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CASE REPORT

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# Isolated distal deep vein thrombosis associated with adenomyosis: Case report and literature review

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**Key Clinical Message**

While adenomyosis is commonly associated with a mild risk of thrombotic complications, the presence of additional thrombophilia factors can increase this risk, particularly in individuals with severe symptoms and elevated CA125 levels.

**KEYWORDS**

adenomyosis, CA125, case report, deep vein thrombosis, pulmonary embolism, stroke

## 1 | INTRODUCTION

Thromboembolism is a common and potentially life-threatening complication that can arise from various medical conditions, including malignancy and a spectrum of benign diseases, such as inflammatory disorders, autoimmune diseases, inherited thrombophilia, obesity, pregnancy, and prolonged immobilization.[1] Adenomyosis, characterized by the presence of endometrial glands and stroma within the myometrium, is a benign uterine disorder that typically presents in middle-aged postpartum women with symptoms of menorrhagia, dysmenorrhea, and chronic pelvic pain. The true prevalence of adenomyosis remains unknown, although estimates derived from patients referred for pelvic imaging suggest a range of 20%–34%.[2] In 1991, Kupryjańczyk described a case of intravascular endometriosis with thrombosis in a patient diagnosed with adenomyosis.[3] Subsequently, several isolated case reports and case series have documented the occurrence of ischemic stroke[4–21] and pulmonary embolism (PE)[22,23] in patients with adenomyosis, suggesting a possible association with hypercoagulability induced by this disorder. However, there are few reports of cases complicated by isolated deep vein thrombosis (DVT).[24,25] In this report, we present a case of isolated distal deep venous thrombosis (IDDVT) of the right lower extremity in a patient with a 1.5-year history of adenomyosis. We also conducted a comprehensive literature review to explore the

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clinical features, treatment approaches, and prognosis of thrombotic complications associated with adenomyosis.

## 2 | CASE HISTORY

A 50-year-old woman presented at our outpatient clinic with acute pain in her right lower extremity after long-distance travel. She complained of a significant exacerbation of the pain over the past 10 h, despite the administration of oral diclofenac sodium. The patient presented with stable vital signs, including a blood pressure of 120/80 mmHg, heart rate of 80/min, respiratory rate of 20/min, and a temperature of 36.2°C. She reported no chest pain, chest tightness, or dyspnea. She married at an adult age (G1, P1), and her husband and child were in good health. She was on the third day of her menstrual cycle. She had no history of hypertension, diabetes mellitus, cardiovascular disease, or venous thromboembolism (VTE). She also denied any family history of these conditions. The patient had previously been diagnosed with adenomyosis 18 months ago and had undergone 3 months of gonadotropin-releasing hormone agonist (GnRHa) therapy. Given the potential diagnosis of DVT, D-dimer and lower extremity venous ultrasound were done, which demonstrated the presence of vein thrombosis in her calf of the right lower extremity (Figure 1A). Her D-dimer and fibrin degradation product levels were found to be markedly elevated at 6.19 μg/mL (normal <0.5 μg/mL) and 25 μg/mL (normal <5.0 μg/mL), respectively. She was admitted to our hospital and initiated anticoagulation therapy using heparin.

## 3 | METHODS

Laboratory investigation revealed a slight reduction in hemoglobin concentration (111 g/L, normal range: 115–150 g/L), along with significantly elevated levels of carbohydrate antigen 125 (CA125) at 687 U/mL (normal range < 35 U/mL) and carbohydrate antigen 199 (CA199) at 64.5 U/mL (normal range < 35 U/mL). There were no significant abnormalities for white blood cell count, platelet count, coagulation function, biochemistry panel, autoantibodies, antiphospholipid antibodies, or lupus anticoagulant tests. A chest computed tomography (CT) scan was unremarkable. Given the elevated tumor biomarker levels, an abdominal CT scan and gynecologic ultrasound were performed to rule out malignancy. No space-occupying lesions were detected, but a significantly enlarged uterine corpus (Figure 1B) confirmed adenomyosis via ultrasonography (Figure 1C).

## 4 | CONCLUSION AND RESULTS

After a 7-day course of heparin anticoagulation therapy, the patient experienced complete resolution of lower extremity pain and a reduction in D-dimer levels to 0.87 μg/mL. However, her CA125 level remained high at 401.8 U/mL (Figure 2). She was discharged on an oral course of rivaroxaban (20 mg QD) which continued until the second month post-discharge when she underwent a hysterectomy for adenomyosis treatment, based on the gynecologist's recommendation and personal preference. One month after the procedure, repeat tests for CA125, CA199,

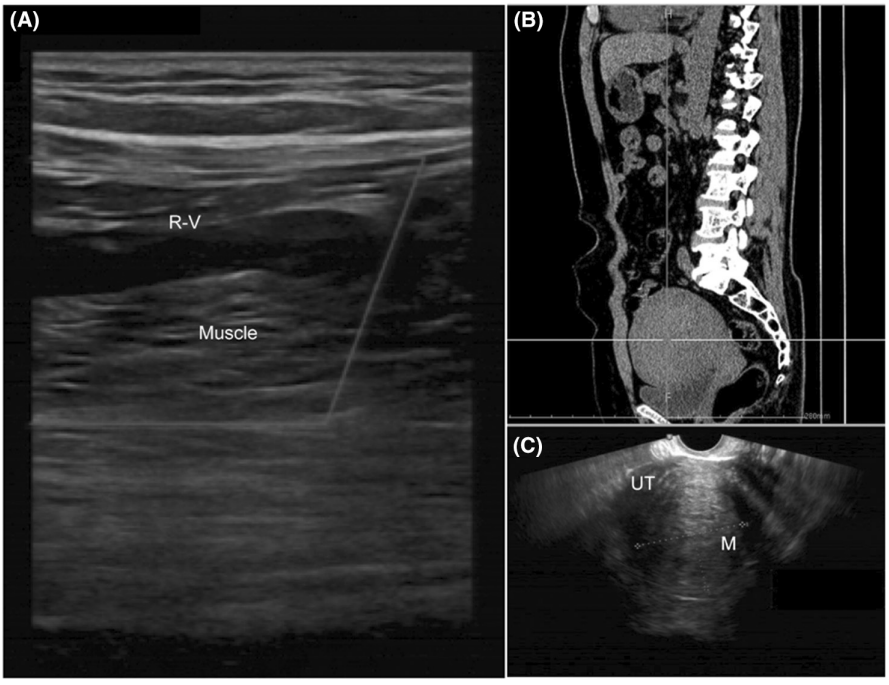


FIGURE 1 Imaging findings of the presented case. (A) Thrombosis of the distal vein of the right lower extremity. The lumen of the vein exhibits a moderately hypoechoic plaque, while color Doppler flow imaging (CDFI) detects a filling defect within the lumen, along with an absence of a blood flow signal. (B) An abdominal CT scan illustrates a substantially enlarged uterus. (C) Gynecologic ultrasound confirms the presence of adenomyosis.

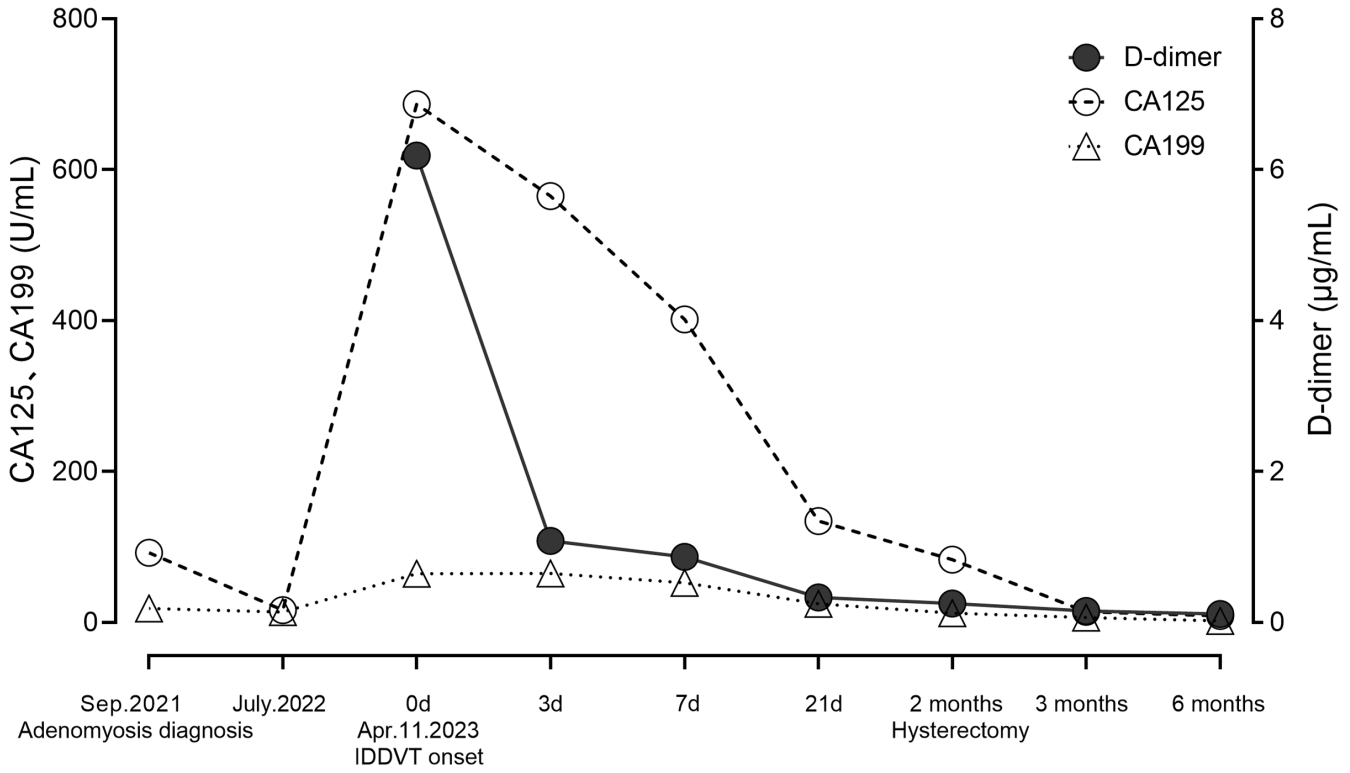


**FIGURE 2** Dynamic changes in CA125, CA199, and D-dimer levels for the reported patient.

and D-dimer revealed values within the normal range. No thrombus recurrence was observed during the 6-month follow-up period.

## 5 | DISCUSSION

This report presents a case of IDDVT that was potentially associated with adenomyosis. The patient experienced a thrombotic episode on the first day following long-distance travel, which coincided with her menstrual phase of the menstruation cycle. We suggest that the combined effects of hypercoagulability related to adenomyosis and blood stasis from long-distance travel may have contributed to the development of IDDVT. The patient was effectively managed using heparin in combination with Panax notoginseng saponins, a traditional Chinese medicine known for its anti-inflammatory, antioxidant, and cardiovascular protective effects. She was discharged with oral rivaroxaban for thromboprophylaxis. Two months post-discharge, she underwent a hysterectomy for the treatment of adenomyosis to reduce the risk of recurrence.

The true incidence of adenomyosis-related thrombotic complications remains uncertain. Ischemic stroke has been observed in 0.1%–0.8% of patients with adenomyosis according to early single-center studies.[26] Limited data are available regarding other types of thrombotic events. To further investigate this association, we conducted a literature search on PubMed using the terms "adenomyosis AND thrombo OR infarction." This search strategy yielded a total of 22 eligible case or series reports (Table 1), including 25 cases (75.7%) of ischemic stroke,[4–21] 6 cases (18.2%) of PE,[22,23] and 2 cases (6.1%) of DVT.[24,25] The median age of these documented patients was 45 years (range 34–59), with a tendency to experience thrombotic events during menstrual cycles. These epidemiological findings align with adenomyosis itself, an estrogen-dependent condition that is seldom diagnosed in premenarchal or postmenopausal women.

As summarized in Table 1, both arterial and VTE have been documented in patients with adenomyosis. Among these cases, multiple cerebral infarctions were the most frequently observed, accounting for 18 out of 33 cases (54.5%). Notably, seven of these cases (38.9%) exhibited systemic embolism,[4,5,10,14,16,18] resembling Trousseau's syndrome commonly seen in cancer patients. These observations suggest that hypercoagulability may play a significant role in the pathogenesis of thrombotic complications related to adenomyosis. Consistent with this speculation, previous studies have identified a procoagulant state in patients with adenomyosis, which is further exacerbated during menstruation and accompanied by activation of fibrinolysis.[27]

The mechanisms underlying hypercoagulability in patients with adenomyosis may be multiple. First, an early study found increased reactivity of tissue factor, a major

**TABLE 1** Reported cases of adenomyosis-associated stroke, PE, and DVT.

| Ref. | Case no. | Age | Onset during menstruation | Diagnosis | Thrombus location | NBTE | Systemic embolism | Recurrence (period) |
|---|---|---|---|---|---|---|---|---|
| *Ischemic stroke* | | | | | | | | |
| [4] | 1 | 50 | Yes | Multiple CIs | Brain, spleen, kidney | Yes | Yes | Yes (1 year) |
| [5] | 2 | 45 | No | Multiple CIs | Brain, left fingers | No | Yes | No |
| | 3 | 44 | Yes | Multiple CIs | Brain, kidney | No | Yes | No |
| | 4 | 50 | Yes | Multiple CIs | Brain | No | No | No |
| | 5 | 42 | Yes | Multiple CIs | Brain | No | No | Yes (1 year) |
| [6] | 6 | 47 | – | CVT | Brain | No | No | No |
| [7] | 7 | 59 | – | Multiple CIs | Brain | Yes | No | No |
| [8] | 8 | 49 | No | Multiple CIs | Brain | Yes | No | No |
| [9] | 9 | 48 | No | Multiple CIs | Brain | Yes | No | No |
| [10] | 10 | 44 | Yes | Multiple CIs | Brain, spleen | No | Yes | Yes (6 months) |
| [11] | 11 | 42 | – | Single CI | Brain | No | No | No |
| | 12 | 50 | – | Single CI | Brain | No | No | No |
| [12] | 13 | 34 | Yes | Multiple CIs | Brain | No | No | No |
| | 14 | 37 | Yes | Single CI | Brain | No | No | No |
| | 15 | 46 | Yes | Multiple CIs | Brain | No | No | No |
| [13] | 16 | 34 | Yes | Multiple CIs | Brain | No | No | No |
| [14] | 17 | 48 | Yes | Multiple CIs | Brain, kidney | No | Yes | No |
| [15] | 18 | 50 | Yes | Multiple CIs | Brain | No | No | Yes (7 days) |
| [16] | 19 | 46 | Yes | multiple CIs + PE + VTE | Brain, lung, right lower extremity | No | Yes | No |
| [17] | 20 | 42 | Yes | CVT | Brain | No | No | No |
| [18] | 21 | 47 | Yes | Multiple CIs | Brain, kidney | No | Yes | Yes (1 month) |
| [19] | 22 | 38 | Yes | CVT | Brain | – | No | Yes (10 days) |
| | 23 | 34 | – | CVT | Brain | – | No | No |
| [20] | 24 | 42 | Yes | Multiple CIs | Brain | – | No | Yes (1 month) |
| [21] | 25 | 47 | Yes | Multiple CIs | Brain | Yes | No | No |
| *Pulmonary embolism* | | | | | | | | |
| [22] | 1 | 38 | – | PE | Lung | – | No | No |
| [23] | 2 | 44 | – | PE + DVT | Lung, left lower extremity | – | Yes | No |
| | 3 | 38 | – | PE | Lung | – | No | No |
| | 4 | 50 | – | PE | Lung | – | No | No |
| | 5 | 45 | – | PE | Lung | – | No | No |
| | 6 | 51 | – | PE + DVT | Lung, left lower extremity | – | Yes | No |
| *Deep vein thrombosis* | | | | | | | | |
| [24] | 1 | 37 | – | DVT | Left femoral vein | – | No | Yes (10 years) |
| [25] | 2 | 34 | – | DVT | Left lower extremity | – | No | No |

*Note*: –: Data not reported.

Abbreviations: CIs, cerebral infarcts; CVT, cerebral venous thrombosis; DVT, deep vein thrombosis; GnRHa, gonadotropin-releasing hormone agonist; IVC, inferior vena cava; NBTE, nonbacterial thrombotic endocarditis; VKA, vitamin K antagonist.

| CA125 (U/mL) | D-dimer (μg/mL) | HGB (g/dL) | Treatment for VTE (initial, subsequent) | Treatment for adenomyosis | Thrombotic recurrence-free follow-up time |
|---|---|---|---|---|---|
| 1579 | 95.7 | 9.8 | Edaravone→Magnesium sulfate | Hysterectomy | 2 years |
| 159 | 1.1 | 8.4 | Heparin→Antiplatelet | GnRHa | – |
| – | – | 7.0 | Heparin→Warfarin | GnRHa | – |
| 42.6 | 0.57 | 6.9 | Aspirin | GnRHa | – |
| 1750 | 6.0 | 8.6 | Heparin→Warfarin | GnRHa | – |
| 784.6 | 6.3 | 7.6 | Heparin→Warfarin→Antiplatelet | Adenomyosis resection | 2 years |
| 334.8 | 7.0 | – | Heparin | None | 6 months |
| 379 | 3.99 | 9.9 | Heparin→Oral VKA | Hysterectomy | 3 months |
| 901 | 1.9 | 8.5 | Heparin→Warfarin | Hysterectomy | – |
| 2115 | 17.0 | 7.3 | Heparin→Rivaroxaban→Warfarin | GnRHa→Hysterectomy | 2 years |
| 395 | 1.4 | – | Warfarin | – | 68 months |
| 143 | 3.7 | – | Rivaroxaban | - | 19 months |
| 937.1 | 1.05 | 13.4 | – | – | – |
| 735.7 | 23.4 | 10.8 | – | – | – |
| 546.5 | 12.04 | 12.1 | – | Hysterectomy | – |
| 937.7 | 27.4 | 11.2 | Heparin→Antiplatelet | None | 4 months |
| 3536 | 79.3 | 8.2 | Thrombectomy→Heparin→Edoxaban | Hysterectomy | 15 months |
| 999 | 6.4 | 9.2 | Heparin→Apixaban | GnRHa →Hysterectomy | 18 months |
| 1477 | 7.4 | 9.6 | Heparin→Antiplatelet→Rivaroxaban | Hysterectomy | 16 months |
| 155 | 2.5 | 8.4 | Heparin→Dabigatran | Progesterone only pills | 2 months |
| 90.3 | 3.8 | 11.3 | Heparin→Edoxaban | Hysterectomy | 5 years |
| – | 3.9 | 7.5 | Heparin→Warfarin | None | – |
| 312.4 | 18.63 | 7.6 | Heparin→Warfarin | Adenomyosis resection | – |
| 293 | – | – | Heparin→Edoxaban | GnRHa→Hysterectomy | 10 months |
| 48 | 30 | 3.4 | Warfarin | Medroxyprogesterone→Hysterectomy | 3 years |
| – | – | – | Thrombolytic and anticoagulant therapies | Hysterectomy | – |
| - | – | 7.3 | Warfarin | GnRHa→Hysterectomy | – |
| – | – | 4.5 | Rivaroxaban | GnRHa→Hysterectomy | – |
| – | – | 6.2 | Warfarin | GnRHa | – |
| – | – | 11.4 | Warfarin | GnRHa | – |
| – | – | 7.9 | Thrombolytic therapy, warfarin, IVC filter | GnRHa→Hysterectomy | – |
| – | – | – | Oral VKA | Hysterectomy | – |
| – | – | – | – | GnRHa | – |

physiological initiator of blood coagulation,[28] in ectopic endometrium obtained from women with adenomyosis compared to normal endometrium.[29] This heightened TF activity was identified to correlate with the severity of adenomyosis.[29] Second, the normal endometrium experiences repeated proliferation, decidualization, and shedding across the menstrual cycle, which is a fine balance between tissue injury and repair tuned by the endocrine, immune, vascular, and coagulation systems.[30] However, adenomyosis may disrupt this balance, and the ectopic endometrium and its associated vascular malformations can lead to impaired spontaneous decidualization, resulting in persistent inflammation and hemorrhage, which subsequently triggers the thromboinflammation pathway.[27,31] Last, it is worth noting that the thickened endometrium during menstruation is rich in mucins, which have been associated with thrombophilia in individuals with mucinous cancer.[32,33] The endometrium serves as the primary source of CA125 in females, which can rise to eight times the upper reference limit (35 U/mL) during menstruation and return to baseline at the conclusion of the menstrual cycle.[34] In the context of adenomyosis, it is plausible to hypothesize that impaired decidualization may lead to sustained elevation of CA125 levels for prolonged durations. The current case, along with previous reports, provides supportive evidence for this hypothesis. Notably, elevated CA125 levels have been observed in certain patients during their nonmenstrual periods,[5,8,9] and in our case, the elevated CA125 level persisted for approximately 2 months until hysterectomy was performed (see Figure 2).

The association between CA125 levels and the severity of adenomyosis remains uncertain. Nonetheless, a pooled analysis of 23 documented stroke cases[4–21] with CA125 measurements revealed a significant increase in CA125 levels among nine individuals (cases 1, 2, 5, 10, 17–19, 21, 24) experiencing systemic embolism (defined as stroke complicating extremity or organ embolism) and/or recurrent embolism, in contrast to the 14 cases (cases 4, 6–9, 11–16, 20, 23, 25) with isolated and nonrecurrent embolism (see Figure 3). This preliminary investigation emphasizes the need for further research to establish the potential value of CA125 in the treatment and monitoring of thrombotic complications associated with adenomyosis.

The source of emboli has been investigated in several previous case studies. In a subset of 21 cases with cerebral infarcts, nonbacterial thrombotic endocarditis (NBTE) was detected in seven cases through transesophageal echocardiography, suggesting the potential presence of cardiogenic emboli. Considering that some cases were reported a decade ago, the postulated incidence of NBTE may be higher under current circumstances due to the use of more sensitive ultrasound technology. Notably, NBTE is

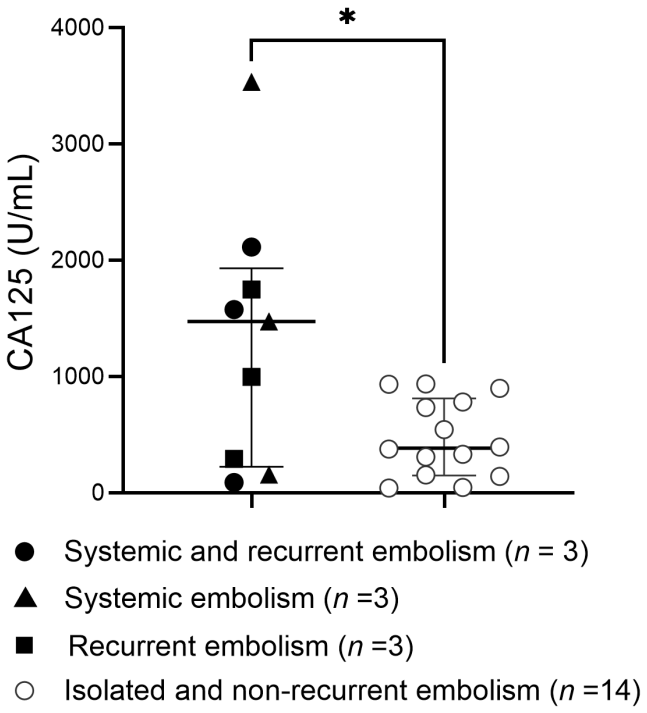


**FIGURE 3** Comparison of CA125 levels between patients experiencing systemic and/or recurrent embolism and those with isolated and nonrecurrent embolism. The central horizontal line shows the median, with the shorter horizontal lines positioned above and below denoting the interquartile range. *$p = 0.015$, according to the Kolmogorov–Smirnov test.

commonly observed in patients with malignancy and connective tissue diseases,[35,36] and yet its potential relationship with adenomyosis remains unexplored. Therefore, future research is essential to elucidate whether adenomyosis acts as a contributing factor or a mere incidental discovery in cases where NBTE serves as the primary trigger for embolic events. To date, there have been six documented cases of PE, with five originating from a single center in Singapore. Of these, two were complicated by lower extremity DVT, indicating the likelihood of peripheral distal emboli. However, the remaining four cases did not exhibit DVT, and other known risk factors for VTE were ruled out. It has been noted that in up to 50% of PE cases, no DVT is found by ultrasonography.[37,38] One possible explanation is the existence of a thrombus in a less common location or previous complete embolization of the whole thrombotic mass.[38] Yamanaka et al. documented how magnetic resonance imaging identified multiple signal hyperintense spots within adenomyotic tissues, likely representing ectopic endometrium or microhemorrhage in the myometrium. They postulated that this condition modifies the coagulation system through local inflammation and the formation of microthrombi, which could lead to embolization into the systemic circulation and subsequent embolic events.[27]

Isolated DVT associated with adenomyosis is rare, with only two documented cases. It is worth noting that one out of these two cases also presented with other thrombotic risk factors in addition to adenomyosis. Specifically, one case had hyperhomocysteinemia,[24] while our case developed DVT after long-distance travel. These findings underscore the necessity for systematic assessment of thrombotic risk and the implementation of thromboprophylaxis education for patients diagnosed with adenomyosis.

The management of thrombotic complications associated with adenomyosis comprises two essential aspects: anticoagulation therapy during the acute phase of thrombophilia and treatment specifically targeting adenomyosis. Consensus regarding the optimal anticoagulation regimens for thrombotic complications related to adenomyosis is lacking. While conventional anticoagulation therapy using heparin, warfarin, or new oral anticoagulants has demonstrated efficacy in most patients, 4 out of 33 individuals experience recurrence within 1 month. Further evaluation is needed to assess the potential benefits of escalating anticoagulant dosage or prolonging therapy duration. Additionally, the effectiveness of integrating anticoagulation with adenomyosis treatment to control thrombotic exacerbations or recurrences remains uncertain. Information on treatment strategies for adenomyosis is available for 26 patients according to the original literature. Among these cases, 15 received initial treatment with hormone therapy, seven of which eventually underwent hysterectomy. Additionally, 11 cases were directly scheduled for surgical procedures, including eight hysterectomies, two adenomyosis resections, and one supracervical hysterectomy. Although the extended therapeutic use of GnRHa effectively alleviated symptoms in select cases, three patients persisted in experiencing thrombosis or recurrence despite GnRHa treatment.[10,15,20] In such cases, hysterectomy is often considered a final option. There was no reported thrombotic recurrence during postoperative follow-up.

We present a rare case of IDDVT that was potentially attributed to adenomyosis-associated hypercoagulability and travel-related blood stasis. This case study highlights the importance of etiologic investigation and treatment in the management of thrombotic complications. A comprehensive analysis of previously documented cases suggests that CA125 may serve as a promising biomarker for predicting recurrent or systemic thromboembolism in patients with adenomyosis. Additionally, it is noteworthy that the risk window for thrombotic events in patients with adenomyosis may extend beyond the menstrual phase of the menstruation cycle, suggesting a longer duration of susceptibility. Therefore, adenomyosis should be regarded as a potential risk factor for thromboembolism. Aggressive thrombotic risk assessment should be considered as part of clinical practice for patients with this condition, particularly those presenting with severe symptoms and significantly elevated CA125 levels.

## AUTHOR CONTRIBUTIONS

**Xiaolong Zong:** Conceptualization; writing – original draft. **Xuechao Wang:** Writing – review and editing. **Shenjia Liu:** Resources; visualization. **Xuemei Tang:** Investigation; resources. **Dayong Zheng:** Conceptualization; supervision.

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## CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

## DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article.

## CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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