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Case Report

The use of calcitonin in the effective preoperative management of neonatal hypercalcemia in congenital mesoblastic nephroma

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ABSTRACT

Subcutaneous administration of calcitonin is effective in the preoperative management of hypercalcemia associated with congenital mesoblastic nephroma (CMN). The short onset of action (within 2 hours) and duration (6 to 8 hours), makes it a viable alternative to bisphosphonates (action 48 hours and duration of 7 to 14 days). A 15-day-old late preterm, male, presented with dehydration, failure to thrive and a large abdominal mass. On admission, he was hypertensive, and a firm mass was palpable in the abdomen. Severe hypercalcemia was noted on the blood work. An abdominal ultrasound shows a large 9×8 cm dominant solid right renal mass. Echo and electrocardiography (ECG or EKG) were normal. The patient initially received IV hydration, nicardipine and furosemide. The hypercalcemia persisted after 24 hours of treatment; thus, one dose of calcitonin (6 units/kg subcutaneously) was given, resulting in a decrease in serum calcium to the upper limits of normal within 4 hours. The patient then underwent a successful radical right uretero-nephrectomy. Pathology reported congenital mesoblastic nephroma (CMN) of the cellular type. This is the third case report describing the use of calcitonin for a likely PTH-rP-mediated severe hypercalcemia in a neonate with CMN.

Keywords: Calcitonin, Neonatal hypercalcemia, Congenital mesoblastic nephroma

INTRODUCTION

Prenatal sonography in the first trimester has an 84% detection rate for major and lethal anomalies. This rate drops to around 60% in the mid-trimester.[1] However, abdominal tumors can still appear later in pregnancy.[2] Abdominal masses in neonates can be caused by a variety of conditions, both benign and malignant, and often originate from the kidney. Congenital renal tumors are relatively rare. The most prevalent is congenital mesoblastic nephroma (CMN), followed by nephroblastoma (Wilms tumor), rhabdoid tumor, clear cell sarcoma, and finally, hamartomas.[3]

CMN is the most common renal tumor before the age of 6 months, accounting for nearly half of renal tumors in this age group, but only 5% of renal tumors before 15 years. It typically behaves as a benign tumor, with favourable outcome following complete surgical excision.[2] However, serious complications can include polyhydramnios, hydrops fetalis, respiratory distress syndrome, or metastases.[3] Hypertension is present in 70% of CMN, and hypercalcemia is seen in 20%, often secondary to paraneoplastic secretion of parathyroid hormone (PTH) or parathyroid hormone related peptide (PTHrP).[4]

Pediatric patients with hypercalcemia of malignancy are generally treated with hyperhydration, loop diuretics, and bisphosphonates.[5,6] Calcitonin, a peptide that antagonizes the effects of PTH inhibits osteoclast-mediated bone resorption and lowers serum calcium levels.[7] While calcitonin is commonly used in adults,[8] there is limited pharmacokinetic data regarding its use in neonates, particularly in those with CMN, which makes its administration challenging due to unclear safety parameters.

We present the third published case of using calcitonin to manage severe hypercalcemia likely mediated by PTH-rP in neonate with CMN.

CASE REPORT

A 2-week-old boy, born at 37 weeks of gestation via scheduled C-section, presented to his pediatrician with lethargy and decreased oral intake. The patient had been breastfeeding and taking 45 ml of formula every 3 hours, but over the last few days the parents noted he would only take 30 ml of formula before tiring out. The mother is a G4P4, who received good prenatal care from the first trimester onward, with no documented abdominal mass on fetal ultrasound. She reported no medications during pregnancy except for prenatal vitamins, iron and folic acid supplements and denied a significant past medical history, substance use disorder, smoking, alcohol consumption or sexual transmitted disease. Her prior pregnancies were all term deliveries via c-section without complications.

On physical exam, a large abdominal mass was palpable in the right upper abdomen. The patient was immediately transferred to the neonatal intensive care unit. On admission, the neonate was afebrile, with a heart rate of 156 bpm, a respiratory rate of 40 breath per minutes, and oxygen saturation of 98% on room air. However, he was hypertensive with his blood pressure above the 99th percentile (138/84 mmHg). His birth weight was 3.265 kg, and his admission weight was 2.813 kg, reflecting a 13.8% weight loss. He appeared severely dehydrated, and a firm mass in the right abdomen crossing the midline was confirmed.

Laboratory results showed no leukocytosis, and hemoglobin and platelets were within normal limits, with no bands present. The complete metabolic panel was normal, including magnesium, phosphorus, alkaline phosphatase, and albumin, except for an elevated serum calcium levels at 3.37 mmol/l (13.5 mg/dl); normal range 2.1-2.6 mmol/l, with an ionized calcium 1.71 mmol/l (normal range 1.15-1.30 mmol/l). PTH-rP and PTH were sent but the sample was insufficient to run the test. Urine analysis showed no hematuria.

Abdominal ultrasound revealed a large, 9.1×8 cm dominant solid mass in the right kidney, with left-sided medullary nephrocalcinosis. A contrast-enhanced computed tomography (CT) scan of the abdomen and pelvis showed a large mass originating from the right kidney. The mass demonstrated central hypodensity with peripheral and heterogeneous internal enhancement, suggestive of internal necrosis, with marked displacement of adjacent structures, but no invasion. An echocardiogram and EKG were within normal limits.

Diagnostic assessment

This case describes a malnourished, hypertensive, lethargic 2-week-old neonate with a large abdominal mass. These symptoms suggest dehydration and feeding difficulties, possibly due to compression of the stomach from the tumor. While the hypertension maybe because of pain, in 80% of cases of CMN, hypertension is related to hyper-reninemia.[9] The significantly elevated serum calcium levels is likely caused by the secretion of parathyroid hormone-related peptide (PTH-rP) by the tumor.[5]

Abdominal masses in neonates can result from a wide range of conditions, both benign and malignant, hence the importance of the abdominal ultrasound in identifying the mass's origin. In our patient, the abdomen ultrasound revelled a large, 9.1×8 cm solid mass in the right kidney, highly suggestive of CMN.

The differential diagnosis should include Wilms tumor or nephroblastoma, the most common renal malignancy of childhood, typically occurring between ages of 2 and 5 but sometimes developing in infancy. Most cases of Wilm's tumor are sporadic, although hereditary forms do exist. Patients may present with abdominal pain, hypertension or be asymptomatic. Unilateral involvement is the most common. Clear cell sarcoma, typically found in children under 4 years of age is the second most common childhood renal malignancy. It can present with hematuria, hypertension, and abdominal pain. Other potential diagnosis includes anaplastic sarcoma, angiomyolipoma, nephroma, rhabdoid tumor; and renal cell carcinoma.[10]

Treatment

The patient received hydration with normal saline bolus and 1.5 maintenance fluids. The hypertension was treated with Nicardipine, and furosemide at 1 mg/kg/day IV every 6 hours was added to correct the hypercalcemia. Despite 24 hours of treatment, the patient's hypercalcemia persisted, with a serum calcium level of 3.67 mmol/l (14.7 mg/dl) and an ionized calcium level of 1.81 mmol/l. Although the definitive treatment is removal of the tumor, and there were no EKG abnormalities, pediatric anesthesia refused to clear the patient for surgery unless the ionized calcium levels were within acceptable limits. Therefore, upon consultation with pediatric endocrinology, the patient received one dose of calcitonin (4 units/kg subcutaneously), resulting in a reduction of serum calcium to 2.87 mmol/l (11.5 mg/dl) within 4 hours (Figure 1).

The patient then underwent a successful radical right uretero-nephrectomy, followed by post-surgery improvements in both cardiovascular and electrolyte status (Figure 2).

Outcome and follow-up

Pathology from the right radical nephrectomy was consistent with CMN, cellular subtype. Surgical margins, including vascular and ureteral sites, were negative for tumor, confirming stage I. FISH analysis demonstrated 12p13.2. Patient was discharged 6 days post-operation

tolerating breastfeeding or formula 45-60 ml every 3 hours. Parents also noted that patient was much more active and alert. At discharge, the patient weighed 3.045 kg, which was 4.2% below his birth weight.

At the 13-month post-surgical clinic visit, the patient was noted to be gaining weight appropriately and meeting his developmental milestones. His blood pressure remained within normal limits for age, and his electrolytes, including calcium, were all normal. An abdominal ultrasound shows no signs of residual or recurrent mass.

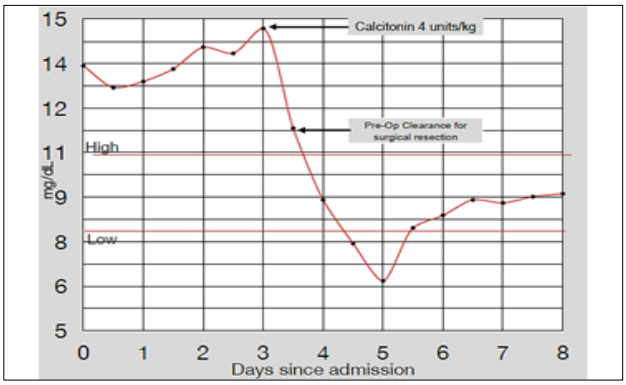

Figure 1: Calcium trends with intervention.

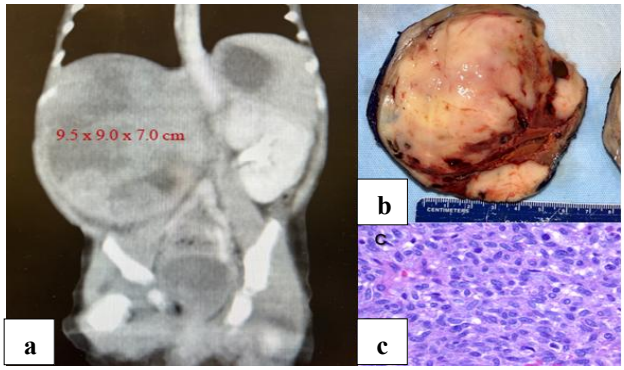

Figure 2: Congenital mesoblastic nephroma, (a) CT abdomen with contrast observing the mass in upper hemiabdomen, (b) surgical piece of the tumor, and (c) under hematoxylin and eosin, sections of predominant tumor show sheets of ovoid, plump tumor cells with sarcomatous-like appearance/fascicular arrangement. Scattered mitoses, that correspond to congenital mesoblastic nephroma cellular subtype.

DISCUSSION

Congenital mesoblastic nephroma was first described by Bolande et al in 1967; however, decades earlier, this tumor had been referred to as fetal renal hamartoma or leiomyomatous renal hamartoma. It is the most common renal neoplasm diagnosed in the first month of life, highlighting the embryonal nature of the disease.[11]

Prenatal screening ultrasounds are typically performed in the first and second trimesters. However, Tongsong et al reported a review of 41 cases of CMN in which the tumor was detected in the third trimester or late second trimester.[2] In our patient, the mother did not have a history of polyhydramnios, and we did not have access to her fetal ultrasounds.

CMN is classified into three histological subtypes: classic, cellular, and mixed type. The cellular subtype, which is identical to infantile fibrosarcoma, is characterized by dense cellularity, a strong hemangiopericytous vascular pattern, and high mitotic activity. However, it exhibits less infiltrative growth into the renal parenchyma compared to the classic subtype that grows into the renal parenchyma and/or perirenal fat. The mixed subtype is a combination of interlacing fascicles of fibroblastic cells (classic CMN) and areas with high cellularity and mitotic activity (cellular CMN).[11] Our patient presented the cellular subtype, which is associated with the most common genetic translocation, (12;15)p13;q25), resulting in a fusion of the genes ETV6 and NTRK3 genes, as confirmed by FISH testing.

CMN presents as an asymptomatic abdominal mass; though it may be associated with hypertension (19%), hematuria (11%), polyhydramnios (15%) and hypercalcemia (4%). Hypercalcemia in CMN can be secondary to paraneoplastic secretion of PTH or PTH-rP. Hypercalcemia of malignancy is typically treated with hyperhydration, loop diuretics, and bisphosphonates. Loop diuretics promote calcium excretion by inhibiting reabsorption in the loop of Henle, though side effects can include dehydration, electrolytes unbalances, hypotension, nauseas, diarrhea, ototoxicity, and in rare cases kidney damage. The effects of loop diuretics are usually observed within 1 hour. Bisphosphonates, a second-line treatment, also inhibits bone reabsorption by interfering with osteoclast recruitment and function. Bisphosphonates require IV infusion, ranging from 15 minutes to 4 hours, and their effects are typically observed in 24 to 48 hours. Significant side effects include flu like symptoms, bone pain and gastrointestinal irritation.

In this case, we initially started with conventional treatments; hydration, antihypertensives and the maximum doses of furosemide for 24 hours. However, both hypertension and the serum calcium level continued to rise. Since the removal of the tumor would resolve the hypercalcemia, and the use of bisphosphonate would take too long to act, we researched other alternative treatments, such as calcitonin. Calcitonin, as the Bisphosphonates, inhibit bone resorption by interfering with osteoclast function and promotes calcium excretion in the urine. After subcutaneous administration, calcitonin has an onset of action within 4 to 6 hours and duration of action lasting up to 48 hours. Side effects may include erythematous rash of the face and neck, rhinitis, swelling, and difficulty breathing. Although there are no specific dose recommendations for children for hypercalcemia of malignancy, a review of the literature reveals only two report cases of calcitonin use in newborn with CMN (Table 1).

Table 1: References with calcitonin use in malignant hypercalcemia.

S. no.	Publication	Location	Journal	Age	Peak serum calcium*	Treatment modalities
1	Srivasta et al, 2011[12]	Kansas City, MO	The Journal of Pediatric Nephrology	29 w, 30 dol	12.8 mg/dl (3.19 mmol/l), 16.7 mg/dl (4.17 mmol/l)	Hydration, furosemide, pamidronate, calcitonin.
2	Kleespies et al, 2022[13]	Chicago, IL	The Journal of Pediatric Pharmacology Therapies	31 w	18.0 mg/dl (4.49 mmol/l)	Hydration, prednisolone, furosemide, calcitonin up to 8 U/kg, q6H
3	Current	El Paso, TX		15 dol	14.7 mg/dl (3.67 mmol/l)	Hydration, furosemide, calcitonin 4 U/kg, 1 time

*Serum calcium normal range: 8.5-10.5 mg/dl or 2.1-2.6 mmol/l; w: weeks; dol: days of life

Srivastava et al described two cases (one in a 29-week and a 1-month-old) with malignant hypercalcemia treated with calcitonin prior to surgery, although they did not specify the doses.[12] Kleespies et al reported a 31-week-old male with left-sided CMN and malignant hypercalcemia, treated with calcitonin at 4 units/kg every 6 hours starting on day of life (DOL) 1, alongside hydration at 1.5 times maintenance and furosemide. The maximum doses of calcitonin (8 units/kg every 6 hours) were reached on DOL 3, and treatment continued for 5 days until tumor resection.[13]

CONCLUSION

This case represents the third reported instance of using calcitonin in a neonate with CMN to manage persistent hypercalcemia. Subcutaneous calcitonin administration at 4 units/kg was effective, with a short onset of action (within 2 hours) and a duration of 6 to 8 hours. This makes calcitonin a viable alternative to bisphosphonates, which take longer to act (approximately 48 hours) and has a longer duration of action (7 to 14 days). The advantages of calcitonin include fewer side effects and faster resolution of hypercalcemia.[8] Additionally, the flexibility of repeated dosing every 6 hours, with the option to adjust the dose as needed, enhances its clinical utility.

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