Case Report

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Spontaneous ovarian hyperstimulation syndrome in a nonpregnant female patient: a case report and literature review

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Abstract

Spontaneous ovarian hyperstimulation syndrome (sOHSS) usually occurs in patients with a spontaneous ovulation cycle, especially in those with multiple pregnancies combined with hypothyroidism and polycystic ovary syndrome. sOHSS rarely occurs in women who are not pregnant. A 23-year-old woman with obvious abdominal distension visited our hospital. The patient was not pregnant and had not undergone controlled superovulation. Apart from abdominal distension, the patient denied any symptom of obvious incentives, abdominal pain, abnormal vaginal bleeding, or drainage. Biochemical analysis showed a high carbohydrate antigen-125 level and low total protein and albumin levels. Abdominal ultrasound and computed tomography showed a large amount of ascites and cystic uneven masses with an irregular shape in the area of the ovaries and fallopian tubes. Post-surgical histopathology indicated the diagnosis of sOHSS. Wedge resection of both ovaries was performed. Symptomatic treatment was further performed and the patient recovered well. Our findings indicate that sOHSS can occur in women who are not pregnant. Additionally, besides the follicle-stimulating hormone receptor gene mutation hypothesis, the pathogenesis of sOHSS should be further studied.

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Introduction

Ovarian hyperstimulation syndrome (OHSS) is a type of fatal disease, which is usually caused by iatrogenic overstimulation of the ovaries. OHSS is always accompanied by pleural effusion, ascites, oliguria, blood concentration, electrolyte disorders, and liver and kidney impairment.[1,2] This disease mainly occurs in patients with controlled superovulation that assists in reproduction.[3,4] Spontaneous OHSS (sOHSS) can be found in patients with a spontaneous ovulation cycle, especially in those with multiple pregnancies combined with hypothyroidism and polycystic ovary syndrome.[2,3] Although spontaneous conception with sOHSS is rare, it also affects embryonic development and fetal survival, and even endangers the life of pregnant women. In 1989, researchers first reported a case of sOHSS in a pregnant woman with hypothyroidism and Down's syndrome.[5] However, to the best of our knowledge, sOHSS has not been reported in a nonpregnant patient. In our study, we report a rare case of sOHSS in a nonpregnant female patient. We also summarize the clinical characteristics, diagnosis, differential diagnosis, pathological features, and treatment methods of sOHSS.

Case report

A 23-year-old woman visited our department with abdominal distension for 3 days. The body mass of the patient was 24.22 kg/m^2. Her current medical history included abdominal distension for 3 days, with no obvious incentives, and no abdominal pain, abnormal vaginal bleeding, or drainage. She visited the local hospital and was diagnosed with ascites and a pelvic mass. To obtain an accurate diagnosis and treatment, this patient then visited our department. During the course of the disease, the patient had a poor diet, good sleep, diarrhea with a sense of urgency, and normal urination. She had gained approximately 5 kg in weight in the most recent 2 weeks. With regard to her past medical history, she was normally healthy, with no history of infectious diseases, surgery or trauma, or drug-induced ovulation induction. She also denied any history of smoking or drinking. Her cycle of menstruation was approximately 1 to 6 months and the menstrual period was 5 days with no dysmenorrhea.

A physical examination showed a slightly swollen abdomen, shifting dullness (+), and fluid thrill (+). A specialist examination showed a normal vulva, an unobstructed vagina with soft mucous membranes, a normal size of the cervix with a smooth surface, and an anterior uterus with a full shape and firm texture. We could touch a 5- × 5-cm mass in the pelvic cavity with poor movement and tenderness.

Biochemical analysis showed the following: total protein level, 52.6 g/L (normal, 65–85 g/L); albumin level, 31.4 g/L (normal, 40–55 g/L); and carbohydrate antigen-125 (CA-125) level, 165.50 U/mL (normal, 0–35 U/mL). Levels of human chorionic gonadotropin (HCG), follicle-stimulating hormone (FSH), luteinizing hormone (LH), progesterone, estradiol, prolactin, and testosterone were normal.

A thyroid function test also showed no abnormal biochemical levels. Vaginal color Doppler ultrasound showed an anterior uterus, which was floating, and the uterine body size was 5.8×4.7 cm with a normal shape, smooth capsule, and uniform echo of the muscle wall. The uterine cavity line was not clear and endometrial thickness was 1.2 cm. There was a 9.5- $\times$ 6.6-cm cystic uneven mass in the right appendix area and an 8.7- $\times$ 8.0-cm cystic uneven mass in the left appendix area (Figure 1). Furthermore, we found free liquid in the pelvic cavity, which was 8.4 cm in depth. Abdominal computed tomography showed a large amount of ascites (Figure 2a) and irregular abnormal density shadows above the uterus in the pelvic cavity (Figure 2b). The largest slice size was 11.5×5.7 cm with uneven internal density. The patient underwent ultrasound-guided peritoneal puncture and drainage was performed to extract pale red liquid. Further cytology of ascites showed no cancer cells. The total volume of extracted ascitic fluid was 2200 mL after 4 days of drainage. The patient felt that the abdominal distension was slightly relieved at this time.

The patient was diagnosed with a pelvic mass, and peritoneal and pelvic fluid. Our clinical team considered that the pelvic mass might have derived from the following. (1) Ovarian cancer in which CA-125 levels can be increased was a possible cause. (2) An ovarian benign tumor was another possibility because the vaginal color Doppler ultrasound examination could not exclude this possibility. (3) A pelvic inflammatory mass might have been involved because this mass can be a cystic solid or solid mass, and is often accompanied by elevated blood CA-125 levels. (4) Metastatic ovarian cancer might have caused the pelvic mass because primary digestive breast tumors can metastasize to the ovaries. Metastatic tumors can be bilateral solid or cystic solid mass. (5) Uterine sarcoma always occurs in perimenopause with irregular vaginal bleeding. Additionally, peritoneal and pelvic fluid

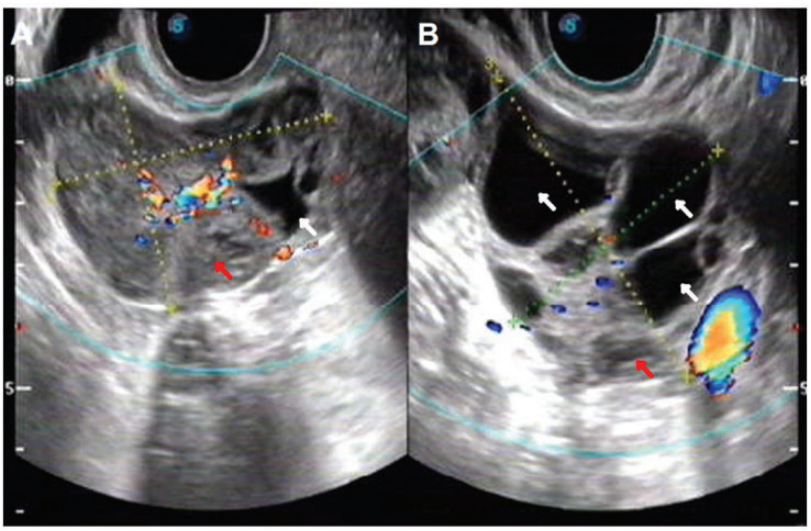

Figure 1. Vaginal color Doppler ultrasound examination. (a) A 9.5- $\times$ 6.6-cm cystic uneven mass (red arrow) in the right appendix area. The white arrow indicates the cystic cavity. (b) An 8.7- $\times$ 8.0-cm cystic uneven mass (red arrow) in the left appendix area. The white arrows indicate cystic cavities.

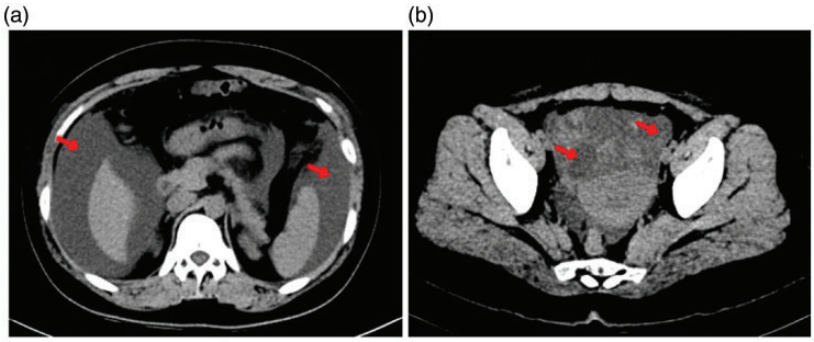

Figure 2. Abdominal computed tomographic examination. (a) A large amount of ascites can be seen (red arrows). (b) Irregular abnormal density shadows (red arrows) above the uterus in the pelvic cavity can be seen.

are not common. Therefore, the patient was unlikely to be diagnosed with uterine sarcoma. (6) sOHSS mostly occurs in patients with controlled hyperovulation, which assists in reproduction. Furthermore, sOHSS is found in a spontaneous ovulation cycle, especially with multiple pregnancies and hypothyroidism. However, the patient did not receive controlled hyperovulation and was not pregnant. Therefore, our clinical team considered that the pelvic mass was likely to be an ovarian tumor and surgery should be performed within a limited period. During the operation, a rapid pathological examination was necessary, and the scope of the operation was determined according to the pathological results.

During the operation, approximately 50 mL of bloody ascites was found in the abdominal cavity. The uterus was in the anterior location and both ovaries were enlarged with polycystic changes. Several hemorrhagic and necrotic lesions were found in the cysts in both ovaries, and the diameter of the cyst cavity was approximately 1.0 to 2.0 cm. Both fallopian tubes were normal. During surgery, this patient was diagnosed with bilateral ovarian cysts, and wedge resection of the ovarian cysts was performed for rapid pathology to exclude malignant ovarian tumors. The scope of resection of the ovaries was reduced as much as possible to prevent extensive bleeding. Rapid pathological results showed a luteal hemorrhagic cyst with cystic follicles and the surgery was finished. A cross-section of both resected masses showed that they were cystic with dark red fluid. Post-surgery pathology was the same as that with the rapid pathological examination. A histopathological analysis showed a luteal hemorrhagic cyst and enlarged cystic follicles (Figure 3). On the basis of the pre-surgical examinations and post-surgical pathology, the patient was diagnosed with sOHSS. The patient recovered well and was discharged from our department on the 4th day post-surgery.

Discussion

sOHSS is an extremely rare disease that usually occurs in the 8th to 12th weeks of pregnancy.[6,7] Unlike sOHSS, recruitment and enlargement of follicles occur during administration of exogenous FSH for OHSS. As a result, iatrogenic OHSS usually occurs at 3 to 5 weeks of pregnancy.[8] The risk factors for sOHSS include a young age, low body mass, polycystic ovary syndrome, a rapid rise in serum estradiol levels, hypothyroidism, and a previous history of

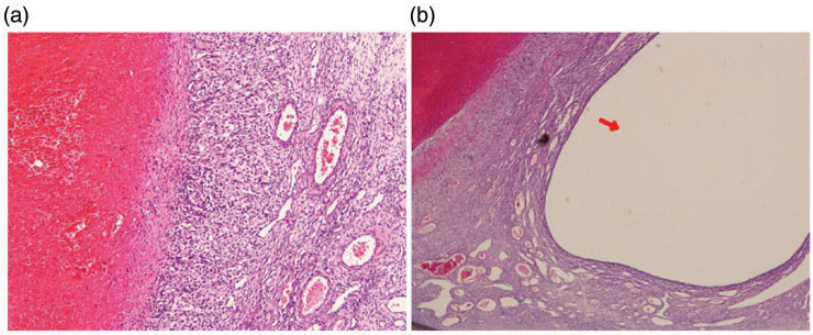

Figure 3. Post-surgery pathology. (a) A luteal hemorrhagic cyst (magnification, ×40). (b) Enlarged cystic follicles (red arrow; magnification, ×100).

sOHSS.[6,7,9] In our study, the patient was a young woman who was not pregnant and had normal thyroid function. Additionally, she denied any controlled hyperovulation treatment. Our case is rare and our findings indicate that sOHSS can occur in nonpregnant patients with normal thyroid function.

The pathogenesis of sOHSS is not fully understood, but it may be due to abnormal sensitivity of HCG to a mutant FSH receptor (FSHR) or excessive secretion of glycoprotein hormones with the same subunit.[10] Because of increased HCG levels in patients with sOHSS, FSH receptor mutations are triggered, thereby increasing the cascade of corresponding downstream hormones.[11] Recent studies have shown that all FSHR gene activation mutations are related to sOHSS.[12,13] These mutations cause loss of specific ligand binding and an increased response to HCG, thus leading to sOHSS.[14,15] Some researchers also consider that sOHSS may be a familial clustering disease. The renin–angiotensin system in the ovary plays a main role in the pathogenesis of sOHSS.[16,17] Our patient was not pregnant with normal levels of HCG, FSH, LH, progesterone, estradiol, prolactin, and testosterone. Our patient also denied any familial history of sOHSS. Therefore, another pathogenesis that is associated with sOHSS may have been present and needs to be further studied.

The main pathological changes of sOHSS are as follows. Multiple ovarian follicles and corpus luteal cysts with interstitial edema can cause ovarian enlargement.[18] Additionally, there is increased capillary permeability and movement of body fluids to the extravascular space, which causes pleural fluid, ascites, pericardial effusion, and even systemic edema.[19] These can lead to low blood volume and increased blood concentration, which can easily result in intravascular thrombosis, and low blood volume shock. Furthermore, low blood volume can easily lead to insufficient renal perfusion, followed by oliguria, hyperkalemia, hypernatremia, azotemia, and acidosis.[20] Sometimes sOHSS can cause acute respiratory distress syndrome. Our patient had multiple ovarian follicles and corpus luteal cysts. A large amount of peritoneal and pelvic fluid was also found, which may have been caused by increased capillary permeability and movement of body fluids to the extravascular space. This patient did not have any symptoms of insufficient renal perfusion or obvious respiratory disorders.

The clinical symptoms of sOHSS are mainly abdominal pain, distension, nausea, vomiting, pleural effusion, ascites,

and systemic edema. Blood biochemical tests can show blood concentration, an increased red blood cell volume, decreased albumin levels, serum ion disorders, and increased levels of serum sex hormones (e.g., hCG, FSH, LH) and CA-125.[7] Besides these symptoms and biochemical changes, controlled hyperovulation should be excluded for the diagnosis of sOHSS. Additionally, a Doppler ultrasound examination is important for diagnosing sOHSS. The size of both ovaries is usually normal before pregnancy or during the conception cycle, and the ovaries are polycystic after natural conception.[21,22] Our patient mainly complained about abdominal distension. We also found peritoneal and pelvic ascites, decreased albumin levels, and increased CA-125 levels. Doppler ultrasound only showed cystic uneven masses in the ovaries and fallopian tubes. Therefore, we could not initially exclude the diagnosis of an ovarian tumor and sOHSS was not initially considered for our case.

For treatment of sOHSS, symptomatic treatment, including correction of a low circulating blood volume, acid–base disorders, and electrolyte imbalance, application of diuretics, thoracocentesis and puncture for ascites, prevention of thrombosis, and thrombolytic therapy, should be performed. For patients who are unsuitable for symptomatic treatment, especially for those with an ovarian cyst with a twisted pedicle or a ruptured ovary, surgery should be performed. The scope of resection of the ovary should be reduced as much as possible. If there is no ischemic necrosis of the ovary, the ovary can be preserved. In our patient, excessive ascites and abnormally enlarged ovaries occurred in a short time. To exclude tumors, laparotomy and wedge resection of the ovary were performed to confirm the pathology. All of the patient's the clinical values rapidly returned to normal post-surgery. After symptomatic treatment, the patient recovered well. However, wedge resection is not an adequate recommended treatment for sOHSS. Even though rapid pathology, which is based on wedge resection of the ovary, is important to exclude malignancy, wedge resection may change stage 1 malignancy to stage 3 or stage 1C malignancy.

Conclusion

We report a rare case of sOHSS in a patient who was not pregnant with normal thyroid function. The patient had normal HCG, FSH, and LH values, which is in contrast to traditionally reported sOHSS cases.[1,2] Our findings indicate that sOHSS can also occur in women who are not pregnant. In addition to the possibility of FSHR genetic mutation, the pathogenesis of sOHSS should be further studied.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Ethics statement

This study was approved by the Ethics Committee and Institutional Review Board of the First Hospital of Jilin University, Changchun, China. The patient provided informed consent for publication of the case.

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