Unusual presentation of more common disease/injury

Cardiac disease in a case of precursor B acute lymphoblastic leukaemia with eosinophilia(ALL/Eo)

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Summary

Acute lymphoblastic leukaemia (ALL) is the most common paediatric malignancy. However, it may rarely associate with eosinophilia. Patients with ALL associated with eosinophilia (ALL/Eo) have a grave prognosis and higher incidence of cardiac complications compared to standard lymphoblastic leukaemia. Reports of ALL/Eo disclosed a few case with cardiac involvement early in the course of leukaemia. Here, the authors report a case of 13-year-old boy who presented with peripheral eosinophilia, chest pain and a large left ventricular mass early in the course of precursor B- cell ALL associated with eosinophilia. He received multi-agent chemotherapy but succumbed to death 25 days after chemotherapy due to a refractory cardio respiratory failure.

BACKGROUND

Precursor B cell acute lymphoblastic leukaemia (ALL) is the most common subtype of ALL in children. However, acute lymphoblastic leukaemia with eosinophilia (ALL/Eo) is a rare subset first described by Spitzer and Garson. ALL/Eo is more refractory to treatment than standard leukaemia.^{1–4} Here, we present a 13-year-old boy initially diagnosed to have hypereosinophilic syndrome who received hydroxyurea and prednisolone. Three months later, he was admitted to our hospital with an acute coronary syndrome. The clinical impression was cardiac disease in hypereosinophilic syndrome. However, the definite diagnosis was precursor B cell ALL/Eo. To our knowledge, there are few cases of precursor B cell ALL/Eo with cardiac disease early in the course of leukaemia.

CASE PRESENTATION

A 13-year-old boy was admitted to the hospital with a crushing pain in the abdomen in early October 2010. He noticed fatigue, loss of strength and weight loss in early June 2010. His diagnosis was hypereosinophilic syndrome. White blood cell count was around 22 000/ μ l and the eosinophils were extremely elevated (44% of total white blood cells).

There was no detection of Bcr/abl fusion; however, the molecular assay for mutation in platelet-derived growth factor receptor was not performed. Serologic tests for fasciola, toxocara, trichinella and strongyloidosis infections were all negative. He received prednisolone 1 mg/kg/day and hydroxyurea late in June and his symptoms improved slightly.

A few hours before admission to the hospital, he felt a severe pain in the abdomen. The pain was over the left upper quadrant of the abdomen. It was a constant pain

radiating to left shoulder. Its intensity did not change with respiration or position changes.

INVESTIGATIONS

On physical examination, the patient was febrile; the blood pressure was 100/65 mm Hg, the heart rate 125 beats per min and the respiratory rate 18 breaths per min. He had profound facial flushing and conjunctival pallor; the rest of head and neck was normal on the examination. The heart and lung were normal on auscultation except for hyperdynamic heart sounds. Abdomen was tender on superficial palpation of left upper quadrant. Extremities, genital and neurologic examinations were normal.

Complete blood counts showed haemoglobin: 11.4 g/dl, total leucocyte count 23 370/ μ l with 71%, eosinophils, 27% neutrophils, 2% lymphocytes and platelet count 47 000/ μ l. Serum bilirubin, liver enzymes, alkaline phosphatase, urea, creatinine, sodium, potassium, uric acid and blood glucose were within normal limits. The abdominal x-ray findings, tests of amylase and lipase were all normal. Ultrasound study of abdomen disclosed a small hypoechoic lesion in the splenic hilum suggestive of a splenic infarction; but the colour doppler study of abdominal veins showed no thrombosis. A few hours later, he developed a severe pain over left hemi-thoracic area along with diaphoresis, and palpitation. The pain radiated to inner aspect of the forearm. The abdominal pain also persisted with less intensity. Cardiac injury biomarkers including troponin were significantly elevated. Troponin was 0.9 ng/ml (reference range: 0.01–0.1). The electrocardiography showed sinus tachycardia with ST segment depression in precordial leads. The clinical impression was acute coronary syndrome; the abdominal pain must have been a referred pain of thoracic origin. Echocardiography revealed

Figure 1 Transthoracic echocardiography shows a large 5×5 cm mass in left ventricle and normal ventricular function.

a 5×5 cm hyper-mobile mass of the left ventricular apex (figure 1, video 1). A tumoural mass or a thrombus ball was probable. There was no regional wall motion abnormality; both of the ventricles were intact in systole and diastole. The left ventricular ejection fraction was 50%. The pericardium was also intact. There was no sign of fibrotic stage or scar formation commonly seen in hypereosinophilic syndromes. He received intravenous nitrate, heparin, morphine and metoprolol. His chest pain persisted despite treatment. Nevertheless, the decreasing platelet count to 13000/μl and the presence of disseminated intravascular coagulation precluded the coronary catheterisation and intervention. Bone marrow examination was performed under conscious anaesthesia.

Video 1 Transthoracic echocardiography shows a large 5×5 cm mass in left ventricle and normal ventricular function.

He remained febrile throughout the hospitalisation; the oral temperature varied between 37.4 and 39.0°C. The results of blood cultures showed *Staphylococcus aureus* growth; thus, he received vancomycin and imipenem intravenously.

The following day, he developed dyspnoea and hypoxemia. Chest radiography result showed frank pulmonary oedema. On the fourth day of admission, the second echocardiography showed the increase in dimensions of ventricular mass, global dyskinesia, apical akinesia and reduced left ventricular ejection fraction to 35 %; probably, the emboli of cardiac mass caused myocardial infarction and recent-onset systolic dysfunction. Increasing trend of troponin level was in favour of the clinical assumption. Treatment with intravenous nitrate, furosemide, morphine and oral captopril continued.

On the same day, the result of bone marrow examination showed hyper-plastic marrow, increased number of

eosinophils and infiltration by 40% lymphoid blasts. Flow cytometric analysis with a panel of fluorescence-labelled antibodies showed the precursor B cell ALL; the blast cell population showed strong reactivity (88%) with B cell markers as CD10, CD19, CD20 and CD22. The blasts did not express lymphoid T cell markers as CD3, CD5 and CD7 and myeloid markers as CD13, CD33 and CD34. HLA-DR showed strong positivity (86.4%). The diagnosis was precursor B- cell ALL with eosinophilia (ALL/Eo) (figure 2).

We reviewed blood and bone marrow aspiration smears of 3 months ago; surprisingly, there were at least 40% lymphoblast in marrow smears not in blood. He had lymphoblastic leukaemia since 3 months ago but the presence of increased number of circulating eosinophils and rarity of blasts on peripheral blood smears led on to misdiagnosis.

TREATMENT

He received induction therapy regimen consisting of four-drug regimens as vincristine, daunorubicin, cyclophosphamide and prednisolone. Asparaginase was not among the administered medicine, as there was fear of further thromboembolic events due to synergistic effect of this drug along with increased eosinophils.

He received intravenous nitrate, furosemide, dobutamine and oral captopril for systolic heart failure.

OUTCOME AND FOLLOW-UP

Thirteen days after the beginning of the chemotherapy regimen, the third echocardiography examination was done. There was severe global hypokinesia. The initial mobile ventricular mass had shrunk, but the apices of both ventricles had been obliterated; left ventricular ejection fraction was nearly 10% (figure 3 or video 2). At the

Figure 2 Peripheral blood smear shows eosinophilia with lymphoid blasts.

same time, blood count analysis showed severe pancytopenia with total white blood cell count reached to 1900/ μ l. There was no longer evidence of eosinophilia in blood exam. Therefore, echocardiography findings meant there was no significant response to the chemotherapy regimen. He was prepared to undergo bone marrow transplantation from a matched donor. Unfortunately, he was expired 25 days after institution of therapy due to a progressive cardio respiratory failure.

Video 2 Transthoracic echocardiography shows the extension of previous mass to the apices of both ventricles along with depressed left ventricular contractility.

DISCUSSION

Eosinophilia is the presence of more than 600 eosinophils per μ l of blood. It is common in the setting of parasitic infections, allergic disorders, collagen vascular diseases and malignancies.⁵

Lymphoblastic leukaemia of both B and T cell origins may be associated with eosinophilia. In patients with precursor B cell ALL/Eo, there is a gene rearrangement due to t(5;14). Interleukin-3 (IL-3) producing locus on chromosome 5 is linked to immunoglobulin heavy chain locus on chromosome 14. The result is over expression of IL-3 locus and overproduction of IL-3. IL-3 as a hematopoietic stimulating factor provokes eosinophilia.

In a small subset of patients with precursor T cell lymphoblastic lymphoma, there is t(8;13); consequently, the fibroblast growth factor receptor 1 locus and a zinc finger protein gene are involved. There is FIP1L1-PDGFR α fusion gene generated by del⁴ in patients with lymphoblastic leukaemia and eosinophilia. However, the exact underlying mechanism of eosinophilia is yet unknown.⁶⁻¹⁰

The majority of patients with ALL/Eo are boys with median age of 14. The paucity of blasts circulating in blood may delay the definite diagnosis. Diagnosis of ALL may be delayed from several months to even 2 years. The cardio respiratory system is frequently involved in ALL/Eo that may be responsible for a poorer prognosis of this entity compared to the standard ALL.^{4 11}

It is not rare to confront cardiac involvement in leukaemia. Cardio toxicity of chemotherapeutic drugs, heart failure and precipitated coronary events are typical examples.^{12 13} Moreover, opportunistic infections such as fungi may invade the cardiac chambers.¹⁴ Tumoural infiltration ranging from gross cardiac masses to microscopic infiltrations may directly involve the heart. Lymphoma/leukaemia may involve myo-pericardium and cardiac valves, but not early in the disease course.^{15 16}

There are few numbers of cases with ALL/Eo initially presented with cardiac disease, so the best therapeutic regimen in such patients is not clear-cut. L-asparaginase should be used cautiously in chemotherapy regimen of ALL/Eo, since there are fears of thromboembolic events triggered by synergistic procoagulant effect of this drug and eosinophilia. Ronald S Go, *et al* reported a case of ALL/Eo treated by L-asparaginase-based regimen that developed fatal deep vein and intracardiac thromboses.¹⁷ It is unknown exactly when a gross cardiac mass disappears with the beginning of chemotherapy in a patient with ALL/Eo. Nie YL *et al* reported a 17-year-old girl with ALL/Eo, presented initially with congestive heart failure and left ventricular endocardial thrombosis. The thrombosis resolved 8 weeks after chemotherapy.¹² Barbaric D *et al* reported a 15-year-old boy with ALL who had a large echo dense mass in the right ventricle at the time of diagnosis. The mass resolved as early as 5 days after commencing chemotherapy.¹⁸

Figure 3 Transthoracic echocardiography shows the extension of previous mass to the apices of both ventricles along with depressed left ventricular contractility.

Aissi K *et al* reported a case of a 29-year-old man with ALL/Eo who had congestive heart failure at the presentation. He had a left ventricular thrombus that subsequently resulted in a cerebral ischemia. They proposed that chemotherapy regimens containing corticosteroid would result in rapid resolution of cardiac complications in such patients. Their patient showed evidence of improvement as early as 7 days after institution of multi-agent chemotherapy.¹⁹

To our knowledge, there are a few numbers of cases with precursor B cell ALL/Eo whose courses are complicated with cardiac disease initially. As ALL/Eo is a rare entity with a poorer prognosis comparing to standard leukaemia, reports of such cases may be of help in increasing our awareness and broadening our knowledge in timely diagnosis and treatment of such patients. Considering the adverse impact of cardiac involvement in haematologic malignancies associated with eosinophilia, we must be vigilant to perform a cardiac imaging such as echocardiography and/or cardiac MRI earlier in the course of such leukaemia.

Learning points

- ▶ Remember that an acute coronary syndrome may present with a referred abdominal pain.
- ▶ Be vigilant to cardiac complications in haematologic disorders associated with eosinophilia.
- ▶ Acute lymphoblastic leukaemia with eosinophilia may not have blast circulating in blood.

Competing interests None.

Patient consent Obtained.

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