**Cerebral Venous Thrombosis in a patient with adenomyosis: a case report**

Jayant Kumar Yadav1, Aakar Thapa2, Anjan Bhattarai2, Ashmita KC3, Samip Jung Budhathoki4, Avinash Chandra1, Reema Rajbhandari1

**1 = Annapurna Neurological Institute and Allied Sciences, Maitighar, Kathmandu**

**2 = Tribhuvan University, Institute of Medicine, Maharajgunj, Kathmandu**

**3 = National Centre for Rheumatic Diseases, Ratopul, Kathmandu**

**4 = Kathmandu Medical College, Sinamangal, Kathmandu**

**Corresponding author:**

Jayant Kumar Yadav, MBBS

Jkyadav22@iom.edu.np

Annapurna Neurological Institute and Allied Sciences

Maitighar, 44700

Kathmandu, Nepal.

**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 CVT. Increased CA-125 and Iron deficiency anemia in adenomyosis may predispose to CVT.

Key words:

Cerebral venous thrombosis, CVT, adenomyosis, Iron deficiency anemia

**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 multitude of risk factors including infections, hypercoagulable states, hematologic conditions, vascular disease, malignancy, and oral contraceptive pills among others(2). 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.

**Case presentation:**

A 42 years lady presented to the emergency department at our center with the 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 two minutes 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 due to adenomyosis but was non-compliant with 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 cranial nerve and ocular examination and sensory exam was normal as well. Fundoscopic examination was normal. Motor power was 4+/5 on 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 haemoglobin (Hb) of 8.4 gm/dl and MCV of 72 fl. Thrombocytosis was noted with levels of 510,000/mm3, most likely secondary to iron deficiency anemia (IDA). Other blood investigations including erythrocyte sedimentation rate (ESR), CRP, renal 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 left cerebral cortex. She was admitted to Intensive care unit where she was managed with subcutaneous heparin 40 U, intravenous leveraticetam, dexamethasone, IV fluids and pantoprazole. Carbamzepine, phenytoin, and Benzodiazepine were added to her treatment regimen following subsequent seizures. She received multiple blood transfusions in view of her ongoing bleeding and declining hemoglobin level. She was 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, two weeks later she was doing well and plans for regular follow up with gynaecologist was done. Gynaecologist 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.

**Discussion:**

We encountered a 42 years 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 were 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. (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 haemoglobin levels with raised CA 125 and D- dimer levels(5). Similar findings were reported by Yin et al. (2018) and Zhao et al. (2020) (6) (7). The profiles consistently pointed out anemia, raised CA 125 levels and ongoing menstruation in the reported cases of infarction with adenomyosis. The lady in our case had raised CA 125 levels and microcytic anemia due to chronic blood loss and IDA. Even though her last menstrual period was 5 days prior to presentation, the onset of her premonitory headache was during her menstruation. These findings suggest probable interplay of more than one factor to contribute to hypercoagulabiity, 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 level of mucinous tumor marker 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 hyperviscous glycoprotien capable of cleaving Factor X to Xa(10). Apart from endometrium, serosal linings can be a source of CA 125. High levels of CA 125 during menstruation has been attributed to the release of endometrial cell surface into blood stream and to the irritation of uterine serosa(11).

Stolz et al (2007) conducted a study comparing 121 prospectively identified patients with CVT and 120 healthy controls and found out that severe anemia (Hb < 9gm/dl) was significantly and independently associated with CVT (12). 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 raise the platelet levels(13,14). On top of it, IDA creates an 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 for 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 two days leading to fall in Hb levels upto 7 gm/dl. We continued with administration of heparin along with iron supplementation and blood transfusion. This challenge during initial treament has been reported by Hong et al (2020) in their retrospective review of Venous thromboembolism (VTE) and adenomyosis(8). They controlled bleeding with a single dose of Gonadotropin releasing hormone analog (GnRHa) in 4 out of 5 cases of venous throboembolism while starting on anticoagulation with warfarin/rivaroxaban. For our patient contraceptive doses of oral progesterone only pills were tried for menorrhagia. Gomes et al (2004) reviewed data on POP-related risk of VTEs from 8 case control studies where none of the studies found statistical significance for POPs used in lower doses(16)

**Conclusion:**

In conclusion, the relation between CVT and adenomosis 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.

**Abbreviations:**

**APTT: Activtated paartial thromboplastin time**

**BT: Bleeding time**

**CRP: C reactive protein**

**CT: Computed tomography**

**CVT: Cerebral venous thrombosis**

**EEG: Electroencephalogram**

**ESR: Erythrocyte sedimentation rate**

**GCS: Glasgow coma scale**

**GnRHa: Gonadotropin releasing hormone agonist**

**IDA: Iron deficiency anemia**

**LFT: Liver function test**

**MCV: Mean cell volume**

**MRI: Magnetic resonance imaging**

**MRV: Magnetic resonance venography**

**NSAIDs: Non steroidal anti inflammatory drugs**

**OCP: Oral contraceptive pills**

**PT: Prothrombin time**

**POP: progesterone only pills**

**VTE: Venous thromboembolism**

**Declarations:**

**Acknowledgements:** None

**Conflict of Interest:** None of the authors has any conflict of interest to disclose.

**Authors Contribution:** AT, JKY, AK, AB wrote the draft manuscript. AC, RR, SJB revised the manuscript. All except AT, AK, AB were involved in the direct care of the patient. All authors agreed on the final draft for submission.

**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.

**Data availability statement:** Not applicable

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**Figure legends:**

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: MRV brain showing absence of flow signals in Left transverse sinus, sigmoid sinus and Left intenal jugular vein.