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A case of severe non-cardiogenic pulmonary edema in a woman treated with atosiban for preterm labor

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Abstract. – BACKGROUND: A 27-year-old primigravid woman with a triamniotic pregnancy presented with preterm labor at 29 weeks of gestation and acute severe pulmonary edema after treatment with atosiban.

CASE REPORT: The severe symptoms and hypoxemia of the patient led to emergency hysterotomy and intensive care unit hospitalization.

CONCLUSIONS: This clinical case prompted us to review the existing literature to examine studies on differential diagnoses in pregnant women with acute dyspnea. The possible pathophysiological mechanisms of this condition and the management of acute pulmonary edema are worth discussing.

Key Words:
Atosiban, Maternal, Multiple pregnancies, Non-cardiogenic pulmonary edema, Nifedipine.

Introduction

Atosiban is a tocolytic agent[1] that competes with oxytocin for oxytocin receptors (OTR) on the membranes of the uterine smooth muscle and thus works by competitively inhibiting the binding of oxytocin and vasopressin receptors. The drug ties to membrane-bound oxytocin receptors on the myometrium and prevents oxytocin-stimulated increases in inositol triphosphate production. This activity inhibits the uterine contractions induced by oxytocin, and a good tocolytic effect is achieved. Atosiban provides more effective inhibition of contractions and has fewer side effects than other tocolytics[2].

Pulmonary edema is a known side effect of other tocolytic agent, especially when they are administered in combination with other drugs. Notably, the conversion of atosiban to β -receptor antagonists in pregnant women was reported to induce pulmonary capillary leakage, which is a rare complication[3,4]. Only a few cases of atosiban-induced pulmonary edema have been reported to date[5-10].

Case Report

A 27-year-old primigravida woman with a triamniotic pregnancy presented with preterm labor at 29 + 2 gestational weeks in another hospital. She took levothyroxine 16 ug per day to supplement her thyroid hormone levels.

The first three days, an induction dose of atosiban (6.75 mg) was administered intravenously over 1 min, followed by 300 mg/min for 3 h, and then 100 mg/min, according to the manufacturer's instructions. On day 4, nifedipine combination therapy was initiated. One hour after nifedipine intake, the patient developed transient fever with a temperature of 37.8°C. Furthermore, she began to cough and felt weakness and generalized muscle ache. Five hours after the first symptoms, her temperature rose to 38.4°C, and her cough aggravated. Thirteen hours after symptom onset, the patient had shortness of breath and dyspnea. Her pulse rate was 130/min, respiratory rate 30/min, blood pressure 110/60 mmHg, SpO_2 75% on room air, arterial PaO_2 was 52 mmHg. The diagnosis was acute respiratory failure, and delivery of high-flow oxygen was initiated by mask. Meanwhile, intravenous injection of cedilanid 0.4 mg and furosemide 20 mg was administered. However, this treatment was ineffective, and a non-invasive ventilator for assisted breathing was used during her transfer to our hospital.

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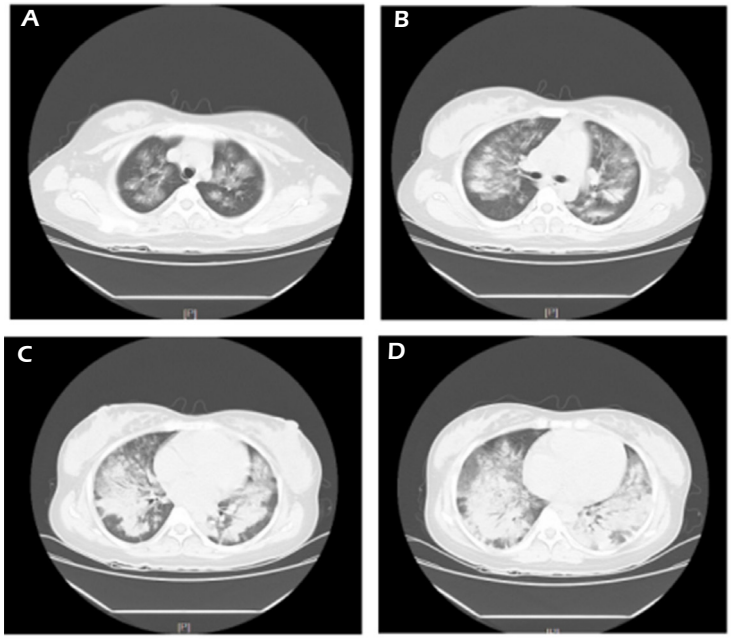

Figure 1. CT scan of the lungs at admission. **A**, Transjugular notch cross-section. **B**, Horizontal cross-section through trachea bifurcation. **C**, Cross section through both inferior pulmonary veins. **D**, Cross-section through phrenic venal foramen.

The following laboratory results were obtained at admission: WBC 13.1 * 10^9/L, HB 98g/L, PLT 178 * 10^9/L, CRP 169.8 mg/L, and PCT 0.25 ug/L (normal). Liver and kidney function and electrolyte levels were normal. The myocardial enzyme findings were as follows: LDH 287 U/L, CK 40 U/L, CK-MB 39 U/L (0-25), and myoglobin 61 U/L (normal). BNP: 874 pg/mL. The Gram-stained sputum smear culture was negative. We obtained the following electrocardiogram (ECG) results: heart rate 112/min, sinus tachycardia. CT scan of the lungs revealed large bilateral pulmonary ground-glass opacities (Figures 1 and 2). After a consultation with experts in the hospital, early termination of pregnancy was recommended. The patient was transferred to the intensive care unit after cesarean section.

At the time of admission, the patient was calm, with ventilator-assisted breathing by endotracheal intubation, FIO_2 100, and arterial PaO_2 69.9 mmHg. Echocardiography showed EF 60%; the systolic and diastolic functions of the left ventricle were normal. There were no obvious abnormalities in the cardiac structure.

After admission, the patient's condition improved after treatment with anti-infection drugs, fluid restriction, diuretics (furosemide), and oxytocin. PaO_2/FIO_2 increased from 175 to 410 mmHg on the second day, and endotracheal intubation was terminated. A CT scan of the lungs on day 4 after admission showed a significant reduction in the large bilateral pulmonary ground-glass opacities (Figures 3 and 4).

On the fifth day after admission, the patient was transferred out of the intensive care unit and returned to the maternity ward. We reviewed the echocardiography and myocardial enzyme spectrum results, which were normal, and cardiomyopathy was ruled out. The postoperative pathological analysis showed no signs of chorioamnionitis. A CT scan of the lungs on day 11 after admission showed that the large bilateral pulmonary ground-glass opacity continued to improve

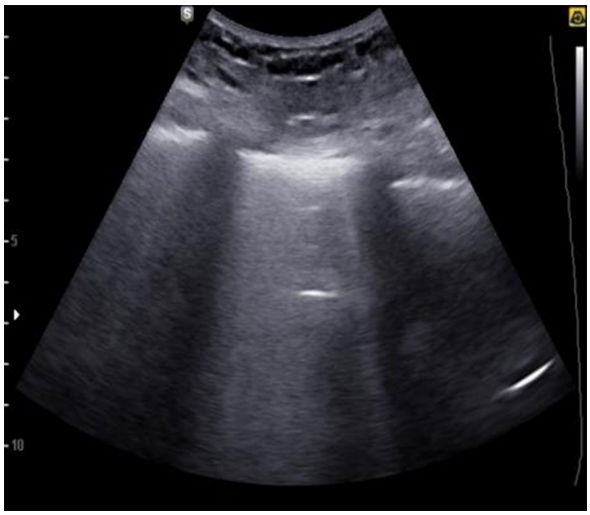

Figure 2. Ultrasound of the lungs after cesarean section.

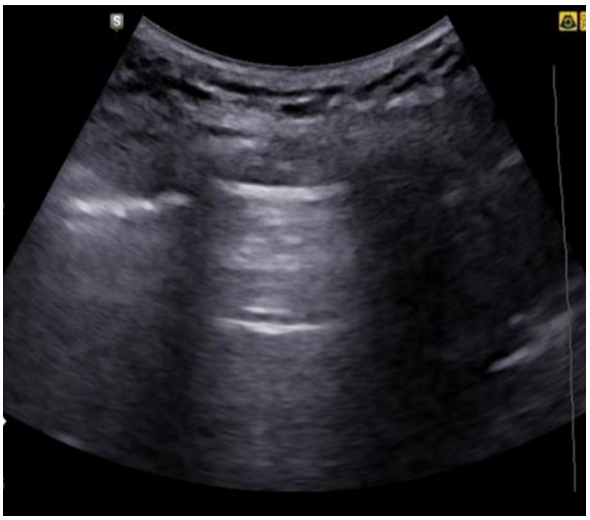

Figure 3. Ultrasound of the lungs on day 3 after admission.

further. On day 13, she was discharged from hospital (Figure 5).

Based on the actual situation of the patient, we choose the Naranjo's Rating Scales to evaluate for adverse drug reactions. The 10 questions were answered, and a score was obtained. The results are presented in Table I.

Discussion

Pulmonary edema is the main clinical manifestation of diseases caused by the extravasation of fluid in the blood vessels of the lung parenchyma into the interstitium or alveoli, resulting in physiological dysfunction and dyspnea. Based on its etiology, pulmonary edema can be classified into cardiogenic (hydrostatic) and non-cardiogenic pulmonary edemas (with increased permeability)[11].

Cardiogenic pulmonary edema is caused by an increase in the hydrostatic pressure of the pulmonary vessels induced by cardiovascular factors such as heart failure. Non-cardiogenic pulmonary edema refers to the absence of left ventricle and left atrium overload, and the absence of increased interstitial or alveolar fluid exudation due to reduced myocardial contractility. Non-cardiogenic pulmonary edema is characterized by various etiologies and complex pathogenesis, including increased pulmonary capillary permeability, decreased plasma colloid osmotic pressure, and increased negative interstitial pressure. Non-cardiogenic pulmonary edema includes neurogenic pulmonary edema, infectious pulmonary edema, pulmonary reopening after pulmonary edema, drug pulmonary edema, etc. Penicillin, amiodarone, anti-tumor medicines have been found to cause drug-induced pulmonary edema[12].

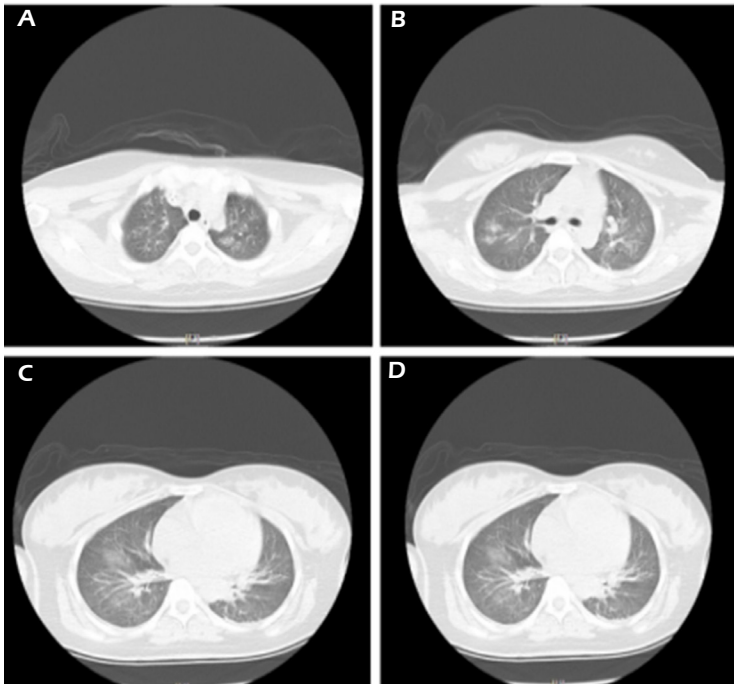

Figure 4. CT scan of the lungs on day 4 after admission. **A**, Transjugular notch cross-section. **B**, Horizontal cross section through trachea bifurcation. **C**, Cross section through both inferior pulmonary veins. **D**, Cross section through phrenic venal foramen.

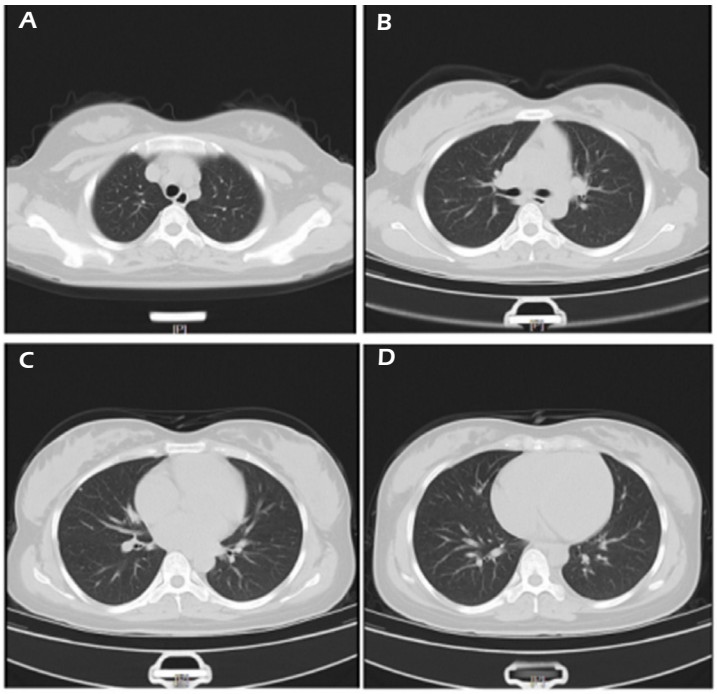

Figure 5. CT scan of the lungs on day 11 after admission. **A**, Transjugular notch cross-section. **B**, Horizontal cross section through trachea bifurcation. **C**, Cross section through both inferior pulmonary veins. **D**, Cross section through phrenic venal foramen.

Table I. The Naranjo's assessment of atosiban induced non-cardiogenic pulmonary edema in patients.

Relevant issues	Score			Score reasons
	Yes	No	Unknown	
1	+1			Atosiban has been reported to cause non-cardiogenic pulmonary edema in pregnant women.
2	+2			Non-cardiogenic pulmonary edema occurred after the use of atosiban.
3	+1			After drug withdrawal, the symptoms of non-cardiogenic pulmonary edema were relieved.
4			0	Never used any of the suspect drugs again.
5			0	It is unknown whether there are other independent factors that may cause non-cardiogenic pulmonary edema.
6			0	No placebo was used for this response.
7			0	Toxic concentrations of atosiban were not determined.
8			0	It is not known whether the patient had exacerbation with increasing dose and remission with decreasing dose.
9			0	It is not known whether the patient had a similar reaction to prior exposure to the same drug.
10	+1			CT Scan and Ultrasound of the Lungs can be regarded as objective evidence of this reaction.
Total	5			

The total score ≥9 points indicated that the causal relationship between the drug and adverse reactions was positive, which was confirmed by objective evidence and quantitative testing data. The total score of 5-8 is very likely to be relevant, that is, the results supported by objective evidence or quantitative testing results. The total score 1-4 is classified as possible correlation, that is, it belongs to the situation that can neither be fully confirmed nor completely denied. The total score less than or equal to 0 is considered suspicious, that is, it is incidental or basically unrelated.

Atosiban is a tocolytic agent[1], which works by competitively inhibiting the binding of oxytocin and vasopressin receptors. It competes with oxytocin for oxytocin receptors (OTR) on the membranes of the uterine smooth muscle. When the oxytocin receptor is antagonized by atosiban, the uterine contractions induced by oxytocin can be inhibited, and a good tocolytic effect is achieved. Atosiban has become the tocolytic therapy of choice because it is better tolerated than other drugs[4,13].

Pulmonary edema is a known side effect of other tocolytic agent, especially in high-risk patients with twin pregnancies or treated combination with other drugs. The conversion of atosiban to β-receptor antagonists in pregnant women was reported to induce pulmonary capillary leakage, which is a rare complication[3,4].

The instructions for atosiban use warn of an increased risk of pulmonary edema in patients with multiple pregnancies. Adverse respiratory reactions, such as dyspnea and pulmonary edema have been reported, particularly in association with other contraction inhibitors, such as calcium antagonists and β-adrenergic receptor agonists, and/or in association with multiple pregnancies.

Although known as a selective oxytocin receptor (OTR) antagonist unique to the uterus of pregnant women, OTRs have been discovered in numerous organs, such as the hypophysis, kidney, ovary, testis, thyroid gland, bone, brain, heart, lung, and the fat tissue of both pregnant and non-pregnant animals. The number of endothelial OTRs are estrogen-dependent and vary in response to the changing physiology of gestation. Atosiban causes vasodilatation through the production of nitric oxide and the transmembrane mobilization of Ca^{2+}. However, this antagonistic effect of atosiban on the vasopressin receptor, leading to inhibition of the anti-diuretic effect, can also be biased by an agonistic effect, depending on the presence of a Gq protein (inhibitory activity) or a Gi protein (stimulatory effect) at the oxytocin receptor, leading to the activation of selective intracellular cascades. Whether this paradoxical agonistic mechanism, which is mainly involved in tumor-cell proliferation, participates also in the pathogenesis of non-cardiogenic lung edema, is currently unknown.

This patient developed pulmonary edema after taking atosiban in combination with calcium channel blockers. There was no evidence of physical heart disease and infection, and thus we ruled out chorioamnionitis. The Naranjo total score for atosiban in patients with non-cardiogenic pulmonary edema was 5 in our study, which means Atosiban probably caused non-cardiogenic. Most likely, a drug adverse reaction or interaction is considered to have occurred. No reports have been published on adverse reactions caused by nifedipine in pulmonary edema. Moreover, no other drugs known to cause non-cardiogenic pulmonary edema were taken by the patient. In this case, the post-delivery termination of atosiban treatment quickly relieved the symptoms of the patient.

Little is known about the side effects of antitocolytics. The side effects of certain drugs may endanger the life of women without heart disease, and thus the related mechanisms are worthy of further research. Life-threatening non-cardiogenic pulmonary edema caused by atosiban is extremely rare, but more vigilance needs to be exercised in clinical practice to reduce adverse clinical outcomes[13].

Conclusions

Atosiban is a tocolytic agent, which works by competitively inhibiting the binding of oxytocin and vasopressin receptors. The administration of this drug is associated with an increased risk of pulmonary edema during pregnancy, especially when used in combination with other contraction inhibitors. The mechanism of this adverse effect is still unclear. Life-threatening non-cardiogenic pulmonary edema caused by atosiban is extremely rare, but more vigilance needs to be exercised in clinical practice to reduce adverse clinical outcomes.

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Ethical Approval
The study was approved by the Research Ethics Committee of the hospital (Research Ethics Board Number: KY-2022060106).

Informed Consent
Informed consent was obtained from the patient included in the study.

Conflict of Interest
The authors declare that they have no conflict of interest.

Authors' Contributions

Yi Chen and Chaoyang Jiang conceived and supervised the study. Ziwei Deng, Zhenxing Duan, and Yuanlu Shu analyzed the data. Yi Chen and Jianliang Zhou wrote the manuscript. Jianliang Zhou revised the manuscript. All authors reviewed the results and approved the final version of the manuscript.

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