Received: 2 January 2021 | Revised: 28 January 2021 | Accepted: 2 February 2021

DOI: 10.1002/ccr3.3945

CASE REPORT

Clinical Case Reports Open Access WILEY

Subcutaneous fat necrosis of the newborn – An atypical case with typical complications

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Abstract

Subcutaneous fat necrosis of the newborn should be considered in newborns with suggestive skin lesions, even in the absence of perinatal distress. SCFN may cause long-standing complications, like hypertriglyceridemia or hypercalcemia. Hypercalcemia can be refractory to therapy and lead to poor weight gain and nephrocalcinosis, which should be closely monitored.

KEYWORDS

hypercalcemia, newborn, subcutaneous fat necrosis of the newborn

1 | INTRODUCTION

Subcutaneous fat necrosis of the newborn (SCFN) is a rare inflammatory disease of the adipose tissue which occurs in full-term or post-term newborns in the first weeks of life.[1-5] Main clinical features include plaques and reddish subcutaneous nodules which usually appear on the thighs, arms, and trunk.[1,2,4]

Diagnosis is essentially clinical[6] and prognosis is generally good, with a complete regression of skin lesions within few weeks.[1,2] Nevertheless, acute complications like hypercalcemia, hypertriglyceridemia, and thrombocytopenia may appear.[1,5,6] Hypercalcemia is the most frequent complication and can be potentially life-threatening.[7]

The pathogenesis of the disease remains unknown, although it has been associated in almost all cases with perinatal stress factors which cause hypoxia and adipocyte necrosis.[1,3,6] Predisposing factors include maternal diseases (gestational diabetes, preeclampsia) and neonatal conditions (hypothermia, infections, hypoxemia).[1,4-6]

We describe an atypical case of a female newborn with SCFN without associated risk factors and with long-standing complications.

2 | CASE PRESENTATION

We present a case of a 4-day-old female born at 39 weeks of gestation via uncomplicated vaginal delivery to a 25-year-old healthy mother. There was no parental consanguinity. Pregnancy was supervised and uneventful; routine prenatal screening and obstetric ultrasounds were normal. Because of a positive result for Group B *Streptococcus* in vaginal swab, intrapartum prophylaxis with ampicillin was administered before delivery. Birth weight was 3150 g and length was 45.5 cm (adequate for gestational age); APGAR score was 9 and 10 at 1 and 5 minutes, respectively. Postnatal course was otherwise unremarkable, and she was discharged from the hospital on the second day of life (DOL).

On the 4th DOL, she presented at the Pediatrics Emergency Department with an extensive skin lesion on the back with notion of local pain. Parents denied other symptoms, such as fever, refusal to eat, or irritability; there was no history of trauma. The baby was clinically well, and physical examination was normal except for the presence of an extensive flat, firm, and erythematous skin lesion localized on the back and left shoulder, with local heat and edema. Blood tests revealed anemia (hemoglobin 11 g/dL), C-Reactive Protein (CRP) of

5.58 mg/dL and a procalcitonin (PCT) of 1.41 ng/mL (high-intermediate risk). She was admitted to the Pediatric ward with the diagnosis of cellulitis and started intravenous antibiotic therapy with flucloxacillin and gentamicin.

From DOL 5 to 6, there was progression of the skin lesions to the upper limbs, thighs, and abdominal region associated with a color change from erythematous to purplish plaques. Due to irritability and worsening of the skin lesions, it was decided to escalate antibiotic therapy to gentamicin, ampicillin, and cefotaxime.

On DOL 7, some erythematous subcutaneous nodules were noted on the back, upper limbs, and thighs, raising the diagnostic suspicion of SCFN. Isolated severe hypercalcemia (total calcium: 14.7 mg/dL) was detected, so the patient was transferred to the Neonatal Intensive Care Unit for continuous cardiac monitoring and started therapy with intravenous fluids, oral furosemide (2 mg/kg/day), and prednisolone (2.5 mg/kg/day).

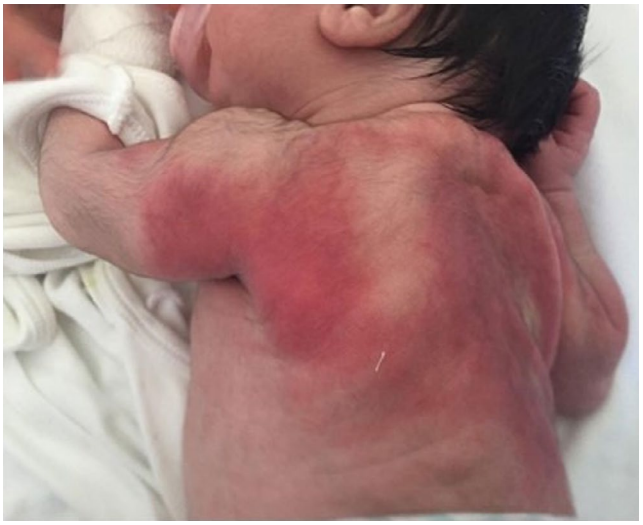

FIGURE 1 Purplish and erythematous plaques and nodules on the upper arms and back on DOL 12

3 | INVESTIGATIONS

3.1 | 4th DOL

Hemoglobin 11 g/dL (normal 13-20.5 g/dL), leukocytes 6.800 u/L (normal 5-20 × 10^3/uL - 67% neutrophils), platelets 316.000/uL (normal 150-500 × 10^3/uL), CRP 5.58 mg/dL (normal <2 mg/dL), PCT 1.41 ng/mL (normal <0.5 ng/mL).

3.2 | 7th DOL

Serum calcium level (which was the highest value detected during follow-up) 14.7 mg/dL (normal 8.1-10.2 mg/dL); CRP 2.62 mg/dL.

3.3 | 9th DOL

Hemoglobin 16.8 g/dL, leukocytes 13.900/uL (78% neutrophils), platelets 717.000/uL, glucose 87 mg/dL (normal 40-90 mg/dL), creatinine 0.4 mg/dL (normal 0.11-0.8 mg/dL), CRP 0.90 mg/dL, phosphorus 7.3 mg/dL (normal 4.5-8 mg/dL), triglycerides 291 mg/dL (normal <150 mg/dL).

4 | OUTCOME AND FOLLOW-UP

Between DOL 10 and 12, there was a decrease in calcium levels (10.9 mg/dL), a progressive improvement of the extension of purplish plaques but an increase in the number and size of the nodules (Figure 1). Antibiotic and corticosteroid therapy were suspended at that time (after 7 and 4-days-therapy, respectively) and furosemide dose was progressively decreased. On DOL 13, she started fever (38.3ºC) which was maintained until DOL 15; nevertheless, CRP values remained low (1.78 mg/dL), and blood cultures were sterile, so it was decided not to restart antibiotic therapy.

Further investigations of hypercalcemia revealed a normal phosphorus, albumin, and 25-OH-vitamin D levels, as well as normal urinary calcium/creatinine ratio; parathormone (PTH) was appropriately suppressed (Table 1). Renal ultrasound showed no alterations. She was discharged at DOL 18 with a remarkable improvement of the skin lesions (Figure 2), and stability of calcium levels (10.8 mg/dL) under a low dose of furosemide (0.8 mg/kg/day).

Performance of an ultrasound of the skin lesion or even a skin biopsy for differential diagnosis was considered in the first days after hospital admission; nevertheless, clinical evolution of the skin lesion was typical for SCFN (extension to the upper and lower limbs and thighs, together with the appearance of subcutaneous nodules) and diagnosis of SCFN was additionally supported by the presence of hypercalcemia. Execution of either an ultrasound or a skin biopsy would have been our next step in case of atypical evolution or clinical worsening.

After discharge, a weekly monitoring of calcium levels was performed. Calcium levels remained stable until DOL 30, when went up to 12.9 mg/dL, despite improvement of the skin lesions (Figure 3), so furosemide was once again increased (1.5 mg/kg/day). Thrombocytosis was resolved at that time (Table 1). Between DOL 30 and DOL 50 total calcium level remained fluctuating between 10.6 and 11.9 mg/dL, despite of progressive furosemide dose adjustments (up to 2.5 mg/kg/day) and no vitamin D taking (Figure 4). At that point, the use of corticosteroids and pamidronate was considered;

TABLE 1 Main blood and urine results during follow-up

Age (days)	Platelets $\times 10^3$/uL (Normal 150-500)	Vitamin D ng/mL (Normal ≥20)	PTH pg/mL (Normal 15-65)	Calcium/creatinine (urine) (Normal <0.5)	Triglycerides mg/dL (Normal <150)
7	316.000				
19	717.000	20	6.6	0.16	292
30	575.000			0.11	453
57				0.5	
90	343.000			0.17	
150	343.000			0.10	
270			47.2	0.37	259

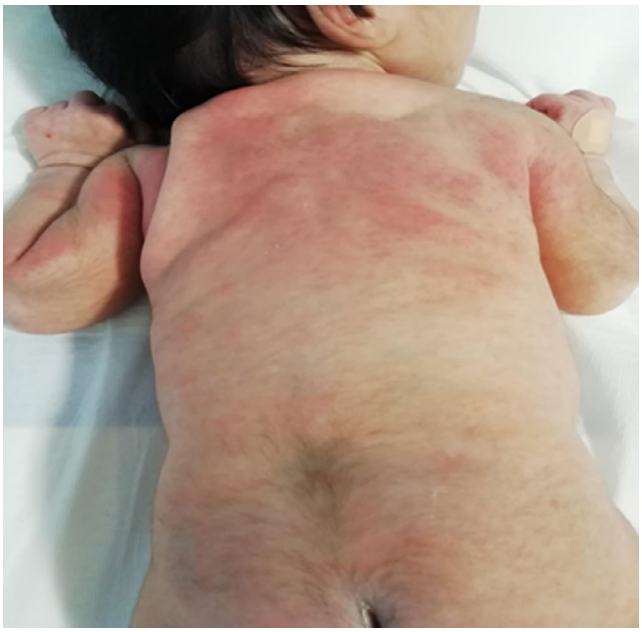

FIGURE 2 Improvement of the skin lesions on DOL 18

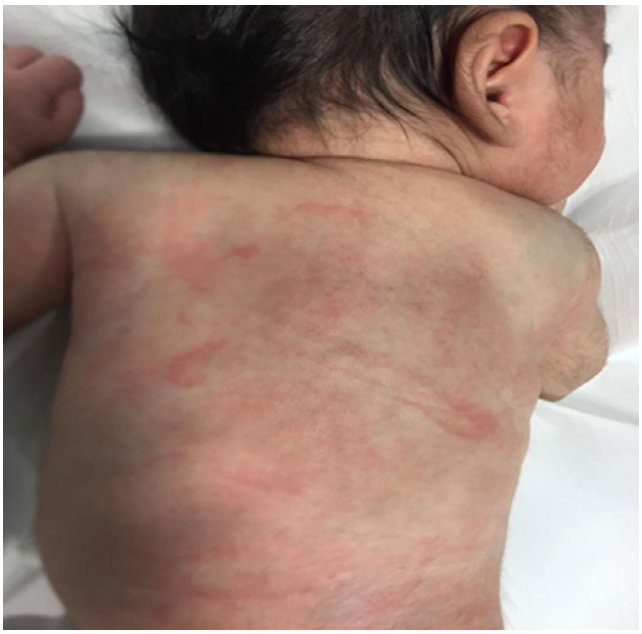

FIGURE 3 Improvement of the skin lesions on DOL 30

nevertheless, it was decided not to start as our patient only had mild hypercalcemia, urinary calcium/creatinine ratio remained normal and renal ultrasounds did not show signs of nephrocalcinosis. After DOL 50, there was a progressive normalization in calcium levels until furosemide was finally stopped (almost at 5 months of life); however, at that time, renal ultrasound revealed grade I/III nephrocalcinosis.

Calcium levels remained normal after diuretic discontinuation; nevertheless, nephrocalcinosis was still present on the last renal ultrasound performed at 9 months old, although slightly improved. Complete resolution of skin lesions was only evident at that time; on the contrary, hypertriglyceridemia has not been resolved yet (Table 1).

During follow-up, anorexia and poor weight progression were noted (weight decrease from percentile 15-50 to percentile 3). Gradual improvement in weight gain began after the introduction of a glycidic supplement and complementary feeding and continued after normocalcemia was reached. She is currently on percentile 15 for age and sex.

5 | DISCUSSION

Subcutaneous fat necrosis of the newborn is a rare panniculitis usually present in the first weeks of life. The pathogenesis of SFCN remains unclear; however, it has been postulated that perinatal stress may cause hypoxia and hypothermia of the immature fat tissue leading to inflammation and necrosis.[2,8]

Typical skin lesions consist of firm, erythematous, or purplish indurated plaques which evolve to subcutaneous hard painful nodules on the back, shoulders and upper limbs, and thighs. Diagnosis is essentially clinical,[9] although a skin biopsy may be useful in case of clinical doubt.[4] Differential diagnosis for SCFN may be difficult and includes *sclerema neonatorum* and cellulitis.[1,2,4]

Several predisposing factors for SCFN have been identified, which include maternal risk factors (preeclampsia, gestational diabetes, drug consumption) or neonatal conditions such as traumatic delivery, asphyxia, meconium aspiration,

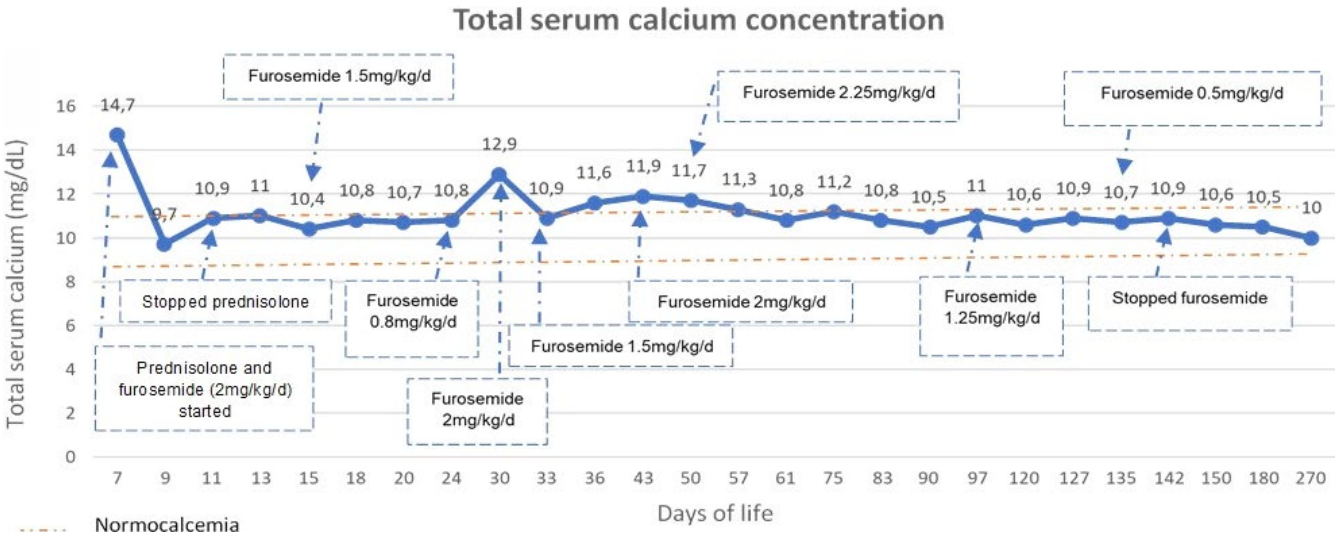

FIGURE 4 Total serum calcium levels during follow-up

macrosomia, or septic shock.[2,9] As published in some systematic reviews, almost 90% of patients experienced pregnancy complications and many were delivered via cesarian section due to fetal distress.[4] Another well-known risk factor is therapeutic hypothermia,[10] present in up to 20% of SCFN cases described in literature.[4] In our case, none of the risk factors could be identified; pregnancy was uneventful, delivery was uncomplicated, and the first days of life were unremarkable. There was concern over the possibility of early neonatal sepsis as initial skin lesions raised the diagnostic suspicion of cellulitis, inflammatory parameters were elevated, and fever was present from DOL 13. However, clinical stability together with typical progression of the skin lesions in SCFN and sterile blood cultures ruled out the possibility of an underlying infection. The elevation of CRP and procalcitonin may merely reflect the underlying inflammation present in SCFN and fever could be induced by elevated levels of prostaglandin E2 found in some cases of SCFN with hypercalcemia due to interleukin-1 present in granulomes.[11]

Subcutaneous fat necrosis of the newborn is usually a benign disease with an uncomplicated course[2]; skin lesions tend to resolve in some weeks without sequelae or, less frequently, evolve into fibrotic scars and fat atrophy.[1] Nevertheless, complications may appear, like thrombocytopenia, hypoglycemia, hypertriglyceridemia, and most frequently, hypercalcemia.[2]

Incidence of hypercalcemia varies widely, from 25% to 65%,[4,12] being more frequent in term or full-term infants and in cases of extensive and truncal skin lesions, according to some reports.[2,4,12] The hypothesized cause of hypercalcemia is that granulomatous inflammatory cells in SCFN express high levels of 1-alpha-hydroxylase, the enzyme that converts 25-OH vitamin D3 to its active form (1,25-dihydroxyvitamin D3), which can stimulate intestinal calcium uptake.[2,7-9,12] Hypercalcemia can also be explained by an increased bone resorption in SCFN due to higher prostaglandin E levels,[1,13] and by an increased calcium mobilization from resolving areas of subcutaneous fat necrosis.[4]

Hypercalcemia usually manifests in the first month after the development of the skin lesions,[4] but can occur as late as 6 months afterward; this is why patients should be long-term monitored.[2,12] Patients with hypercalcemia may be asymptomatic or present with symptoms such as lethargy, irritability, hypotonia, vomiting, polyuria, polydipsia, dehydration, and constipation.[7,8,12] It may lead to severe complications, both acute (cardiac arrest and renal failure), as well as chronic problems (metastatic calcifications).[1,7] Almost 54% of patients with hypercalcemia may have complications or symptoms, according to some reviews.[4]

Treatment options include restriction of calcium and vitamin D intake, intravenous rehydration, and most specific measures. Furosemide is used to induce calciuresis and avoid calcium reabsorption. For most severe cases of hypercalcemia, glucocorticoids are recommended, as they reduce intestinal calcium absorption, increase renal calcium excretion and degradation of vitamin D. Last therapeutic option should be bisphosphonates, such as pamidronate or zoledronic acid, which inhibit osteoclast function.[1,2,7]

In our patient, severe hypercalcemia was detected at the time of the diagnosis of SCFN (DOL 8), earlier than usual. Despite she had a good initial response with intravenous rehydration, glucocorticoids, and furosemide in high dose, mild hypercalcemia was long-standing, and our patient was dependent on diuretic treatment until she was 5-month-old. This differs from most cases described in literature, where the median time to achieve normocalcemia was 9 days,[11] and in more than 90% of cases it was resolved in the first 3 months of life.[4]

Failure to thrive is one of the most important side effects of hypercalcemia and usually ameliorates after the normalization of calcium levels. In our case, anorexia and

poor weight progression were detected, which improved shortly after dietary changes and after normocalcemia was reached.

Nephrocalcinosis may appear even in cases of mild hypercalcemia, although there is no current evidence that persistent nephrocalcinosis can be associated with adverse renal outcomes in infants with SCFN.[11] There are few cases described in literature about SCFN and hypertriglyceridemia. The pathophysiology of this association is not well established; it may be due to mobilization of fatty acids from the adipose tissue following hypoxia.[8] Clinical significance of this association is not clear either; it can be a sign of an underlying metabolic disease. In our patient, hypertriglyceridemia appeared at the time of the diagnosis and although there was an improvement over time, has not been resolved yet.

Although thrombocytopenia is frequent in SCFN due to sequestration of platelets in the subcutaneous tissue, our patient showed thrombocytosis. There is only one report in literature of a patient with thrombocytosis, according to our knowledge[14]; it may be attributed to the reactive inflammatory response of SCFN.

ACKNOWLEDGMENTS

None

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

All authors (CL, AR, JM, and PC): were present in the daily approach and management of the patient to whom the case report refers to and approved the final version. CL: planned and conducted the initial design of the present case report and drafted the initial manuscript. AR: carried out the bibliographic research and then proceeded with acquisition and analysis of data regarding the clinical and laboratory evolution of the patient. JM and PC: did additional research concerning SCFN and revised the initial draft.

ETHICAL APPROVAL

Ethical approval prior to publication was obtained from our institution's ethics committee (Hospital Garcia de Orta, EPE), as well as parental written informed consent.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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How to cite this article: Lorenzo C, Romana A, Matias J, Calhau P. Subcutaneous fat necrosis of the newborn – An atypical case with typical complications. *Clin Case Rep*. 2021;9:2069–2073. https://doi.org/10.1002/ccr3.3945