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UNMASKING THE HIDDEN THREAT: A CASE AND REVIEW OF PRIMARY HYPERPARATHYROIDISM-INDUCED PANCREATITIS DIAGNOSED IN PREGNANCY

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ABSTRACT

Primary hyperparathyroidism is a very well-documented and understood endocrine pathology that includes the overproduction of parathyroid hormone, leading to an exaggerated effect of hypercalcemia. However, its prevalence leading to pancreatitis, specifically in pregnant patients, is underreported and widely undiagnosed. In this case, we present a case of a 23-year-old female in her second pregnancy who presented with pancreatitis after already being treated and diagnosed with pancreatitis in her first pregnancy. It was later discovered that this patient had a nodule believed to be a parathyroid adenoma. We believe this parathyroid adenoma alone could have gone unnoticed, but with concurrent changes and physiology of pregnancy, caused a significant burden of pancreatitis on our patient, not only in one pregnancy, but in both of her pregnancies.

KEYWORDS

Primary hyperparathyroidism, pancreatitis, pancreatitis in pregnancy, parathyroid hormone, hypercalcemia

LEARNING POINTS

- Hyperparathyroidism is rarely diagnosed in pregnancy and is widely unrecognized.
- This carries threats to mother and baby, which include pancreatitis.
- If a parathyroid adenoma is present, surgical removal in the second trimester is the preferred treatment.

INTRODUCTION/BACKGROUND

Primary hyperparathyroidism (PHPT) leading to pancreatitis, especially in pregnancy, is a rare phenomenon that has been reported in a very small number of cases[1]. PHPT alone is a prevalent endocrine pathology that could go undiagnosed due to the small percentage of patients who develop symptoms[2-4]. The symptoms of PHPT include lethargy, nausea, polyuria, and constipation[4]. These symptoms are also found in many pregnant patients, making it challenging to differentiate from pathological PHPT. The simultaneous physiology of pregnancy and release of parathyroid-related protein from the foetus leads to increased intestinal

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absorption of calcium and maternal bone resorption. In this case, we discuss the pathology of PHPT, which is usually be insignificant alone, and the exaggeration of physiological changes in pregnancy that lead to complications such as pancreatitis in pregnant patients.

CASE DESCRIPTION

A 23-year-old G2P1 10+1-week gestation presented to the emergency department complaining of epigastric pain radiating to her back. The pain was not associated with nausea, vomiting, fever, or other symptoms. She was found to have acute pancreatitis and was admitted for further evaluation and treatment. Further history revealed a prior episode of acute pancreatitis which occurred a year prior during the third trimester of her first pregnancy, at 34 weeks. During this first bout of pancreatitis, she was hospitalized for one month and underwent early delivery at 38 weeks. The infant was born healthy with no postpartum complications. Medical records obtained from the patient's prior admission confirmed a history of acute pancreatitis secondary to hypercalcemia in the setting of hyperparathyroidism. Laboratory work at that time was significant for elevated amylase at 2,198 U/l (normal range: 25-115 U/l), lipase of 7,251 U/l (normal range: 73-393 U/l), total calcium corrected to albumin of 12.2 mg/dl (normal range: 8.5-10.1 mg/dl), ionized calcium of 6.1 mg/dl (normal range: 4.7-5.5 mg/dl), and normal urinary calcium levels. Parathyroid hormone (PTH) was markedly elevated at 387.9 pg/ml (normal range: 18.4-80.1 pg/ml), while PTH-related peptide was within normal limits 12 pg/ml (normal range: 11-20 pg/dl). Unfortunately, the patient did not follow up after delivery, believing she was well enough not to warrant further evaluation. She remained asymptomatic until her second pregnancy and experienced no reported hypercalcemia-related complications.

Upon presentation, physical examination revealed epigastric tenderness, but her abdomen was non-distended, and bowel sounds were present in all four quadrants. Murphy's sign was negative. The patient was afebrile with stable vital signs: blood pressure 138/89 mmHg, heart rate 102 bpm, respiratory rate 18 breaths per minute, and oxygen saturation within normal limits on ambient air. Initial laboratory tests showed leucocytosis. Her white blood cell count was 14.8 $\times 10^9$/l (reference range: 4.5-11 $\times 10^9$/l) with neutrophil predominance, Haemoglobin 15.6 g/dl (reference range: 12-16 g/dl), and haematocrit of 48.3% (reference range: 36-46%), suggestive of dehydration. Lipase was elevated at 1,035 U/l (reference range: 11-82 U/l), alkaline phosphatase at 143 U/l (reference range: 34-104 U/l), with normal transaminases, kidney function, and triglycerides 149 mg/dl (reference range: <149 mg/dl). Hypercalcemia was noted, serum calcium level was 12.7 mg/dl (reference range: 8.6-10.3 mg/dl) with albumin at 4.4 g/dl (reference range: 3.5-5.7 g/dl). The beta-human chorionic gonadotropin (hCG) level was 165,000 mIU/ml, consistent with a 10-week gestation. The patient was started on intravenous fluids, analgesics, and ceftriaxone for a concurrent urinary tract infection. Repeat laboratory testing after rehydration revealed persistent hypercalcemia at 11.9 mg/dl with albumin at 3.4 g/dl. Abdominal ultrasound showed hepatic steatosis, a normal gallbladder, and a patent common bile duct, with no evidence of cholelithiasis or choledocholithiasis. Transvaginal ultrasound confirmed a single live intrauterine pregnancy measuring 9 weeks and 4 days. Given the confirmed diagnosis of acute pancreatitis based on symptoms and elevated lipase levels, a computed tomography scan of the abdomen was not done due to the risks of radiation exposure in pregnancy and its limited utility in altering management. Further workup revealed a vitamin D deficiency at 7 ng/ml (reference range: 30-100 ng/ml) and an elevated PTH at 253 pg/ml (reference range: 11.1-79.5 pg/ml). High-resolution sonography of the neck revealed a 2.3×1×1.7 cm hypoechoic nodule inferior to the left thyroid lobe, which was suspicious for parathyroid adenoma. Sestamibi scan was deferred secondary to its contraindication in pregnancy. The patient's symptoms improved with conservative treatment, including intravenous hydration. Due to the recurrent nature of pancreatitis in this patient, it was recommended that patient undergo parathyroidectomy to prevent further complications on the patient and her baby. She was started on vitamin D supplements to improve the levels of vitamin D before surgery to avoid post-surgical hypocalcaemia. Extensive discussion was had with the patient, and she agreed to have surgery in the second trimester. Based on a literature review and endocrinology consultation, it was recommended to undergo surgical intervention after the first trimester to minimize pregnancy complications. The patient was discharged 2 days later with close follow-up with endocrinology to arrange for parathyroidectomy.

DISCUSSION

There are few reports of PHPT induced pancreatitis in pregnancy documented in the medical literature, starting in the mid-20th century[1]. PHPT prevalence has been reported in different studies and published work, but all account for one of the more common endocrine diseases[2,3]. A large portion of patients with PHPT may go undiagnosed as only 20% of patients develop symptoms, making it difficult to account for the incidence and prevalence[4]. Diagnosing PHPT in pregnancy has proven even more difficult as clinical symptoms are non-specific and could be attributed to the physiological changes of pregnancy itself[5]. Symptoms such as lethargy, nausea, fatigue, polyurea and constipation are commonly seen in pregnancy; it is not until patients develop worsening symptoms or complications such as acute pancreatitis that patients are evaluated[4]. Also, even with increased calcium requirements and calcium consumption by a foetus, total calcium levels can be normal in patients with PHPT due to physiologic changes in pregnancy. In our case, the patient developed acute pancreatitis in both of her pregnancies and presented to our hospital in the first trimester of her second pregnancy. Medical records were obtained from the hospital to which she presented during

her first pregnancy, and she was found to have high calcium levels as well as high PTH levels but the patient was lost to follow-up after delivery, so no further workup was done. It can be theorized that many pregnant patients do present with signs of hypercalcemia, but no workup is completed due to the nonspecific symptoms and normal total calcium levels. Augustine et al., the largest systematic review published to date on acute pancreatitis secondary to PHPT, accounted for only 54 cases from the early 20th century until today[1].

The physiology of pregnancy plays a significant role in calcium level regulation. PHPT, primarily secondary to a parathyroid adenoma, may go undetected for many years or never be detected at all. The physiology of pregnancy includes increased calcium requirements and absorption due to the foetal demand for sufficient bone formation[6]. The placenta and foetus release PTH-related protein to increase calcium transport through the placenta, maternal bone resorption, and intestinal absorption of calcium[6]. Other maternal changes include an increase in intravascular volume and hypoalbuminemia. This is important to note, as the total calcium levels are expected to be lower, whereas ionized calcium fraction remains the same[6]. The effect of PTH-related protein also facilitates the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, which should, in fact, lower PTH levels[6,7]. Understanding this mechanism is essential when diagnosing PHPT, as calcium levels may appear normal, but that may be due to the increased calcium consumption by the foetus. This may lead to a missed diagnosis, but because pregnancy leads to lower calcium levels, any high normal or elevated calcium level should be further investigated[7]. Elevated PTH should also be considered, as pregnant and lactating patients should have lower PTH levels. In the patient we present in this case, the PTH and total calcium were significantly elevated. This emphasized the point that her calcium was elevated considerably from what was expected, which in turn could have been the provoking factor of her acute pancreatitis. Of note, a patient with mild hypercalcemia may be asymptomatic, but that can be attributed to the high calcium transport to the foetus. In our review of these cases, there were also documented cases of acute pancreatitis secondary to PHPT in the postpartum period[8,9]. It can be theorized that this could be due to the absence of foetal calcium consumption that was present during pregnancy.

The diagnosis of PHPT is similar in both pregnant patients and non-pregnant patients. The elevated PTH level in hypercalcemia is diagnostic and warrants further evaluation for the underlying cause. In 85% of cases, a single parathyroid adenoma is the culprit, followed by parathyroid hyperplasia and carcinoma[5]. There are no published guidelines for the treatment of PHPT in pregnancy, but the published case reports and literature reviews do agree on parathyroidectomy in the second trimester. In fact, 0.8% of patients who do undergo parathyroidectomy are pregnant[7]. Unfortunately, in patients such as ours, symptoms can begin as early as the first trimester. This leads to the discussion about using calcitonin, cinacalcet, and intravenous bisphosphonates[1]. The incidence of acute pancreatitis in pregnant patients and non-pregnant patients is similar at 1 in 2500 cases[10]. The treatment is also identical and includes intravenous hydration, early enteral feeds when tolerated, and pain control[1,10]. Regardless of this, the ultimate goal is to minimize complications to the pregnant mother and foetus. Thus far, neonatal mortality is 9.3% in the 54 cases reviewed in the abovementioned systematic review[1]. Foetal complications of hypercalcemia include spontaneous abortions, intrauterine growth restrictions, or postpartum hypocalcaemia and subsequent tetany[9]. In regard to the mother, other than pancreatitis, complications such as eclampsia, renal stones, bone disease, or lethal hypercalcemia crisis can develop[9]. We believe that the true incidence of PHPT-induced pancreatitis in pregnancy is under-reported due to a lack of evaluation and clinical awareness. PHPT during pregnancy has only been reported in less than 1% of cases, and pancreatitis from PHPT occurs in 10% of these cases[7,11]. This is indicative of a significant burden.

CONCLUSION

We conclude that PHPT induced pancreatitis in pregnant patients are rarely reported due to low clinical awareness. PHPT alone presents with symptoms very similar to those of pregnancy that make it difficult to differentiate from a more serious diagnosis. The prevalence of PHPT patients who are symptomatic is low leading to unclear true prevalence of the disease. The physiological changes of pregnancy lead to increased overall calcium absorption and consumption, but we theorize that concurrent PHPT leads to increased burden of symptoms and symptom severity. We hope that shedding further light on the subject will lead to more diagnostic evaluation and reveal the true prevalence of PHPT in the hope of minimizing complications such as spontaneous abortions or pancreatitis in pregnancy.

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