Generalized periosteal reaction and tissue swelling secondary to prolonged prostaglandin E1 infusion and venous stasis: a case report

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Prostaglandin E1 (PGE1) is the drug of choice for providing ductal patency in cyanotic congenital heart disease (CCHD) for a short period of time until essential surgical management. Occasionally, prolonged use of PGE1 is required when the surgical procedure is delayed due to certain clinical conditions. Prolonged use of PGE1 may lead to bone and tissue changes such as pretibial and soft tissue swelling of the extremities and reversible cortical proliferation of the bones. Venous stasis as an additional risk factor can result in generalized periosteal reaction that initially can cause the separation of the periosteum from the cortex. We report an infant with CCHD who developed severe tissue swelling and generalized periosteal reaction due to coexistence of prolonged use of PGE1 and venous stasis. To the best of our knowledge, this is the first case report with both of these risk factors.

Key words: cyanotic congenital heart disease, newborn, periosteal reaction, prostaglandin E1, venous stasis.

Periosteal reaction results when cortical bone reacts to one of many possible insults[1]. Neonates may have a physiological reaction of the periosteum, though subperiosteal new bone formation is a common finding in early infancy[1,2].

Prostaglandin E1 (PGE1) is the drug of choice for providing ductal patency in cyanotic congenital heart disease (CCHD) for a short period of time until essential surgical management[3]. Occasionally, prolonged use of PGE1 is required when the surgical procedure is delayed due to certain clinical conditions. Although rare, prolonged use of PGE1 may lead to bone and tissue changes such as pretibial and soft tissue swelling of the extremities and reversible cortical proliferation of the bones[3-5]. We herein present a newborn who developed severe tissue swelling and generalized periosteal reaction due to prolonged use of PGE1 in addition to venous stasis.

Case Report

A 3279 g female newborn was born vaginally to a 24-year-old mother at 39 6/7 weeks after an uneventful pregnancy. The newborn had no dysmorphic features and was admitted to routine nursery care.

Cyanosis and 3/6 systolic murmur over the mesocardiac area and continuous murmur over the second intercostal space along the left parasternal border were detected during the physical examination on the first day of life. The rest of the physical examination was normal. Echocardiography demonstrated pulmonary atresia, ventricular septal defect (7.3 mm, with right-to-left shunting), a constricted 1.5 mm, tortuous, patent ductus arteriosus, and a patent foramen ovale with right-to-left shunting. PGE1 (Alprostadil®, PINT-Pharma GmbH, Vienna, Austria) was started intravenously at a dose of 0.01 μg/kg/minute. A modified Blalock-Taussig shunt between the right subclavian and right pulmonary artery was performed on the second day of life. After surgery, PGE1 had to be continued due to shunt thrombosis. Unfortunately, after the second surgery, the shunt was re-occluded even under effective heparinization. Congenital thrombophilia screening revealed normal results. She had to be kept on PGE1 infusion for 128 days. The dose of PGE1 during the infusion period ranged from 0.01 to 0.07 μg/kg/minute. The total dose received was 14 mg, with a mean dosage of 118 μg/day.

On day 44 of life, she was noted to have fever and painful bilateral swelling of the lower extremities, which was not pitting edema. Both pretibial areas were tender and had a hard consistency. Since acute phase reactants were positive under broad spectrum antibiotic coverage, osteomyelitis was suspected. Radiographs of the lower long bones showed extensive periosteal reaction or cortical thickening of the diaphysis, symmetrically. Upper extremities showed a similar swelling, and X-rays demonstrated periosteal reaction in the upper limbs and clavicles, which were not present on admission (Fig.1). 18F-fluorodeoxyglucose (FDG) whole-body positron emission tomography scan excluded osteomyelitis.

Serum calcium, phosphate and liver function tests were normal except alkaline phosphatase (ALP), which increased to 644 U/L (150-420 U/L). No drug had been used in the patient that could have led to periosteal reaction except for PGE1. The maternal and child syphilis serology was negative. Therefore, the patient was diagnosed as periosteal reaction secondary to prolonged use of PGE1 infusion. On the postnatal 52nd day, angiography was performed for stent implantation of the ductus arteriosus, which failed because of femoral and iliac vein thrombosis. Low molecular weight heparin was started and continued until recanalization. After recanalization on the postnatal 119th day, angiography was performed from the left axillary artery for stent implantation for the remaining ductus arteriosus, and the operation was completed successfully; PGE1 infusion was stopped. The patient was discharged on the postnatal 132nd day and followed as an outpatient.

Discussion

Duct-dependent CCHD like pulmonary atresia usually presents as an emergency. PGE1 infusion can keep the duct patent and should be started early in these patients at the slightest indication of impending ductal closure[6].

Common (6%-15%) side effects of PGE1 therapy include apnea, hypotension, fever, leukocytosis, cutaneous flushing, and bradycardia. Hypokalemia has also been reported with long-term therapy (longer than 20 days), especially with doses greater than 0.05 μg/kg/minute. Gastric outlet obstruction and reversible cortical proliferation of long bones after prolonged treatment (>120 hours) were also reported. Seizures, hypoventilation, tachycardia, cardiac arrest, edema, sepsis, diarrhea, and disseminated intravascular coagulation are among the

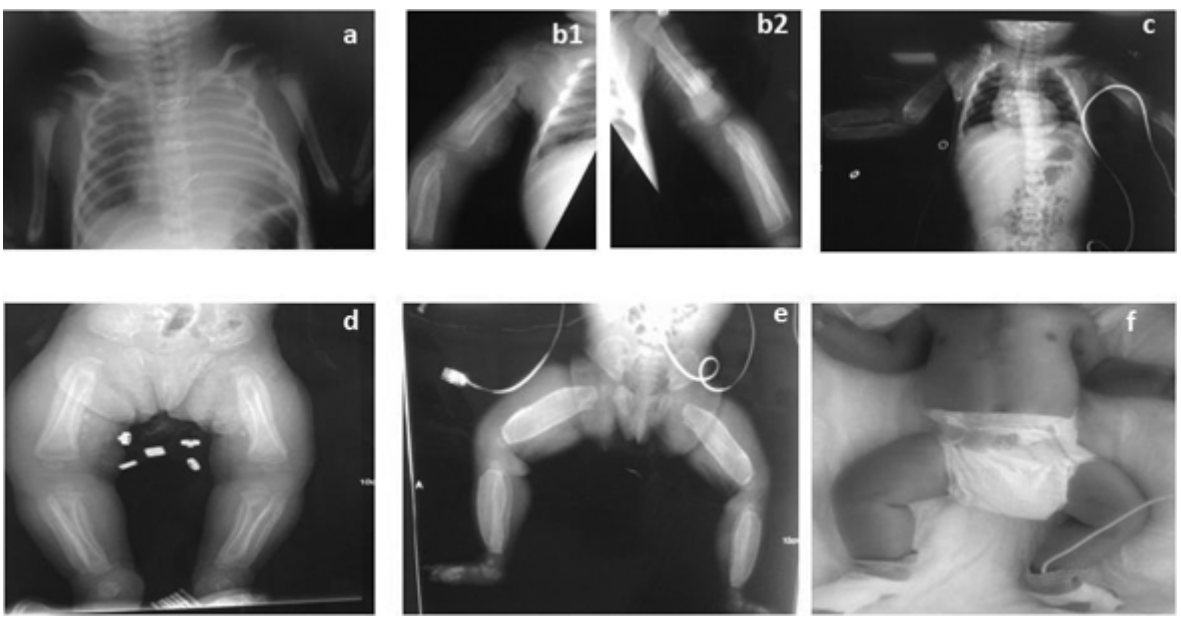

Fig.1.
(a) Chest X-ray, 23 days of age, shows no periosteal reaction on upper limb and clavicles.
(b1, b2) Upper limb X-rays, 39 days of age, show marked periosteal reaction.
(c) Upper limb X-ray, 118 days of age, shows more marked cortical thickening.
(d) Lower limb X-ray, 39 days of age, shows marked cortical thickening.
(e) Lower limb X-ray, 118 days of age, shows more marked cortical thickening.
(f) Bilateral tissue swelling of the legs.

uncommon (1%-5%) side effects. Urticaria, bronchospasm, hemorrhage, hypoglycemia, and hypocalcemia are also rare reported side effects (<1%)[7]. Musculoskeletal changes, such as widened fontanels and pretibial and soft tissue swelling of the extremities, may occur after the use of prostaglandins. Cortical hyperostosis and periostitis may also occur with long-term (>3 months) therapy[8]. In the case described here, there were no acute adverse events except fever during the hospitalization.

The periosteum in children is more active and less adherent to the cortex than in adults. The rapid growth of the infant and loosely adherent periosteum may account for this finding[9]. PGE1 is believed to decrease osteoclastic bone resorption, which can result in periosteal reaction associated with limb pain and considerable swelling of the extremities[1]. These changes are responsible for the increase in serum ALP concentrations that occurs in 53% of the patients[9]. In some cases, when there is infection or absence of a specialized hospital for transfer, PGE1 infusion duration can extend for months[10]. In our case, the first and second surgical processes were complicated with the thrombotic occlusion of the shunt; therefore, the patient had to receive PGE1 for up to 128 days. The percentage of infants who develop hyperostosis with continuous PGE1 infusion increases with duration of PGE1 infusion[9,10]. Considering the skeletal side effects, Kaufman et al.[5] suggested encouragement of dosage titration and limiting the duration of the drug use in neonates. However, Brodlie et al.[11] reported two preterm infants with ductal-dependent CCHD who received PGE1 infusion for 152 and 98 days, respectively, but they did not observe multiple periosteal reaction.

An additional unusual issue in our patient was the presence of venous thrombosis. In our case, PGE1 use might have an additive effect on painful tissue swelling and severe periosteal reaction together with the venous thrombosis caused by venous stasis. It is already known that venous stasis, especially in the lower extremities, can result in generalized solid undulating periosteal reaction that initially can be separated from the cortex[1]. Although our patient did not have this type of periosteal reaction, coexistence of venous stasis might have worsened her condition.

The differential diagnosis of cortical thickening in infants includes metabolic disorders such as scurvy, rickets, Caffey's disease, and hypervitaminosis A and D, prostaglandin administration, infections such as congenital syphilis, and physiologic periosteal reaction[2]. Generalized cortical thickening or periosteal reaction may present as a normal physiologic response of bone to growth. However, cortical thickening of a single bone is always pathologic and develops due to conditions such as osteomyelitis, trauma (accidental, abuse) and malignancies (neuroblastoma, leukemia)[2,4]. We screened our patient for all possible causes and ruled out these diseases either by history, physical examination or laboratory findings.

In conclusion, although rare, prostaglandin-induced cortical thickening seems to be related to duration and total dosage. Coexistence of venous stasis due to thrombosis may have an additional effect on periosteal reaction and painful tissue swelling.

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