CASE REPORT

Transient Hyperthyroidism Following L-asparaginase Therapy for Acute Lymphoblastic Leukemia

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Summary

The effect of L-asparaginase on the thyroid gland has not been well documented. We report the first two cases of hyperthyroidism associated with thyroid nodule following L-asparaginase therapy for acute lymphoblastic leukemia (ALL). The thyroid function abnormalities were not severe, short-lived and did not require specific therapy.

Key Words: Acute lymphoblastic leukemia (ALL), L-asparaginase, Hyperthyroidism, Thyroid nodule

Introduction

L-asparaginase is one of the "standard" drugs used in induction remission therapy of ALL. Major toxic effects of L-asparaginase include hypersensitivity reactions, coagulopathy, acute pancreatitis, liver and renal function abnormalities, and central nervous system changes[1]. Thyroid abnormalities resulting from L-asparaginase therapy is uncommon. The following report describes 2 patients who developed transient hyperthyroidism associated with thyroid nodule following L-asparaginase therapy. Other possible causes of hyperthyroidism were excluded.

Case Report

An 18-year-old patient presented with a 3-day history of unexplained fever one week after receiving a total of 81,000 I.U. of subcutaneous L-asparaginase. She was diagnosed to have T-ALL one month earlier and had achieved remission with induction chemotherapy consisting of vincristine, daunorubicin, and high dose prednisolone. There was no previous history of thyroid disorder. Infective causes of the fever were excluded. Examination revealed a thyroid nodule measuring 4 x 5 cm. There were fever temperature of 30°C heat intolerance, fine tremor, tachycardia and brisk tendon reflexes. Serous fluid was noted on aspiration of the thyroid nodule and cytological study of the specimen was consistent with thyroiditis. Culture of the fluid was negative. Serum free thyroxine (T_4) level was 53 (NR 10-22 pmol/l) and TSH less than 0.06 (NR 0.5-6 U/l). Thyroid autoantibodies were not detected. The full blood count was normal. The fever and neck pain improved 7 days later with analgesics. There was no recurrence of the thyroid nodule and thyroid function test was normal when she was last seen 3 weeks after the onset of the thyroid abnormalities.

The second case was a 52-year-old patient who received 63,000 I.U. of L-asparaginase as part of induction chemotherapy for ALL. She developed palpitations, heat intolerance, and loose stool 2 days after the last dose of L-asparaginase. A thyroid nodule measuring 4x5 cm

was evident on examination. Thyroid function test was consistent with moderate hyperthyroidism (serum free T_4 68 pmol/l and TSH < 0.06 U/l). Aspiration of the thyroid gland was not performed in view of severe thrombocytopenia and hypofibrinogenemia. The thyroid nodule disappeared and the thyroid function test returned to normal 5 days later. The patient subsequently died of pulmonary hemorrhage. Anti thyroid therapy was not instituted in both patients as there were few toxic symptoms and it was thought that the thyroid dysfunction would recover spontaneously upon discontinuation of the L-asparaginase.

Discussion

Several factors may contribute to the thyroid dysfunction in patients with ALL. These include severe systemic disease, steroid administration, radiotherapy, and L-asparaginase therapy. The following factors suggested that the abnormal thyroid function was related to L-asparaginase. Firstly, symptoms of hyperthyroidism first appeared following administration of L-asparaginase and disappeared 5-7 days after withdrawal of the drug. The plasma half-life of L-asparaginase is 3.24 ± 1.83 days in patients who were previously sensitive to L-asparaginase and 5.69 ±3.25 days in non-hypersensitive patients[2]. These could explain the brief period of thyroid function abnormalities observed in our patients. Secondly, other possible causes of thyroiditis were not evident. Both patients did not have past or family history of thyroid disorders and thyroid autoantibodies were not detected. Thirdly, the patients did not receive other drugs or radiation therapy that could affect the thyroid. Drugs that are known to cause goitre and interfere with the thyroid function include amiodarone, ethionamide, para-aminosalicylic acid and iodine containing drugs. Fourthly, L-asparaginase has been reported to interfere with the interpretation of thyroid function tests by producing a rapid and marked reduction in serum concentrations of thyroxine-binding globulin (TBG) within 2 days after the first dose[3]. Serum concentration of TBG returned to pretreatment values within 4 weeks of the last dose of L-asparaginase. Apart from this report, there was only one other report that studied the effect of L-asparaginase therapy on thyroid hormones[4]. Parameters of thyroid function were measured in 9 children with ALL who received induction chemotherapy with L-asparaginase (5000 U/m^2) daily on days 1-21, vincristine, anthracycline drugs and corticosteroids. There was a significant reduction in the total T_4, free T_4, total T_3, and TBG. It was concluded that the low T_3 and TBG levels during late intensification were primarily due to steroid administration, while during induction, the even lower T_3 and TBG values were mainly attributable to L-asparaginase. The hypothyroidism was transient and did not require treatment. In contrast, our patients had elevated free T_4 level.

The mechanism of thyroid abnormalities following L-asparaginase is not known. Unlike amiodarone, it does not contain iodine[1,2]. The major toxic effects of L-asparaginase are due to its ability to inhibit protein synthesis in normal tissues[5]. Inhibition of protein synthesis in the liver will result in hypoalbuminemia, a decrease in clotting factors and serum lipoproteins. This can account for the reduction in TBG levels and hypothyroidism that have been noted after L-asparaginase therapy. There is however no report on a direct toxic effect of L-asparaginase on the thyroid gland.

In patients who are critically ill with ALL, signs and symptoms of hyperthyroidism or hypothyroidism may be difficult to detect. Thus, thyroid function should be included in the work-up of a patient who develops unexplained or persistent fever following L-asparaginase administration. As the effect of L-asparaginase on the thyroid gland has not been well documented, there is uncertainty regarding the natural history, outcome and management of this uncommon problem. Nevertheless, it should be used with caution in patients with thyroid dysfunction. In our patients the hyperthyroidism was not severe, short lasting, and did not require anti thyroid drugs. To the best of our knowledge, this report represents the first 2 cases of hyperthyroidism associated with thyroid nodule following administration of L-asparaginase.

References

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