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Single Case

Spontaneous Bacterial Peritonitis and Anasarca in a Female Patient with Ovarian Hyperstimulation Syndrome Complicated by Respiratory and Kidney Failure

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Keywords

Spontaneous bacterial peritonitis · Ovarian hyperstimulation syndrome · Acute kidney injury

Abstract

Ovarian hyperstimulation syndrome (OHSS) was first described in 1960. It may occur as a complication of gonadotropin hormone therapy during assisted pregnancy or for primary infertility. A 26-year-old female patient with polycystic ovarian syndrome and primary infertility was treated to conceive. She received intravenous gonadotropin-releasing hormone (GnRH) along with follicle-stimulating hormone in an outside private clinic. She presented to the emergency department with abdominal and chest pain, loose stool, vomiting, shortness of breath and decreasing urine output. She was found to have edema, ascites, effusion and acute kidney injury (AKI). Considering the symptoms preceding the drug history and anasarca, a diagnosis of severe OHSS was made. Ascites was further complicated by spontaneous bacterial peritonitis (SBP), which had already been reported before. We speculate that low immunity due to decreased immunoglobulin in patients with OHSS makes them prone to SBP. In our case, septicemia secondary to SBP and fluid loss due to capillary leakage from

OHSS resulted in AKI and respiratory failure. This critically ill patient was treated in a special care unit, and she fully recovered with supportive measures. Severe OHSS may present as anasarca including ascites which can develop SBP leading to sepsis and multiorgan failure.

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Introduction

Ovarian hyperstimulation syndrome (OHSS) is a serious and potentially life-threatening physiological complication observed in women who undergo ovulation induction therapy [1, 2]. The syndrome develops several days after induction therapy with gonadotropin. This leads to ovarian enlargement due to multiple ovarian cysts. There is increased permeability of capillaries to plasma proteins leading to fluid shift from the intravascular to the extravascular compartment, which clinically manifests as ascites, pleural effusion, oliguria, hemoconcentration and electrolyte imbalances [3]. Vasoactive substances such as interleukins, tumor necrosis factor- α , endothelin-1, and VEGF secreted by the ovaries have been implicated in increasing vascular permeability. Age younger than 35 years, low body mass index, gonadotropin treatment, high estradiol concentrations, large number of follicles, a history of polycystic ovarian syndrome, administration of exogenous hCG, and endogenous hCG from treatments resulting in pregnancy increase a patient's risk of developing OHSS.

The severity of symptoms can be mild, moderate or severe. Mild symptoms include abdominal bloating and feeling of fullness, nausea, diarrhea, and slight weight gain. Moderate symptoms include excessive weight gain (weight gain of greater than 2 pounds per day), increased abdominal girth, vomiting, diarrhea, darker urine and less in amount, excessive thirst, and skin and/or hair feeling dry (in addition to mild symptoms). Severe symptoms are fullness/bloating above the waist, shortness of breath, pleural effusion, urination significantly darker or has ceased, calf and chest pains, marked abdominal bloating or distention, and lower abdominal pains (in addition to mild and moderate symptoms). OHSS may present various complications. It results in the accumulation of fluid causing ascites and effusion. It can also be complicated by electrolyte imbalance, acute kidney injury (AKI), thrombosis, twisting of ovaries, rupture of ovarian cyst and intraperitoneal bleeding, respiratory failure, pregnancy loss or rarely death. Death has been reported from cerebral thromboembolism, AKI, acute respiratory distress syndrome (ARDS) and cardiorespiratory arrest [3–6].

In this case report, we describe a woman with OHSS secondary to intravenous therapy with gonadotropin-releasing hormone (GnRH) and follicle-stimulating hormone for primary infertility due to polycystic ovarian syndrome. She received 18 injections of intravenous GnRH agonist for induction of pregnancy along with 11 injections of follicle-stimulating hormone. She developed severe OHSS as evident by ascites, effusion, respiratory failure and AKI. Interestingly, she developed SBP secondary to *Stenotrophomonas maltophilia* leading to septicemia. SBP has rarely been reported in the literature. We think that the cause of infected ascitic fluid could be from infected cyst which could have migrated into the peritoneal cavity in the absence of cyst rupture. There was no evidence of intestinal perforation which could have resulted in secondary peritonitis. The patient's course of the disease was complicated by severe AKI and she needed dialysis. Our patient also developed AKI most likely due to a combination of sepsis and intravascular depletion from capillary leakage. Beside AKI, the patient had respiratory failure needing bimanual positive airway pressure (BIPAP). We are sharing this case with multiple complications and the rare association with SBP and its successful management in a special care unit.

Case Report

A 26-year-old housewife and resident of Karachi, Pakistan with a known history of polycystic ovarian syndrome was admitted to the emergency department with complaints of abdominal and chest pain, loose stool, vomiting, shortness of breath and reduced urine output. She developed abdominal pain 5 days prior to the admission. The pain was generalized, and nonradiating in nature. Her pain scored 8/10 on the pain scale. It was also associated with nausea, vomiting and abdominal distension. She also had had loose watery nonbloody stools with a frequency of 4–5 episodes per day in the previous 4 days. This was accompanied by progressive shortness of breath, reduction in urine output and peripheral edema. Her past medical history included primary infertility from polycystic ovarian syndrome, which had been diagnosed 8 years back. She was started on intravenous GnRH agonist for induction of pregnancy, and she had received 18 intravenous injections in the past 20 days before admission. On top of this, she had also received 11 injections of follicle-stimulating hormone. Keeping in mind the drug history, gastrointestinal symptoms and anasarca, a diagnosis of OHSS was made. At the time of presentation to the emergency department, she was drowsy with a regular pulse of 120 beats/min and had a blood pressure of 70/50 mm Hg. She was afebrile, but was tachypneic with a respiratory rate of 32/min. Her oxygen saturation was 85% on room air. She was pale, with ankle and sacral edema. Cardiovascular examination revealed sinus tachycardia and normal first and second heart sound. Respiratory examination showed bilateral basal rales and decreased air entry at the bases. Her abdomen was tender with evidence of tense ascites. Neurological examination showed a decreased mental state with no evidence of focal neurological deficit. Our patient underwent various laboratory tests shown in [table 1](#) and [table 2](#). In view of the hemodynamic instability, she was managed in a special care unit with intensive monitoring. She required ventilatory support through BIPAP because of increasing respiratory compromise and type I respiratory failure. She was started empirically on intravenous piperacillin/tazobactam (Tazocin) 2.25 g every 6 h because of raised white blood cell counts, C-reactive protein and raised procalcitonin. Her ascites was drained through a pigtail catheter as it was felt that this was impeding her respiratory effort. She was also supported by renal replacement therapy (hemodialysis) primarily for fluid removal in the first dialysis. However, after the first dialysis, she had a persistently low central venous pressure (6–8 mm Hg) and hypotension, and no fluid was removed during the subsequent 3 sessions. After draining of ascites, her tachypnea improved. She was cautiously given boluses of saline along with albumin intermittently to keep the central venous pressure between 10 and 12 mm Hg.

Her ascitic fluid analysis showed glucose of 100 mg/dl, protein 3.8 g/l, and her total leukocyte count was 1,397/ μ l. Her differential leukocyte count was 80% neutrophils and 20% lymphocytes. Her blood and urine cultures were negative but the ascitic culture grew *S. maltophilia* which was sensitive to piperacillin-tazobactam. The patient started producing urine on day 5. Her supportive management was continued. She did not need any further dialysis.

Our patient made a gradual recovery through medical supportive measures and was able to come off dialysis and BIPAP. Her repeat procalcitonin and white blood cell counts showed a decreasing trend. Her care was deescalated to a general ward after 4 days and she was discharged home after 9 days. She was followed in clinic after 1 week. A total of 14-day course of antibiotics was completed. She completely regained her kidney function and her follow-up creatinine was 1.1 mg/dl.

Discussion

OHSS is a rare complication of GnRH agonist treatment used for induction of ovulation in patients undergoing assisted reproductive techniques. Young age (under 35 years), low body mass index, polycystic ovarian syndrome, and atopic syndrome and pregnancy are common risk factors associated with OHSS. The less serious forms of OHSS are observed in between 25 and 30% of cases, while the more serious forms have an incidence of 0.5–5% [3].

Death has also been reported from cerebral thromboembolism, AKI, ARDS and cardiorespiratory arrest [3–6]. The disease has been classified into various stages on the basis of the seriousness of the condition according to the Golan criteria [7] and modifications by Navot et al. [6]. OHSS can be graded according to severity as follows:

- *mild OHSS*: grade 1 (abdominal distention and discomfort), grade 2 (grade 1 disease plus nausea, vomiting and/or diarrhea plus ovarian enlargement from 5 to 12 cm);
- *moderate OHSS*: grade 3 (features of mild OHSS plus ultrasonographic evidence of ascites);
- *severe OHSS*: grade 4 (features of moderate OHSS plus clinical evidence of ascites and/or hydrothorax and breathing difficulties), grade 5 (all of the above plus a change in the blood volume, increased blood viscosity due to hemoglobin concentration, coagulation abnormalities and diminished renal perfusion and function);
- *chronic OHSS*: grade 6 (ascites ± hydrothorax, Hct >55%, white blood cell count $25 \times 10^9/l$, oliguria, creatinine ≥ 1.6 , creatinine clearance < 50 ml/min, renal failure, thromboembolism, ARDS).

OHSS is characterized by increased capillary permeability leading to ascites and effusion [8]. The hyperstimulation causes large amounts of estrogens, progesterones and cytokines to be released. This results in the secretion of vascular endothelial growth factor which causes vascular hyperpermeability, leading to a shift of fluids from the intravascular system to the abdominal and pleural cavity. As fluid accumulates in the third space, a patient may become hypovolemic and is at a risk of circulatory and renal failure. This is consistent with the clinical presentation of our patient.

Our patient suffered from SBP due to *S. maltophilia*. Infections are common in OHSS [1]. However, the occurrence of SBP associated with OHSS is very rare. Our literature reviews revealed only two previous cases of peritonitis from OHSS. There is a case report by Taniguchi et al. [9] of *Escherichia coli* SBP associated with OHSS in a 36-year-old Brazilian woman 5 weeks after in vitro fertilization. There is also a case report of secondary peritonitis by Fujimoto et al. [10] in a case of OHSS as a result perforated appendix. The case implied that OHSS might not only mask typical presentations of appendicitis but may also worsen concurrent intraperitoneal infection. Cirrhotic ascites are low in protein and hence are more prone to SBP [11, 12]. In contrast, ascites in OHSS has a high protein level with elevated albumin and high immunoglobulin G (IgG). So, theoretically, patients having ascites should be less prone to have SBP. However, immunity is somehow low in OHSS as infections other than SBP are common in OHSS [1]. *S. maltophilia* is a hospital-acquired bacterium and can infect patients with reduced immunity. Hypogammaglobulinemia has been reported in severe OHSS [13]. A very high white blood cell count, high C-reactive protein and procalcitonin with a low blood pressure pointed out to severe sepsis. We think that sepsis was potentially due to underlying SBP. The patient also had AKI. We assumed that her kidney injury was a result

of septicemia and intravascular depletion from capillary leakage. Despite edema, effusion and ascites, our patient's central venous pressure was persistently low. This could have been due to leakage of fluid from the vascular compartment through increased capillary permeability leading to decreased kidney perfusion causing AKI. AKI can be a potential complication because of decreased renal circulation [14]. At the same time, sepsis from SBP could also have contributed to decreased effective circulation, thus further exacerbating the situation. There has been a case report of compression of the ureter by enlarged ovaries causing AKI due to in vitro fertilization [15]. However, this does not hold true for our case as there was no ultrasonographic finding of obstruction of the kidneys and ureters.

Early antibiotic treatment is crucial in the management of SBP. Our supportive treatment and management in a high-dependency setup with antibiotics, renal replacement therapy and BIPAP has helped the patient to overcome this potentially life-threatening illness. Intravascular compartment fluid depletion is often seen in OHSS and successful treatment with plasma has been shown. Our case could not tolerate ultrafiltration, and we gave small boluses of saline and albumin to keep the central venous pressure around 10 mm Hg. Our case is unique because SBP is a rarely described complication of OHSS. This infectious complication can be treated effectively with a timely administration of antibiotics and supportive care. AKI can occur as a result of a constellation of multiple factors including septicemia and intravascular depletion. It is important to understand the risks and complications of OHSS to pre-empt corrective and supportive measures [16].

Conclusion

SBP is a rare finding in patients with OHSS and can result in sepsis. The combination of sepsis and capillary leakage in OHSS can result in the damage of various organs including the kidney. In patients with OHSS having unexplained sepsis and ascites, SBP should be looked for.

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Statement of Ethics

Written consent was obtained from the patient for publication of this case report. For this case report, approval by the local ethics committee was not necessary.

Disclosure Statement

The authors declare that they have no competing interest.

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Table 1. Laboratory tests

| Item | Values |
|---------------------------------------|---|
| pH | 7.34 |
| PCO ₂ | 25 mm Hg |
| PO ₂ | 65 mm Hg |
| HCO ₃ | 14 mEq/l |
| Base excess | 9.6 |
| SO ₂ (oxygen saturation) | 97.40% |
| BUN | 21 mg/dl |
| Creatinine | 2.6 mg/dl |
| Sodium | 129 mEq/l |
| Potassium | 4.2 mEq/l |
| Chloride | 100 mEq/l |
| Bicarbonate | 13.3 mEq/l |
| Calcium | 8.0 mg/dl |
| Albumin | 2.3 g/dl |
| Magnesium | 1.2 mg/dl |
| Phosphate | 4.2 mg/dl |
| Total bilirubin | 0.8 mg/dl |
| Direct bilirubin | 0.5 mg/dl |
| Indirect bilirubin | 0.3 mg/dl |
| γ-Glutamyltransferases | 44 unit/l |
| Alanine transaminase | 40 units/l |
| Aspartate aminotransferase | 82 units/l |
| Alkaline phosphatase | 60 units/l |
| CRP | 27.45 mg/dl |
| Procalcitonin | 91.08 µg/ml |
| Lactic acid | 4.5 mEq/l |
| Troponin I | negative |
| Hemoglobin | 13.2 g/dl |
| Hematocrit | 40.8% |
| MCV | 80.2 fl |
| WBC | 72.5 × 10 ⁹ /l |
| Neutrophils | 93% |
| Lymphocytes | 2.1% |
| Platelets | 201 × 10 ⁹ /l |
| Prothrombin time | 14.1 s |
| International normalized ratio | 1.36 |
| Activated partial thromboplastin time | 33.8 s |
| D-dimer | 25.08 mg/ml |
| FLT | 730 |
| Estradiol | 2,086 pg/ml |
| Progesterone | >40.0 pg/ml |
| β-hCG | 25.5 pg/ml |
| TSH | 2.751 mU/l |
| Chest X-ray | bilateral pleural effusion |
| Ultrasound abdomen | moderate ascites with no visceromegaly and enlarged ovaries with multiple large cysts |

Table 2. Ascitic fluid analysis

| Items | Values |
|------------------------|---------------|
| Glucose | 100 mg/dl |
| Protein | 3.8 g/dl |
| White blood cell count | 1,397 μ l |
| Neutrophils | 80% |
| Lymphocytes | 20% |