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Case Report

L-ASPARAGINASE-INDUCED HYPOFIBRINOGENEMIA: A CASE REPORT

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ABSTRACT

Anticancer therapy is always known to cause various side effects. L-asparaginase used in the treatment of adult T-cell lymphoblastic leukemia is a novel class of drug, an enzyme produced from plants as well as microorganisms except human. It is known to cause various adverse reactions including life-threatening neurological complications and thrombotic disorders. Hence, we report a case of hypofibrinogenemia associated with L-asparaginase in a patient treated for T-cell adult lymphoblastic leukemia.

Keywords: L-asparaginase, Hypofibrinogenemia, Adverse effect, Leukemia.

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INTRODUCTION

L-asparaginase is a novel chemotherapeutic agent present obtained from various plants, bacteria, fungus except humans. It is used in the treatment of adult as well as pediatric lymphoblastic leukemia. L-asparaginase enzyme plays a very crucial role in the production of aspartate family of amino acids, namely, threonine, lysine, and methionine. L-asparaginase is known to cause severe thrombotic complications. Hence, we report a case of L-asparaginase-induced hypofibrinogenemia in a 16-year-old male, T- cell adult lymphoblastic leukemia (ALL) patient in a tertiary care hospital in South India

CASE REPORT

Informed consent was taken from the patient. A 16-year-old male patient diagnosed of ALL of T-cell type on September 09, 2016 and was started on September 10, 2016, with injection vincristine 2 mg and injection daunorubicin 64 mg. After completion of the first cycle with above two drugs, the second cycle was started with L-asparaginase on October 02, 2016, at a dose of 16,000 IU/m^2 along with vincristine and daunorubicin. The latter two drugs were given on the same day once at the dose as used in the first cycle. L-asparaginase was continued, and after 10 days on October 13, 2016, patient's routine blood investigation revealed a drop in fibrinogen levels to a very low level of 67.6 mg/dl. Other laboratory parameters were normal, and liver function test was also normal. There was no bleeding or thrombotic events, and finally, L-asparaginase was suspected to be the cause, and other causes were ruled out. L-asparaginase was stopped on October 19, 2016, and the patient's fibrinogen assay returned to normal levels on October 20, 2016 (Table 1).

DISCUSSION

L-asparaginase is a tetrameric protein, and it plays a pivotal role in the hydrolysis of free L-asparaginase enzyme into aspartic acid and ammonia [1]. L-asparaginase enzyme accounts for almost 40% worldwide sale as a potential therapeutic antileukemic agent [2]. It is also used in the treatment of Hodgkin's lymphoma, chronic lymphocytic leukemia, and melanosarcoma as antineoplastic agent apart being a novel class of drug used in the treatment of adult T-cell lymphoblastic leukemia. Mashbrun and Wriston first isolated L-asparaginase from *Escherichia coli*, and this kick started the production of this enzyme in large scale for the treatment of leukemia [2].

An interesting mechanism of L-asparaginase has made it the blockbuster agent in the treatment of leukemia. The mechanism of action is, as cancer cells are dependent on exogenous supply of asparagine, due to lack of L-asparaginase synthetase enzyme; when L-asparaginase is given therapeutically in leukemic patients, this drug drains out all the available asparagine, and later cancer cells starve to death due to the lack of asparagine [3]. L-asparaginase is known to cause various side effects due to its effect on normal body cells which includes hepatic dysfunction, skin rashes, breathlessness, acute pancreatitis, leucopenia, thrombosis, hemorrhage, depression, seizures, fatigue, and severe neurological toxicity [3].

Hypofibrinogenemia, defined as fibrinogen levels below 150 mg/dl, can be caused by both congenital as well as acquired causes. Congenital abnormalities include Type I afibrinogenemia which is caused by mutations in both chromosomal alleles of fibrinogen gene whereas Type II dysfibrinogenemia is basically due to mutations in one chromosomal allele of fibrinogen gene [4,5]. Acquired causes include reduced synthesis due to liver disease, increased consumption due to sepsis, cancer, and tissue plasminogen activator therapy, and hemodilution due to massive transfusions and due to autoantibody against fibrinogen in case of autoimmune diseases [6]. Many drugs are also known to cause hypofibrinogenemia including prednisolone, alteplase, tigecycline, isotretinoin therapy, autoantibodies produced due to isoniazid, and also bovine fibrin glue used in surgeries. There are case reports of hypofibrinogenemia induced by L-asparaginase [7]. Mechanism attributed to this adverse reaction is mainly decreased synthesis of fibrinogen, and rapid death of cancer cells may also contribute to fall in fibrinogen levels due to consumption coagulopathy [7].

In our case, the patient was diagnosed of adult T-cell lymphoblastic leukemia and was started with vincristine and daunorubicin. At the end of first cycle, fibrinogen levels were normal. After induction of L-asparaginase in the second cycle, the patient showed decreased fibrinogen levels after 10 days of starting the treatment. Hence, with this evidence by ruling out other potential acquired as well as congenital causes of hypofibrinogenemia, L-asparaginase was found to be causative agent of decreased fibrinogen levels in the study patient. Furthermore, after stopping the drug, the patient recovered back immediately supporting our finding. Hence, to establish a causal relationship, causality assessment using Naranjo's scale [8] was

performed, and a probable causal relationship was ascribed. Severity scale was performed using Hartwig's scale [9], and adverse reaction was found to be of mild severity. Furthermore, preventability assessment was done as per Thornton's scale [10], and adverse reaction was found to be not preventable (Table 2).

CONCLUSION

L-asparaginase, a very useful drug in the treatment of leukemia causes many adverse reactions and hypofibrinogenemia, is one among them. Severe hypofibrinogenemia can lead to life-threatening complications in some patients. Hence, proper monitoring of fibrinogen levels using fibrinogen assays is of at most importance, and further clinical studies can be performed to find the incidence of hypofibrinogenemia associated with L-asparaginase treatment in leukemia patients.

Table 1: Fibrinogen levels before and after L-asparaginase

Date	Fibrinogen levels (mg/dl)
September 30, 2016	306
October 04, 2016	167
October 13, 2016	67.6
October 20, 2016	208.7

Table 2: Adverse drug assessment

Scales	Assessment
Naranjo's	Probable
Hartwig's	Mild severity
Thornton's	Not preventable

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