CASE REPORT

Spontaneous bacterial peritonitis complicating ovarian hyperstimulation syndrome-related ascites

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INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is a life-threatening iatrogenic complication of *in vitro* fertilization (IVF).[1] One of the characteristic features of OHSS is increased vascular permeability due to the overproduction of vasoactive mediators from hyperstimulated and enlarged ovaries. Such altered permeability leads to fluid shifts from intravascular to interstitial or third-space compartments.[2-4] Clinical manifestations, therefore, include hemoconcentration, hypovolemia, decreased renal perfusion, hypotension, electrolyte imbalance, and in severe forms (0.5%–5% of cases), tense ascites.[5,6] In addition, lower-than-normal levels of plasma immunoglobulin have been detected in patients with severe OHSS,[7] which may predispose patients to serious infections.[8] In this report, we describe a woman with OHSS without previous liver disease who developed a previously unreported infectious complication: spontaneous bacterial peritonitis (SBP).

CASE DESCRIPTION

A 36-year-old woman was admitted to Hospital das Clínicas, University of São Paulo, Brazil during her pregnancy five weeks after IVF was performed at another health service. She was previously healthy but had attempted IVF three times without success. The previous IVF procedure had been complicated with mild OHSS that did not require hospitalization or treatment. The protocols for ovarian stimulation and ovulation induction were unknown. The patient had also noticed abdominal enlargement at the time of oocyte retrieval (25 oocytes collected). Five days later, two embryos were transferred, and human albumin was administered intravenously.

Three weeks after embryo transfer, she was admitted to our service due to abdominal discomfort, hyperemesis, low urine output, and weight gain (7 kg in the previous seven days). The patient's core temperature and blood pressure were normal. Her abdomen was distended, and ascites was detectable during physical examination. Although her breathing and oxygen saturation in room air were normal, small bilateral pleural effusions were observed on the thoracic radiographs.

Transabdominal ultrasonographic examination at admission revealed a viable intrauterine twin pregnancy with bilateral multiloculated cystic ovaries (right ovary 5.8×4.4×4.8 cm, estimated volume 64 cm^3; left ovary 5.9×4.5×5.3 cm, estimated volume 86 cm^3) and ascites. Laboratory values were as follows: hemoglobin, 15 g/dL; hematocrit, 42.7%; leukocyte count, 18,540/mm^3; platelet count, 450,000/μL; serum sodium, 133 mmol/L; potassium, 4.7 mmol/L; creatinine, 0.6 mg/dL; and albumin, 3.5 g/dL. The levels of hepatic transaminases were slightly elevated (AST 45 IU/L, ALT 27 IU/L), but the bilirubin levels were normal. The results of a hormonal assay for thyroid function were normal. The serum E_2 level was 6,204 pg/mL, and the human chorionic gonadotropin level was 14,765 mIU/mL. Serology results for viral hepatitis were negative.

OHSS was suspected, and supportive care in the intensive care unit (ICU) was initiated. Intravenous crystalloid hydration and 20% albumin (150 mL/day) was started. Heparin (5,000 IU three times a day) was administered for thromboembolic prophylaxis. The patient responded well and maintained adequate urine output. The hemoconcentration resolved, and the patient was discharged to an obstetric ward.

After one week, the patient developed fever, shivering, and renal failure (creatinine 1.68 mg/dL). C-reactive protein increased from 42.7 to 116 mg/L. Because of the respiratory compromise, transvaginal paracentesis was performed during which 4 L of ascites was aspirated. Fluid analysis revealed 520 cells/mm^3 with 400 polymorphonuclear (PMN) cells/mm^3 and a total protein concentration of 5.0 g/dL. *Escherichia coli* was recovered from the ascitic fluid culture. Ceftriaxone was initiated, guided by a culture antibiogram. Human albumin was administered at 1.5 g/kg on the first day and at 1.0 g/kg on the third day of antibiotic treatment. The patient's general condition and renal function improved. No other source of infection was discovered. After 48 h of treatment, another transvaginal paracentesis was necessary to alleviate discomfort from tense ascites. Fluid analysis demonstrated improvement of the cell count (from 520/mm^3 to 280/mm^3). Ceftriaxone was discontinued after eight days of treatment.

The patient remained in the hospital for another month because of two further episodes of bacteremia documented by blood cultures (one episode with *Escherichia coli* ESBL and the other with *Acinetobacter baumannii*). Both episodes were successfully treated with antibiotics (*E. coli* treated

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with piperacillin/tazobactam and *A. baumannii* with meropenem) and by transvaginal paracentesis (5 L of ascites aspirated) with albumin infusion for the alleviation of abdominal hypertension and discomfort. The patient was discharged from the hospital after a total of two months of hospitalization.

At 31 weeks of gestation, the patient was readmitted for assessment of fetal vitality. At 34 weeks of gestation, premature rupture of membranes occurred. Caesarean section was performed without complications. The mother and both babies were discharged in good condition two days after the delivery.

DISCUSSION

Ovarian hyperstimulation syndrome is an iatrogenic complication of the ovarian stimulation commonly used for IVF. The condition is potentially life-threatening; therefore, it represents one of the most serious complications of assisted reproduction treatments.[9] In this case report, we describe SBP as a new infectious complication of OHSS.

Summary of the case report and SBP as a novel infection in OHSS

We presented a patient with serious illness due to OHSS. Some laboratory findings for our patient were characteristic of severe OHSS, including leukocytosis (white blood cell count >15,000), electrolyte imbalances (hyponatremia: sodium <135 mEq/L), and elevated liver enzymes.[1] The evolution of this condition was complicated by the occurrence of SBP due to *E. coli*, which was successfully treated with antibiotics and intravenous human albumin administration.

SBP is characterized by the spontaneous infection of ascitic fluid in the absence of an intraabdominal source of infection.[12] The occurrence of peritonitis associated with OHSS was the subject of a previous case report, but in that case, the infection was due to perforated appendicitis.[13] No previous report of an association between SBP and OHSS was found. Therefore, the occurrence of this infectious complication during OHSS appears to be novel.

The occurrence of SBP in OHSS

The most important aspect of our case report is the evidence of SBP as a cause of sepsis during OHSS. The presence of >250 PMN cells/mm^3 in the ascitic fluid is diagnostic of this condition and mandates immediate treatment.[12] Ascitic fluid cultures are negative in 30-50% of cases and, when positive, usually grow gram-negative enteric bacteria (typically *Escherichia coli* and *Klebsiella pneumoniae*). When ≥250 PMN cells/mm^3 are present in ascites, patients with positive or negative ascitic fluid cultures share common clinical, prognostic, and therapeutic characteristics. A delay in antibiotic treatment could result in a significant and potentially fatal deterioration in clinical status.[14] Such infections are typically associated with advanced cirrhosis, rather than non-cirrhotic ascites.[14] This finding probably reflects the constellation of derangements that occur with cirrhosis, such as increased intestinal permeability with bacterial translocation into the bloodstream, alteration in the systemic immune system, and impaired ascitic fluid defense mechanisms.[14] Specifically, a low protein concentration in the ascitic fluid predisposes patients to SBP.[15-17] The ascitic fluid in OHSS patients typically has a high protein concentration, with elevated levels of albumin and IgG.[7,18] Therefore, elevated opsonic activity is expected, and SBP is likely to be a rare event. Nevertheless, hypogammaglobulinemia occurs in cases of severe OHSS and might predispose patients to severe infections.[7,8] Our patient had 400 PMN cells/mm^3 and a positive culture for *Enterobacteriaceae*, which is diagnostic of SBP, and two additional severe infections, suggesting a predisposition for infections.

Albumin administration has been suggested to be an effective plasma expander in OHSS, and it has also been demonstrated to be beneficial in the treatment of cirrhotic patients with SBP.[1,11,19] Sort et al.[19] established that in addition to antibiotics, albumin reduces mortality and renal impairment if given early at a dose of 1.5 g/kg of body weight at the time of diagnosis followed by 1 g/kg on day 3. The mechanisms of action might be related to the prevention of circulatory dysfunction and to the subsequent activation of vasoconstrictor systems. Because the pathogenesis of OHSS and cirrhosis share some features (low arterial pressure, vasodilation, activation of vasoconstrictor systems),[18,20] albumin administration for the prevention of hemodynamic derangement in patients with OHSS may be beneficial. Clinical trials specifically designed to evaluate this aspect are needed. In our case, we decided to treat the patient as suggested for cirrhotic patients despite the lack of evidence for good recovery when applied to OHSS.

Risk factors and the prevention of OHSS

Recognition of the risk factors for OHSS is a crucial step in the identification of patients with a high-risk profile who would demand careful follow-up after ovulation induction and might benefit from prevention strategies. The described risk factors for OHSS include young age, low body weight, polycystic ovary syndrome, and previous episodes of OHSS.[1,6-8] The large number of retrieved oocytes in this case is also of concern because it may be associated with OHSS.[11] Our patient also reported a previous episode of OHSS, and importantly, described symptoms at the time of embryo transfer. The transfer of two embryos into a patient with this condition, as in this case, is perhaps inadvisable for a high-risk patient already exhibiting OHSS symptoms. The transfer of a single embryo would eliminate the possibility of multiple pregnancies and, perhaps, reduce the incidence of OHSS.[5]

Several strategies have been reported to prevent OHSS, including albumin administration, coasting, dopamine agonists, *in vitro* maturation of oocytes, reduced human chorionic gonadotropin (hCG) dosage, non-steroidal anti-inflammatory administration, GnRH antagonist protocol, and using a GnRH agonist instead of hCG to induce oocyte maturation.[4,5,9] The last two strategies have been reported to achieve good results in preventing OHSS.[4] A recent update of a Cochrane review comparing GnRH antagonists with agonists demonstrated that the OHSS rate in women receiving antagonists is significantly lower than in those treated with the agonist protocols.[21] Although albumin was administered and has previously been used in high-risk women for OHSS prevention,[4,5] most recent evidence does not support this practice.[22]

In conclusion, we describe SBP as a novel life-threatening infectious complication of OHSS. In cases of sepsis with unknown causes, prompt paracentesis to determine the cell count may reveal SBP. The timely administration of

antibiotics is indicated if the diagnosis of SBP is made. Minimizing the risk of OHSS is a key issue, and the importance of the prevention of OHSS cannot be overemphasized.

AUTHOR CONTRIBUTIONS

All authors collected the data and helped to draft the manuscript. All authors read and approved the final manuscript.

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