Malignant osteopetrosis obscured by maternal vitamin D deficiency in a neonate

Abstract A neonate presented with clinical, biochemical, endocrine and radiographic features consistent with vitamin D deficiency rickets of maternal origin. Persistent hypocalcemia and subsequent development of pancytopenia, hemolysis and hepatosplenomegaly prompted further studies that led to the diagnosis of infantile osteopetrosis.

Conclusion Osteopetrosis is an important differential diagnosis of neonatal rickets and is not excluded by low vitamin D levels.

Key words Malignant infantile osteopetrosis · Rickets · Neonate · Vitamin D deficiency

Abbreviations 25OHD 25-Hydroxyvitamin D · 1,25(OH)₂D 1,25-Dihydroxyvitamin D · PTH Parathyroid hormone · ALP Alkaline phosphatase

Introduction Malignant infantile osteopetrosis is a rare autosomal recessive disorder of osteoclast function and hence decreased resorption of calcified cartilage. Accumulation of sclerotic bone results in reduced marrow space and narrowed osseous foramina. Major consequences include marrow failure and nerve entrapment [6, 13]. If untreated, death usually occurs in mid-childhood due to anemia, bleeding or infection. While partial amelioration may be achieved by treatment with corticosteroids [15], parathyroid hormone (PTH) [1, 7], high-dose calcitriol [9] or gamma interferon [10, 11], the disease can be cured by bone marrow transplantation providing hematopoietic stem cells that can differentiate into functioning osteoclasts [5].

Rickets is a seemingly paradoxical but characteristic feature of infantile osteopetrosis (osteopetrorickets) [3, 8]. In severe osteopetrosis, 1,25-dihydroxyvitamin D [1,25(OH)₂D] synthesis is usually maximally stimulated and 25-hydroxyvitamin D (25OHD) plasma concentrations are normal. Here, we report a patient with infantile osteopetrosis in whom the diagnosis was obfuscated by vitamin D deficiency of maternal origin.

Case report A 2-week-old boy was referred to our hospital because of recurrent convulsions starting on the 6th day of life. He was the first child of healthy, non-consanguineous parents of Turkish origin. Pregnancy and birth at term were uneventful.

Physical examination was normal. Laboratory data at admission showed hypocalcemia, hypophosphatemia, elevated serum PTH and alkaline phosphatase (ALP) levels. Both plasma 25OHD and 1,25(OH)₂D concentrations were markedly decreased (Table 1). Complete blood count, serum electrolytes, albumin, creatinine, blood gases and glucose were normal.

Radiography of the knee showed signs of florid rickets, characterized by an increased gap between the ossification center of the epiphysis and the visible end of the metaphysis, including widening and fraying of the metaphysis with longitudinal stripes of different bone densities. However, instead of osteopenia there was remark-
able increase in bone density and no differentiation of cortex and spongiosa (Fig. 1A).

Investigation of the mother’s biochemical and endocrine status revealed markedly reduced plasma 25OHD and 1,25(OH)2D levels. Serum calcium, phosphorus and PTH were in the normal range. ALP was slightly elevated and bone density was normal. Of note in the mother’s history were her dark skin, avoidance of sunlight, the timing of pregnancy between May and February, and a diet low in vitamin D. Vitamin D was not supplemented during pregnancy. After exposure to ultraviolet light, her levels of 25OHD and 1,25(OH)2D rapidly normalized.

Since clinical, laboratory and radiographic findings suggested vitamin D deficiency rickets of maternal origin in her newborn, treatment with 25OHD (5,000 IE/day orally), high dose supplementation of elemental calcium given as calcium gluconate (600 mg/day i.v. and 200 mg/day orally, i.e., 200 mg/kg per day) and phosphorus administered as sodium glycerophosphate (6 mmol/kg per day, i.e., 186 mg/kg per day inorganic phosphorus) was initiated.

After 3 weeks of treatment the radiographic signs of rickets had improved albeit not disappeared. The width of the epiphyseal growth plates had decreased, the metaphyses had become more sharply defined and some superiostial new bone formation was visible along the diaphyses due to remineralization of osteoid in this area. However, there was still a marked increase in radiodensity of the bones with lack of sufficient bone modeling and splayed metaphyses (Fig. 1B). Plasma levels of PTH, 25OHD and 1,25(OH)2D and ALP activity had normalized. Remarkably, serum calcium values rarely exceeded 2.1 mmol/l (8.4 mg/dl) under treatment, and urinary calcium excretion remained very low (3 l mol/kg per day; urinary calcium/creatinine ratio: 0.03). 25OHD and calcium supplementation were continued for another 4 weeks, since radiographic and laboratory features still showed altered mineral homeostasis.

During the subsequent 4 weeks the boy successively developed thrombocytopenia, anemia, hemolysis, reticulocytosis, leukocytosis and leukoerythroblastosis. Physical examination revealed hepatosplenomegaly. These signs and symptoms were consistent with malignant osteopetrosis. Radiography of the knee was repeated (Fig. 1C). The radiographic features of rickets had now almost completely resolved but the bone density was still highly increased with obliteration of the corticomедullary junction and poorly defined medullary canals. X-rays of skull and spine also displayed characteristic features of osteopetrosis. The diagnosis was confirmed by a trephine bone marrow biopsy performed at 10 weeks of age (Fig. 2). On microscopical examination, inadequately remodelled bone was observed.