CLINICAL VIGNETTE

Acute Dural Venous Sinus Thrombosis Associated with Oral Contraceptive Use

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A 49-year-old woman presented to the emergency department with nausea and vomiting and gradually worsening frontal headache associated with tinnitus in her right ear. Her past medical history included mixed hyperlipidemia, trace tricuspid regurgitation, and use of oral contraception pills. Her headache began two days prior to presentation. She described it as throbbing 8/10 pain at its worst with radiation from her right ear to her frontal sinuses. There were no exacerbating factors and Ibuprofen improved pain to 5/10. She went to urgent care the prior day and was prescribed amoxicillin for possible otitis media. However, her headache persisted and the development of nausea and vomiting prompted her to seek emergent care.

She also had poor oral intake and photophobia with otherwise negative review of systems. There was no trauma or falls. She was an ICU nurse currently caring for COVID-19 patients. She was married with one child and was taking oral contraceptives (OCPs). She never smoked or used illicit drugs and rarely drank alcohol. Family history included autoimmune cirrhosis. She did not have a known personal or family history of clotting disorder.

Computed tomography (CT) and computed tomography venography (CTV) of the head performed in the emergency department showed superior sagittal venous thrombosis with involvement of bilateral transverse and sigmoid sinuses. Trace subarachnoid hemorrhage (SAH) was suggested by CT.

She was admitted to the ICU for further evaluation and management. Additional imagery included magnetic resonance imaging (MRI) to assess for SAH and magnetic resonance venography (MRV) to better visualize the drainage from the superior sagittal sinus to the transverse sinus, as well as to visualize the confluence, the internal jugular veins, and possible enlargement of the superior sagittal sinus. MRI showed no evidence of infarct or SAH. MRV confirmed extensive cerebral venous thrombosis involving the superior and inferior sagittal sinuses and bilateral transverse and sigmoid sinuses.

Notable labs included elevated D-dimer (1752 ng/mL), negative rapid SARS-COV-2, and negative human immunodeficiency virus and rapid plasma reagin. Hypercoaguable testing included normal Factor V Leiden, Protein C & S, antithrombin III, homocysteine, and a negative lupus antibody. Antinuclear antibody test was normal. White blood cell count (15,300/CMM), c-reactive protein (2.21 mg/dL), and interleukin-6 (2.9 pg/mL) were elevated. Ferritin (95.1 ng/mL) and procalcitonin (< 0.15 ng/mL) were normal. Urinalysis was not indicative of infection. No growth was found on blood, urine, or sputum cultures. Respiratory polymerase chain reaction was negative. Lumbar puncture was not recommended. The leukocytosis was ultimately attributed to a leukemoid reaction due to extensive clot burden. Nonetheless, empiric ampicillin/sulbactam was continued throughout her hospitalization for persistent leukocytosis.

Additional management included initiation of a heparin drip without bolus and maintaining Anti-Xa un-fractionated heparin levels between 0.3-0.51 IU/mL. Consultations included neurology, neurosurgery, infectious disease, and critical care. Levetiracetam was started for seizure prophylaxis and was changed to divalproex in attempt to also help alleviate her persistent headache. Magnesium sulfate 1 gram intravenously (IV) daily for three days was given to manage photophobia. Surgical intervention was not recommended. Antiemetics helped control her nausea and vomiting. Blood pressure was maintained less than 140/100 with the use of antihypertensives.

Heparin drip was change to enoxaparin 1mg/kg twice a day, then to oral dabigatran to continue for at least six months. Repeat MRI and MRV showed persistent thrombus that had decreased in size. After seven days of hospitalization, she discharged home with dabigatran 150mg twice a day and pain medications for headache control. She was advised to discontinue OCPs.

Outpatient follow up one month after hospitalization found that her headache was improving, but still required acetaminophen every six hours. She also continued to have tinnitus in her right ear. Dabigatran was changed to apixaban due to development of a drug rash. Repeat MRI, MRV was recommended two months after her hospital presentation. The subsequent MRV showed persistent dural venous thrombosis with new thrombosis of the right internal cerebral vein. She continued on apixaban, applied for disability and was referred to hematology.

Cerebral Venous Thrombosis

This case is noteworthy because cerebral Venous Thrombosis (CVT) (also called dural sinus thrombosis or cerebral venous sinus thrombosis) is an uncommon cause of stroke. Incidence is believed to be 5 per million annually and accounts for 0.5-1% of all strokes.[1] CVT is more common in women than men by a 3:1 ratio.[2] The imbalance may be due to pregnancy and oral

contraceptive use, as with the patient in this case. When compared with patients affected by arterial types of stroke, CVT affects younger individuals with a median age of 37.[2]

There are a multitude of risk factors for CVT. The etiology for venous thrombosis is rooted in Virchow's triad (venous stasis, endothelial injury/dysfunction, hypercoagulability). Risk factors are often separated into acquired vs genetic or transient vs permanent. The following is a list of the most common risk factors: prothrombotic conditions (either genetic or acquired), oral contraceptives, pregnancy and the puerperium, malignancy, infection, head injury and mechanical precipitants. Other risk factors include: sinusitis, trauma and surgery, intracranial hypotension, dehydration, lumbar puncture, medications (oral contraceptives, corticosteroids, tamoxifen, phytoestrogens, erythropoietin), additional disease risk factors such as IBD, hematologic conditions (PNH, TTP, SCD, polycythemia), collagen vascular diseases, hyperhomocysteinemia, nephrotic syndrome, and sarcoidosis.[1,2] The main risk factor for the patient in this case was using oral contraceptives.

Pathogenesis is incompletely understood due to high variability in the anatomy of the venous system and paucity of experiments in animal models. Despite this limited understanding, the current hypothesis of pathogenesis was outlined by Coutinho in 2015. Venous thrombosis leads to obstruction of blood drainage from brain tissue causing cerebral parenchymal lesions (stroke) or dysfunction. Venous thrombosis also causes increased venous and capillary pressure with disruption of the blood brain barrier.[3] This leads to vasogenic edema with leakage of blood plasma into the interstitial space. Localized cerebral edema and venous hemorrhage can occur due to venous or capillary rupture. Increases in intravenous pressure can cause increased intravascular pressure, decrease in cerebral perfusion pressure, resulting in a decrease in cerebral blood flow (CBF) and failure of energy metabolism. This leads to failure of the Na/K ATPase pump and consequent cytotoxic edema.[4]

A second pathogenic pathway involves occlusion of venous sinuses leading to increased venous pressure, which leads to impaired CSF absorption (arachnoid granulations in superior sagittal sinus) causing increased intracranial pressure.[3]

Clinical presentation of CVT can be highly variable with acute, subacute or chronic onset. Clinical symptoms and signs vary by age and gender, the site and number of occluded sinuses and veins, the presence of parenchymal brain lesions, and the interval from CVT onset to presentation. Typical presentation is a new headache or with the syndrome of isolated intracranial hypertension with headache, decreased visual acuity, and papilledema. Other clinical presentations include seizures, focal neurological deficits, and encephalopathy. Less common signs and symptoms includes cavernous sinus syndrome, subarachnoid hemorrhage, and multiple cranial nerve palsies.[3]

Urgent neuroimaging is the first step to diagnosis. Three imaging techniques are used to diagnose CVT: Magnetic resonance imaging (MRI) with MR venography, computed tomography (CT) venography, and catheter angiography.[3] MRI is the most widely used. Diagnosis requires visualization of the thrombus within the vein in combination with absent flow on MR-venography.[3] In addition to absent flow in the cerebral venous system, other lesions of the brain parenchyma can be seen on imaging. These include intracerebral hemorrhage (ICH), which is found in 30-50% of all patients,[2] localized cerebral edema, and subdural and subarachnoid hemorrhages.[3] Routine blood studies including chemistry panel, complete blood count, PT and aPTT should be performed on patients with CVT.[3] D dimer testing is limited by low sensitivity and possibility for false negatives.[3] Screening for thrombophilia is recommended with antithrombin, protein C and S, Factor V Leiden, Prothrombin G20210A mutation, lupus anticoagulant, anticardiolipin, and anti-bet2 glycoprotein-I antibodies.

Heparin is the mainstay therapy for CVT and is recommended by international guidelines.[1,3,5] Endovascular treatment (ET) (ie: mechanical thrombectomy and thrombolysis) has been documented in case reports and case series but there have been no randomized trials or large prospective trials and currently is not recommended due to limited data. Decompressive surgery may be necessary if patients develop large venous hemorrhagic infarcts that result in mass effect, brain displacement, and/or transtentorial or subfalcine herniation.[3] To prevent recurrence of CVT, long term anticoagulation is recommended with dabigatran 150mg twice daily or warfarin at an INR goal of 2-3 (RE-SPECT CVT trial[6]). Anticoagulation should continue for 3-6 months for provoked CVT and 6-12 months for unprovoked. Patients with thrombophilia, recurrent CVT, or other VTE after CVT require indefinite anticoagulation. Approximately 5% of patients die in the acute phase of CVT, most commonly due to transtentorial herniation secondary to a large hemorrhagic lesion with mass effect.[7]

The patient in this case had provoked dural sinus thrombosis due to the use of OCPs. The size of her thrombosis decreased while receiving heparin. She discharged home on dabigatran, but developed a drug rash and switched to apixaban. Outpatient imaging revealed persistent and new thrombosis while on apixaban. Literature suggests that her anticoagulation be changed to warfarin. Lifelong therapy is a consideration for this patient, as it is unclear if extension of her thrombosis to the right internal cerebral vein is due to the use of apixaban instead of dabigatran or warfarin versus a factor inherent in her disease process. Repeat hypercoaguable testing, including prothrombin G20210A mutation, anticardiolipin, and anti-bet2 glycoprotein-I antibodies, may be considered.

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