Primary hyperparathyroidism, presenting with acute kidney injury in the first trimester of pregnancy; a case report

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Abstract
Primary hyperparathyroidism (PHPT) is the leading cause of hypercalcemia. Total serum calcium level >3.5 mmol/L is associated with a high risk of a hypercalcemic crisis, manifesting with nausea, vomiting, dehydration, myalgia's, abdominal pain, acute pancreatitis, acute kidney injury (AKI), cardiac rhythm disorders and disturbances of consciousness. We report here a case of PHPT, manifested with hypercalcemic crisis during pregnancy. A 30-year-old woman in the first trimester of pregnancy admitted complaining on loss of appetite, nausea, vomiting, lower abdomen pain, weakness, and leg pain during the last 10 days. She had a history of two uncomplicated pregnancies, and two episodes of renal colic, her kidney function was normal 2 weeks prior to admission. Work-up showed hypochloremia, hypokalemia, hyponatremia, total serum calcium was 5.34 mmol/L, and serum creatinine 226 µmol/L, and she underwent urgent hemodialysis (HD). Her parathyroid hormone (PTH) was 948 pg/ml, and imaging revealed missed miscarriage 9-10 weeks, soft tissue mass 30x20x33mm near the lower pole of the left lobe of the thyroid gland, small stones in renal calices, and polysegmental pneumonia. She received antibiotics, calcimimetics, and every-day hemodiafiltration (HDF), and underwent vacuum aspiration of uterine cavity and surgical removal of the parathyroidoma. Her PTH shortly returned to the reference level, and serum creatinine dropped to 140 µmol/L after kidney replacement therapy (KRT) secession. Pathology confirmed the diagnosis of parathyroid adenoma. PHPT should be included in the diagnostic algorithm of AKI in pregnancy along with vomiting of pregnant, sepsis, pre-eclampsia and other causes. Successful management of PHPT complications in pregnancy demands multidisciplinary team.

Keywords: Hypercalcemia, Parathyroid adenoma, Kidney damage, Intensive care, Hemodialysis, Missed miscarriage


Case Presentation
A 30-year-old Caucasian woman in the first trimester of pregnancy admitted to the emergency room complaining on loss of appetite, nausea, vomiting, lower abdomen pain, weakness and leg pain, which progressed over the last 10 days. Two weeks prior to admission, she experienced condition manifesting with nausea, uncontrollable vomiting, dehydration, myalgia's, abdominal pain, acute pancreatitis, acute kidney injury (AKI), cardiac rhythm disorders and QT interval shortening, and disturbances of consciousness, including coma (3,4). We report here a case of PHPT, manifested with hypercalcemic crisis during pregnancy.

Introduction
Primary hyperparathyroidism (PHPT) is one of the most common endocrine diseases worldwide, and the third most prevalent endocrine disease in our Region, yielding only diabetes mellitus and thyroid gland diseases (1,2). PHPT can remain quiescent until development of its overt complications. Clinical manifestations of PHPT mostly depend on the severity of hypercalcemia. Hypercalcemia with the total calcium level ≤3.5 mmol/L is usually asymptomatic or pauci-symptomatic with nonspecific complaints on muscle weakness, fatigue, decreased appetite, nausea and polyuria. Total serum calcium level >3.5 mmol/L is associated with a high risk of a hypercalcemic crisis – a life-threatening condition manifesting with nausea, uncontrollable vomiting, dehydration, myalgia's, abdominal pain, acute pancreatitis, acute kidney injury (AKI), cardiac rhythm disorders and QT interval shortening, and disturbances of consciousness, including coma (3,4).
right-side renal colic, her creatinine and urea levels then were within normal range. She received volume repletion, antibiotics and painkillers, and in a few days' kidney stone passed out. Her previous medical history was remarkable for the first episode of renal colic with spontaneous stone passage 5 years ago; and two pregnancies (6 and 8 years ago) which both were uneventful. She declined taking any medications or supplements, and her family history was unremarkable.

At admission, she was slightly confused, her body temperature, and vital signs were normal, and physical examination was unremarkable. Neurology examination found nothing but decreased muscle strength to grade 4.5-4 both in upper and lower extremities.

The absence of abdominal wall defense and peritoneal signs, along with normal WBC count and otherwise normal results of abdomen X-ray and ultrasound allowed excluding surgical abdomen and renal colic; however pelvic ultrasound found missed miscarriage 9-10 weeks and retrochorial hematoma. Work-up showed mild iron deficiency anemia and mild thrombocytopenia with a normal level of lactate dehydrogenase, hypochloremia, hypokalemia, hyponatremia, and increased serum creatinine up to 226 μmol/L and urea up to 16.5 mmol/L; electrocardiogram showed rhythm 62 bites per minute. She was diagnosed with pre-renal AKI, referred to the intensive care unit, and started on normal saline and potassium repletion. However, her condition did not improve, and work-up revealed hypercalcemia with increased serum calcium up to 2.93 mmol/L. Urgent hemodialysis (HD) with calcium-free dialysis solutions was initiated, and total calcium decreased to 3.98 mmol/L. Next day she got vacuum aspiration of uterine cavity and removal of the altered fetal egg, followed by antimicrobial therapy and second HD session, after which total serum calcium decreased to 2.93 mmol/L.

We performed a work-up in search of her hypercalcemia cause. Neck ultrasound revealed a large nodular mass in the left lower parathyroid gland location, and blood test found increase of parathyroid hormone (PTH) up to 948 pg/mL, with vitamin D level as low as 11.0 ng/mL, suggesting PHPT. The whole-body CT confirmed ultrasound findings, and revealed soft tissue well-contoured irregularly shaped mass 30×20×33 mm with heterogeneous density near the lower pole of the left lobe of the thyroid gland. CT did not find neither osteolytic lesions nor intrathoracic lymphatic nodes hyperplasia, however, it showed bilateral poly-segmental pneumonia. In addition, small stones were found in the calices of both kidneys. Panel for lupus, antiphospholipid syndrome and broad spectrum of infections, including tuberculosis, viruses and mycoplasmas was negative, and bone marrow smear was unremarkable.

Daily HD sessions did not allow correcting hypercalcemia, therefore she was started on calcimimetics (cinacalcet 60 mg BID), and got a subcutaneous injection of receptor activator of nuclear factor-xB ligand (RANKL) inhibitor (denosumab 60 mg). Surgical removal of the parathyroid mass was scheduled, but on the 3rd day of the hospital stay patient's condition worsened, SPO2 decreased from 97% to 75%, and she was started on non-invasive respiratory support. Echocardiography demonstrated an increase in the pulmonary artery pressure up to 49 mm Hg.

CT angiopulmonography, however, did not confirm pulmonary embolism, but showed progression of bilateral polysegmental pneumonia with an increase of areas of consolidation with "ground glass opacity" features, and a soft tissue mass 35x24 mm with heterogeneous structure, located pretracheally in the anterior mediastinum below the level of the thyroid gland (Figure 1).

Patient's condition demanded postponing of surgical intervention. Kidney replacement therapy (KRT) was switched to daily veno-venous low-flow prolonged hemodiafiltration (HDF) with unfractionated heparin anticoagulation under coagulation tests control; antimicrobial treatment was enhanced.

Within two days her condition significantly improved, SPO2 returned to 98% on the room air, and repeated CT showed regress of pneumonia. Given the pneumonia regression, normalization of vital signs, and lack of efficacy of conservative AKI, referred to the intensive care unit, and started on normal saline and potassium repletion. However, her condition did not improve, and work-up revealed hypercalcemia with increased serum calcium up to 2.93 mmol/L. Urgent hemodialysis (HD) with calcium-free dialysis solutions was initiated, and total calcium decreased to 3.98 mmol/L. Next day she got vacuum aspiration of uterine cavity and removal of the altered fetal egg, followed by antimicrobial therapy and second HD session, after which total serum calcium decreased to 2.93 mmol/L.

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The patient underwent surgery on the 6th day of her hospital stay. Figures 2 and 3 display surgical removal of parathyroid gland, and significantly enlarged parathyroid gland after removal.

Pathology examination confirmed the diagnosis of parathyroid adenoma. PTH level dramatically decreased intraoperative from 971.8 pg/mL to 147.9 pg/mL, with further fast return to the reference level. Patient’s condition improved significantly, HDF procedures were discontinued, and she was referred to nephrology department. Her serum creatinine level after the cessation

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**Implication for health policy/practice/research/medical education**

Primary hyperparathyroidism (PHPT) is a leading cause of hypercalcemia, which can be life threatening if serum total calcium level exceeds 3.5 mmol/L. Hyperparathyroid crisis manifestations include nausea, vomiting, dehydration, myalgia’s, abdominal pain, acute pancreatitis, acute kidney injury (AKI), cardiac rhythm disorders and disturbances of consciousness. PHPT in pregnant women is associated with extremely high risk of complications for the mother and the fetus; successful management of PHPT complications in pregnancy demands multidisciplinary approach.
of the KRT procedures decreased spontaneously to 140 µmol/L.

Subsequent “hungry bone” phenomenon with a fast decrease of serum calcium level demanded immediate initiation of calcium supplementation in combination with alfalcaldol, which allowed avoiding hypocalcemia symptoms, and the patient was discharged on the 27th day of the hospital stay.

Discussion

Primary hyperparathyroidism is the leading cause of hypercalcemia is the general population, however, among hospitalized patients the most common causes of hypercalcemia are lung and kidneys neoplasms and blood malignancies; other causes, like granulomatous disorders, familial hypercalciuria and vitamin D toxicity are much rarer (5). In our patient, extensive work-up ruled out malignancies, granulomatous disorders and vitamin D excess, her family history was unremarkable. Highly elevated PTH and neck soft tissue mass without a history of a late stage of chronic kidney disease suggested PHPT.

Hypercalcemia in pregnant women often remains underestimated due to its nonspecific symptoms. Thus, nausea and vomiting, as initially in our case, traditionally considered as vomiting of pregnant, and AKI, again as in our case at admission - as consequence of hypovolemia and hyponatremia caused by vomiting. At the same time, PHPT is the most common cause of hypercalcemia in pregnant women, and once hypercalcemia detected in pregnant women, a high “index of suspicion” for PHPT is required, since the delayed diagnostics is threatening. PHPT in pregnant women is associated with extremely high risk of complications for the mother and the fetus (67% and 80% respectively). Without treatment this condition in 20%-30% can lead to the pregnancy loss, as in our case, or to the perinatal death of newborns (6,7).

The most common causes of hypercalcemia in patients with AKI are hyperparathyroidism and multiple myeloma - 43.3% and 33.3%, respectively. In our patient, presenting with AKI, which did not resolve after volume repletion, the diagnosis of multiple myeloma was ruled out, and targeted work-up allowed confirming PHPT diagnosis in two days after admission. The main mechanism of AKI, associated with hypercalcemia is the decrease of the glomerular filtration rate due to the vasoconstrictive effect of calcium on the intrarenal vasculature. In addition, calcium deposition in the kidney medulla leads to the tubular and collecting ducts damage, which affects the concentration ability of the kidneys, polyuria and hypovolemia, and also contribute to AKI pathogenesis (8). AKI is usually reversible, and kidney function recovers with normalization of calcium level, as it happened in our case.

Acute kidney injury and other target organs, including heart, central nervous system, gastrointestinal tract damage due to calcium toxicity is commonly observed when total calcium level exceeds 3.75 mmol/L, and more often is described in multiple myeloma or parathyroid carcinoma cases (9,10). However, the maximum level of total calcium up to 6.0-6.9 mmol/L was observed in patients with PHPT and AKI (11,12). In the recently reported case of PHPT in a pregnant woman, who developed a hypercalcemic crisis with AKI and acute pancreatitis at the 23rd week
of gestation, PTH level was 2500 pg/mL, total calcium level was 3.9 mmol/L, and serum creatinine level was 199 µmol/L (7). As in our case, HD treatment was required to correct hypercalcemia.

Another common manifestation of PHPT is nephrolithiasis, detected in ~20% of patients with PHPT; and vice versa in ~5% of patients with nephrolithiasis, its cause is hyperparathyroidism (13). In our patient, the first episode of renal colic with stone passage occurred 5 years prior current admission, suggesting that PHPT existed for a long time and gradually progressed asymptotically. We speculate that pregnancy triggered parathyroid adenoma progression with hypercalcemic crisis.

In our case, very high level of calcium is a remarkable point. There is evidence of the possibility of a long-term benign course of asymptomatic PHPT in most patients. However, in some patients, the disease progresses over time with the development of specific symptoms (14). In addition, we observed an extremely high level of PTH, which is more specific for malignant parathyroid tumor (10,15). However, the final pathology diagnosis in our case confirmed benign parathyroid adenoma.

The case is also noteworthy due to the low efficacy of calcimimetics, and the rapid increase in calcium levels by 0.4-0.8 mmol/L in the intradialytic intervals, and daily KRT procedures remained the only way to correct hypercalcemia before surgery, postponed for 3 days due to severe pneumonia.

Conclusion
In conclusion, the early diagnosis of PHPT is difficult, first, because of the low awareness of physicians regarding this disease and the non-specific clinical features. The “high index of suspicion” towards PHPT in hospitalized patients with hypercalcemia is the only way to diagnose this condition timely and avoid complications. PHPT should be included in the diagnostic algorithm of AKI in pregnancy along with vomiting of pregnant, sepsis, pre-eclampsia and other causes. Successful management of PHPT complications in pregnancy demands multidisciplinary team, including endocrinologists, nephrologists, gynecologists, intensivists and surgeons.

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Author's contribution

Ethical issues
Informed consent was obtained from the individual participant included in the study. Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Conflicts of interest
The authors declare that they have no competing interests.

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