Case Report

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Cerebral sinuses thrombosis prior to the diagnosis of acute lymphoblastic leukemia in a child: A case report

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Abstract

Acute lymphoblastic leukemia is the most common malignancy in children. In children, venous thromboembolism is relatively common. In most cases, venous thromboembolism manifests in patients who are diagnosed with acute lymphoblastic leukemia. Several risk factors associated with acute lymphoblastic leukemia predispose patients to the development of venous thromboembolism. Unlike most reported cases of venous thromboembolism, herein we report a child who developed cerebral venous sinus thrombosis prior to the diagnosis of acute lymphoblastic leukemia. The patient recovered from an attack of acute gastroenteritis with sepsis, pancytopenia, and disseminated intravascular coagulation 2 weeks before the development of thrombosis. Her laboratory workup for coagulopathy and disseminated intravascular coagulation was normal at the time of diagnosis of cerebral sinus thrombosis. The genetic workup for thrombophilia risk identified several genetic thrombophilia mutations: the homozygous factor XIII V34L and MTHFR A1298C mutations and heterozygous factor V Leiden mutation. Three weeks later, the patient was diagnosed with acute lymphoblastic leukemia. However, it remains questionable whether the thrombotic event was caused by the previous infection of gastroenteritis, sepsis, and disseminated intravascular coagulation picture (which was augmented by her genetic thrombophilia risk), or was it caused by acute lymphoblastic leukemia (that was not detected at early stages with its associated hypercoagulable state), or was it caused by a type of paraneoplastic syndrome. A multifactorial etiology is proposed.

Keywords

Genetic risk, thrombophilia, pediatric, acute lymphoblastic leukemia, mutation

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Introduction

Acute lymphoblastic leukemia (ALL) is considered the most common type of cancer in pediatrics which represents about one-fourth of all forms of cancers in the 0–14 age group.[1]

Venous thromboembolism (VTE)—symptomatic and asymptomatic—had been found in 14% and 50%, respectively, of children with ALL.[2] The majority of these thrombotic events were reported during the induction phase of chemotherapy. There are many predisposing factors—for thrombotic events in pediatric cancer patients—that contribute to the long-term morbidity as well as early mortality.[2,3] Those factors include associated coagulopathy, cancer type (T-cell ALL), cancer with tumor burden (presence of mediastinal mass), administration of chemotherapeutic agents for example L-asparaginase (ASP) and steroids, use of central venous catheters (CVCs), as well as being older than 10 years and having a non-O blood group. However, the role of inherited thrombophilia as a predisposing factor for VTE in pediatric cancer patients is still unclear because of conflicting results.[4]

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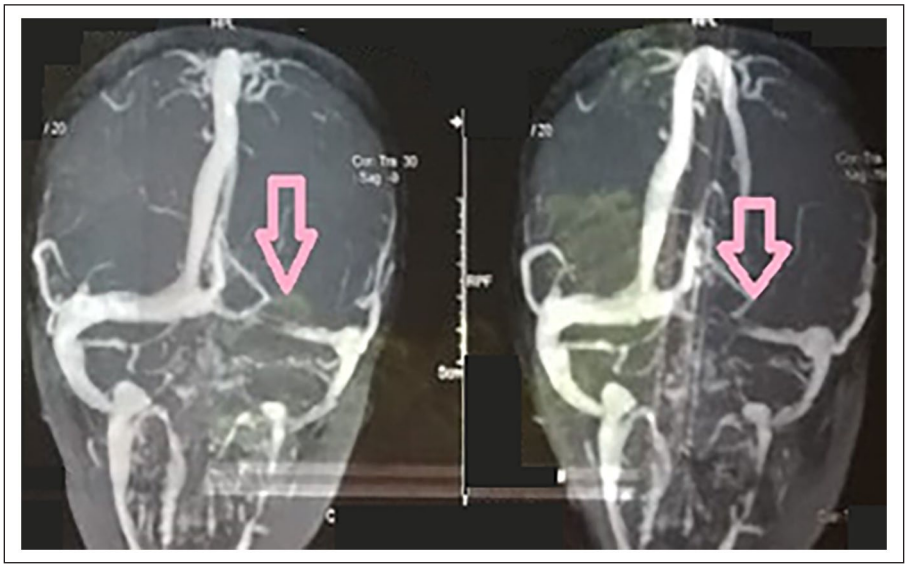

Figure 1. Magnetic resonance venography showing reduced flow to left transverse sinus.

The involvement of the central nervous system (CNS) in ALL can occur due to CNS infiltration, CNS radiation, and intrathecal or systemic chemotherapy. Herein, we report a child who developed cerebral venous sinus thrombosis (CVST) prior to the diagnosis of ALL and propose possible underlying pathogenesis.

Case report

A previously healthy 3-year-old female patient presented to the emergency department with fever, diarrhea, abdominal pain, and severe dehydration. The patient was critically ill necessitating pediatric intensive care unit admission.

On assessment, the child was feverish (temperature was 39.5°C) and tachypneic with rapid shallow breathing (respiratory rate was 40 breaths/min). She was also hypotensive with blood pressure of 60/40 mm Hg. There was evidence of severe dehydration with dry tongue, sunken eyes, poor skin turgor, and oliguria (urine output < 1 mL/kg/h). The patient was pale with purpuric eruption all over the body with no organomegaly or lymphadenopathy.

Her initial laboratory investigations revealed pancytopenia with absolute neutropenia (white blood cells (WBCs): 500/mm^3, absolute neutrophil count: 200/mm^3, Hb: 6.4 gm/dL, platelets: 2000/cm^3) and renal impairment with electrolyte imbalance (BUN: 104 mg/dL, creatinine: 2.5 mg/dL, K: 6.5 mmol/L, ph: 21.9 mg/dL, Na: 128 mmol/L, Ca: 5.3 mg/dL).

It also revealed hyperuricemia (uric acid: 37 mg/dL), coagulopathy with disseminated intravascular coagulation (prothrombin time (PT): 16.3 s, partial thromboplastin time (PTT): 40.1 s, and D-dimer: 17 ng/mL), and high inflammatory markers (CRP: 287 mg/L). Her stool and blood cultures were positive for gram-negative *Bacilli Escherichia coli*.

Management with intravenous fluid therapy, blood components transfusion, correction of electrolyte disturbance, and antibiotic therapy was started. She was provisionally diagnosed with acute infectious gastroenteritis with sepsis complicated by severe dehydration, acute renal failure, and disseminated intravascular coagulation (DIC).

Her pelvi-abdominal ultrasound was normal. Bone marrow aspirate was done to investigate her severe pancytopenia with absolute neutropenia. It revealed hypocellular bone marrow and was negative for any abnormal cells.

During the course of hospital admission, the patient showed gradual improvement in her general condition. Her laboratory data including her electrolytes, renal functions, blood indices, coagulation parameters, and inflammatory markers were restored to normal values. She was discharged after 2 weeks in good general condition with a clinic follow-up visit.

Three weeks after discharge, she developed unexplained irritability, abnormal behavior, and hallucinations with failure to recognize her parents. She was vitally stable, well hydrated, and had normal hematological indices, coagulation parameters, renal panel, and serum electrolytes. Brain imaging studies in the form of magnetic resonance imaging (MRI), magnetic resonance arteriography (MRA), and magnetic resonance venography (MRV) revealed thrombosis in both the left sigmoid and the transverse sinuses (Figure 1). Workup of thrombophilia revealed no thrombocytosis, normal coagulation profile (PT, PTT, and D-Dimer), normal protein C and S, and antithrombin III. Genetic testing for the thrombophilia mutations panel was requested. The assessment of the pediatric cardiologist, electrocardiogram, and echocardiography were normal.

Low molecular weight heparin was initiated at a dose of 1 IU/kg every 12 h. The patient improved and was discharged on a therapeutic dose of low-molecular-weight (LMW) heparin with a follow-up appointment for her clinical condition. The parents were to be updated with the results of

thrombophilia genetic testing, which was supposed to be released after 1 month.

Two weeks later, the patient was readmitted for the third time with fever (temperature: 39.5°C), pallor, and abdominal enlargement. Her blood picture showed leukocytosis (total leukocytic count: 68,000/mcL), anemia (hemoglobin level: 8.4 g/dL), and thrombocytopenia (platelet count: 20,000/mcL). Peripheral smear revealed many blast cells and abdominal ultrasonography revealed hepatosplenomegaly.

Bone marrow examination was repeated, which revealed hypercellular bone marrow which is heavily infiltrated with 96% blast cells. Immunophenotyping was done with positive CD10, CD20, and CD79a.

The diagnosis of Common ALL was established, and we immediately started the ALL protocol adopted from St. Jude's total XV protocol. She received induction therapy followed by consolidation.

The thrombophilia mutations panel result was received 2 weeks after starting the treatment. It revealed positive factor XIII V34L and MTHFR A1298C homozygous mutations and heterozygous positive factor V Leiden mutation.

The follow-up MRV was done during the induction phase, which showed complete recanalization of the thrombosed sinuses with no new thrombi. Hence, we did not modify the chemotherapeutic regimen or reduce the L-asparaginase dose. She is currently in complete remission with regular follow-up with no other thrombotic events or leukemia relapses.

Discussion

Most thrombotic events in ALL occur initially during the induction phase of treatment due to the intense treatment protocol, especially during the use of asparaginase in combination with corticosteroids.[5]

Our patient had a thrombotic event in the form of left sigmoid and transverse sinus thrombosis before the diagnosis of ALL (normal bone marrow aspiration at first admission). The possibility that ALL was present since the first admission cannot be excluded. It might be explained by the bone marrow patchy leukemic infiltration in the early stages of ALL. Another possibility is that the patient was in an aplastic phase of leukemia; hence, no blast cells were detected on bone marrow aspiration. If we propose that an aplastic phase of leukemia was present, then this bone marrow aplasia was the cause of immunodeficiency and the development of severe infection and sepsis.

The associated prothrombotic state even at the earliest phase of leukemia[6] might explain the cerebral sinus venous thrombosis (CSVT) developed by our patient. De Stefano et al.[6] reported that increased VTEs can take place even prior to the diagnosis of ALL, like the situation seen in solid tumors. A possible hypothesis is that it could be a type of paraneoplastic syndrome.

This is open for further investigations, as we could not find supportive literature in ALL patients.

Another plausible hypothesis of thrombosis is the severe sepsis and DIC at first admission. During infection, inflammatory cells and mediators can induce the expression of tissue factors on monocytes and endothelial cell surfaces, which is a major activator of coagulation. This can lead to widespread intravascular fibrin deposition.[7]

Moreover, enhanced fibrin formation is caused by tissue factor–mediated thrombin generation. Another risk factor of thrombosis is the suppression of the inhibitory mechanisms, such as the protein C and S system and the impairment of the endogenous thrombolysis secondary to high circulating levels of plasminogen activator inhibitor.[1] To sum up, a state of imbalance between procoagulant and anticoagulant occurs during infection, which might overwhelm the balance of hemostasis and result in microthrombi.[8]

In our patient, although CSVT was diagnosed 2 weeks after infection and sepsis resolution, it might be that microthrombi started to build up during her septic state with DIC and that when those thrombi grew large enough to occlude the sinuses, the clinical symptoms started. We cannot comment on protein C, S, and antithrombin III during the first admission, as they were not requested at that time, but they were normal during the second admission at the time of CVST diagnosis.

We requested thrombophilia mutations genetic panel to investigate possible genetic risk, which came positive for homozygous MTHFR A1298C mutation and heterozygous factor V Leiden mutation. Unfortunately, the results of the genetic panel were delayed and were only received after the third admission with a whole month. Although those mutations are proposed genetic risk factors, their role remains questionable. Tripathi et al.[9] reported a 14-year-old boy with ALL who had MTHFR mutation and presented with recurrent venous thrombosis in the absence of asparaginase therapy. On the contrary, Akın et al.[10] found that Factor V Leiden 1691 G-A and PT 20210 G-A mutations are not associated with the development of thrombosis in pediatric leukemia patients.

A discussion was raised in literature trying to correlate the genetic variants of inherited thrombophilia and the risk of development of childhood ALL, but has yielded discordant opinions which cannot used as evidence.[11–13] Kałużna et al.[11] studied the relation between the inheritance of MTHFR C677T and A1298C polymorphisms and the risk of ALL development in a population under 18 years of age of Caucasian ancestry. They reported that The MTHFR 677T allele alone or in combination with the MTHFR 1298C allele significantly increases the risk of development of ALL (twofold compared to control).[11] However, Roy Moulik et al.[12] examined this association in North Indian children with ALL, and they found that polymorphisms in the MTHFR gene could possibly modulate the risk of ALL in North Indian adults, but not in children.[12] Many other studies denied such association.[13,14] Atashrazm et al.[13] reported in their studies on pediatric ALL patients that the MTHFR C677T and A1298C gene variants lack a major influence

on the susceptibility for pediatric ALL. Similarly, Sazawal et al.[14] reported no statistically significant difference in the susceptibility to ALL in children between those with and without MTHFR C677T and A1298C polymorphism. Moreover, Bahari et al.[15] documented that MTHFR rs1801131 (A1298C) heterozygous genotype decreased the risk of ALL in comparison with AA homozygous genotype (odds ratio (OR) = 0.43, 95% confidence interval (CI) = [0.21, 0.90], $p = 0.037$).

Although two thrombophilia mutations were detected in our patient, but we could not confidently attribute her CVST event to the detected mutations due to the lack of consistency in supporting evidence in the literature. It seems that a multifactorial pathogenesis could explain the CVST developed by our patient. The factors include (1) the infectious process and the DIC picture with microthrombi development which became symptomatic after occlusion of the sinuses, (2) the genetic susceptibility, (3) the questionable aplastic phase of leukemia with prothrombotic state, and (4) a possibility of paraneoplastic syndrome.

This report paves the way for future research in the area of VTEs prior to the documented diagnosis of ALL. Worthy of mention is that we did not modify the protocol of ALL management including L-asparaginase dose because the results of genetic thrombophilia risk were delayed. We performed MRI studies for the previously thrombosed sinuses which were completely canalized. We strictly monitored our patient for any evidence of VTEs, and there was no development of further thrombotic events. Currently, the patient is in complete remission with regular follow-ups.

Conclusion

VTEs are well known in ALL patients. Their development prior to the diagnosis of ALL might be explained by an aplastic phase of ALL with a procoagulant state even at the very early stages of leukemia. This bone marrow aplasia might precipitate severe infections and sepsis, which might lead to imbalanced coagulation pathways and DIC with VTEs. A genetic thrombophilia risk might play a role, but there is no literature consensus. Further research focused on VTEs prior to ALL is needed to help clarify the possible underlying pathogenesis.

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Author contributions

All authors contributed substantially to writing the manuscript; reviewing the literature; the concept and design, acquisition, and interpretation of data; drafting the article; revising it critically for important intellectual content; and final approval of the version to be published. L.S. submitted the work.

Availability of data and materials

All data and materials related to the study are included in the current manuscript.

Consent for publication

Parents signed written informed consents for publication of the current case report.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics approval

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Informed consent

Written informed consent was obtained from legally authorized representatives (parents) for anonymized patient information to be published in this article.

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