

Adenomyosis-associated Recurrent Acute Cerebral Infarction Mimicking Trousseau's Syndrome: A Case Study and Review of Literature

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Abstract

Adenomyosis is a common, benign uterine disease. Acute cerebral infarction (CI) associated with adenomyosis is rarely reported and difficult to treat. We experienced successful treatment for this disease. A 50-year-old woman presented with a two-day history of visual disturbance. Magnetic resonance imaging showed multiple tiny diffusion-weighted high-density spots on several lobes. No common risk factors for stroke were detected. Cancer antigen 125 Level was 999 U/mL, along with massively expanded uterus and adnexa. Based on the diagnosis of benign adenomyosis, direct oral anticoagulants and GnRH agonists were administered for CI and adenomyosis, respectively. Acute CI recurred seven days after admission. We suspected a relationship between infarction and adenomyosis, and concluded hysterectomy as a proper treatment strategy based on literature. Eighteen months after hysterectomy, no recurrence of CI without anti-thrombus medications has been detected. Hysterectomy is a radical therapy that is effective in preventing acute CI due to adenomyosis.

Keywords: Acute cerebral infarction • Adenomyosis • CA 125 • Hysterectomy • Trousseau's syndrome

Abbreviation: TS: Trousseau's Syndrome; MRI: Magnetic Resonance Imaging; CT: Computed Tomography; MRA: Magnetic Resonance Angiography; CI: Cerebral Infarction

Introduction

Adenomyosis is a common, benign uterine disease. A pathological trait of the disease is the formation of uterine glands and stroma in the endometrial membrane. It presents with abnormal uterine bleeding, pelvic pain, and uterine growth in volume, with a prevalence of 20–35% in women [1]. The exact diagnosis is based on pathological findings, but the images obtained by radiological tests and tumor markers may be sufficient to diagnose adenomyosis by radiologists or gynecologists.

Trousseau's syndrome (TS) is characterized by cancer-related embolic events, such as deep vein thrombosis/pulmonary embolism and cerebral infarction (CI) [2]. Acute CIs are mainly caused by smoking, hypertension, dyslipidemia, abnormal glucose tolerance, and aging. Clinicians usually consider TS when observing patients with acute CIs of an unknown origin. TS accounts for a small number of patients among all stroke diseases as a cause, but it should not be misdiagnosed due to its fatality. To date, 16 cases of adenomyosis that resemble TS have been reported [3,4]. This disease shows relatively similar radiographical and demographical presentations to gynecological cancers, which confuses patients and doctors. Additionally, no standardized treatments have been verified to date. Here, we report a successfully treated extremely rare case of adenomyosis associated with recurrent acute CI.

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Case Report

A 50-year-old woman presented with a two-day history of visual disturbance that was later identified as left-sided hemianopsia. Magnetic Resonance Imaging (MRI) revealed multiple acute CIs in almost all lobes (Figure 1). The patient had a medical history of mild hypertension and adenomyosis with relatively severe symptoms that had not yet been officially diagnosed. An Electrocardiogram (ECG) showed no abnormal findings, such as arrhythmia

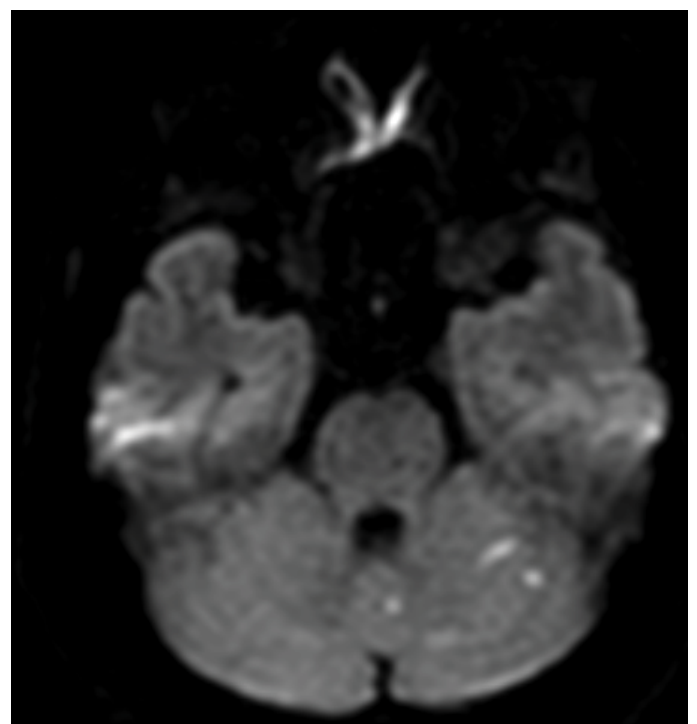


Figure 1. MRI showing spotty multiple cerebral infarction in the frontal, parietal, occipital lobes and cerebellum.

or ST-wave changes. The results of common laboratory tests were as follows: Hb 9.2 g/dL and D-dimer 6.4 $\mu\text{g/mL}$. The patient's recent menstruation was initiated two days before the onset of visual disturbance and appeared heavier than ever before. Considering the distribution of acute CIs, elevated D-dimer levels, and gynecological medical history, TS was initially suspected. As a primary treatment, the patient was administered a 10,000 U/day dose of heparin to prevent recurrence of ischemia. In addition to routine screening tests, such as carotid sonography and echocardiography which turned out to be within normal later, malignancy confirmation checks, such as abdominal computed tomography (CT) or tumor markers, were performed; the analyses suggested cancer antigen (CA) 125 level to be 999 U/mL (normal value <35 U/mL) and CA 19-9 level to be 112 U/mL (normal value <37 U/mL). The values of protein C/S, anti-thrombin III, and homocysteine were within the normal range. Pelvic CT (Figure 2) showed massively expanded uterus and adnexa that were considered as malignant lesions, such as ovarian cancer. However, detailed radiological interpretation revealed no expanded lymph nodes, and thus, adenomyosis was the first differential diagnosis. We mistakenly excluded the relationship between adenomyosis and stroke. First, conservative therapy (GnRH agonist therapy) was administered for adenomyosis, and direct oral anticoagulant (DOAC; apixaban 5.0 mg 2T2x) was prescribed for preventing ischemia. One day after discharge (on the 7th day after the first admission), the patient experienced recurrent acute CIs presenting with moderate dysarthria without any limb weakness. MRI showed several tiny acute CIs in the bilateral cerebellum (Figure 3). A review of literature on the relationship between acute CI and adenomyosis indicated simple hysterectomy to be a possible radical treatment for recurrent acute CI. The surgery was performed on the 14th day after the initial symptoms that revealed no histopathological malignancy in the uterine specimens. One month after the operation and after discontinuing DOAC, the CA 125 and CA 19-9 levels were within normal ranges. The patient had not experienced any CI relapse for 18 months.

Discussion

Adenomyosis is a relatively common disease affecting approximately 20–30% of women worldwide [1]. Acute CI induced by adenomyosis has rarely been reported in the literature. We hypothesized that this enigma is based on the values of CA 125. The past literature elucidated the average value of CA 125 in adenomyosis ($n=80$) has been reported to be slightly elevated; 91.2 U/mL (38.8 U/mL–151.8 U/mL). In the meantime, in adenocarcinoma ($n=11$) and serous adenocarcinoma ($n=11$), the mean CA 125 levels are

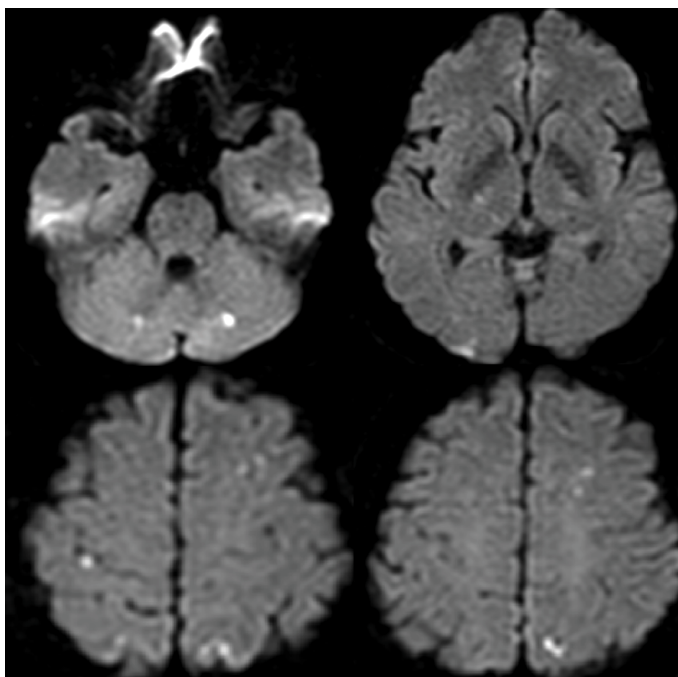


Figure 2. MRI showing tiny multiple cerebral infarctions in the cerebellum.

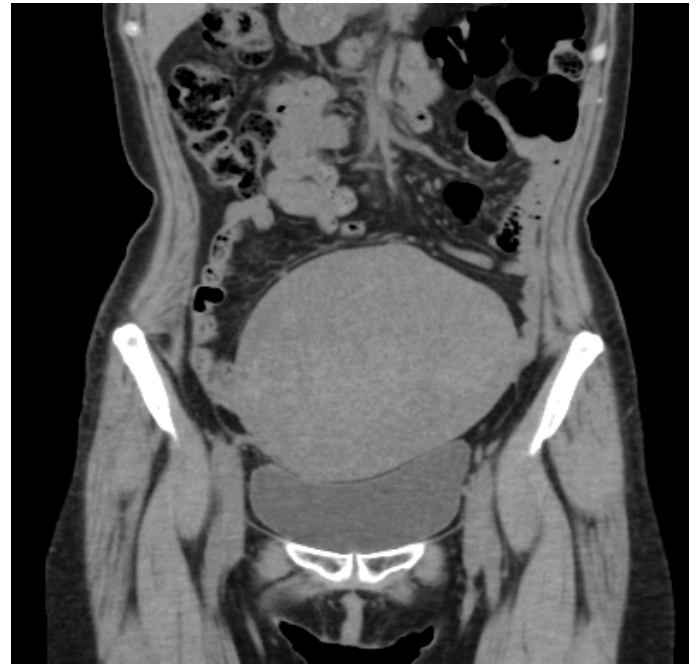


Figure 3. Plain CT showing expanded organ in the pelvis without any enlarged lymph nodes.

significantly elevated to 415.2 U/mL and 126.3 U/mL, respectively [5]. We summarize the previously reported cases. According to the previous reports [3,4], the median levels of CA 125 in cases of adenomyosis with acute CIs are significantly higher (645.1 IU/mL) than these levels. It is true that several studies have reported that infection or anemia is key factor for the development of infarctions in adenomyosis [3]. It is more important that menstruation may be a potent inducing point for CI. The serum CA 125 levels vary depending on the menstrual cycle, reaching the highest levels during menstruation [6]. In the literature, 10 out of all reported 17 cases (59%) experienced CI during menstruation that support the risk of coagulation with CA 125. Based on these facts, we strongly hypothesize that CA 125 is the main causative coagulation-activating factor. CA 125 is a member of the mucin family of glycoproteins that is commonly elevated in women with ovarian tumors, pelvic inflammatory disease, and endometriosis [7]. This glycoprotein activates the coagulation system by stimulating factor X. CI with a high level of mucinous tumor markers, but without cancer, has been reported [8]. Moreover, literature suggests that the median levels of CA 125 in the CI recurrent group (1374.5 IU/mL) are higher than those in CI non-recurrent groups (395 IU/mL), although this difference is not statistically significant due to the small number of patients. In this calculation, one patient who underwent hysterectomy as early as six days after onset was excluded from the non-recurrent group. CA 125 is a potential biomarker for detecting adenomyosis that can lead to acute CI and also for differentiating the less curable adenomyosis from benign ones.

Hysterectomy is the radical treatment for adenomyosis associated with acute CI. The present case showed recurrent CI with anticoagulant administration. Two similar cases with recurrent CI under anti-thrombus medication with GnRH agonists for adenomyosis have been reported previously [3,4]. The anti-thrombus medication may theoretically exacerbate menorrhagia and should possibly be avoided for patients with massive uterine bleeding. In a previous study [3], a patient with CA 125 levels of 3,341 mg/day and presumed to have a high possibility of recurrent acute CI was successfully cured by early radical hysterectomy (only 6 days after the initial ischemic symptoms) and survived without any recurrent CI. We firmly propose that in patients with high CA 125 levels and not planning to have babies, radical hysterectomy is an appropriate treatment. The previously reported cases recurred between 43 days and 15 months after the initial stroke [3,4]. Our case recurred at seven days after the initial stroke. Considering these periods, it may be better to prevent CI when planning to perform hysterectomy within seven days after CI. In addition, against general stroke, hysterectomy was reported to be protective in certain literature [8]. The most controversial point is the choice of therapy

for women planning to have babies, especially those with high CA 125 levels, although the average patient age (45.3 years) is beyond the fertility period for a majority of the women [3,4]. Study of a greater number of patients can help elucidate the best treatment for such cases. In the near future, by collecting data on CA 125 levels in benign adenomyosis, the threshold of CA 125 for determining its potentiality as a biomarker in acute CIs can be obtained.

Conclusion

Adenomyosis can lead to recurrent acute CIs. Hysterectomy may be a radical and appropriate treatment for such conditions.

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