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L-Asparaginase Induced Intracranial Haemorrhage in Acute Lymphoblastic Leukemia

H L Lim, C P Teo, K Wong, Y K Kueh

ABSTRACT

A 20-year-old national serviceman with acute lymphoblastic leukaemia, developed a large left parieto-occipital haemorrhage 7 days after completion of induction chemotherapy. Severe hypofibrinogenemia had been noted while he was receiving L-asparaginase. The haemorrhage could not be attributed to thrombocytopenia, disseminated intravascular coagulopathy, arterio-venous malformation, berry aneurysm or leukaemic infiltration because each of these causes was carefully investigated into and excluded. We conclude that the intracranial haemorrhage was likely L-asparaginase induced, an uncommon but recognised complication associated with L-asparaginase therapy.

Keywords: acute lymphoblastic leukaemia, L-asparaginase, intracranial haemorrhage, hypofibrinogenemia

CASE REPORT

L-asparaginase is an enzyme derived from *Escherichia coli*, which has anti-neoplastic activity particularly in lymphoid malignancies. It is often used in the induction therapy of acute lymphoblastic leukaemia (ALL). However, its toxicities include haemostatic abnormalities (both thrombotic and haemorrhagic), hyperglycaemia, hypertriglyceridemia and hypoproteinemia. The haemostatic problems are due to decreased production of both natural anti-coagulants like anti-thrombin III (AT III), protein C and S and coagulation factors like fibrinogen, factor IX and others[1].

Although hypofibrinogenaemia had been shown to occur in 50% to 100% of cases studied, actual haemorrhagic complications were not common. It was first reported in 1980 that L-asparaginase could cause haemorrhagic problems[2]. Since then various large studies had estimated the incidence of either thrombotic or haemorrhagic complications with L-asparaginase to be about 1.0% to 2.4%[3-5]. Feinberg reported that the incidence of haemorrhagic events was roughly the same as thrombotic events[6]. We report a case of intracranial haemorrhage which was probably L-asparaginase induced.

CASE REPORT

A 20-year-old national serviceman presented with fever, sorethroat and exertional dyspnoea for about one week's duration. The initial physical examination revealed mild pallor, generalised lymphadenopathy and a hepatomegaly of 3 cm below the right costal margin. No neurological deficits were noted.

The initial investigations were as follows: haemoglobin 11.5 g/dL (normal 14.0 – 18.0 g/dL), white cell count 12.44 x 10^9/L (normal: 4.0 – 11.0 x 10^9/L) with 29% blasts, and the platelet count was 107 x 10^9/L (normal: 130.0 – 400.0 x 10^9/L). The coagulation times were normal. The prothrombin time (PT) was 11.6 seconds (normal: 10.0 – 14.0s), the activated partial thromboplastin time (APTT) was 30.6 seconds (normal: 25.0 – 40.0s), and the thrombin clotting time (TCT) was 13.5 seconds (normal: 12.0 – 19.0s). The serum fibrinogen level was 5.74 g/L (normal: 2.0 – 4.0 g/L). D-dimers were measured at 2,000 – 8,000 ng/mL (normal: < 200 ng/ml), and soluble monomers were absent. The serum total protein was 60 g/L (normal: 60 – 82 g/L), and the serum albumin was 31 g/L (normal: 39 – 50 g/L).

Bone marrow aspiration revealed a dry tap. Imprints from the bone marrow trephine biopsy as well as the biopsy showed a hypercellular marrow extensively replaced by immature cells morphologically compatible with those of acute lymphoblastic leukaemia, L_2 by the French-American-British classification. These cells were PAS and Sudan black negative. Immunophenotyping was positive for CD10 and B-cell markers. Cytogenetic analysis of the blast cells from the peripheral blood revealed an abnormal karyotype, 46, XY, 10p+.

He was prescribed a modified UKALL X induction chemotherapy protocol, comprising of vincristine 1.4 mg/m^2 weekly, daunorubicin 45 mg/m^2 on day one and day two, and prednisolone 40 mg/m^2 daily. L-asparaginase was started on day five and was initially administered three times a week at 6,000 units/m^2. However this was decreased to twice weekly as his fibrinogen level dropped to 0.92 g/L. The total number of 9 doses of L-asparaginase was given over four weeks, instead of the usual 3-week period. The induction therapy was uncomplicated. The day 14 marrow examination was hypocellular but the patient achieved complete remission by day 28. He was then started on cranial irradiation and intrathecal methotrexate for central nervous system (CNS) prophylaxis.

Department of Medicine
National University Hospital
5 Lower Kent Ridge Road
Singapore 119074

H L Lim, M Med (Int Med)
Consultant Oncologist

Y K Kueh, FRCP
Associate Professor

Department of Medical Oncology
Singapore General Hospital
Outram Road
Singapore 169608

K Wong, M Med (Int Med), MRCP (UK)
Consultant Oncologist

6 Napier Road
Gleneagles Medical Centre
Singapore 258499

C P Teo, M Med (Int Med)
Consultant Haematologist

Correspondence to:
A/Prof Y K Kueh

On day 37 (7 days after the last dose of L-asparaginase and the fourth dose of intrathecal methotrexate), he complained of headache, nausea and vomiting. The initial neurological examination including fundoscopy was normal. A lumbar puncture was performed to look for meningitis or CNS leukaemia. However, he rapidly developed a right homonymous hemianopia and terminal neck stiffness several hours after the lumbar puncture. An urgent CT scan of the head was performed which revealed a large parieto-occipital haemorrhage with some surrounding oedema.

The investigations at this point of time were: haemoglobin 8.9 g/L, white cell count 2.85 x 10^9/L with a normal differential count, and a platelet count of 140 x 10^9/L. The PT was 12 seconds, PTT 31.1 seconds, and the TCT was 17.9 seconds. Serum fibrinogen concentration was 2.16 g/L. D-dimer concentration was less than 500 ng/mL, and soluble monomer was not detected. Serum total protein level was 52 g/L, and the serum albumin level was 28 g/L. A microscopic examination of the cerebrospinal fluid (CSF) showed an absence of blast cells. There were 333 red blood cells, and less than one white cell per cubic millilitre of CSF.

Patients' progress

Despite the left parieto-occipital haemorrhage, he was conscious and alert. Other than the right homonymous hemianopia, the only other neurological deficit was impaired higher intellectual function. There was a marked impairment of short-term memory, and he had difficulty doing simple mathematical subtractions.

He was treated conservatively with mannitol and dexamethasone. Five hundred millilitres of fresh frozen plasma was transfused despite the normal clotting times and serum fibrinogen level. His visual field defect resolved rapidly and was not clinically demonstrable the following day. However, his impaired intellectual function persisted.

A search was made to elucidate a local cause for the haemorrhage. Carotid angiography showed no evidence of an arterio-venous malformation or a berry aneurysm. Leukaemic infiltration of the central nervous system was excluded by the absence of blast cells in the CSF and a normal magnetic resonance imaging of the brain.

Serial serum fibrinogen concentrations dropped progressively from 2.16 g/L on the day of the haemorrhage to 1.92 g/L, then 1.03 g/L and 0.8 g/L by day 3. After the third day, the level gradually rose, normalising nine days after the bleed. He recovered gradually and was able to complete his cranial radiotherapy prophylaxis, although intrathecal methotrexate was not continued.

DISCUSSION

Acute neurological crises are not uncommon problems in the management of ALL. They range from definite cerebrovascular events (either L-asparaginase-related or otherwise) to leukostasis from hyperleukocytosis and CNS disease. Eden reported 21 out of 821 patients (2.5%) with such neurological crises in the UKALL VIII trial[7]. A definite aetiology was not possible for most of the cases, though it was felt that L-asparaginase probably accounted for the majority.

In our patient, there was a definite intracranial haemorrhage to account for his right homonymous hemianopia. The aetiology of the haemorrhage is a point of contention though the most likely cause is due to L-asparaginase. His fibrinogen level was normal at the commencement of induction therapy but it fell rapidly to rather low levels during L-asparaginase treatment. At the time of the haemorrhage, the fibrinogen level, although within the lower range of normal level, 2.16 g/L, was probably the result of a rapid, transient rise because fibrinogen, being an acute phase reactant, would respond to the haemorrhage. The actual fibrinogen level at the instant of the haemorrhage could have been much lower. This argument is substantiated by the rapid fall of the fibrinogen level to 0.8 g/L within three days.

Haemorrhagic complications in ALL are commonly due to severe thrombocytopenia and less often, to disseminated intravascular coagulation (DIC). However, the platelet level in our patient was normal three days before as well as on the actual day of the bleed. There were no clinical features or laboratory evidence of DIC. The clotting times were normal, and plasma soluble monomers were absent. Leukostasis can sometimes cause intracranial haemorrhage but this usually occurs at the time of diagnosis when the blast cell count is very high. This is definitely not the case here as the white cell count was only 2.58 x 10^9/L at the time of haemorrhage. Non-ALL related causes such as a berry aneurysm or an arterio-venous malformation was excluded by a normal carotid angiogram.

The mechanism by which L-asparaginase causes haemorrhage is still not absolutely certain. Though it is known that L-asparaginase can cause severe hypofibrinogenaemia, very few cases actually develop bleeding problems. The low incidence of bleeding in the face of a low fibrinogen level is thought to be due to a concomitant decrease in anti-thrombin III, protein C and S, which are the body's natural anticoagulants, and the fibrinolytic factors like plasminogen and alpha$_2$ anti-plasmin.

At present, there is no general agreement on the need to monitor the coagulation/fibrinolytic systems in patients treated with L-asparaginase. There are also no guideline on ways to avoid either the haemorrhagic or thrombotic complications. Muntean[8] suggested replacing the coagulation factors with fresh frozen plasma and at the same time, giving AT III and heparin; but the general consensus is to treat expectantly. An alternative is to use asparaginase derived from Erwinia carotovora, which had been reported to cause less haemostatic disturbances as it has less hepatotoxicity[9]. Patients who develop haemostatic complications may complete their induction therapy with Erwinia-derived asparaginase without any further complication[10].

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