CASE REPORT

Calcium maelstrom: recalcitrant hypocalcaemia following rapid correction of thyrotoxicosis, exacerbated by pregnancy

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SUMMARY

A 29-year-old pregnant woman with Graves' disease presented with severe persistent hypocalcaemia after thyroidectomy. Six months prior to presentation she was diagnosed with Graves' disease and remained uncontrolled with methimazole. She was confirmed pregnant prior to radioactive iodine ablation (RAI), and underwent total thyroidectomy during her second trimester. After surgery, continuous intravenous calcium infusion was required until delivery of the fetus allowed discontinuation at postoperative day 18, despite oral calcium and calcitriol administration. A total of 38 g of oral and 7.5 g of intravenous elemental calcium was administered. We report an unusual case of recalcitrant hypocalcaemia thought to be due to a combination of postoperative hypoparathyroidism, combined with thyrotoxic osteodystrophy and pregnancy, after surgical correction of Graves' disease. Increased vigilance and early calcium supplementation should be a priority in the management of these patients.

BACKGROUND

The German pathologist, Von Recklinghausen, was one of the first to describe the effects of hyperthyroidism on bone. In 1891, he wrote a case of a young woman with uncontrolled Graves' disease who reported constant pain in her back and limbs.¹ The autopsy was notable for thin bones with striations and fibrosis.¹ The prolonged and severe stimulation of thyroid hormone increases a high bone turnover state described as thyrotoxic osteodystrophy.² The sudden removal of thyroid hormone stimulation such as thyroidectomy on bone can create a state of avid calcium retention or hungry bone syndrome. Pregnancy can induce calcium bone resorption in the mother in order to provide adequate fetal calcium despite maternal serum hypocalcaemia.³ We speculate that the combination of postoperative hypoparathyroidism and thyrotoxic osteodystrophy in pregnancy can induce severe hypocalcaemia, which has rarely been described in the literature.

CASE PRESENTATION

A 29-year-old pregnant woman presented with recalcitrant hypocalcaemia after total thyroidectomy. She had been diagnosed with Graves' disease 6 months prior, after she was discovered to be in atrial fibrillation with rapid ventricular response. Methimazole was initiated, and thyroid-stimulating hormone remained below 0.015 mIU/mL (0.465–

4.68 mIU/mL). Free thyroxine (FT4) ranged between 5.46 and 5.95 ng/mL (0.78–2.19 ng/dL) after 6 months of therapy. Review of laboratories was otherwise unremarkable except for a serum alkaline phosphatase level that was elevated at 218 U/L (38–126 U/L). Radioactive iodine ablation was planned. However, on the day of the procedure, human chorionic gonadotropin was found to be positive. Methimazole was changed to high-dose propylthiouracil without correction of overt clinical and biochemical thyrotoxicosis despite titrating to maximum dose. The decision was made to proceed with total thyroidectomy in the second trimester of pregnancy.

At 20 weeks gestation, daily super saturated potassium iodide was initiated 10 days before the surgery date. On the day prior to the scheduled thyroidectomy, the patient had leakage of vaginal fluid and was admitted to the labour and delivery floor for premature rupture of membranes. Thyroidectomy occurred as planned. Fifty milligrams of intravenous hydrocortisone was given every 8 h as prophylaxis for adrenal insufficiency. The patient's operative course was uncomplicated; propylthiouracil and hydrocortisone were discontinued after surgery. Pathology results of thyroid reported diffuse thyroid hyperplasia without evidence of parathyroid gland tissue.

The day after surgery, serum corrected calcium dropped to 7.3 mg/dL from a preoperative value of 9 mg/dL (ref 8.8–10.2 mg/dL). Ionised calcium was 0.86 mm/L (ref 1.12–1.30), 25 vitamin D levels were at 25 ng/mL (ref 30–100) and intact parathyroid hormone (PTH) was 4.6 pg/mL (ref 15–88 pg/mL). The patient's physical examination was unrevealing without clinical signs of hypocalcaemia. ECG revealed QT prolongation. Her hypocalcaemia was presumed to be due to postoperative hypoparathyroidism, and she was placed on 1 g elemental calcium and 400 IU of cholecalciferol four times per day. After 2 days of persistently low calcium levels, calcitriol was initiated along with a continuous intravenous calcium gluconate infusion containing 81 mg of elemental calcium/100 mL. Ionised calcium levels fluctuated between 0.86 and 1.15 mm/L. After a prolonged calcium infusion requirement, 24 h urine calcium was checked (postoperatively day 7), which was low normal at 117 mg/24 h (ref 100–300 mg/24 h). Concomitant hypomagnesaemia to 1.0 mg/dL was replete to normal levels without significant improvement in hypocalcaemia. Repeat PTH levels returned at 20.4 pg/mL.

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At 23 weeks gestation, 15 days postoperatively from her thyroidectomy, the patient developed prolapsed cord with discovery of chronic placental abruption requiring emergency caesarean section. Three days postdelivery, the patient's calcium stabilised and intravenous infusion was discontinued (18 days postoperatively from her thyroidectomy). She was discharged on calcium/cholecalciferol 4 g/1600 IU divided four times per day, calcitriol 2.25 µg daily and sevelamer hydrochloride 4.8 g divided three times per day. Over the 17-day period from thyroidectomy to calcium level normalisation, the patient received a total of 7.5 g of intravenous elemental calcium and 38 g of oral elemental calcium. PTH levels were rising prior to discharge at 30 pg/mL and 25 vitamin D levels increased to 27 ng/mL.

The patient's calcium remained stable after discharge and at follow-up. Over the course of the year the patient had intermittent drops in her calcium below 8 mg/L when she was non-compliant with her calcium supplementation. But ultimately she was weaned off calcium and calcitriol supplementation after a year without recurrence of hypocalcaemia.

DISCUSSION

Thyrotoxic osteodystrophy was described by Michie *et al* in patients who had evidence of osteoporosis, osteitis fibrosa, or osteomalacia in the setting of thyrotoxicosis. Thyrotoxic osteodystrophy is secondary to increased osteoclastic resorption and excessive osteoblastic remineralisation. Elevated alkaline phosphatase, as seen in our patient, can be suggestive of increased bone turnover. In vitro rat-based studies found that T4 and triiodothyronine (T3) increase osteoclastic activity leading to bone resorption.^{4 5} Histological examination of bone in active thyrotoxic patients revealed increased osteoclast and osteoblast activity resembling osteitis fibrosa in hyperparathyroidism.² Patients typically had simultaneous loss of calcium through stool and urine with continued demineralisation of bone and maintenance of near normal calcium levels.³ See and Soo⁶ reported a series of 146 thyrotoxic patients post-thyroidectomy, where 46% of cases developed hypocalcaemia. The high incidence of hypocalcaemia after thyroidectomy suggests that rapid loss of T3 and T4 compounded by temporary loss of PTH stimulation can potentially induce a 'hungry bone syndrome', which predisposes bone to avid calcium reabsorption and remineralisation. Thus calcium loss through urine was not demonstrated in our patient.

Though data are limited on pregnant patients, animal studies have demonstrated transport of calcium to the fetus independent of maternal serum calcium levels or hormone deficiencies. Placental perfusion studies on pregnant sheep found that the rate at which fetal and placental calcium transfer occurred was unchanged after iatrogenic hypocalcaemia from maternal parathyroidectomy.⁷ In fetal rat studies, the rate of placental calcium transfer was upregulated despite parathyroidectomy-induced chronic maternal hypocalcaemia.⁸ Fetal calcium absorption remained persistent and maternal rats died in tetany during delivery due to severe hypocalcaemia.⁸ Experiments also revealed that fetuses of parathyroidectomised maternal rats actively absorb calcium with maternal intravenous calcium infusion.⁵ We postulate that pregnant human subjects may have similar physiological mechanisms where the fetus independently depletes calcium stores despite hypocalcaemia in the maternal patient. This would explain why this patient was unable to be weaned off the calcium infusion until after delivery of her baby.

While the fetus may have been a contributor to the patient's hypocalcaemia, we do not believe that fetal absorption of calcium was the primary cause of maternal hypocalcaemia. Research of ashen aborted fetuses revealed the total amount of calcium in a term fetus was approximately 21 g.² This level is significantly lower than the amount of calcium supplementation required in our case and does not support pregnancy as the primary driver of our patient's hypocalcaemia. The aetiology of our patient's recalcitrant hypocalcaemia was likely multifactorial. We speculate that a calcium debt was likely created from a prolonged thyrotoxic state even before surgery. Postoperative hungry bone syndrome resulting from sudden elimination of the thyrotoxic state was made worse by postoperative hypoparathyroidism, and further increased by perinatal calcium requirements. We theorise that delivery of the fetus may have eliminated a significant calcium requirement in the mother, which finally allowed rapid restoration of bone calcium to allow homeostasis on her oral regimen.

Maintaining normal calcium levels in pregnancy should be a priority in pregnant patients post-thyroidectomy. In addition to the known risks of hypocalcaemia, such as tetany, laryngospasms and cardiac arrhythmias, there are serious fetal risks. Hypocalcaemia can induce reactive hyperparathyroidism that may progress to intracranial bleeding and neonatal rickets.⁸ Undercorrection of calcium and vitamin D is thought to cause uterine irritability and increase the risk of preterm labour.⁹

We recommend a high index of concern for thyrotoxic pregnant patients undergoing rapid preparation with oral iodine for total thyroidectomy. Preoperative optimisation of vitamin D and calcium levels while undergoing oral iodine treatment should be considered. Perioperative monitoring of calcium levels is the standard of care, but a low threshold should be kept for initiating intravenous calcium infusion, particularly when there is evidence of postoperative hypoparathyroidism, as calcium debt due to thyroid osteodystrophy may be higher than expected.

Learning points

- ▶ Hungry bone syndrome is a recognised but rare complication after thyroidectomy in patients with long-standing thyrotoxicosis.
- ▶ Increased vigilance should be maintained for severe hypocalcaemia in thyrotoxic pregnant patients who undergo total thyroidectomy.
- ▶ Diagnosis and early intervention with intravenous calcium for hypocalcaemia is important in pregnancy due to the risk for preterm birth.

Competing interests None declared.

Patient consent Obtained.

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