A Unique Case of Deep Cerebral Veins Thrombosis in an Adolescent Affected by Acute Lymphoblastic Leukemia Treated with Peg-Asparaginase

Elvira Pota; Mario Diplomatico; Martina Di Martino; Daniela Di Pinto; Mario Cirillo; Francesca Rossi*

1Department of Women, Child, and General and Specialized Surgery, University of Campania Luigi Vanvitelli, 80138 Naples, Italy.
2Department of Advanced Medical and Surgical Science, University of Campania Luigi Vanvitelli, 80138 Naples, Italy.

*Corresponding Author(s): Francesca Rossi
Department of Women, Child, and General and Specialized Surgery, University of Campania Luigi Vanvitelli, 80138 Naples, Italy.
Tel: +393358184429;
Email: Francesca.ROSSI@unicampania.it

Abstract
The most common malignancy in childhood is Acute Lymphoblastic Leukemia (ALL). Survivors need a regular follow-up after the cessation of chemotherapy for the long-term complications that are related to the type and intensity of the treatment regimen. Asparaginase is a milestone in the ALL treatment and even though a direct neurotoxicity is uncommon, it is associated with coagulopathy causing both hemorrhagic and thrombotic complications, particularly hemorrhagic stroke and cerebral sinovenous thrombosis, typically after several weeks of treatment. We report a unique case of ischemic stroke in an adolescent affected by ALL due to the unusual occlusion of deep cerebral veins only nine days after the infusion of PEG-asparaginase. With our report, we want to highlight the possibility (not previously reported) of cerebral deep veins thrombosis during asparaginase treatment with a possible favorable outcome as CSVT.

Keywords: Leukemia; Asparaginase; Stroke; Thrombosis; Chemotherapy.

Introduction
The most common malignancy in childhood is Acute Lymphoblastic Leukemia (ALL) [1]. The actual outcome for ALL approaches 90 percent of five-year event-free survival but survivors need a regular follow-up after the cessation of chemotherapy for the long-term complications that are related to the type and intensity of the treatment regimen. Asparaginase is a milestone in the ALL treatment and even though direct neurotoxicity is uncommon, it is associated with coagulopathy causing both hemorrhagic and thrombotic complications, particularly hemorrhagic stroke and cerebral sinovenous thrombosis, typically after several weeks of treatment [2,3]. We report a unique case of ischemic stroke in an adolescent affected by ALL due to the unusual occlusion of deep cerebral veins only nine days after the infusion of PEG-asparaginase.

Case report

A 15-year-old girl was diagnosed with ALL-L2 CALL+ at our tertiary referral hospital presenting with hepatosplenomegaly, weakness, cervical spine and wrists pain during the last month. Her blood tests showed: RBC 2.06x10⁶/ul, Hb 6.2 g/dl, PLT 156000/ul, WBC 8880/ul (neutrophils 2%, lymphocytes 4%, blasts 94%). Bone marrow examination showed 95% of blasts CD19+ CD10+ without chromosomal aberrations. Her coagulation, hepatic and renal function tests were in the normal range; neurological examination, electroencephalogram, brain MRI and lumbar puncture were normal. She received induction with “AIEOP-BFM ALL-2009 protocol” (high-risk cytogenetics and persistent minimal residual disease on the fifteenth day assessed by multiparameter flow cytometry=70.367%) and only nine days after the first infusion of PEG-asparaginase she had two episodes of loss of consciousness, urinary urgency and incontinence, deambulatory and speech difficulties. As for this reason we performed cardiological evaluation, ECG and echocardiography that resulted all normal, Factor V Leiden, MTHFR, protein C and protein S resulted all in the normal range, PT, aPTT and fibrinogen could not be measured properly, D-dimer resulted 2699 mg/ml and antithrombin activity was of 49%. Electroencephalography showed a diffuse deregulation of the electrical activity without focality and an urgent MRI showed multiple white matter hyperintensities compatible with acute thromboembolic lesions (Figure 1 A-B). We treated her replacing Antithrombin (AT) to get antithrombin activity above 70% and Low-Molecular-Weight Heparin (LMWH) for 5 months. Neurologically she recovered swiftly, and we monitored the patient by brain-MRI every month showing a major radiological improvement after six months (Figure 2). In the meantime, she continued her chemotherapy without asparaginase and now she is into complete remission for three years.

Discussion

Children affected by leukemia and treated with only chemotherapy or low-dose radiation (<30 Gy) didn’t have an increased risk for late-occurring stroke compared to age-matched siblings [4]. The reported incidence of thrombosis during the treatment course of childhood ALL is variable from 1 to 37% in different populations and treatment protocols [5]. Cerebral Sinus Venous Thrombosis (CSVT) is a complication well known to occur during childhood ALL therapy and it is associated with high mortality rate (8-13 %) and long-term neurological sequelae [6]. The most common sites of involvement are the dural sinuses and cortical veins with a higher incidence during the induction phase [7,8]. The most common symptoms/signs are seizure, headache, vomiting, hemiparesis and altered mental status depending on the site and size of thrombosis. CSVT pathophysiology is related to hyperleucocytosis, possible sepsis and prothrombotic predisposition of the patient. Risk factors associated with CSVT were age >10 years, T immunophenotype, intermediate/high risk, antileukemic drugs (as asparaginase and steroids). The last AHA/ASA scientific statement published in 2019 suggests a close monitoring of anticoagulation with serial assessment of anti-factor Xa level for LMWH therapy and even though there are no indication about the length of treatment, the most common approach is to treat CSVT for 3 to 6 months and longer if there is an inherited thrombophilia or persistent risk factors for venous thrombosis (as asparaginase therapy). It is also suggested to often repeat neuroimaging to monitor for clot stability and the degree of recanalization [9]. According to the literature, we treated our patient as for standard CSVT with enoxaparin (LMWH) 1 mg/kg every 12 hours to achieve an anti-Xa activity between 0.5 and 1 IU/ml for 5 months; the treatment was stopped only for lumbar puncture for 24 hours before and 4 hours after [10]. After the treatment of a common CSVT, it is suggested a secondary prophylaxis with a daily dose of 1 mg/kg/day of LMWH until asparaginase treatment is completed [8]. As mentioned previously, we decided to exclude asparaginase from her chemotherapy because of the singularity of her cerebral deep venous thrombosis and the lack of data reported in literature about her long-term outcome.

Conclusion

To reduce the risk of thrombosis during chemotherapy, a complication already due to the drugs used and the presence of central venous lines that has a negative impact on the achievement of complete remission, life expectancy and long-term quality of life, we consider as reasonable to perform a complete screening for inherited thrombophilia in all patients affected by...
ALL before starting therapy (test should include factor V Leiden (G1691A), factor V (H1299R), MTHFR (C677T), MTHFR (A1298C), factor II (G20210A), Protein C, protein S, lipoprotein (a), fibrinogen, Antithrombin (AT) activity and lupus antibodies) in addition to a close monitoring of laboratory tests for thrombosis and hemostasis in patient with high leukemic burden during PEG-asparaginase treatment. In October 2020, Rank et al. published a Cochrane review entitled “Prophylaxis of thromboembolism during therapy with asparaginase in adults with acute lymphoblastic leukaemia” concluding that there are no evidences for clinically appreciable benefits suggesting thromboprophylaxis in adults with ALL treated with asparaginase-based regimens [11]. To the best of our knowledge, also in pediatric patients with ALL there are insufficient data to support a thromboprophylaxis and for this reason we consider of great importance to report our case hoping to improve the clinical practice with future research and to highlight the possibility (not previously reported) of cerebral deep veins thrombosis during asparaginase treatment with a possible favorable outcome as CSVT.

Disclosure statement

The authors have no conflicts of interest to declare. We declare that there is no competing interest in the submission we have made. We declare that each author listed on the manuscript has seen and approved the submission of this version of the manuscript and takes full responsibility for the manuscript.

Funding sources

We declare that none of the authors received any honorarium, grant, or other form of payment for this study.

Statement of ethics

This research was conducted in compliance with the guidelines for human studies and ethically in accordance with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from the parents prior to any study-related procedures.

Author Contributions

E.P. contributed to the design, methodology, investigation, supervision and writing of the study.

M.D. contributed to the investigation, data curation, resources and writing of the study.

M.D.M., D.D.P., M.C. contributed to conceptualization, formal analysis and editing of the study.

F.R. contributed to the methodology, formal analysis, and review of the manuscript.

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