Spontaneous fractures secondary to primary hyperparathyroidism in pregnancy: a case report

Fracturas espontâneas secundárias ao hiperparatiroidismo primário na gravidez: um relato de caso

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ABSTRACT
Objective: To report a case of hyperparathyroidism secondary to a parathyroid adenoma, presenting a high level of hypercalcemia associated with spontaneous fractures in young pregnant woman. Case report: The patient underwent an emergency cesarean after presenting premature amniorrhexis and tolerated the procedure without complications. The newborn evolved satisfactorily, without symptoms of hypocalcemia. The postpartum woman was then submitted to left lower parathyroidectomy and, in the postoperative period, she developed bone hunger syndrome, despite previous administration of bisphosphonate. There was a progressive resolution of PTH and serum calcium levels, with a consequent improvement in the clinical condition. Conclusion: This report highlights the need and the difficulty regarding the early diagnosis of primary hyperparathyroidism, which is a potentially fatal pathology for the maternal-fetal binomial. Therefore, it is essential to institute proper treatment early, with individualization according to the patient's clinical condition, to minimize the risks of complications and mortality.

Keywords: Bone fractures. Cesarean section. Hypercalcemia. Hyperparathyroidism. Parathyroid Neoplasms.

RESUMO
Objectivo: Relatar um caso de hiperparatiroidismo secundário a um adenoma paratiróide, apresentando um elevado nível de hipercalcemia associado a fracturas espontâneas em mulheres grávidas jovens. Relato de caso: A paciente foi submetida a uma cesariana de emergência após apresentar amniorrexia prematura e tolerou o procedimento sem complicações. O recém-nascido evoluiu de forma satisfatória, sem sintomas de hipocalcemia. A mulher pós-parto foi então submetida a uma paratiroidectomia inferior esquerda e, no período pós-operatório, desenvolveu síndrome de fome óssea, apesar da administração prévia de bisfosfonato. Houve uma resolução progressiva dos níveis de PTH e soro de cálcio, com uma consequente melhoria da condição clínica. Conclusão: Este relatório realça a necessidade e a dificuldade no que diz respeito ao diagnóstico precoce do hiperparatiroidismo primário, que é uma patologia potencialmente fatal para o binómio materno-fetal. Por conseguinte, é essencial instituir um tratamento adequado precoce, com individualização de acordo com a condição clínica do paciente, para minimizar os riscos de complicações e mortalidade.

Palavras-chave: Fracturas ósseas. Secção de cesariana. Hipercalcemia. Hiperparatiroidismo. Neoplasias paratiróides.

1 INTRODUCTION

Primary hyperparathyroidism (PHPT) results from the exacerbated production of parathyroid hormone (PTH) by one or more parathyroid glands [1]. The PTH main function is to increase blood calcium levels by increasing its renal reabsorption in the distal tubule, as well as its absorption in the small intestine, the stimulation of bone resorption, besides activating the conversion of vitamin D to calcitriol [2].

PHPT is the third most prevalent endocrinological disorder, after diabetes and other thyroid diseases [3]. Its prevalence in the general population varies from 0.4 to 21.6 cases per 100,000 people/year [1]. PHPT occurs more frequently in 40-65 years-old women, hardly affecting children and adolescents [1]. Less than 1% of the diagnosis is made during pregnancy, which leads to an underdiagnosis, explained by the exclusion of the serum calcium measurement as a routine examination during pregnancy [3]. It is the main cause of outpatient hypercalcemia. However, as it is not a characteristic symptom of the disease, PHPT requires a differential diagnosis for other pathologies, leading to delayed diagnosis [3-4].

The clinical picture of hyperparathyroidism is usually asymptomatic, presenting in a non-specific way, and usually confused with physiological changes in pregnancy [5]. The manifestations can include bone and/or renal involvement, hypercalcemic crisis, pancreatitis, hyperemesis in pregnant women and spontaneous abortion, fetal death, low birth weight, and neonatal hypocalcemia in the newborn [6].

Thus, the present work aims to report the case of a young patient diagnosed with severe PHPT during pregnancy, who experienced complications during the pregnancy process, with a focus on the pathophysiology of the disease.

2 CASE REPORT

Female patient, 33 years old, G2Pc1A0, 29 weeks pregnancy. The patient was admitted to a public health referral service with reports of spontaneous fractures in the left clavicle and right forearm in the current pregnancy. She denied previous episodes of fractures but referred previous pain in his right foot. When referred to an X-ray, osteopenia was evidenced. She was unable to walk due to severe pain in her hip. On physical examination, she showed painful bulging in the left clavicle and right forearm, and limited flexion in the lower limbs. She only brought to her first appointment an ultrasound examination (USG) of the urinary tract, which indicated right renal lithiasis and medullary nephrocalcinosis.

After some initial lab tests results (Table 1), a hypercalcemia was identified, thus PTH measurements and cervical imaging tests were requested. The patient's PTH value was 1169.3 pg/mL, while USG and magnetic resonance imaging (MRI) of the cervical region showed a solid nodule in the topography of the left lower parathyroid (Figure 1). The clinical and laboratory findings led to the hypothesis of a parathyroid adenoma as the cause of PHPT. A subsequent MRI of the cervical spine revealed lytic and inflationary

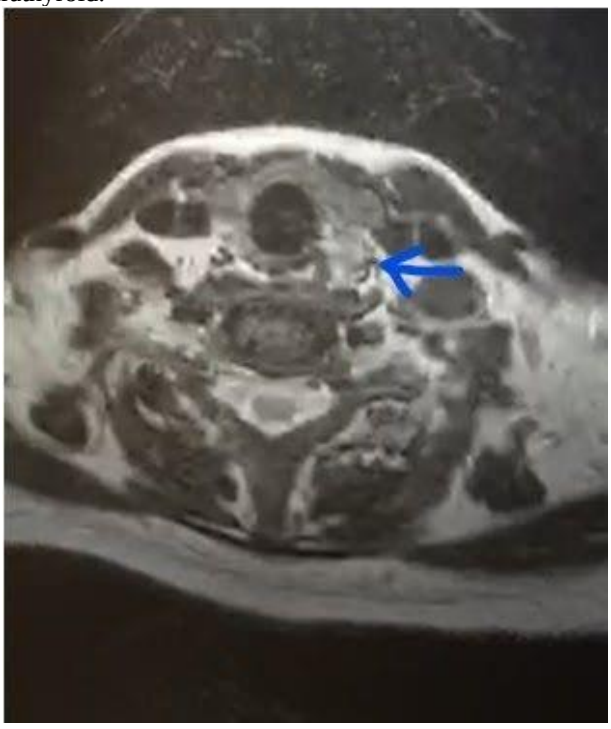
bone lesions in the posterior elements of C2, C4 and D1 and two in the left clavicle, which may correspond to brown tumors (osteitis fibrosa cystica) and pathological fracture of the T4 vertebra.

Table 1. Lab results on admission

	Result*	Reference range
Hemoglobin	**6,95 g/dL**	13.0 a 18.0 g/dL
Hematocrit	**22,3 %**	38 a 52%
Leucocites	**10.100 uL**	4.500 a 10.000 uL.
Platelets	286.000 uL	140 000 a 450 000 µL
C-reactive protein	**11,6 mg/L**	< 3 mg/L
Erythrocyte sedimentation test	**102 mm**	5 a 20 mm
Urea	22 mg/dL	16 a 40 mg/dL
Creatinin	0,78 mg/dL	0,6 a 1,2 mg/dL
Albumin	**3 g/dL**	3,5 a 4,7 g/dL
Serum calcium	**14,1 mg/dL**	8,5 a 10,2 mg/dL
Urinary calcium 24h	**13 mg/dL**	< 0,25 mg/dL
Phosphate	3,8 mg/dL	2,5 a 4,5 mg/dL
Vitamin D	**18,2 ng/mL**	> 20 ng/mL
ALP	**329 uL**	36 a 110 u/L
TSH	1,32 Mu/L	0,4 a 4,5 mU/L

*Altered levels are presented in bold.

Figure 1. Cervical region MRI, axial plan, showing an intermediate nodule in T1 and T2, located in the topography of the left parathyroid.



The patient evolved with premature amniorrhexis and onset of uterine contractions, thus undergoing an emergency cesarean section. Patient tolerated the procedure without complications. 32-week-old newborn, weighing 1900 grams, 30 cm

head circumference, 37 cm chest circumference, 39 cm height, 9/9 Apgar, without hypocalcemia symptoms. After the procedure, he received neonatology care and was referred to the neonatal ICU, having progressed satisfactorily over the days, with subsequent discharge from hospital in good general condition.

Regarding the pregnant woman, after the establishment of HPTP secondary to a parathyroid adenoma diagnosis, recovery from childbirth, the patient underwent a left lower parathyroidectomy with cervical emptying, with previous administration of pamidronate, a normalization of vitamin D levels were achieved after oral supplementation in the beginning of hospitalization. The anatomopathological result of the surgical specimen (weight: 4g; size: 2.5 × 1.5 × 0.9cm) confirmed a histological picture compatible with parathyroid adenoma. The PTH dosage intraoperatively, after parathyroidectomy, was 228 pg / mL. The patient developed bone hunger after surgery, with calcium levels reaching up to 7.7 mg / dL, being adequately treated. Late postoperative exams showed a significant reduction in PTH and serum calcium values, with normalization in the following days (34 pg / mL and 9.6 mg / dL, respectively).

3 DISCUSSION

The prevalence of primary HPTP in pregnancy is not known, remaining rare and commonly underdiagnosed due to the physiological changes of pregnancy, which end up hiding the symptoms and delaying the disease diagnosis, as in the case described [3]. It is likely that, in this case report, the first manifestations of HPTP appeared even before pregnancy, due to a history of osteopenia in the patient's feet X-rays, with a sudden evolution to spontaneous bone fractures during pregnancy. Hyperparathyroidism in pregnancy is associated with severe morbidity, both maternal and fetal, however, mortality decreases dramatically if an early diagnosis and treatment is performed [5].

HPTP' manifestations are very rare during pregnancy. Most pregnant women are asymptomatic, even in the presence of high serum calcium levels [5]. However, when symptoms occur, they may include pancreatitis and neurological symptoms [7]. Within the bone manifestations, osteitis fibrous cystic appears as a pathognomonic skeletal change of HPTP [8].

In HPTP patients, there is a predominant loss of cortical bone, which occurs because PTH has a catabolic function in the appendicular skeleton and anabolic function in the axial skeleton. Bone pain, pathological fractures and muscle weakness are the main manifestations related to these and other bone diseases [9]. However, being most

asymptomatic, bone involvement is revealed only through complementary exams. In this case report, the initial symptoms curiously began with spontaneous bone fractures.

For diagnostic purposes, the relevant initial lab tests are serum calcium levels, phosphorus, albumin, alkaline phosphatase, PTH, urea, creatinine, 25OHD, calcium and phosphorus in 24-hour urine. Complementary imaging tests include kidneys and urinary tract USG, radiological inventory, bone densitometry and parathyroid scintigraphy [10-11]. However, in this case report, as the patient is a high-risk pregnant woman, there is a restriction related to radiation-based diagnostic methods to protect the fetus against malformations. However, as it is a rare and uncommon condition, it was necessary to perform these tests to reach the patient's final diagnosis. Thus, the medical staff prioritized low radiation exams, and understood that the benefits outweigh the risks.

The management of HPTP during pregnancy should be carried out individually, based on the symptoms, gestational age, and hypercalcemia severity. The treatment of choice is usually parathyroidectomy, preferably at the beginning of the second pregnancy trimester. Conservative treatment may be indicated for patients with mild or asymptomatic symptoms during pregnancy, as well as surgical failure or when facing contraindications [12]. Such patients are then treated with venous hydration with 0.9% saline and calcitonin, as literature points no adverse effects on the fetus [4]. Hydration is recommended in all cases for volemic correction, as it increases the excretion of calcium in the urine and decreases the reabsorption of the electrolyte by increasing the glomerular filtration rate. Calcitonin, in turn, acts by inhibiting osteoclast precursors [8]. In this case report, due to the delay in diagnosis, the patient was only submitted to parathyroidectomy after the completion of pregnancy.

Other conservative treatment is based on the use of cinacalcet and bisphosphonates which, despite successfully used in some already reported cases, are not commonly indicated because they are embryotoxic. The efficacy and safety of treatments in pregnant women are poorly known due to the lack of cases described in the literature [4]. Thus, parathyroidectomy is still considered the best treatment and, as serum calcium levels increase, it becomes increasingly indicated [13]. In the case described, the pregnant woman was not submitted to surgery in the appropriate time because she developed premature amniorrhexis, thus undergoing an emergency cesarean section.

Bisphosphonates are contraindicated when pregnancy / lactation is suspected or ongoing. However, in some cases, the expected treatment benefits outweigh possible congenital risks. In the reported case, along with the instituted therapy, vitamin D

replacement was performed to normalize levels that were previously below those recommended [8,14].

If left untreated during pregnancy, HPTP can trigger, in most times, several and serious problems in the newborn, including neonatal death, fetal growth restriction, premature birth and low birth weight [4]. In approximately 50% of cases, neonate's postpartum fetal hypocalcemia occurs, due to the high levels of maternal calcium that suppress the fetal parathyroid gland. However, this condition is usually not permanent. In the case described, despite the severity of hypercalcemia, the newborn was born without complications related to the disease [15].

4 CONCLUSION

Delayed diagnosis of HPTP in pregnancy can lead to serious complications in both maternal and fetal conditions, ranging from muscle weakness to pancreatitis. Early identification of the pathology becomes an essential tool for the outcome of pregnancy and maternal-fetal prognosis. This report highlights the importance of adequate investigation to help and expedite the diagnosis, in addition to the development of routine serum calcium and parathyroid hormone tests in these cases.

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