L-Asparginase induced cortical venous thrombosis in a patient with acute leukemia

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ABSTRACT

L-Asparginase is used for remission induction in acute lymphoblastic leukemia. We describe a case of 16-year-old boy who developed cortical venous thrombosis following the administration of L-Asparginase.

Key words: Acute lymphoblastic leukemia, cortical venous thrombosis, L-Asparginase

INTRODUCTION

L-Asparginase is an active anti-cancer drug exclusively used in the treatment of Acute Lymphoblastic Leukemia. The common side effects include Hypersensitivity reactions, Pancreatitis and Coagulation abnormalities. Cortical venous thrombosis (CVT) is an uncommon side effect and can result in a life threatening complication. Here we report a case of a young boy with leukemia who developed CVT on treatment with L-Asparginase.

CASE REPORT

A 16-year-old boy diagnosed as acute lymphoblastic leukemia (ALL) was started on multicentric protocol (MCP) 841 protocol. The drugs used during the induction phase include vincristine, L-asparginase, daunorubicin, and steroids. He received L-asparginase 6000 IU/m^2 on alternate days for five doses during the repeat induction phase. He presented with headache, vomiting, and multiple episodes of seizures. On examination, he was afebrile, there was no evidence of neurological deficit and fundus examination revealed no evidence of papilledema. Hemogram was normal with no evidence of blasts on the peripheral smear. A contrast enhanced CT brain was taken which revealed cortical venous thrombosis (CVT) [Figure 1]. He was started on low molecular weight heparin (enoxaparin) at a dose of 1 mg/kg twice a day for 6 months and his symptoms improved. A repeat CT taken after a month revealed a normal study.

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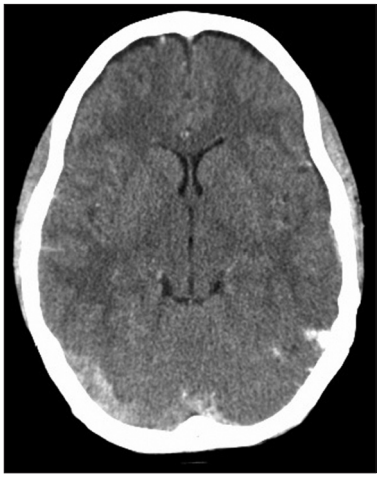

Figure 1: CT brain—showing cortical venous thrombosis

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L-Asparaginase is a bacteria-derived enzyme that provides specific therapy for lymphoid malignancies such as acute lymphoblastic leukemia (ALL) by catalyzing the hydrolysis of L-Asparagine to L-Aspartic acid and depleting the circulating pools of this amino acid. Although the capacity to synthesize L-asparagine is constitutive in most normal tissues, malignancies of the lymphoid origin lack the enzyme (asparagine synthetase) that catalyzes the transformation of L-Aspartic acid to L-asparagine and therefore depend on exogenous sources of L-Asparagine. Despite this apparent specificity for lymphoblasts, however, therapy with L-asparaginase is often limited by significant toxicity such as coagulation abnormalities and hypersensitivity reactions.[1]

Venous thrombosis may cause as many as 30% of the acute central nervous system events in acute leukemias. Children with ALL during treatment have a 5% risk of thrombosis, and it is life threatening when the central nervous system is involved.[2,3] L-Asparaginase may impair the hemostatic system by reducing the synthesis of coagulation factors (including fibrinogen, factor II, IX, and X) and inhibitors of coagulation (such as antithrombin, protein C, and protein S) as a consequence of asparagine depletion. There is a state of hypercoagulability despite a reduction of both procoagulant and anticoagulant activity. L-Asparaginase-induced deficiency of antithrombin III is responsible for the increased risk of sinovenous thrombosis in the brain.[4] About 2% of children treated with L-asparaginase develop hemorrhagic or nonhemorrhagic infarcts consequent to CSVT.[3]

Early diagnosis demands a low threshold for imaging, and MRI should be preferred over CT. The findings of venous infarcts, the empty delta sign, and absent flow in the dural sinuses on CT and MR venography help in proper diagnosis and management.[5,6]

Treatment of CVT resulting from L-asparaginase-induced antithrombin deficiency includes general supportive measures, anticonvulsants for seizures, and anticoagulation. Further L-Asparaginase is contraindicated. However, the key to management is early diagnosis by imaging as delayed institution of anticoagulation may be futile. For therapeutic anticoagulation, low molecular weight heparin is given initially and this may be continued or it may be substituted by oral anticoagulants for 3–6 months.[3]

CONCLUSION

We conclude that diagnosis of CSVT in leukemic patients being treated with L-Asparaginase requires a high index of clinical suspicion in the presence of seizures, a focal neurological deficit, and features of raised intracranial tension. Early diagnosis demands a low threshold for imaging, and MRI should be preferred over CT.

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