KenKyu

Clinical Case Reports, Research & Trials 2:57-60 (2017)

Case Report

Four simultaneous serious complications following L-asparaginase / Dexamethasone therapy in acute lymphoblastic leukemia: case report

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Received July 13, 2017; **Accepted** November 14, 2017; **Published** November 16, 2017

Introduction

Acute lymphoblastic leukemia (ALL) is characterized by the overproduction and accumulation of cancerous, immature white blood cells called lymphoblast. L-asparaginase represents the key chemotherapeutic agent for this kind of hematological malignancies [1] However, it is well known to induce several toxicity effects, the most common are hypersensitivity reactions and dysfunctions of the liver and pancreas [2].Although these side effects are widely described in the literature and generally reported as having a favorable evolutionary genius [3]. The simultaneous occurrence of several life threatening complications is rare. We report a case of 18-year-old female patient who developed acute pancreatitis, new onset severe diabetic ketoacidocis, intravascular disseminated coagulation and myelosuppression following L-asparaginase containing regimen in remission induction phase of (ALL).

Keywords: L-asparaginase, toxicity, acute pancreatitis, diabetic ketoacidosis

Case report

An 18-year-old girl diagnosed as B-cell acute lymphoblastic leukemia (ALL). Initially, Hyper-CVAD chemotherapy protocol was started, two cycle have been given and prematurely therapy was discontinued for intolerance (significant muscle atrophy) and switch to St Jude low risk chemotherapy protocol, a complete remission with bone marrow blast count at 4% obtained two month later, she received a total dose of L-asparaginase 375000 /m^2 divided into 5 series, each containing 6 doses of intramuscular L-asparaginase 12500 / m^2 / dose at 1-6 weeks intervals to be administered discontinuously, with a total of 30 dose. She was in remission induction phase therapy, at the last dose of the protocol, with Vincristine 1.6 mg/m^2 intrathecal, L-asparaginase 12500 UI/m^2 intramuscular and dexaméthasone 50mg/m^2 orally. On the third day of therapy, she developed abdominal pain, vomiting, polyuria, polydepsia and confusion. Two days after, she presented to emergency department in shock, the blood pressure was 80/50 mmHg, heart rate 130 bpm, and temperature 35 °C. Glasgow coma score was 13/15. She was tachypneic, tenderness on abdominal palpation. Investigations revealed Arterial blood gases with a pH 7.07, sodium bicarbonate 3.6mmol/L, Pco_2 12mmHg, Po_2 153 mmhg, SaO_2 98%; blood sugar 27.6 mmol/L(3.9-6.1 mmol/L); urea 22 mmol/L(2.5-7.5 mmol/L); creatinine 140 µmol/L(70-130 µmol/L); serum sodium 124 mmol/L(136-146 mmol/L); potassium 4.4 mmol/L(3.9-6.1 mmol/L) (3.6-4.6 mmol/L); serum osmolarity 318µmol/L; lipase 1630 UI/L(23-300 UI/L); lactate 1.6 mmol/L(0.55-2.2mmol/L) . Urine revealed ketonuria and glycosuria. The diagnosis of diabetic ketoacidosis complicated with hypovolemic shock associated with pancreatitis was made.

She was stabilized by intravenous fluid resuscitation with physiological saline, intravenous infusion of insulin and transferred to ICU. Initially we witness a worsening of the circulatory condition requiring the introduction of noradrenaline 2.3mcg/kg/min and a significant volume expansion (up to 6L) that improve circulatory condition. A abdominal contrast-enhanced Computed Tomography was performed and showed acute pancreatitis Baltazard C classification, Ranson's score was 2 in admission and 0 at 48 hours into admission. Other investigations such as Complete blood count revealed hemoglobin 8.4 g/dL (12–16 g/dL), platelet count 21000/µL (150000-450000/µL), white blood cells count 1.4 .10^3cells/L (4-10 .10^3cells/L), Absolute neutrophil count 29%; Prothrombin Time 40%(70-100%); D-dimer units > 0.5 µg/ml (≤ 0.5 µg/ml) Fibrinogen 2.95 g/L; normal range liver function tests. Intravenous fluids along with noradrenaline, intravenous insulin were continued. She received Paracetamol as an analgesic agent, empiric antibiotic therapy with Imipénème 500 mg IV q6hr, vancomycine 2 g/day, which covering the only Staphylococcus

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Epidermidis cultivated in blood cultures. She was made NPO (nothing to eat).On subsequent days the hemodynamic status improved allowing to soft stop noradrenaline the abdominal pain and confusion resolved, patient's abnormal lipase, complete blood count, coagulopathy begun to decrease rapidly to the normal values. The patient was discharged from ICU on the eighth day

Discussion

This case represents may be the first case described in the limit of our knowledge which combines at least four serious adverse effects related to protocol treatment including L-asparaginase during the remission induction phase of treatment in a patient with (ALL).

L-asparaginase acts on the lymphoblastic cells by depletion of the external reserves of asparagine, hydrolyzing it into aspartic acid and ammonium, as the lymphoblastic cells have low asparaginase synthetase activity, the result of lack of asparagine leads to cell death and apoptosis. [4]

Acute pancreatitis induced by L-asparaginase is now a well known complication and widely described in the literature. Its Incidence is ranging from 2 to 18% [4,5]

The physiopathology of the pancreatic toxicity of L-asparaginase remains unclear. but it seems that the main mechanism is related to the systemic decrease in asparagine, which will induce a decrease in protein synthesis, that will be more pronounced in organs that have a significant protein turn-over such as liver and pancreas[4].

In a serie of 786 children ongoing Nordic Society of Paediatric Haematology and Oncology protocol, 45 were diagnosed with L-asparaginase associated pancreatitis witch occurred after a median of five doses (range 1-13), and 11 days (median) from the last administration of the chemotherapeutic drug[6]. For the reported patient, Pancreatitis was clinically suspected because the onset of excruciating abdominal pain which occurred three days after the 30 dose. Two days later, the elevated serum lipase level and the abdominal CT scan, both performed on the day of her hospitalization, confirmed the diagnosis.

On the other hand, L-asparaginase can cause commonly hyperglycaemia. [3],nevertheless diabetic ketoacidocis (DKA) remains rare condition with a reported prevalence of 0.8% .The age greater than 10 years was identified as the only risk factor.[7]

L-asparaginase and glucocorticoids are commonly associated in the treatment protocol of ALL; The first drug induce hypoinsulinemia [7] with possibly a decrease in the expression of insulin receptors. On the other hand glycocorticoides promotes insulin resistance and increases hepatic gluconeogenesis [8]. Therefore, pancreatitis represents most likely an additional risk factor of hyperglycemia and (DKA) [9]. However, the combination of (AP) and (DKA) associated with L-asparaginase use represents few cases reported [10].

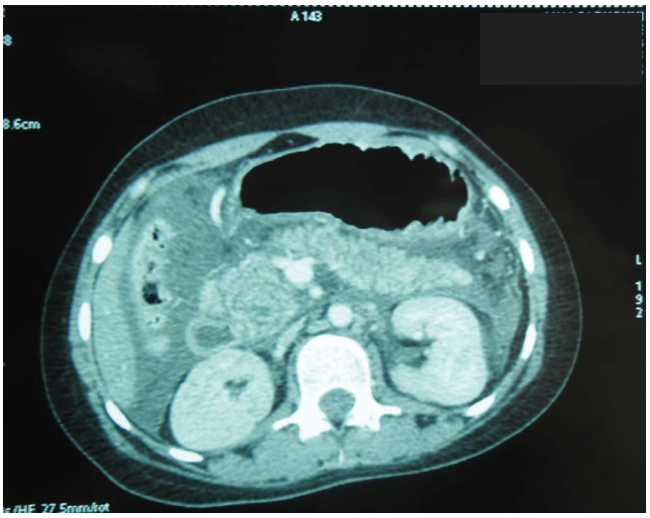

Figure 1: CT abdominal scan showing acute pancreatitis Baltazar C classification with fluid effusion around the pancreas.

Among the existing two types*: Erwinia*-derived and E. *coli* derived L-asparaginase, the second is recognized provider of adverse effects more than the first [11]. Indeed, our patient was 18 years old and she received Saint Jude protocol including dexamethasone and E. coli derived L-asparaginase(separ). She had no evidence of pre-existing insulin resistance or hyperglceamia during follow-up consultations. Ten units per hour of insulin were required to manage her (DKA) the first two days surely because of Epidermidis Staphylococcus induced sepsis. On the one hand, the clinical presentation of diabetic ketoacidocis combining abdominal pain and digestive disorders that can mimic surgical emergency or acute pancreatitis .The high level of lipase was a decisive element for diagnosis suspicion of acute pancreatis. On the other hand, pancreatic reaction was described in cases of diabetic ketoacidosis especially severe [12]. Nonetheless, the chronological relationship with the taking of asparaginase and association with other side effects including coagulopathy and myelosuppression was very evocative of the toxic origin of clinical picture.

Therapy with ulinastatin, octreotide, glucocorticoid could relieve abdominal pain significantly [13]. For the reported case, we just used Paracetamol as an analgesic agent with a clear regression of abdominal pain concomitantly with improved biological parameters.

L-Asparaginase treatment is also known to be usually complicated by level lowering of fibrinogen, plasma clotting factors IX and X, plasminogen, and antithrombin. Intra vascular disseminated coagulation can occur with more frequently thrombotic events. [14]

E coli derived asparaginase is more involved in this haemostatic alterations [11].

the depletion of asparagine and the consequent decrease in protein synthesis, including coagulation factors, is the main mechanism that can explain the effects of L-asparaginase on hemostasis [15]. Other abnormalities can be seen as a high level of d-Dimer, which seems to be more persistent during treatment with L-asparaginase [16]

There is evidence on the combination L-asparaginase with vincristine and prednisolone induced myelosuppression, particularly of the granulocytic series, resulting in an increase in Gram-negative sepsis and death during the neutropenic phase induced by L-asparaginase [17].

For our patient, we noted biologic intravascular disseminated coagulation at day four with a normal plasma fibrinogen level. There was no evidence of hemorrhagic nor thromboembolic events during ICU stay. The coagulopathy spontaneously improved without any supportive therapy. The myelosuppression observed at day 6 was transient. In fact, bone marrow regeneration was obtained after two days under growth factor. A broad spectrum antibiotic covering the only Staphylococcus Epidermidis cultivated in blood cultures and was maintained until ICU discharge.

For decades, L-asparaginase is increasingly used in adolescents and young adults with (ALL). Since the treatment in question has largely proved its effectiveness. Aware that occurrence of asparaginase associated pancreatitis could have poor outcome [18]. Its association with diabetic ketoacidosis, coagulopathy and myelosuppression even rare, increases significantly morbidity and mortality. The simultaneous occurrence of such life threatening complications represents therapeutic dilemma. In fact, re-exposure is associated with recurrence and treatment interruption has been linked to increased relapse rate [19]. Clinical criteria were proposed in order to reduce the risk of relapse without compromising safety [4] Erwinia derived, which is safer than E coli derived L-asparaginase should be considered in first intention in acute lymphoblastic leukemia treatment [11] especially during the occurrence of adverse effects induced by the latest.

Conclusion

L-Asparaginase is a effective component of (ALL) protocol treatment but is associated with multiple potential toxicities. Asparaginase associated pancreatitis (AAP) is a common complication. (AAP) is exceptionally combined, with (DKA), coagulopathy and myelosuppression, in same patient and in the same episode. Awareness of these life threatening side effects is imperative. This observation must alert hematologist who widely prescribe this chemotherapeutic agent, and represents serious therapeutic dilemma.

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