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LETTER TO THE EDITORS

CORTICAL HYPEROSTOSIS SECONDARY TO PROLONGED USE OF PROSTAGLANDIN E1

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INTRODUCTION

Prostaglandin E1 (Alprostadil), a drug used for ductal patency in cyanotic congenital heart disease, comprises an essential part of the treatment of infants waiting for cardiac surgery in hospitals with no specialized medical staff or in situations of inadequate weight for surgery. Prostaglandin E1 (PgE1) can also be used in elevation of presurgical oxygenation status in more severe cases.[1,2]

The duration of infusion is often short (from 6 hours to 20 days).[3] However, in some cases, when there is low birth weight, infection, or absence of a specialized hospital to transfer the patient to (all of these being common situation in developing countries), the infusion time can extend for weeks or months.[4,5]

Common side effects of prostaglandin therapy include apnea, fever, convulsions, rash, skin flushing, vasodilatation with hypotension, diarrhea, and gastric outlet obstruction.[3] These effects are related to short-term use of PgE1, and the Pediatric Intensive Care Unit staff has the expertise to easily recognize and treat them.

In rare situations of prolonged use of alprostadil, the most important side effects include soft tissue swelling and reversible cortical hyperostosis in the large bones.[4,5] We describe the case of an infant presenting this complication secondary to prolonged use of PgE1, with typical and extensive radiological findings.

CASE REPORT

A 6-month-old male neonate, born at 38 weeks of gestation with APGAR scores of 7 and 9 at the first and fifth minute, respectively, weighed 2930 g at birth. His mother had no pregnancy or labor antecedent.

In the first hours of life, the neonate started to develop respiratory distress and cyanosis. On physical exam, a systolic murmur of a patent ductus arteriosus was found. The child had no dysmorphic features.

The echocardiography revealed Ebstein's anomaly, with a dysplastic tricuspid valve, nonrestrictive atrial septal defect (ostium secundum) of 7.5 mm, single aortic outlet from the left ventricle, and patent ductus arteriosus. The systolic function of the left heart was normal, with a left ventricular ejection fraction (LVEF) of 65%.

Intravenous infusion of PgE1 was started on the first day of life, at a dosage of 0.05 μg/kg/minute.

The child progressed with mechanical ventilation dependency and had systemic and respiratory infections, requiring use of antibiotics. On 60th day, he underwent a tracheostomy procedure. Despite the use of multiple and prolonged empirical antibiotic treatments, the infant sustained a persistent fever and had a C-reactive protein (CRP) level of 188 mg/L.

At this time, the clinical and laboratory diagnosis of persistent nosocomial sepsis was made, due to positive blood cultures that isolated an uncataloged, nonfermenting, Gram-negative bacillus. The patient had a number of positive blood and catheter cultures with the same bacillus. At the time, the antibiotic schedule included piperacillin and tazobactam associated with trimethoprim-sulfamethoxazole guided by the antibiogram. The cardiac surgical correction was delayed, and the time of utilization of PgE1 was increased.

After 3 months, the child was transferred from another state to our hospital. On examination, he was noted to have painful bilateral swelling of ankles and fists. The pain with manipulation was intense in the 4 limbs and unresponsive to regular analgesics. The radiography of the large bones revealed an intense periosteal reaction with bilateral corticoperiosteal thickening of the diaphyses in clavicles, femur, tibia, humerus, radius, and ulna. The lesions were distributed along the middle portion of the large bones described, with the exception of the humerus, where the affection was distributed more distally (Figures 1, 2, and 3).

Regarding laboratory findings, the maternal and child syphilis serology were negative. Alkaline phosphatase was 399 U/L (normal range, 145-320 U/L) with normal calcium and phosphate.

With these results and considering the dose and dura-

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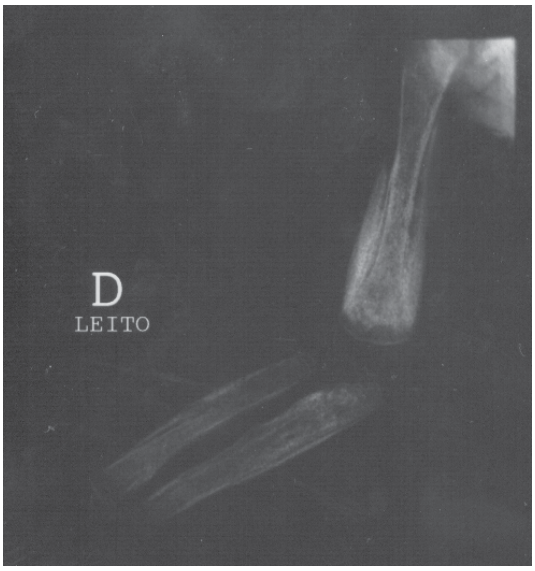

Figure 1 - Radiograph of the right arm showing intense cortical thickening of the distal portion of the humerus. Note the periosteal reaction and less intense cortical thickening of the radius and ulna.

Figure 2 - Radiograph of the right lower extremity showing cortical thickening of femur and tibia.

tion of PgE1 utilization, the diagnosis of cortical hyperostosis secondary to intravenous prostaglandin was made.

After this diagnosis, 2 attempts at reduction and interruption of the intravenous PgE1 were made. The goal was to reduce the existing adverse events: hyperostosis, fever, and abdominal distention. The fever started within the first month of life, and the highest temperature was 38.6ºC with 1 or 2 episodes per day. Even considering the infection to

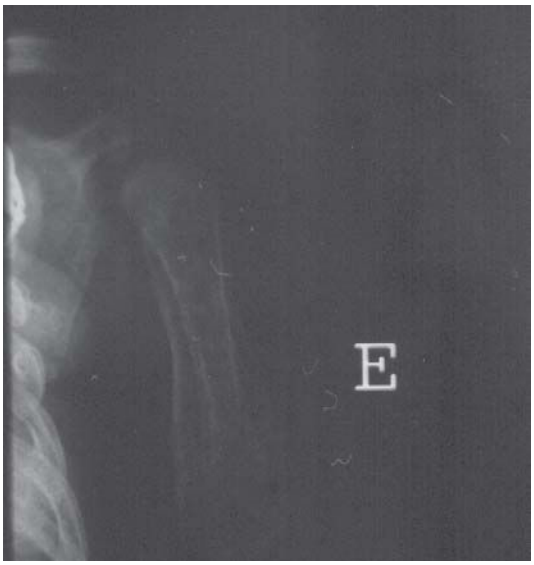

Figure 3 - Cortical hyperostosis of the left clavicle and humerus

be the main reason for the fever, the hypothesis of an adverse event secondary to PgE1 could not be ruled out. Abdominal distension was moderate, accompanied by vomiting or gastric residual content in the nasogastric tube.

The infant did not tolerate the reduction of the drug, experiencing rapid decrease in the arterial saturation (pulse oximetry saturation of 55% after 1 hour of reduction).

He was kept on PgE1 infusion for 162 days (5.4 months). The dose of PgE1 during the infusion period ranged from 0.025 to 0.1 μg/kg/minute. The total dose received was 45 mg, with mean dosage of 279 μg/day (0.043 μg/kg/minute).

After a period of 1 week during which the child received the drug by peripheral vascular access, the blood cultures become negative (3 samples). At this point, the cardiothoracic surgeons performed a modified Blalock-Taussig shunt. The patient had a good recovery from surgery, permitting the interruption of the drug in the operating room.

After 2 weeks, the swelling of ankles and fists disappeared, and the child had no longer pain after manipulation, with complete clinical regression. A radiograph of the left humerus after 47 days showed radiological regression of the bone hypertrophy (Figure 4).

DISCUSSION

The presence of cortical hyperostosis is frequent in infants with prolonged use of intravenous prostaglandin, but the final diagnosis is not always achieved. The investigation performed by pediatricians and neonatologists is generally focused on the more immediate and frequent adverse

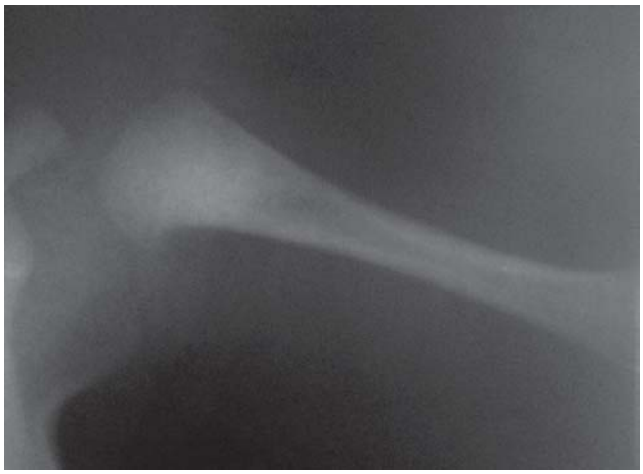

Figure 4 - Radiograph of the left humerus 47 days after the withdrawal of PgE1, showing complete regression of the cortical thickening.

events such as apnea (19%), abdominal distension (16%), bradicardia (13%), enterocolitis (6.5%), hypotension (6.5%), fever (1.6%), and flushing (1.6%).[3]

In the case described above, our patient presented only fever and abdominal distension as acute adverse events. The fever, which had a clear infectious trigger, was probably related to the infusion of PgE1. This fact was corroborated by the maintenance of the presurgical fever even after the fall of CRP from 188 mg/L (highest value) to < 1 mg/L and the presence of negative blood cultures (sepsis treatment success). One day after interruption of the drug the fever disappeared.

Histological examination of bones with cortical hyperostosis shows rapid formation of primitive bone, extensive resorption of the outer cortical surface, and bone formation in the inner surface. These changes are responsible for the increase in serum alkaline phosphatase concentrations that occurs in 53% of the patients.[6,8]

The cortical thickening seems to be related with the duration or dosage of continuous intravenous infusion of PgE1.[5–7] Forty-two percent of infants receiving PgE1 infusion for more than 30 days develop hyperostosis; this increases to 100% in infants receiving the infusion for more than 60 days.[8]

It is notable that in many cases, the degree of hyperostosis is higher due to delay in diagnosis. There are reports of extremely early cortical changes, with initiation of radiographic findings in 9 days.[5,8,9]

The clinical history and physical exam are usually sufficient to elucidate the diagnosis. The most important differential diagnoses of this condition include congenital syphilis, infantile congenital hyperostosis, scurvy, and hypervitaminosis A. In contrast, when the cortical thickening is restricted to 1 bone, it is usually secondary to trauma, tumor, or osteomyelitis.

In this case, the diagnosis of syphilis was unlikely due to absence of compatible clinical history and negative serology. In hypervitaminosis A, the cortical hyperostosis appears after months or years of excessive ingestion. Regarding scurvy, the cortical thickening occurs during the healing process of subperiosteal hematomas, which requires months of evolution and was unlikely in this patient.

Finally, infantile cortical hyperostosis is the diagnosis with the most difficult differentiation from prostaglandin-induced hyperostosis. Infantile cortical hyperostosis or Caffey disease is a genetic disorder, with autosomal dominant inheritance in its usual form, with incomplete penetrance. However, the severe and lethal form of the disease appears to be inherited as an autosomal recessive disorder. Recently, a novel gene mutation on the alpha-1 chain of type I collagen has been described in patients with the autosomal dominant form of the disease.[12] Clinically, infantile cortical hyperostosis is characterized by hyperirritability, soft tissue swelling, and cortical hyperostosis. The median age of presentation is around 9 weeks of age. Fever is present and may be due to the high prostaglandin levels or excessive metabolic activity in the bones.[10,11] In the light of the fact that both diseases have the same clinical aspects and radiological findings, differentiation is possible only due to the antecedent of prolonged therapy with prostaglandin. Because our patient had clinical, laboratory, and radiological aspects of the disease concomitant with the use of PgE1 of more than 5 months, we could determine the diagnosis of prostaglandin-induced cortical hyperostosis. This fact was confirmed after the interruption of the drug and the subsequent reduction in the radiological and clinical findings.

Our patient had a similar evolution as for some other cases described in the literature, with an extremely prolonged infusion period and a relatively rapid decrease in clinical and radiological findings after withdrawal of the drug as the most notable points. One unusual issue in this case was the presence of cortical hyperostosis involving the clavicles. The first description of clavicle involvement in PgE1 hyperostosis was made by Nadroo et al in 2000.[5] Our patient had clear bilateral clavicle involvement as seen in Figure 3, reinforcing the probability of bone hypertrophy in these bones.

CONCLUSION

Pediatric intensivists and neonatologists must be alert to the adverse effects of continuous intravenous infusion of prostaglandin. Attention must be given to the acute and more common adverse effects as well as to the ones related to prolonged use. Early and frequent radiological investigation

should be made in patients undergoing intravenous PgE1 treatment for more than 7 days. All efforts must be made to attempt interruption of the drug as soon as possible, aiming at preventing the potential complications.

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