A Case of Thromboembolism After Injection of Gonadotropin-releasing Hormone Agonist

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Gonadotropin-releasing hormone agonist (GnRH-a) was one of the most used therapies in the treatment of endometriosis. But unfortunately, no literatures realized GnRH-a may be related to thrombosis until now. The case below was exactly about thromboembolism taking place after using GnRH-a because of estradiol (E2) peak short-time after injection.

A 50-year-old woman presented to our institution with menorrhagia. Her medical history was notable for adenomyosis and dysmenorrhea for more than 10 years.

In January 2014, the patient had blood transfusion because of anemia and progestogen (norethisterone) to control the menorrhagia. Two months later, after stopping norethisterone for 2 days, her vaginal bleeding increased. Subsequently, she was prescribed Marvelon for 3 months.

On April 15, the patient went to our institution, the physical examination showed that her uterine was enlarged to 26-week size. She had curettage (dilation and curettage) followed by GnRH-a (leuprorelin acetate microspheres for injection, Shanghai Livzon Pharmaceutical Co., Ltd., China) 3.75 mg subcutaneous injection, and was advised to stop Marvelon. Vaginal bleeding recurred 3 days later, and she continued to take oral norethisterone 5 mg every 8 h. After 24 h, she felt unwell with decreased urine output. The blood test showed sodium 130 mmol/L, blood urea nitrogen 11.4 mmol/L, creatinine 436 μmol/L, C-reactive protein 303.6 mg/L, white blood cell count 27.6×10^9/L, hemoglobin 56 g/L, carbohydrate antigen 125 (CA125) 334 U/ml, alanine transaminase 103 U/L, aspartate aminotransferase 110 U/L, and D-Dimer 1.5 μg/ml. She was admitted to hospital subsequently.

Upon admission, the patient was transfused with 4 units packed red blood cell. Further, blood test showed β2-glycoprotein 1 Immunoglobulin AGM (Ig AGM) antibody positive, anticardiolipin antibody (ACA) 35.5 RU/ml, and antinuclear antibodies negative. Upper abdominal and pelvic computerized tomography showed hematomata and bilateral pulmonary exudative process with bilateral pleural effusion. Ultrasound of bilateral kidney and renal artery: bilateral kidney diffuse lesions, sparse renal blood flow, and abnormal bilateral renal artery spectrum.

We gradually reduced the dose of norethisterone. Her vaginal bleeding subsided. However, the renal function continued to deteriorate. As a result, the patient was transferred to nephrology department for hemodialysis. Her renal condition was improved after hemodialysis treatment. Nevertheless, her pulmonary ventilation and perfusion scanning [Figure 1a and 1b] showed a defect in lower lobe of the left lung, which did not match the pulmonary ventilation imaging, led to the diagnosis of "pulmonary embolism." Her renal biopsy showed: 3/17 glomerular sclerosis, 7/17 coagulation necrosis, a portion of tubular epithelial necrosis, bare basement membrane formation, a large number of cellular pipe, particle of tube formation; a large number of lymph plasma cells and eosinophil granulocyte infiltration in interstitium, arteriolar wall thickening, and hyaline degeneration. The Seldinger technique of renal arteriography taken on May 8 showed that left renal artery–vascular distribution was sparse, and the right was in normal vascular distribution. Brain magnetic resonance imaging suggested that there was ischemia in the white matter region of right frontal lobe. ACA was retested

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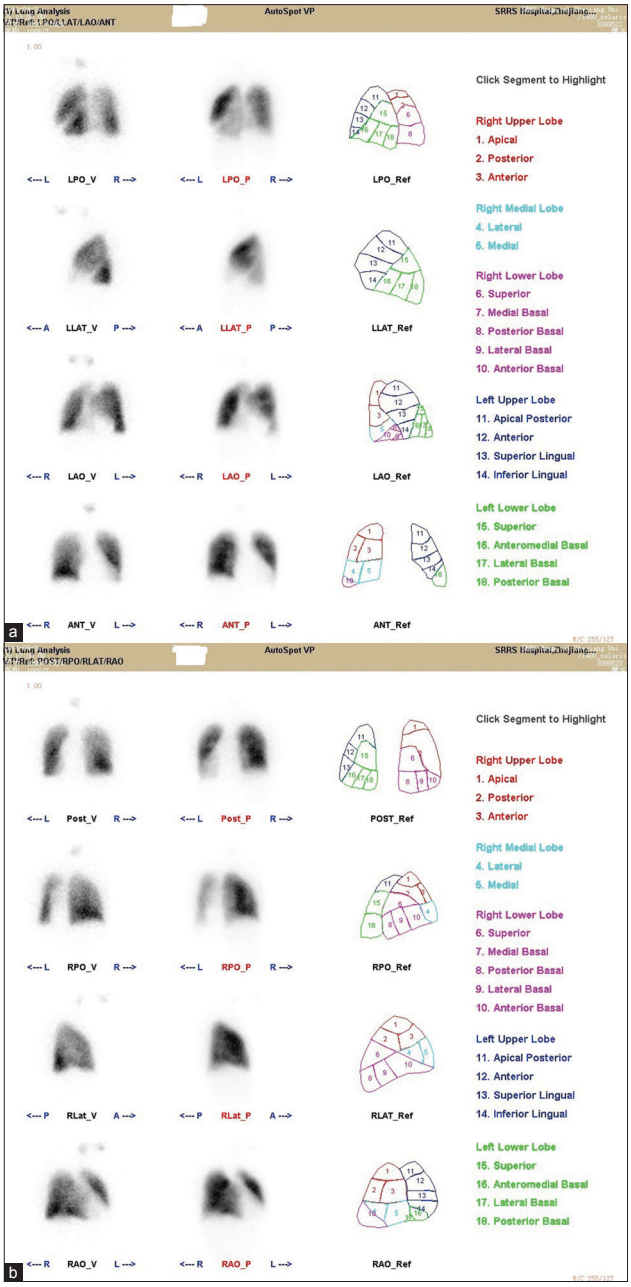

Figure 1: (a and b) Pulmonary ventilation and perfusion scanning: defect in left lower lobe of lung, which did not match the pulmonary ventilation imaging.

and the value was 21.4 RU/ml, β2-glycoprotein 1 IgAGM antibody was positive. At this point, the patient was diagnosed as catastrophic antiphospholipid syndrome (CAPS) because of the onset of acute kidney injury with kidney embolism, pulmonary embolism, and cerebral infarction within 1 week. The patient received low molecular weight heparin and methylprednisolone (40 mg daily), amlodipine tablet 5 mg daily. Her physical condition was gradually improved. Five months later, she underwent hysterectomy + bilateral tubal resection + bilateral ovarian cystectomy.

In this report, we observed a case of a woman with adenomyosis who developed pulmonary embolism and multiple organs failure shortly after the injection of GnRH-a. GnRH-a was a synthetic derivative of GnRH. In the initial stage, it could promote secretion of luteinizing hormone (LH) and follicle stimulating hormone (FSH) by binding to GnRH receptor competing with GnRH. When continuously administered, pituitary was desensitized, releasing of GnRH would be suppressed. Therefore, there was a short E2 peak in early stage. Some research data showed that within 12 h after injection, the concentration of serum FSH increased by 5 times, LH increased by 10 times, and E2 increased by 4 times. Estrogen could lead to increase of synthesis of several coagulation factors including fibrinogen, factor II, VII, and X, and at the same time, thrombin inhibitors such as synthetic and activities of antithrombin III, protein C, and protein S were reduced, which made the blood easier to coagulate, more prone to cause thrombosis. Hence, we speculated that the patient was in high coagulation state during the long history of adenomyosis, thrombosis took place because of triggering of E2 peak after injection of GnRH-a.

It was notable that the patient had multiple risk factors which led to hyper-coagulation state, the details were as follows:

Estrogen Therapy

The effect of oral contraceptive on coagulation function was mainly related to estrogen. Early literature showed that there was a risk of thrombosis caused by oral contraceptive, such as Marvelon. It could lead to 8.6/millions fatal venous thrombosis, especially when the patient complicated with genetic defects which could induce thrombosis. It was also found that the risk of thrombosis due to oral contraceptives was not increased during therapy time, the greatest risk was in the 1st year.[1] The patient in this study had a history of taking Marvelon orally for nearly 6 months; it might be one of the risk factors that led to high coagulation in blood.

Chronic Anemia and High Level of Carbohydrate Antigen 125

In 2012, Yamashiro *et al*.[2] reported 4 cases of adenomyosis complicated with cerebral infarction. This same team reported a case of adenomyosis patient with occurrence of cerebral thrombosis without apparent cause in 2014.[3] The authors thought blood loss anemia caused by adenomyosis and elevated levels of CA125 could promote the high coagulation state and lead to cerebral thrombosis. There were many studies taking anemia as a risk factor of embolism. By investigating its pathogenesis, some people thought that was due to thrombocytosis after anemia, but other theories thought that[4] quantity of platelet did not increase when anemia, the thrombosis was caused by hematic high coagulation state because of long-time blood loss. Moreover, some studies indicated that hypoxia damage of terminal arteries caused by anemia would result in thrombosis. CA125 was a marker of epithelial ovarian tumor, and a kind of sticky protein that could lead to hematic high coagulation state. This case had long-term severe blood loss anemia, accompanied

by abnormally high CA125 level, these factors made blood in a high coagulation state for a long time, and eventually led to thrombosis on a stimulation of E2 peak caused by GnRH-a.

Thrombophilic Condition

Notably, the patient was diagnosed as CAPS finally. The titers of ACA of the patient were not high, but β2-glycoprotein 1 IgAGM antibody was continuing positive for a period of 6 weeks. Positive result of antiphospholipid antibodies was one of the high risk factors of thrombosis. It was reported[5] that β2-glycoprotein 1 antibody had strong correlation with thrombosis. Because of the limitation of our clinical laboratory, we could not examine other coagulation factors, such as protein C or S, antithrombin III. Deficiencies of those factors were also the cause of embolism.

In conclusion, this case of thrombosis may be multi-factorial, but the occurrence of thrombosis had close temporal relationship to GnRH-a administration. Many investigations believed that GnRH-a could reduce inflammation and angiogenesis, relieve pain, improve anemia condition, and could be considered as an effective therapy to preserve the uterus. The case suggested that GnRH-a should be used with caution in adenomyosis patients who had recently used oral contraceptive agents or other estrogenic drugs, chronic severe anemia, or high CA125. Coagulation function should be checked before the use of GnRH-a, perhaps, it should be used after anemia has been corrected and blood coagulation status has been improved. It may be necessary to give prophylactic anticoagulation therapy in high coagulation state. More importantly, we should inform patients about the risk of thromboembolism.

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Conflicts of interest

There are no conflicts of interest.

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