

Osteopetrorickets Presenting with Failure to Thrive and Hypophosphatemia

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Osteopetrosis is a rare group of bone disorders characterized by defective osteoclast bone resorption causing high bone mineral density. A high bone mineral density in combination with defective skeletal mineralization results in a phenotype of osteopetrorickets. We present a rare presentation of infantile osteopetrorickets in an 8-week-old female who presented with failure to thrive, hypophosphatemia, anemia, and thrombocytopenia. A skeletal survey showed increased bone density with rachitic changes. She was found to have a homozygous T-cell immune regulator 1 (*TCIRG1*) pathogenic mutation consistent with osteopetrosis. This highlights the importance of a clinical suspicion of osteopetrosis with this symptom constellation.

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Osteopetrosis represents a clinically and genetically heterogeneous group of sclerosing bone dysplasias characterized by high bone mineral density due to abnormal osteoclast formation or function [1]. Patients can develop hypocalcemia, compressive neuropathies, fractures, obliteration of the bone marrow space, and anemia with extramedullary hematopoiesis. Before many of the defective genes of osteoclast activity were identified, Shapiro et al classified osteopetrosis as autosomal recessive “malignant” or “infantile” osteopetrosis [2], autosomal recessive intermediate osteopetrosis, and autosomal dominant osteopetrosis [3]. Currently, the Nosology and Classification of Genetic Skeletal disorders has further differentiated several forms of osteopetrosis based on the genetic defect [4]. Autosomal recessive osteopetrosis (ARO) is rare, with an overall estimated incidence of 1:200000 [5].

We present an unusual case of osteopetrosis in an 8-week-old infant who presented with failure to thrive, anemia, thrombocytopenia, and severe hypophosphatemia prior to manifesting severe hypocalcemia secondary to a pathogenic mutation in T-cell immune regulator 1 (*TCIRG1*).

1. Case Presentation

An 8-week-old female twin born at 36 weeks had a history of frequent diarrhea and emesis, with feeds resulting in failure to thrive (FTT). Her length was 2.64 SD below the mean and her weight was 2.04 SD below the mean when adjusted for gestational age. Initial screening

laboratory evaluation was significant for hypophosphatemia (2.5 mg/dL), relatively normal calcium (9.1 mg/dL), anemia (hemoglobin 7.9g/dL), and thrombocytopenia (platelet count $66 \times 10^3/\text{uL}$). Subsequent evaluation revealed elevated serum parathyroid hormone level (400 pg/mL) and normal 25-hydroxyvitamin D concentration (33 pg/mL). Nutritional hypocalcemia with secondary hyperparathyroidism and resultant hypophosphatemia was suspected. She was started on 20 mg/kg/day of elemental calcium and her calorie intake was optimized. A wrist x-ray showed dense bones as well as widening, cupping, and fraying of the metaphyses. Patient had an elevated white cell count ($28.4 \times 10^3/\text{uL}$) and lactate dehydrogenase level (1948 U/L). In view of worsening anemia and thrombocytopenia, elevated white cell counts, and serum lactate dehydrogenase, the differential diagnoses included osteopetrosis, juvenile myelomonocytic leukemia, and erythroid leukemia.

Subsequently, bone marrow biopsy was performed, which revealed monocytosis with increased nucleated red blood cells. Fluorescence in situ hybridization (FISH) for Myelodysplastic syndrome and trisomy 21 were negative. During her hospitalization, she required multiple platelet and packed red blood cell transfusions due to anemia and thrombocytopenia.

A skeletal survey (Fig. 1) revealed increased diaphyseal bone density along with rachitic changes of cupping, fraying, and fragmentation of metaphysis. At 10 weeks of life, she developed hypocalcemia, which continued to worsen despite treatment with calcitriol 1 mcg BID (0.6 mcg/kg/day) and elemental calcium up to 125 mg/kg/day. She also required large doses of phosphorous replacement, up to 9.5 mmol/kg/day (294.5 mg/kg/day). Despite increasing calcitriol and calcium doses, her hypocalcemia remained refractory and difficult to manage. She required multiple intravenous (IV) calcium boluses in addition to IV maintenance dosing. Although a slow continuous IV calcium drip would have been the preferred management of hypocalcemia, the treatment was limited by IV access, the need for multiple transfusions, total parenteral nutrition (TPN), antibiotics, and other IV medications. The patient also had feeding intolerance and received multiple doses of parenteral calcium boluses. Details regarding laboratory results and medication doses are in Table 1.

Brain magnetic resonance imaging (MRI) showed thickening of the skull, narrowing of the optic nerve canal, and narrowing of the internal auditory canal. Visual and auditory evoked potentials suggested left-sided blindness and sensorineural hearing loss. Genetic testing from GeneDx laboratories revealed a homozygous *TCIRG1* pathogenic mutation confirming malignant infantile osteopetrosis. Complete deletion was ruled out with a normal comparative genomic hybridization (CGH) array.

With her brother being a good match, the patient underwent a matched-related donor hematopoietic stem cell transplant (HSCT) at 4 months of age. Most recent FISH for XY showed 95% donor indicating success of the transplant. The patient's post-transplant clinical course was complicated. She was treated with defibrotide for possible veno-occlusive disease as well as methylprednisolone for graft versus host disease. She also developed



Figure 1. Skeletal survey on initial presentation. Legend: skeletal survey illustrating rachitic changes of cupping, fraying, and fragmentation of metaphysis (A) and increased diaphyseal bone density (B).

Table 1. Clinical and laboratory course of the patient

Age (Weeks)	8.5	9	10	10*	11	12	17	20**	20.5	22.5
Calcium (mg/dL)	9.1	8.0	8.8	8.9	7.1	5.8	6.8	5.8	5.6	9.2
Phosphorus (mg/dL)	2.8	2.4	2.5	2.2	3.5	3.5	3.3	4.5	7.7	4.5
Alkaline phosphatase (U/L)	---	---	456	518	---	460	522	441	259	449
PTH (pg/mL)	---	400	252	---	---	---	---	---	---	---
Albumin (g/dL)	3.9	---	3.7	3.4	3.3	3.0	2.8	3.1	3.3	3.5
25(OH)D (ng/mL)	---	30	33	---	---	17	---	---	---	21
1,25(OH) ₂ D (pg/mL)	---	---	383	---	---	386	---	---	---	331
WBC (10 ³ /uL)	19.3	12.8	28.4	24.6	---	10.9	2.1	2.47	1.4	1.0
Hemoglobin (g/dL)	7.9	8.0	6.9	6.5	---	7.4	6.3	5.8	10.6	8.5
Platelets (10 ³ /uL)	66	63	47	46	---	26	40	17	85	54
Reticulocyte count (%)	---	---	13.8	15.13	15.94	---	---	---	0.43	0.49
Calcium supplementation (mg/kg/day)	20	20	20	20	59	118	55	72	125	67
Phosphorus supplementation (mmol/kg/day)	---	---	---	---	2.4	5.3	8	9.5	2.7	---
Calcitriol (mcg/kg/day)	---	---	---	---	---	0.3	0.6	0.5	0.5	0.2

Abbreviations: 1,25-dihydroxyvitamin D, 1,25(OH)₂D; 25-hydroxyvitamin D, 25(OH)D; PTH, parathyroid hormone; WBC, white blood cell.

*Date of inpatient admission.

**Date of bone marrow transplant.

persistent hypertension, acute kidney injury, and fluid overload, which required continuous renal replacement therapy (CRRT), a form of slow ultrafiltration and hemodialysis. She continued to have persistent hypocalcemia for about 3 weeks post-transplant. After that, the dose of calcitriol and calcium gluconate were gradually reduced. At about 4 weeks post-transplant, she no longer required calcium or phosphorous supplementation. Repeat x-ray about 7 weeks post-transplant demonstrated hyperdensity of marrow and early healing cortex and periosteal changes (Fig. 2).

The patient is now 16 months old, transfusion independent, and no longer on immunosuppressive treatment. She continues to catch-up on developmental milestones. Her calcium and phosphorous levels have remained normal. Repeated visual testing through visual evoked potentials now indicates intact visual pathways, although they do not equate to normal visual acuity in her.

2. Discussion

The initial presentation of FTT and hypophosphatemia with normal calcium and 25-hydroxyvitamin D levels presented a diagnostic and management conundrum in this patient with osteopetrorickets. In osteopetrosis, dysfunctional osteoclastic bone resorption results in significant accumulation of calcium in the skeleton, thickening of cortical and lamellar bone, and defective skeletal mineralization of the newly formed bone. The ineffective bone resorption leads to hypocalcemia, secondary hyperparathyroidism, and hypophosphatemia, eventually resulting in osteopetrorickets. It should be kept in mind that patients with osteopetrosis can present with hypophosphatemia prior to the onset of hypocalcemia [6].

The most frequent mutation, accounting for over 50% of the cases of ARO, is in the *TCIRG1* gene, which encodes the $\alpha 3$ subunit of the V0 domain of the vacuolar ATPase (V-ATPase) proton pump on osteoclasts and gastric parietal cells on the apical membrane [7]. Normal activity of V-ATPase proton pump is needed to dissolve both the inorganic and organic bone matrix. Without this acidification, bone resorption is ineffective, leading to dense bones [7].



Figure 2. Skeletal survey post-transplant. Legend: x-ray at 7 weeks post-transplant showing hyperdensity of marrow and early healing cortex and periosteal changes (C).

In the gastric mucosa, normal pump activity is needed to maintain an acidic environment conducive to absorb calcium [8]. In our patient, it was difficult to treat the refractory hypocalcemia. A review of children with the same genetic defect has speculated that this is likely secondary to impaired gut absorption as well as the inability of the bone to mobilize calcium stores [8, 9]. This led to secondary hyperparathyroidism and resultant hypophosphatemia. As a result, she developed paradoxical rickets in the bone despite osteopetrotic changes [10]. This phenomenon of poor gastric and intestinal absorption has now been described in both animal models and human studies [2, 11]. It is important to maintain a serum calcium of 8 to 9 mg/dL before transplant to avoid hyperparathyroidism. Fractures are frequently seen due to the poor quality of bone in osteopetrosis but were absent in our patient. Her biochemical features, including hypocalcemia, hypophosphatemia, secondary hyperparathyroidism, normal serum levels of 25-hydroxyvitamin D, and persistently elevated serum levels of 1,25 dihydroxy vitamin D, are akin to type 2 hereditary vitamin D dependent due to the mutations of *VDR*. In this case, these were secondary to the refractory hypocalcemia.

Defective bone resorption led to infringement of the bone upon the marrow, causing anemia and thrombocytopenia in our patient [12]. Narrowing of the optic foramina caused compressive optic neuropathy and the resultant left-sided blindness [13]. Visual findings have previously been described as a common initial presentation [5, 12]. Our patient also had sensorineural hearing loss secondary to bony compression of the nerve and sclerosis of the middle ear ossicles. Neuroimaging is important to evaluate for cranial nerve involvement, as bony compression can lead to hearing and vision loss.

Although it is common to encounter hypercalcemia post-transplant [5], it can be avoided with close monitoring and gradual withdrawal of calcium and calcitriol therapy. At present, the only curative treatment for ARO remains HSCT. In patients with the *TCIRG1* mutation, it currently offers the best chance of long-term survival [14]. Additionally, as osteoclasts are hematopoietic in origin, a transplant should allow for bony resorption by the donor-derived cells. Donor osteoclasts differentiate and mature, leading to bone remodeling and hematopoiesis. Although rapid resolution of hypocalcemia is usually expected, this case presentation showed that supportive care is still needed following transplant. Patients are also at risk for further post-transplant complications, including engraftment failure, graft versus host disease, and infection. A multidisciplinary approach is important to provide optimal care for patients with osteopetrosis. Some future directions include animal studies using in utero transplantation of donor stem cells or gene-corrected autologous stem cells [15] and synthetic RANKL therapy [16], but these remain experimental options in humans.

3. Conclusion

Autosomal recessive osteopetrosis is a rare disease that can present with nondescript symptoms, such as FTT. Thorough evaluation by skeletal survey and serial monitoring is extremely important in infants with hypophosphatemia and FTT. It is important to effectively

diagnose and manage rickets and sequelae of secondary hyperparathyroidism—even in cases where the bones are dense.

Additional Information

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