The successful non-invasive management of pulmonary thromboembolism in a child with acute lymphoblastic leukemia

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ABSTRACT
In childhood, pulmonary thromboembolism (PTE) is an uncommon but potentially life-threatening disease. The greater numbers of venous thromboembolism (VTE) are complications of underlying risk factors such as malignancies, chemotherapy (L-asparaginase), and central venous catheter. We report a patient with acute lymphoblastic leukemia and PTE, who presented with near-syncpe, and was successfully treated with low molecular weight heparin and calcium channel blockers.

Key words: pulmonary embolism, leukemia, children.

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INTRODUCTION
Pulmonary thromboembolism (PTE) is an obstruction of the main artery of the lung or one of its branches by a thrombus. In childhood, PTE is an uncommon but potentially life-threatening disease. Thromboembolism registry data has reported the annual incidence of childhood PTE as 0.14-0.9 per 100,000 children. Risk factors of venous thromboembolism (VTE) are central venous catheter, malignancies, chemotherapy (L-asparaginase), congenital heart disease, infections, surgery, trauma, immobility, hypovolemia, lupus erythematosus, hemoglobinopathies (thalassemia, sickle cell disease), and inherited thrombotic disorders.

The diagnosis of PTE is difficult on clinical signs and pulmonary computed tomography angiography is the most widely used method in diagnosing PTE. Anticoagulation is the mainstay of therapy for PTE.

Pulmonary arterial hypertension (PAH) is defined as a mean pulmonary artery pressure (PAP) of more than 25 mmHg at rest. PAH is rare in childhood and is a complex disorder with various etiologies.

We report a case of PTE because of venous thrombosis at left brachial system, successfully and non-invasively managed in a teenage boy with leukemia.

CASE REPORT
A 16-year-old male patient presented with persistent leg pain and swelling of the lymph nodes in the neck which did not resolve with antimicrobial treatment. On physical examination he had bilateral sub-mandibular lymphadenopathy, hepatomegaly extending 5-6 cm below the right costal margin and splenomegaly extending 6-7 cm below the left costal margin. Additionally he had petechial rashes on his face and all extremities. Laboratory test results were as follows; hemoglobin: 9.1 g/dl; leukocyte: 258x10^9/L; platelet: 36 x10^9/L; potassium: 5.7 mEq/L; aspartate aminotransferase (AST): 103 IU/L; alanine aminotransferase (ALT): 47 IU/L; uric acid: 11.6 mg/dl (N: 2.40-7.00); lactate dehydrogenase: 4569 IU/L (N: 266.0-500.0).

Lymphoblasts were the predominant cells in the peripheral blood smear. Flow cytometry analysis revealed CD45, CD117, CD5, CD7, intracytoplasmic CD3 and CD22 positivity and the patient diagnosed as myeloid antigen-positive acute lymphoblastic leukemia (ALL) and TR-ALL BFM 2000 treatment protocol was started.

Since leukocyte count raised as high as 408 x10^9/L leukopheresis using left jugular central venous line was performed. Crystallized insulin due to secondary hyperglycemia following steroid use and teicoplanin, meropenem and fluconazole therapy for febrile neutropenia was administered. On day 24th, the catheter was removed without...
any complication. At second month of treatment, when there was a peripheral vascular catheter at left antecubital vein, hyperemia and pain appeared on the medial part of the left upper extremity. Doppler ultrasonography revealed increased intraluminal echogenicity, increased vascular calibration and weak flow pattern at left internal jugular vein, brachiocephalic junction, subclavian, axillary, brachial and basilic veins.

These findings were thought as the signs of recanalized thrombosis at subacute stage. Although, enoxaparin 100 U/kg/dose q12h was initiated, the patient developed a near-syncope episode lasting for 1-2 seconds after the second dose. Respiratory rate was 24/min; heart rate was 120/min, blood pressure was 100/70 mmHg and oxygen saturation was 95%. Echocardiographic examination was performed for evaluation for near-syncope and right ventricular dilation, moderate tricuspid valve insufficiency (3.5 m/s, estimated systolic right ventricle pressure was 54 mmHg), mild pulmonary valve insufficiency (2.6 m/s, estimated mean PAP was 27 mmHg) and as a result mild pulmonary hypertension was detected. Nasal oxygen (2 L/min), furosemid (1 mg/kg/day, 1x, PO) and amlodipin (0.1 mg/kg/day, 1x, PO) were started as well as enoxaparin. Because echocardiographic assessment revealed 27 mmHg mean PAP, which was previously documented to be in the normal range, PTE was suspected.

The ventilation/perfusion scintigraphy and also computerized tomographic angiography (CTA) of the pulmonary vascular bed revealed bilateral thrombi with partial flow at all lobar arteries of right main pulmonary artery and at all segmental arteries of left lower lobar artery (Figures 1 and 2). The dosing of enoxaparin was adjusted so as to keep anti-factor Xa level between 0.5-1.0. We did not undertake embolectomy because of the hemodynamic stability and good oxygenation of the patient. Protein C and S, factor V Leiden, prothrombin gene mutation 20210A, antithrombin III, homocysteine and antiphospholipid antibody levels were all in the normal range at that time.

Following medical treatment PAH gradually resolved (Figure 3), the patient achieved bone marrow remission and was discharged after the last TR ALL BFM 2000 High Risk consolidation therapy. Unfortunately, patient died because of neutropenic sepsis 5 months later from the diagnosis of ALL.

DISCUSSION
Pulmonary thromboembolism is a severe disorder with substantial mortality, especially when the diagnosis or treatment is delayed. Certain risk factors such as central venous catheterization, infection and congenital heart disease may increase the risk of PTE in children. The incidence of PTE in children with central venous catheters has been reported to be between 33 to 64%. Previous studies reported that around 2.9% of children with malignancies sustained...
Echocardiography may demonstrate directly the thrombus within the heart or the main pulmonary artery. Additionally, it may reflect several indirect findings associated with embolism such as right ventricle dilatation, hypokinesia, or abnormal inter-ventricular septum motion, tricuspid valve regurgitation, and absence of the inferior vena cava collapse during inspiration. Following the observation of several indirect findings of PTE in echocardiography, we performed V/Q and CTA to confirm the diagnosis.

In a series of 405 children with VTE, the rate of mortality was 16% and 2.2% of which were due to VTE. Of the nine patients who died due to VTE, seven were of pulmonary origin and had a documented thrombus in the upper extremity as well as a central venous catheter. Embolectomy is rarely performed in children with a venous thrombosis and it is indicated merely in hemodynamically unstable children in whom thrombolysis fail or is contraindicated.

A single massive PE or repeated pulmonary emboli can lead to right ventricular failure, shock, and sudden death. Pulmonary arterial hypertension secondary to PE is considered a relatively rare complication. Various management strategies such as supportive therapy and lifestyle changes have been implemented for patients with PAH. Supportive therapy involves oral anticoagulant treatment, supplemental oxygen together with diuretic and digoxin therapy in right-heart failure. Calcium channel blockers...
inhibit calcium influx into smooth muscle cells across the slow motion channels and result in vasodilatation of the smooth muscles of pulmonary vasculature. Our patient was hemodynamically stable and was prescribed a calcium channel blocker for PAH and a diuretic and digoxin for right-heart failure. His clinical status improved and pulmonary hypertension resolved gradually.

In the current report, we aimed to demonstrate that patients with hematologic malignancies are predisposed to thrombosis and that these patients required repetitive echocardiographic assessment to closely monitor the risk for pulmonary embolism.

REFERENCES