An unexpected cerebral sinovenous thrombosis in a boy with acute lymphoblastic leukemia: A case report

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Abstract

Acute Lymphoblastic Leukemia (ALL) is the most common malignancy in children. Prednisone, Vincristine, Cytarabine and also L-Asparaginase are usually used in induction chemotherapy. Thrombovascular events such as Cerebral Sinovenous Thrombosis (CSVT) are one of the most common complications of the disease that may arise during or even after the treatment. Majority of the cases of CSVT are either directly attributed to ALL or considered as a consequence of using chemotherapy agents mentioned above. In this manuscript we present an 8-years-old boy diagnosed with ALL who exhibited seizure attack following his first chemotherapy cession. CSVT was finally diagnosed due to manifestations and assessments.

Keywords: Acute Lymphoblastic Leukemia (ALL), Cerebral Sinovenous Thrombosis (CSVT), Intrathecal Injection, Children.

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Introduction

Acute Lymphoblastic Leukemia (ALL) is the most common malignancy in children and accounts for one-fourth of all cancers in 0-14 age-group. The survival has increased over the last four decades and cure rates were improved from 10% to 90% approximately [1].

Prednisone, Vincristine, Anthracyclines (mostly Daunorubicin) and also L-Asparaginase are frequently applied for induction chemotherapy. There are protocols according to which Cyclophosphamide, Cytarabine (either in conventional or high doses), and Mercaptopurine are added to the aforementioned regimen. Dexamethasone may exert higher anti-leukemic activity and it is used instead of prednisone [2,3].

Prevalent acute Central Nervous System (CNS) complications in ALL may result from CNS leukemia, CNS radiation intrathecal chemotherapy and less frequently systemic chemotherapy [3-6].

Acute Intracerebral Hemorrhage is a known CNS complication of ALL that may occur in patients due to severe thrombocytopenia, extremely high leukocyte counts or disseminated intravascular coagulation [7].

Cerebral Sinovenous Thrombosis (CSVT) is a rare complication of the disease that accounts for 0.5-1% of all stroke cases [8]. The most common etiologies and triggers of CSVT include dehydration, hypoxia, infection, systemic lupus erythematosus, inflammatory bowel disease, anaemia, iron deficiency, sickle cell disease, B-thalassemia, paroxysmal nocturnal hemoglobinuria, autoimmune haemolytic anaemia, malignancies and their treatment, cardiac disease and related medications, nephrotic syndrome, down syndrome, homocystinuria, head injury, hydrocephalus, Behcet disease, medications such as Oral Contraceptives, L-Asparginase, Corticosteroids and Epoetin-alfa [7,9].

Different chemotherapy agents or administration protocols can cause a wide array of subsequent venous thromboembolic events during or even after receiving chemotherapy [10-12].

Furthermore, CSVT was observed in some studies following intrathecal injections. Lumbar Puncture (LP) was also considered as one of the rare risk factors for CVST and some reports have suggested the association between LP and CVST [13].

CSVT imaging studies may include cerebral Computed Tomography (CT) Scan, Cerebral Computed Tomography Angiogram (CTA) and Magnetic Resonance Angiography imaging (MRA).

Trials by Abdel Razek et al., shows that Computed Tomography Angiography (CTA) is a trustworthy and non-invasive imaging tool for the diagnosis and classification of head and neck vascular stenosis and thrombosis [14,15].

Due to the rare incidence of CSVT in children and the challenging possibility of the association between CSVT and lumbar puncture we decided to publish the sequence of events from the first manifestations to the final managements for this case.

Case Presentation

In January 2016 an 8-year-old boy with a 5-month history of fever and cervical lymphadenopathy was referred to Doctor Sheikh Hospital as a tertiary referral centre for paediatrics in Mashhad, Iran. His past medical history was unremarkable.

His initial Complete Blood Count (CBC) showed anaemia and leukopenia. Suspected for possible malignancy, he underwent different diagnostic tests including bone marrow aspiration and biopsy. BMA showed more than 20% lymphoblast and cells were found positive for CD10, CD19, CD22 using flow cytometry while no cytogenetic abnormalities were reported. The patient was subsequently diagnosed with B-precursor Acute Lymphoblastic Leukemia (ALL).

Initial induction chemotherapy was started based on the Children's Oncology Group (COG) AALL-0031 treatment protocol for paediatric ALL; the regimen consisted of Vincristine, Dexamethasone, L-Asparaginase, Cytarabine and Methotrexate (intrathecal and systemic).

According to paediatric oncology references due to importance and frequency, initial intrathecal therapy based on individualized treatment schedule is suggested for cases with diagnosed ALL to prevent any possible CNS involvement. Therefore, once the diagnosis was made, the CNS involvement was ruled out by analyzing cerebrospinal fluid. The cell counts, glucose, protein, and bacterial cultures of the CSF were normal in all samples. Intrathecal (IT) Cytarabine was also given at the time of lumbar puncture. The patient received the other treatment as seen in Figure 1.

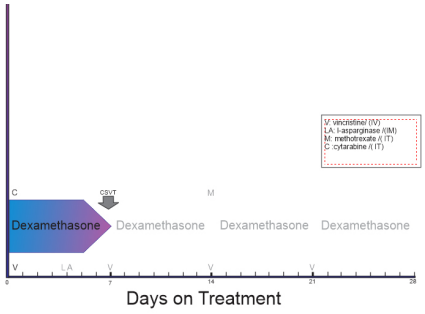

Figure 1: Timing of remission induction chemotherapy and the onset of stroke symptoms. Some of the drugs which were not prescribed at that time are shown by grey color in algorithm.

Despite all normal result of initial CNS evaluations, the patient complained from headache on the 6th day of treatment and then his first convulsion happened on day 7.

He exhibited generalized tonic seizure with upward gaze twice in 3 hours before they could be ceased by administrating phenytoin and phenobarbital.

We started to investigate the causes of his seizures. First brain Computed Tomography (CT) was obtained which revealed areas of haemorrhage and ischemic lesions in the left frontal region, suggestive of Intra Cranial Haemorrhage (ICH) (Figure 2). Therefore, CT-Angiography (CTA) was performed as the next step. The CTA showed an enlarged and engorged dilated vein near the haemorrhage site and a filling defect in the superior sagittal sinus suggestive of possible cortical vein thrombosis (Figure 3).

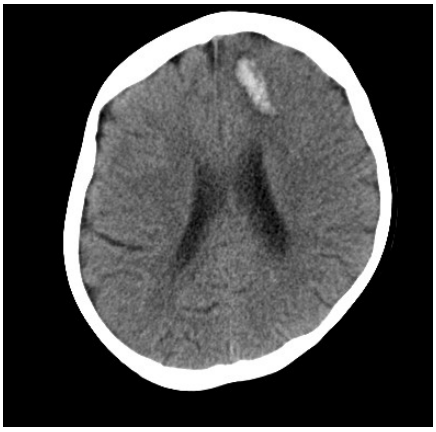

Figure 2: Cerebral Computed tomography, hyperdensity in the left frontal region (white arrow); suggestive of Intracerebral hemorrhage.

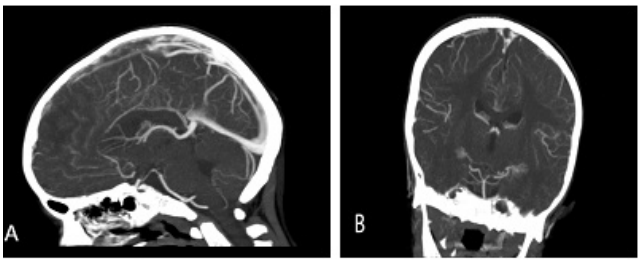

Figure 3: Cerebral computed tomography angiogram; (A) Sagittal view; filling defect in superior sagittal sinus (white arrow) (B) Coronal view; empty delta signs (white arrow) in confluence site; suggestive of thrombosis.

The patient blood test results came back with low level of Haemoglobin (7.5 g/dl), normal platelet (244,000/µl) normal Prothrombin Time (PTT) and Thromboplastin Time (PT).

As the final step, Magnetic Resonance Venography (MRV) manifested filling defects in superior sagittal sinus and confirmed the diagnosis of CSVT (Figure 4).

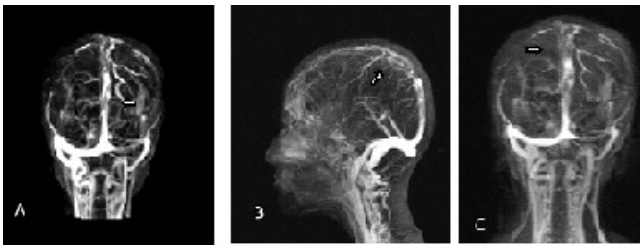

Figure 4: Brain Magnetic Resonance Venography (MRV); filling defects in the superior sagittal sinus demonstrate the diagnosis of CSVT (white arrows). (A) 3-Dimensional Contrast enhanced MRV; coronal view. (B) Sagittal view. (C) Coronal view.

As soon as the diagnosis was confirmed, analgesic for his headache and anticoagulant (Enoxaparin) for his brain lesion was administered. Seven days later he was discharged from hospital advised to continue oral anticoagulant for 3 months.

Ultimately, the patients hemorrhagic stroke was considered to be due to CSVT. Although we could not find a definite reason for CSVT, but intrathecal chemotherapy and corticosteroid consumption (oral or intrathecal) were the most probable responsible for the event.

Discussion

We described a new onset ALL in an 8 year old boy who manifested frontal lobe hemorrhagic stroke shortly after starting induction chemotherapy; which was due to CSVT and clinically presented with seizure.

Venus Thromboembolism (VTE) frequently occurs in childhood Acute Lymphoblastic Leukemia (ALL). The prevalence of symptomatic VTE varies depending on the employed chemotherapy protocol [16].

Risk factors of VTE in ALL patients are mentioned in many articles; e.g. L-Asparaginase (ASP) alone or in combination with vincristine or corticosteroids, applying Central Venus Lines (CVLs) and inherited thrombophilia [17]. Central nervous system is one of the most common areas where symptomatic VTEs occur [16].

Some studies verified the correlation between spinal anaesthesia or intrathecal chemotherapy and CSVT. There has been a study suggesting that CSVT mostly occurs in the induction phase and that the Asparaginase and steroids were equally responsible for the induced CSVT [13,18].

Another article demonstrated increased risk of CVST in ALL children who received prednisone [6,19].

In addition to chemotherapy drugs, intrathecal injection can also lead to CSVT. In one study authors stated that intrathecal glucocorticoid injections can be followed by cerebral venous thrombosis in patients with stroke [20].

As we mentioned in our case presentation, seizure in our case occurred just one week after lumbar puncture.

Methotrexate (MTX) can cause serious clinical neurotoxicity such as somnolence, confusion, and seizures within 24 hours of treatment but no increase in risk of thrombosis is reported yet [21].

Recent studies indicate that, contrary to infants, older children with ALL may be at higher risk of developing VTE. But, the epidemiology or the exact pathogenesis of this idea has not been clarified yet [22].

Having an unclear etiology, thrombin production tends to increase in children with ALL. Although, Thromboembolism (TE) in children with ALL is mostly reported after the beginning of anti-leukemic therapy, a possible interaction between the disease and the therapy should also be considered. Anti-leukemic drugs affect the haemostatic system either by direct influence of the chemotherapy agents or indirectly via the side effects of supportive managements such as infectious complications secondary to immunosuppression or Central Venous Line (CVL) [9,10].

That's why our patient's blood and CSF were analyzed and cultured and found to be completely normal.

Cerebral Sino Venous Thrombosis (CSVT) imaging studies may include cerebral Computed Tomography (CT) Scan, Cerebral Computed Tomography Angiogram (CTA) and Magnetic Resonance Angiography imaging (MRA) witch show the signs of CSVT encompasses changes in signal intensity or in the size and silhouette of the Cerebral Sinuses [23].

Post-Lumbar Puncture (PLPH) headache is a common side effect occurs in 10–30% of patients due to persistent Cerebrospinal Fluid (CSF) leakage after a lumbar puncture performed for anaesthesia or diagnostic purposes [24]. PLPH is mostly mild and resolves spontaneously so for the first 24 hours, conservative therapy (bed rest, oral analgesics) is recommended [25]. Epidural blood patch, oral and intravenous caffeine, oral gabapentin are suggested treatments (26). Our patient's headache did not resolve despite trying all these.

In our patient, there was no evidence of a definite predisposing factor for bleeding. The headache was probably due to the dural tear and the leakage of Cerebrospinal Fluid (CSF) led to intracranial hypotension. Intracranial hypotension can induce a downward shift of the brain and the resultant traction and disruption of the veins/sinus may lead to venous dilatation and thrombosis [27,28].

Heparin or Low Molecular Weight Heparin (LMWH) is used for antithrombotic treatment in acute events. Antiplatelet drugs can be used instead in case of contraindications. Direct endovascular interventions may be used as a substitute treatment in some patients [29].

Conclusion

Acute Lymphoblastic Leukemia (ALL) is the most common malignancy in childhood. One of the remarkable complications of the disease is Venous Thromboembolism (VTE). Utilizing appropriate screening measures in high risk children with ALL and tracing the development of neurologic impairments can prevent CNS complications of the disease and provides more life expectancy.

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