

Important hypercalcemia due to subcutaneous fat necrosis treated with pamidronate in an infant with severe hypoxic-ischemic encephalopathy

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Abstract

Subcutaneous fat necrosis (SCFN) of the newborn is an uncommon form of panniculitis that occurs after fetal distress and involves fatty areas during the first weeks of life. This rare disorder is generally self-limiting and undergoes complete regression. However, it can be complicated with a potentially life-threatening hypercalcemia. We report a case of severe hypercalcemia due to SCFN occurring after serious perinatal hypoxic injury, which resolved by intravenous administration of pamidronate. This treatment was rapidly effective and well tolerated. We suggest that pamidronate could be the first-line therapy for severe hypercalcemia in SCFN.

Keywords

Subcutaneous fat necrosis, hypercalcemia, pamidronate, hypoxic-ischemic encephalopathy.

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How to cite

Quitadamo PA, Villani A, Cristalli PP, Marinelli M, Riganti A, Bisceglia M, Gatta A. Important hypercalcemia due to subcutaneous fat necrosis treated with pamidronate in an infant with severe hypoxic-ischemic encephalopathy. *J Pediatr Neonat Individual Med.* 2016;5(2):e050226. doi: 10.7363/050226.

Case report

A full-term male infant with severe fetal distress was delivered by emergency cesarean section in critical condition. The baby was pale and flaccid with undetectable heart rate and no respiratory effort. He was unresponsive to full resuscitation with an Apgar score of 0 at 1, 5, and 10 minutes, and 4 at 20 minutes. Since the patient suffered from severe hypoxic-ischemic encephalopathy, therapeutic hypothermia was induced. An acute multi-organ dysfunction syndrome rapidly occurred with a quickly worsening clinical condition.

On the 6th day of life, he developed erythematous subcutaneous nodules over the back (Fig. 1), which resulted in extensive indurated plaques in the next few days (Fig. 2). A diagnosis of subcutaneous fat necrosis (SCFN) of the newborn was made.

At the age of 33 days, the infant was admitted again to the hospital for failure to thrive, hypotonia, hyporeactivity, fever (38°C) and anemia. A blood transfusion was administered. Even if slowly disappearing, subcutaneous nodules were still detectable. Serum calcium level was 16.8 mg/dl (n.v.: 7.9-10.7 mg/dl). Parathyroid hormone was undetectable (< 3 pg/ml; n.v.: 10-65 pg/ml) while the 1,25-dihydroxyvitamin D3 level was normal (52 pg/ml; n.v.: 16-81 pg/ml). Protein-C-Reactive was slightly increased (2.05 mg/dl; n.v.: < 0.32 mg/dl). Blood cultures were negative. Triglycerides were 233 mg/dl. A mild hypereosinophilia was found in complete blood count (Eo: 11.6% – 1,250/mcl).

The infant had developed severe hypercalcemia due to SCFN. He was fed with a low-content vitamin D and calcium formula preparation. After about 24 hours of treatment with hyperhydration, two doses of i.v. furosemide and betamethasone, serum calcium level increased to 17.2 mg/dl. Therefore, pamidronate was given by slow intravenous infusion at a rate of 0.25 mg/kg of body weight over 2 hours. The clinical response was excellent. Serum calcium level significantly decreased (13.8 mg/dl) after the first administration of pamidronate and returned within the normal range (8.8 mg/dl) after the third dose. According to literature, pamidronate at a dose of 0.25-0.5 mg/kg shows persistent and prolonged effectiveness and is well tolerated. We observed a rapid decrease in serum calcium just 12 hours after the first dose and a complete normalization of calcium levels after 24 hours, with no side



Figure 1. Erythematous subcutaneous nodules over the back on the 6th day of life.



Figure 2. Extensive indurated plaques in the next few days.

effects. In our experience pamidronate was used almost as a first-line treatment. A renal ultrasound examination showed only a moderate bilateral nephrocalcinosis. The infant was discharged in good clinical conditions with weight gain and with a follow-up program. Parents of the newborn were advised to closely monitor serum calcium levels for at least 6 months and to be alert to any signs or symptoms of hypercalcemia. No further pamidronate treatment was necessary. At 9 months of age, all skin lesions due to SCFN had spontaneously disappeared. Although a persistent yet stable bilateral nephrocalcinosis was found on renal ultrasound examination, renal function was unaffected.

Discussion

SCFN of the newborn is a rare [1-3] form of localized panniculitis which is usually found in full-term infants during the first weeks of life. SCFN is a transient inflammatory disorder of the adipose tissue associated with several perinatal events, including fetal and neonatal stress.

The etiology of SCFN is still unclear, despite several hypotheses. Perinatal hypoxia is the most frequently recognized etiologic factor [1, 4]. Any neonatal distress may probably interfere with normal blood supply to the fat tissue, creating an environment of ischemia, hypoxia and hypothermia, which is believed to damage the immature adipose tissue causing fat to crystallize in necrotizing granulomas. In addition, subcutaneous fat composition is unique in its high concentration of saturated fatty acid with a high melting point, which makes them more likely to crystallize under colder conditions. Even therapeutic hypothermia for hypoxic-ischemic encephalopathy may play a role in the development of SCFN [5].

Characteristic lesions consist of single or multiple subcutaneous nodules, often painful to the touch, or indurated plaques with or without erythema. The affected areas are usually the back, shoulders, buttocks and the base of the limbs. The diagnosis is essentially clinical. In case of doubt the confirmation is obtained by skin biopsy, that shows focal necrosis of the subcutaneous adipose tissue, granulation tissue and lipid crystals. The main clinical differential diagnosis of SCFN is the Sclerema Neonatorum (SN), but children with SN are usually severely ill premature babies. Moreover, SN more extensively affects the skin

with the exception of the palms, soles of the feet and genitals, and it has a poor prognosis [6].

SCFN is generally a self-limiting condition and the skin lesions disappear within 3-6 months without treatment. However, it may be complicated by metabolic and hematological alterations including hypoglycemia, hypertriglyceridemia, thrombocytopenia and anemia, conditions that typically resolve spontaneously. On the contrary, hypercalcemia is a rare and serious complication [2, 4, 5, 7-9]. Novel findings include the occurrence of eosinophilia and fever, which were described for the first time in a series of 2014 [2]. The authors hypothesize that they may be caused by SCFN itself in some cases. The onset of hypercalcemia can be delayed up to 6 months after the development of skin manifestations, emphasizing the importance of prolonged follow-up. Hypercalcemia may be asymptomatic or may present with irritability, lethargy, hypotonia, vomiting, polyuria, polydipsia, constipation, poor weight gain. Rarely, it may present with the most serious sequelae of acute hypercalcemia, like cardiac arrest for increased risk of dysrhythmia, seizures and renal failure. Untreated hypercalcemia may lead to severe chronic complications such as metastatic calcification of skin, liver, heart, vessels and gastric mucosa [7, 10].

The pathogenesis of hypercalcemia in SCFN of the newborn is unknown [3]. High levels of 1,25-(OH)₂D with low or undetectable PTH are observed in hypercalcemic patients, supporting the hypothesis of an uncontrolled production of 1,25-(OH)₂D [3, 11]. A recent report found increased bone turnover markers in patients with SCFN [12]. A combination of factors is probably responsible for the hypercalcemia seen in these patients, including increased extrarenal 1,25 Vit D production and increased bone turnover.

The presentation of hypercalcemia with calcification of the dermo-hypodermic lesions has led to believe that it can be consequent to the release of calcium by the subcutaneous nodules in the process of resorption [10], and to the osteoclast activation mediated by prostaglandins [2, 13] or other unknown factors.

The first choice treatment for hypercalcemia in SCFN involves hyper-hydration, calcium wasting diuretics such as furosemide, potassium citrate to inhibit the formation of kidney stones, and a preferential use of low-content calcium and vitamin D feeding formulas. The second choice in case of failure of the previous strategy is the use

the low dose corticosteroids, which, in general, act quickly and improve renal calcium excretion, with consequent increase of the risk of nephrocalcinosis [14]. After the unsuccessful use of this classic treatment regimens, the use of pamidronate should be considered. Some authors [14-16], however, offer it as a first choice drug. The main effect of pamidronate is the inhibition of the osteoclast-driven bone resorption with consequent decrease in serum calcium and in renal excretion of calcium, with reduced risk of nephrocalcinosis. Possible adverse effects of pamidronate are transient and include slight hyperthermia, myalgia, bone pain, vomiting and hypocalcemia. However, no side effects were reported in any of the cases reported in literature [14-18].

A dosage of 0.25-0.5 mg/kg is indicated for 3-4 administrations. Normalization of serum calcium occurs quickly, with a decrease already after 12 hours following the first dose. Given that hypercalcemia is the most serious complication of SCFN, effective and immediate resolution is needed.

In conclusion, this report is further evidence that physicians should be aware that infants with a history of fetal distress or asphyxia at birth are at risk of SCFN. The presence of localized skin changes with the previously described characteristics should suggest the diagnosis of SCFN with potential severe hypercalcemia. Early identification of hypercalcemia is crucial to prevent fatal complications. All newborns who develop skin lesions consistent with SCFN should be followed up for the possible onset of hematological and metabolic alterations and should have their serum calcium level monitored regularly for at least 6 months.

Eosinophilia and fever were also observed in our patient and they were probably both caused by SCFN.

Therapeutic cooling hypothermia may be an additional risk factor of SCFN.

Our case report confirms the safety of pamidronate, that has proven to be rapidly effective and well tolerated. In cases of severe hypercalcemia in SCFN, we believe that this treatment may be the first choice.

It would be interesting to know through other reports the long term evolution of nephrocalcinosis, which is common and may persist for several years without evidence of renal dysfunction, and the impact of pamidronate on the natural history of SCFN.

Declaration of interest

The Authors declare that there is no conflict of interest.

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