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BRIEF REPORT

Parathyroid-hormone-related protein-mediated hypercalcemia in benign congenital mesoblastic nephroma

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Abstract Parathyroid hormone-related protein (PTHrP) mediated hypercalcemia of malignancy is rare in children, and even more so in the setting of a benign tumor. We report two infants with PTHrP-mediated hypercalcemia secondary to congenital mesoblastic nephroma and their outcome after removal of the benign tumor. Pre-operatively hypercalcemia was corrected with saline hydration, furosemide, calcitonin and/ or pamidronate. Following resection of the tumor serum PTHrP normalized. Immunohistochemical staining of tumor cells was positive for PTHrP. Post-operatively the infants developed elevated serum parathyroid hormone with low- normal serum Ca and P, and undetectable urinary Ca and P, probably due to their movement into bone. Children needed treatment with calcitriol, Ca and P supplementation for 6-12 weeks until PTH normalized and urinary Ca and P were detected, suggesting bone replenishment. We conclude that benign congenital mesoblastic nephroma can secrete PTHrP that can cause severe hypercalcemia; and following excision one should anticipate the development of a transient modified "hungry bone"-like condition requiring Ca, P and calcitriol therapy for several weeks accompanied by careful monitoring of mineral homeostasis.

Keywords PTHrP · Congenital mesoblastic nephroma · Hypercalcemia · Hungry bone

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Introduction

Hypercalcemia associated with malignancy is either due to local osteolysis from metastases in bone or a humoral-mediated process, the latter being a result of production of parathyroid hormone-related protein (PTHrP) or, rarely, parathyroid hormone (PTH). Humoral hypercalcemia of malignancy (HHM) is a paraneoplastic feature characterized by minimal or no radiographic skeletal involvement and reversal of hypercalcemia following resection or treatment of the tumor. For many years, PTHrP was theoretically suspected to be the cause of HHM, and it was finally isolated, cloned, and the gene mapped in the 1980s [1–3]. PTHrP is homologous in structure to PTH, but in contrast to PTH works in a paracrine and autocrine fashion. It is found in both fetal and adult tissues, such as epithelial and mesenchymal tissues, endocrine glands, and central nervous system [4]. Although PTHrP is now a well-recognized cause of HHM, PTHrP-mediated hypercalcemia is extremely rare in the setting of benign tumors [5–7]. A review of the literature for PTHrP-mediated hypercalcemia in benign tumors found only several case reports in adults [5–12]. Hypercalcemia in pediatric malignancies is a rare event, occurring in about 0.2–0.7% children with cancer [13]. Moreover, in the setting of benign tumors, there is only a single case report of a child with hypercalcemia

secondary to renal metanephric adenoma [14]. We hereby report two infants who developed hypercalcemia from increased PTHrP secretion from congenital mesoblastic nephroma (CMN). Successful tumor resection led to resolution of the hypercalcemia, transient hyperparathyroidism, and the need for vitamin D and mineral supplementation secondary to increased movement of calcium (Ca) and phosphorus (P) into the "hungry bones".

Case reports

Case 1

A 29-week premature baby was transferred to the hospital at birth with known abdominal mass detected on fetal ultrasound. On examination, he had a distended abdomen with a palpable mass in the left flank, bilateral syndactyly of the second and third toes, and postaxial left-foot polydactyly. On presentation, blood work showed sodium (Na) 131, potassium (K) 3.6, chloride (Cl) 99, carbon dioxide (CO_2) 26 mmol/L, and blood urea nitrogen (BUN) and creatinine (Cr) 16 and 0.9 mg/dl, respectively. Total serum Ca was 12.8 mg/dl and ionized calcium (iCa) 1.97 mmol/L (normal 1.13–1.37). The blood work showed normal blood counts, P, magnesium (Mg), albumin (Alb), and alkaline phosphatase (ALP). Additional workup showed undetectable serum PTH <3 pg/ml, normal thyroid studies, low 25 vitamin D (14 ng/ml), normal 1,25 vitamin D (92 pg/ml), and elevated PTHrP at 17 pmol/L (normal <2, Mayo Medical Laboratories). Urine Ca/Cr ratio was 0.09 and tubular phosphate reabsorption per glomerular filtration rate (TP/GFR) 5.3 mg/dl. The abdominal ultrasound and subsequent computed tomography (CT) scan showed a mass arising from the left kidney measuring approximately 7.0 cm×6.7 cm×4.3 cm (Fig. 1, upper panel). To control his hypercalcemia, he was treated with saline hydration, furosemide, and calcitonin. On day 16, when his total

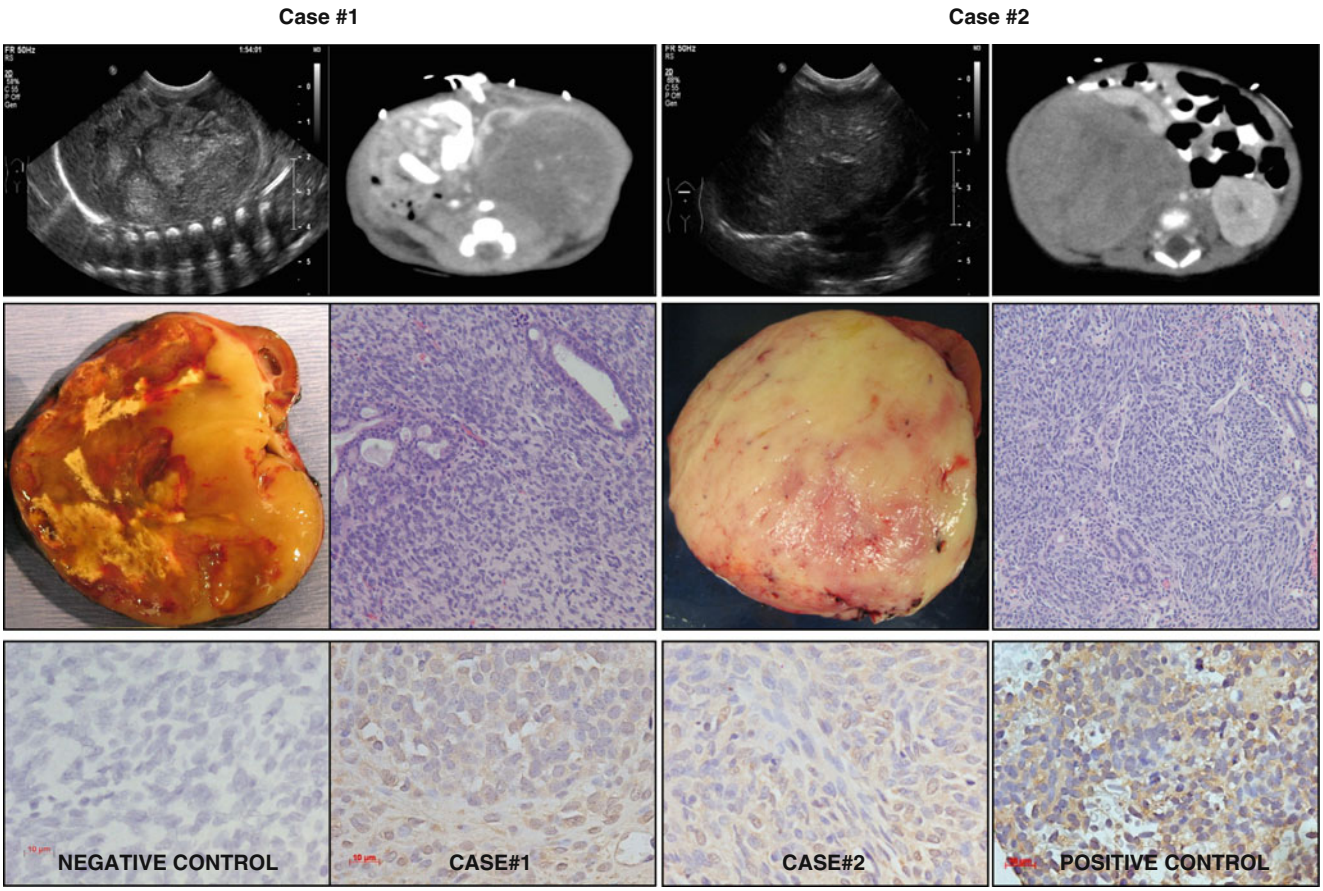

Fig. 1 *Upper panel* shows congenital mesoblastic nephroma (CMN) in case 1 from the left kidney on ultrasound (*left*) and computed tomography (CT) (*right*) and in case 2 from the right kidney on ultrasound (*left*) and CT (*right*). The *middle panel* shows CMN gross appearance (*left*) and light microscopy on hematoxylin–eosin stain (*right*) in both cases. The *lower panel* shows immunohistochemistry performed on the excised tumor tissue with polyclonal rabbit antibody 1904 raised to the human parathyroid-hormone-related protein (PTHrP) peptide containing amino acids 1–14 [PTHrP(1–14)] using the standard method, as described in Danks et al. [15]. The congenital mesoblastic nephroma from both cases showed positive cytoplasmic staining for PTHrP. Also shown are negative and positive controls for PTHrP staining

serum Ca was 9.2 mg/dl, he underwent a complete surgical resection of the abdominal mass. The excised mass represented the left kidney, which weighed 149 g and revealed a large 8.0 cm×5.5 cm×4.5 cm pale tannish yellow tumor with firm to friable cut surface and extensive areas of hemorrhage and necrosis (Fig. 1, middle panel). Microscopic evaluation revealed tumor cells that were spindle to plump with ill-defined cytoplasm, fine granular chromatin, and inconspicuous nucleoli arranged in intersecting fascicles. The tumor focally entrapped tubules, and some of the entrapped tubules showed embryonal metaplasia and/or epithelial hyperplasia. Tumor morphology and immunophenotype were consistent with mixed variant of CMN with predominant classic pattern. Using the standard method described by Danks et al. [15], immunohistochemistry was performed on the excised tumor tissue with polyclonal rabbit antibody 1904 raised to the human PTHrP peptide containing amino acids 1–14 [PTHrP(1–14)]. It showed positive expression of PTHrP (Fig. 1, lower panel).

Case 2

A 1-month-old boy presented to the hospital with symptoms of projectile emesis, lethargy, weight loss, and constipation. He was born after an uneventful 38-week pregnancy by an uncomplicated caesarean section for placenta previa. On examination, he was emaciated, with a sallow complexion, sunken anterior fontanel, and palpable mass in the right flank. The rest of the physical examination was unremarkable. On presentation, blood work showed Na 135, K 4.1, Cl 96, CO_2 27 mmol/L, and BUN and Cr 13 and 0.7 mg/dl, respectively. Serum total Ca was 16.7 mg/dl, iCa 2.12 mmol/L, and P 4.1 mg/dl. Blood work showed normal blood count, Mg, ALP, Alb, glucose, lactate dehydrogenase (LDH), and uric acid (UA). Additional workup showed undetectable serum PTH (<3 pg/ml), normal thyroid studies, low 25 vitamin D (10 ng/ml), low 1,25 vitamin D (25 pg/ml), and elevated PTHrP at 378 pg/ml (normal: 14–27, Quest Diagnostics). Urine Ca/Cr ratio was high at 1.4 and TP/GFR low at 2.0 mg/dl. The abdominal ultrasound and subsequent CT showed a mass arising from the right kidney measuring approximately 7 cm×6 cm×5 cm (Fig. 1, upper panel). The left kidney showed medullary nephrocalcinosis. To control hypercalcemia, he was treated with saline hydration, furosemide, and calcitonin and subsequently received two doses of pamidronate 0.25 mg/kg per dose on days 4 and 5. On day 8, when his total serum Ca was 10.0 mg/dl, he underwent surgical resection of the mass, with a small part of the tumor being left attached to the major blood vessels.

The excised right kidney weighed 155 g and was affected by a large tumor that was whitish tan in color, with small focal areas of hemorrhage (Fig. 1, middle panel). Microscopically, the tumor showed intersecting bundles of short spindle cells with vesicular nucleus and a small amount of cytoplasm with low mitotic figures. The tumor showed an abnormal male karyotype with extra copies of chromosomes 11 and 18 and reciprocal translocation between chromosomes 12 and 15 that results in the *ETV6* gene rearrangement. The tumor was classified as a cellular variant of congenital mesoblastic nephroma. On immunohistochemistry, tumor cells showed a positive expression for PTHrP (Fig. 1, lower panel).

Postoperative course following excision of PTHrP secreting congenital mesoblastic nephroma

Postoperative course from the surgical perspective was uneventful in both children. Changes in mineral metabolism were significant for decreased serum Ca, iCa, and P within 24 h of tumor resection. In the following days, the postoperative course was characterized by low to low–normal serum Ca, iCa, and P concentrations associated with elevated serum PTH levels (Table 1) and concomitant undetectable or low urinary excretion of Ca and P. The serum PTHrP level had normalized when checked at 1 week in both children following CMN excision. The persistent elevation in serum PTH with undetectable urinary Ca and P suggested a modified "hungry-bone-like" state. Thus, the children were supplemented with calcitriol, Ca, and P. In the following weeks, the therapy was quantitatively slowly decreased, with gradual normalization of serum Ca, P, and PTH and reappearance of urinary Ca and P, suggesting repletion of the hungry bones. Case 1 required calcitriol, Ca, and P supplementation for 8 weeks and case 2 for 12 weeks. Tests done at last follow-up, which was 16 weeks after discontinuation of all supplementation in case 1 and 6 weeks in case 2, showed normal serum Ca, iCa, P, ALP, PTH, and PTHrP (Table 1). The children are now being followed for long-term care of solitary kidney.

Discussion

Hypercalcemia associated with malignancy is either due to local osteolysis from metastases in bone or humoral effects from PTHrP production. Although there is no normative reference range for PTHrP in premature newborns and neonates, it is likely that the high circulating PTHrP levels in our two cases were tumor-related and that PTHrP caused the hypercalcemia. This is due to the observation that at the time of presentation, with pathological hypercalcemia, PTH was suppressed and vitamin D metabolites were low, and following tumor resection, PTHrP levels fell dramatically, remaining normal on follow-up. Moreover, in both cases,

Table 1 Serum levels of calcium (Ca), phosphorus (P), ionized calcium (iCa), parathyroid hormone (PTH), alkaline phosphatase (ALP) and PTH-related peptide (PTHrP) upon presentation, 24 h following excision of congenital mesoblastic nephroma (CMN), on therapy with calcitriol, Ca, and P supplementation, and at last follow-up off all therapy

	Case 1				Case 2			
	On presentation	24 h postexcision	Postexcision on therapy	Last follow-up	On presentation	24 h postexcision	Postexcision on therapy	Last follow-up
Ca (mg/dl)	12.8	7.5	7.5–9.4	10	16.7	6.8	4.4–8.6	10.8
P (mg/dl)	5.6	4.6	4.0–5.4	5.6	4.1	3.0	2.2–5.2	6.2
iCa (mmol/L)	1.97	1.17	1.07–1.36	1.32	2.12	0.96	0.96–1.28	1.31
PTH (pg/ml)	<3	–	184–215	64	<3	43	39–83	22
ALP (IU/L)	56	–	420–672	340	358	159	129–159	247
PTHrP	17[a]		0.2	0.2	378[b]		31	33

[a] Serum PTHrP: normal <2 pmol/L performed at Mayo Medical Laboratories

[b] Serum PTHrP: normal 14–27 pg/ml performed at Quest Diagnostics

Normal ranges of PTH and iCa in our laboratory are 7–75 pg/ml and 1.13–1.37 mmol/L, respectively

immunohistochemistry convincingly demonstrated the presence of PTHrP in tumor tissue (Fig. 1).

Hypercalcemia of malignancy is relatively rare in children, and while not uncommon in children with leukemia, it is seen in only 0.4–0.7% of children with solid tumors [13, 16]. In pediatric tumors of the kidneys, hypercalcemia has been described exclusively in infants with either malignant rhabdoid tumor or CMN and has been attributed to secretion of PTH or prostaglandin E_2; however, that report was from the era prior to identification of PTHrP [17]. PTHrP-mediated hypercalcemia in benign tumors is rare. A review of the literature found a few case reports in adults with ovarian dermoid cyst [5], uterine leiomyomas [6–9], intestinal leiomyoma [10], and pheochromocytomas [11, 12], but only a single case report in the pediatric population in a child with renal metanephric adenoma [14].

PTHrP is a polyhormone processed by members of the prohormone convertases to several biologically active peptides, each of which is thought to have its own receptor [4]. The amino-terminal sequence of PTHrP and PTH are similar and function through the G-protein-coupled receptor, PTH/PTHrP receptor (PTHR1), linked to adenylate cyclase activation. In contrast to PTH, which circulates systemically and thus functions as a hormone; PTHrP is found locally in many tissues in both the fetus and adult, including in epithelia, mesenchymal tissues, endocrine glands, and the central nervous system, and functions in an autocrine and paracrine fashion. Activated by either PTH or PTHrP, PTHR1 stimulates formation of osteoclasts in bone and restricts Ca loss in the kidney [4]. In our two cases, at presentation, the skeletal and renal effects of elevated PTHrP were similar to those seen in a child with hyperparathyroidism—namely, hypercalcemia, mild non-oliguric acute renal failure and, in case 2, hypophosphatemia. The serum PTHrP assay used in our patients detected the N-terminal region, which has PTH-like biological effects mediated via PTHR1. The clinical presentation was thus consistent with the proposed biological activity of PTHrP, with corresponding suppression of serum PTH due to the hypercalcemia caused by PTHrP.

The changes in mineral metabolism observed in our two cases postoperatively could be best explained by hypothesizing that following the removal from circulation of PTHrP, Ca and P previously removed from the bone began to move back into the bone. This phenomenon is analogous to the changes observed in mineral metabolism and postparathyroidectomy and is called hungry bone [18]. Thus, the biochemical profile observed in our two cases in the immediate postsurgical period might be best explained by the earlier suppression of the parathyroid glands by the hypercalcemia caused by pathologic serum levels of PTHrP. In case 1, PTH was measured for the first time only 1 week after surgery, when our service was consulted (TS and USA), and at that time showed appropriate response of elevated serum PTH level. Even though the picture in the latter case was less clear, due to his TPN, he too demonstrated hypocalcemia in the first few days after surgery. In both cases, once the parathyroid glands were able to provide the normal physiological response to hypocalcemia, only a moderate decline in serum iCa at the cost of elevated PTH was noted.

The observation of near absence of urinary P excretion despite elevated levels of PTH would suggest that mobilization of Ca and P continued into the bone despite elevated serum PTH levels. In case 2, despite ongoing treatment with Ca, P, and calcitriol, we saw no appreciable amount of urinary P until 6 weeks postsurgery. We previously reported this clinical observation, of undetectable urinary P excretion, in a child with hereditary 1,25-dihydroxyvitamin-D-resistant rickets during the phase of active bone healing,

brought about by intravenous Ca therapy [19]. In adults with PTHrP-mediated hypercalcemia from benign tumors, Ravakhah et al. [8] reported a similar postsurgical tumor removal of an increase in serum PTH and need for Ca supplementation for 3 months. Similarly, Mune et al. [12] reported a series of adults with pheochromocytoma and elevated PTHrP-like immunoreactivity with or without hypercalcemia that exhibited decreased serum Ca and increased serum PTH levels following tumor resection.

In essence, it seems that all the time Ca was moving into the bones to replenish it, PTH was recruited to try to maintain serum Ca within the normal range. It thus seems that in order to replenish the hungry bones while at the same time maintaining normal serum Ca concentration, it is important to supplement patients with high enough amounts of Ca and vitamin D. One can argue that in our cases even more Ca was needed and that the indication of adequate supplementation would have been maintaining serum PTH and concomitant urine Ca within their normal ranges. Thus, in future cases, it might be worth trying a higher dose of Ca while simultaneously monitoring serum Ca, P, and PTH and urinary Ca and P, and making sure that the patients are replenished with active vitamin D.

In summary, the above two cases bring to the attention of the pediatric nephrology community the occurrence of PTHrP-mediated hypercalcemia in benign CMN. Tumor removal leads to normalization of PTHrP, movement of Ca and P into bone, and rapid decrease in serum Ca. The latter results in a state of reactive hyperparathyroidism in an attempt to maintain serum Ca within its normal range, thus requiring supplementation with Ca and calcitriol. A careful attention to serum Ca, P, and PTH and simultaneously urinary Ca and P can guide therapy in these infants until bone healing is complete and hyperparathyroidism subsides.

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