 kg (86% of expected) and his head circumference was normal (39 cm). His elder sibling aged 4 years was normal. On examination he had severe pallor with massive splenohepatomegaly (spleen 7cm below left costal margin and liver 6cm below right costal margin). He also had classic features of rickets with craniotabes, wide open anterior fontanel and rachitic rosary.

His hemoglobin was 3.9 g/dL while peripheral smear suggested pancytopenia with atypical lymphocytes (TC 3,700/mm^3, DC: lymphocyte 79%, neutrophils 21%, platelets 65,000/mm^3). He also had hypocalcemia (serum calcium-7.9 mg/dL and ionized calcium-0.9 mmol/L), hypophosphatemia (serum inorganic phosphorous 2.9 mg/dL) with normal magnesium levels. Renal function tests were normal and liver function tests revealed markedly elevated alkaline phosphatase levels (2697 IU/L). His bone marrow aspiration turned out to be a dry tap and bone marrow trephine biopsy showed normocellular to hypocellular marrow with serial sections showing few megakaryocytes. There was a mild to moderate reduction in erythroid and granulocytic series of cells. The interstitium showed moderate infiltration of lymphocytes, histiocytes and scattered osteoclastic giant cells and there were also occasional large histiocytes with eosinophilic cytoplasm. There was mild to moderate increase in interstitial reticulin with an occasional intertrabecular space showing significant mineralisation. The cortical fibroblastic reaction was suggestive of defective mineralisation and urine-screening tests for metabolic disorders were negative. Ultrasonogram of the abdomen revealed massive spleno-hepatomegaly with normal kidneys. Skeletal survey suggested active rickets. Blood, urine and CSF cultures were sterile. Serological tests for HIV, TORCH and VDRL were negative. Serum 25-hydroxy-cholecalciferol was 5 ng/mL (9-37.6 ng/mL) and parathyroid hormone level was 180 pg/mL (12-65 pg/mL), thus confirming the diagnosis of vitamin D deficient rickets. Since the infant was exclusively breast-fed, maternal 25 hydroxycholicalciferol and parathyroid hormone assay were done which showed low 25 hydroxycholecalciferol –8.9 ng /mL and increased parathyroid hormone - 130 pg/mL.

The infant was managed with intravenous antibiotics, antimalarials (in view of persisting fever spikes) and oral calcium. A single dose of vitamin D_3 6,00,000 IU was given intramuscularly. Multiple transfusions were required to maintain his hemoglobin levels.

Within 4 weeks of therapy following a single dose of vitamin D_3 and oral calcium, his calcium, phosphorous, ALP levels became normal. His repeat serum calcium was 8.9mg/dL, inorganic phosphorus –3.7 mg/dL and ALP- 543 IU/L thus confirming that vitamin D deficiency rickets had responded to treatment. However, pancytopenia and spleno-hepatomegaly persisted. Within 2 months, he needed 240mL/kg of packed cells to maintain his hemoglobin level and by 8 months of life, he died due to sepsis and ARDS.

Discussion

Myelofibrosis is the descriptive term referring to excessive reticulin deposition in the bone marrow. Primary (idiopathic) myelofibrosis is characterized by bone marrow fibrosis with no apparent cause and is very rare in children. Secondary myelofibrosis due to neoplastic causes includes acute lymphoblastic leukemia, acute myeloid

leukemia, acute megakaryocytic leukemia, non Hodgkin's lymphoma *etc*. and due to non neoplastic causes includes vitamin D deficient rickets, hyperparathyroidism, renal osteodystrophy, SLE, Fanconi's anemia, *etc.*(1). Vitamin D deficient rickets is an important cause for secondary myelofibrosis, as an active metabolite of this vitamin normally inhibits the proliferation of megakaryocytes and promotes the maturation of monocytes and macrophages that degrades collagen(1,3). In vitamin D deficient rickets there is secondary hyperparathyroidism, which is the cause for myelofibrosis(4). In our case, the diagnosis of vitamin D deficient rickets was confirmed by clinical findings, investigations and by its prompt response to vitamin D therapy. The other neoplastic and non-neoplastic causes of myelofibrosis were also considered and excluded with the detailed clinical work up and investigations. Myelofibrosis associated with rickets has been reported almost exclusively in Turkish children(2,5). Stephen, *et al.*(4) have reported myelofibrosis due to vitamin D deficiency and its prompt response to vitamin D therapy in 1999. Exclusive breast-feeding and lack of exposure to sunlight are the risk factors for vitamin D deficiency, which can easily be prevented with vitamin D supplementation and with adequate exposure to sunlight(6,7). In our patient, though the rickets resolved with vitamin D therapy, the hematological problems persisted and the infant became transfusion dependant and finally succumbed to septic shock due to pancytopenia that was secondary to intense myelofibrosis. Therapy for secondary myelofibrosis consists of treating the underlying disease and it has been reversed concomitantly with therapeutic control of primary condition(3). In contrast primary myelofibrosis has a poor prognosis in spite of treatment with various modalities like androgens, corticosteroids, chemotherapeutic agents, irradiation and splenectomy.

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