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Case Report

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Hydatidiform Mole With Coexisting Fetus and Syndrome of Inappropriate Antidiuretic Hormone Secretion: A Case Report

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Abbreviations: ADH, antidiuretic hormone; CHMCF, complete hydatidiform mole with a coexisting fetus; hCG, human chorionic gonadotropin; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

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Abstract

Context: Molar pregnancies have been associated with hyperthyroidism and hypertensive disorders. Coexisting molar and fetal pregnancies, which are very rare, have an even higher risk of complications.

Case Description: We describe a case of hyponatremia due to syndrome of inappropriate antidiuretic hormone secretion (SIADH) associated with a molar pregnancy. A 36-year-old patient at 13 weeks gestation with a coexisting molar pregnancy presented with headache, nausea, and vomiting. She was found to have hypertension, hyperthyroidism, and hyponatremia. The hyponatremia was further assessed with an isotonic saline challenge which resulted in a diagnosis of SIADH. The patient underwent dilation and curettage and her hyponatremia resolved. She later developed gestational trophoblastic neoplasia.

Conclusions: A molar pregnancy can present with unusual associated conditions, such as SIADH. Hyponatremia in a patient with molar pregnancy may be mistakenly attributed to other side effects of trophoblastic tissue (hyperthyroidism, pre-eclampsia, or hyperemesis gravidarum). Hyponatremia in a patient with a molar pregnancy warrants evaluation for SIADH.

Key Words: mole, pregnancy, SIADH, hyponatremia

Complete hydatidiform mole with a coexisting fetus (CHMCF) is extremely rare, with an estimated incidence rate of 1 in 22 000 to 100 000 gestations and only 244 cases reported in the literature over the past 40 years [1]. CHMCF pregnancies have a higher risk of complications compared with normal twin pregnancies and single molar pregnancies. The most commonly reported complications include pre-eclampsia, intrauterine fetal demise, and preterm delivery. The incidence of maternal complications in 1 study was 81%, with hyperthyroidism reported in 23%

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and pre-eclampsia in 14% of cases [1]. Hyponatremia or syndrome of inappropriate antidiuretic hormone secretion (SIADH) associated with CHMCF pregnancies has not been reported. CHMCF pregnancies are often terminated due to these increased risks, with live births occurring in 37% to 50% of reported cases [1, 2]. Cases associated with more favorable outcomes are those with lower human chorionic gonadotropin (hCG) and the absence of pregnancy-induced hypertension, hyperthyroidism, or hyperemesis gravidarum, which are likely related to less molar growth [2].

We report our experience with the management of a molar pregnancy with coexisting single living uterine pregnancy and associated complications, including SIADH. The patient provided written informed consent for publication of this report and accompanying images.

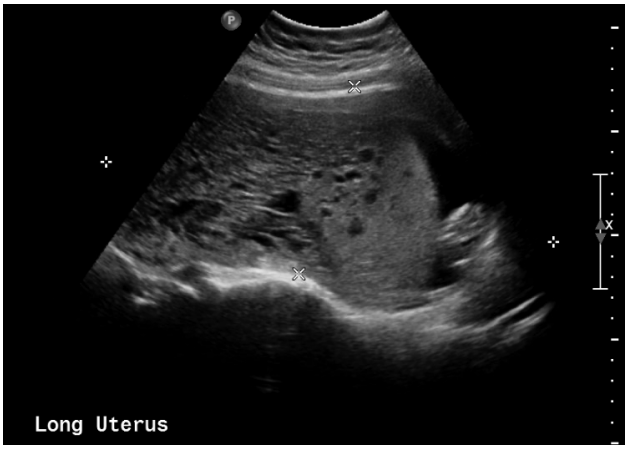

Figure 1. An ultrasound image demonstrating heterogenous appearance of the uterine endometrium within the mid and upper uterine segments. Numerous internal cystic spaces are seen.

Case

A 36-year-old woman, gravida 2 para 0, presented to the emergency department complaining of 6 weeks of headache, nausea, and vomiting, with acute worsening of the headache 1 day before presentation. The patient was 13 weeks pregnant by intrauterine insemination, and her obstetrician recently referred her for a high-risk consultation for coexisting molar pregnancy and expanding bilateral ovarian cysts seen on ultrasound. Her past medical history included an ectopic pregnancy managed with methotrexate 8 months prior, polycystic ovarian syndrome, gastroesophageal reflux disease, hypertriglyceridemia, and morbid obesity (body mass index of 40 kg/m^2). Transabdominal ultrasound confirmed the diagnosis of a molar pregnancy in the upper uterine segment and single living pregnancy measuring 13 weeks 0 days gestational age in the lower uterine segment, seen in Fig. 1. Additionally, her ovaries were enlarged with multiple theca-lutein cysts.

Further evaluation revealed: (1) severe range hypertension (blood pressures 147-178/88-106 mmHg); (2) hyperthyroidism (free thyroxine 3.3 ng/dL, thyrotropin < 0.01 mcU/mL); and (3) hyponatremia (sodium 127 mmol/L). She received 1 dose of hydralazine 10 mg intravenously, followed by daily nifedipine XL 60 mg for her hypertension. Her hyperthyroidism was treated with daily methimazole 10 mg. Her thyroid ultrasound revealed a multinodular goiter, all sub-centimeter except for 1 larger nodule in the right mid-thyroid lobe.

Hypotonic, hyponatremia was noted on the patient's labs on admission with a serum osmolality of 261 mOsm/kg and sodium level of 127 mmol/L. Clinically, the patient was euvolemic without lower extremity edema. Her urine output was normal at 828 mL over 24 hours. Urine osmolality was elevated at 394 mOsm/kg on the second day of admission. Isovolemic hypotonic hyponatremia was noted with an elevated urine osmolality and no signs of hypothyroidism or glucocorticoid deficiency. In conjunction with the finding of hyperthyroidism and hypertension, her clinicians suspected SIADH. Typically in SIADH, urine sodium is > 30 mmol/L, whereas this patient's urine sodium level was < 10 mmol/L [3]. This level of urine sodium is more commonly seen in hyponatremia due to low effective arterial blood volume such as heart failure, dehydration, and third spacing. The labs relevant to the hyponatremia workup are listed in Table 1.

The etiology of the hyponatremia remained unclear on the third day of admission and the patient did not have other symptoms to point to a cause of low effective arterial blood volume. Therefore, the patient underwent an isotonic saline challenge to help differentiate between hypovolemic and euvolemic hyponatremia. This was performed by checking a basic metabolic profile and urine sodium, creatinine, and osmolality before and after 1 L of isotonic saline. In hypovolemic hyponatremia, a rise in serum sodium is expected. In SIADH, isotonic saline may worsen hyponatremia [3]. The patient's lab values changed as follows: serum sodium decreased from 126 to 123 mmol/L, urine sodium rose from 11 to 12 mmol/L, urine creatinine decreased from 114 to 110 mg/dL, and urine osmolality decreased from 370 to 332 mOsm/kg. Because her low serum sodium decreased further and urine osmolality rose with isotonic saline, the patient was diagnosed with SIADH.

The patient received counseling about these findings and complications associated with molar pregnancies. An induced abortion was recommended to prevent maternal morbidity and mortality. Dilation and suction curettage of the pregnancy was planned. The patient received 100 mcg buccal misoprostol the morning of the

Table 1. Serum and urine laboratory values relevant to hyponatremia during the patient's admission

Lab	Day 1	Day 2	Day 3	Day 4	Day 5 surgery date	Day 6	Day 7	Day 8
Serum Na (mmol/L)	127	128 128	126 126	123	124 122 125 125 259 261 259	127 133 137 132 262 275 282 273	136 132 136 280 272 281	136 280
Serum osmolality (mOsmol/kg)	261	264 265	263	257	256 253 259 261			
Urine Na (mmol/L)		<10	11	12	18			
Urine osmolality (mOsm/kg)		394	370	332	331			
Blood pressure range	(143-162) /(79-101)	(139-143)/(82-86)	(150-155)/(85-95)	(136-154)/(79/86)	(136-168)/(84-92)	(144-159)/85-92)	(144-151)/ (84/92)	(135-144)/ (79-82)
Medications	Nifedipine 60 mg XL, Hydralazine 10 mg IV	Nifedipine 60 mg XL	Nifedipine 60 mg XL	Nifidipine 60 mg XL Atenolol 25 mg	Lisinopril 10 mg Nifidipine 90 mg XL	Lisinopril 10 mg Nifidipine 90 mg XL	Lisinopril 10 mg Nifidipine 0 mg XL	Lisinopril 10 mg Nifidipine 90 mg XL

procedure. Preoperatively, the patient was hypertensive and tachycardic. She received atenolol due to concerns for thyrotoxicosis. The patient's preoperative hemoglobin had decreased to 7.6 g/dL from 9.9 g/dL on admission. The patient underwent dilation and suction curettage and was given 1 unit packed red blood cells intraoperatively. Total blood loss was 1 L. Pathology reported the products of conception with a complete hydatidiform mole.

The patient was admitted to the medical intensive care unit postoperatively to monitor her hyponatremia. She was transferred to a medical-surgical floor 2 days later. Her hemoglobin further decreased to 6.7 g/dL 2 days after surgery, so she received 1 L blood transfusion. The patient's hyponatremia was treated with free water restriction. She did not appear volume overloaded on exam. Her serum sodium reached a nadir of 122 mmol/L on the day of the procedure. Postoperatively, her sodium levels trended upwards and remained stable in the 132-137 mmol/L range until discharge.

The patient remained hypertensive so lisinopril 10 mg was added to the nifedipine 90 mg XL. She was discharged on both medications until a blood pressure check appointment 1 week later. Her total T3 remained elevated at 218 ng/dL postoperatively. Per endocrinology's recommendations, the patient remained on methimazole 10 mg daily until her hCG dropped below 100 000 U/L, and atenolol 10 mg daily to keep her heart rate within normal limits. She was discharged on postoperative day 3.

When the patient initially presented to the emergency department, her hCG was 1 927 240 U/L. The first and second week following the dilation and curettage, the hCG trended downward to a nadir of 39 908 U/L. Three weeks postoperatively, her hCG increased to 54 930 U/L, prompting a referral to gynecologic oncology. At this time, transvaginal ultrasound showed 5 cm thickening of the endometrium and she was diagnosed with Stage 1, World Health Organization score 4 invasive molar pregnancy. She was treated with 6 cycles of dactinomycin. Her hCG level plateaued around 5000 U/L and her therapy transitioned to EMA-CO chemotherapy. She completed 6 cycles of EMA-CO chemotherapy and her hCG levels have since remained at 1 U/L. Her hCG is being checked monthly at the time of writing this case report. The patient's serum sodium levels have remained within normal limits in the several months since the dilation and suction curettage.

Discussion

We present a rare case of hyponatremia with a molar pregnancy. We found no reported cases of SIADH in association with molar pregnancy with a literature search using

PubMed, Embase, and Web of Science in July 2020 using the search terms *hydatidiform mole, SIADH, hyponatremia*.

Pregnancy normally results in a mild decrease in serum osmolality by 10 mOsm/kg and serum sodium by 5 mEq/L [4]. This patient, however, presented with a serum osmolality 19 mOsm/kg below normal range and serum sodium 10 mEq/L below the normal limit. One explanation for this finding could be extreme hypertension causing renal secretion of antidiuretic hormone (ADH). Hypertension and constricted renal afferent vessels may cause the juxtaglomerular cells in the kidney to sense a decrease in blood volume and renal perfusion. In response, prorenin is secreted and the renin-angiotensin-aldosterone system is activated. Angiotensin II stimulates the release of ADH from the posterior pituitary. ADH, in turn, acts on the collecting duct of the kidney to increase water reabsorption, which can result in hyponatremia via a dilutional effect [5].

Hydatidiform moles are associated with hormonal imbalances, including hyperthyroidism, caused by the high levels of hCG which has the same alpha subunit as thyrotropin (thyroid stimulating hormone, TSH). There has been a case report of trophoblastic tissue producing leptin, disrupting caloric homeostasis [6]. Therefore, it is also reasonable that a molar pregnancy could also alter sodium and water homeostasis via increasing ADH levels.

Serum hCG is also known to reduce the osmotic threshold for ADH release. In a study by Davison et al, participants given different doses of intramuscular hCG had proportional decreases in osmotic thresholds for release of ADH. This study also presented a molar pregnancy case in which the thresholds for ADH secretion remained decreased until 6 weeks post-evacuation of the mole, which was the same time hCG levels diminished [7]. An extremely elevated hCG due to a molar pregnancy, as seen in the presented case, could have also resulted in a decreased osmotic threshold leading to inappropriate ADH secretion.

While mild hyponatremia is often asymptomatic, moderate to severe hyponatremia can present with cognitive side effects including confusion, vomiting, seizures, and impaired consciousness [8]. Treating hyponatremia that has been present for 2 or more days has risks, as cells have adapted to their new environment. Raising serum sodium too quickly can result in osmotic demyelination syndrome resulting in neurologic symptoms including coma, locked-in syndrome, and quadriparesis. For this reason, it is recommended that serum sodium is only increased 8-10 mmol/L per day [3]. First-line treatment for chronic hyponatremia is fluid restriction of less than 1 L per day. Fluid restriction is effective in 59% of patients with SIADH, with decreased response seen in patients with urine sodium > 130 mmol/L and urine osmolality > 500 mOsm/kg [9].

There have been case reports of hypovolemia and SIADH in the setting of pre-eclampsia, with the average gestational age at presentation of 33 weeks [10]. Hyponatremia in association with pre-eclampsia has been reported to be associated with a greater risk of obstetric complications including eclampsia, placenta abruption, preterm delivery, and HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count), although these associations have not been reproduced in all studies [10]. It has been postulated that SIADH in these instances is due to both hypovolemia and placental secretion of ADH [11]. There has also been a case report of a patient with polycystic ovarian syndrome undergoing ovulation induction who developed hyponatremia and was found to have acute intermittent porphyria. This case is similar to our patient's history, although our patient was several weeks remote from ovulation induction [12].

This case illustrates SIADH as a possible side effect of molar or CHMCF pregnancies. The SIADH improved after the removal of the molar tissue and fluid restriction. Because patients often have severe symptoms from other side effects of the trophoblastic tissue (hyperthyroidism, pre-eclampsia, or hyperemesis gravidarum), hyponatremia may be mistakenly attributed to other symptoms rather than evaluated for SIADH.

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Additional Information

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