Received: 26 June 2022 | Revised: 22 November 2022 | Accepted: 14 December 2022

DOI: 10.1002/ccr3.6796

CASE REPORT

Clinical Case Reports Open Access WILEY

Cerebral venous thrombosis in a patient with adenomyosis: A case report

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Abstract

Cerebral venous thrombosis can be caused by different conditions such as infectious, structural, hypercoagulable states, hematological, hormonal, collagen, vascular diseases, and oral contraceptive pills among other causes. Adenomyosis has been rarely associated with Cerebral venous thrombosis (CVT). Increased CA-125 and iron deficiency anemia in adenomyosis may predispose to CVT.

KEYWORDS

adenomyosis, cerebral venous thrombosis, iron deficiency anemia

1 | BACKGROUND

Cerebral venous thrombosis (CVT) is an important cause of stroke in young adults caused by complete or partial occlusion of the major cerebral venous sinuses or the smaller feeding cortical veins. The estimated prevalence of CVT is 1.3–1.6 cases per 100,000 people and accounts for 0.5% of all stroke cases.[1] Compared with the general population, the incidence of CVT is higher in children and women. It is caused by a multitude of risk factors including infections, hypercoagulable states, hematologic conditions, vascular disease, malignancy, and oral contraceptive pills among others.[2] Uterine adenomyosis is a condition in which endometrial glands and stroma are present within the myometrium. Although the majority of cases are asymptomatic, these patients often present in the hospital with abnormal uterine bleeding, dysmenorrhea, and uterine enlargement. Adenomyosis as a possible cause of CVT has been rarely reported.

We herein present a case of CVT of a 42-year-old female suffering from adenomyosis who presented with cerebral venous thrombosis.

2 | CASE PRESENTATION

A 42-year-old lady presented to the emergency department at our center with complaints of sudden aggravation of a frontal headache which was mild at onset and present for the last 3–4 days. It was followed by a focal seizure of left lower limb lasting for around 2 min with no postictal confusion. The headache was associated with nausea but no vomiting and partially relieved by NSAIDs. She described her headache as continuous, throbbing in nature, not associated with fever, photophobia/photophobia, or auras. There was no diurnal or nocturnal variation without any associated neck rigidity. There was no history of loss of consciousness, visual disturbances, or weakness of any part of her body. She is non-smoker, non-alcoholic, or had history of drug abuse.

Further inquiry revealed that she had menorrhagia secondary to adenomyosis and was under treatment with progesterone only pill (POP). However, she was non-compliant with her treatment. Her menstrual period had concluded a few days before her presentation to the hospital.

On examination, she had conjunctival pallor with no other significant general physical findings. Her GCS level was E4V5M6. No abnormalities were detected on a cranial nerve and ocular examination and sensory exam was normal as well. Fundoscopic examination was normal. Motor power was 4+/5 on the right upper and lower limb while it was 5/5 on left upper and lower limb. Plantar response was flexor. Systemic examinations were within normal limits. She was subjected for Non-contrast Computed tomography (CT) scan of head which showed left cortical hematoma with surrounding edema in the temporo-occipital region (Figure 1). Venous bleed was suspected and Magnetic Resonance Imaging (MRI) brain with Magnetic Resonance Venography (MRV) was ordered which revealed intra-axial cortical based hematoma with complete absence of flow signal involving the left transverse sinus, sigmoid sinus and the internal jugular vein with filling defects in contrast images suggestive of cerebral venous sinus thrombosis (Figure 2). Blood parameters showed microcytic anemia with hemoglobin (Hb) of 8.4 gm/dl and MCV of 72 fl. Thrombocytosis was noted with levels of 510,000/mm^3, most likely secondary to iron deficiency anemia (IDA). Other blood investigations including erythrocyte sedimentation rate (ESR), CRP, renal

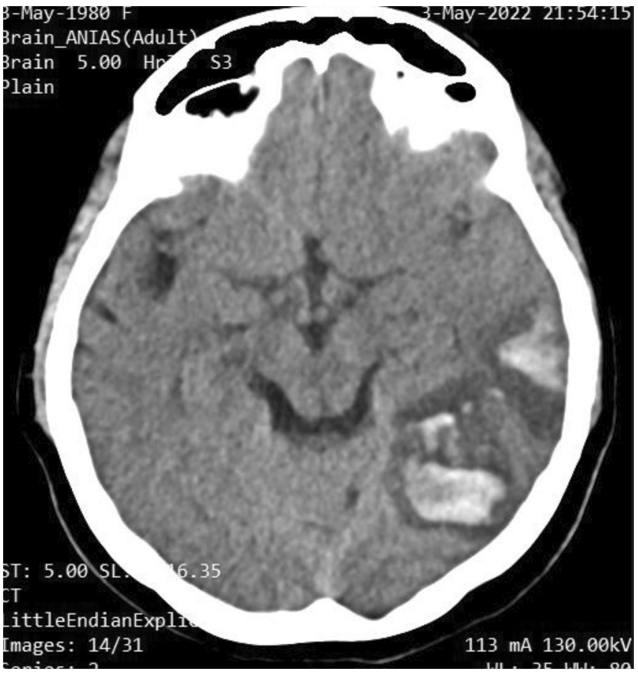

FIGURE 1 Non-contrast CT scan of the head showing intraparenchymal hematoma with surrounding edema in the left temporo-occipital region with mild mass effect.

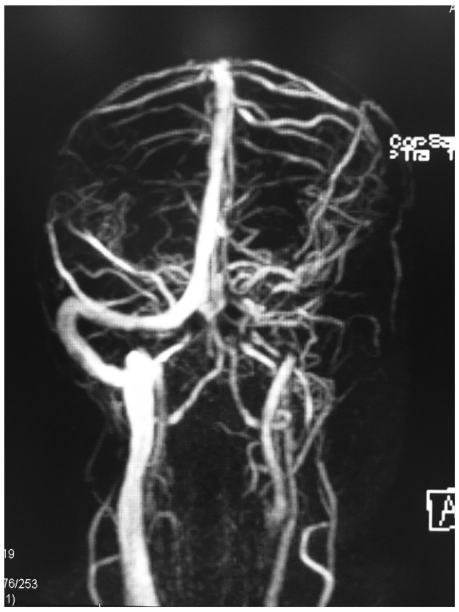

FIGURE 2 Magnetic resonance venography brain showing absence of flow signals in left transverse sinus, sigmoid sinus, and left internal jugular vein.

function test (RFT), liver function test (LFT), thyroid function test (TFT), bleeding time (BT), clotting time, APTT, and PT/INR were within normal limits. D-dimer level was elevated (2.5 μg/ml). Homocysteine level was 12.8 micromol/L which was within normal limits. ANA level was normal. In view of her heavy vaginal bleed and her history of adenomyosis, USG of the abdomen was done which showed bulky posterior myometrium in the uterus with heterogeneous echotexture consistent with adenomyosis. CA-125 level was raised to 155 IU/ml.

Following admission, she suffered two episodes of generalized tonic clonic seizures. Electroencephalogram (EEG) revealed abnormal awake EEG record with interictal seizure pattern arising from the left cerebral cortex. She was admitted to the intensive care unit where she was managed with treatment dose low-molecular weight heparin (Enoxaparin) 40 mg twice daily in accordance to her weight <50 kg, intravenous levetiracetam 1 g twice daily, dexamethasone, IV fluids, and pantoprazole. Before transferring her to the ICU, SARS-CoV-2 PCR was done as per the institutional protocols which came out to be negative. During her stay, she suffered from several episodes of generalized seizures. Intravascular lorazepam was used to abort the seizures. However, she suffered from additional seizure episode, and therefore she was commenced on phenytoin (loading dose: 15 mg/kg and maintenance dose of 100 mg thrice daily), and carbamazepine (200 mg twice daily) following subsequent seizures. She did not suffer additional seizure episodes thereafter. She received multiple blood transfusions in view of her ongoing bleeding and

declining hemoglobin level. She was then commenced on oral iron and folate therapy. Her conditions gradually improved during the course of the week and she was shifted to ward. She was discharged 10 days later on oral dabigatran, iron tablets, and antiepileptics. She was discharged with no deficits with mRS score of 1. On follow up, 2 weeks later she was doing well and plans for regular follow-up with the gynecologist was done. The gynecologist offered her hysterectomy which she declined and plans were made for conservative management. She was then placed on contraceptive dose progesterone only pills (POP). She continues to do well at 2 months post discharge with menorrhagia under control and no recurrence of CVT.

3 | DISCUSSION

We encountered a 42-year-old lady under oral progestins for menorrhagia secondary to adenomyosis seeking help immediately after her menses for a severe frontal headache which had gradually reached its peak over days and a focal seizure. A diagnosis of cerebral venous thrombosis was made. A multitude of possible risk factors was explored. Up to 44% of the cases have more than one risk factors, and the presence of one of them should not lead to cessation of the search for others.[1] On literature search, we came across few case reports and case series of cerebral infarction with adenomyosis. However, only one case of CVT with adenomyosis has been reported.[3] One other case of CVT with adenomyosis was found; however, the cause of CVT could be well attributed to combined oral contraceptive pills (COCPs) that she was taking for adenomyosis.[4]

Aiura et al.[5] (2021) tabulated the clinical profiles of 15 cases of cerebral infarction associated with adenomyosis which showed that almost half of them had presented during menstruation, and most of the patients had low hemoglobin levels with raised CA 125 and D- dimer levels. Similar findings were reported by Yin et al. (2018) and Zhao et al. (2020)[6,7] The profiles consistently pointed out anemia, increased CA 125 levels, and ongoing menstruation in the reported cases of infarction with adenomyosis. The lady in our case had increased CA 125 levels and microcytic anemia due to chronic blood loss and IDA. Even though her last menstrual period was 5 days before presentation, the onset of her premonitory headache was during her menstruation. These findings suggest a probable interplay of more than one factor to contribute hypercoagulability, cerebral Infarction, and CVT in adenomyosis. As of yet, causation has not been established between venous thromboembolism and adenomyosis. However, several theories are in place to link the two conditions.[8]

Increased levels of mucinous tumor markers like CA 125, menstruation-related coagulopathy, and increase in tissue factor levels could contribute to the development of cerebral infarction in adenomyosis.[9] CA 125 is a mucinous and hyper-viscous glycoprotein capable of cleaving Factor X to Xa.[10] Apart from the endometrium, serosal linings can be a source of CA 125. High levels of CA 125 during menstruation have been attributed to the release of the endometrial cell surface into the bloodstream and the irritation of uterine serosa.[11]

Stolz et al.[12] (2007) conducted a study comparing 121 prospectively identified patients with CVT and 120 healthy controls and found that severe anemia (Hb < 9 gm/dl) was significantly and independently associated with CVT. Even though the anemia was not stratified, it suggested that most of the cases could be iron deficiency anemia because 63% had microcytic anemia, 81% of severe anemia cases had a rise in platelet levels, and there was female predominance. Various mechanisms have been put forth regarding the role of IDA in hypercoagulability. Low iron levels have been shown to disinhibit megakaryocyte activity and consequently increase platelet levels.[13,14] On top of it, IDA creates a hypoxic environment in the brain, which consequently increases blood flow and thus greater turbulence and more contact of platelets with the blood vessel wall.[15] All of the above in combination could contribute to the biological plausibility and temporality of CVT in IDA.[1]

During the course of the hospital stay, we faced difficulty in establishing anticoagulation because she again started having heavy vaginal bleeding which lasted for 2 days, leading to a decrease in Hb levels up to 7 gm/dl. We continued with the administration of heparin along with iron supplementation and blood transfusion. This challenge during initial treatment has been reported by Hong et al.[8] (2020) in their retrospective review of venous thromboembolism (VTE) and adenomyosis. They controlled bleeding with a single dose of gonadotropin-releasing hormone analog (GnRHa) in four out of five cases of venous thromboembolism while starting on anticoagulation with warfarin/rivaroxaban. At discharge, we started our patient on dabigatran instead of warfarin for several reasons. First, the current evidence suggests that DOACs are non-inferior to warfarin for the prevention of the recurrence of CVT.[16] Second, the patient hailed from rural Nepal with limited access to healthcare services and regular follow-up was not an option. As DOACs do not require regular blood monitoring, dose adjustments, fewer drug interactions, and lack of dietary restrictions compared to warfarin, DOACs was preferred. For our patient, contraceptive doses of oral progesterone only pills (POP) were tried for menorrhagia. Gomes et al.[17] (2004) reviewed data on the POP-related risk of VTEs from eight case–control studies where none of the studies found statistical significance for POPs used in lower doses.

4 | CONCLUSION

In conclusion, the relationship between CVT and adenomyosis could extend beyond anecdotal evidence and further research is warranted. CVT is usually multifactorial and when associated with adenomyosis, other parameters like CA 125, IDA, and relation with menstruation could signpost to the association between the two.

AUTHOR CONTRIBUTIONS

Jayant Kumar Yadav: Writing – review and editing. **Aakar Thapa:** Writing – original draft. **Anjan Bhattarai:** Resources; writing – review and editing. **Ashmita KC:** Writing – original draft. **Samip Jung Budhathoki:** Resources. **Avinash Chandra:** Conceptualization; supervision. **Reema Rajbhandari:** Supervision.

ACKNOWLEDGEMENT

None.

CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

Not applicable.

ETHICAL APPROVAL

Ethical approval of case report is not needed in accordance with local ethical guidelines.

CONSENT

The patient provided written informed consent for publication of this case report and accompanying images.

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REFERENCES

1. Ferro JM, Canhão P, Stam J, Bousser MG, Barinagarrementeria F. Prognosis of cerebral vein and Dural sinus thrombosis: results of the international study on cerebral vein and Dural sinus thrombosis (ISCVT). *Stroke*. 2004;35(3):664-670.
2. Saposnik G, Barinagarrementeria F, Brown RD, Al E. Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011;42(7):1158-1192.
3. Nishioka K, Tanaka R, Tsutsumi S, et al. Cerebral Dural sinus thrombosis associated with Adenomyosis: a case report. *J Stroke Cerebrovasc Dis*. 2014;23(7):1985-1987.
4. Matsushima T, Akira S, Asakura H, Takeshita T. Low-dose gonadotropin-releasing hormone agonist therapy (draw-back therapy) for successful long-term management of adenomyosis associated with cerebral venous and sinus thrombosis from low-dose oral contraceptive use. *Clin Exp Obstet Gynecol*. 2017;44(1):143-145.
5. Aiura R, Nakayama S, Yamaga H, Kato Y, Fujishima H. Systemic thromboembolism including multiple cerebral infarctions with middle cerebral artery occlusion caused by the progression of adenomyosis with benign gynecological tumor: a case report. *BMC Neurol*. 2021;21(1):14.
6. Yin X, Wu J, Song S, Zhang B, Chen Y. Cerebral infarcts associated with adenomyosis: a rare risk factor for stroke in middle-aged women: a case series. *BMC Neurol*. 2018;18(1):213.
7. Zhao Y, Zhang Y, Yang Y. Acute cerebral infarction with adenomyosis in a patient with fever: a case report. *BMC Neurol*. 2020;20(1):210.
8. Hong E, Lin H, Fong Y. Venous thromboembolism and adenomyosis: a retrospective review. *Gynecol Minim Invasive Ther*. 2020;9(2):64-68.
9. Yamashiro K, Tanaka R, Nishioka K, et al. Cerebral infarcts associated with adenomyosis among middle-aged women. *J Stroke Cerebrovasc Dis*. 2012;21:e1-e5.
10. Yamashiro K, Furuya T, Noda K, Urabe T, Hattori N, Okuma Y. Cerebral infarction developing in a patient without cancer with a markedly elevated level of mucinous tumor marker. *J Stroke Cerebrovasc Dis*. 2012;21(7):619.e1-619.e2.
11. Nakamura Y, Kawamura N, Ishiko O, Ogita S. Acute disseminated intravascular coagulation developed during menstruation in an adenomyosis patient. *Arch Gynecol Obstet*. 2002;267(2):110-112.
12. Stolz E, Valdueza JM, Grebe M, et al. Anemia as a risk factor for cerebral venous thrombosis? An old hypothesis revisited. *J Neurol*. 2007;254(6):729-734.
13. Beguin Y. Erythropoietin and platelet production. *Haematologica*. 1999;84(6):541-547.
14. Habis A, Hobson WL, Greenberg R. Cerebral sinovenous thrombosis in a toddler with iron deficiency anemia. *Pediatr Emerg Care*. 2010;26(11):848-851.
15. Hartfield DS, Lowry NJ, Keene DL, Yager JY. Iron deficiency: a cause of stroke in infants and children. *Pediatr Neurol*. 1997;16(1):50-53.
16. Yaghi S, Shu L, Bakradze E, et al. Direct Oral anticoagulants versus warfarin in the treatment of cerebral venous thrombosis (ACTION-CVT): a multicenter international study. *Stroke*. 2022;29(2):728-738.
17. Gomes MPV, Deitcher SR. Risk of venous thromboembolic disease associated with hormonal contraceptives and hormone replacement therapy: a clinical review. *Arch Intern Med*. 2004;164(18):1965-1976.

How to cite this article: Yadav JK, Thapa A, Bhattarai A, et al. Cerebral venous thrombosis in a patient with adenomyosis: A case report. *Clin Case Rep*. 2022;10:e06796. doi:10.1002/ccr3.6796