Image Diagnosis: Weber Syndrome: A Rare Presentation of Acute Leukemia—A Case Report and Review of the Literature

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CASE STUDY

A 13-year-old boy had fever, fatigue, and breathlessness for two weeks before presenting to the Emergency Department. He also had painless lymphadenopathy on both sides of his neck, axilla, and groin. Four hours before presentation to the Emergency Department, he developed drooping of the right upper eyelid. There was complete ptosis and no associated diplopia. The pupil of the right eye was dilated and nonreactive. The extraocular movements and pupil of the left eye were normal. There was no headache, vomiting, or seizures. Two hours after presentation the patient developed sudden-onset complete weakness of the left side of his body along with left upper motor neuron facial palsy. With a clinical diagnosis of acute cerebrovascular accident, an urgent noncontrast computed tomography scan of the head was performed. It showed multiple hemorrhages, one of which was located in the ventral midbrain on the right side (Figure 1), possibly explaining the contralateral hemiplegia and ipsilateral oculomotor palsy.

Investigations revealed hyperleukocytosis (454,000/μL), hemoglobin of 9.2 g/dL, and thrombocytopenia (42,000/μL), with greater than 99% lymphoblasts and many degenerated cells seen in the peripheral smear examination (Figures 2 and 3). Prothrombin time and activated partial thromboplastin time were 13 seconds and 37 seconds, respectively (reference value 12 seconds and 35 seconds, respectively). Fibrinogen concentration was 2.5 g/L, and there was no laboratory finding to suggest disseminated intravascular coagulation. Renal and liver functions were normal. Serum lactate dehydrogenase was elevated (9 times the upper limit of the reference value). Serum potassium was 6 mmol/L, but there were no accompanying electrocardiographic abnormalities of hyperkalemia. Serum calcium was 9.3 mg/dL, whereas serum uric acid was elevated to 11.4 mg/dL.

We diagnosed acute leukemia, probably acute lymphoblastic leukemia (ALL), on the basis of peripheral blood film. Tumor lysis syndrome was suspected and the patient was hydrated well. Emergency leukapheresis was planned in view of hyperleukocytosis and breathlessness. But before we obtained additional samples for flow cytometry to confirm the diagnosis and before the initiation of leukapheresis, the patient developed seizures, after which he became comatose and died. Clinical course suggested a possible fatal intracranial hemorrhage as the preterminal event.

DISCUSSION

Neurologic manifestations in patients with leukemia can have multiple etiologies, depending on whether the time of presentation is pre- or postchemotherapy. In prechemotherapy, intracranial hemorrhage and leukemic infiltration are the important causes of neurologic symptoms, whereas in postchemotherapy, infections are the most important cause.[1,2] In children with ALL, neurologic manifestations can occur in up to 9% of cases, and in those patients with ALL with extreme leukocytosis (total leukemia blood cell count > 400,000/μL), 2% can have intracranial hemorrhage.[3] In patients with acute leukemia, intracranial hemorrhage portends a poor prognosis, with a mortality rate approaching 19.7% in the first 72 hours and 32.7% at 30 days.[4] Acute nonlymphoblastic leukemias present more commonly with intracranial hemorrhage than ALL and are more frequently fatal early in the course of the disease (7% in acute myeloblastic leukemia vs 1% in ALL in one series).[5,6]

Brain stem strokes or cerebrovascular accidents are relatively uncommon, particularly in children. Midbrain strokes commonly result from ischemia or hemorrhage as in any other cerebrovascular territory. Though both

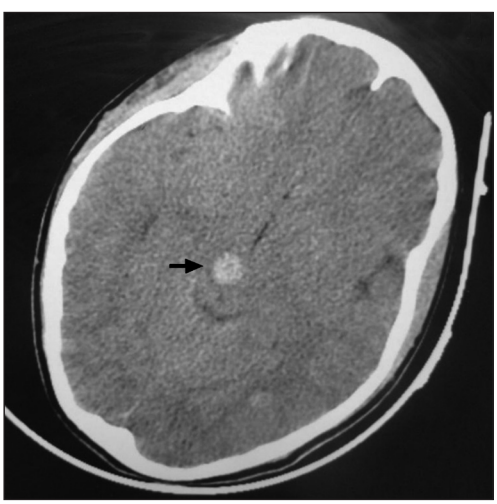

Figure 1. Noncontrast computed tomography scan of the head showing blood in the ventral midbrain on the right side.

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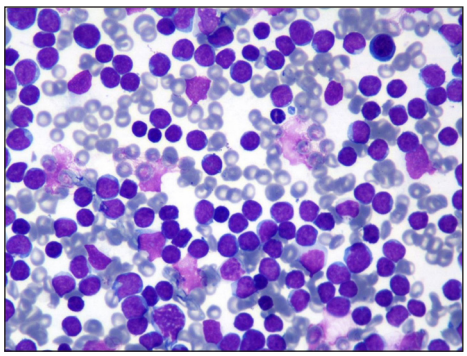

Figure 2. Peripheral blood film showing marked leukocytosis with greater than 99% lymphoblasts and many degenerated cells (Leishman stain, x400).

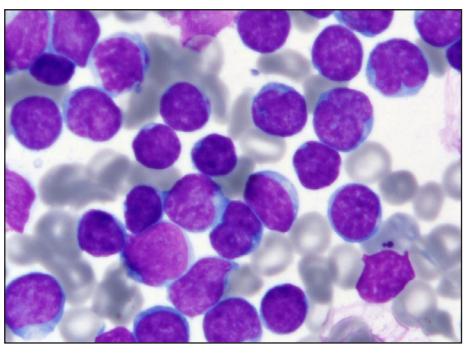

Figure 3. Higher-power view of peripheral blood film revealing variably sized lymphoblasts ranging from smaller (1 to 2 times the size of mature lymphocytes), with coarse, clumped chromatin and very high nucleocytoplasmic ratio, to larger, with nuclear indentations, 0 to 2 inconspicuous nucleoli, and modest amounts of basophilic agranular cytoplasm (Leishman stain, x1000).

ischemia and hemorrhage can lead to stroke in children, the latter seems to be a more important cause in children with cancer and leukemia.[7,8] Eponymous syndromes of brainstem strokes are often heard but seldom seen. The presence of ipsilateral oculomotor palsy and contralateral hemiplegia constitutes Weber syndrome. Weber syndrome occurs as a consequence of a lesion located in the cerebral peduncle of the midbrain, which includes the pyramidal fibers (causing contralateral hemiplegia) and the third nerve fascicle (causing ipsilateral oculomotor paresis).[9] This patient's neuroimaging demonstrates a strategically located small bleed in this region of the midbrain, which correlates with the clinical presentation. We undertook a systematic search of PubMed for similar cases. Search terms for our PubMed searches are listed in the Sidebar: PubMed Search Terms. We found that the index case was the first case of leukemia reported in the literature to have presented clinically as Weber syndrome.

Presence of hyperleukocytosis, thrombocytopenia, and acute promyelocytic leukemia are well-known risk factors for hemorrhage in leukemia.[10] Acute promyelocytic leukemia is the most common leukemia to be associated with a deranged coagulation profile and hemorrhagic manifestations.[11,12] Hyperleukocytosis (with subsequent intracranial bleeding) is more common in ALL patients with translocations involving the chromosomal abnormalities t(4;11)(q21;q23) and t(9;22)(q34;q11) (Philadelphia-positive ALL).[13,14] In treatment-naïve leukemia patients, bleeding related to hyperleukocytosis has been noted to be one of the most important causes of death.[1] The use of L-asparaginase may also be a cause of intracranial hemorrhage in leukemia patients receiving chemotherapy.[15] Our patient had hyperleukocytosis and thrombocytopenia, both of which could have predisposed him to intracranial hemorrhage.

Hyperleukocytosis (usually defined as a white blood cell count > 100,000/μL) generally results in leukostasis, wherein intravascular accumulation of leukemic or nonleukemic white blood cells results in various clinical manifestations, particularly respiratory distress and neurologic disturbances. Hyperleukocytosis is a medical emergency; its management includes supportive care (hydration, prevention, and treatment of tumor lysis syndrome) and urgent cytoreductive therapy. Cytoreduction may be achieved by hydroxyurea, leukapheresis, or conventional chemotherapy.[16] Despite such aggressive measures, mortality remains high in these patients, especially in those with intracranial hemorrhage. Though leukapheresis may reduce circulating lymphoblast cells, thereby effectively controlling leukostasis in cerebral circulation, it has not been consistently shown to improve outcomes.[16] The approach in patients with thrombocytopenia and leukostasis who are at risk of intracranial bleeding should be to identify the type of leukemia as early as possible. Provision of leukapheresis, platelet transfusion, and cytoreductive agents, along with appropriate chemotherapy, may improve outcomes. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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PubMed Search Terms

("leukaemia"[All Fields] OR "leukemia"[MeSH Terms] OR "leukemia"[All Fields]) AND (("intracranial hemorrhages"[MeSH Terms] OR ("intracranial"[All Fields] AND "hemorrhages"[All Fields]) OR "intracranial hemorrhages"[All Fields] OR ("intracranial"[All Fields] AND "bleed"[All Fields]) OR "intracranial bleed"[All Fields]) OR ("haemorrhage"[All Fields] OR "hemorrhage"[MeSH Terms] OR "hemorrhage"[All Fields]) OR ("cns"[All Fields]) AND ("hemorrhage"[MeSH Terms] OR "hemorrhage"[All Fields] OR "bleed"[All Fields])) OR (("brain stem"[MeSH Terms] OR ("brain"[All Fields] AND "stem"[All Fields]) OR "brain stem"[All Fields] OR "brainstem"[All Fields]) AND ("hemorrhage"[MeSH Terms] OR "hemorrhage"[All Fields] OR "bleed"[All Fields])) OR weber[All Fields]).

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Waterworks

The physics of a man's circulation are the physics of the waterworks of the town in which he lives, but once out of gear, you cannot apply the same rules for the repair of the one as of the other.

— *Aequanimitas, with Other Addresses,* Sir William Osler, MD, 1849-1919, physician, clinician, pathologist, teacher, diagnostician, bibliophile, historian, classicist, essayist, conversationalist, organizer, manager, and author