

A rare presentation of isolated right-sided pleural effusion in the context of ovarian hyperstimulation syndrome: A case report

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ABSTRACT

An isolated pleural effusion as the sole manifestation of early ovarian hyperstimulation syndrome (OHSS) is rare. A 38-year-old woman who had undergone *in vitro* fertilization presented with OHSS. Six days after transvaginal oocyte pickup, she presented with only an isolated right-sided pleural effusion and restricted respiratory capacity. A thoracentesis was successful. Clinicians must be aware of unilateral pleural effusion, with a higher incidence on the right side, as a single-symptom presentation of OHSS. The case reported here illustrates the diversity and severity of OHSS.

1. Introduction

Ovarian hyperstimulation syndrome (OHSS) is usually an iatrogenic disorder. The incidence of moderate to severe OHSS is 1–5% of all *in vitro* fertilization (IVF) cycles, with a mortality rate of 1:45000–1:50000 [1]. Most cases of OHSS arise only 2–7 days after oocyte pickup (OPU) due to the administration of exogenous human chorionic gonadotropin (hCG) on the day of ovulation induction, a so-called “early-onset OHSS.” A decline in serum hCG concentration 7–10 days after hCG-induced ovulation leads to improved OHSS symptoms. In contrast, “late-onset OHSS” occurs 12–17 days after hCG administration almost exclusively due to endogenous hCG production resulting from pregnancy [2].

Knowledge of the risk factors enables preventive management of OHSS. Young patients with PCOS or high antral follicle count (AFC) and those who have received a high dose of gonadotropins are at an increased risk of OHSS. An additional risk factor is low BMI, related to high hormone responsiveness. The administration of hCG to induce ovulation considerably increases the risk of OHSS. An individually selected patient-specific dosage of gonadotrophins and careful monitoring during stimulation are of utmost importance in preventing OHSS. The use of an antagonist protocol for ovarian stimulation halves the risk of OHSS [3]. In addition, patients at increased risk of OHSS should cryopreserve all the embryos that are acquired. To reduce the risk of OHSS, a gonadotropin-releasing hormone (GnRH) agonist should be used to trigger ovulation. We present a rare case of OHSS with isolated pleural effusion following controlled ovarian hyperstimulation.

2. Case Presentation

A 38-year-old woman (gravida I, para I) presented with secondary infertility for about 2 years. Her medical history included endometriosis stage I according to the revised American Society for Reproductive Medicine classification (rASRM) without deep endometriosis or adenomyosis and the endometriosis fertility index (EFI) was 6. Due to a unilateral tubal occlusion (re+ / li-) the previous pregnancy resulted from insemination therapy. The sperm quality of the partner was normal. Her ovarian reserve showed no evidence for PCO-like ovaries during transvaginal sonography, and her AMH level was 18 pmol/L. Her BMI was 21 kg/m².

For ART, stimulation of the ovaries was performed using an antagonist protocol which included 225 IU hMG/day for a total of 12 days and ganirelix 0.25 mg/day for eight days, starting on day 6. For seven follicles >17 mm, ovulation induction was performed with rHCG (s.c. 250 µg of r-hCG [Ovitrelle®]) 36 h before OPU. Progesterone on the trigger day was 2.0 nmol/L. A total of 16 oocytes were retrieved, 13 of which were mature, and nine of which were suitable for *in vitro* fertilization. After five days, embryo transfer (one blastocyst 4AB) was performed. Four blastocysts were subsequently cryopreserved. One day after embryo transfer, the patient presented with a new onset of dyspnea in the right lateral position and nausea without vomiting. The patient's weight was 48.8 kg (pre-treatment weight 48 kg), had an abdominal circumference of 72 cm, was afebrile, and had a stable circulation. At the time of presentation after embryo transfer, the patient had a weight increase of 0.8 kg, a pulse rate of 76 beats/min, and a respiratory rate of 18

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Fig. 1. Sonographic presentation of enlarged ovaries without presence of ascites intraabdominally.

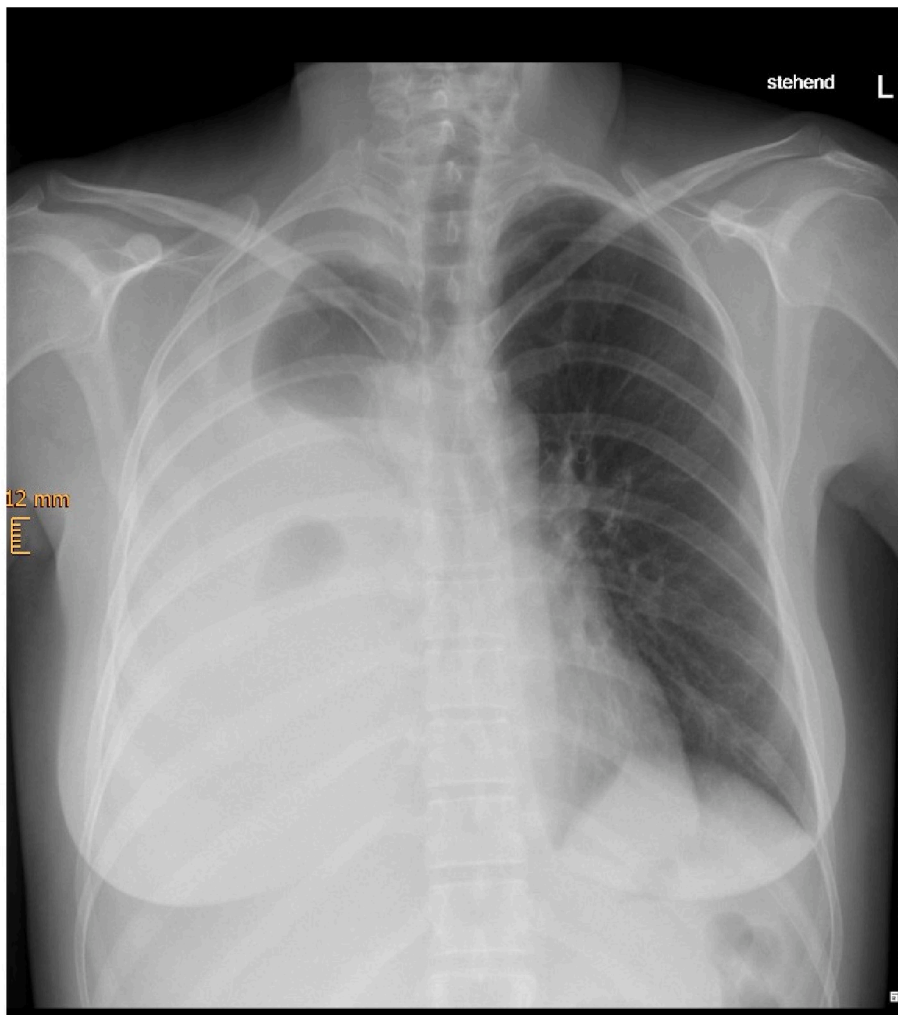


Fig. 2. Chest X-ray reveals a severe pleural effusion on the right side.

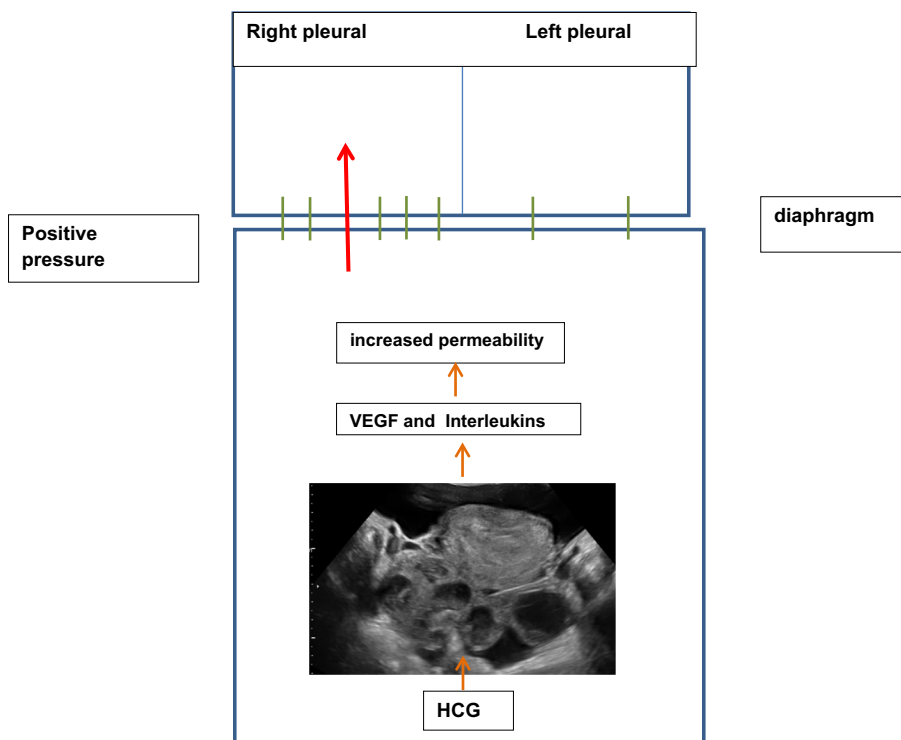


Fig. 3. Pathophysiology of right-sided pleural effusions during ovarian hyperstimulation.

breaths/min.

Transvaginal and transabdominal ultrasound showed enlarged ovaries: right ovary 80x51x30 mm, left ovary 45x31x65 mm, without intraabdominal ascites, but the patient presented with a unilateral pleural effusion on the right side (Fig. 1). Laboratory tests showed hematocrit, electrolytes, and renal function values within the normal range. The patient was admitted to hospital for monitoring due to the diagnosis of OHSS. The management of OHSS was commenced with 1.5 L of intravenous fluids, and thromboembolic prophylaxis with heparin (prophylactic dosage) was started.

During the patient's hospital stay, her dyspnea worsened, and her weight increased to 82 kg. Laboratory tests revealed a hematocrit value of 0.47, mild hyponatremia, and hyperkalemia. The patient had an oxygen saturation level of 94%. Chest X-rays showed a large right pleural effusion with almost complete atelectasis of the right lung (Fig. 2). The left lung was regularly ventilated. Cardiac decompensation was ruled out by the massive pleural effusion evident on echocardiography, and thoracic drainage led to a total of 2 L of fluid being removed. hCG blood tests confirmed pregnancy 14 days after OPU.

The chest X-ray showed an apical pneumothorax 10 mm wide on the right side and a regressive pleural effusion. The infusion therapy was stopped after laboratory values were normalized. Due to an inadequate increase of hCG and the sonographic detection of a disturbed early pregnancy, drug therapy with misoprostol was begun. Subsequently, rapid improvement of symptoms followed a drop in hCG. Fortunately, after three months, an embryo transfer during a thawing cycle resulted in a further pregnancy and delivery without any complications.

3. Discussion

OHSS is a serious complication of IVF that presents at different times of onset and with various degrees of severity. The most frequent symptoms are abdominal discomfort, nausea, and vomiting, which are exographically related to ascites and ovarian enlargement [4,5]. OHSS is associated with increased vascular permeability, which is influenced by the renin-angiotensin-aldosterone system (RAAS) and the release of

Table 1

Classification based on symptoms and severity according to the Royal College of Obstetricians and Gynaecologists (RCOG).

| Depending on the severity | |
|---|--|
| Grade I (mild) | No clinical symptoms, flatulence, size of the ovaries <8 cm each |
| Grade II (moderate) | moderate clinical symptoms, nausea, vomiting, abdominal pain, size of the ovaries each approx. 8–12 cm |
| Grade III (severe) | ascites, pleural effusion, oliguria, hypovolemia, hemoconcentration>0.45, hypoproteinemia, electrolyte depletion, ovarian size>12 cm each. |
| Grade IV (life-threatening) | ascites, pleural effusion, oliguria, hypovolemia, hemoconcentration>0.55, leukocytes>25,000 / ml, thrombosis, ARDS. |
| Depending on the occurrence of the symptoms | |
| Early onset | within 7 days of HCG administration |
| Late onset | 10 or more days after HCG administration, mostly endogenous HCG when pregnancy has occurred |

vasoactive substances, such as vascular endothelial growth factor (VEGF) and interleukins (IL) -1, -2, and - 6, which alter the permeability of the vascular bed and, as a consequence, this typical symptomatology appears. [6,7].

We present here a case of isolated pleural effusion in a patient with severe OHSS. In 2017, a systematic review was published which included ~30 patients with an atypical pleural effusion but only one patient presented with an ovarian manifestation of OHSS [5,7,8]. Most patients with atypical isolated pleural effusion suffer from shortness of breath (oxygen saturation up to ~87%) and an exudative component. The findings in our case of isolated right-sided pleural effusion are correlated with the reports of the above-mentioned systematic review [5].

The pathophysiology of OHSS is not fully understood. After the release of vasoactive substances (especially VEGF, IL-1, IL-2, and IL-6),

vascular permeability is increased, which can lead to fluid displacement with a consecutive accumulation of fluids intraperitoneally and in the pleural space. The mechanism for the development of pleural effusion is still unclear, but it has been hypothesized that a pressure gradient is responsible for effusion. Fluid buildup in the peritoneum can lead to excess pressure, which can impair the normal function of the diaphragm. Negative intrathoracic pressure then draws fluid from the peritoneum into the pleura, which may explain findings of minimal to absent ascites, as observed in our case. These defects usually occur on the right side (Fig. 3, [7]).

Prevention and early diagnosis of OHSS driven pleural effusion are very important; time of diagnosis determines whether a patient receives ambulatory or intensive care treatment. In our case, we found the appearance of pleural effusion after day 6 of OPU. Unfortunately, an isolated finding of pleural effusion as a presentation of severe OHSS is not recognized under the OHSS classification [9]. There is currently no consensus for the classification of OHSS, although in 2016 the Royal College of Obstetricians and Gynaecologists (RCOG) proposed a classification system based on symptoms and severity (Table 1, [9]).

We propose here the following strategies that should be considered to prevent OHSS [4,5,10,11]. As primary prevention, individualized stimulation with gonadotropin should take into account risk factors. In addition, before stimulation, potential complications such as OHSS should be clarified (for informed consent). The dose of gonadotropins in ovarian stimulation should be adapted to AMH and AFC, and where there is the possibility of a good response to ovarian stimulation, a GnRH antagonist should be administered. In secondary prevention, GnRH agonist administration should be given instead of hCG administration; all blastocysts should be frozen and a fresh transfer avoided, thus preventing endogenous hCG production according to the clinical guidelines from the ASRM and ESHRE [3,5]. OHSS is an iatrogenic complication, and despite close monitoring during ovarian stimulation, it can have significant morbidity and mortality. Meticulous fluid management, physical examinations, and blood tests are key to patient management. Outpatient management is possible only in mild to moderate OHSS. If symptoms worsen, hospital admission is advised for rehydration, electrolyte correction, and thrombosis prophylaxis. In our case, a thoracentesis was performed due to the large right-sided effusion causing pulmonary compromise. The result was a significant reduction of dyspnea, improved respiratory function, and reduced further complications such as pulmonary embolism, infections, and abdominal ascites. The possibility of a patient undergoing hormonal treatment being at risk of OHSS or endometriosis presenting with unilateral pleural effusion should be kept in mind when assessing these patients.

4. Conclusion

In conclusion, the very early appearance of a unilateral right-sided pleural effusion without ascites can be an atypical course of OHSS. Such a diagnosis necessitates prompt hospital management for any associated complications. Before ovarian stimulation treatment is begun, primary prevention of OHSS should be carried out if risk factors are present.

Contributors

Angela Vidal was involved in patient care, conception of the case report, wrote the initial manuscript draft, revised it critically for

important intellectual content and approved the final submission.

Christiane Wachter revised the manuscript critically for important intellectual content and approved the final submission.

Alexandra Kohl Schwartz revised the manuscript critically for important intellectual content and approved the final submission.

Carolyn Dhakal was involved in patient care, assisted in the literature review, revised the manuscript critically for important intellectual content and approved the final submission.

Conflict of interest

The authors declare that they have no conflict of interest regarding the publication of this case report.

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Patient consent

Informed consent was obtained from the patient for the publication of this case report and the accompanying images.

Provenance and peer review

This case report was peer reviewed.

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