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Clinical vignette: An unusual cause of cerebral venous thrombosis

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EPSTEIN-BARR VIRUS CAUSING BOTH THROMBOCYTOPENIA AND CEREBRAL VENOUS SINUS THROMBOSIS

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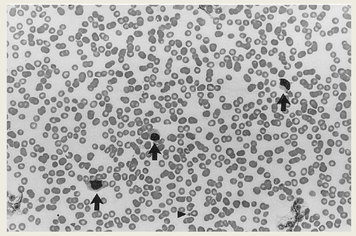
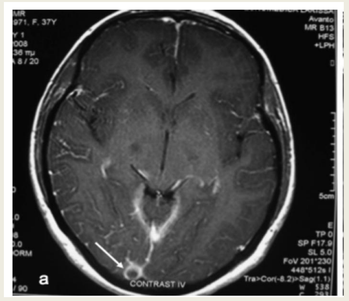
CASE PRESENTATION

An 18 year old female with no past medical history awoke with a severe generalized headache associated with nausea, vomiting and photophobia. Two weeks prior, she had nasal congestion, mild sore throat, and productive cough with yellow sputum which resolved but fatigue persisted. She was taking oral contraceptives. Physical exam was normal except for significant fatigue. Pertinent labs included a normal WBC, H/H, PT/INR and aPTT. Platelets were 20,000 platelets/mm^3. CT Head demonstrated right transverse sinus thrombosis, with empty delta sign. MRI revealed extensive right transverse sinus thrombosis with extension into the right internal jugular vein. Peripheral smear showed marked thrombocytopenia with occasional large and giant forms, some neutrophils with toxic granulation, and occasional reactive-appearing lymphocytes. Her LFTs were mildly elevated with AST 116, ALT 120 Unit/L. Abdominal ultrasound revealed hepatomegaly with mild echogenicity and a normal sized spleen. Viral hepatitis screen was negative. Absolute CD4 count was low (182/mm^3); HIV negative. Hypercoagulable workup negative. ANA negative. Anti-heterophile antibody negative. Epstein-Barr antibody to early antigen positive. Epstein-Barr viral capsid antigen IgG positive but IgM negative. Epstein-Barr antibody to nuclear antigen positive. She was diagnosed with Epstein-Barr virus infectious mononucleosis causing immune thrombocytopenia, for which she was treated with dexamethasone and intravenous immunoglobulin (IVIG). The infection plus oral contraceptives likely resulted in the cerebral venous sinus thrombosis, for which she was treated with a heparin drip and then transitioned to warfarin. Oral contraceptives were discontinued. She received Keppra for seizure prophylaxis. On day 2, her platelets dropped to 9,000 platelets/mm^3, but then rose to normal by day 12. Her low CD4 count, mildly elevated LFTs, hepatomegaly and severe fatigue were attributed to the Epstein-Barr virus.

Peripheral smear in EBV with atypical lymphocytes (arrows) and thrombocytopenia



MRI head showing filling defect after contrast (empty delta sign)



EPSTEIN-BARR VIRUS (EBV) AND IMMUNE THROMBOCYTOPENIA (ITP)

Background. Epstein-Barr virus infection has been associated with a variety of hematologic abnormalities, including immune thrombocytopenia, hemolytic anemia, aplastic anemia, thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome, and disseminated intravascular coagulation. EBV appears to be a fairly common cause of ITP in children. A study in China found EBV infection in 35/108 (32.4%) children diagnosed with ITP[1]. Another study in China studied spleens of patients with ITP and controls and found EBV expression in nine (21.4%) with ITP compared to none in the control group[2]. Mild thrombocytopenia (100-150,000 platelets/mm^3) occurs in 25-50% cases of acute EBV infections, but severe thrombocytopenia (<20,000 platelets/mm^3) is rare; most cases occur in children and young adults[3,4].

Etiology. The etiology of thrombocytopenia in EBV is thought to be immune-mediated[5]. In a review of EBV cases with thrombocytopenia, 7/16 patients (43%) had anti-platelet antibodies[5]. Historically splenomegaly was considered etiologic; however, only half of EBV patients with severe thrombocytopenia have splenomegaly, with no correlation between thrombocytopenia and splenic size[3].

Diagnosis. Heterophile antibodies may be absent at the time of hematologic complications of EBV, so serologic studies should be done to get the diagnosis[3].

Treatement and Prognosis. In cases of ITP due to EBV, the thrombocytopenia usually resolves spontaneously in days to weeks. Treatment may not be needed, but often standard treatment for ITP including steroids and immunoglobulins is given. Chronic thrombocytopenia is very rare. Fatal cases are rare but may occur due to cerebral hemorrhage or splenic rupture[3].

CEREBRAL VENOUS SINUS THROMBOSIS (CVST)

Background. CVST is rare, with the incidence in children at 7 cases per million and in adults at 3-4 cases per million, and it is more common in women.

Etiology. The main risk factors are genetic or acquired prothrombotic state and infection. Dual or multi-factorial causes have been identified in 44% of cases. Oral contraceptives are a well-identified risk factor, as well as pregnancy and post-partum.

Clinical Presentation. Headache is the most common presenting symptom (89%); it is usually acute and severe, non-localized, and worsened with Valsalva. Presentation can be variable. Some patients get focal neurologic signs, like hemiparesis or acute aphasia (left transverse sinus). Seizures occur in 40% of patients. Some patients present with encephalopathy. Cavernous sinus syndrome is the least common presentation, with oculomotor nerve palsies, facial pain, sensory loss in the trigeminal nerve distribution, proptosis, and chemosis.

Treatment. Anticoagulation is recommended, with a goal INR 2-3. The recommended duration varies, from 3 months for a known acute cause, to 6-12 months for idiopathic cases, to lifelong if the patient has multiple prothrombotic factors or antiphospholipid antibody syndrome. Other recommendations include aggressive management of intracranial hypertension and medication for seizure prophylaxis. There are no guidelines for endovascular treatment, which should be reserved for severe cases.

Prognosis. Mortality for CVST is 8-14%, with death usually due to intracerebral hemorrhage. Most cases (87%) result in complete recovery, with the venous recanalization rate at 3 and 12 months at 85%. The recurrence rate is 2.8%[6].

TEACHING POINTS

1. Epstein-Barr virus can cause immune thrombocytopenia, particularly in children and young adults.
2. The usual screening test for Epstein-Barr virus infectious mononucleosis, the anti-heterophile antibody, can be negative at the time of presentation with hematologic complications, so serology is necessary for the diagnosis.
3. Cerebral venous sinus thrombosis main risk factors are prothrombotic state (including oral contraceptives) and infection. Many cases have multiple risk factors present.

CONCLUSIONS

This case illustrates a rare presentation of Epstein-Barr virus infection causing both immune thrombocytopenia and cerebral venous sinus thrombosis at the same time. The oral contraceptive pills likely played a contributing role in addition to the Epstein-Barr virus infection in causing the cerebral venous sinus thrombosis.

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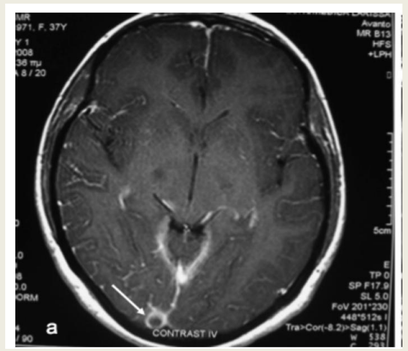
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