JCEM Case Reports, 2025, **3**, luaf066
https://doi.org/10.1210/jcemcr/luaf066
Advance access publication 15 April 2025
Case Report

Severe Hypercalcemia Associated With Perinatal Hypophosphatasia While Receiving Enzyme Replacement Therapy

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Abstract

Hypophosphatasia (HPP) is characterized by defective bone mineralization due to reduced function of tissue-nonspecific alkaline phosphatase (TNSALP) caused by pathogenic *ALPL* gene variants. Hypercalcemia is more common in the perinatal and infantile forms and may be mitigated or prevented with enzyme replacement therapy asfotase alfa (AA). Here, we report a patient who developed severe hypercalcemia while receiving AA. Hypercalcemia was initially managed with intravenous fluids, dietary calcium restriction, and maximizing AA dose. Despite these measures, she required an additional hospital admission, at which time calcitonin 4 IU/kg every 12 hours was initiated. On this regimen, her calcium normalized without recurrence of severe hypercalcemia. Over the subsequent 8 months, restrictions of calcium intake were slowly lifted, and calcitonin was tapered and discontinued with maintenance of calcium within the normal range. This case underscores the significance of vigilant monitoring of calcium levels and dietary intake in infants diagnosed with HPP. While calcitonin is typically not considered as a sustained treatment for hypercalcemia, the present case illustrates the efficacy of adjunct calcitonin therapy, in conjunction with restricted calcium intake and maximum AA dosing, in managing severe hypercalcemia in an infant with perinatal HPP.

Key Words: hypophosphatasia, hypercalcemia, asfotase alfa, calcitonin

Abbreviations: AA, asfotase alfa; HPP, hypophosphatasia; TNSALP, tissue-nonspecific alkaline phosphatase.

Introduction

Hypophosphatasia (HPP) is an inherited metabolic bone disorder that is characterized by a wide spectrum of clinical manifestations and that mainly affects bone and dental mineralization. It can also manifest with neuromuscular, respiratory, and renal disease [1]. HPP is caused by reduced function of tissue-nonspecific alkaline phosphatase (TNSALP) from pathogenic *ALPL* gene variants localized on chromosome 1p36.12 [2]. The enzyme TNSALP is highly expressed at the extracellular surface of the plasma membrane where it dephosphorylates and hydrolyzes extracellular inorganic pyrophosphate (PPi), which is a potent inhibitor of mineralization that leads to impaired deposition of hydroxyapatite in bone and teeth [3]. TNSALP deficiency or absence will lead to accumulation of PPi in the extracellular matrix with subsequent inhibition of bone mineralization [4, 5]. The clinical spectrum of HPP is broad and has been classified into different clinical phenotypes depending on age of onset, disease severity, and clinical manifestations. Perinatal HPP is considered the most severe form, while adult onset HPP and odontohypophosphatasia are the milder forms of the disease [1].

HPP can be inherited in an autosomal dominant or recessive pattern with more than 400 *ALPL* gene variants identified [6]. Autosomal recessive inheritance is more often associated with severe disease (perinatal and infantile HPP) [2], with milder forms typically inherited as an autosomal dominant manner. Autosomal recessive disease typically leads to complete penetrance while the dominant form of the disease has incomplete penetrance [2].

In severe perinatal HPP, fetal imaging may reveal chest deformities complicated with pulmonary hypoplasia, under-mineralization, and fractures. Postnatal imaging demonstrates skeletal abnormalities including short, bowed long bones with or without fractures, varying degrees of skeletal under-mineralization, cup-shaped metaphysis and osteochondral spurs that are associated with skin dimpling on forearms and legs [1, 7].

Perinatal severe HPP is a life-threatening disease if left untreated [1, 8]. Asfotase alfa (AA) is a human recombinant TNSALP that promotes bone mineralization. It is approved for the treatment of childhood-onset HPP. Hypercalcemia is common in infants with untreated, severe HPP [9]. AA may mitigate or prevent hypercalcemia [10]. Here we report a patient who developed severe hypercalcemia while receiving AA and describe her clinical course and our management strategy (Fig. 1).

Case Presentation

A now 4-year-old girl, with perinatal hypophosphatasia treated with AA (6 mg/kg/week) since day 2 of life, presented with severe hypercalcemia at 9 months of age.

Received: 10 December 2024. **Editorial Decision:** 13 March 2025. **Corrected and Typeset:** 15 April 2025

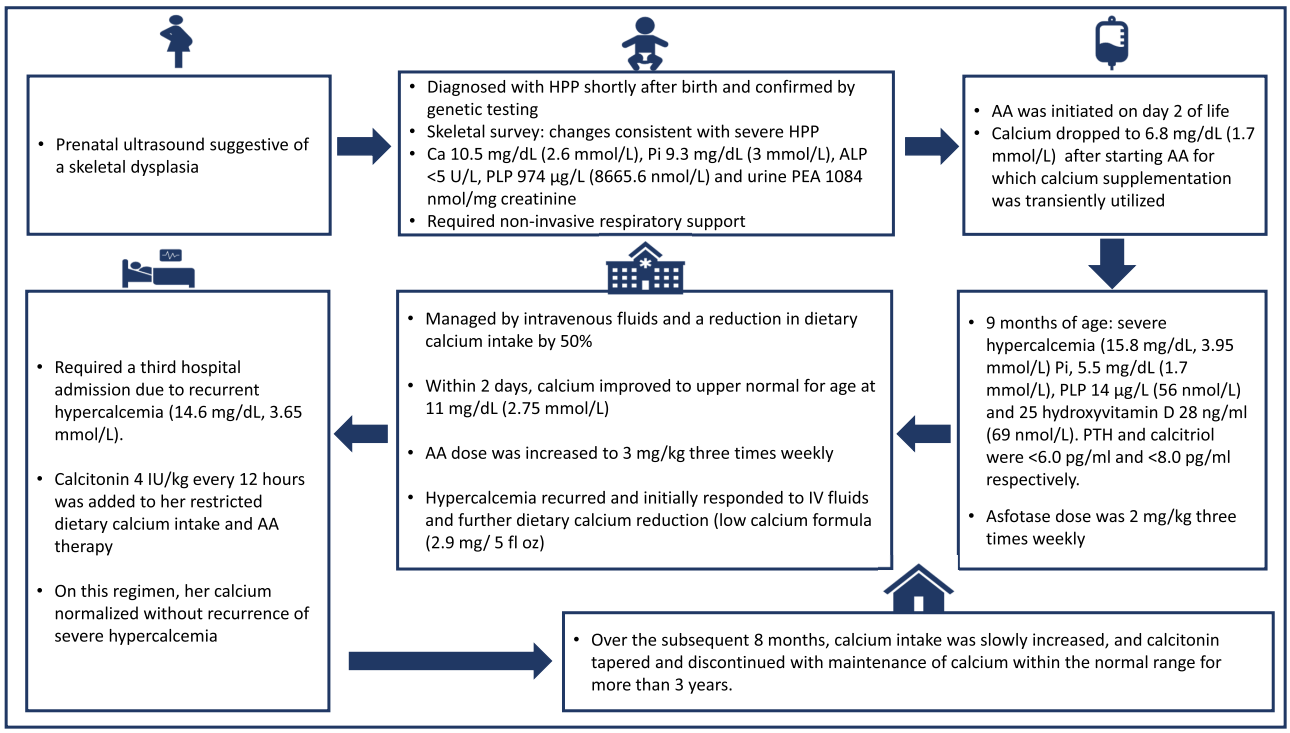

Figure 1. This figure illustrates the progression of the patient's clinical course, including her diagnosis of perinatal hypophosphatasia (HPP), subsequent laboratory evaluations, and medical interventions at different stages.

Abbreviations: AA, asfotase alfa; ALP, alkaline phosphatase; Ca, calcium; PEA, urine phosphoethanolamine; Pi, phosphorus; PLP, pyridoxal 5-phosphate; PTH, parathyroid hormone.

Prenatal ultrasound was suggestive of a skeletal dysplasia. She was born to a 24-year-old G3 P2 mother at 38 weeks gestation. She developed respiratory distress shortly after birth requiring noninvasive respiratory support. Skeletal survey obtained at day 2 of life revealed diffuse metaphyseal splaying, bone under-mineralization, platyspondyly, and thin ribs. Long bones appeared foreshortened. There were no obvious fractures on the initial skeletal survey. She developed one episode of seizure on day 2 of life confirmed by electroencephalogram (EEG), which revealed a moderately severe diffuse disturbance of cerebral function consistent with a focal or multifocal seizure disorder. Renal ultrasound was unremarkable.

Diagnostic Assessment

Initial laboratory evaluation at day 2 of life revealed a normal calcium of 10.5 mg/dL (2.6 mmol/L), phosphorus 9.3 mg/dL (3 mmol/L), total alkaline phosphatase <5 U/L, pyridoxal 5-phosphate 974 µg/L (8665.6 nmol/L) (reference range, 5-50 µg/L), and urine phosphoethanolamine to creatinine ratio of 1084 nmol/mg (1084 µmol/mmol) (reference range, 15-341 nmol/mg). Genetic testing subsequently revealed 2 pathogenic variants in the *ALPL* gene (c.661G>C/p.Gly221Arg and c.1471G>A/p.Gly491Arg). AA was initiated at a dose 2 mg/kg 3 times weekly. One day after initiating AA, her calcium dropped to 6.8 mg/dL (1.7 mmol/L), for which calcium supplementation was transiently utilized. At 9 months of age, she developed severe hypercalcemia (15.8 mg/dL, 3.95 mmol/L). Phosphorus was 5.5 mg/dL (1.78 mmol/L), pyridoxal 5-phosphate 14 µg/L (56 nmol/L), and 25 hydroxyvitamin D 28 ng/mL (69 nmol/L). Parathyroid hormone and calcitriol were appropriately suppressed at <6.0 pg/mL (<0.64 pmol/L) and <8.0 pg/mL (<19.2 pmol/L), respectively. Her dose of AA remained 2 mg/kg 3 times weekly.

Treatment

Initial management of hypercalcemia included intravenous fluids and a reduction in dietary calcium intake by 50% (receiving approximately 200 mg of calcium daily). After 2 days, serum calcium declined to the upper end of normal range for age at 11 mg/dL (2.75 mmol/L). Although radiographs identified worsening changes of hypophosphatasia at the wrists and persistent changes in the knees, imaging was markedly improved compared to pre-AA at birth (Fig. 2). The dose of AA was subsequently increased to 3 mg/kg 3 times weekly due to hypercalcemia and mildly worsening radiographic findings. Hypercalcemia recurred after 10 days and initially responded to intravenous (IV) fluids and further dietary calcium reduction (low calcium formula containing 2.9 mg/5 fluid oz) (receiving approximately 17 mg of elemental calcium daily). Despite these measures, she required a third hospital admission 13 days after her second hypercalcemic episode, at which time calcitonin 4 IU/kg every 12 hours was added to her restricted dietary calcium intake and AA therapy. On this regimen, her calcium normalized without recurrence of severe hypercalcemia.

Outcome and Follow-Up

Over the subsequent 8 months, calcium intake was slowly increased, and calcitonin tapered and discontinued with maintenance of calcium within the normal range for more than 3 years (Fig. 3).

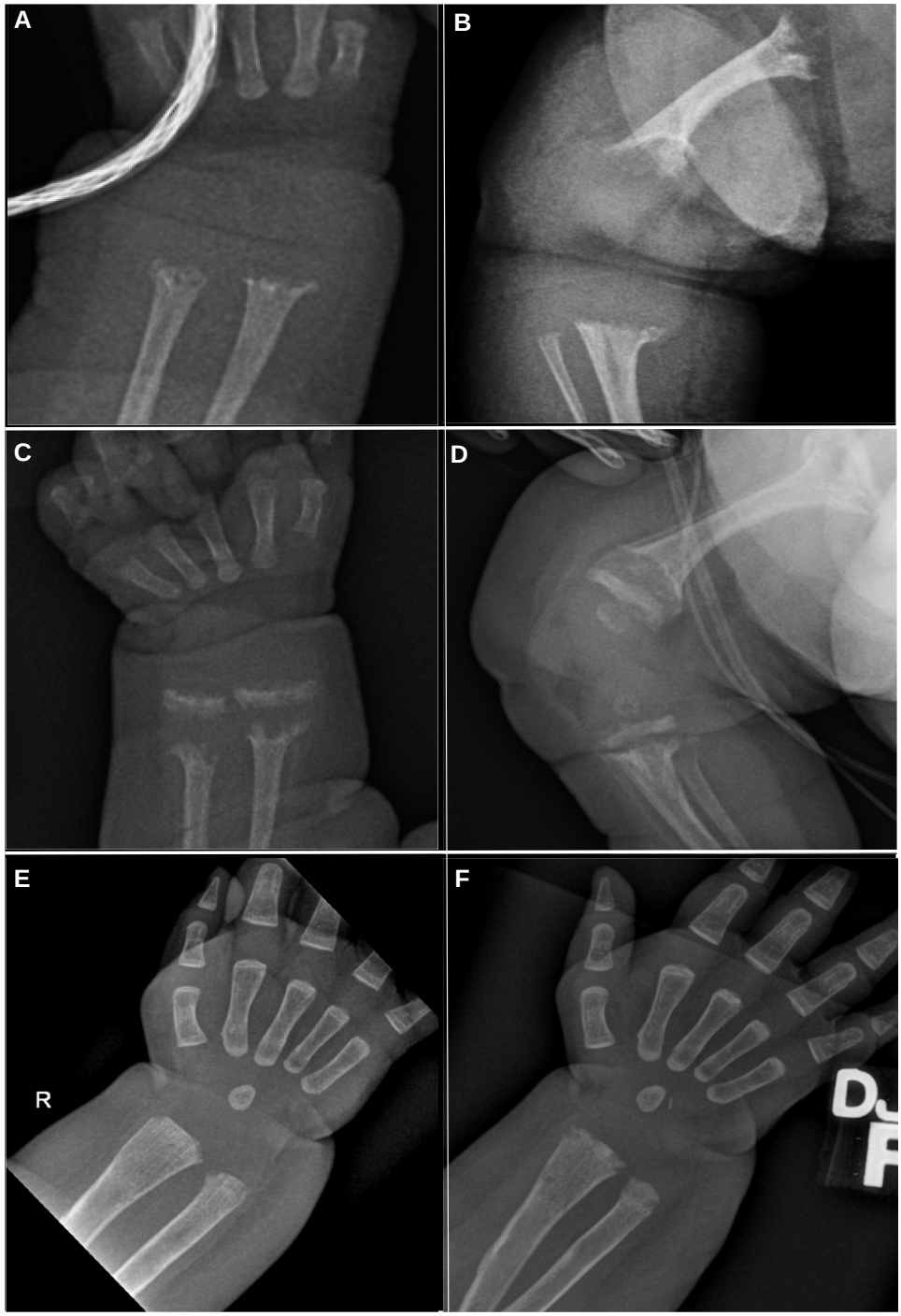

Figure 2. (A) Wrist radiograph at day 2 of life and (B) knee radiograph at day 2 of life, both demonstrating abnormal metaphyseal changes with lack of mineralization. (C) Wrist radiograph at 2 months of age and (D) knee radiograph at 2 months of age, demonstrating interval improved but incomplete mineralization. (E) Wrist radiograph at 6 months of age, demonstrating considerable improvement in mineralization of the distal radius and ulna. (F) Wrist radiograph at 9 months of age, demonstrating increased irregularity along the distal metaphyses of the radius and ulna.

Discussion

Calcium and phosphate homeostasis is a dynamic process influenced by many factors, including gastrointestinal absorption, renal excretion, and bone formation and resorption [11]. More than 99% of calcium resides in bone as hydroxyapatite to provide skeletal strength and act as a calcium reservoir that can be utilized to maintain serum calcium concentrations within a normal range [11]. Due to impaired bone mineralization, hypercalcemia and hyperphosphatemia are known complications of the more severe forms of HPP [1, 9]. A retrospective review that included 48 newborns with perinatal or infantile HPP described the clinical and biochemical phenotype in the untreated state. Of all the patients in the cohort, 28 of 39 (72%) were found to have either high serum or urine calcium [9], and nephrocalcinosis was reported in 16 of 31 (52%) [9]. Another cohort included 50 children with HPP; 4 (8%) perinatal, 17 (34%) infantile and 29 (58%)

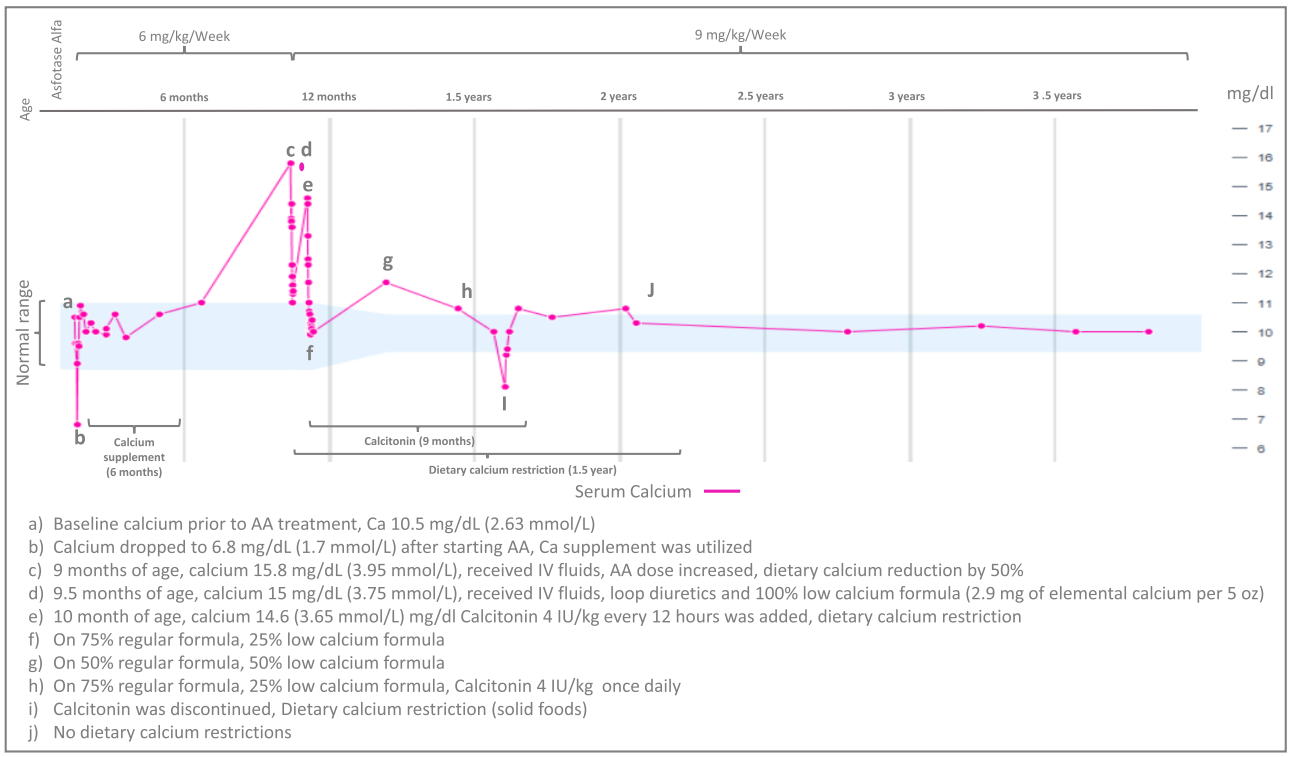

Figure 3. The trajectory of calcium levels across various stages of the patient's clinical course, highlighting different interventions implemented to manage hypercalcemia.

childhood HPP: the median calcium concentration in the perinatal HPP group was 11.3 mg/dL (2.825 mmol/L) compared to 10 mg/dL (2.5 mmol/L) and 9.9 mg/dL (2.475 mmol/L) in the infantile and childhood-onset HPP, respectively [12]. Nephrocalcinosis was reported in 50% and 76% of the perinatal and infantile HPP groups, respectively, relative to only 17% in the childhood HPP group [12]. In infants and children with HPP, nephrocalcinosis can develop with a normocalcemic status. In a global HPP registry, 68% of those with nephrocalcinosis did not have a documented history of hypercalcemia; however, the presence of hypercalcemia was a predictor of nephrocalcinosis [13]. Our patient's initial renal ultrasound at birth did not show nephrocalcinosis; however, repeat imaging at 9 months of age revealed bilateral nephrocalcinosis.

A variety of treatment approaches can be utilized for management of hypercalcemia in HPP. This includes intravenous fluids, calcitonin, and loop diuretics for short-term management. Longer-term glucocorticoid therapy and low dietary calcium intake have previously been reported [14-16]. Bisphosphonates are avoided in patients with HPP as they may worsen the severity of bone disease by further impairing bone mineralization in patients already predisposed to defective skeletal development [17, 18]. As the main cause of hypercalcemia and hypercalciuria in HPP is felt to be due to impaired calcium deposition in bone, AA would seem an effective treatment for hypercalcemia associated with HPP [10]. In an open-label, 7-year follow-up, single-arm phase 2 trial that included 11 children ≤3 years of age with perinatal or infantile hypophosphatasia, the baseline median serum calcium concentration was at the upper normal range with a maximum concentration slightly above 12 mg/dL (3.0 mmol/L). The median calcium concentration after treatment remained relatively stable throughout the treatment duration [19]. Nephrocalcinosis was reported in 2 patients, one with evidence of bilateral nephrocalcinosis at baseline. The second child had questionable calcium deposits at 6 months treatment duration and nephrocalcinosis after 3 years of therapy [19]. Another study included 69 children aged ≤5 years with HPP followed for up to 6 years while on AA treatment (dose: 6 mg/kg/week). Their mean serum calcium concentration at baseline was 10.4 mg/dL (2.6 mmol/L) (upper/lower concentration, 7.21/16 mg/dL) and only small fluctuation was observed during the duration of the study. However, 3 patients developed hypercalcemia after starting enzyme replacement therapy (14.4 mg/dL (3.6 mmol/L) at week 3, 13.2 mg/dL (3.3 mmol/L) at week 6, and 12.4 mg/dL (3.1 mmol/L) at week 120) [20]. Our patient developed significant hypercalcemia up to 15.8 mg/dL (3.95 mmol/L) after 9 months of AA (dose, 2 mg/kg 3 times/week). Her hypercalcemia recurred despite increasing the AA dose to 3 mg/kg 3 times/week and lowering her dietary calcium intake (low calcium formula [2.9 mg/5 fluid oz]). Therefore, calcitonin 4 IU/kg every 12 hours was added to her regimen. Calcitonin is typically used for acute management of hypercalcemia for a duration of 2 to 3 days, which is typically followed by tachyphylaxis. The impact of calcitonin on serum calcium usually fades after such duration, likely due to receptor downregulation [21]. Due to resistant hypercalcemia in our patient, calcitonin was utilized for almost 8 months with successful stabilization of serum calcium. Our patient's clinical course highlights that hypercalcemia in HPP can be challenging to manage and may occur despite use of enzyme replacement therapy and warrants close laboratory monitoring with assessment of calcium and vitamin D intake. Multiple modalities may be required to normalize the calcium concentration.

Hypercalcemia is common in infants with untreated severe HPP and is likely mitigated for most when treated with AA. This case highlights the importance of monitoring calcium concentration and intake in infants with HPP. Although calcitonin is generally not considered a long-term therapy for hypercalcemia, bisphosphonates may worsen the bone disease of HPP and should be avoided. This case demonstrates the utility of calcitonin therapy added to low calcium intake and maximal AA dosing to treat severe, persistent hypercalcemia in an infant with perinatal HPP.

Learning Points

- Vigilant monitoring of calcium levels and dietary intake is crucial in infants with HPP.
- Treatment of hypercalcemia in HPP should not include a bisphosphonate.
- Adjunct calcitonin therapy, along with restricted calcium intake and maximal asfotase alfa dosing, may be used to manage severe hypercalcemia in HPP.
- This case highlights the importance of individualized treatment approaches in managing complications of HPP, such as hypercalcemia.
- Long-term calcitonin may be considered when hypercalcemia is persistent/recurrent.

Contributors

All authors made individual contributions to authorship. M.S. conceptualized the study, drafted the initial manuscript, and reviewed and revised the manuscript. P.T. and A.A.N. conceptualized the study and critically reviewed and revised the manuscript. All authors were involved in the diagnosis and management of this patient, manuscript submission and approval of the final manuscript as submitted, and agree to be accountable for all aspects of the work.

Funding

No public or commercial funding.

Disclosures

None declared

Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient's relatives or guardians.

Data Availability Statement

Original data generated and analyzed during this study are included in this published article.

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