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OLGU SUNUMU **CASE REPORT**

A Rare and Unique Complication: Pleural Effusion Associated With Ovarian Hyperstimulation Syndrome

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Abstract

Ovarian Hyperstimulation Syndrome (OHSS) is defined as an excessive response and hypersensitivity to the treatment administered to stimulate the ovaries, which can also occur iatrogenically. It can present a wide range of clinical and laboratory findings. As a result of ovarian stimulation, serum fluid can shift from the intravascular compartment to the third space, leading to complications such as ascites and pleural effusion.

This article presents two cases of patients who underwent ovulation induction therapy and were found to have pleural effusion during follow-up, along with a review of the literature. Following an intervention with paracentesis to manage ascites, regression of the pleural effusion and improvement in the patients' clinical condition were observed.

With the increasing use of assisted reproductive techniques, OHSS may be encountered more frequently. Therefore, we aim to discuss OHSS, a rare cause of pleural effusion, through these cases and emphasize the importance of determining appropriate treatment and follow-up strategies at the initial stage.

Keywords: *ascites, ovarian hyperstimulation syndrome, pleural effusion*

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Nadir ve Özel Bir Komplikasyon: Over Hiperstimülasyon Sendromuna Bağlı Plevral Efüzyon

Özet

Ovarian Hiperstimülasyon Sendromu (OHSS); iatrojenik olabildiği gibi overlerin uyarılması için verilen tedaviye karşı aşırı bir yanıt ve hassasiyet olarak tanımlanmaktadır. Çok farklı klinik ve laboratuvar bulgularıyla görülebilmektedir. Overlerin stimülasyonun bir sonucu olarak, serum intravasküler alandan üçüncü boşluğa geçiş yaparak; assit ve plevral efüzyon gibi komplikasyonlara yol açabilir.

Bu yazıda ovulasyon indüksiyonu tedavisi uygulanan ve takiplerinde plevral mayi tespit edilen iki olgu literatür eşliğinde sunuldu. Assite parasentez ile yapılan müdahale sonrasında plevral mayini geriledği, hastanın kliniğinin düzeldiği görülmüştür.

Yardımcı üreme tekniklerinin gün geçtikçe daha yaygın kullanımıyla OHSS daha sık görülebilir. Bu sebeple Plevral efüzyonun nadir nedenlerinden biri olan OHSS'yi olgular eşliğinde tartışmayı, uygun tedavi ve takip stratejilerin ilk aşamada belirlenmesinin önemini hatırlatmak istedik.

Anahtar Kelimeler: *assit, over hiperstimülasyon sendromu, plevral efüzyon*

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INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic complication that occurs in patients undergoing ovulation induction and controlled ovarian hyperstimulation treatment (1). It has been associated with high morbidity and low mortality risk (2). Due to variations in diagnostic and reporting criteria, determining the true incidence remains challenging; however, moderate to severe OHSS has been reported to occur in approximately 1–5% of in vitro fertilization (IVF) cycles (3).

The primary pathophysiological mechanism of OHSS involves exposure to luteinizing hormone (LH) or human chorionic gonadotropin (hCG) following ovarian stimulation (4). Additional risk factors include young age (<30 years), low body mass index (BMI), and polycystic ovary syndrome (PCOS) (5). After hCG exposure, vascular endothelial growth factor (VEGF) is released, leading to increased vascular permeability. As a result, fluid shifts into third spaces, leading to the development of edema, ascites, and pleural effusion. In severe cases, this may progress to acute respiratory distress syndrome (ARDS) (6). Patients who were found to have fluid accumulation in at least two of the pleural, pericardial, and peritoneal cavities were monitored with the diagnosis of polyserositis (7). In this report, we aim to present two cases that were referred to our center after undergoing ovarian hyperstimulation for IVF at an external facility, subsequently developed polyserositis, and were ultimately diagnosed with OHSS, accompanied by a review of the relevant literature.

CASE REPORT

Case 1: A 28-year-old female patient under evaluation for infertility was found to have bilateral polycystic ovarian morphology and a right ovarian endometrioma. Prior to the initiation of IVF treatment, her body weight was 65 kg, height was 168 cm, and her BMI was 23.04. In her first IVF cycle, daily 250 IU recombinant human follicle-stimulating hormone (rFSH; Gonal-F) was administered for controlled ovarian stimulation. Metformin and medroxyprogesterone acetate were also included in the treatment protocol.

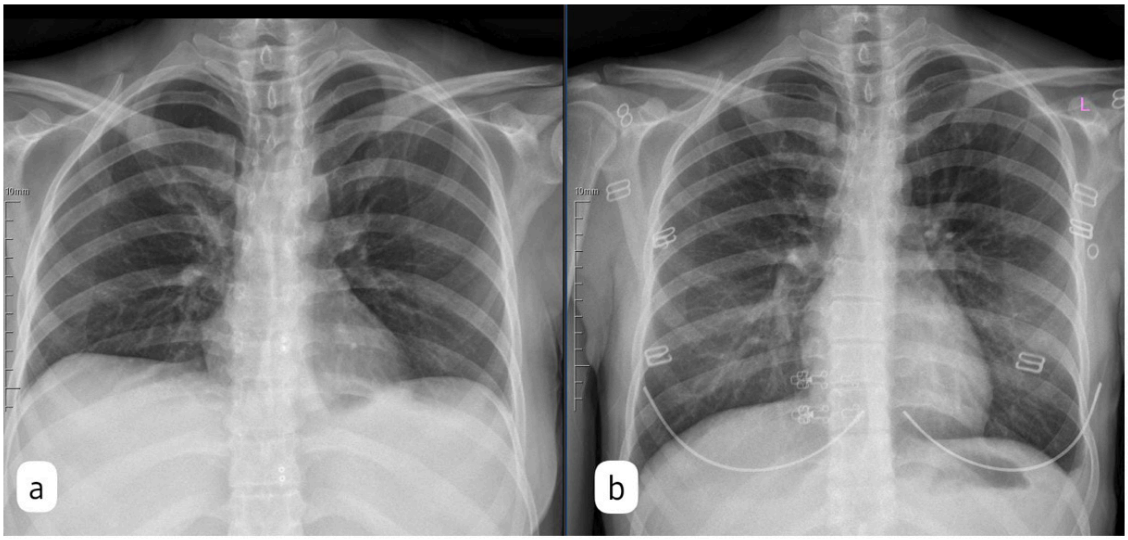
Table 1: Severity levels of ovarian hyperstimulation syndrome (8).

Category	Manifestations
Mild	Mild nausea/vomiting Abdominal bloating Enlarged ovaries Diarrhea No significant biochemical features
Moderate	In addition to mild symptoms, there is also evidence of ascites based on an ultrasound not clinically seen.
Severe	Mild and moderate features are present plus: Clinical evidence of ascites Pleural effusion Oliguria Severe dyspnea Hemoconcentration (Hct >0.45) Serum Cretain >1.5 mg/dL Hyperkalemia (K^+ >5 mEq/L) Elevated liver enzymes Hyponatremia (Na^+ <135mEq/L) Hypoprotinemia (serum albumin <35 g/l)

Critical	Tense ascites Oliguria/ Anuresis Thromboembolism Renal insufficiency Massive hydrothorax Respiratory distress syndrome Haematocrit >0.55 White blood cell (WBC) >25000/microL

Five days after oocyte pickup (OPU), she presented with complaints of weight gain, abdominal bloating, and edema. The retrieved oocytes were cryopreserved, and no fresh embryo transfer was planned. At the time of admission, her serum estradiol (E2) level was 8706 ng/L, and albumin level was 2.9 g/dL. Abdominal ultrasonography (USG) revealed ascites, and a catheter was placed for paracentesis. Approximately 7000 mL of serous fluid was drained over three days with concurrent albumin replacement therapy. Chest radiography performed prior to catheter insertion showed no clear evidence of pleural effusion, although blunting of the costophrenic angle was not observed (Figure 1a). Follow-up was continued with thoracic and abdominal ultrasonography.

Figure 1. Posteroanterior chest radiographs of Case 1 are presented:
a) Five days after the OPU procedure, during which the patient experienced symptoms.
b) On the third day following the paracentesis. USG revealed a lesion measuring 15 mm in the right thorax and 20 mm in the left thorax.



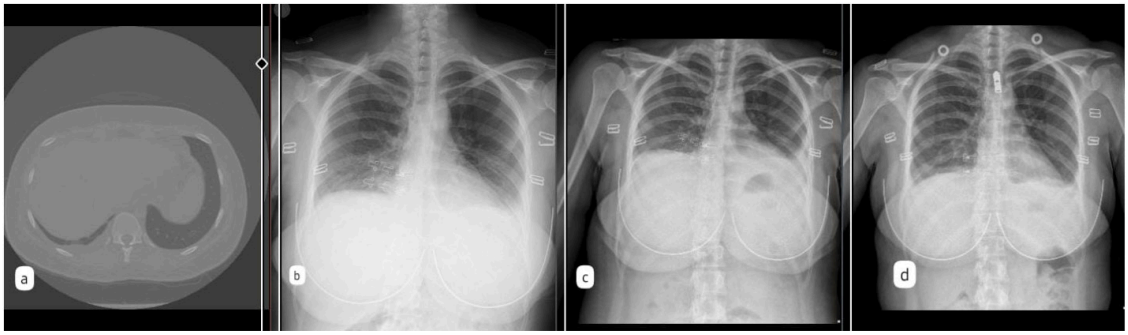
On the second day of paracentesis, thoracic ultrasonography revealed free fluid with a depth of 40 mm in the right hemithorax and 30 mm in the left. On the third day, the fluid depth had decreased to 15 mm on the right and 20 mm on the left. As drainage ceased, the interventional radiology team removed the catheter. The patient was referred to our clinic for evaluation of the pleural effusion following catheter removal.

On physical examination, the patient showed no signs of respiratory distress. The abdomen was edematous and distended. Vital signs were stable (blood pressure: 110/60 mmHg, SpO_2: 92%, pulse: 80 bpm, temperature: 36°C, respiratory rate: 20/min). Clinically, the patient reported significant relief after paracentesis and a decrease in exertional dyspnea. Follow-up chest radiography showed no significant pleural effusion or costophrenic angle blunting (Figure 1b). The pleural fluid detected by thoracic USG did not require intervention. The patient was discharged after regression of the effusion.

Case 2: A 25-year-old female patient with known bilateral polycystic ovarian morphology had a body weight of 68 kg, height of 162 cm, and BMI of 25.9 prior to her first IVF treatment. The treatment protocol included daily administration of 250 IU Gonal-F, metformin, and medroxyprogesterone acetate. Following OPU, all oocytes were cryopreserved, and no fresh embryo transfer was planned.

One day after the OPU procedure, the patient developed nausea and vomiting, but the etiology could not be determined. As her symptoms persisted, she presented again to a healthcare facility five days post-procedure. At that time, her serum estradiol level was recorded as 2809 ng/L and albumin level as 3.47 g/dL. Evaluation revealed the presence of free fluid in the abdomen, and paracentesis was planned. Approximately 3600 mL of serous fluid was drained over two days with concurrent albumin replacement therapy.

Figure 2. Imaging Findings of Case 2:
a) Thoracic section of the abdominal computed tomography scan obtained one day after the OPU procedure, during the symptomatic period. Minimal fluid is observed on the right side, with no fluid detected in the abdomen.
b) Thoracic imaging obtained five days after the OPU procedure, showing sinus blunting on the left side during the symptomatic phase.
c) Chest X-ray on the second day of paracentesis. USG revealed a pleural effusion measuring 40 mm in the right hemithorax and 48 mm in the left hemithorax.
d) Chest X-ray obtained 11 days after the OPU procedure.



On the first day of paracentesis, thoracic ultrasonography performed by the interventional radiology team revealed pleural effusion measuring 52 mm in the right hemithorax and 68 mm in the left. A simultaneous chest radiograph taken prior to paracentesis showed blunting of the left costophrenic angle (Figure 2b). On the second day of paracentesis, thoracic USG demonstrated a decrease in fluid depth to 40 mm on the right and 48 mm on the left. Blunting of the left costophrenic angle was still present on chest radiography performed the same day (Figure 2c).

The patient was referred for consultation regarding pleural effusion. She did not exhibit respiratory distress but reported exertional dyspnea. The abdomen was edematous and distended, and bilateral pretibial edema was present. Vital signs were stable (blood pressure: 120/70 mmHg, SpO_2: 93%, pulse: 87 bpm, temperature: 36.8°C, respiratory rate: 20/min). On review of abdominal CT images obtained at an external facility on the day her symptoms began, minimal isolated right-sided pleural effusion was noted in the thoracic slices, while no intra-abdominal fluid was reported (Figure 2a). No intervention was performed for the pleural effusion. Both the symptoms and radiological findings improved following paracentesis. The patient was discharged 11 days after OPU, with chest radiography showing complete pulmonary re-expansion (Figure 2d).

DISCUSSION

Pharmacologic ovarian stimulation is a commonly used procedure in the treatment of infertility. The most serious and potentially life-threatening complication of this treatment is OHSS (1-3). Clinically, OHSS presents with a

broad spectrum of severity, ranging from mild symptoms to life-threatening conditions. The stages of OHSS are presented in Table 1 (8). The risk of developing OHSS is particularly higher in women with PCOS (9). In both of the presented cases, PCOS was present; in addition, one case also had a coexisting ovarian endometrioma.

In a study evaluating the risk of OHSS development during IVF treatment in women with PCOS, no statistically significant difference was found in BMI between patients who developed OHSS and those who did not. However, the same study reported that all cases of OHSS had a lower BMI compared to those who did not develop OHSS. Additionally, there was no significant difference in BMI between patients who developed mild or moderate OHSS (5). In our cases, the recorded BMIs were 23.04 and 25.9, respectively.

It has been reported that the risk of OHSS is higher in women aged between 24 and 30 years (10). Both of our patients were under the age of 30.

In a study conducted by Sun et al. in 2021, elevated serum E2 levels were shown to increase the incidence of moderate and severe OHSS (5). In both of our cases, serum E2 levels were found to be markedly elevated. High serum E2 concentrations have been demonstrated to induce the overproduction of VEGF and various inflammatory cytokines (11). Increased VEGF levels lead to impaired vascular permeability (6).

One leading hypothesis regarding the pathogenesis of fluid accumulation in OHSS describes the movement of fluid from the peritoneal cavity into the pleural space. This process is believed to be facilitated by the release of vasoactive substances such as VEGF, IL-1, IL-2, and IL-6, which increase capillary permeability (12). In the second case presented, the absence of intra-abdominal fluid on abdominal imaging on the first day of symptoms, accompanied by the early presence of right-sided pleural effusion, suggests that increased capillary permeability may have initially occurred in the pulmonary circulation prior to the translocation of fluid from the peritoneum.

Man et al. suggested that pleural effusion may occur in many cases of OHSS, but is often underreported due to the lack of routine chest imaging or because many cases resolve spontaneously (13). In a Canadian study involving 771 patients, 22 patients (3%) developed severe OHSS, 5 patients (0.65%) had pleural effusion, and only 1 patient (0.12%) required thoracentesis (14). Pleural effusion is observed in approximately 10% of severe OHSS cases and is typically accompanied by significant ascites, while isolated pleural effusion is considered extremely rare (12).

In our cases, no massive pleural effusion was visible on chest radiographs. However, bilateral pleural effusion was identified via ultrasonographic follow-up, and it regressed in both cases following paracentesis. In the second case, pleural effusion was observed prior to the development of ascites, indicating a presentation that began with isolated pleural involvement.

Palomba et al. reported that, despite numerous interventions proposed over the past decade to reduce or prevent the risk of OHSS, most of these strategies have shown limited preventive efficacy and remain controversial or ineffective (15).

With the increasing use of IVF and other assisted reproductive technologies, OHSS can present with varying degrees of severity. As a result, pleural effusion or polyserositis may occur, particularly in younger women, highlighting the need for increased vigilance in this population. Isolated right-sided hydrothorax is a rare, unexpected, and unpredictable manifestation, and may even arise in cases of mild OHSS. It may progress to ascites and bilateral pleural effusions during follow-up. Therefore, timely monitoring and appropriate management are of great importance.

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Patient consent for publication: A written informed consent was obtained from the patient.

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