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Case Report

Reversible myelofibrosis due to severe Vitamin D deficiency rickets

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A 10-month-old male infant, third born of a 3rd degree consanguineous marriage, belonging to lower socioeconomic class (as per Kuppuswamy's scale), was brought with complaints of delay in motor developmental milestones since 6 months of age and associated lethargy, progressive pallor with abdominal distension since preceding 2 months of presentation. He had an uneventful antenatal and perinatal period, with a birth weight of 3 kg. He was exclusively breastfed till 6 months, with a subsequent deficit of protein (3 g) and calories (250 kcal) in the complementary diet with no supplementation of iron or any vitamins. There was no history of irritability, fever, petechiae, easy bruising, bony pains, prolonged jaundice, polyuria, or swelling anywhere else on the body. The family lived in a congested slum area with minimal sun exposure inside the house and the mother–infant dyad was indoors during most of the time. Anthropometry revealed weight: 7.2 kg (−1 to −2 z scores), length: 70 cm (1–2 SD), and OFC: 45 cm (0–1 SD). Clinically, he had pallor, wide wrists, double malleoli, wide open anterior fontanelle (4 cm × 4 cm), craniotabes, absent dentition, Harrison's sulcus, rachitic rosary, hepatomegaly (liver span 11 cm, 6.5 cm below right costal margin in midclavicular line), and firm splenomegaly (5 cm along left long axis of spleen). There were no dysmorphic or coarse facies, lymphadenopathy, icterus, bony tenderness, or evidence of bleeding tendency. Rest of the systemic examination was normal (Fig. 1). Clinical possibilities of

Introduction

Myelofibrosis is an uncommon condition in infants with very few cases of reversible myelofibrosis reported in literature.¹ Vitamin D deficiency (VDD) rickets is a rare but well-defined cause of this condition. With a reported recent increase in prevalence of VDD among exclusively breast fed infants and identification of newer roles of Vitamin D in modulation of hematopoiesis and immune regulation, this assumes importance.² In this report, we describe a 10-month-old rachitic infant with anemia and hepatosplenomegaly secondary to marrow fibrosis whose clinical features improved after Vitamin D therapy.

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Fig. 1 – The patient with rickets. Notice the large head, widening of wrists.

rickets associated with storage disorders, congenital infections, and primary hematological disorders were considered.

On investigations, he was found to have anemia (Hb – 8.1 g/dL), TLC-17300 (neutrophils 47%, lymphocytes 36%, basophils 4%, eosinophils 4%, monocytes 5%, myelocytes 2%, metamyelocytes 2%), platelets 240,000/mm³. Peripheral blood smear (PBS) showed normocytic normochromic anemia with leucoerythroblastic picture, few nucleated RBCs, anisopoikilocytosis with RDW 18.5%. Corrected reticulocyte count was 1.6%. Other biochemical parameters were: LDH – 240 IU/L, calcium 6.5 mg/dL, phosphate 3.2 mg/dL, alkaline phosphatase 4020 IU/L radiograph wrists showed irregular metaphyseal ends with cupping, splaying and fraying with generalized osteopenia (Fig. 2). Iron studies showed low serum ferritin [6.23 ng/mL (21–274)] and high total iron binding capacity [688 mcg/mL (250–450 mcg/mL)]. Hemoglobin electrophoresis and renal function tests were normal. Vitamin D3 level, as assessed by chemiluminescence assay, was 20.99 nmol/L (severe VDD). iPTH level was 738 pg/mL (14–72 pg/mL). The mother of the child also had VDD (22.6 nmol/L). Serological markers for congenital infections (Toxoplasma, Rubella, Syphilis, Cytomegalovirus, Herpes and HIV viruses) were negative. Montoux test was negative and there were no other

Fig. 2 – Radiograph wrists of the child depicting cupping, fraying of the metaphyseal ends.

evidences of Tuberculosis or Malaria. Flow cytometry of the peripheral blood showed increased number of CD34 (15.3%) cells (normal <1%). Bone marrow CD34 could not be assessed due to dry tap, while biopsy showed features of myelofibrosis on reticulin stain (grade IV) (Fig. 3).

The child and mother were treated with megadose of oral Vitamin D (600,000 IU), iron, vitamin supplementation, and optimization of diet. After 3 weeks, the child showed clinical improvement and radiograph revealed healing rickets with zone of provisional calcification. With favorable response, the child was continued on Vitamin D (60,000 IU sachet given once every 3 weeks), elemental calcium 500 mg for the next

Fig. 3 – Bone marrow biopsy depicting infiltration by fibrous tissue on reticulin stain suggestive of myelofibrosis.

4 months; followed with daily maintenance of Vitamin D 400 IU. Clinical examination at 6 months of treatment showed marked reduction in hepatomegaly (reduced to 3.5 cm below right costal margin), splenomegaly (2 cm), improvement in achieved milestones and improvement of anemia (Hb 11.5 g/dL), with reversal of PBS picture to normalcy. The peripheral CD34 reduced to 2.5%. The parents of the child refused any further bone marrow studies on follow-up.

Discussion

Primary myelofibrosis is rare in children with multiple secondary causes, ranging from malignancies to systemic illnesses.³ Despite high prevalence of VDD and its casual relationship for myelofibrosis being well known, only a few cases have been reported.^{1–5} Though the present case also had evidence of iron deficiency anemia as per biochemical reports, presence of normochromic normocytic anemia with leucoerythroblastic picture prompted us to perform bone marrow study and further evaluation.

The activities of hematopoietic stem cells and osteoblasts are closely interrelated. Defective osteoblastic activity as in rickets is known to hamper haematopoiesis.⁶ CD34, a surface glycoprophosphoprotein expressed on committed and primitive hematopoietic stem cells, is a surrogate marker for hematopoiesis.⁷

In a similar case of rickets, Yetgin et al found a high yield of CD34+ cell count in the samples from splenic aspirate and peripheral blood with a corresponding low count in bone marrow corroborating with underlying myelofibrosis with secondary extramedullary hematopoiesis from spleen. These levels of CD34+ cells normalized in the respective compartments after treatment with Vitamin D.⁸ A similar response of reduction in percentage of CD34+ cell in peripheral blood sample (from 15% to 2%) along with clinical and radiological improvement of rickets was seen in our case on treatment with Vitamin D, thus demonstrating a reversal of underlying bone marrow fibrosis. Bone marrow studies could not be repeated after treatment in our case due to refusal by the parents.

The plausible mechanisms of bone marrow fibrosis in rickets could be: absence of an active metabolite of Vitamin D3

which normally facilitates the maturation of the monocytes and megakaryocytes and degrades collagen via production of various cytokines and presence of high levels of PTH, which is known to induce fibrous tissue growth in bone marrow (as has been demonstrated in patients with chronic kidney diseases).^{8,9}

Though this secondary marrow fibrosis is potentially reversible; case reports of fatality due to sepsis related to severe pancytopenia have been reported.⁴ With increasing prevalence of VDD rickets being identified, myelofibrosis as a cause of anemia in such patients with hepatosplenomegaly should be strongly considered.

Conflicts of interest

The authors have none to declare.

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