Case Report

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Mechanical thrombectomy by stent retriever for the treatment of arterial ischemic stroke in a pediatric patient with acute lymphoblastic leukemia: a case report

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Introduction: Arterial ischemic stroke (AIS) caused by occlusion of large vessels in childhood is a devastating rare condition that can contribute to long-term disabilities. Childhood leukemia is identified as a recognized risk factor for ischemic strokes. Mechanical thrombectomy is the standard of care for large vessel occlusions in adults. However, there are still no definite recommendations regarding the application and outcomes of endovascular thrombectomy and the devices used for pediatric patients with arterial ischemic stroke.
Case presentation: The authors report a 13-year-old female with acute lymphoblastic leukemia who developed AIS due to thrombosis in the left internal carotid and proximal middle cerebral artery in the induction phase of treatment. The patient underwent successful mechanical thrombectomy via Solumbra by using "Embolus Retriever with Interlinked Cages (ERIC)" stent retriever and Sofia plus catheter, which resulted in successful recanalization of ICA and MCA.
Discussion: Selected pediatric patients with AIS due to large vessel occlusions can benefit from mechanical thrombectomy. Although the recently published literature demonstrated the efficacy and safety of MT in children, strong guideline recommendations are still absent. At present, the last AHA/ASA guidelines for early management of AIS recommends intravenous thrombolysis and endovascular therapy in adults, whereas controversy still exists in children. An urgent approach within the defined therapeutic time frame and a multidisciplinary team specialized in pediatric stroke with professionally trained interventional neuroradiologist is essential for achieving optimal results.
Conclusion: Mechanical thrombectomy provides promising results with high rates of arterial recanalization and favorable outcomes in pediatric patients with AIS.

Keywords: acute lymphoblastic leukemia, arterial ischemic stroke, large vessel obstruction, malignancy, mechanical thrombectomy, pediatric

Introduction

Pediatric arterial ischemic stroke (AIS) is an important cause of neurologic morbidity in children. There is limited data on its incidence in pediatrics. According to a systematic review and meta-analysis up to October 2021, the incidence of AIS has been reported 1.28 per 100 000 person-years[1].

HIGHLIGHTS

- Acute leukemia has the highest risk of thrombosis among malignancies in children.
- Pediatric patients with acute leukemia are at an increased risk of stroke.
- Arterial strokes comprise the minority of strokes in children with leukemia.
- Mechanical thrombectomy (MT) is suggested in pediatric leukemia with AIS.
- This is the first report of MT via a modern stent retriever in a child with leukemia.

Many factors have been contributed to the increased risk of stroke in children with cancer. The underlying etiology is either directly due to cancer itself or a hypercoagulable state due to the cancer treatments[2]. In a literature search performed in PubMed, Cochrane, and Google Scholar during 1995–2022, incidence of stroke in pediatric cancer patients fluctuated between 0.47 and 2.9%, and prevalence between 1 and 3%[3]. International Pediatric Stroke Study (IPSS) determined the history of cancer in 99 out of 2968 children with AIS (3.3%), showing brain tumors in 48% and hematologic malignancies in 40%[4].

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Pediatric acute lymphoblastic leukemia (ALL) has the highest risk for thrombosis compared to other malignancies in children. In a study conducted by the division of Hematology, L'Aquila University, Italy, the incidence of thrombosis in 1752 children with ALL was found to be 5.2% which almost half of them (2.9%) occurred in the central nervous system (CNS). In a retrospective cohort study including 3968 pediatric ALL patients, the incidence of CNS thrombosis was reported to be 1.8% (venous: 1.5%, arterial: 0.03%)[5].

Large vessel occlusion (LVO) is reported to be responsible for ~25% of AIS in adults[6,7]. Endovascular therapy (EVT) or mechanical thrombectomy (MT) has been recommended as the standard treatment for AIS due to LVO in adults particularly in those with occlusion in internal carotid, anterior and middle cerebral arteries up to 24 hours from the onset of symptoms[8]. There is a lack of standard approaches for diagnosing and treating pediatric patients with AIS due to the paucity of evidence-based data in children and differences in risk factors, etiology, clinical manifesta tions, and therapeutic strategies between children and adults.

In this case report, we present a 13-year-old female with newly diagnosed B-cell-ALL who experienced AIS due to LVO in anterior circulation during the induction phase of the treatment. She underwent successful MT with a modern device without serious complications. To the best of our knowledge, this is the first case of MT in a teenage female with ALL; in Iran, who developed AIS. To the best of our knowledge, this is the first case of MT in a teenage female with ALL; in Iran, who developed AIS. This work has been reported in line with the SCARE criteria[9].

Case presentation

A 13-year-old girl, known case of high-risk ALL at the end of the induction phase was admitted to the emergency department due to abrupt onset of right-sided hemiplegia and facial palsy, expressive aphasia and some degrees of decreased level of consciousness. The parents mentioned that the last known normal time was about four hours ago when she woke up early in the morning. The neurological examination on arrival was remarkable for loss of the muscle force of the right upper and lower limbs as 0/5 based on the Medical Research Council (MRC) scale for muscle strength, right-sided facial palsy, and upward right plantar reflex. The patient's National Institutes of Health Stroke Scale (NIHSS) score was estimated to be about 20 upon arrival to the hospital.

The patient had received weekly vincristine and daunorubicin for the last 4 weeks and a single dose of Pegaspargase (pegylated L-asparaginase) two weeks before the onset of symptoms. She underwent non-contrast computed tomography, which was negative for intracranial hemorrhage. Brain MRI and MRA was scheduled for the patient at five hours of onset of symptoms, which showed mild hyperintensity in the left insular cortex in T2-weighted and fluid-attenuated inversion recovery sequences along with mild hyperintensity in left basal ganglia in diffusion-weighted sequences compatible with acute ischemic infarct. Occlusion in M1 segment of left middle cerebral artery (MCA) in 3D time-of-flight (TOF) sequence was observed on MRA of the patient (Fig. 1). Accordingly, she was transferred to a specialized comprehensive stroke center to go through emergent MT after nine hours of the onset of symptoms.

An ultrasound-guided right common femoral artery puncture was performed. A 90 cm long 7-F femoral sheath was advanced in the aorta up to the level of the left internal carotid artery. In the DSA, tandem thrombosis of left distal ICA and M1 segment of MCA was observed. The procedure was proceeded via SOFIA Plus aspiration catheter for two times, which was not successful. Then the technique was changed to Solumbra by using "Embolus Retriever with Interlinked Cages (ERIC)" 6×40 mm stent retriever and Sofia plus catheter, which resulted in recanalization of ICA and MCA after two attempts. Post-thrombectomy angiography showed complete revascularization of left ICA and MCA and "Thrombolysis in cerebral infarction (TICI)" grade 3 was achieved in the patient. Immediate post-thrombectomy CT scan showed hyperdensity in the left basal ganglia due to contrast extravasation, which disappeared 12 hours after thrombectomy (Fig. 2). MRI, three days after thrombectomy showed basal ganglia hyperintensity in T2 and fluid-attenuated inversion recovery images and hypointensity in T1 weighted images in favor of stabilized infarct (Fig. 3).

Right-sided hemiplegia improved to 1/5 and 2/5 in the muscle force of the right arm and leg, respectively. Follow-up MRA after

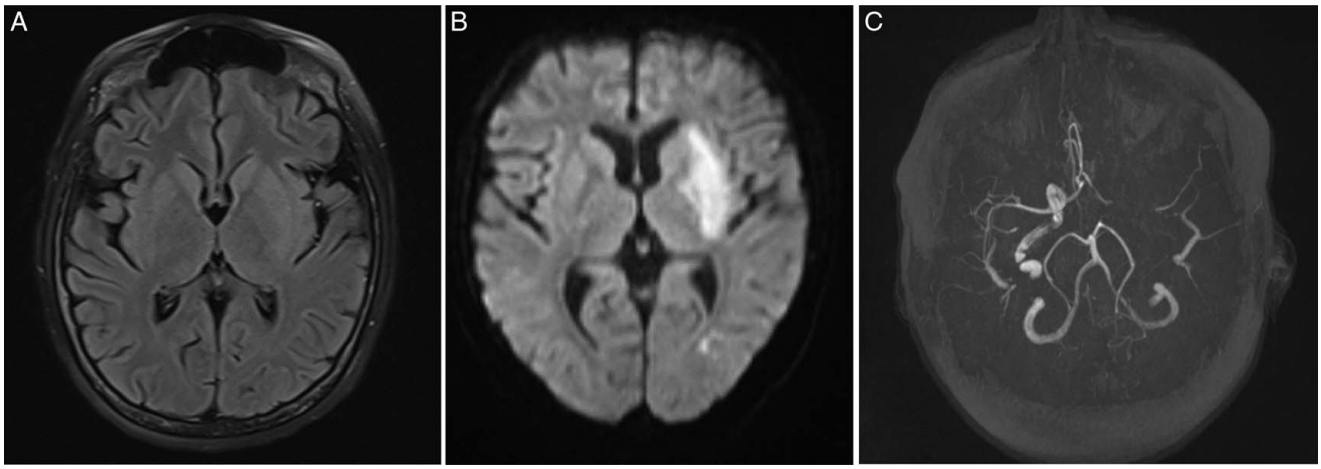

Figure 1. MRI, before thrombectomy at 6 h of onset of patient's symptoms. (A) Mild hyperintensity in the left insula cortex in the FLAIR sequence. (B) Mild hyperintensity in left basal ganglia in the DWI sequence. (C) Occlusion in M1 segment of left MCA in 3D-TOF sequence. FLAIR, fluid-attenuated inversion recovery; 3D-TOF, 3D time of flight; DWI, diffusion weighted imaging; MCA, middle cerebral artery.

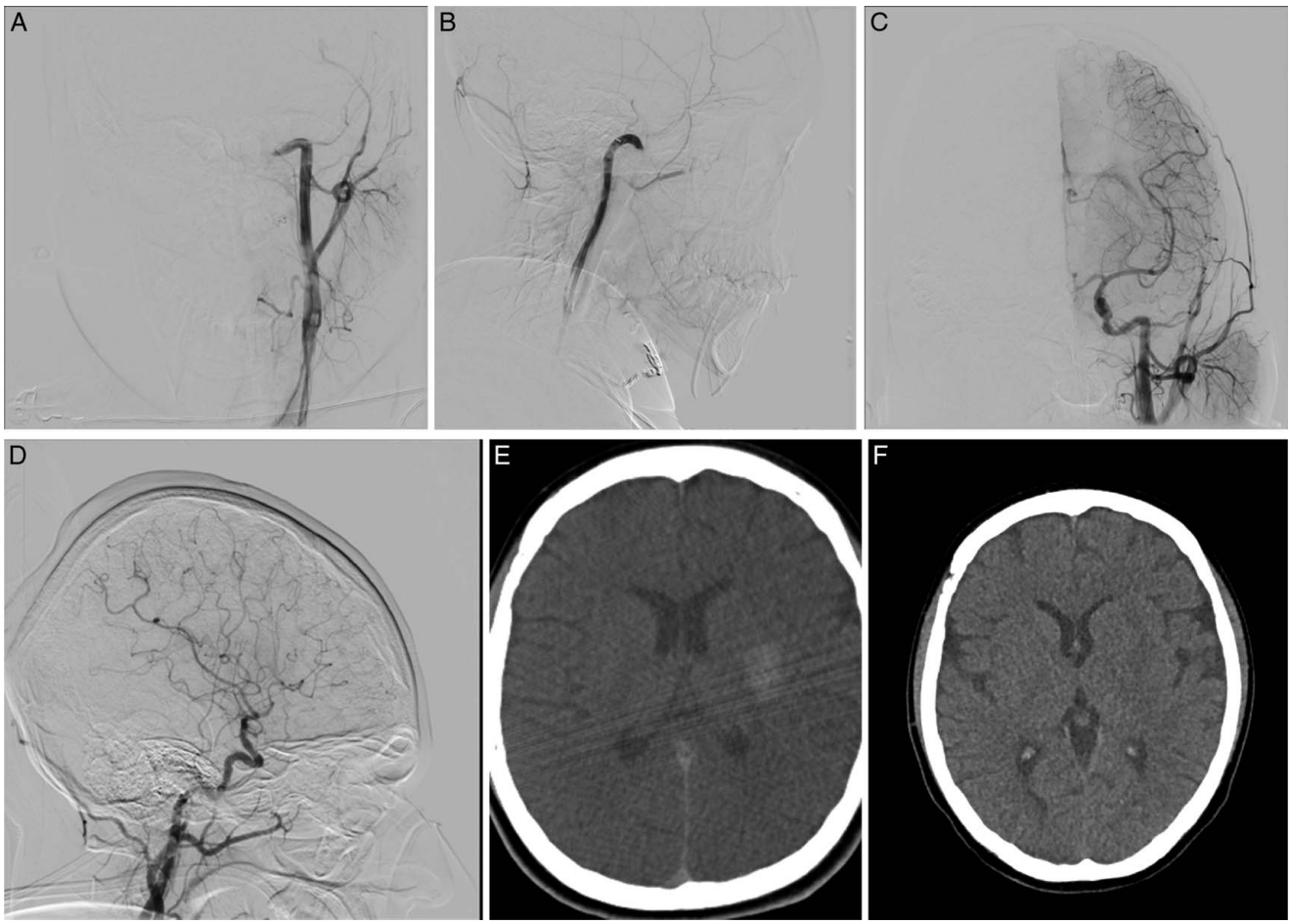

Figure 2. (A, B) Digital subtraction angiography (DSA) showed left distal internal carotid (ICA) occlusion in PA and lateral view of ICA. (C, D) Post-thrombectomy angiography of left ICA in PA and lateral views show complete revascularization of left ICA and MCA territories. (E) Immediate post-thrombectomy computed tomography scan shows hyperdensity in the left basal ganglia due to contrast extravasation. (F) Disappearance of contrast extravasation 12 h after thrombectomy. MCA, middle cerebral artery; FLAIR, fluid-attenuated inversion recovery.

10 days showed recanalized ICA on the left side with evidence of an ischemic pattern on MRI (Fig. 4).

The patient returned back to the referral hospital to follow her recovery course. There was an uneventful period with improving physical abilities through rehabilitation therapies along with physiotherapy sessions. The speech returned to normal with a low weak voice. After 3 months, some degrees of improvement in muscle strength of the right lower limb were observed. She achieved a modified Rankin Scale (mRS) of 2 in 90 days; however, there was still severe disability in upper extremity mainly in the wrist and fingers after 8 months.

Discussion

The occurrence of venous thrombosis in childhood ALL is a well-recognized complication. The majority of symptomatic thromboses in childhood ALL are related to central venous catheters and involve the upper venous system. CNS thrombosis involving the cerebral venous sinuses is the major feature of asparaginase-related thrombosis and is reported to occur in 1–3% of patients with ALL. Asparaginase contributes to a hypercoagulable state with decreased production of anticoagulant proteins of antithrombin, protein C, and protein S[10,11]. It is also noteworthy to mention that age is reported as an independent risk factor of thrombosis in acute leukemia with rates more than 40% in some cohorts of patients above 30 years of age[12,13]. Rate of thrombosis appears to be similar for PEGylated versus native E-coli asparaginase in pediatric populations[14]. Although, treatment with anthracyclines and prednisone (instead of dexamethasone) and asparaginase for long periods are reported to be associated with the highest incidence of thrombosis[15], high-risk patients may develop thrombosis even with first doses of asparaginase[16].

In a retrospective cohort study on 346 pediatric patients with ALL who received asparaginase, CNS thrombosis occurred in 3·8% (13/346) of the patients. Obesity (body mass index above 95th percentile) and different asparaginase formulation were the only factors associated with CNS thrombosis[17]. The present case was an obese teenage with BMI greater than 40 that we had to prescribe her high doses of dexamethasone during induction.

Interestingly, it is reported that the majority of thrombotic events in ALL patients occur during the initial phases of chemotherapy with about half of the episodes occurring even prior to administration of asparaginase. This could be explained by the fact that the event of thrombosis in ALL is a multifactorial process in which steroid administration and placement of venous

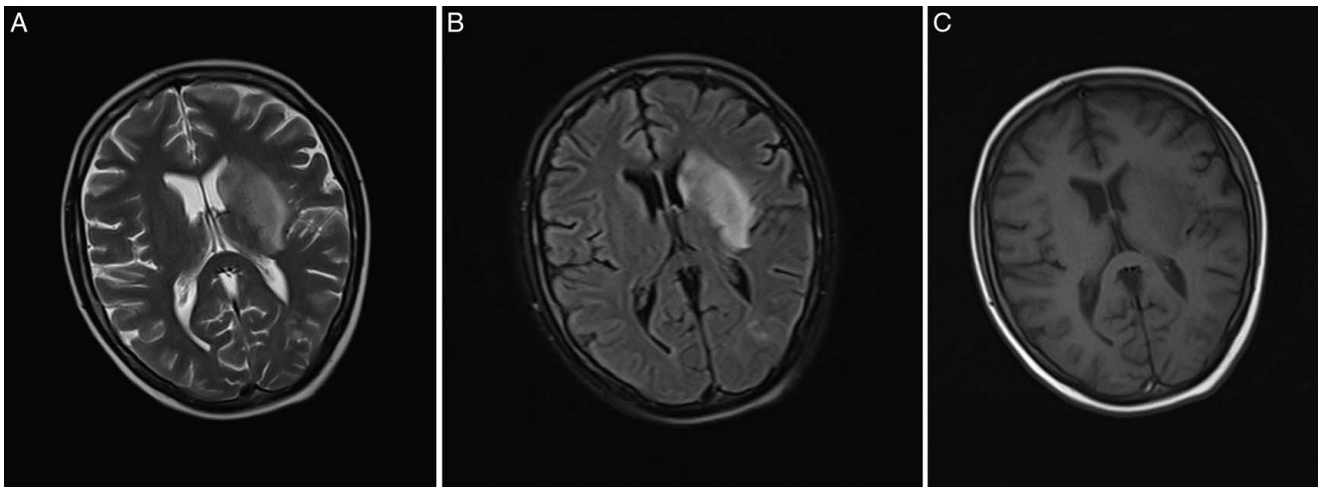

Figure 3. (A, B) MRI, 3 days after stroke onset and thrombectomy showed basal ganglia hyperintensity in T2 and FLAIR images. (C) Basal ganglia hypointensity in T1 weighted images.

catheters are among the most significant contributing factors[18]. The present case developed AIS within 2 weeks after injection of a single dose of pegylated asparaginase according to the protocol of high-risk ALL.

Review of the literature shows very few cases of AIS in children with ALL. In a retrospective review from four referral hospitals of Midlands, 10 cases of ALL with cerebral thrombosis is reported over a 5-year period that only 2 out of 10 patients had developed cerebral arterial thrombosis on days 15 and 19 of induction[16].

Severe vasospasm of cerebral arteries with subsequent infarcts have been reported in four ALL cases in children who showed neurological symptoms following intrathecal cytarabine[19–21]. Cerebral MRI/MRA in these patients indicated large areas of diffusion restriction in frontal and parietal lobes and diffuse vasospasm and narrowing involving the anterior and posterior circulations. A unique case of neonatal leukemia with focal seizure-like activity has been reported with right MCA infarct on MRA[22].

Arterial recanalization therapies, including intravenous tissue plasminogen activator (tPA) and endovascular MT has been shown to be significantly beneficial in adults with AIS when applied within the golden time period of 4.5 hours and 6 hours from the onset of symptom, respectively[23,24]. In a study published on behalf of the "American Heart Association" in adults, the efficacy of MT in patients with LVO was compared between two time frames (<6 and 6–24 h) and the results demonstrated similar outcomes[25,26]. Although the recently published literature demonstrated the efficacy and safety of MT in children[27,28], robust recommendations are still lacking. At present, the 2018 AHA/ASA guidelines for early management of AIS recommends intravenous thrombolysis and endovascular therapy for adults older than 18 years, whereas controversy still exists in children with AIS[29].

In a national study performed in Denmark, 28 out of 133 children with AIS demonstrated LVO on angiography (21%) which MT was successful with recanalization in 93% of the subjects[30].

A retrospective cohort study reported 166 pediatric patients with AIS of whom 39 (23.5%) had an LVO[31]. In this cohort, about 30% of patients with LVO underwent MT with or without intravenous thrombolysis. pediatric patients with LVO who did not receive MT had poor neurological sequels suffering from moderate to severe disability or death[31].

Delayed diagnosis of stroke in children may lead to missing the therapeutic window of 6-h between onset of symptoms to the time of MT. However, due to the presence of rich cerebral

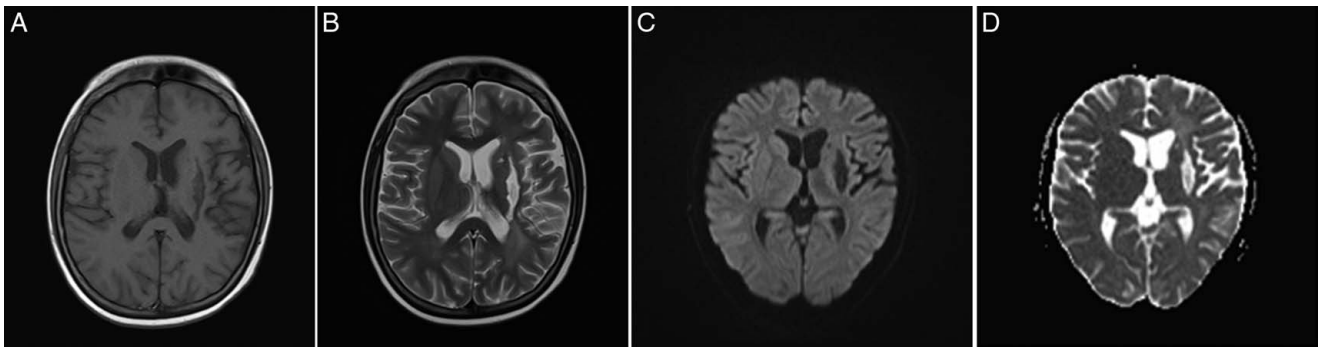

Figure 4. (A,B) MRI, 10 days after thrombectomy showed basal ganglia hypointensity in T1 and hyperintensity in T2 weighted images in favor of encephalomalacia. (C, D) There is no evidence of restricted diffusion in ADC and DWI images, respectively. ADC, apparent diffusion coefficient; DWI, diffusion weighted imaging.

collateral blood flow in children and also the change in this time frame already discussed, they might benefit from delayed MT beyond the therapeutic window period[32,33]. Our case underwent successful MT after about 10 h of onset of symptoms of stroke with favorable functional outcomes in 90 days.

Conclusion

Pediatric ALL patients are susceptible to thrombotic events due to both primary disease and chemotherapeutic agents, which may contribute to both AIS and cerebral venous thrombosis. Although L-Asparaginase is strongly associated with cerebral venous thrombosis, the authors suggest that the stroke in this case was due to a number of factors including PEG-asparaginase, severe obesity and high dose of corticosteroids during induction.

Accurately selected pediatric patients with AIS-LVO might benefit from endovascular MT even with an extended therapeutic window period. However, more case and observational studies are required to justify safe utilization of this procedure in children.

Ethical approval

For case reports, we need to have the approval of ethics committee of department of pediatric hematology/oncology of Mofid Children Hospital. It was taken accordingly.

Consent

The written informed consent was obtained from the patient's parent.

Source of funding

There was no financial support or any kind of funding for reporting this case.

Author contribution

A.K.B.: interventional neuroradiologist performing the main procedure of intervention and study concept. M.K.: radiologist imaging of the patient, Data analysis and interpretation. S.A.: writing the paper. Z.K.: pediatric oncologist, study design along with the other colleagues. M.A. and A.Z.: pediatric hematology/oncology fellowships, finalyzing the draft. P.M.: data collection.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

Research registration unique identifying number (UIN)

This was a case report.

Guarantor

Samin Alavi.

Data availability statement

This is a case report.

Provenance and peer review

It was not invited.

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