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Subcutaneous fat necrosis of the infant

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Subcutaneous fat necrosis of the newborn and infant is a rare disease, with still unknown incidence, which usually occurs in term or post-term newborns that have experienced perinatal stress. It usually occurs within the first six weeks of newborn's life; however, onset of the disease may be delayed for several months. A 6-week-old female infant was admitted to our department due to failure to thrive, irritability and vomiting. Physical examination in the area of the inner thighs, hips, back and shoulders, revealed the presence of subcutaneous infiltrations, which were firm, slightly livid, and did not seem painful to touch. Laboratory analysis showed hypercalcemia, ultrasonographic review of body fat revealed hyperechogenicity, while abdominal ultrasound revealed nephrocalcinosis. Computerized tomography detected the presence of calcifications in the brain. Deep skin biopsy confirmed the diagnosis of subcutaneous fat necrosis. Treatment included fluid loading, termination of vitamin D substitution, and low calcium diet. Single doses of calcitonin and pamidronate were administered. After this therapy, calcium levels returned to normal range. Subcutaneous infiltrates gradually decreased and became softer. In most reported cases, regression of skin lesions is expected after a few months, often without any residue on the skin. Elevated serum calcium may persist long after the withdrawal of cutaneous lesions, which is the reason for continuous monitoring of serum calcium and appropriate treatment in case of hypercalcemia in order to prevent metastatic calcification.

Keywords: fat necrosis; hypercalcemia; infant, newborn

INTRODUCTION

Subcutaneous fat necrosis (SFN) of the newborn is a rare disease, with still unknown incidence, which usually occurs in term or post-term newborns that have experienced perinatal stress in the form of asphyxia, meconium aspiration, or hypothermia. Gender and race have no effect on the onset of the disease (1-4). It usually occurs within the first six weeks of life; however, the onset of the disease may be delayed for several months. The precise pathophysiology of this disease is still unknown. It is believed that stress in the neonatal period, followed by hypoperfusion of the skin and hypothermia, with still insufficiently developed enzyme system, leads to an inability to desaturate saturated fatty acids, which causes crystallization, necrosis and the granulomatous inflammatory reaction in adipocytes. This is clinically manifested by the appearance of firm, erythematous plaques and nodes, predominantly localized on the trunk, arms, thighs, gluteal region and cheeks (5-9). These lesions are usually painless (1). Patients are usually afebrile and in good general condition. The disease is self-limiting and transient, and in most cases there is spontaneous restitution of skin lesions and no specific therapy is required. However, in some cases, the disease may lead to hypercalcemia, a complication usually occurring several weeks after the appearance of skin lesions. Associated hypercalcemia can lead to significant morbidity (calcification of tissues, irritability, vomiting, hypotonia, constipation, failure to thrive, seizures, blindness), and even death. In such instances, therapy should be geared towards lowering serum calcium. Since hypercalcemia may be present for some time following

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withdrawal of cutaneous lesions, periodical monitoring of serum calcium is needed in these children (8, 12). Besides hypercalcemia, hypertriglyceridemia, thrombocytopenia, anemia and hypoglycemia may also be found in SFN (10).

CASE REPORT

A 6-week-old female infant was admitted to our department due to failure to thrive, irritability and vomiting. She was born at term, by vaginal delivery, pelvic presentation, with foul-smelling meconium in amniotic fluid. There was a delay in the expulsion of the child. Body weight at birth was 3270 g, body length 53 cm, head circumference 33 cm, Apgar score 1/3/5 (1′, 5′, 10′). After birth, the child was hospitalized at the Clinical Department of Pediatrics due to meconium aspiration syndrome and subarachnoid hemorrhage complicated with neonatal sepsis. During hospital stay, she had neonatal jaundice and hypoglycemia, and was diagnosed with ventricular septal defect. She was released after four weeks of hospital stay in good general condition. After discharge from the hospital, at home, she refused meals, was tearful, irritable and slept insufficiently, with occasional vomiting, and after two weeks, at the age of 6 weeks, the child was readmitted to our Department.

On admission, she was alert, hypotonic and irritable, afebrile, with respirations of 40 *per* minute and heart rate 132 *per* minute, hypotrophic (body weight 2920 g, length 53 cm, head circumference 34 cm, all under the 5th percentile). Physical examination in the area of the inner thighs, hips, back and shoulders, revealed the presence of subcutaneous infiltrations, which were firm, slightly livid, and did not seem painful to touch. There were also signs of dehydration (sunken fontanel, shriveled and dry skin, dry and sticky mouth). There was second/third degree systolic murmur over the precordium (punctum maximum over the Erb's point).

Laboratory analysis showed hypercalcemia of 3.04 mmol/L, high urinary calcium/creatinine ratio, anemia, hypertriglyceridemia, low HDL cholesterol, elevated AST, gamma GT and LDH with significantly lower levels of PTH (<2.5 pg/mL), while vitamin D was within the normal range. Ultrasonographic review and computerized tomography of body fat revealed hyperechogenicity (Figures 1 and 2), while abdominal ultrasound revealed nephrocalcinosis. Computerized tomography detected the presence of calcifications in the brain. Electromyoneurography findings were normal. Karyotype was normal, 46,XX. Biopsies of subcutaneous adipose tissue confirmed the diagnosis of SFN. The subcutaneous adipose tissue contained necrotic fat tissue infiltrated with multinucleated giant cells with numerous cholesterol crystals, needle-shape clefts and mixed inflammatory infiltrate. The inflammatory infiltrate was present in the entire lobules, however, more prominent in the peripheral parts of the lobules (Figure 3).

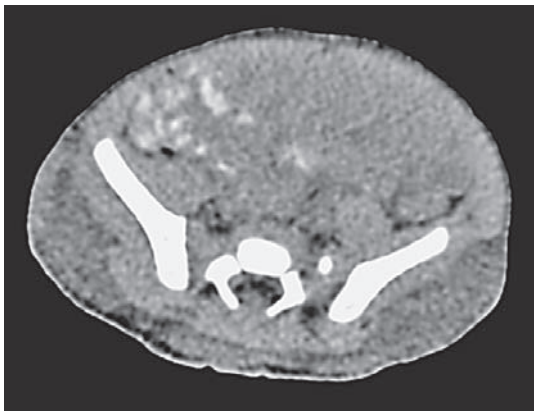

FIGURE 1. Computed tomography: hyperdensity in the gluteal region.

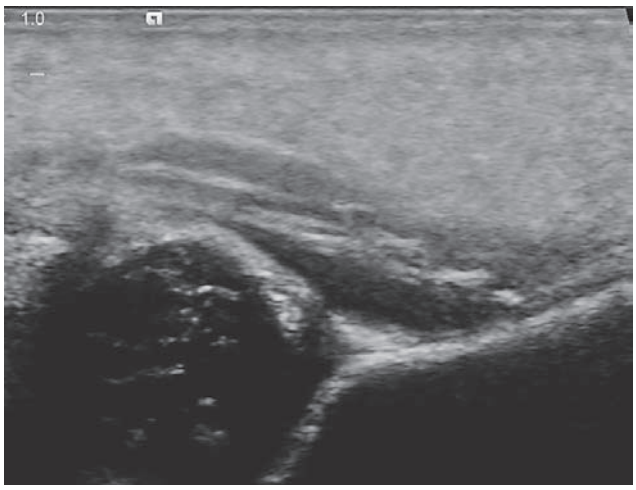

FIGURE 2. Necrosis of subcutaneous fat tissue, presented as extremely increased echogenicity of subcutaneous fat on ultrasonography

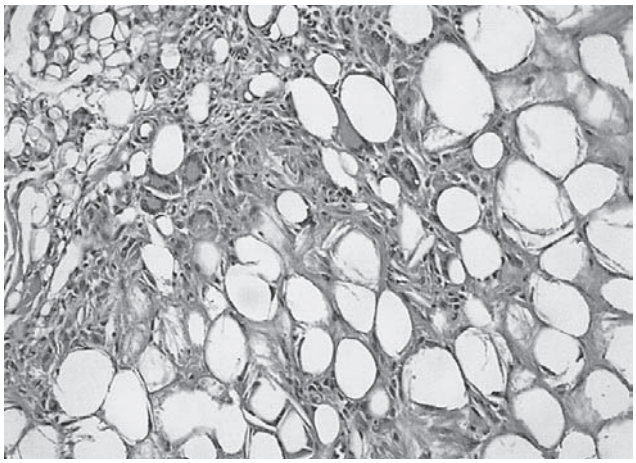

FIGURE 3. Histopathologic findings: focal necrosis of subcutaneous fat tissue with multinucleated giant cells with numerous cholesterol crystals and mixed inflammatory infiltrate (HE, X200).

Treatment included fluid loading, termination of vitamin D substitution, and low calcium diet. Single dose of calcitonin was administered. Despite this therapy, the serum calcium levels were still at the upper limit. Therefore, the patient was given one dose of bisphosphonates (pamidronate, 2 mg/kg in i.v. infusion). After this therapy, calcium levels returned to the normal range. During hospitalization, the child's general condition was good, with satisfactory gain weight. Subcutaneous infiltrates gradually decreased and became softer. The child was discharged after two months of hospital stay with normal calcium values and complete regression of subcutaneous changes.

DISCUSSION

Subcutaneous fat necrosis is a rare disorder that is associated with perinatal complications such as asphyxia, hypothermia, meconium aspiration, a primary defect in the subcutaneous tissue, as well as preeclampsia and gestational diabetes. It is obvious that neonatal stress has an important role in initiating necrotic processes in adipose tissue (1, 13). This was the case in our patient as well, who had severe asphyxia and meconium aspiration.

This disorder occurs more frequently in children born at term, as well as in post-term neonates (5, 13), as seen in our patient. The appearance of skin lesions generally occurs within the first six weeks of life (10). Our patient was diagnosed with skin lesions at the age of six weeks, with no information available on their possible earlier existence. Lesions occurred on the interior part of the thigh, the left and right hip, back, and in the shoulder area, which corresponds to the predilection sites described in the literature. These lesions are usually solid erythematous nodules, without an increase in local temperature. Pain is present in 25% of cases and is caused by the existing inflammation (1). In the case of our patient, subcutaneous nodules were slightly livid, were not warm, but were firm to touch and did not seem painful.

The diagnosis of SFN usually requires deep skin biopsy, since it may be difficult to exclude *sclerema neonatorum*, which carries a mortality rate of 75%, while the prognosis of SFN is good (2). In most reported cases, regression of skin lesions is expected after a few months, often without any residue on the skin (5, 7, 8), which proved to be the case in our patient. In some patients, drainage of necrotic tissue through the skin may occur, as well as the formation of scars or skin atrophy (1). If there are no associated complications, these children are usually in good general condition and afebrile. The most frequent complication of SFN is hypercalcemia. It usually occurs a few weeks after the onset of the disease, leading to various disorders and even death of the patient (4, 8).

The cause of the occurrence of hypercalcemia is thought to be increased bone resorption (due to the effect of prostaglandin E), the release of calcium from necrotic cells and, for the most part, unregulated extrarenal production of calcitriol by macrophages of granulomatous infiltrates (5, 8, 9). Hypercalcemia can often cause calcification of tissues and organs (8, 10), as seen in our patient. It is the most frequent and dangerous complication of SFN because of its potential lethal effects on cardiovascular and renal systems. Therapy is focused on the elimination of excessive calcium and vitamin D intake, and adequate hydration with intravenous normal saline. Furosemide may be helpful to induce calciuresis, but has to be used carefully in order to avoid dehydration and consequent worsening of hypercalcemia. Corticosteroids, calcitonin, citrate and bisphosphonates may be required as second-line therapy in resistant cases (10, 15). Hypertriglyceridemia and anemia may also occur, as well as thrombocytopenia and hypoglycemia (8, 10, 14).

CONCLUSION

Regression of skin lesions is expected after a few months, often without any residue on the skin. Elevated serum calcium may persist long after withdrawal of cutaneous lesions, which is the reason for continuous monitoring of serum calcium and appropriate treatment in case of hypercalcemia in order to prevent metastatic calcification.

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SAŽETAK

Nekroza potkožnog masnog tkiva kod dojenčeta

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Nekroza potkožnog masnog tkiva kod novorođenčeta i dojenčeta je rijetka bolest još uvijek nepoznate incidencije, koja se obično javlja kod novorođenčadi rođene u terminu ili poslije termina izložene perinatalnom stresu. Najčešće nastaje u prvih šest tjedana djetetova života, no moguć je i odgođeni nastup bolesti za nekoliko mjeseci. Žensko dojenče staro 6 tjedana primljeno je na naš odjel zbog slabog napredovanja, razdražljivosti i povraćanja. Fizikalni pregled otkrio je na unutarnjem dijelu bedara, bokovima, leđima i ramenima potkožne infiltrate koji su bili tvrdi, blago modrosivi i nisu se činili bolnima na dodir. Laboratorijske pretrage pokazale su hiperkalcemiju, dok je ultrazvučni pregled tjelesne masti otkrio hiperehogeničnost, dok je ultrazvuk abdomena pokazao nefrokalcinozu. Kompjutorizirana tomografija otkrila je prisutnost kalcifikacija u mozgu. Duboka kožna biopsija potvrdila je dijagnozu nekroze potkožnog masnog tkiva. Liječenje je provedeno opterećenjem tekućinom, uz prestanak nadomještanja vitamina D i prehranu s niskim sadržajem kalcija. Dijete je dobilo po jednu dozu kalcitonina i pamidronata. Nakon ove terapije razine kalcija vratile su se na normalu. Potkožni infiltrati postupno su se smanjili i omekšali. U većini opisanih slučajeva regresija kožnih promjena očekuje se kroz nekoliko mjeseci, često bez ikakvih zaostalih tragova na koži. Povišena razina kalcija u serumu može potrajati još dugo nakon što se kožne promjene povuku pa je potrebno stalno praćenje serumskog kalcija i odgovarajuće liječenje u slučaju hiperkalcemije kako bi se spriječila metastatska kalcifikacija.

Ključne riječi: nekroza masnog tkiva; hiperkalcemija; novorođenče