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Myelofibrosis in Severe Vitamin D Deficiency Rickets

Pages with reference to book, From 174 To 177

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Vitamin D deficiency is prevalent in infants and children in the underdeveloped countries¹. Infants with mild deficiency tend to present with complications like hypocalcemic seizures whereas occurrence of pathological features in advanced rickets is well elucidated². Secondary myelofibrosis has been reported as a complication of severe rickets and in these children anemia, myeloid metaplasia and bone marrow aplasia strongly suggested myelofibrosis. Despite the high prevalence of rickets in the Indo-Pakistan subcontinent, there has been no report on this complication. We present a case of severe clinical rickets who had developed secondary myelofibrosis with hepatosplenomegaly. The purpose of presentation is to highlight this rare complication and increase clinician's awareness. The pathogenesis of myelofibrosis in rickets is discussed with emphasis on the reversible nature of the disease.

Case Report

Eighteen months old girl, AK, was admitted to the Aga Khan University Hospital with cough and fever for 3 weeks and breathlessness for 3 days prior to presentation. The child, born to healthy consanguineous parents, had been suffering from recurrent bouts of fever and cough from the age of 5 months and was treated for reactive airway disease in her hometown. She had received all the primary immunizations and there was no history of tuberculosis in the family. The child's motor milestones were grossly delayed but her intellectual development was normal. The nutritional intake was very poor, comprising of diluted buffalo milk and small quantities of home cooked cereals. The child severely malnourished, weighing 4.2 kg and her length was 67 cms. She was anemic, had a widely open anterior fontanelle and florid clinical rickets (figure 1).

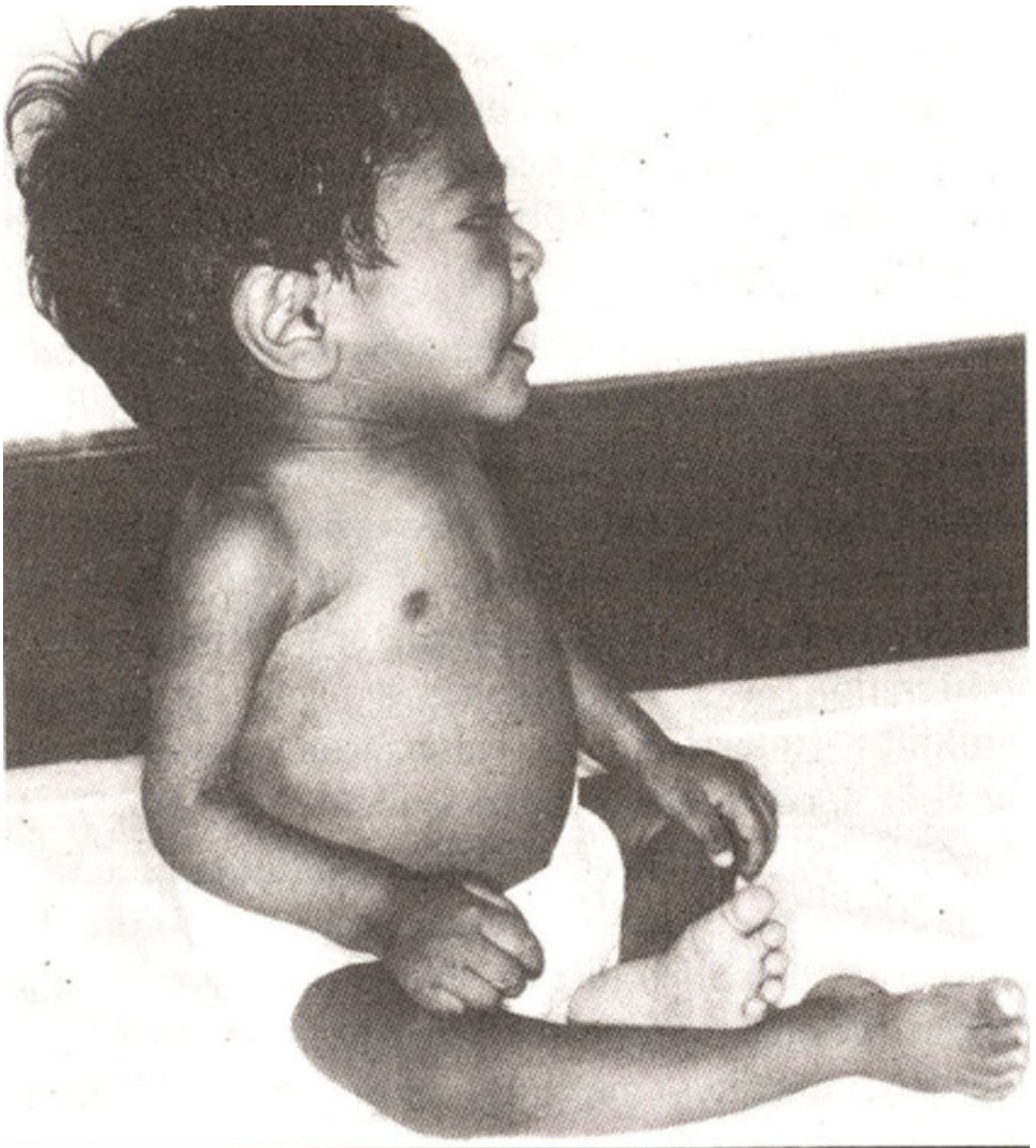


Figure 1.

Both wrists and ankles were very broad with double lateral malleoli, prominent rachitic rosary and Harrison's sulcus were present on the chest. The child had bilateral pneumonia and significant hepatosplenomegaly (liver 4 cms and spleen 3 cms below the Costal margin). There were no neurological abnormalities except for a mild generalized hypotonia.

The laboratory investigations revealed a hemoglobin of 8 gm/dl, hematocrit of 25%, a total leukocyte count of $13.2 \times 10^9/L$ (with 20% polymorphs and 75% lymphocytes). The platelet count was $100 \times 10^9/L$. The peripheral film showed no malarial parasites and the anemia was normocytic normochromic. The

electrolytes were normal and there was no acidosis. The serum creatinine was 0.4 mg/dl (normal~0.1-1 mg/dl), the prothrombin time and the activated partial thromboplastin time were both normal. The reticulocyte count was 1.4%, glucose-6-phosphate dehydrogenase was not deficient and the serum ferritin was 55 ng/ml (normal=7-200 ng/ml).

The serum calcium and phosphorus were 8 mg/dl (normal= 8.1-10.1 mg/dl) and 1 mg/dl (normal=4-5.3 mg/dl) respectively and the alkaline phosphatase was 2333 iu/L (normal=97 to 366 iu/L). The urinary aminoacid and sugar chromatography were inconclusive and the serum parathormone level was 191 pg/ml (normal=12-72 pg/ml). The sweat chloride was 22 mmol/L. The total serum proteins were 5.9 g/dl and the serum albumin was 3.9g/dl (normal=3.2-5.0 g/dl). Serum immunoglobulin levels were normal excepting mildly raised levels of IgE (92 iu/ml). Several cultures were performed including mycobacterial and PCR (polymerase chain reaction) for detection of DNA of mycobacterium tuberculosis and all were negative.

Radiological survey of the bony skeleton showed severe generalized osteopenia. extensive rickets of the thoracic cage and ends of long bones with splaying, cupping and fraying of metaphyses. No pathological features were noted. Liver biopsy revealed normal architecture of the liver parenchyma with no fibrosis in portal tracts and no granuloma formation. Significant extramedullary hemopoiesis was seen in the liver. Bone trephine clearly depicted replacement of hemopoiesis by fibroblasts with very occasional erythroid and myeloid precursors and no megakaryocytes were seen. Reticulin stain revealed significantly increased fibrosis, findings being consistent with myelofibrosis (Figure 2).

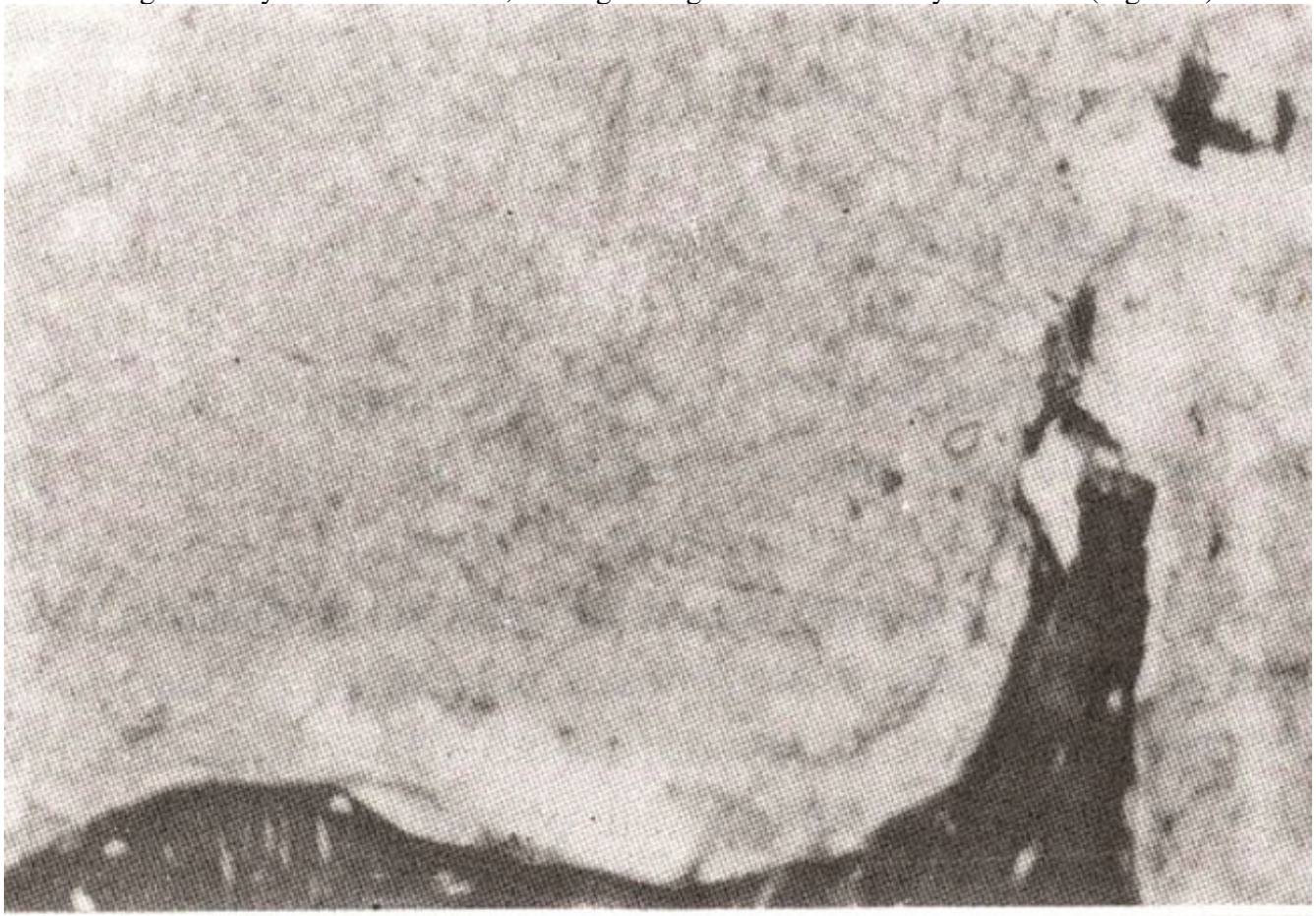


Figure 2. Reticulin stain showing increased fibrosis before therapy.

Therapy and Clinical Course

The child was treated with antibiotics and bronchodilators. She was given oral sodium phosphorus,

intravenous calcium gluconate (later made oral) and oral aiphacalidiol in the dosage of 0.25 ug daily; After 12 weeks of therapy, there was a complete regression of hepatosplenomegaly with normalization of complete blood count and serum alkaline phosphatase and a complete radiological healing of rickets. Bone trephine at that time revealed a cellular specimen containing all the hemopoetic precursor cells including megakaryocytes (Figure 3).

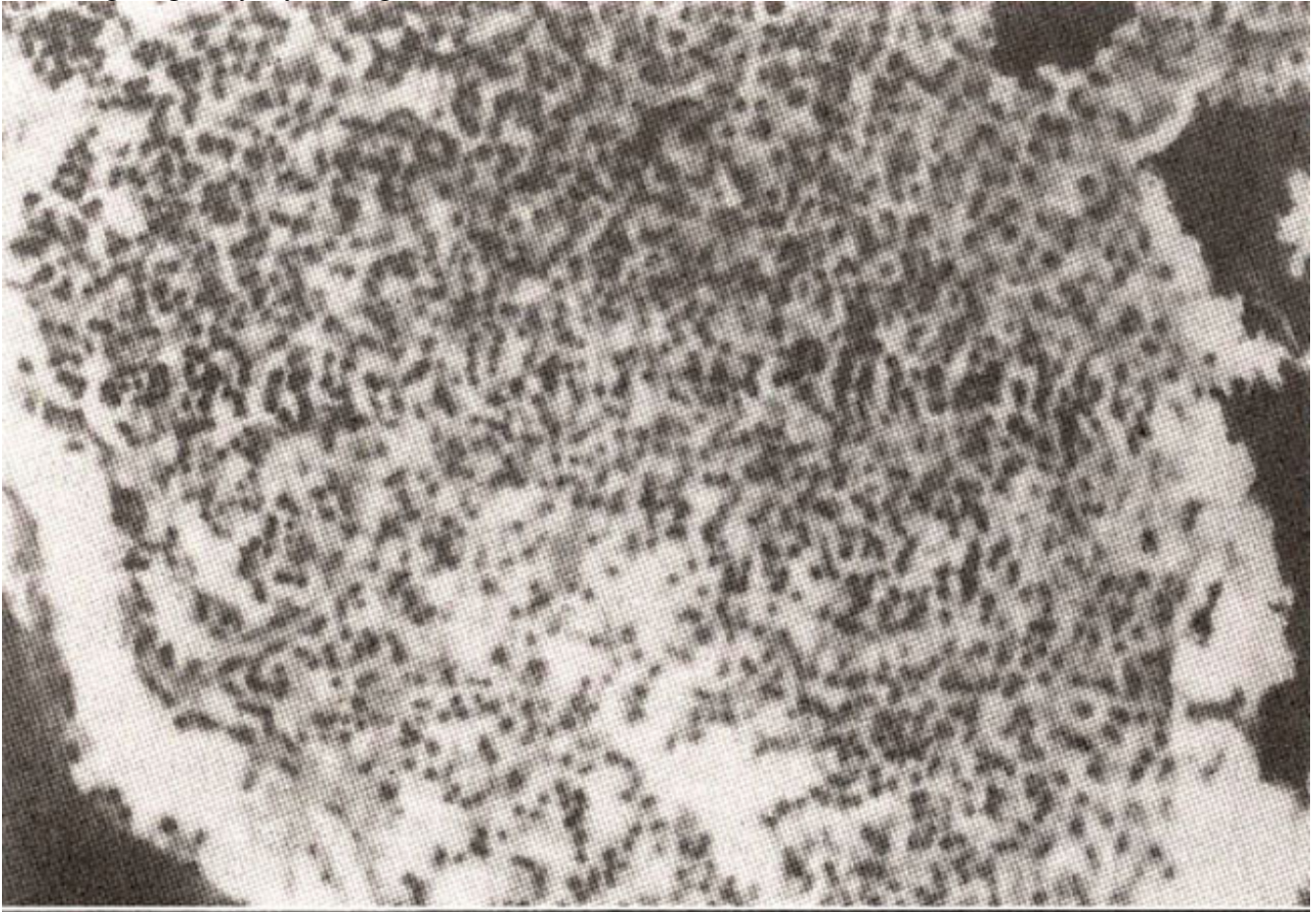


Figure 3. Histopathological sections showing cellular bone marrow after therapy. The reticulin stain showed none to minimal fibrosis (Figure 4).

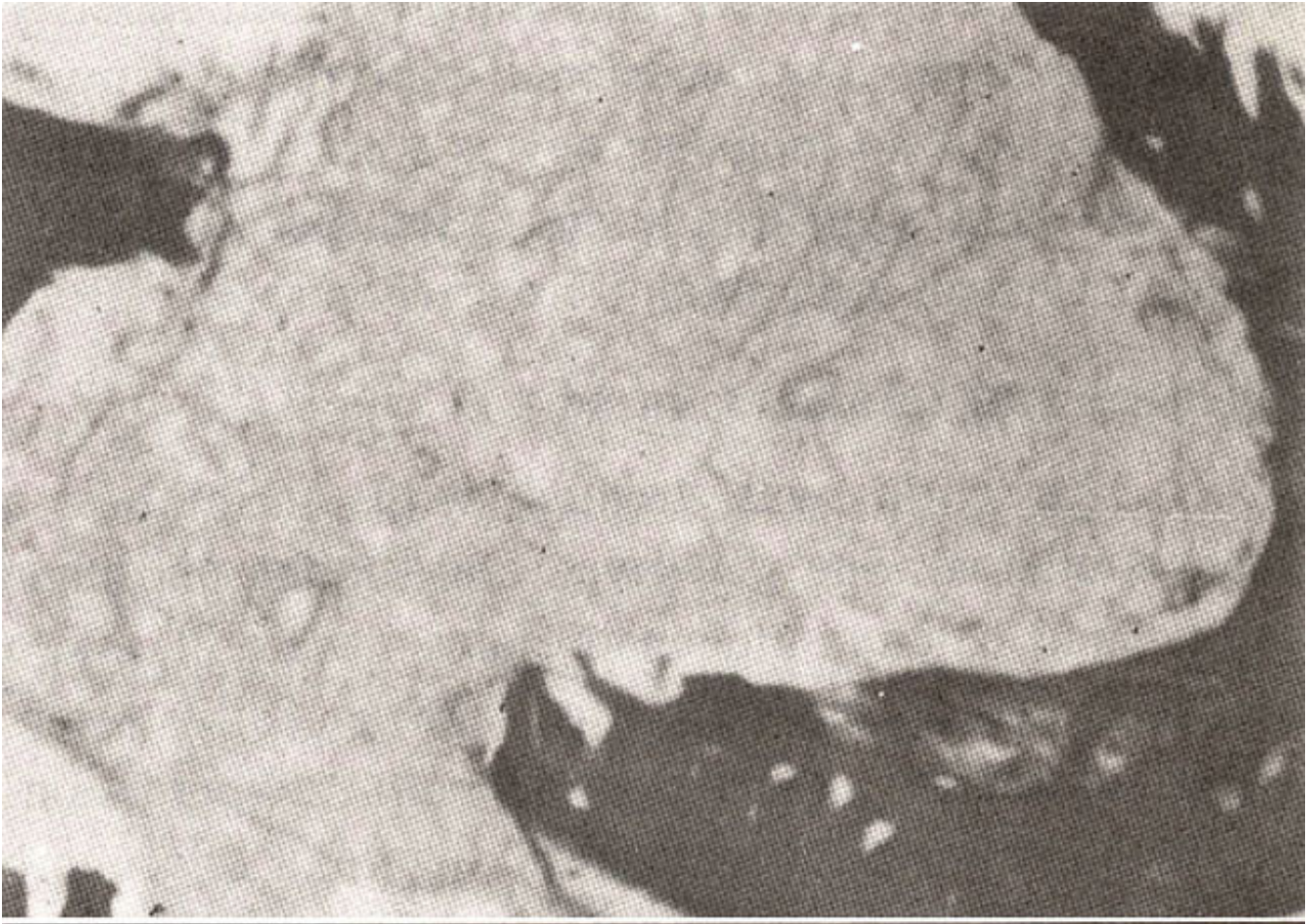


Figure 4. Reticulin stain showing minimal fibrosis after therapy.

Discussion

Vitamin D is essential for normal skeletal growth in children and along with parathormone it plays a central role in calcium and phosphorus homeostasis⁵. Casual exposure to sunlight is the major source of vitamin D for most infants and children, because dietary source is poor in the underdeveloped countries¹. Recently, it has been recognized that a wide variety of tissues and cells, related or unrelated to calcium metabolism, are target sites for 1,25-dihydroxyvitamin D₃ (OH)₂D₃. This has made vitamin D an endocrine system acting on the gut, kidneys, bones, cells of immune system and several other tissues⁶.

Vitamin D essentially increases intestinal calcium absorption, helps calcification of osteoid tissue in bones and also stimulates stem cells in the marrow to mobilize calcium from the bones⁵. Non-calcemic tissues that possess receptors for 1,25 (OH)₂ D₃ respond to the hormone in different ways. Of great and recent interest is the role of 1,25 (OH)₂ D₃ as a potent anti-proliferative and pro-differentiation mediator^{5,7}. Monocytes, macrophages, activated lymphocytes, thymocytes and hemopoietic stem cells have a vitamin D receptor (VDR), a 50-k Da unit. There are several effects of 1,25 (OH)₂ D₃ on these hemolymphopoietic tissues: It modulates the production of a plethora of monocytes, lymphocytes and bone marrow stromal cell products including several interleukins and cytokines⁸. 1,25 (OH)₂ D₃ is also involved in the differentiation of myeloid lineage and stimulates fusion and differentiation of

hemopoietic progenitors in bone marrow into several cell lines including osteoclasts which help in bone resorption. Vitamin D is therefore essential for normal hemopoiesis and its deficiency may cause suppression of marrow cell lines, clinically evident as anemia, neutropenia and thrombocytopenia^{9,10}. 1,25 (OH)² D₃ also behaves as a paracrine factor in the immune system¹⁰. It has potent actions on all the cellular components of the immune defence mechanisms and deficiency of vitamin D has long been associated with recurrent infections⁹. Vitamin D analogues have been proven to have immune modulatory activity and the proliferation of T lymphocytes as well as release of cytokines (interleukin 2, interferon gamma, tumor necrosis factor) are suppressed by 1,25 (OH)² D₃. Therefore, there is also an indirect inhibition of antibody production by B cells. These properties have been exploited and applied to clinical and pre-clinical settings such as rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, diabetes mellitus type I, several cancers including leukaemias and myeloproliferative disorders^{6,8}.

The association of rickets and myelofibrosis was first described in 1889 and as yet its causal association is unclear. A central role of vitamin D₃ in bone marrow collagen disposition has been claimed^{7,11}. It is proposed that the active hormonal metabolite, 1,25 (OH)₂ D₃ inhibits formation of fibrous tissue, mainly collagen, in the bone marrow and also enhances its degradation. The hormone inhibits proliferation of megakaryocytes which promote collagen synthesis. Degradation of fibrous tissue is mediated by the collagenases contained in monocytes and macrophages. Thus deficiency of vitamin D may allow abnormal accumulation of collagen in the bone marrow^{11,12}.

Deficiency of vitamin D stimulates secondary hyperparathyroidism which is a well recognized stimulus for formation of fibrous tissue. Severe hyperparathyroidism not only leads to extreme bone demineralization, but also to marked myelofibrosis with bone marrow displacement, osteosclerosis and reduction in bone marrow cavity. This effect has been well elucidated in uremic patients¹³⁻¹⁵, and in them parathyroidectomy alleviates that problem.

Secondary myelofibrosis in advanced rickets may therefore be the result of severe deficiency of active 1,25 (OH)² D₃ or secondary hyperparathyroidism or perhaps both. Myelofibrosis leads to compensatory extramedullary hemopoiesis resulting in hepatosplenomegaly. This is reversible after therapy with vitamin D, as was shown in our patient. The case reported herein had severe rickets and myelofibrosis which reversed after twelve weeks of the therapy with alphacalcidol. We are inclined to agree with other authors³ that rickets take a longer time to get treated in the severely malnourished. We conclude that, since vitamin D deficiency is so common in our part of the world, clinicians must be aware of its diverse functions and rare complications like myelofibrosis. Prevention of vitamin D deficiency should be emphasized by dietary supplementation and adequate sunlight exposure.

References

1. Atiq M, Suria A, Nizami SQ, et al. Vitamin D status of breastfed Pakistani infants. *Acta Pediatr.* 1998;87:737-40.
2. Fraser D, Kooh SW, Sciver CR. Hypoparathyroidism as the cause of hyperammonaciduria and phosphaturia in human vitamin D deficiency. *Pediatr. Res.*, 1967;1:425-9.
3. Yetgin S, Ozsoy Iu S, Ruacan S. et al. Vitamin D deficiency rickets and myelofibrosis. *J. Pediatr.*, 1989;114:213-7.
4. Cooperberg AA, Singer OP. Reversible myelofibrosis due to vitamin D deficiency rickets. *Can. Med. Assoc. J.*, 1966;94:392.
5. Holick MF. Non-calcemic actions of 1,25-dihydroxyvitamin D₃ and clinical applications. *Bone.* 1995; 17:1075-1115.
6. Deluca HF, Zierold C. Mechanisms and functions of vitamin D. *Nutr, Rev.* 1998;56:54-75.

7. Manolagos SC, Yu XP, Girasole G, et al. Vitamin D and the hematolymphopoetic tissue. A 1994 update. *Semin Nephrol.* 1994; 14:129-43.
8. Muller K, Bendtzen K. 1-25 dihydroxyvitamin D₃ as a natural regulator of human immune functions, *J. Investig. Dermatol., Symp. Proc.*, 1996;1: 68-71.
9. Walka M, Daumling S, Hadorn MB, et al. Vitamin D dependent rickets type 11 with myelofibrosis and immune dysfunction. *Eur. J. Pediatr.*, 1991;150:665-8.
10. Casteels K, Bouillon R, Waer M, et al. Immunomodulatory effects of 1,25-dihydroxyvitamin D₃. *Cur. Opin Nephrol., Hypertens* 1995;4:313-8.
11. McCarthy DM, Hibbin JA, Goldman JM. A role for 1-25 dihydroxyvitamin D₃ in control of bone marrow collagen disposition? *Lancet*, 1984;1:78-80.
12. Yetgin S, Ozsoylu S. Myeloid metaplasia in vitamin D deficiency rickets. *Scan. J. Hematol.*, 1982;28:180-5.
13. Cundy T, Kanis JA, Earnshaw M, et al. Comparative effects of alphacalcidol and parathyroidectomy with vitamin D in hyperthyroid renal bone disease. *Q. J. Med.*, 1986;60:659-70.
14. Barbour OL. Effect of parathyroidectomy on anemia in chronic renal failure. *Arch. Intern. Med.*, 1979; 139:889-91.
15. Rao DS, Shih MS, Mohini R. Effect of serum parathyroid hormone and bone marrow fibrosis on the response to erythropoietin in uremia. *N. Engl. J. Med.*, 1993;328:171-5.