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EDITED BY

Tomasz Szczepanski,
Medical University of Silesia, Poland

REVIEWED BY

Tomasz Urasinski,
Pomeranian Medical University, Poland
Sachin Gajanan Damke,
Dr Rajendra Gode Medical College, India

*CORRESPONDENCE

Feiqiu Wen
✉ fwen62@163.com

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Case Report: A successful outcome of nadroparin calcium therapy for cerebral venous sinus thrombosis in a child with acute lymphoblastic leukemia

Lichun Xie^{1,2}, Ye Xu¹, Guichi Zhou², Fen Chen², Changgang Li², Lian Ma^{1,2} and Feiqiu Wen^{2*}

¹Department of Pediatrics, The Third Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong, China, ²Department of Hematology and Oncology, Shenzhen Children's Hospital, Shenzhen, China

Background: The appearance of cerebral venous sinus thrombosis (CVST) in childhood acute lymphocytic leukemia (ALL) is a rare life-threatening disease that can cause significant morbidity, neurological sequelae, and potentially poor outcomes.

Case presentation: We present the case of a 13-year-old boy with ALL who developed CVST and intrinsic hemorrhage approximately 30 days after receiving chemotherapy with vincristine, dexamethasone, daunorubicin, and pegylated-asparaginase (PEG-Asp). He complained of a severe headache and then developed a generalized seizure at night. T1- and T2-weighted magnetic resonance imaging (MRI) and cerebral magnetic resonance venography sequences revealed superior sagittal sinus thrombosis and intrinsic hemorrhagic changes in the bilateral frontoparietal lobes. He received nadroparin calcium as the anticoagulant treatment and was switched to Erwinia asparaginase (Erwinia Asp) rather than PEG-Asp. Oxcarbazepine and clonazepam were started with good seizure control. Intrathecal treatment was delayed until 1 month later. Anticoagulation treatment was stopped for 24 h before and 6 h after lumbar puncture. Platelet transfusion was administered to ensure the platelet count remained at $>50 \times 10^9/L$. Oral acetazolamide (500–1,000 mg, daily) was administered to relieve headache and reduce intracranial pressure. Three months later, brain MRI showed a complete resolution of or significant improvement in the filling defect. Nadroparin calcium was administered for 1 week after switching to Erwinia Asp to prevent clot recurrence. He completed the 6-month chemotherapy and is doing well with no neurological sequelae and no recurrence of bleeding or thrombosis.

Conclusions: Nadroparin calcium therapy appears to be safe and effective for pediatric CVST with ALL. The reintroduction of Erwinia Asp should be accompanied by anticoagulant therapy with nadroparin calcium.

KEYWORDS

cerebral venous sinus thrombosis, anticoagulation, nadroparin calcium, childhood acute lymphoblastic leukemia, pegylated-asparaginase

Abbreviations

ALL, acute lymphocytic leukemia; APTT, activation of blood coagulation time; CNS, central nervous system; CVST, cerebral venous sinus thrombosis; LMWH, low molecular weight heparin; LP, lumbar puncture; MRI, magnetic resonance imaging; PEG-Asp, pegylated-asparaginase; SCCLG-ALL, South China Children's Leukemia Group; UFH, unfractionated heparin.

1 Introduction

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer. Venous thromboembolism (VTE) is a well-known complication of the treatment of pediatric ALL (1, 2). Cerebral venous sinus thrombosis (CVST) is a rare treatment-related but life-threatening complication of childhood ALL. The incidence of CVST in the population is 1%–2% in children treated for ALL and the mortality is approximately 10% (3). Because the symptoms and signs are non-characteristic and variable, early diagnosis of CVST is quite challenging. We present the case of a 13-year-old boy with parenchymal hemorrhage during induction chemotherapy.

2 Case report

A 13-year-old boy was diagnosed with B-cell immune phenotype ALL according to the South China Children's Leukemia Group (SCCLG-ALL) guidelines. Chromosomal translocations, intrachromosomal rearrangements, and genetic alterations were negative. Evidence of central nervous system (CNS) leukemia was negative. He was undergoing induction chemotherapy with vincristine, dexamethasone, daunorubicin, and pegylated-asparaginase (PEG-Asp) when he presented with a headache, and 30 days later, he developed a generalized seizure. Brain T₁- and T₂-weighted magnetic resonance imaging (MRI) and cerebral magnetic resonance venography revealed superior sagittal sinus thrombosis and intrinsic hemorrhagic alterations in the bilateral frontoparietal lobes (Figure 1). Anticonvulsants were administered. Hereditary thrombotic hemophilia was excluded. Plasma-infusion-corrected coagulation and fibrinogen level remained above 0.5 g/L. Platelet transfusion maintained a platelet count of $>50 \times 10^9/L$. Oxcarbazepine and clonazepam were used to control the seizures. Papilledema was ruled out. Two days

later, his symptoms resolved slightly. One week later, brain MRI showed that intracranial hemorrhage had been effectively controlled, and chemotherapy for the SCCLG-ALL was reintroduced in combination with anticoagulation with nadroparin calcium. Nadroparin calcium treatment was started at a dose of 1 mg/kg twice daily subcutaneously. The second part of induction therapy included cyclophosphamide, mercaptopurine, and cytarabine. PEG-Asp was switched to Erwinia asparaginase (Erwinia Asp) in subsequent treatment phases. CNS leukemia was stratified into CNS-3 status. Intrathecal lumbar puncture (LP) was delayed for 1 month due to intracranial hemorrhage. The number of LPs with triple i.t. agents was modified to the CNS-3 status of the treatment protocol. The patient complained of headache, which is considered asymptomatic of chronic intracranial hypertension. Oral acetazolamide relieved the symptoms of chronic intracranial hypertension. Nadroparin calcium treatment was discontinued for 24 h before and 6 h after lumbar puncture. The nadroparin calcium dose was adjusted based on the platelet counts and antithrombin activity. Platelet transfusion was administered to ensure that the platelet count remained at $>50 \times 10^9/L$. Follow-up brain MRI at 3 months showed an improvement (Figure 2). Nadroparin calcium was adjusted to a once-a-day dose from that point. The total duration of nadroparin calcium treatment was extended to 1 week post-Erwinia Asp to prevent clot recurrence. No recurrence of bleeding or thrombosis occurred during treatment. The patient completed 6 months of chemotherapy and is doing well with no evidence of neurological deficit.

3 Discussion and literature review

CVST can present with various symptoms, including severe headache, focal neurological dysfunction (such as motor or sensory deficits), seizures, and altered consciousness (4). Early

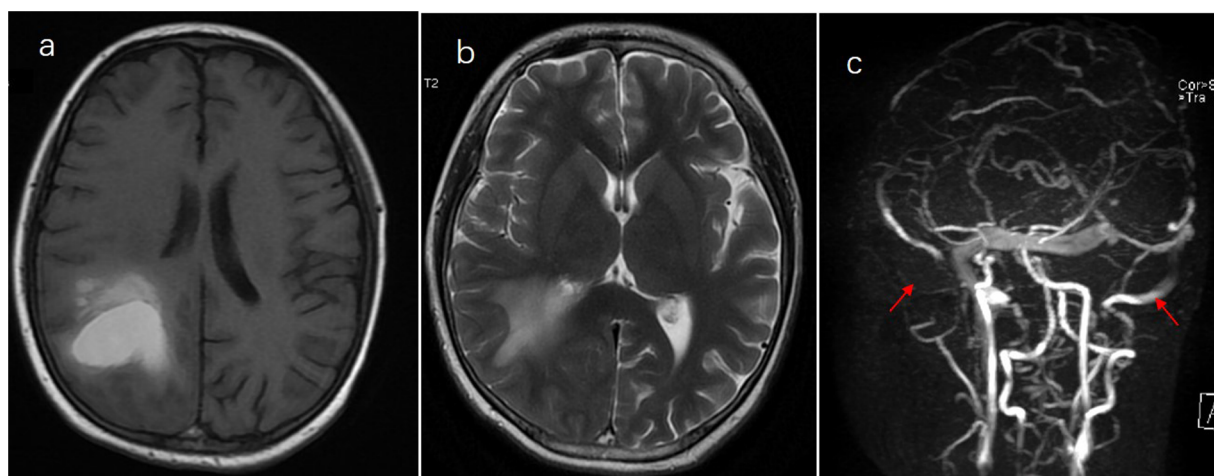


FIGURE 1
Thrombosis of the superior sagittal sinus and internal hemorrhage on the bilateral frontoparietal lobes. (a) T1. (b) T2+. (c) Cerebral magnetic resonance venography.

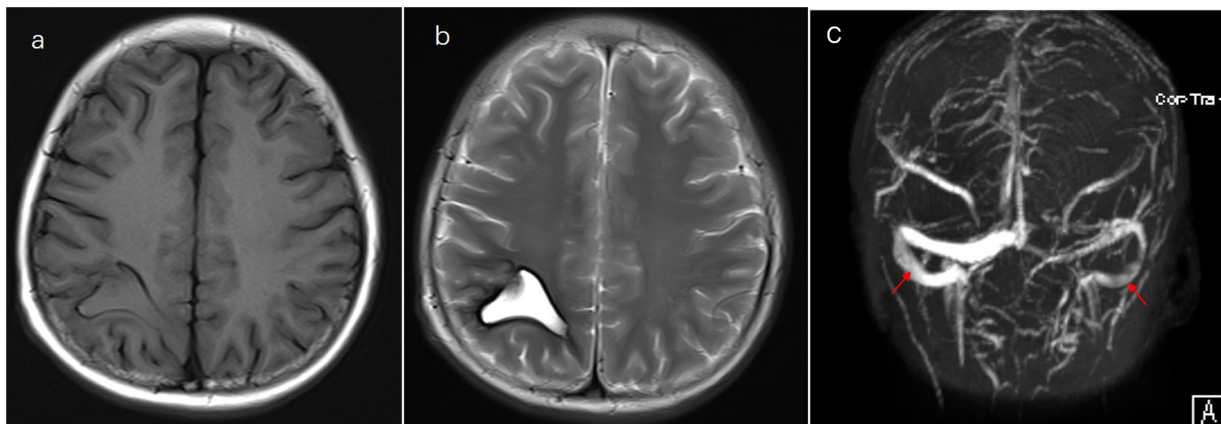


FIGURE 2

Evolution of changes on follow-up. (a) T1- and (b) T2-weighted MRI and (c) magnetic resonance venography imaging performed after the treatment.

recognition of these symptoms is crucial for prompt diagnosis and treatment (5).

Idiculla et al. recommended that computed tomography (CT) and MR angiography should be the preferred diagnostic methods for CVST (6), as CT imaging without contrast agents has limitations and presents a false-negative rate of up to 40%. Additional sequences, such as diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR), can improve diagnostic accuracy (7).

Anticoagulant therapy is the mainstay of CVST treatment and should be started quickly (8, 9). Common anticoagulant options in pediatrics include unfractionated heparin (UFH), administered by continuous infusion, subcutaneous low molecular weight heparin (LMWH), and warfarin. In general, prophylactic LMWH does not significantly affect the activation of blood coagulation time (APTT), has minimal food interactions, and offers advantages due to its short half-life and flexibility in invasive surgical procedures (10). UFH is administered by continuous infusion. Nadroparin calcium can be administered subcutaneously at a dose of 86 IU/kg every 12 h. However, the pain associated with the subcutaneous nadroparin calcium administration and the need to involve parents in drug administration pose challenges. Nadroparin calcium eliminates the need for blood monitoring, making it more convenient. Warfarin, on the other hand, is available only in tablet form, which complicates its use in younger children. Furthermore, the prolonged duration of warfarin effects exhibits significant variability due to different factors. Concomitant use of sulfonamides, broad-spectrum antibiotics, and corticosteroids (commonly used in children with ALL) can affect the efficacy of warfarin, which requires close monitoring during clinical use (11). PREVAPIX-ALL was a phase III clinical trial in which no statistically significant treatment benefit was identified in pediatric ALL or lymphoma patients who received apixaban (12). The management of pegylated-asparaginase (PEG-Asp) re-administration after CVST in children with ALL during induction chemotherapy remains uncertain due to the lack of epidemiological studies. As ASP is a crucial drug in ALL treatment, there is controversy

surrounding its association with venous thrombosis (13). In particular, Erwinia Asp, which has a shorter biological half-life than *Escherichia coli*-derived ASP and ASP-Peg, is recommended for patients with childhood ALL with CVST who need to return to ASP treatment after treatment suspension.

Children with ALL and extensive CVST can experience intracranial hypertension. This condition may be the result of damage to the arachnoid villi, which are present in the dural sinuses (14). The sagittal sinuses are particularly affected, leading to visual impairment, severe pain, difficulty concentrating, memory loss, and learning disabilities that can persist for months. To alleviate intracranial hypertension, oral acetazolamide therapy or repeated lumbar puncture therapy is recommended (15). In our case, oral acetazolamide was administered to relieve intracranial hypertension, along with oxcarbazepine and clonazepam to control epilepsy, resulting in a successful recovery.

4 Conclusion

We believe that the reintroduction of ASP treatment is safe with monitoring of antithrombin levels. Randomized controlled trials investigating the prevention and treatment of CVST will play a crucial role in determining effective clinical management.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by the ethics committee of Shenzhen Children's Hospital. The studies were

conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

LX: Writing – original draft. YX: Software, Writing – original draft. GZ: Data curation, Writing – original draft. FC: Visualization, Writing – original draft. CL: Writing – review & editing. LM: Supervision, Writing – review & editing. FW: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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