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Severe hypercalcemia due to subcutaneous fat necrosis: presentation, management and complications

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Abstract

Objective—Subcutaneous fat necrosis (SCFN) is a rare form of panniculitis in infants that generally occurs following birth trauma, meconium aspiration, or therapeutic cooling. Severe hypercalcemia occurs in a subset of patients, but data on its presentation, management, and outcomes are limited. This report details the clinical course and complications of infants treated for severe hypercalcemia (peak serum calcium ≥3.0 mmol/L) due to SCFN.

Design—Chart review of all infants with SCFN seen at a single pediatric center over a 13-year period.

Patients—Seven infants with SCFN developed severe hypercalcemia, with median peak serum calcium 4.1 mmol/L (range 3.3–5.1).

Results—Severe hypercalcemia occurred before 6 weeks of age, and was asymptomatic in 3/7 patients (43%). Most patients were treated with intravenous hydration, furosemide, glucocorticoids, and low-calcium formula, which restored normocalcemia in a median of 9 days (range 2–42). Fever developed during treatment in 4/7 infants (57%): two patients had bacterial infections and two had no infectious source identified. Nephrocalcinosis was present in 5/6 patients (83%) who were evaluated by renal ultrasound. Nephrocalcinosis failed to resolve in all

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Daniel E. Shumer: Dr. Shumer participated substantially in conceptualization and design of the study, acquisition and analysis of data, drafted the initial manuscript, and approved the final manuscript as submitted.

Vidhu Thaker: Dr. Thaker participated substantially in conceptualization and design of the study, acquisition and analysis of data, reviewed and revised the manuscript for important intellectual content, and approved the final manuscript as submitted.

George A. Taylor: Dr. Taylor participated substantially in analysis and interpretation of ultrasound data, reviewed and revised the manuscript for important intellectual content, and approved the final manuscript as submitted.

Ari J. Wassner: Dr. Wassner participated in conceptualization and design of the study, acquisition and analysis of data, reviewed and revised the initial manuscript for important intellectual content, and approved the final manuscript as submitted.

All authors agree to be accountable for all aspects of the work.

cases over a median follow up of 20 months (range 8–48), but no renal dysfunction was observed. Eosinophilia, which has not been reported previously in SCFN, was present in 6/7 patients (86%).

Conclusions—In this largest series to date of infants with severe hypercalcemia due to SCFN, novel findings include the common occurrence of fever and a high incidence of persistent nephrocalcinosis without evidence of adverse renal outcomes.

Keywords

subcutaneous fat necrosis; infant; hypercalcemia; fever; nephrocalcinosis

Subcutaneous fat necrosis (SCFN) is a rare form of panniculitis most often seen in term infants following birth trauma or asphyxia, meconium aspiration, or therapeutic cooling.[1] Hypercalcemia is a potentially life-threatening complication that occurs in a subset of patients.[2–4] Data on the clinical course and outcomes of infants with SCFN who develop severe hypercalcemia are limited to case reports and small series with short follow-up.

Methods

We searched the electronic medical record for patients under age 12 months presenting between 2000–2012, using the search term “fat necrosis.” Cases of SCFN were defined by the presence of characteristic clinical features documented by the examining physician. Severe hypercalcemia was defined as peak serum calcium ≥3.0 mmol/L because hypercalcemia in this range is frequently symptomatic and clinically significant.[5] Hypercalcemia was considered to be due to SCFN if no clinical or laboratory evidence of another cause was present, including hyperparathyroidism, hypophosphatasia, vitamin D intoxication, malignancy, or Williams syndrome. For patients with severe hypercalcemia due to SCFN, data on presentation, clinical course, treatment, and complications were extracted from the medical record. Renal ultrasounds were evaluated by a single radiologist blinded to clinical course. This study was approved by the Boston Children’s Hospital Institutional Review Board.

Results

Seven patients were identified with severe hypercalcemia due to SCFN (Table 1). Perinatal risk factors were similar to those previously reported, including meconium aspiration, hypotension, and therapeutic cooling.[3,6] Clinical signs including poor feeding, lethargy, and failure to thrive were present in 4/7 patients. Hypercalcemia was diagnosed at a median age of 28 days (range 16–38), and the median peak serum calcium level was 4.1 mmol/L (range 3.3–5.1).

Four of seven infants (57%) developed fever during treatment. One infant had bacteremia related to a central venous catheter, and another had both a urinary tract infection and respiratory syncytial virus (RSV) infection. One infant with increased erythema of the areas of fat necrosis and another infant with no localizing signs or symptoms had no infectious cause detected by a complete sepsis evaluation, and their fevers resolved spontaneously.

All patients were admitted to the hospital and treated with intravenous hydration, and all received furosemide (1–1.5mg/kg/dose every 6–12 hours) for a median of 5 days (range 3–18). Glucocorticoids (prednisolone or methylprednisolone 1–2mg/kg divided once or twice daily) were administered to six patients for a median of 56 days (range 19–155). Low-calcium formula was given to five infants and continued for 1–5 months. Calcitonin was transiently effective when given to one patient with hypercalcemia refractory to hydration and furosemide, but normocalcemia was not achieved until glucocorticoids were added. Pamidronate was given to one patient who failed to achieve normocalcemia after 15 days of hydration, furosemide, and glucocorticoids. Serum calcium normalized within 12 hours of pamidronate infusion, and normocalcemia was subsequently maintained with low-calcium formula alone. The median time to achieve normocalcemia was 9 days (range 2–42). The median duration of initial hospitalization was 16 days (range 10–37), and 2/7 patients required readmission for recurrent hypercalcemia.

Hypercalciuria (defined as peak calcium/creatinine ratio >1.5 mmol/mmol in infants younger than 12 months, measured in a random spot urine sample)[7] was present in all patients. Renal ultrasonography was performed in six patients, and nephrocalcinosis was identified in five of these (83%). All infants with nephrocalcinosis had serial renal ultrasounds, and their median age at last follow-up was 20 months (range 8–48). In all cases, nephrocalcinosis was persistent on the most recent ultrasound, but renal growth was normal and no patient had evidence of chronic renal dysfunction or hypertension. Linear growth was normal at last follow up in the 4/7 patients for whom data were available.

Asymptomatic mild hypoglycemia was observed in two patients and resolved with feeding. No hyperglycemia was observed. Two of seven infants (29%) had mild initial polycythemia. Thrombocytopenia was not observed, but four infants had initial thrombocytosis. Three patients had leukocytosis at presentation, and 6/7 infants had eosinophilia (median 900 eosinophils/uL, range 520–2870; reference range 0–500). Serum triglycerides were measured in one infant and were normal.

Discussion

Hypercalcemia due to SCFN is rare and data are limited regarding its clinical course. Prior series have documented hypercalcemia in 36–56% of infants with SCFN, but in many cases hypercalcemia was mild and follow-up short.[3,4] We therefore chose to study infants with severe hypercalcemia, who are presumably at highest risk of complications. These seven patients constitute the largest such cohort described to date.

Severe hypercalcemia was diagnosed in all patients within the first 6 weeks of life. This timing is consistent with prior reports[3,4,8] and likely represents the period of highest risk for clinically significant hypercalcemia in SCFN. The importance of screening all infants with SCFN for hypercalcemia is highlighted by the fact that 3/7 infants were asymptomatic despite severe hypercalcemia.

Fever occurred in 4/7 infants in this cohort. While two patients had serious bacterial infections, two had no apparent infectious etiology, leading us to hypothesize that fever may

be caused by SCFN itself.[9] Fever could be induced by elevated levels of the potent pyrogen prostaglandin E2 found in some hypercalcemic patients with SCFN,[10,11] or by elaboration of interleukin-1 by the granulomas of SCFN, analogous to that observed in sarcoidosis.[12] This hypothesis may provide reassurance in well-appearing febrile infants with SCFN in whom no infectious source is identified. However, a diagnosis of SCFN does not obviate the need to evaluate for serious bacterial infection, particularly in infants with additional risk factors.

Nephrocalcinosis was a common complication (83%) in this cohort. Whereas others have reported resolution of nephrocalcinosis in most cases,[3,8] nephrocalcinosis failed to resolve in any of our patients after up to 4 years of follow-up. This difference is likely related to more severe hypercalcemia and hypercalciuria in our cohort, an element of our study design.[3,4,8] While nephrocalcinosis is a complication of hypercalcemia and hypercalciuria, its clinical significance depends on the etiology.[13,14] We found no evidence that persistent nephrocalcinosis is associated with adverse renal outcomes in infants with SCFN.

In one patient in this series, treatment with pamidronate yielded rapid, permanent resolution of otherwise refractory hypercalcemia, consistent with prior reports of its efficacy in this setting.[8,15,16] Although SCFN-related hypercalcemia may be due partly to excess intestinal calcium absorption (due to unregulated 1α-hydroxylation of 25-hydroxyvitamin D by activated macrophages),[17] the efficacy of bisphosphonates suggests a possible additional contribution from bone resorption, perhaps mediated by PGE2 or other unknown factors.[10,11]

Variable abnormalities of glucose, triglycerides, and hematologic parameters have been reported in SCFN.[3,9] Besides two episodes of clinically insignificant hypoglycemia, the only consistent abnormality we observed was mild eosinophilia present in 6/7 patients (86%). This finding has not been reported previously in SCFN and is of uncertain significance, but may prove useful in cases of infantile hypercalcemia in which the diagnosis of SCFN is unclear.

Although limited by its small size and possible referral bias, this series is the largest and has the longest follow-up to date describing the clinical course, treatment, and outcomes of patients with severe hypercalcemia due to SCFN. Novel findings include the frequent occurrence of mild eosinophilia and of fever, which we hypothesize may be caused by SCFN itself in some cases. Finally, nephrocalcinosis is common and may persist for several years without evidence of renal dysfunction, but its long-term clinical significance remains uncertain.

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Abbreviations

SCFN	subcutaneous fat necrosis

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What is already known on this topic

Subcutaneous fat necrosis (SCFN) is a rare form of panniculitis in infants.

Risk factors for SCFN include traumatic birth or asphyxia, meconium aspiration and therapeutic cooling.

Severe hypercalcemia is a life-threatening complication seen in a subset of infants with SCFN.

What this study adds

This report describes clinical course and complications of seven infants treated for severe hypercalcemia due to SCFN.

Novel findings include the common occurrence of fever and eosinophilia, and a high incidence of persistent nephrocalcinosis without evidence of adverse renal outcomes.

Table 1

Clinical Characteristics, Treatment, and Complications of Patients with Severe Hypercalcemia due to Subcutaneous Fat Necrosis

Patient	1	2	3	4	5	6	7
Sex	Male	Male	Male	Female	Male	Male	Female
Age at presentation (days)	38	32	16	35	21	20	28
Peak serum Ca (mmol/L)	4.4	5.1	3.5	4.1	3.8	3.3	4.8
PTH (pmol/L)	<0.3	<0.1	<0.1	<0.3	<0.3	N/A	0.3
25(OH)D (nmol/L)	8.7	46.7	54.9	204.7	49.9	N/A	54.9
$1,25(OH)_2D$ (pmol/L)	185	N/A	N/A	114	320	320	354
Peak urine Ca/Cr (mmol/mmol)	2.5	15.7	9.5	9.8	7.0	8.7	13.4
Treatments received[1]	IV,F,GC, DCR	IV,F,GC,C, DCR,CIT	IV,F,GC	IV,F,GC	IV,F,GC,PM, DCR,CIT	IV,F,DCR	IV,F,GC, DCR,CIT
Time to normocalcemia (days)	2	5	18	5	14	42	9
Fever	Yes	Yes	No	No	Yes	Yes	No
Result of sepsis evaluation	Negative	Bacteremia	N/A	N/A	UTI, RSV	Negative	N/A
Eosinophils (cells/uL)	460	930	2870	900	520	570	910
Nephrocalcinosis (months of follow up)	Persistent (10)	Persistent (20)	Not Assessed	Persistent (8)	Persistent (48)	No	Persistent (36)

General abbreviations: Ca calcium; **Cr** creatinine; **PTH** parathyroid hormone; **25(OH)D** 25-hydroxyvitamin D; **$1,25(OH)_2D$** 1,25-dihydroxyvitamin D; **UTI** urinary tract infection

Reference ranges: Ca 2.0–2.6 mmol/L; **PTH** 1.1–6.9 pmol/L; **25(OH)D** 75–250 nmol/L; **$1,25(OH)_2D$** 39–195 pmol/L; **urine Ca/Cr** < 1.5 mmol/mmol; **eosinophils** 0–500 cells/uL

[1]**Treatments abbreviations: IV** intravenous hydration; **F** furosemide; **GC** glucocorticoid; **DCR** dietary calcium restriction; **C** calcitonin; **PM** pamidronate; **CIT** citrate

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