Subcutaneous fat necrosis (SCFN) of the newborn is a rare condition characterized by painful, firm and erythematous nodules or plaques. This condition usually occurs in term infants within the first week of life, mostly following a complicated delivery causing hypoxemia. The prognosis of the disease is generally favorable, with complete spontaneous regression of the skin lesions within several weeks to months, but it may be complicated by serious metabolic abnormalities. The most important complication of SCFN is hypercalcemia, which may cause potentially life-threatening problems affecting the renal and cardiovascular systems. Subsequent complications of SCFN, including hypoglycemia, thrombocytopenia and hypertriglyceridemia, are usually transient and may improve spontaneously without sequelae.

We present a case with SCFN following perinatal asphyxia secondary to meconium aspiration, complicated by all metabolic complications, including hypoglycemia, thrombocytopenia, hypertriglyceridemia, and hypercalcemia, with bilateral nephrocalcinosis. In the report, we focus specifically on the hypercalcemia and subsequent nephrocalcinosis, which persisted despite therapy over four years of follow-up.

Case Report
A four-month-old female infant, who had a history of perinatal asphyxia secondary to meconium aspiration syndrome, was referred to our hospital to evaluate bilateral nephrocalcinosis. She had been born at full term, weighed 4250 g, and was delivered by cesarean section because of fetal distress after an uncomplicated pregnancy. Her Apgar scores had been 0, 7, and 10 at 1, 5 and 10 minutes, respectively. The newborn had been observed for seven days in the neonatal intensive care unit (NICU). According to her medical history while in the NICU, she had hypoglycemia (15 mg/dl), hypocalcemia (7.1 mg/dl), thrombocytopenia (58000/mm³), and increased aspartate aminotransferase (AST: 1400 U/L), alanine aminotransferase (ALT: 1200 U/L), blood urea nitrogen (BUN: 34 mg/dl), and creatinine (3.3 mg/dl) levels, indicative of perinatal asphyxia in the first day of life. At three days old, the platelet count fell to 26000/mm³ and she was treated with two transfusions of a platelet suspension. Sepsis was ruled out with negative blood cultures, and then the infant was discharged after one week of hospitalization with serum creatinine of 0.6 mg/dl and calcium of 7.9 mg/dl, and a platelet
count of 59000/mm³. At the age of 20 days, her mother noticed reddish nodular swellings on the arms, cheeks, legs, back, and buttocks. Neither investigation nor treatment was done at that time. At the age of three months, the infant was taken to her pediatrician with complaints of failure to grow, constipation and polydipsia. Nephrocalcinosis was detected on her abdominal ultrasonography, so the infant was referred to our hospital.

On admission, she was four months of age. The physical examination was normal, with the exception of the irregular, firm and erythematous plaques and the soft tissue masses on the lateral part of both thighs (Fig. 1). Serum glucose, BUN, creatinine, AST, and ALT levels were within normal limits. Her serum levels of calcium (13.5 mg/dl) and triglyceride (536 mg/dl) were high. The parathyroid hormone was suppressed, at 3.3 pg/ml (normal: 12-72 pg/ml), while the 25-hydroxyvitamin D₃ (23.7 ng/dl) and 1,25-dihydroxyvitamin D₃ levels (45.0 ng/L) were within the normal ranges. The urinary calcium/creatinine ratio was elevated, at 1.2 mg/mg (normal value: <0.8 mg/mg for infants <6 months old). The renal ultrasonography showed bilateral increased echogenicity of the medullary pyramids, suggesting nephrocalcinosis (Fig. 2a). The infant was diagnosed as having a SCFN, complicated by hypercalcemia and nephrocalcinosis, based on her medical history and the clinical and laboratory evidence.

The hypercalcemia was treated with intravenous hydration and the discontinuation of vitamin D, in addition to a low-calcium diet. Neither corticosteroids nor bisphosphonate was required for the normalization of calcemia. The patient was discharged after seven days, with serum level of calcium of 10.9 mg/dl. At the age of 12 months, the subcutaneous lesions had reduced markedly in size, and the serum creatinine was 0.6 mg/dl, calcium 10.7 mg/dl and urine calcium/creatinine ratio 0.55 mg/mg; however, the abdominal ultrasonography indicated persistence of the medullary nephrocalcinosis despite the potassium citrate therapy. She is now five years old and still in a good clinical condition with a normal renal function; however, bilateral grade III nephrocalcinosis persists (Fig. 2b).

Discussion

Subcutaneous fat necrosis (SCFN) of the
newborn is an uncommon and transient inflammatory disorder of the adipose tissue. The etiology of the disorder is unknown, but multiple risk factors are responsible for its development. Hypoxemia of the newborn induced by local trauma (forceps delivery) or more diffuse cutaneous trauma (macrosomic infants) is a well-described risk factor. Recently, therapeutic hypothermia in hypoxic ischemic newborns has recently been noted as a predisposing factor. Maternal factors may also be associated with SCFN, including gestational diabetes, preeclampsia, smoking, thrombosis, and dyslipidemia. In our patient, there were no maternal risk factors; however, there was a history of perinatal hypoxemia probably induced by macrosomia and meconium aspiration.

Despite the fact that SCFN is usually known as a benign condition, it may lead to potentially serious complications, including thrombocytopenia, hypoglycemia, hypertriglyceridemia, and hypercalcemia. Thrombocytopenia is an early complication of SCFN that usually appears before or at the same time as the onset of skin lesions. It can be caused by peripheral sequestration of platelets within the subcutaneous tissue. Hypoglycemia is another early complication of SCFN that may be associated with perinatal distress and maternal gestational diabetes. In the present case, hypoglycemia may be explained by perinatal distress and also macrosomia or as a complication of SCFN. Hypertriglyceridemia is another complication of SCFN that may be due to mobilization of fatty acids from the adipose tissue. In addition to those three complications, which did not cause any serious problem, our patient also had hypercalcemia, which led to persistent nephrocalcinosis. Therefore, we herein have focused on this complication.

Hypercalcemia is the most serious complication of SCFN and usually occurs between one to six months after the development of subcutaneous nodules. The frequency of this complication has been reported to be as high as 69% in a case series of 13 patients evaluated for hypercalcemia. The underlying etiology of hypercalcemia is unclear, but there are several hypotheses to explain the causes of this metabolic abnormality. One of the most accepted theories is the increased secretion of 1,25-dihydroxyvitamin D3 from the granulomas of subcutaneous lesions, leading to an increased intestinal calcium uptake. Another possible mechanism for hypercalcemia is increased levels of inflammatory mediators like prostaglandin E, resulting in the activation of osteoclasts and the release of calcium from necrotic fat cells. In our infant, both normal vitamin D levels and suppressed parathyroid hormone levels suggest the second mechanism in the development of the hypercalcemia.

Hypercalcemia should be treated immediately and aggressively to decrease the serious complications. The initial therapy for hypercalcemia is hyperhydration, low dietary calcium intake and the restriction of vitamin D; however, this first line of therapy may be insufficient and does not change the natural course of the disease and its complications. Furosemide and prednisolone are also used for hypercalcemia, but there is evidence that they increase renal calcium excretion, raising the risk of nephrocalcinosis. There is evidence of the positive effect of pamidronate on hypercalcemia in patients with SCFN, reducing the renal calcium load and the risk of nephrocalcinosis.

Untreated hypercalcemia may lead to serious complications, such as nephrolithiasis, nephrocalcinosis and renal failure. Nephrocalcinosis due to SCFN usually appears within 4-6 weeks, and may occur following persistent hypercalcemia. Mahe et al. reported three cases complicated by nephrocalcinosis among nine hypercalcemic newborns with SCFN. One of them also had transient renal insufficiency. Those infants were treated with furosemide, prednisolone and pamidronate (in 1 patient) for hypercalcemia in addition to a low-calcium diet and vitamin D restriction. The authors observed that the calcium levels normalized within seven days and the nephrocalcinosis disappeared within 3-11 months in all three infants. Alos et al. reported two cases with SCFN complicated by nephrocalcinosis that did not persist at follow-up. Both of them were treated with pamidronate for hypercalcemia after treatment with intravenous hydration, furosemide and a diet low in calcium and vitamin D. Their pamidronate treatment was started at the age of 33 days and 45 days, respectively. In our
patient, hypercalcemia therapy was initiated at the age of four months, when she was referred to us with a severe nephrocalcinosis. It is unfortunately not possible to know either the severity or the duration of hypercalcemia due to the lack of follow-up before the admission. Hypercalcemia had most probably occurred earlier and reached much higher levels than detected, and persisted up to admission. The long-term persistence of hypercalcemia and later initiation of therapy most likely led to the severe nephrocalcinosis in our case.

In summary, SCFN of the newborn is a rare clinical entity. Although it seems to be a benign, transient and self-limited disease, it may be complicated by irreversible conditions in infants receiving a delayed diagnosis. Therefore, SCFN should be kept in mind in the diagnosis of neonates who develop skin lesions within the first week of life, and these neonates should be monitored regularly and closely for potential complications. Most importantly, clinicians need to be aware of hypercalcemia and its serious complications. Hypercalcemia should also be treated immediately and appropriately in order to decrease the risk of nephrocalcinosis.

REFERENCES