Humoral hypercalcaemia in an infant: a diagnostic dilemma

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Hypercalcaemia is seldom encountered in paediatric patients, and calcium levels are not routinely included in investigations. Associated symptoms such as nausea, vomiting, dehydration and abdominal pain are non-specific, thus sustained hypercalcaemia may result in delipidating calcifications, neurological and renal impairment.[1] Physiologically, primary role players in calcium metabolism include parathyroid hormone (PTH) and vitamin D3 (calcitriol). It is important to establish whether hypercalcaemia is PTH or non-PTH related so that targeted treatment may be planned.

Epithelioid haemagioendothelioma (EHE) is a vascular malignant tumour that mostly affects the liver, lung, bone and soft tissue.[2] Colonic EHE is uncommon. The clinical course of EHE is highly variable ranging from asymptomatic and mild disease with prolonged survival even without any treatment to severe disease with some patients succumbing to the disease within a few months post diagnosis.[3] Immunohistochemical evaluation of CD31, CD34 and factor VIII are used to confirm EHE.

Although paraneoplastic syndrome is not common in these patients, others[4] have also reported hypercalcaemia in a setting of EHE. The patient in this case report presented mainly with PTH-related peptide (PTHrP)-mediated hypercalcaemia. PTHrP expression from the resected tumour was confirmed using both western blot and real-time quantitative reverse transcription-PCR. Testing for PTHrP poses a diagnostic challenge when humoral hypercalcaemia is suspected.

Moreover, quantitative evaluation of PTHrP is not practical and not currently available for routine use, being mostly limited to research laboratories. Arrival at the diagnosis of PTHrP-mediated hypercalcaemia requires extensive investigations in an attempt to exclude all other potential causes for which testing can be performed in clinical laboratories.[5] Differential diagnoses for hypercalcaemia in infants are primary hyperparathyroidism, including multiple endocrine neoplasia syndromes, disorders of calcium sensing receptors such as severe neonatal hypercalcaemia and familial hypocalciuric hypercalcaemia, granulomatous diseases and vitamin D toxicosis.[6] Unfortunately, this exercise involves multiple investigations, which are not cost effective, inconvenient to the patient and may delay the diagnosis. In resource restrained centres, the diagnosis may be missed.

Mechanisms of PTHrP activity are both autocrine and paracrine. It is a 141 amino acid peptide, which bears similarity to the N-terminal PTH, mimicking PTH activity.[7] Both bind to the PTH-1 receptor stimulating calcium tubular reabsorption and phosphaturia, but PTHrP is not implicated in calcitriol synthesis. Excessive PTHrP secretion causes hypercalcaemia through both increased renal retention and bone resorption, thus patients may develop osteolytic lesions.[5]

PTHrP in paediatric populations has been reported in patients with haematological malignancies, including acute lymphocytic leukaemia[8] These were excluded by the normal full blood count in this patient. However, elevated PTHrP levels have also been reported in infants with renal anomalies, without any tumours or haematological malignancies.[9]

Resection of the tumour is the preferred treatment method and has potential to completely resolve the symptoms and biochemical derangements.[6,10] In this report, PTHrP-mediated hypercalcaemia associated with EHE was diagnosed, further illuminating the diagnostic dilemma that may be encountered by clinical laboratories owing to the unavailability of PTHrP testing.

References

1 Reynolds BC, Cheetham TD. Bones, stones, moans and groans: hypercalcaemia revisited. *Arch Dis Child Educ Pract Ed* 2015; 100:44–51.

2 Hettmer S, Andrieux G, Hochrein J, et al. Epithelioid hemangioendotheliomas of the liver and lung in children and adolescents. *Pediatr Blood Cancer* 2017; 64: e26675.

3 Lau K, Massad M, Pollak C, et al. Clinical patterns and outcome in epithelioid hemangioendothelioma with or without pulmonary involvement: insights from an Internet registry in the study of a rare cancer. *Chest* 2011; 140:1312–8.

4 Boukhris I, Azzabi S, Kéchaou I, et al. Hypercalcemia related to pth- rp revealing malignant hepatic epithelioid hemangioendothelioma. *Ann Biol Clin* 2016; 74:98–102.

5 Davies JH. *Approach to the child with hypercalcaemia. Calcium and bone disorders in children and adolescents*. Karger Publishers, 2015: 101–18.

6 Davies JH, Shaw NJ. Investigation and management of hypercalcaemia in children. *Arch Dis Child* 2012; 97:533–8.

7 Gardella TJ, Jüppner H, Ju H. Interaction of pth and pthrp with their receptors. *Rev Endocr Metab Disord* 2000; 1:317–29.

8 Martins AL, Moniz M, Nunes PS, et al. Severe hypercalcemia as a form of acute lymphoblastic leukemia presentation in children. *Rev Bras Ter Intensiva* 2015; 27:402.

9 Kodous N, Filler G, Sharma AP, et al. Pthrp- related hypercalcaemia in infancy and congenital anomalies of the kidney and urinary tract (cakut). *Can J Kidney Health Dis* 2015; 2:52.

10 Mehrabi A, Kashfi A, Schemmer P, et al. Surgical treatment of primary hepatic epithelioid hemangioendothelioma. *Transplantation* 2005;80: S109–12.