İSTANBUL UNIVERSITY PRESS

Çocuk Dergisi - Journal of Child 2022;22(3):244-247
DOI: 10.26650/jchild.2022.833032

CASE REPORT / *OLGU SUNUMU*

Severe Hypercalcemia in an Infant with Subcutaneous Fat Necrosis: Successful Management with Bisphosphonate Treatment

Subkutan Yağ Nekrozu Olan Süt Çocuğunda Ciddi Hiperkalsemi: Bifosfonat Tedavisi ile Başarılı Yönetim

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Citation/Atıf: Yavas Abali Z, Collu M, Poyrazoglu S, Darendeliler F. Subkutan yağ nekrozu olan süt çocuğunda ciddi hiperkalsemi: Bifosfonat tedavisi ile başarili yönetim. Çocuk Dergisi - Journal of Child 2022;22(3):244-247. https://doi.org/10.26650/jchild.2022.833032

ABSTRACT

Subcutaneous fat necrosis (SFN) in infancy is a rare condition and usually presents with panniculitis, especially within the first few weeks of life. These skin lesions may improve spontaneously but the most life-threatening complication of SFN is severe hypercalcemia.

Here, we report the case of an infant with severe hypercalcemia due to SFN. The infant was managed for sepsis and evaluated for nodular erythematous skin lesions, which revealed SFN. Hypercalcemia was severe and unresponsive to the usual treatment regimens. Therefore, bisphosphonate (pamidronate) was used to correct the hypercalcemia.

Hypercalcemia is a serious complication in SFN and needs prolonged follow-up. Calcium levels should be monitored regularly in these patients. We report that pamidronate may be appropriate as the first line therapy to treat severe hypercalcemia due to SFN.

Keywords: Subcutaneous fat necrosis, hypercalcemia, bisphosphonate

ÖZ

Subkutan yağ nekrozu (SYN) nadir görülen bir durumdur ve genellikle yaşamın ilk birkaç haftasında pannikülit ile kendini gösterir. SYN'e bağlı cilt lezyonları kendiliğinden iyileşse de yaşamı tehdit eden şiddetli hiperkalsemi en önemli komplikasyonudur.

Sepsis nedeniyle tedavi edilmekte olan yenidoğanda gözlenen nodüler eritemli cilt lezyonları SYN tanısı koydurdu. Olguda gelişen ciddi hiperkalsemi olağan tedavi rejimlerine yanıt vermemişti. Bu nedenle, hiperkalsemiyi düzeltmek için bifosfonat (pamidronat) tedavisi kullanıldı.

Hiperkalsemi, SYN'nin ciddi bir komplikasyonudur ve uzun süreli izlem gerektirir. Bu olgularda kalsiyum seviyeleri düzenli olarak takip edilmelidir. Pamidronatın SYN'e bağlı hiperkalsemide güvenlidir ve ciddi hiperkalseminin tedavisinde ilk seçenek olarak tercih edilmelidir.

Anahtar Kelimeler: subkutan yağ nekrozu, hiperkalsemi, bifosfonat

INTRODUCTION

Subcutaneous fat necrosis (SFN) is a rare form of panniculitis. Lesions can occur on the face, back, shoulders and buttocks and may present as plaques and nodules in the first six weeks of life (1). Hypoxic ischemia, sepsis, hypothermia, meconium aspiration, Rh incompatibility, sepsis, obstetric trauma, macrosomia, exposure to smoking, maternal or paternal thrombosis, gestational diabetes, and preeclampsia have been described as risk factors (2, 3). It is frequently self-limited but may become serious and life-threatening when complicated with hypercalcemia. The frequency of hypercalcemia in infants with SFN is uncertain. Hyperhydration, calciuric diuretics, and corticosteroids are frequently used as first-line regimens for the treatment of hypercalcemia. In resistant cases, bisphosphonates may be life-saving. It is reported that pamidronate may be appropriate as the first line therapy in severe hypercalcemia (4-6).

Here, we report the case of a severely hypercalcemic neonate who was unresponsive to hyperhydration, diuretics, and methylprednisolone.

CASE PRESENTATION

A term male infant was born to a 27-year-old healthy primigravida mother. During pregnancy, she was routinely

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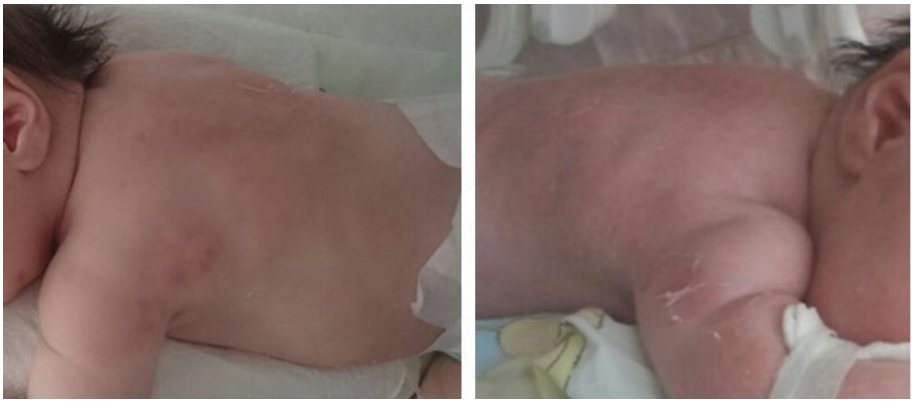
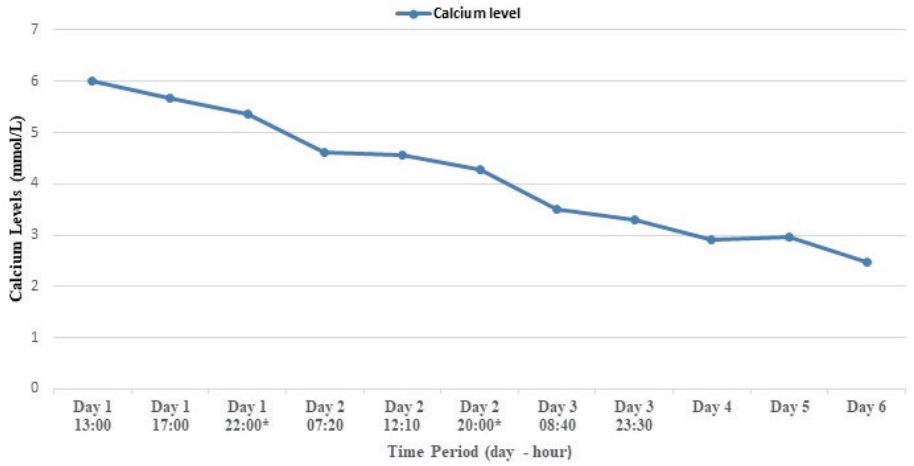
Submitted/Başvuru: 29.11.2020 • **Revision Requested/Revizyon Talebi:** 13.07.2021 • **Last Revision Received/Son Revizyon:** 22.09.2021 • **Accepted/Kabul:** 27.09.2021 • **Published Online/Online Yayın:** 20.12.2022

followed as an uncomplicated pregnancy. The mother reported that she had smoked cigarettes occasionally during and after pregnancy. The child was born via emergency cesarean section due to the entanglement of the umbilical cord around his neck. Birth weight, birth length, and head circumference were -0.4 SDS, 1.1 SDS, and -0.7 SDS, respectively. Umbilical cord blood gas analysis and Apgar score were not recorded. The child had transient respiratory distress in the early postnatal period and stayed a night in the hospital. In the second postnatal day, he was admitted to the neonatal intensive care unit (NICU) with the diagnosis of sepsis, due to high C-reactive protein levels and sickly appearance. In the following few days, irregular, indurated, subcutaneous lesions over his back and shoulders were observed (Figure 1). These lesions were followed initially and after recovery of the sepsis and discharge from NICU, the patient was referred to the dermatology clinic for the skin lesions. On the postnatal 49th day, severe hypercalcemia with a serum calcium level of 24.4 mg/dl (N:8.7-11.3), ionized calcium level of 2.86 mmol/L (N:1.22-1.4), and urinary calcium/creatinine ratio of 2.8 was detected. There was no report concerning the hypercalcemic state during NICU care. Urgent treatment to restore normocalcemia was commenced. The patient was breastfeeding, so no other nutritional restriction was necessary, apart from eliminating vitamin D supplementation. Following hyperhydration, four doses of intravenous furosemide (1mg/kg/dose) and two doses of methylprednisolone (0.05 mg/kg/dose) were applied in a total of 6 hours, and the calcium level was still 21.5 mg/dl. Intravenous pamidronate sodium (1 mg/kg/dose) was given by infusion over four hours. After twenty-one hours, with a calcium level of 18.2 mg/dl, the second dose of pamidronate was infused (1 mg/kg/dose). The steepest declines in calcium levels were achieved following the pamidronate infusions (Figure 2). The calcium level was normalized (9.8 mg/dl) on the fourth day following the second dose of pamidronate. The calcium levels were regularly monitored and the child had no hypocalcemia after pamidronate treatment. Bilateral nephrocalcinosis was detected in the renal ultrasonography. The urinary calcium/creatinine level was 0.23 on the fifth day of treatment. Furosemide and methylprednisolone therapies were gradually stopped. The parathyroid hormone level was as low as 2.8 pg/mL (N: 15-60) when the serum calcium level was 22.7 mg/dl and the 1,25-dihydroxy vitamin D (1,25-OHD) level was 60.9 ng/ml (N:24-86). 25-hydroxyvitamin D (25-OHD) level



Figur 1: Demonstrations of nodular, erythematous lesions in an infant with subcutaneous fat necrosis. Lesions are more prominent in his shoulders and back.



Figur 2: Schematic representation of response to pamidronate treatment.

*Pamidronate infusion

was 48.4 ng/mL (N:30-60). The skin lesions almost disappeared in the following weeks.

DISCUSSION

Subcutaneous fat necrosis (SFN) in infancy is a rare condition and usually presents with panniculitis, especially within the first few weeks of life. A life threatening complication of SFN is severe hypercalcemia. Here, we report the case of a severe hypercalcemic neonate who was unresponsive to standard first-line treatment regimens for hypercalcemia.

Several perinatal risk factors play a role in the etiology of SFN. The mother's smoking history and umbilical cord entanglement during delivery were important risk factors for SFN in our patient. As moderate hypothermia in hypoxic-ischemic encephalopathy is becoming a standard treatment in clinical practice, there are concerns about hypothermia-related SFN. In a study including 1239 newborns treated with moderate whole-body hypothermia for the hypoxic-ischemic encephalopathy, 12 cases developed SFN (7). In 10 infants with serum calcium measurements, 8 had moderate/severe hypercalcemia. Our case had a history of umbilical cord entanglement and a pre-diagnosis of sepsis but he had no ischemic encephalopathy. There was no history of whole-body hypothermia.

Complications related to SFN are hypercalcemia, hypoglycemia, thrombocytopenia, and hypertriglyceridemia (8). The exact frequency of accompanying hypercalcemia is unknown. Once the diagnosis of SFN is made, patients must be followed cautiously for these complications. Although SFN is a self-limited condition, it may be life-threatening when complicated with severe hypercalcemia. Hypercalcemia was also severe in our patient. Subcutaneous, indurated erythematous lesions were detected during the first postnatal days but the child was not hypercalcemic during NICU follow-up. After discharge from the hospital, checking of routine serum calcium levels was not advised because the diagnosis of SFN had not been considered during his care. He was referred to dermatology for the skin lesions. Pediatricians must also be aware of SFN and its skin lesions for early diagnosis of the disease and to take precautions for complications.

The etiopathogenesis of hypercalcemia in SFN is unclear but adipocyte crystallization and necrosis due to hypothermia is a proposed mechanism (9). The most accepted mechanism for hypercalcemia is the uncontrolled production of 1,25 hydroxyvitamin D by the granulomatous structure in the lesion (10, 11). Other mechanisms include the production of prostaglandin E2 stimulating osteoclasts, macrophages differentiating into osteoclasts, and necrotic fat cells excreting calcium (12). Both, 25-OHD and 1,25-OHD levels were normal in our case and parathyroid hormone was suppressed secondary to hypercalcemia.

The usual treatments of calcium-restricted nutrition, hyperhydration, and furosemide were insufficient in several reported cases, as in our case, and also furosemide increases the risk of nephrocalcinosis. Prednisone and pamidronate emerge as the second-line treatment (4-6). Prednisone acts via stimulating osteoclasts and the degradation of 1,25-OHD and 25-OHD. It also decreases intestinal calcium absorption and increases renal excretion which creates a predisposition for nephrocalcinosis (6). However, it becomes inadequate when a fast response is needed. Hypercalcemia in our patient was unresponsive to hyperhydration, furosemide, and steroids.

Pamidronate, a nitrogenous bisphosphonate, comes forth as the solution. Similar to all bisphosphonates, it is an inorganic derivative of pyrophosphate, and it directly binds to the hydroxyapatite crystals on the bone and inhibits bone resorption (6, 13, 14). Calcium level was normalized on the fourth day following the second dose of pamidronate and the child had no hypocalcemia after this treatment. No other adverse effect was observed related to pamidronate.

Regarding other complications related to SFN, as a result of hypercalcemia, nephrocalcinosis was also present in our case. In a case series reported by Shumer et al (6) the prevalence of nephrocalcinosis was as common as 83.0 %. It was reported to be still present after 20 months' follow-up, without any further apparent complication. Our patient did not suffer from other complications related to SFN.

CONCLUSION

SFN is a rare, transient skin lesion in newborns. It may become life-threatening when complicated with hypercalcemia. Hyperhydration, loop diuretics, and corticosteroids may be insufficient in severe cases. Pamidronate is a fast-acting alternative that resolves the hypercalcemia associated with SFN.

Peer Review: Externally peer-reviewed.

Author Contributions: Data Acquisition- Z.Y.A, M.Ç.; Data Analysis/Interpretation- Z.Y.A, F.B, S.P.; Drafting Manuscript- M.Ç., Z.Y.A.; Final Approval and Accountability- S.P., F.B., F.D, Z.Y.A., M.C.

Conflict of Interest: Authors declared no conflict of interest.

Financial Disclosure: Authors declared no financial support.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Veri Toplama- Z.Y.A, M.Ç.; Veri Analizi/Yorumlama- Z.Y.A, F.B, S.P.; Yazı Taslağı- M.Ç., Z.Y.A.; Son Onay ve Sorumluluk- S.P., F.B., F.D, Z.Y.A., M.C.

Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.

Finansal Destek: Yazarlar finansal destek beyan etmemişlerdir.

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