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Hyperemesis Gravidarum Revealing Primary Hyperparathyroidism

Loubna Benaddi, Amine Raja, Yassine Hafiani, Amine Berrada, Harit Marouane El, Badr Mouhaoui, Smail El Youssoufi, Said Salmi

Obstetrical and Gynecological ICU, Mother and Child University Hospital of Harouchi, Casablanca, Morocco
Email: loubnabenaddi19@gmail.com

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Abstract

Primary hyperparathyroidism is among the most common endocrinopathy in the general population. However, this entity is rare in women of childbearing age, and even rarer during pregnancy. Patients with hyperparathyroidism have a highly aspecific symptomatology, with symptoms as those found physiologically in pregnant women during the first trimester, making the diagnosis difficult to identify. Furthermore, calcemia assessment is not usually performed during routine pregnancy follow-up. Thus, primary hyperparathyroidism with severe hypercalcemia is at high risk of being left untreated during pregnancy, a situation that could lead to serious complications. There are not only obstetrical complications but also fetal complications such as neonatal hypocalcemia. During pregnancy, not many treatments are allowed such as Zoledronate due to the lack of information concerning its effects on the fœtus. On the other hand, some treatments may not be as efficient as the 7/8th parathyroidectomy, which remains the treatment of choice for symptomatic pregnant patients with primary hyperparathyroidism due to parathyroid hyperplasia with very high blood calcium levels. This article presents the case of a 28-year-old woman who was initially admitted for hyperemesis gravidarum. The lack of clinical improvement led us to further our research. Not only did we diagnose a primary hyperparathyroidism due to parathyroid hyperplasia but we also discovered that she had developed central pontine myelinosis probably because of refractory hypokaliemia related to hypercalcemia, making this case a real challenge.

Keywords

Hyperemesis Gravidarum, Primary Hyperparathyroidism, Parathyroid Hyperplasia, Severe Hypercalcemia, Zoledronate, Central Pontine Myelinosis

1. Introduction

Primary hyperparathyroidism is defined as excessive production of parathyroid hormone, leading to hypercalcemia. The most frequent causes are parathyroid adenoma and parathyroid hyperplasia. This entity is rare in women of childbearing age, and even rarer during pregnancy, although its prevalence is unknown [1].

Symptoms are mainly related to hypercalcemia. It is therefore not very specific, and often confused with the clinical manifestations of vomiting in pregnancy.

In addition to the dreaded complication of severe hypercalcemia, there are obstetrical complications such as polyhydramnios or intrauterine growth retardation, and fetal complications such as neonatal hypocalcemia [1]. The incidence of peripartum hyperparathyroidism is unknown, but it is certainly rare. In fact, it carries high risks of perinatal morbidity and maternal mortality, which worsen with the delay of diagnosis and treatment. According to other cases found in the literature, only surgical treatment is curative [2]. Therefore, treating pregnant women with hyperparathyroidism is a challenge that requires a multidisciplinary team focusing not only on maternal but also fetal well-being.

In this article, we present a case of severe hypercalcemia due to primary hyperparathyroidism encountered in our obstetrical ICU.

2. Observation

This is the case of a 28-year-old pregnant woman at 22 weeks of amenorrhea admitted for hyperemesis gravidarum, which did not improve with symptomatic treatment and needed a second hospitalization, this time in our intensive care unit. On admission, she was dehydrated, pale, asthenic and slightly polypneic, with respiratory rate of 20 cycles/min. Hemodynamically, she was stable with a BP of 11/5 and a HR of 100 bpm. She had no jaundice, no abdominal sensibility, nor masses on palpation. Abdominal ultrasonography was performed twice, both times coming back normal with progressive pregnancy. An initial blood test showed hypokalemia at 2.4 mmol/L with no electrical repercussions, requiring a central line and continuous correction with symptomatic treatment of vomiting: metoclopramide, chlorpromazine and a 5HT3 receptor antagonist. Her liver function tests were normal with no cytolysis nor cholestasis, lipasemia levels were normal, and her renal function tests were correct, with creatinemia at 9.4 mg/l. However, she had a microcytic microchromic anemia at 8.3 g/L, for which she received IV martial supplementation. In the absence of clinical improvement, a further workup revealed corrected calcemia at 4.24 mmol/l, and albuminemia at 32 g/L. Regarding this severe hypercalcemia, an electrocardiogram was performed, showing sinus tachycardia without QT shortening. Apart from digestive signs, she had polyuria but no renal failure and no neurological signs.

An etiological workup was performed. PTH was high: to 925 pg/ml and phosphatemia was low about 18 mg/L. Given these results, we concluded to hyperparathyroidism of primary origin. Cervical ultrasound revealed bilateral parathyroid

nodules, suggesting parathyroid hyperplasia.

Concerning the treatment, rehydration was started as soon as possible at 3 L/m²/D, without diuretics as she had mild hypokalemia and polyuria. Corticosteroid therapy was started and then stopped as the possible etiology didn't require steroids. An electrocardiogram was performed twice daily to detect any signs of severity. Fetal cardiac activity was monitored several times a day. In parallel, endocrinologists and ENT specialists were contacted. In view of the young, progressive pregnancy and calcium levels that remained above 3.8 mmol/l despite rehydration and corticosteroid therapy, a calcimimetic agent, cinacalcet, was prescribed by endocrinology team at 30 mg × 2/d with the aim of lowering PTH and thus achieving a concomitant reduction in calcium levels. Biological monitoring showed no significant drop, with blood calcium still high at 3.14 mmol/L.

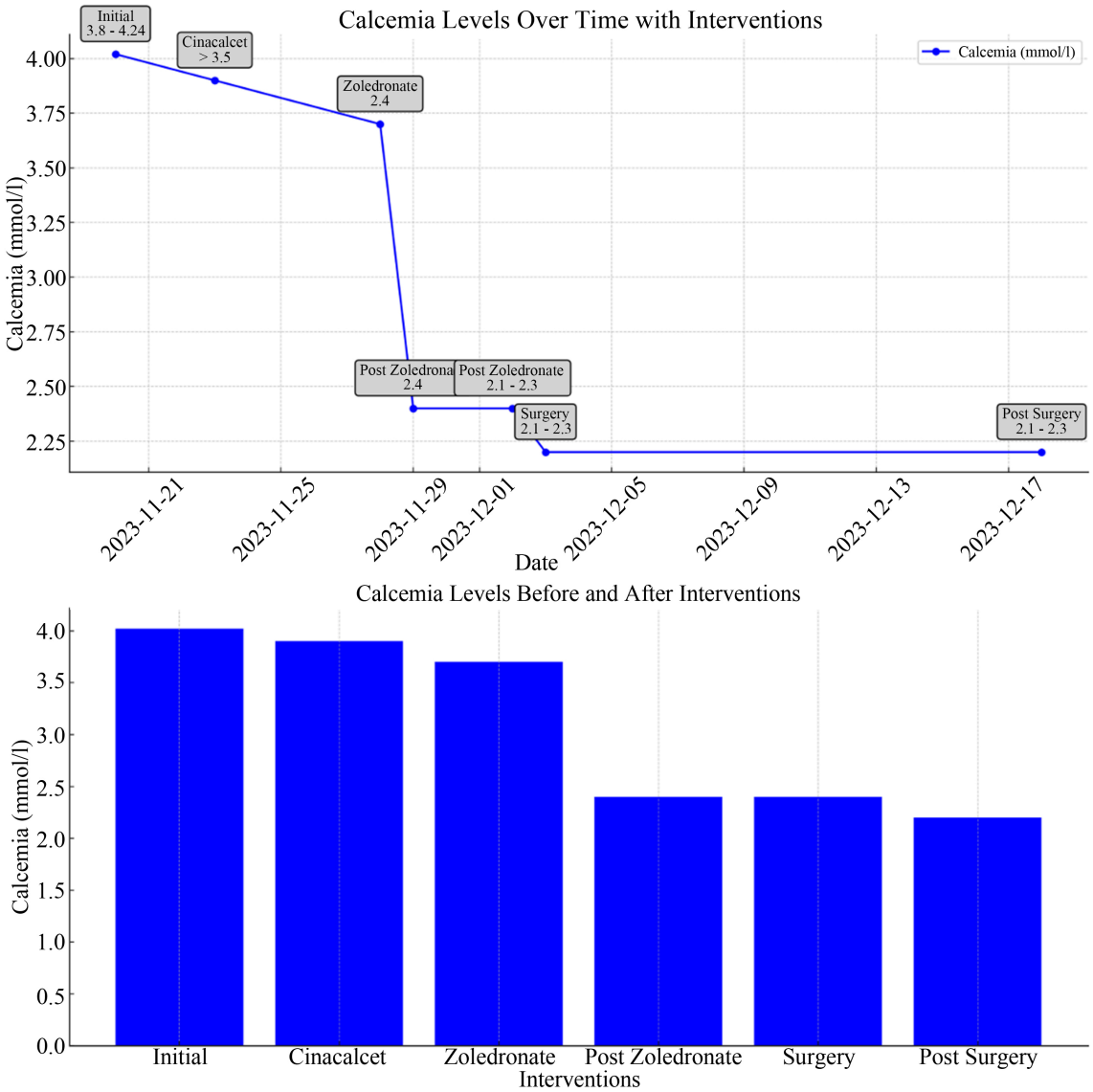

Figure 1. Charts showing the evolution of blood calcium levels during the patient hospitalization depending on therapeutic interventions.

The multidisciplinary decision, taken by endocrinologists, ENT specialists, obstetricians, intensivists and anesthesiologists, was to give a dose of zoledronate to lower blood calcium levels to prepare the patient for surgery. Following a 4 mg dose of zoledronate, blood calcium levels returned to 2.4 mmol/l. The patient underwent a 7/8th parathyroidectomy in the following 48 hours. The postoperative period was uneventful, with no hypocalcemia at daily check-ups, and the pregnancy progressed well (**Figure 1**).

During her hospitalization, she developed severe sepsis, requiring the introduction of norepinephrine and C3G-based antibiotic therapy. Subsequently, blood and urine cultures identified Escherichia Coli C3G-sensitive. This infectious episode was treated with clinical improvement and vasopressor withdrawal. Then, the patient developed confusion with hallucinations and behavior disturbance, not concomitant with the onset or worsening of hypercalcemia. A cerebral MRI was performed, showing a well-limited central pontine nodular lesion, hypo signal T1, hypersignal T2/FLAIR, all in favor of a start of central pontine myelinosis (**Figure 2**). Knowing that the patient had never presented dysnatremias or severe and prolonged variations of blood glucose levels, they were ruled out as possible etiologies for the central pontine myelinosis. However, she had hypokalemia which recurrencies despite repeated correction. As blood potassium levels improved following its correction, we noticed improvement and gradual regression of patient's neurological symptoms.

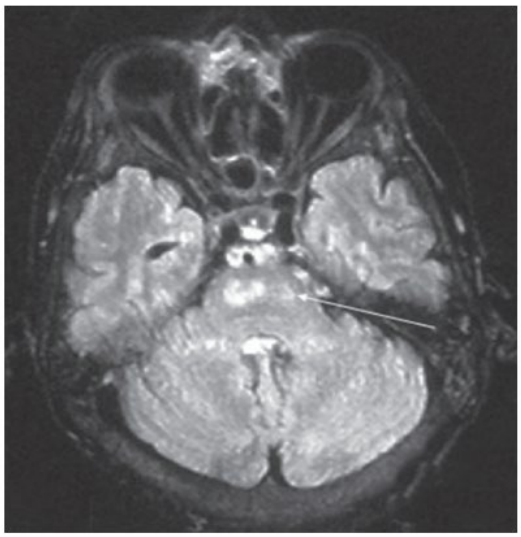

Figure 2. Centro-pontine nodular lesion in hypersignal in T2, findings consistent with central pontine myelinosis.

Calcium and potassium blood levels normalized with clinical improvement and disappearance of vomiting. The evolution was favorable (**Figure 3**). The patient was transferred to endocrinology for appropriate follow-up, with consultations scheduled for her pregnancy check-ups. She delivered a female neonate weighing 3.4 kg, with Apgar scores of 10/10 at birth. A 24-hour assessment revealed no ne-

onatal hypocalcemia.

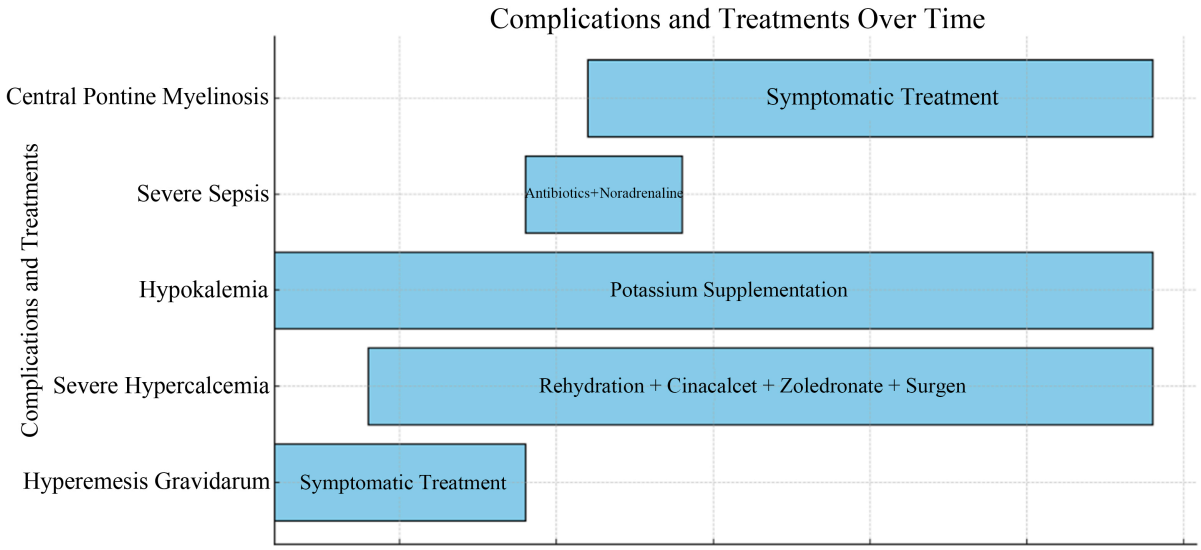

Figure 3. Complications and treatments received during our patient ICU stay.

3. Discussion

Primary hyperparathyroidism is the third most common endocrinopathy in the general population [3]. The first cause of primary hyperparathyroidism is parathyroid adenoma, and the second is parathyroid hyperplasia. The incidence of peripartum hyperparathyroidism is unknown, but it is certainly rare. Over 150 cases were documented in the English literature up to 1999, and since then, isolated cases have been reported [4]. Patients with hyperparathyroidism have a highly aspecific symptomatology, with symptoms as those found physiologically in pregnant women, making the diagnosis difficult to identify [5]. Signs include hyperemesis, fatigue, intense thirst, abdominal pain, sometimes depression, constipation and rarely cardiac rhythm disorders. Blood calcium levels assessment is not usually performed during routine pregnancy follow-up and is not requested as a first-line treatment when these symptoms are present during pregnancy [5]. It was because of the lack of clinical improvement that the test was carried out in our patient.

Primary hyperparathyroidism with severe hypercalcemia left untreated during pregnancy is at high risk of complications. Indeed, in some reviews of the literature, the maternal complication rate has been found to be 67%, the fetal complication rate may be as high as 73%, and the neonatal complication rate may reach 53% [6]. Complications arise in the absence of early diagnosis. Maternal complications include digestive signs, neurological signs and, rarely, rhythm disorders, which must be monitored and prevented.

Obstetrical complications are mainly intrauterine growth retardation and delivery complications due to polyhydramnios [6]. Studies by Abood *et al.* show no increase in the rate of spontaneous miscarriage [1], in contrast to studies by Nor-

man *et al.*, who found a 3.5 fold increase in the miscarriage rate in a population sample [7]. Miscarriages are most often late (second trimester of pregnancy) and associated with repeated miscarriages. Pathophysiologically, the risk of miscarriage and aborted pregnancy may be explained by the fact that PTH-rp; the PTH like hormone secreted by various fetal organs, the placenta and certain tumors; may act as a promoter of calcium transfer to the fetus, and also acts as a smooth muscle relaxant, particularly in the uterus, which could explain the increased rate of premature delivery and hence Caesarean section [7]. The inclusion of blood calcium levels in the assessment of recurrent miscarriage is justified by these results, but more studies are still needed to establish the links between these findings.

Neonatal hypocalcemia with tetany is usually a transient phenomenon linked to suppression of the fetal parathyroid glands due to maternal-fetal hypercalcemia, but can be more prolonged, with the risk of asphyxia at birth, in addition to the risk of convulsions [6].

According to the literature, cases of asymptomatic hyperparathyroidism with blood calcium levels in the upper limits of normal can benefit from conservative treatment with rehydration, thus avoiding the risks of surgery [2]. Cinacalcet, which was initially used in our patient, is a calcimimetic molecule that lowers PTH by increasing the extracellular calcium sensitivity of the calcium-sensitive receptor present on parathyroid cells, thus lowering blood calcium levels. The first case in the literature was described by Horjus *et al.*, who explained that Cinacalcet monotherapy is probably not useful for a severe form and should be combined with calcitonin [8]. According to CRAT, published data on pregnant women exposed to Cinacalcet in the 2nd and/or 3rd trimester are limited to a few numbers of pregnancies, with variable efficacy in hyperparathyroidism of various etiologies, but no specific fetal or neonatal effects attributable to it [8] [9]. Calcitonin does not cross the placental barrier due to its high molecular weight, and the limited data available is in favor of a treatment suitable for pregnant women. However, efficacy is low. In addition, this hormone inhibits bone resorption and increases renal calcium elimination [5]. Thus, it is of no interest in the etiological treatment in our case.

Thus, 7/8th parathyroidectomy is the treatment of choice for symptomatic pregnant patients with primary hyperparathyroidism due to parathyroid hyperplasia with very high blood calcium levels [10]. However, surgery in the first trimester of pregnancy results in exposure of the fetus to anesthetic products during the period of organogenesis. On the other hand, surgery in the third trimester has been shown in several case series to threaten premature delivery. Surgery should generally be performed in the 2nd trimester of pregnancy [11]. Yet, the study by Schnatz *et al.* found no significant increase in morbidity when surgery was performed in the 3rd trimester rather than the 2nd [10]. Most postoperative maternal complications are hypocalcemia secondary to surgery, treatable by calcium supplementation [10].

In our case, surgery was the only effective treatment. However, given the very

high blood calcium levels and the risks associated with anesthesia, it was necessary to lower its level before the intervention. Initially, Cinacalcet was not as effective as the studies reported in the literature. It was only after a single dose of Zoledronate, authorized by obstetricians given the high maternal risk of mortality and complications of severe hypercalcemia, that the rate could be lowered slightly and surgery performed. The surgery went well without a complication, with no post-operative hypocalcemia and no repercussions on the pregnancy.

In our patient, refractory hypokalemia appears to be correlated with hypercalcemia. In fact, hypokalemia had improved only when calcium levels were reduced despite the repeated intravenous corrections. It has been postulated that calcium intake increases sodium supply to the distal tubule, resulting in Na-K exchange with excessive potassium loss [12]. In addition, the secondary aldosteronism caused by polyuria also leads to an increase in urinary potassium excretion [13]. Thus, central pontine myelinosis, in this patient seems to be attributable to hypokalemia in a context of severe hypercalcemia. In fact, there were no dysnatremias, neither were there prolonged periods of high blood glucose levels or high blood pressure. A similar rare case has been reported in the literature. In this case, the hypercalcemia was due to MEN type 1, and the patient also benefited from medical and surgical treatment [14].

4. Conclusions

Primary hyperparathyroidism during pregnancy needs to be diagnosed promptly, so that treatment can be initiated without delay, and fetal and maternal complications can be reduced. Thus, any pregnant woman presenting with vomiting in pregnancy that has not improved after adequate symptomatic treatment should be screened for primary hyperparathyroidism.

The therapeutic approach must be individualized and discussed with a multidisciplinary team. Surgical treatment remains the treatment of choice for symptomatic primary hyperparathyroidism with severe hypercalcemia. It would be interesting to enhance this case with other retrospective studies in the context of this rare disease, as it seems necessary to establish the causal links between hyperparathyroidism and its maternal-fetal consequences.

Ethics

Patient's consent obtained and adhering to ethical guidelines of Helsinky.

Conflicts of Interest

There are no conflicts of interest.

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