Clinical Vignettes

Thoracic Endometriosis Unmasked by Ovarian Hyperstimulation for in vitro Fertilization

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Thoracic endometriosis syndrome is a well-described, rare manifestation of endometriosis. We present a case of a 35-year old woman undergoing controlled ovarian stimulation prior to in vitro fertilization (IVF) who developed bilateral hemorrhagic pleural effusions. She was initially diagnosed with ovarian hyperstimulation syndrome, a complication of infertility therapy; however, she was later found to have occult thoracic endometriosis. We describe ovarian hyperstimulation syndrome and review the manifestations of thoracic endometriosis syndrome. Although endometriosis is a hormone-dependent disease, the rate of IVF complications related to endometriosis is low.

KEY WORDS: endometriosis; in vitro; ovarian hyperstimulation syndrome; thoracic diseases.

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Endometriosis is defined as the growth and function of endometrial tissue outside of the uterine cavity. It affects 6–10% of women of reproductive age and up to 50% of women with infertility.¹ When endometrial tissue is present within the lungs or along the pleural surface it may result in one of the following thoracic endometriosis syndromes: Catamenial hemoptysis, catamenial pneumothorax, catamenial hemothorax or lung nodules.²

We present a rare case of hemorrhagic pleural effusions that developed after ovarian hyperstimulation for in vitro fertilization (IVF). The patient was initially diagnosed with ovarian hyperstimulation syndrome (OHSS), a well-described complication of infertility therapy; but ultimately the effusions were found to be due to occult thoracic endometriosis.

CASE

A 35-year-old gravida-0, para-0 woman with a history of endometriosis who was undergoing in-vitro fertilization (IVF) presented to her fertility clinic complaining of a recent onset of shortness of breath, orthopnea, and right-sided pleuritic chest pain. Twelve days prior to presentation to our institution the patient had begun controlled ovarian stimulation for IVF. She received two ampoules of follicle-stimulating hormone (FSH) and two ampoules of human menopausal gonadotropins (hMG, 150 IU/d, respectively) (Gonal-f®, Pergonal®, Serono Laboratories, Randolph, MA) in divided doses. This was followed by one ampoule FSH and one ampoule HMG and the ovulatory bolus injection of human chorionic gonadotropin. Peak estradiol level was 1339 pg/ml (expected level is approximately 1000–4000 pg/ml). A total of 30 oocytes were collected and cul-de-sac fluid was noted at the time of egg retrieval.

Three days after oocyte retrieval, she complained of increasing abdominal girth, bloating and shortness of breath. A pelvic ultrasound in fertility clinic showed a 10 cm×5 cm pocket of cul-de-sac fluid with the right and left ovaries measuring 9 cm×6 cm and 9 cm×7 cm, respectively (length×width; normal range 3–5 cm×1.5–3 cm).

She was sent from clinic to the emergency department, where she was given the presumptive diagnosis of OHSS and embryo transfer was postponed. Her shortness of breath worsened and she was admitted to the internal medicine service. On admission she did not endorse fever, chills, cough, hemoptysis, nausea, vomiting, diarrhea, prior pulmonary symptoms, personal or family history of thromboembolic disease, tuberculosis, or asthma.

Admission physical examination revealed a well-appearing woman who became moderately dyspneic when reclining. She was afebrile, pulse 110 beats/min, blood pressure 113/65 mmHg, respiratory rate 16, and oxygen saturation 100% on room air. Her lung examination revealed reduced breath sounds and dullness to percussion midway up both lungs. Her cardiovascular exam was

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tachycardic and regular without murmurs or gallops. There was no jugular venous distention. Her abdominal and extremity exams were unremarkable.

Initial serum laboratory studies revealed a normal basic chemistry panel. There was a leukocytosis of $18.0 \times 10^3/\mu\text{L}$ (normal $4.0\text{--}11.0 \times 10^3/\mu\text{L}$). Hematocrit and platelets were normal (40.8 % and 359,000 cells/uL). Serum protein was 6.9 g/dL and lactate dehydrogenase was 136 U/L. A chest radiograph revealed bilateral large pleural effusions with evidence of loculation on the right side. A chest computed tomography (CT) showed a large complicated right hydropneumothorax with extensive pleural thickening and a large left pleural effusion (Fig. 1).

Bilateral thoracenteses removed 1300 mL from the left and 400 mL from the right of serosanguinous exudative fluid (Table 1). Her shortness of breath resolved. A pulmonology consultation was obtained. Based on the timing of her symptoms, the pleural effusions, and the recent hormonal therapy for IVF, the diagnosis of OHSS was felt to be most likely. However, given the presence of blood in the pleural fluid and her prior history of endometriosis, a diagnosis of thoracic endometriosis was also considered. Her pleural fluid cytology revealed no evidence of endometrial cells. She remained stable and was discharged home.

Her pulmonary symptoms continued to improve at home. A repeat CT scan 1 month later showed resolution of the left pleural fluid and a decrease in size of the right hydropneumothorax. Additionally, small sub-pleural bullae were visualized in both lungs that, in retrospect, were also apparent on the original imaging. These findings were felt to be suggestive, though not diagnostic, of thoracic endometriosis.

Three months after the hospitalization she underwent a frozen embryo transfer cycle, conceived, and delivered a healthy infant. Immediately post partum, she developed gastroenteritis with elevated liver transaminases and hepatomegaly. Abdominal magnetic resonance imaging (MRI)

Figure 1. Chest CT performed 3 days after oocyte retrieval showing a large complicated right hydropneumothorax with pleural thickening and large left pleural effusion.

Table 1. Pleural Fluid Laboratory Analyses

Pleural fluid studies	Left pleural fluid	Right pleural fluid
Protein (g/dL)	3.98	3.30
LDH* (U/L)	119	123
Amylase (U/L)	34	35
Glucose (mg/dL)	121	115
Red cell count (cells/mm ³)	166,600	374,000
White cell count (cells/mm ³)	840	1330
Segmented neutrophils (%)	33	16
Lymphocytes (%)	30	43
Monocytes (%)	17	13
Macrophages (%)	18	28
Pleural/Serum LDH ratio	0.9	0.9
Pleural/Serum protein ratio	0.6	0.5

*Lactate dehydrogenase

revealed a diaphragmatic defect with herniation of the right lobe of the liver, compression of the right hepatic vein at the IVC confluence and passive congestion of the right lobe (Fig. 2). She underwent repair of her hernia and video assisted thoracoscopy (VATS) with pleural biopsy. Operative findings were consistent with congenital diaphragmatic agenesis. Histologic sections of pleural tissues were initially read as negative for endometrial tissue. However, over the following months she had persistent air in her pleura by CT evaluation. The pathology slides were re-evaluated at that time and were found to have endometrial tissue present (Fig. 3). With the diagnosis of thoracic endometriosis confirmed, her initial presentation was felt to be due to TES rather than OHSS.

Two years later the patient had a spontaneous pregnancy and delivered a healthy infant. Recently, six years after the initial pregnancy, she was hospitalized twice

Figure 2. MRI showing herniation of much of the right lobe of the liver into the thoracic cavity.

Figure 3. Pleural pathology specimen demonstrating hemorrhage, pleural tissue and a tubular endometrial gland (arrow).

for catamenial pneumothoraces. She was treated with chest tubes on both occasions. After the second pneumothorax she underwent pleurectomy and pleurodesis. One year later, the patient has remained free of hospitalization and is back to routine activities.

DISCUSSION

This case highlights an unusual presentation of thoracic endometriosis, unmasked by ovarian hyperstimulation for

IVF, and initially misdiagnosed as OHSS. OHSS is an iatrogenic complication of pharmacologic ovarian stimulation used in infertility therapy.³ It occurs with a frequency of 0.6% to 38% of IVF cases,⁴ though the estimated incidence of severe cases is 0.1-2%.⁵ OHSS results from an increase in capillary permeability and subsequent extravascular extravasation of protein-rich fluid, or “third spacing”.^{3,6} Symptoms range from mild abdominal pain, diarrhea and nausea to severe disease characterized by ascites, rapid weight gain, hemodynamic instability, tachypnea and oliguria. Onset of symptoms typically occurs soon after ovulation, or after oocyte retrieval.⁶

Laboratory abnormalities in patients with severe OHSS include hemoconcentration (hematocrit >45%), leukocytosis (>15,000), and electrolyte imbalances (hyponatremia, hyperkalemia). In the most severe cases renal failure, adult respiratory distress syndrome (ARDS), ovarian rupture, and thromboembolism may ensue.⁶ Several classification systems have been proposed to assess severity of symptoms; however, currently there exists no consensus definition.^{3,6} Risk factors for the development of OHSS include young age, low body weight, polycystic ovary syndrome, higher doses of exogenous gonadotropin, high or rapidly rising serum estradiol levels, higher numbers of developing follicles and prior episodes of OHSS.⁶ Consultation with a fertility specialist may be warranted.

Pulmonary complications of OHSS include dyspnea, pneumonia, ARDS, pulmonary embolism and pleural effusions (Table 2). In a retrospective review of 130

Table 2. Comparison of Pulmonary Manifestations and Key Features of Ovarian Hyperstimulation Syndrome (OHSS) and Thoracic Endometriosis Syndrome (TES)

	OHSS	TES
Symptoms and pulmonary manifestations	Symptoms Dyspnea Pulmonary manifestations: Pleural effusion* Elevated diaphragms Pulmonary embolism Pneumonia ARDS†	Symptoms: Chest pain Dyspnea Cough Hemoptysis Pulmonary manifestations: Catamenial pneumothorax‡ Catamenial hemothorax‡ Catamenial hemoptysis Lung nodules
Symptom onset	Soon after ovulation or oocyte retrieval	< 2 days of onset of menses
Mechanism	Lung restriction due to “third spacing” of fluid into the pleural space.	Functional endometrial tissue located in the pleura, the lung parenchyma, and the airways
Imaging findings	Chest X-ray: Pleural effusions, bilaterally elevated diaphragms, atelectasis, pneumonia, ARDS	Chest X-ray: Pleural effusions, opacities, nodules Chest CT/MRI: Opacities, nodules, thin-walled cavities, bullae VATS: Diaphragmatic perforations, endometrial deposits (brown, violet)
Key diagnostic features	“Third space” fluid accumulation Hemoconcentration (Hct>45%) Leukocytosis (white blood cell count >15,000) Extra-pulmonary symptoms may be predominant Hemodynamic instability	Temporal relationship of symptoms with onset of menses Imaging insensitive- highest yield if performed during menses

* In OHSS pleural effusions are typically unilateral and right sided. Fluid is most often exudative
† Adult respiratory distress syndrome
‡ Both catamenial pneumothorax and hemothorax are most often unilateral and right-sided

dyspneic patients with severe OHSS (defined as massive ascites/hydrothorax, hemodynamic instability, oliguria, anasarca, liver dysfunction and hemoconcentration), 38 (29%) were found to have pleural effusions. Of these approximately 71% were unilateral.⁷ Pleural fluid is typically accompanied by marked ascites; however, isolated pleural effusions without ascites have been described.^{4,8} Most reports have described exudative fluid composition; however, to our knowledge hemorrhagic pleural effusions have not been described in this syndrome.^{6,9,10} In our patient, the onset of respiratory symptoms after oocyte retrieval is consistent with the initial diagnosis of OHSS; however, several features did not fit with this syndrome. In particular, she had only minimal free pelvic fluid without ascites, no evidence of abdominal distention, and no evidence of hemoconcentration on admission and, as noted above, had hemorrhagic pleural fluid.

Endometriosis is common among women of reproductive age.¹ Implantation of endometrial tissue within the pelvis is the most common manifestation and is thought to result from retrograde menstruation of endometrial cells.¹ The “gold standard” for diagnosis of these lesions is laparoscopy. Distant endometrial implants, such as on the diaphragm, pleura and pericardium, are less common and the mechanism is unknown; lymphatic or hematogenous embolization, metaplastic transformation, and transdiaphragmatic migration have all been proposed.^{1,2}

Thoracic endometriosis syndrome is a rare manifestation of functional endometrial tissue located in the pleura, the lung parenchyma and the airways.^{2,11} There are four clinical syndromes including catamenial pneumothorax (from the Greek *katamenios*, meaning “monthly”), catamenial hemothorax, catamenial hemoptysis and lung nodules. Of these, catamenial pneumothorax is the most frequent presentation, occurring in approximately 70% of women in the two largest series of patients with thoracic endometriosis.^{12,13} Catamenial hemothorax was a less frequent manifestation in these series, occurring in 12-14% of patients. There is a right-sided predilection for all manifestations of thoracic endometriosis (70-90% of cases), though the reason for this is unclear.^{13,14}

Transdiaphragmatic migration through diaphragmatic defects, either congenital or acquired, has been associated with at least some cases of intrathoracic endometriosis.² However, not all patients with thoracic endometriosis have concomitant pelvic endometriosis and there is some evidence to suggest that extrapelvic endometriosis may start as an independent thoracic process.¹¹ Furthermore, it is possible that the diaphragmatic defects found in some patients are acquired from cyclical proliferation and shedding of endometrial implants on the diaphragm (i.e. a consequence, rather than a cause).^{2,13} Interestingly, our patient was found to have a large, probably congenital diaphragmatic defect which may have served as a portal for intrathoracic spread of endometriosis.

The diagnosis of TES requires a high index of suspicion and can be difficult to confirm. It should be considered in any patient with periodic symptoms (e.g. cough, chest pain, and hemoptysis) that occur within 2 days of the onset of menstruation. Imaging may show findings suggestive of TES (Table 2); however, it is often normal. Consultation by cardiothoracic surgery may be warranted as VATS is currently the preferred method for surgical assessment of patients with suspected catamenial pneumothorax or hemothorax.² As in our case, pleural fluid cytology lacks sensitivity and is seldom helpful.¹¹ Our patient's follow-up imaging findings of sub-pleural, thin walled bullae are also consistent with the diagnosis of TES.

There have been prior case reports of ovarian hyperstimulation resulting in an “unmasking” of latent or previously undiagnosed endometriosis.¹⁵⁻¹⁷ Recently, the first case of TES due to ovarian stimulation for IVF was published. The patient was a 32-year-old woman who developed a catamenial pneumothorax after controlled ovarian hyperstimulation.¹⁸ Although in our case hemothorax could not be confirmed as pleural fluid hematocrit was not checked, to our knowledge this is the first case of endometriosis presenting as hemorrhagic pleural effusions due to ovarian hyperstimulation for IVF.

Although endometriosis is a hormone-dependent disease, the rate of IVF complications related to endometriosis is low.¹⁶ Interestingly, recent studies have shown that ovarian stimulation for IVF does not increase the risk for recurrence of pelvic endometriosis.^{19,20} Nevertheless, our hypothesis is that ovarian hyperstimulation triggered preexisting thoracic endometrial implants to become inflamed resulting in bloody pleural effusions; a mechanism that is also suggested by previous reports.^{16,17} Further research into the consequences of ovarian stimulation on endometriosis is warranted.

SUMMARY

In conclusion, this case highlights a rare case of TES unmasked by ovarian hyperstimulation, and initially misdiagnosed as OHSS. Due to the increased use of hormonal therapies for infertility, internists should be familiar with OHSS and consider this common, potentially life-threatening diagnosis in all patients who undergo ovarian hyperstimulation.^{5,10,21} Patients with hemorrhagic pleural effusions or periodic symptoms related to the onset of menses should prompt consideration of the diagnosis of thoracic endometriosis, such as was found in our patient.

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