

Subcutaneous Fat Necrosis as a Complication of Whole-Body Cooling for Birth Asphyxia

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Background: Subcutaneous fat necrosis (SCFN) of the newborn is a form of panniculitis that affects full-term neonates who often have suffered either birth asphyxia or hypothermia. The induction of hypothermia in newborns is becoming frequently used to reduce the neurologic sequelae associated with birth asphyxia. The risk of SCFN in neonates undergoing this therapy is unknown.

Observation: We describe a neonate who developed an abscesslike presentation of SCFN and subsequent asymp-

tomatic hypercalcemia after undergoing whole-body cooling for hypoxic-ischemic encephalopathy.

Conclusions: Hypothermia protocols may be placing newborns at increased risk for the development of SCFN. Clinicians should recognize this association, and newborns who undergo therapeutic cooling should have frequent dermatologic assessments.

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SUBCUTANEOUS FAT NECROSIS (SCFN) of the newborn is a self-limited inflammation of the subcutaneous adipose tissue that typically develops in the first week of life in full-term neonates. Complications include pain, scarring, and hypercalcemia that can develop weeks after SCFN is noted on physical examination. Birth asphyxia and hypothermia are the most commonly associated risk factors for the development of SCFN. Large, randomized, double-blind control trials have indicated neuroprotective benefits of inducing hypothermia in neonates with birth asphyxia; therefore, a growing number of neonatal intensive care units are implementing whole-body cooling programs.^{1,2} We describe a patient who developed SCFN on the sixth day of life after undergoing whole-body cooling for hypoxic-ischemic encephalopathy.

fluid resuscitation. He remained flaccid and unresponsive, suggesting an encephalopathy. Whole-body cooling was initiated to minimize the morbidity associated with hypoxic-ischemic encephalopathy according to standard protocol in the intensive care nursery at the Children's Hospital of Philadelphia, Philadelphia, Pennsylvania.

Cooling was initiated at 2 hours of life. A cooling blanket was set to maintain a target temperature of 33.5°C for 72 hours and then was gradually rewarmed by 0.5°C per hour until a temperature of 36.5°C was reached. At 24 hours of life, the patient's neurologic status had markedly improved; he was alert and responsive to stimuli, and the results of his neurologic examination were normal. Magnetic resonance imaging of the brain on the fourth day of life revealed a small area of acute ischemia in the left thalamus, consistent with a perinatal hypoxic-ischemic insult.

The dermatology service was consulted on the sixth day of life when the neonate developed red and violaceous subcutaneous nodules on the upper back area and buttocks and indurated plaques on the posterior aspect of the arms. There was a red and inflamed, soft, fluctuant central abscess surrounded by similar indurated plaques on the lower back area (**Figure 1**). A biopsy of the abscess revealed drainage of purulent fluid, raising the concern for a bacterial infection and prompting broad-spectrum antibiotic coverage with oxacillin sodium and gentamicin sulfate until the wound culture revealed no growth. Labo-

REPORT OF A CASE

A full-term boy was born to a 32-year-old mother via an emergency cesarean section for placental abruption and late fetal heart decelerations. His mother's pregnancy had been uncomplicated until she came to the hospital with severe pelvic pain. At delivery, the neonate was cyanotic, floppy, and apneic. His initial Apgar scores were 1 at 5 minutes, 4 at 10 and 15 minutes, and 8 at 20 minutes. The cord blood gas indicated a severe metabolic acidosis, and the neonate was intubated in the delivery room and received

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Figure 1. Clinical photograph of subcutaneous fat necrosis on a neonate's back on the sixth day of life. This fluctuant nodule would later drain a chalky white fluid after biopsy.

ratory tests revealed a normal white blood cell count without bacteremia. However, the patient's C-reactive protein level, which was less than 0.2 mg/dL (to convert to nanomoles per liter, multiply by 9.524) at birth, was elevated at days 6 and 8 (4.7 and 8.1 mg/dL, respectively). Calcium levels throughout the intensive care nursery stay were within normal limits.

A punch biopsy specimen of the fluctuant abscess (Figure 1) revealed necrosis of the fat lobules in the subcutaneous adipose tissue. These areas contained an infiltrate consisting of an admixture of inflammatory cells, including predominantly histiocytes with scattered neutrophils and a few lymphocytes (Figure 2). Also, there were numerous deposits of crystalline fat, which appeared as radially oriented needle-shaped clefts in the cytoplasm of adipocytes and some histiocytes (Figure 3).

The patient was discharged on day 10 of life with instructions to have his serum calcium levels checked at least weekly until the lesions clinically resolved and for up to 6 months. At day 22 of life, he was evaluated in the emergency department for asymptomatic hypercalcemia (total calcium, 11.2 mg/dL [reference range, 9.3-10.9 mg/dL]; and ionized calcium, 6.04 mg/dL [reference range, 4.00-4.68 mg/dL]) (to convert calcium values to millimoles per liter, multiply by 0.25). The results of his examination were normal, and he was sent home with instructions to continue calcium checkups as an outpatient. After this peak at day 22 of life, the calcium levels were normal, and the patient was feeding and gaining weight as expected.

COMMENT

Subcutaneous fat necrosis of the newborn affects full-term to postterm neonates. The clinician typically observes areas of firm, mobile, circumscribed nodules and plaques overlying bony prominences on the trunk, buttocks, extremities, and cheeks. The overlying skin may be flesh-colored, red, or violaceous. Neonates typically develop SCFN by days 3 to 7, with isolated cases developing as late as 4 weeks.^{3,4} Lesions heal over weeks to months, with minimal scarring; there have been a few reports of subcutaneous atrophy at old sites of SCFN.⁴

The development of fluctuant and draining nodules has been described in the literature, and this abscesslike

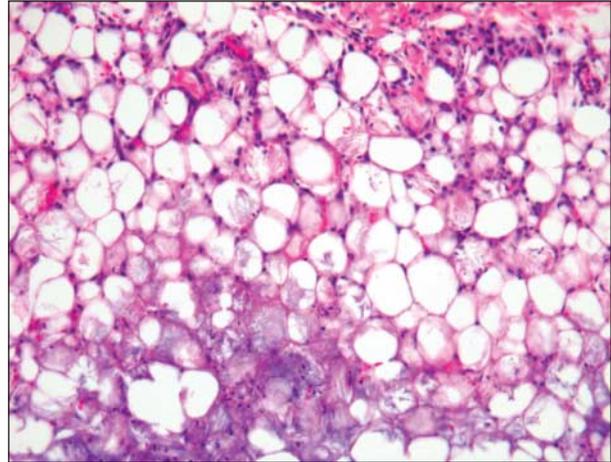


Figure 2. Fat necrosis with histiocyte-predominant inflammatory infiltrate and needle-shaped fat crystals in the cytoplasm of adipocytes and a few histiocytes (hematoxylin-eosin, original magnification $\times 20$).

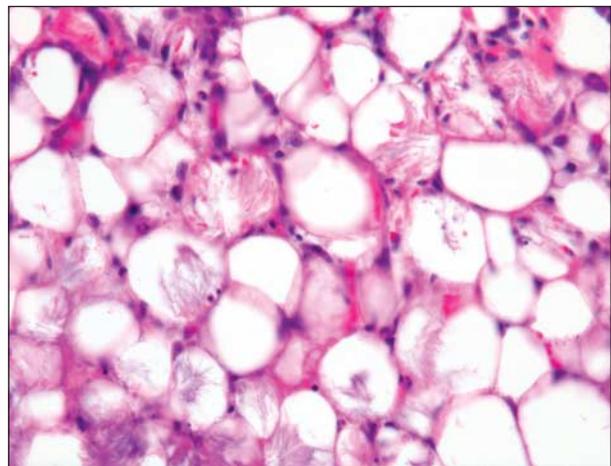


Figure 3. Radially oriented fat crystals in the cytoplasm of damaged adipocytes (hematoxylin-eosin, original magnification $\times 40$).

presentation is highlighted by our case. As subcutaneous fat liquefies, multicystic plaques may develop and affected skin may become taut and undergo epidermal necrosis.^{5,6} In some cases, liquefaction may be so severe that serial aspiration is required to minimize pain and skin breakdown.⁶ Our patient had drainage of a chalky, white substance from a fluctuant nodule for 1 to 2 days after biopsy. With a presentation of erythema, induration, and fluctuance, bacterial cellulitis, erysipelas, and abscess formation are often initially considered in the differential diagnosis. However, neonates with SCFN remain normothermic; lesions do not typically spread; and cultures reveal no growth. The mild elevation of C-reactive protein levels in our patient is consistent with SCFN being an inflammatory process, as past reports have demonstrated other markers of neonatal inflammation, such as thrombocytopenia and elevated ferritin levels.^{7,8}

Beyond infection, the differential diagnosis of SCFN includes other causes of subcutaneous nodules, including dermoid cysts; benign tumors such as hemangiomas and infantile myofibromatosis; malignant tumors such as rhabdomyosarcoma, infantile fibrosarcoma, neuroblastoma, and congenital leukemia; and sclerema neonato-

rum. The criterion standard in confirming the diagnosis of SCFN is punch biopsy. Histopathologic analysis reveals lobular panniculitis with adipose cell necrosis and dense inflammatory infiltrates involving lymphocytes, histiocytes, lipophages, giant cells in granuloma formation, and rare eosinophils. Characteristic needle-shaped, doubly retractile clefts in radial arrangement are noted in giant cells and adipocytes. These clefts are believed to be composed of triglycerides in crystallized form.⁹ As an alternative to skin biopsy, some authors have proposed the use of fine-needle aspiration or touch preparation for spontaneously draining lesions to confirm the diagnosis of SCFN.^{10,11} While these methods likely lack the sensitivity of biopsy and are dependent on the clinician's technique and the amount of material obtained, they may provide a more rapid and less invasive method to diagnose SCFN.

A number of risk factors, including gestational diabetes, preeclampsia, maternal cocaine use, birth asphyxia, meconium aspiration, and neonatal hypothermia, have been associated with SCFN.³ Birth asphyxia is overwhelmingly the most commonly identified predisposing factor. The 2 largest case series on SCFN describe 10 of 11 cases and 13 of 16 cases occurring in the setting of birth asphyxia.^{3,4} Birth asphyxia triggers the "diving reflex" whereby blood is shunted from the skin and splanchnic beds to the brain, heart, and adrenal glands in neonates. The shunting of blood away from subcutaneous tissue creates an environment of hypoxia and hypothermia, which is believed to lead to a cycle of granulomatous inflammation and necrosis of adipose tissue. Furthermore, neonatal adipose tissue is unique in that it is composed of a higher concentration of saturated fatty acids that have a higher melting point (64°C), making them more likely to crystallize under cold stress.¹²

Our case highlights the fact that induced hypothermia may play a further role in the development of SCFN. Early cases of SCFN were documented in neonates who underwent whole-body cooling before being placed on cardiopulmonary bypass for cardiovascular surgery.¹³ Clinicians should be aware of this association as more neonates are undergoing therapeutic cooling to minimize the mortality and morbidity due to hypoxic-ischemic encephalopathy. To date, 2 large, randomized controlled studies have been published documenting a reduction in disability at 18 months of age when infants with hypoxic-ischemic encephalopathy underwent whole-body cooling during the first 6 hours of life and for a total of 72 hours (Total Body Hypothermia for Neonatal Encephalopathy and National Institute of Child Health and Human Development trials).^{1,2} The Total Body Hypothermia for Neonatal Encephalopathy trial did not comment on adverse dermatologic outcomes. However, the National Institute of Child Health and Human Development trial demonstrated that 4 of 102 infants in the cooling arm had dermatologic complications described as erythema, sclerema, cyanosis, and SCFN. No children in the control arm of the study developed SCFN.¹ To our knowledge, our case serves as the first published case report of SCFN during the routine clinical application of a cooling protocol for hypoxic-ischemic encephalopathy. Since neonates undergoing cooling have experienced sig-

nificant hypoxemic stress and are therefore at a distinctive risk for SCFN, our case suggests a possible association and does not establish a direct causal relationship between cooling and SCFN. However, the development of SCFN in areas directly exposed to the cooling blanket in our patient highlights that direct cooling may have an additive effect in the development of SCFN and that further research exploring this association is needed.

While most cases of SCFN spontaneously resolve, complications such as pain, hypoglycemia, thrombocytopenia, hypertriglyceridemia, and hypercalcemia have been reported.⁶ Alterations in glucose levels and platelet counts are often seen in neonatal stress, yet hypercalcemia seems unique to SCFN. Similar to neonates with other granulomatous disorders, neonates with SCFN have unregulated, increased extrarenal production of 1,25-dihydroxyvitamin D₃, leading to increased intestinal absorption of calcium.¹² Hypercalcemia may be asymptomatic, as in our case. However, when it is severe, infants may develop failure to thrive, vomiting, lethargy, and even metastatic calcinosis, as indicated by separate reports of SCFN causing nephrocalcinosis and atrial septum, inferior vena cava, and hepatic calcifications.¹⁴⁻¹⁶ The neonate in our case did not require any treatment for hypercalcemia. Treatment options include conservative management by switching patients to low calcium and vitamin D formula, promoting calciuresis through fluids, and furosemide or anti-inflammatory treatment with low-dose corticosteroids. The use of pamidronate has also been shown to be safe and to normalize calcium levels rapidly in refractory cases.^{15,17}

In summary, our case report emphasizes 3 points that clinicians should recognize when caring for a neonate with SCFN. Subcutaneous fat necrosis of the newborn may have an abscesslike presentation on examination as subcutaneous fat undergoes necrosis. Therapeutic cooling may place neonates at increased risk for SCFN; therefore, it is recommended that these neonates undergo frequent skin examinations and that they be turned regularly to avoid prolonged direct pressure against the cooling interface. Finally, hypercalcemia often arises after the patients are discharged from the hospital so all infants with SCFN should undergo weekly calcium checkups at least until the lesions clinically resolve and for up to 6 months to prevent the significant morbidity that can occur with hypercalcemia.

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REFERENCES

1. Shankaran S, Laptook AR, Ehrenkranz RA, et al; National Institute of Child Health and Human Development Neonatal Research Network. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *N Engl J Med*. 2005; 353(15):1574-1584.
2. Azzopardi DV, Strohm B, Edwards AD, et al; TOBY Study Group. Moderate hypothermia to treat perinatal asphyxial encephalopathy. *N Engl J Med*. 2009; 361(14):1349-1358.
3. Burden AD, Krafchik BR. Subcutaneous fat necrosis of the newborn: a review of 11 cases. *Pediatr Dermatol*. 1999;16(5):384-387.
4. Mahé E, Girszyn N, Hadj-Rabia S, Bodemer C, Hamel-Teillac D, De Prost Y. Subcutaneous fat necrosis of the newborn: a systemic evaluation of the risk factors, clinical manifestations, complications and outcome of 16 children. *Br J Dermatol*. 2007;156(4):709-715.
5. Balfour E, Antaya RJ, Lazova R. Subcutaneous fat necrosis of the newborn presenting as a large plaque with lobulated cystic areas. *Cutis*. 2002;70(3):169-173.
6. Tran JT, Sheth AP. Complications of subcutaneous fat necrosis of the newborn: a case report and review of the literature. *Pediatr Dermatol*. 2003;20(3):257-261.
7. Lewis A, Cowen P, Rodda C, Dyall-Smith D. Subcutaneous fat necrosis of the newborn complicated by hypercalcemia and thrombocytopenia. *Australas J Dermatol*. 1992;33(3):141-144.
8. Zaulyanov LL, Jacob SE, Elgart GW, Schachner L. Subcutaneous fat necrosis of the newborn and hyperferritinemia. *Pediatr Dermatol*. 2007;24(1):93.
9. Zeb A, Darmstadt GL. Sclerema neonatorum: a review of nomenclature, clinical presentation, histological features, differential diagnoses and management. *J Perinatol*. 2008;28(7):453-460.
10. Walker WP, Smith RJ, Cohen MB. Fine-needle aspiration biopsy of subcutaneous fat necrosis of the newborn. *Diagn Cytopathol*. 1993;9(3):329-332.
11. Lund JJ, Xia L, Kerr S, Stratman EJ, Patten SF. The utility of a touch preparation in the diagnosis of fluctuant subcutaneous fat necrosis of the newborn. *Pediatr Dermatol*. 2009;26(2):241-243.
12. Cook JS, Stone MS, Hansen JR. Hypercalcemia in association with subcutaneous fat necrosis of the newborn: studies of calcium-regulating hormones. *Pediatrics*. 1992;90(1, pt 1):93-96.
13. Chuang SD, Chiu HC, Chang CC. Subcutaneous fat necrosis of the newborn complicating hypothermic cardiac surgery. *Br J Dermatol*. 1995;132(5):805-810.
14. Vijayakumar M, Prahlad N, Nammalwar BR, Shanmughasundharam R. Subcutaneous fat necrosis with hypercalcemia. *Indian Pediatr*. 2006;43(4):360-363.
15. Alos N, Eugene D, Fillion M, Powell J, Kokta V, Chabot G. Pamidronate: treatment for severe hypercalcemia in neonatal subcutaneous fat necrosis. *Horm Res*. 2006;65(6):289-294.
16. Dudink J, Walther FJ, Beekman RP. Subcutaneous fat necrosis of the newborn: hypercalcemia with hepatic and atrial myocardial calcification. *Arch Dis Child Fetal Neonatal Ed*. 2003;88(4):F343-F345.
17. Aucharaz KS, Baker EL, Millman GC, Ball RJ. Treatment in hypercalcemia in subcutaneous fat necrosis is controversial. *Horm Res*. 2007;68(1):31.

The Best of the Best

Top-Accessed Article: Dermoscopy of Amelanotic and Hypomelanotic Melanoma

Menzies SW, Kreuzsch J, Byth K, et al. Dermoscopic evaluation of amelanotic and hypomelanotic melanoma. *Arch Dermatol*. 2008;144(9):1120-1127.

Amelanotic and hypomelanotic melanomas of the skin pose a considerable diagnostic challenge. In this retrospective, multicentered study, Menzies and colleagues identified key dermoscopic features for distinguishing 105 amelanotic and hypomelanotic melanomas from 222 nonmelanocytic and 170 benign melanocytic lesions that lacked significant pigmentation. The most notable positive predictors include a blue-white veil, scarlike depigmentation, multiple blue-gray dots, irregularly shaped depigmentation, and irregular brown dots or globules. The morphological features, which include predominant central vessels, milky red-pink areas, more than 1 shade of pink, and a combination of dotted and linear irregular vessels, are also important for diagnosis. It is noteworthy that the images were captured with glass-plate dermoscopy devices, with compression of the underlying vessels varying according to the amount of pressure applied. It is very likely that more significant vessel details may be found using cross-polarized noncontact dermoscopes.

In summary, the dermoscopic features in this study provide valuable clues for diagnosing amelanotic and hypomelanotic melanomas. Future studies with polarized devices may offer additional diagnostic features.

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