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Case Report

Association of hemorrhagic shock and pulmonary embolism following the administration of dienogest in a patient diagnosed with adenomyosis ☆

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ABSTRACT

Adenomyosis is a chronic disease associated with abnormal uterine bleeding and debilitating pain with severely reduced quality of life in many affected women. Primary strategies for its management encompass surgical interventions, hormonal therapy, or a synergistic blend of these therapeutic modalities. Dienogest (DNG), a new progestin, is primarily utilized to treat adenomyosis due to its exceptional selectivity for the progesterone receptor. In this uncommon case report, we introduce a 42-year-old woman who experienced hemorrhagic shock as a result of uterine bleeding and pulmonary embolism that occurred while a patient was undergoing dienogest therapy for uterine adenomyosis. This situation necessitated blood transfusion and introduction of drugs then an emergency hysterectomy was scheduled followed by the initiation of anticoagulation. We hypothesize that the emergence of pulmonary embolism was intimately tied to adenomyosis, and the occurrence of hemorrhagic shock was likely due to the intake of dienogest.

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Introduction

Uterine adenomyosis is a chronic disorder characterized by the presence of endometrial tissue within the myometrium,

resulting in uterine enlargement, abnormal uterine bleeding, pelvic pain, and infertility [1]. The main management options include surgery, hormone therapy, or a combination of these 2 approaches [2]. Commonly used hormone therapies include gonadotropin-releasing hormone agonists, estrogen/

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progestin combinations, and progestins [3]. Dienogest is a progestin widely used as a first-line therapy in symptomatic women and in situations where surgery is either not feasible or declined by the patient [4].

Progestin is often regarded as an optimal choice for the long-term management of adenomyosis due to its minimal adverse effects [5].

Here, we outline a case involving hemorrhagic shock and pulmonary embolism occurring during dienogest therapy for uterine adenomyosis, necessitating emergency hysterectomy and anticoagulation therapy. Additionally, we investigate the root causes of bleeding and the risk of embolism.

Case report

A 42-year-old woman, previously diagnosed with uterine adenomyosis, presented to our emergency department with abrupt chest pain, breathing difficulties, and significant menometrorrhagia.

One month prior, the patient had initiated a progestin-only hormone treatment regimen of 2 mg per day (Dienogest).

The patient was dyspneic and resting sinus tachycardia was observed, with a heart rate of 110 beats per minute, a systolic blood pressure of 70 mmHg, an oral temperature of 36.5°C, and a saturation level of 85%.

The gynecological examination revealed significant uterine bleeding. However, both the cardiovascular and pleuropulmonary examinations yielded normal results, and there were no clinical signs of deep vein thrombosis.

The patient did not have any recent prolonged periods of immobilization, nor did she have a personal or family history of prothrombotic conditions. Additionally, there were no signs or documented history of COVID-19 infection, and she had received her third vaccine dose 6 months prior.

The electrocardiogram revealed sinus rhythm with a heart rate of 110 beats per minute, an S1Q3 pattern, and negative T waves in the anteroseptal leads.

Initial blood tests revealed severe anemia with a hemoglobin level of 5.9 g/dL and a platelet count of $8 \times 10^3/\mu\text{L}$. Serum liver enzymes and renal function were within normal limits, with albumin at 3.7 g/dL and a PT-INR of 1.46. D-dimer levels were elevated, peaking at 920 mg/L (reference limit: 500 mg/L), and CA125 levels were also high before starting medication and during the hemorrhagic episode.

Initially, a diagnosis of hemorrhagic shock secondary to uterine bleeding was established, and the patient underwent blood transfusion, receiving 5 units of red blood cell concentrate, fresh frozen plasma, and platelets. Additionally, drugs were initiated, resulting in an improvement in her hemodynamic parameters.

Subsequent investigation with computed tomography pulmonary angiography (CTPA) revealed bilateral pulmonary embolism (PE) affecting segmental branches of the lower lobes (Figs. 1 and 2). Doppler ultrasound of the lower limbs did not reveal any evidence of deep vein thrombosis.

Transthoracic echocardiogram revealed significant dilation of the right heart along with paradoxical septal motion and normal right ventricular systolic function. The left ventricular

ejection fraction (LVEF) was found to be normal at 67%. Additionally, a small pericardial effusion was observed (Fig. 3).

Additionally, a pelvic MRI was conducted, revealing Type I adenomyosis with a uterine size measuring 102×93 mm (Fig. 4) with an estimated volume of 500 cm³.

Various common causes of pulmonary embolism (PE) were investigated. A PCR test for SARS-CoV-2 conducted on a nasal swab sample was negative. Furthermore, laboratory assessments for thrombophilia and autoimmune disorders, including anti-nuclear and antiphospholipid antibodies, were conducted and all yielded negative results. Additionally, a search for underlying malignancy was carried out, but no abnormalities were detected.

After a multidisciplinary discussion, systemic anticoagulation with low molecular weight heparin was started immediately and an emergency hysterectomy was considered due to the high bleeding risk.

After hysterectomy, the histological examination of the uterus revealed regular-appearing endometrial glands surrounded by an endometrial-type stroma within the myometrium (b: H&E, x40). Furthermore, several endometrial glands were observed near the uterine serosa (a: H&E, x40) (Fig. 5).

The patient had an uneventful recovery and was discharged after 2 weeks on direct oral anticoagulant for the ensuing 6 months.

Discussion

We are confronted with an unusual case report involving the occurrence of both pulmonary embolism and severe uterine bleeding following the administration of dienogest in a patient diagnosed with adenomyosis.

Often affecting women in their late reproductive years, between the ages of 40 and 50, uterine adenomyosis is a chronic and benign condition characterized by the presence of endometrial tissue within the myometrium [1].

Dysmenorrhea, dyspareunia, persistent pelvic discomfort, abnormal uterine hemorrhage, and infertility are some of the clinical signs; nevertheless, about one-third of these cases are entirely asymptomatic [2].

In symptomatic women, the main management options include surgery, hormone therapy, or a combination of these two approaches [3].

Hysterectomy is the definitive treatment. Hormone treatments, on the other hand, are frequently utilized as a first-line therapy when surgery is either not feasible or the patient refuses it.

Hormonal treatment options such as oral contraceptive pills, high doses of progestin, levonorgestrel-releasing intrauterine device (LNGIUD), gonadotropin-releasing hormone agonist (GnRH-a), and danazol are viable therapeutic approaches for managing both adenomyosis and endometriosis [4].

A novel progestin, known as dienogest (DNG), distinguished for being classified as a 19-nortestosterone derivative, exhibits notable bioavailability and potent progestational ef-

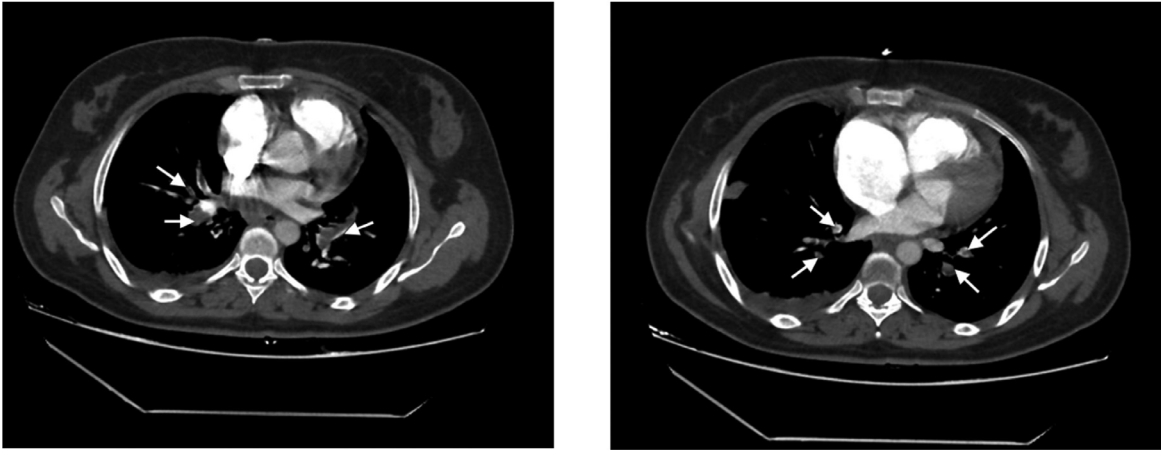


Fig. 1 – Axial section of CTPA showing bilateral PE (white arrow).

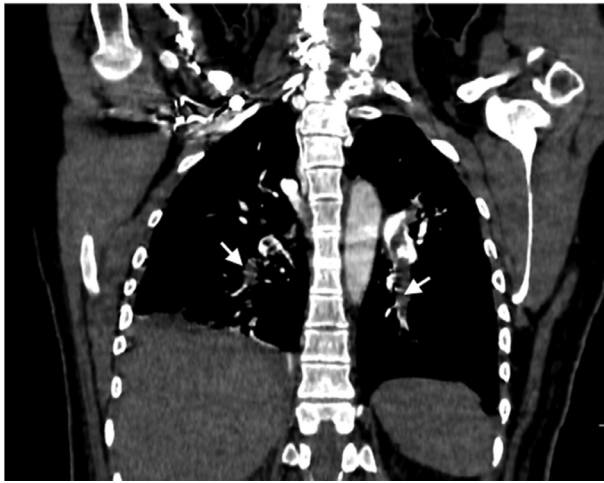


Fig. 2 – Cross section of CTPA showing bilateral PE (white arrow).

ficacy, primarily attributable to its remarkable selectivity for the progesterone receptor is used to treat adenomyosis [6].

A randomized study, double-blind, multicenter, and placebo-controlled conducted in Japan, revealed that nearly all patients with adenomyosis who were treated with DNG (Dienogest) experienced metrorrhagia. This phenomenon was commonly observed during the initial months of therapy. Furthermore, the majority of genital bleeding reported in the DNG group consisted of spotting or breakthrough bleeding [7].

Nevertheless some patients with adenomyosis can experience a non-tolerated bleeding following the administration of DNG, a retrospective cohort study showed that subtype I adenomyosis could predict the probability of significant, unpredictable bleeding episodes during uninterrupted DNG therapy [8]. It is noteworthy that our patient had Type I adenomyosis.

Therefore, careful consideration should be given when prescribing dienogest to patients with adenomyosis due to the increased risk of significant bleeding during therapy [9].

Another study conducted in Japan observed parameters linked to the coagulation and fibrinolysis systems during menstruation in 8 adenomyosis patients. The findings revealed that the coagulation system was significantly active



Fig. 3 – Echocardiogram showing right heart dilatation (white arrow).

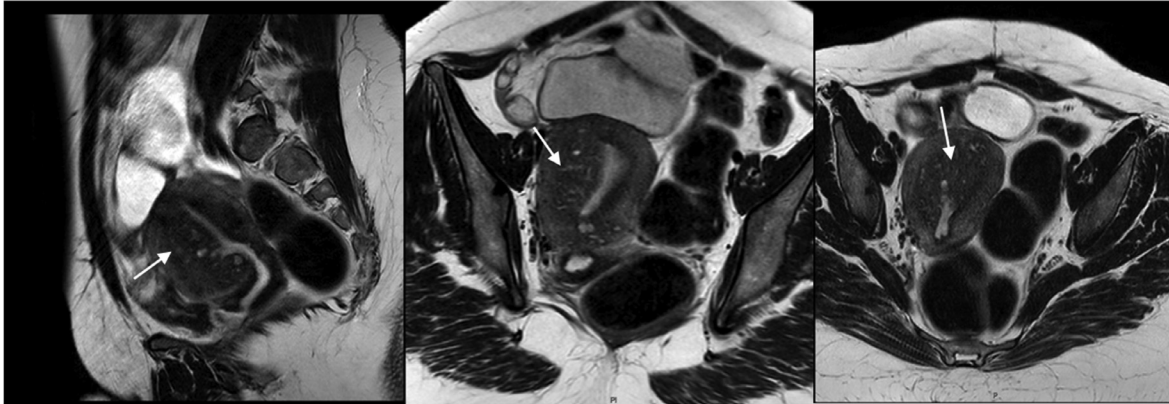


Fig. 4 – MRI images showing type I adenomyosis (white arrow).

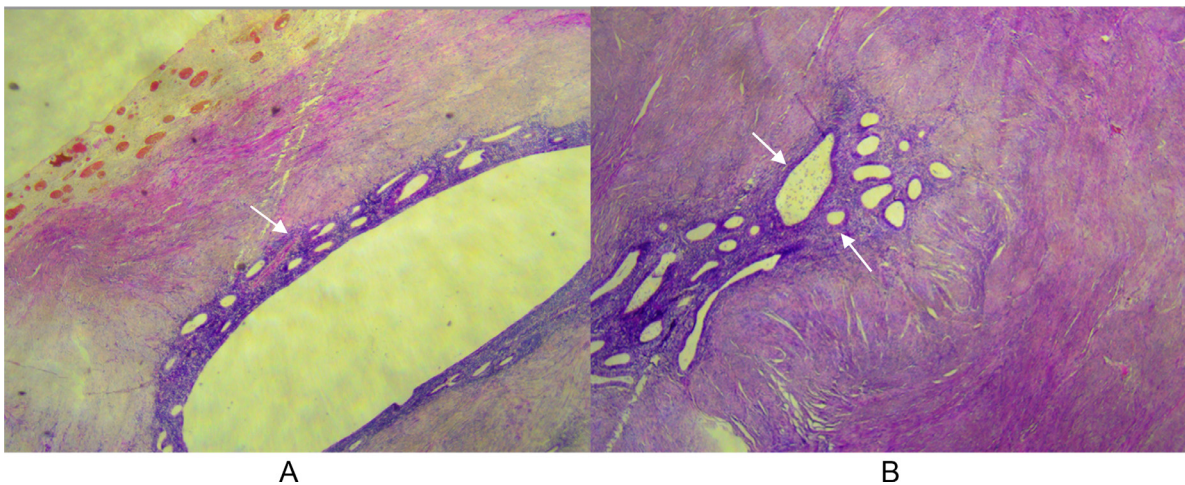


Fig. 5 – (A and B) Histopathological images showing an eutopic endometrium (white arrow in A) and a myometrium with adenomyosis (white arrows in B).

in most patients with a uterine volume exceeding 100 cm³, whereas the fibrinolysis system exhibited activation in a subset of these patients [10]. We noted in our case that uterine volume was surmounting 100 cm³.

We also observed that our patient exhibited a high level of CA125 before starting medication and during the hemorrhagic episode, this elevation is suggested to simultaneously contribute to the hypercoagulable state in patients [11], and to uterine bleeding during treatment with dienogest in adenomyosis [5].

From a similar perspective, Yamashiro et al. reported four cases of cerebral infarction linked to adenomyosis they suggested that patients with adenomyosis could be prone to developing infarctions due to hypercoagulability associated with menstruation-related coagulopathy or increased tissue factors [12].

In light of these findings and in conjunction with the current results we hypothesize that adenomyosis affects both the coagulation and fibrinolysis systems.

It might be quite challenging to manage PE in adenomyosis patients. The risk of bleeding must be taken into account when deciding whether to use anticoagulant treatment.

In the case studies reported, anti-coagulation associated with hysterectomy was the most commonly used treatment [13]. And indeed, this is the approach we pursued with our patient.

Patient consent

Written informed consent for the publication of this case report was obtained from the patient.

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