Case Report

Cerebral venous sinus thrombosis in a young child with acute lymphoblastic leukemia: a case report and literature review

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Abstract
Acute lymphoblastic leukemia (ALL) is a hematological malignancy. There are many risk factors for thrombus development in patients with ALL, and thrombi may develop in different parts of the body. Cerebral venous sinus thrombosis (CVST) is a rare complication of ALL that usually appears during treatment. We present a patient who developed CVST twice, once before diagnosis and once after treatment for ALL. We also reviewed the literature describing ALL and CVST.

Keywords
Acute lymphoblastic leukemia, cerebral venous sinus thrombosis, hemorrhage, pediatrics, malignancy, risk factor

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Introduction
Acute lymphoblastic leukemia (ALL) is characterized by the clonal expansion and accumulation of abnormal immature lymphoid precursor cells in the bone marrow. Owing to the considerable therapeutic progress made in the past, the mortality of young patients with ALL has decreased dramatically. Cerebral venous sinus thrombosis...
(CVST) is a rare complication of ALL. CVST is an uncommon disease with possible severe consequences that may have a negative impact on ALL. We present a patient with ALL who developed CVST, and we reviewed the related literature.

**Case report**

A 9-year-old boy was admitted to our hospital with a history of headache and vomiting for 2 days, accompanied by a single episode of transient weakness in his legs, and altered consciousness for half a day. Ten days before admission, he hit his head against an ice surface in a fall. He experienced no neurological symptoms after hitting his head and did not go to the hospital. Upon arrival, he was conscious, his muscle strength was symmetrical, and deep tendon reflexes were normal and symmetrical. His neck was stiff, but he had no other neurological deficits. His weight was 52 kg; height: 145 cm; body mass index: 24.7 kg/m\(^2\) (>P97). Magnetic resonance imaging (MRI) of vascular plaque in the patient’s head and neck revealed right internal jugular vein, transverse sinus, and sigmoid sinus thrombosis (Figure 1a–c). MRI of the head showed right temporal-parietal lobe hemorrhage (Figure 1d). The results of a comprehensive thrombophilia workup constituting protein C activity, protein S activity, antithrombin III, antiphospholipid syndrome antibody, and homocysteine concentration were normal. A thrombophilia workup was performed routinely to evaluate acute thrombosis of unknown cause. The D-dimer level was 90.65 nmol/L (range: 0–16.13 nmol/L), and routine blood laboratory evaluation revealed hemoglobin: 120 g/L, platelets: 182 \(\times\) 10\(^9\)/L, and leukocytes: 13.2 \(\times\) 10\(^9\)/L with neutrophilia. Tumor marker concentrations were within normal ranges and constituted free prostate-specific antigen, alpha-fetoprotein, prostate-specific antigen, non-small cell lung cancer-associated antigen, neuron-specific enolase, carbohydrate antigen 199, carbohydrate antigen 72-4, and carcinoembryonic antigen. He was treated with glycerol fructose. Thrombectomy was not performed owing to his stable condition and mild symptoms, and because of the intracranial hemorrhage, anticoagulant therapy was not started. His neurological symptoms resolved, and he was discharged. One month after discharge, repeat brain MRI showed that the thrombus had not disappeared, although the signal intensity was lower than in the first scan. MRI also showed that the intracranial hemorrhage was smaller; therefore, we did not initiate anticoagulation.

He returned to our hospital with an intermittent fever, 3.5 months after discharge. In the outpatient department, the attending doctor considered infection and performed routine blood evaluation, which showed hemocytopenia. Therefore, leukemia was suspected, and the patient was admitted to the hospital. Bone marrow aspiration and immunophenotyping revealed ALL with intermediate risk owing to central nervous system leukemia. Brain magnetic resonance venography (MRV) revealed right transverse sinus and sigmoid sinus thrombosis (Figure 2a), which was noted previously. The child had no neurological symptoms; therefore, we did not initiate anticoagulation. He was started on induction therapy comprising vincristine, daunorubicin, L-asparaginase, and corticosteroids. Cerebrospinal fluid pressure was within normal limits, and flow cytometry of the cerebrospinal fluid analysis revealed 27.32% abnormal immature B cells and only 5 white blood cells. After chemotherapy, bone marrow analysis demonstrated that the leukemia was in remission. The patient presented with severe vomiting 22 days after chemotherapy. The fibrinogen concentration had decreased to 0.72 g/L (range: 1.8–4.0 g/L), and cerebral MRV showed right sigmoid
Figure 1. Magnetic resonance imaging (MRI) of vascular plaque in our patient’s head and neck revealed right internal jugular vein, transverse sinus, and sigmoid sinus thrombosis (a, b, c). Head MRI showed right temporal-parietal lobe hemorrhage (d).

Figure 2. Brain magnetic resonance venography (MRV) revealed right transverse sinus and sigmoid sinus thrombosis (a). Cerebral MRV showed right sigmoid sinus, transverse sinus, and sagittal sinus thrombus (b, c).
sinus, transverse sinus, and sagittal sinus thrombosis (Figure 2b, c). Computed tomography (CT) of the head revealed hemorrhage alongside the cerebral falx (Figure 3a). L-asparaginase was stopped, and owing to the intracranial hemorrhage, we did not start anticoagulation. Four days after developing the new CVST, the patient presented with persistent seizures and left-sided weakness. CT of the head showed right frontal lobar hemorrhage (Figure 3b). Because he was receiving anti-epileptic drugs, mannitol, and glycerin fructose, he showed remarkable improvement in the left-sided hemiplegia with only residual grade II weakness in his upper left extremity and focal seizures. However, the parenchymal hemorrhage worsened (Figure 3c). He continued to receive dehydrating therapy and antiepileptic drugs, and eventually, his neurological symptoms resolved completely. Brain CT showed that the hemorrhage had been absorbed, and he received L-asparaginase again 50 days after L-asparaginase cessation.

Discussion

Inherited thrombophilia, elevated coagulation factors, chemotherapeutic agents, elevated lipoprotein concentration, antiphospholipid antibodies, and other factors contribute to thrombus formation in children with ALL. A meta-analysis showed that the presence of at least one primary thrombophilia factor increased the risk of thrombosis eight times in children with ALL. L-asparaginase causes deficiencies in natural anticoagulants, and corticosteroids induce a procoagulant state by increasing plasminogen-activator inhibitor type-1, von Willebrand’s factor, and thrombin. Some patients with ALL developed CVST after receiving methotrexate. The induction therapy in our patient included L-asparaginase and corticosteroids, and chemotherapy was the primary risk factor in our patient regarding developing CVST during leukemia treatment. A previous study found that obesity was strongly associated with venous thrombosis, and our patient was obese. Another study reported that some patients represented with neurological symptoms and developed CVST 24 days after head injury. CVST is an uncommon complication of head injury; however, we consider that our patient’s mild head injury was the possible cause of the first CVST. At that time, routine blood examination findings were normal, and his symptoms improved quickly; therefore, we did

Figure 3. Head computed tomography (CT) at different times revealed hemorrhage alongside the cerebral falx (a), right frontal lobar hemorrhage (b), and right frontal and parietal lobe hemorrhage (c).
not perform bone marrow aspiration or blood smear examination. It is difficult to determine whether he was in the early stages of leukemia at that time.

Patients with ALL may develop thrombi in different parts of the body.3 CVST is a rare complication of ALL, which may lead to death,10 and the clinical symptom are nausea, vomiting, headache, seizures, lethargy, and altered consciousness.11 CVST can also be asymptomatic.12 Our patient developed CVST and presented with vomiting, seizures, and weakness.

Patients with ALL may develop thrombi during the treatment. Some patients developed neurological symptoms 2 to 27 days after the first exposure to L-asparaginase.10 CVST may also occur after induction therapy but before L-asparaginase infusion.13 Our patient developed CVST after hitting his head against an ice surface, and when he was diagnosed with ALL, the CVST had not yet resolved. After chemotherapy, the size of the CVST increased, and this is the special feature of our case.

CVST may impact ALL treatment. We stopped L-asparaginase when our patient developed severe thrombosis and intracranial hemorrhage.12 Receiving less L-asparaginase significantly impacts outcomes.14 However, a previous study showed that a patient with CVST received all of the planned L-asparaginase infusions without recurrence, and that stopping L-asparaginase therapy in some patients during the management of thrombosis did not significantly affect overall survival.13 A patient who did not receive anticoagulation and discontinued L-asparaginase still remained in remission from ALL after nearly 11.7 years.15 Debate continues whether to stop L-asparaginase when thrombosis occurs. We restarted L-asparaginase after our patient experienced complete recovery from his neurological symptoms.

After treatment with heparin, MRV in a patient showed that the superior sagittal sinus had mostly reopened.16 Some patients in previous reports also achieved resolution of both neurological symptoms and CVST following treatment with apixaban or rivaroxaban.17,18 A girl with extensive CVST and hemorrhage was treated with heparin and eventually showed recanalization and brain reperfusion on imaging.11 Another patient with rapidly progressive CVST underwent neurointerventional clot extraction and experienced a successful outcome.19 In another study of a patient with worsening clinical and radiological progression, in situ thrombolysis was performed.20 For children with CVST with significant hemorrhage, guidelines suggest initial anticoagulation as for children without hemorrhage, or radiological monitoring of the thrombosis for 5 to 7 days and anticoagulation if thrombus extension is noted at that time.21 Our patient did not receive anticoagulation because of the presence of intracranial hemorrhage, but his neurological symptoms resolved despite the lack of anticoagulation therapy.

Thromboprophylaxis can prevent thrombosis, but ALL and its therapy may lead to hemorrhage.22 It is important to identify people at high risk of thrombosis to determine the correct use of thromboprophylaxis.22 One study showed that 18.2% of children with ALL had a single established prothrombotic risk factor among TT677 methylenetetrahydrofolate reductase genotype, factor V G1691A mutation, G20210A prothrombin mutation, protein C deficiency, protein S deficiency, antithrombin deficiency, and increased Lp (a) concentration.23 Patients with prothrombotic risk factors who received thromboprophylaxis did not develop thromboembolism during chemotherapy.23 One guideline recommends prophylactic anticoagulation with risk factor recurrence in children with CVST,21 and another study recommended thromboprophylaxis with enoxaparin for children and adolescents receiving ALL during induction
therapy. Prophylactic administration of antithrombin III or fresh-frozen plasma did not demonstrate significant beneficial effects in preventing thrombosis in children with ALL.

In conclusion, CVST is an uncommon complication in patients with ALL. We should pay more attention to CVST, especially when patients with ALL develop neurological symptoms. When the cause of thrombosis is unknown, thrombophilia screening may be needed. If necessary, preventive thrombotic therapy should be given.

Author contributions
All authors contributed to the manuscript writing. The authors read and approved the final manuscript.

Ethics statement
This case report was approved by the ethics committee of the First Hospital of Jilin University (approval number: 2019-308). Informed consent for publication was obtained from the patient’s legal surrogates prior to publication of this report.

Declaration of conflicting interest
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