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Case 2: Beware of Lumps and Bumps after Cooling!

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PRESENTATION

The infant is born to a 31-year-old primigravida mother by cesarean delivery due to nonreassuring fetal heart rate and chorioamnionitis. Rupture of membranes is prolonged at 47 hours with meconium-stained amniotic fluid.

At birth, the newborn is noted to have poor tone and respiratory effort. He undergoes intubation and is admitted to the NICU for further observation and management. Apgar scores are 2, 5, and 7 at 1, 5, and 10 minutes, respectively. Arterial cord gas has a pH of 6.8 and a base deficit of 24 mEq/L (24 mmol/L).

The patient demonstrates signs and symptoms of moderate hypoxic-ischemic encephalopathy and meets the criteria for whole body hypothermia therapy. He is started on parental nutrition. He has evidence of pulmonary hypertension on echocardiography and requires inhaled nitric oxide for 2 days while undergoing hypothermia treatment. He maintains adequate blood pressures and does not have any hemodynamic decompensation. He receives 2 doses of fresh frozen plasma to correct laboratory indices that demonstrate abnormal coagulation profiles. Following rewarming and after obtaining a brain magnetic resonance imaging scan (which is unremarkable) he undergoes successful extubation on the 4th postnatal day. His respiratory support is gradually weaned and he remains in room air from day 6 of age onwards. He is slowly introduced to enteral feeds and reaches full oral feeds by 9 days of age. His neurologic examination findings are normal.

Erythematous, indurated plaques are noted over the upper back, shoulders, and back of the head on the 10th day consistent with a diagnosis of subcutaneous fat necrosis (SCFN). During the NICU admission, his total calcium levels remain within normal range (Fig 1A). The patient's ionized calcium the day before his discharge is 5.4 mg/dL (1.3 mmol/L; normal range 4.5–6.2 mg/dL [1.1–1.55 mmol/L]). On the day of discharge, the ionized calcium is 6.0 mg/dL (1.5 mmol/L) and the patient receives a dose of intravenous (IV) furosemide. The plan at discharge is for the pediatrician to follow up the calcium weekly until the SCFN resolves.

AUTHOR DISCLOSURE Drs Vali and Lakshminrusimha have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

DISCUSSION

Diagnosis

The first outpatient calcium follow-up blood sample cannot be evaluated because the sample quantity was deemed insufficient. A few days later, a repeat sample was obtained and reported at 19.8 mg/dL (4.9 mmol/L; approximately 2 weeks from discharge). The patient was instructed to present to the children's hospital emergency department (ED) immediately. He remains asymptomatic with no signs or symptoms of hypercalcemia.

The Condition

SCFN is an uncommon condition, usually observed in a minority of newborn infants with a history of hypoxic-ischemic encephalopathy treated with therapeutic hypothermia.

Following 3 large randomized controlled trials, in newborns with hypoxic-ischemic encephalopathy, therapeutic moderate hypothermia has become the standard of care and is being increasingly implemented in NICUs. The original trials were not powered to detect rare adverse events and the recognition that moderate hypothermia increases the risk of SCFN has become more widespread with rising cases. Currently, the incidence of SCFN is estimated around 1% to 3%.

SCFN is characterized by erythematous, firm, indurated, nonpitting plaques or nodules over the back, buttocks, thighs, posterolateral surface of the forearms, and rarely, involving the face. Although the exact pathophysiology remains unknown, hypothermia can further compromise skin perfusion in the asphyxiated newborn, exacerbating ischemic injury to immature fat cells that can result in necrosis and solidification. SCFN is usually a self-limiting disorder of adipose tissue presenting in the first week after birth and resolving by 6 months of age.

The associated complication of hypercalcemia, reported in up to 80% of SCFN cases (sometimes presenting with critically elevated calcium levels as observed in the current patient), requires aggressive treatment. This makes the recognition of SCFN by the parents and pediatrician imperative to the well-being of the newborn. A widely accepted hypothesis explaining the development of hypercalcemia in SCFN is that the release of 1,25-dihydroxy vitamin D during necrosis of granulomatous fat cells results in increased intestinal calcium absorption.

SCFN can be distinguished from sclerema neonatorum (SN), also a disorder of fat necrosis, by the presentation of SCFN as circumscribed lesions that are mobile and self-limited; SN, however, is generalized and characterized by hardening of the skin that gets bound down to the muscle and bone. SN hinders breathing and movement in the neonate, and is associated with a high incidence of fatality.

Treatment

Given the overall rare occurrence of SCFN, and even less frequent associated severe complications, the potentially serious adverse effects of hypercalcemia may be underappreciated by caregivers. In the ED, the patient in the current case was aggressively

fluid resuscitated and admitted to the PICU for possible dialysis. He received maintenance IV fluids, IV furosemide, and methylprednisolone for 2 days. He did not have any signs of arrhythmia and did not require dialysis. With improving calcium levels, he was transferred to the inpatient floor for further management and observation. He received 1 dose of IV pamidronate with only a transient effect and therefore continued to take oral steroids until his calcium levels normalized before discharge from the hospital (Fig 1B).

In symptomatic patients, treatment relies on low-calcium and low-vitamin D diets, IV hydration and loop diuretics, corticosteroids, and bisphosphonates with the possible need for dialysis.

Lessons for the Clinician

Because there are currently no guidelines for pediatricians on how best to manage newborns at risk for SCFN, we propose the following recommendations:

- In the event that the newborn shows signs of SCFN during the hospitalization, neonatal care clinicians should document normal calcium levels before discharge.
- Calcium levels should be routinely followed on an outpatient basis, and vitamin D supplementation deferred, until nodules have resolved.
- In newborns who do not show any signs of SCFN at discharge, parents should be instructed to notify pediatricians if they notice any redness or firmness on their child's skin.
- Pediatricians are encouraged to be diligent in their examination, particularly when examining the newborn's skin to make sure developing SCFN is not missed.

By increasing parental and pediatrician awareness of the rare, albeit serious, complications of SCFN with the help of this infographic (Fig 2) we hope to limit cases of hypercalcemia associated with SCFN.

Acknowledgments

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Suggested Readings

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American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the etiology and clinical manifestations of neonatal hypercalcemia.
- Know the laboratory features and approach to therapy of neonatal hypercalcemia.

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Figure 1.

A. Total and ionized calcium levels during NICU admission. Arrowheads indicate period of whole body hypothermia. B. Total and ionized calcium levels during readmission. Arrow indicates initiation of intravenous (IV) maintenance fluids, IV furosemide, and methylprednisolone. # represents cessation of IV fluids and medications, and initiation of prednisolone until discharge.

Figure 2. Infographic showing the pathophysiology and management of hypercalcemia in neonatal subcutaneous fat necrosis. Hypoxic-ischemic encephalopathy and therapeutic hypothermia can increase the risk of subcutaneous fat necrosis in newborn infants. Necrosis of fat cells is thought to release active vitamin D, which leads to increased absorption of calcium and hypercalcemia. Management (shown in black boxes) includes limiting calcium and vitamin D intake and promoting excretion of calcium.