A Case of Pediatric Marfan Syndrome with Acute Myeloid Leukemia and Deep Vein Thrombosis

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ABSTRACT

We are demonstrating a 9-year-old girl, newly diagnosed Marfan syndrome, presented with deep vein thrombosis and acute myeloid leukemia. A few reports of Marfan syndrome with acute myeloid leukemia were published, none could identify correlation among them. To the best of our knowledge this would be the first pediatric case of Marfan syndrome with acute myeloid leukemia and thrombosis.

KEYWORDS: Marfan syndrome, Acute myeloid leukemia, Thrombosis.

Introduction

Marfan syndrome (MFS) is caused by mutations of the FBN-1 gene on Chromosome 15.[1] The incidence varies from 2-3 per 10000 to 1 per 9802 individuals.[2] Their appearances are tall stature, scoliosis, chest deformity and arachnodactyly.[1] Leukemia is the most common malignancy in pediatric patients. There are about 500 new cases per year in Thailand.[3] Acute myeloid leukemia (AML) is an abnormal proliferation and differentiation of myeloid precursor in the bone marrow. Peak incidence is in neonate and adolescence.[3] It is less common than acute lymphoblastic leukemia (ALL) in childhood.[4] AML contributed to about 22% of all diagnosed leukemia.[3] Pediatric thrombosis is a rare event, overall incidence in children is 0.7-1.9 per 100,000 children[5]. Pediatric thrombosis events include deep vein thrombosis (DVT), stroke and purpura fulminans. Risk factors include dwelling catheters, hyper-viscosity, autoimmune disease, surgery or trauma, and chemotherapy (L-asparaginase and prednisone)[5]. Factor V gene mutation is the most common cause of inherited thrombophilia in Northern American[5], but not in Thai.[6]

The objective of this report is to describe a case of Marfan syndrome presented with thrombosis and AML

Case Presentation

Patient information

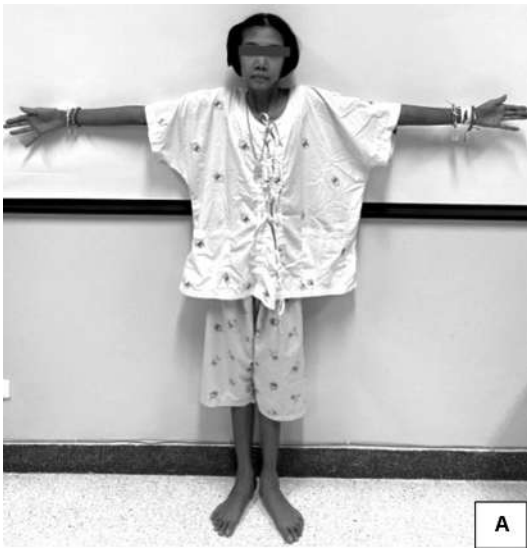
A Thai 9-year-old girl, transferred from provincial hospital, was diagnosed with DVT and acute repetitive seizure. Nine days prior to be transferred, she began to have low grade fever and right foot pain, which later became more swelling and painful. One day prior to be transferred, she was admitted to provincial hospital, complaining

of progressive right foot swelling and weakness. She was treated with intravenous ceftriaxone. Her hematocrit was 20 vol%, and was given red cell transfusion. A doppler ultrasound was done, acute DVT at the right common femoral vein down to popliteal vein was found. Seven hours prior to be referred, she developed acute repetitive seizure. CT Brain was done, the result was unremarkable.

Her previous medical records were unremarkable. Her family history, her father, reported by her mother, had similar physical features with this case. However, he passed away many years from tearing of a great vessel that led to paraplegia and pneumonia. Her mother claims that his doctor also suspected him to have Marfan syndrome.

Clinical findings

At Khon Kaen Hospital, upon physical examination, she weighed 34 kg, her height was 140 cm, upper/lower body ratio was 0.75 and arm span/height ratio was 1.06 (shown in figure 1A). Her body temperature was 41 degrees Celsius, heart rate of 118 beats per minute, blood pressure was 112/61 mmHg and respiratory rate 24/minute. She was lethargic, mildly pale, no jaundice. Her facial features included malar hypoplasia, dolichocephaly, enophthalmos and retrognathia. Her heart sound was pansystolic murmur grade II/VI at apex with friction rub. Janeway lesions were noted. Liver and spleen were not palpable. Her right leg was swelling (pitting edema 2+), warm and tender, with limited range of motion of right knee and hip due to pain. Her left leg was grossly normal, but pes planovalgus were noted. Her fingers were arachnodactyly, wrist and thumb signs were positive (shown in figure 1B and 1C). A complete neurological examination was unremarkable.



Patient pictures
Figure 1A. Patient showing reduced upper / lower Segment and increased arm span / height

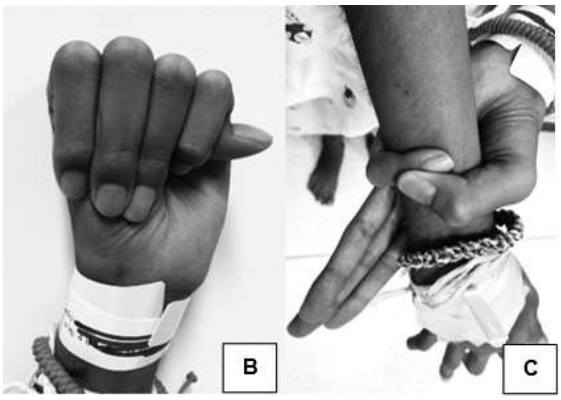
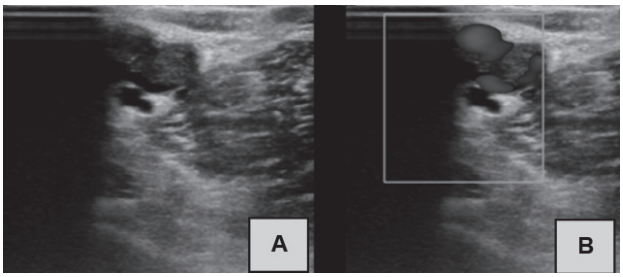


Figure 1B and 1C. Patients demonstrating positive wrist and thumb signs

Diagnostic assessment

Her complete blood count, hemoglobin 7.8 g/dl, hematocrit 24.9 %, white blood cell 8,400 cell/mm^3 (neutrophil 42.2 % lymphocyte 30 % monocyte 27.6 %) platelets 149,000/mm^3. Her coagulogram showed PT 15.8 seconds (reference range 12.4 +/- 0.78)[5], PTT 38.2 seconds (reference range 33.5 +/-3.44)[5], INR 1.4 and D-dimer 26.37 mcg/dL (reference range 0-0.55). Lupus anticoagulants, anti-cardiolipin IgG and IgM, Beta-2 glycoprotein IgG and IgM were all negative. Inherited thrombophilia reviewed protein C was 65% (reference range 70-140),

protein S was 74.2 % (reference range 54.7-123.7), antithrombin III was 25 % (reference range 83-128), homocysteine was 17.7 micromol/litre (reference range 5-15). Immunologic tests showed negative ANA and Anti-dsDNA, C3 and C4 levels were 1.64 g/L (reference range 0.9-1.8) and 0.36 (reference range 0.36 g/L), respectively. ESR, CRP and procalcitonin were 92 mm./hr (reference range 0-20), 88.8 mg/dL (reference range 0.0-0.5) and 0.83 ng/mL (reference range 0-2.0) respectively. Three hemocultures were taken, none had positive growth. ASO titer was negative. Doppler ultrasound of her right leg revealed hyperechoic intraluminal filling defect with increased caliber of right common femoral vein (shown in Figure 2A and 2B). Echocardiography revealed mitral valve prolapse, floppy mitral valve, non-sessile mass attached at anterior mitral valve leaflet, sized 1.1 x 0.8 cm (suspected vegetation), pericardial effusion 8 mm at superior heart border, and 5 mm in thickness along left ventricular border, aortic valve 21 mm (z-score 2.73)[7], ST junction 21 mm.



Colored doppler ultrasound

Figure 2A, B. Colored doppler ultrasound shows absence of color flow filled lumen of these venous structure compatible with deep vein thrombosis

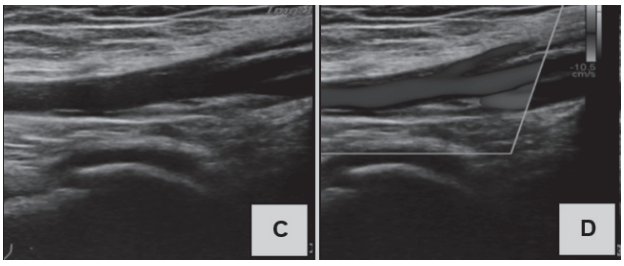


Figure 2C, D. A follow-up Doppler ultrasound after 3 months; completely compressible of veins. Demonstrating resolved DVT

Therapeutic intervention

She was diagnosed with Marfan syndrome and possible infective endocarditis (Modified Duke's criteria; 1 Major and 3 minors) and treated with ampicillin-sulbactam. Low molecular weight heparin (LMWH) was also given for DVT.

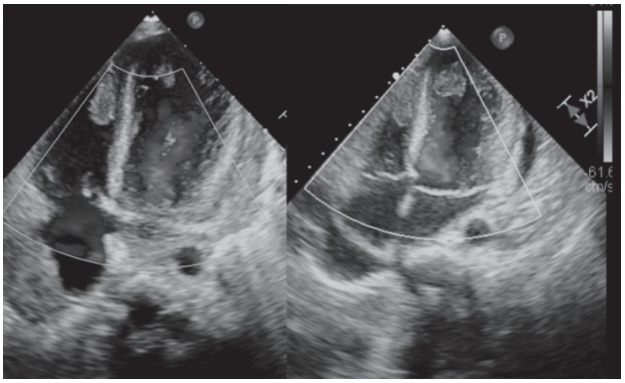
After a week of escalating new antibiotics, her symptoms improved apart from fever and her complete blood count revealed bicytopenia and blast cells (hemoglobin 8.3 g/dl, hematocrit 25.6% white blood cell 6,000 cell/mm3 (neutrophil 48% lymphocyte 6% monocyte 10% eosinophil 4% promyelocyte 4% blast 28%) platelets 112,000/mm^3. Bone marrow aspiration was done, hypercellularity was observed (myeloid: erythroid ratio was more than 20:1), myeloid cells were blasts (medium-sized with 2-3 nucleoli, high nucleocytoplasmic ratio, seen granulation, no Auer rod was seen) 65%, promyelocyte 6%, and metamyelocyte 16%. Flow cytometry for acute leukemia panel was positive for CD13, CD 33, CD 34, CD 64, CD 117 and MPO. Chromosome could not be done due to no metaphase. These findings led to the diagnosis of AML, M2. She was treated with chemotherapy; Thai Pediatric Oncology Group AML-1301 protocol.[8]

Follow-up and outcomes

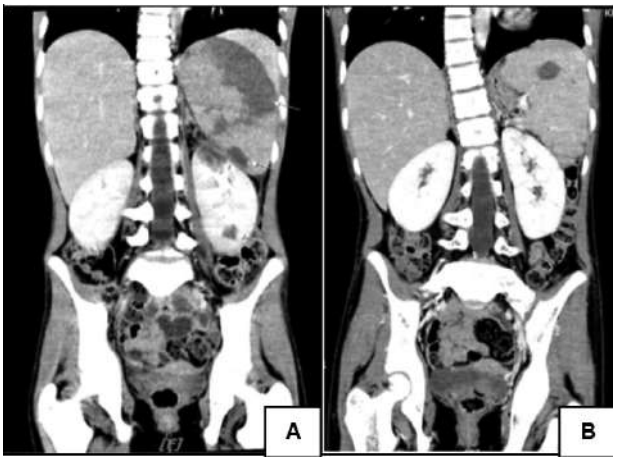
Serial echocardiography was done, vegetation slowly decreased in size and disappeared. A month after admission, echocardiography found multiple intracardiac thrombus (sized 1.7x1.6 cm in left ventricles, 3.5x1.4 cm in right ventricle apex and hyperechoic mass 2.5*1.5 cm in intrapericardial cavity) (shown in figure 3). Corresponding to patient's complaint of left upper quadrant tenderness and splenomegaly was examined; CT abdomen was done, findings included splenomegaly with wedge-shaped noncontrast-enhanced intrasplenic foci and infiltration in upper & lower poles left kidney, which led to diagnosis of splenic infarction. (shown in figure 4A)

She responded well to chemotherapy and LMWH. Her bone marrow aspiration was repeated, the result showed remission. There was no evidence of minimal residual leukemia by flow

cytometry. She was clinically well. Her Doppler ultrasound of the right lower extremity was repeated, showed normal caliber of right common femoral, superficial femoral and popliteal veins with normal venous flow pattern. Complete compressible of these veins are demonstrated. No evidence of intraluminal thrombus is detected (shown in figure 2C and 2D). CT abdomen was repeated; decrease size of multiple peripheral wedge shaped non-enhancing hypodense areas in spleen; suggestive of partially improvement of splenic infarction (shown in figure 4B). Unchanged small peripheral wedge-shaped hypodense lesions with renal capsule retraction at upper and lower pole of left kidney; could be renal scar. Echocardiogram revealed slightly decreased in size of hyperechoic mass at right ventricle apex 1.4x1 cm in size and at left ventricle apex 1x0.6 cm in size. Homocysteine was 9.2 micromol/litre (reference range 5-15), and antithrombin III was 96% (reference range 83-128).



Echocardiography
Figure 3. Echocardiography demonstrating floppy mitral valve with intracardiac thrombi



CT Whole Abdomen
Figure 4A. Ill-defined non-enhancing infiltrative intrasplenic lesion; revealed splenic infarction.
Figure 4B. Decreased size of multiple peripheral wedge shaped non-enhancing hypodense areas at spleen are observed; suggestive of partially improvement of splenic infarction.

DISCUSSION

This is a case of a Thai girl, first diagnosed Marfan syndrome with possible infective endocarditis, deep vein thrombosis, acute myeloid leukemia, intracardiac thrombus and splenic infarction.

There is a nested case-control study in Taiwan showing association between MFS and solid organ tumor, highest being head and neck tumors.[9] There were many reported cases on MFS and AML, but none has concluded their correlation.[10-13]

There was a case report of 39-year-old man with Marfan syndrome presented with multiple pulmonary emboli, renal, hepatic and splenic infarction[14], however due to rarity of report, it could not conclude that Marfan syndrome is known to increase risk of thromboembolism.

Neglecting the uncertainty of her father's diagnosis into account, we use aortic root dilatation score with systemic score instead. This patient was diagnosed Marfan syndrome based on revised Ghent nosology (systemic score = 9; positive "wrist and thumb sign", plain flat foot, facial features (malar hypoplasia, dolichocephaly,

enophthalmos and retrognathia), upper/lower body ratio: 0.75 (<0.85) and Arm Span/Height Ratio: 1.06 (>1.05).

There was a study showing ALL and its treatment as an important risk for a thrombosis event.[5] There was an observational cohort study showed that thrombosis could be presenting symptoms of acute leukemia in adult (3.4%, 95%, CI 1.8%-5.8%), highest in acute promyelocytic leukemia (APL, M3). However, it failed to conclude the thrombotic risk associated with AML due to absence of intensively evaluating inherited thrombophilia.[15]

The occurrence of thromboemboli in a relatively young patient without apparent risk factors prompted an evaluation for hypercoagulability. No evidence for deficiencies of proteins C, protein S or antithrombin III were found. No antiphospholipid antibody was detected. The only problem was factor V mutation was not studied here because of rarity in Asian population and unavailability of testing in general. In this patient, the initial low level of protein C and antithrombin might be due to consumption in thrombus formation[16]. Interval analysis of these levels are essential to support our hypothesis.

In summary, this would be the first report of a case of Marfan syndrome with AML and thrombosis (deep vein thrombosis, splenic infarction and intracardiac thrombus). Further study on their correlation should be carried out in large cohort.

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รายงานผู้ป่วยเด็ก Marfan Syndrome และ Deep Vein Thrombosis และ Acute myeloid leukemia

ภคิน กวักเพฑูรย์, สุอร ชัยนันท์สมิตย์, อำนวยพร อภิรักษากร, สุพัตรา สมจิตต์

รายงานนี้นำเสนอ ผู้ป่วยเด็กหญิงไทย อายุ 9 ปี ที่ได้รับการวินิจฉัยมาร์แฟนซินโดรมครั้งแรก ที่มาด้วยภาวะลิ่มเลือดอุดตันที่หลอดเลือดดำและมะเร็งเม็ดเลือดขาวเฉียบพลันชนิดไมอิลอยด์จากการทบทวนวรรณกรรม มีการรายงานผู้ป่วยมาร์แฟนซินโดรมที่ได้รับการวินิจฉัยเป็นมะเร็งเม็ดเลือดขาวเฉียบพลันชนิดไมอิลอยด์ แต่ยังหลักฐานไม่เพียงพอที่จะหาความเชื่อมโยงระหว่าง 2 โรคนี้รายงานนี้เป็นรายงานแรกที่ผู้ป่วยมาร์แฟนซินโดรมมาด้วย ภาวะลิ่มเลือดอุดตันที่หลอดเลือดดำและมะเร็งเม็ดเลือดขาวเฉียบพลันชนิดไมอิลอยด์

คำสำคัญ มาร์แฟนซินโดรม, มะเร็งเม็ดเลือดขาวเฉียบพลันชนิดไมอิลอยด์, ภาวะลิ่มเลือดอุดตัน

ที่ทำงาน สำนักงานกุมารเวชกรรม โรงพยาบาลขอนแก่น 54 ถนนศรีจันทร์ ตำบลในเมือง อำเภอเมือง ขอนแก่น จังหวัดขอนแก่น 40000 โทรศัพท์ 043-009-900 ต่อ 4014