Isolated Protein S Deficiency Presenting as Thromboembolic Pulmonary Arterial Hypertension in a Young Child

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Received September 27, 2014; Revised December 04, 2014; Accepted December 10, 2014

Abstract A 13 months male child presented with progressive dyspnea of three months and recent cyanosis. Cardio-respiratory examination revealed tachypnea, cyanosis, left parasternal heave and loud P2. Echocardiography revealed thrombus in pulmonary artery and severe pulmonary arterial hypertension. Tests for thrombophilia demonstrated protein S deficiency. Treatment included anticoagulants, sildenafil, bosentan and supportive measures without embolectomy. The child get stabilized soon with echocardiographic evidence of thrombus resolution, however, tachypnea and oxygen dependency persisted. He discharged on bosentan, warfarin and home O2 inhalation. Follow-up CT pulmonary angiography showed organized thrombus in pulmonary artery and cystic lesions in lungs. During 14 months of follow-up he remained tachypneic and oxygen dependent despite discharge medication and additional sildenafil, and subsequently died of right ventricular failure and pulmonary hemorrhage. Thromboembolic pulmonary arterial hypertension due to protein S deficiency can present in early childhood and treatment with anticoagulants, bosentan and sildenafil without embolectomy may not be appropriate.

Keywords: protein S deficiency, thromboembolism, pulmonary arterial hypertension, Wegener granulomatosis, Langerhans cell histiocytosis


1. Background

Pulmonary thromboembolism is a rare cause of pulmonary arterial hypertension (PAH) in children, common being congenital heart disease, pulmonary disease or idiopathic [1,2]. Congenital or acquired thrombophilia are frequent risk factors for thromboembolic pulmonary hypertension in children [3]. Protein S is a natural anticoagulant, acts as cofactor to facilitate action of activated protein C which in turn inhibits factor VIIIa and factor Va. Its deficiency can manifest as venous thromboembolism, occasional arterial thrombosis, and rarely, with severe deficiency as purpura fulminans in young children and in association with bacterial or viral infections [4,5,6,7]. Pulmonary thromboembolism causing PAH is rare and hardly been reported in children [4,8]. We describe case of a young child who presented as PAH secondary to pulmonary thromboembolism, and had isolated protein S deficiency with subsequent fatal outcome.

2. Case Presentation

A 13 month old boy presented with illness of 3 months duration, with fast breathing, initially on exertion but later at rest; easy fatigability; cough especially on exertion/ cry and cyanosis since three days prior to admission. The child had received multiple courses of antibiotics, bronchodilators and short duration steroid without significant improvement. He was first born child, a product of non consanguineous marriage, delivered at term gestation and has average birth weight. Antenatal, perinatal, neonatal and early infancy periods were uneventful. His growth and development was age appropriate. There was no family history of cardiopulmonary disease. On admission he was centrally cyanosed with oxygen saturation 80 % at room air, tachypnic (RR 76/ min) with mild chest retractions and nasal flaring. He was afebrile, normotensive, and all peripheral pulses were palpable. There was no edema, significant pallor, icterus and lymphadenopathy but grade two clubbing of nails. Chest auscultation showed equal and adequate air entry with bilateral scattered crepitations. Cardiac examinations suggested tachycardia (HR 162/min), left parasternal heave and loud pulmonary component of S2 without any obvious murmur. Other systemic examinations were within normal limits. Arterial blood gas analysis at admission showed hypoxemia and metabolic acidosis. A clinical diagnosis of pulmonary
hypertension was made; however, there was no clinical clue of thromboembolic, pulmonary or cardiac causation.

3. Investigations

Initial investigation revealed hemoglobin of 9.2g/dL, total leucocyte count 9780/cumm (N58L39M5E0), ESR 15mm, platelet count 2.73 lac/cumm, prothrombin time 13 sec (control 13 sec), prothrombin concentration 100%, INR 1.0 and activated partial prothrombin time 29 sec (control 25 sec). Peripheral blood smear showed microcytic, hypochromic RBCs along with anisocytosis, there were no immature cells and screening test for sickling (deoxygenation) was negative. Serum electrolytes, serum urea, creatinine and liver enzymes were within normal range. Chest radiograph showed normal CT ratio, bilateral hilar prominence with interstitial thickening in both lungs (Figure 1). Blood cultures (3times) were sterile. Workup for tuberculosis including mantoux test, gastric aspirate for acid fast bacilli and TB interferon-gamma assay in blood were negative; test for influenza virus, and HIV were also negative. Analysis of pulmonary secretion for hemosiderin laden macrophages was negative, and urine analysis was normal. Lupus anticoagulant and factor V Leiden mutation were absent. Antiphospholipid IgG antibodies in serum, dilute russell’s viper venom (DRVV) screen titer, plasma antithrombin activity (77%), protein C activity (69%), and homocysteine level were within normal range. Plasma protein S activity (clotting based assay: normal value 77-143%) performed twice and was low, 16% & 10%, done after 14 & 28 days of discontinuation of heparin and before initiating warfarin. Electrocardiogram showed right ventricular hypertrophy. Echocardiography revealed severe tricuspid regurgitation (TR) with severe PAH (peak TR velocity 4.3 m/sec; pressure gradient across TV 77 mm Hg), dilatation of right atrium and ventricle and thrombus above pulmonary valve, extending to main and right pulmonary artery (Figure 2). Venous Doppler study of lower limbs was normal. Subsequent echocardiography demonstrated regression in degree of tricuspid regurgitation, PAH and size of thrombus (Figure 3 & Figure 4). Initial spiral CT pulmonary angiography was possible three month later showed filling defect along lateral wall of main pulmonary artery extending up to bifurcation suggestive of organized thrombus; and multiple thin walled cystic lesions in both lungs (Figure 5 & Figure 6). Test for antinuclear antibodies and sweat chloride test for cystic fibrosis were negative, and X-ray skull was normal. Follow-up contrast enhanced CT showed persistent and even larger cysts in lungs along with pulmonary arterial dilatation (Figure 7 & Figure 8).
4. Differential Diagnosis

Clinical finding of respiratory insufficiency along with left parasternal heave and loud pulmonary component of S2 lead clinical diagnosis of pulmonary hypertension in this case. There was no clinical or investigative evidence towards cardiac anomaly. Chronic pulmonary conditions like interstitial lung disease and pulmonary complication of connective tissue diseases seems unlikely, as these conditions are rare in young children, may have other system involvement and have varied radiological findings. Pulmonary function test and lung biopsy are useful to establish the diagnosis, however, it could not become possible. Interestingly, CT pulmonary angiography performed during follow-up showed multiple thin walled small cystic lesions in both lungs distributed widely in all the lobes. Possibly, it could be because of chronic embolization and infarction of lung tissue; however, the cystic changes in such condition are more common in peripheral region of lungs. Wegener granulomatosis (WG), a small vessel vasculitis can have cavitory lesions in the lungs. However, it is rare in young children, presents with constitutional symptoms; upper airway involvement as sinusitis, nasal ulceration, epistaxis, otitis media; lower respiratory tract as cough, wheezing, dyspnea and hemoptysis; and has renal involvement [9]. Pediatric pulmonary Langerhans cell histiocytosis (LCH) can have chronic respiratory symptoms with reticulonodular or cystic changes in lungs [10], is typically part of multisystem LCH, with occurrence of PAH as a late phenomenon, which were not in the present case [11]. Both WG and LCH require lung biopsy for confirmation of the diagnosis, but it could not be performed in this patient because of parents did not give consent for same. Moreover, in view of suboptimal response to initial treatment and lack of lung histopathology, a course of oral corticosteroid was tried during the initial follow up period, but it was discontinued after a month due to no response. One would expect response to corticosteroid in cases of interstitial lung disease, WG, and LCH, however, it was not the case, minimizing the possibility of these conditions. Finally, thromboembolic etiology for pulmonary arterial hypertension in the present patient was established by echocardiography and investigations for thrombophilia indicated the cause of thrombosis due to protein S deficiency.

5. Treatment

The treatment began with oxygen by mask, intravenous fluid, injection vitamin K single dose.

Oral sildenafil, bosentan and unfractionated heparin infusion were started after the echocardiography findings suggestive of thrombus and pulmonary arterial hypertension. Injection vancomycin, meropenam and voriconazole were given for four weeks owing to remote possibility of septic embolization, though the supportive evidences were lacking. As the patient got stabilized and subsequent echocardiographic examination found pulmonary thrombus no more, heparin infusion was discontinued after 14 days. Oral warfarin was started only after the investigations for thrombophilia demonstrated protein S deficiency, targeting INR 2-2.5. Though, the patient had improved in due course of time with regression of pulmonary hypertension and disappearance of thrombus, he remained tachypneic and require low flow oxygen to maintain normal saturation. Finally, he discharged from the hospital after a stay of 2 ½ months, on oral bosentan and warfarin along with home oxygen inhalation with intermittent oxygen saturation monitoring.

6. Outcome and Follow-up

After discharge, the patient was followed-up in outdoor; however, the visit was infrequent, 3-4 monthly. Each time, the patient was found to have tachypnea, tend to develop cyanosis on brief discontinuation of oxygen inhalation; however he used to remain comfortable for about 30 min without oxygen despite having desaturation. Echocardiography done 6 & 12 months after discharge revealed no further thrombus but there remained evidence of mild pulmonary hypertension. Meanwhile, the patient also visited at two apex tertiary centres of our country and was advised to continue on oral warfarin and bosentan.
Repeat spiral CT pulmonary angiography performed 12 months after initial presentation showed thickened and dilated pulmonary arteries along with persistent and enlarged cystic lesions of the lung (Figure 7 & Figure 8). Till 14 months after being discharged, his condition remained stationary with having persistent mild tachypnea and oxygen dependency. However, over the last 5 days his breathing became worsened, developed legs and facial swelling; and he again hospitalized in very critical stage. This time, he had severe dyspnea, hypoxemia, right heart failure; and developed massive pulmonary hemorrhage within hours. He was managed on respiratory support, injection vitamin K despite having INR of 2.5 and other supportive measures, but succumbed to death.

Figure 7. Follow up CECT thorax axial view showing marked dilatation of main pulmonary (the ratio of ascending aorta and main pulmonary artery is reversed)

Figure 8. Follow up CECT thorax axial view lung window showing persistent and enlarged cysts bilateral lung fields

7. Discussion

Pathogenesis of PAH has been recognized to be multifactorial: vasoconstriction, proliferation, inflammation and thrombosis, which may have therapeutic implication [12]. Thromboembolic PAH is thought to result from single or recurrent pulmonary thromboemboli from sites of venous thrombosis [13], or de-novo pulmonary artery thrombosis [14]. Probably, our patient developed thrombosis primarily in pulmonary artery, as there was no evidence of thrombosis in the major vein of extremities on Doppler study. For unknown reason, resolution of thrombus does not occur completely in some of survivors of acute pulmonary thromboemboli, which then evolve into organized obstruction inside the pulmonary artery, eventually causing an increased pulmonary vascular resistance [15,16]. One may get misguided of false thrombus resolution process because of ongoing recurrent embolization leading to reduction in thrombus size. This appears true if despite embolectomy or thrombolytic therapy, apparent resolution of thrombus as demonstrated on serial imaging is not being accompanied by clinical improvement, as happened in our case. Thrombophilic conditions encountered in children includes protein C & S deficiency, activated protein C resistance, antithrombin III deficiency, factor V Leiden mutation, elevated homocysteine level, abnormal lipid profile, antiphospholipid syndrome and thrombocytopenia; the risk is more when multiple conditions exists and in familial cases. Sdogou et al [17] have reported deep vein thrombosis and pulmonary embolism in a young child with diabetic ketoacidosis who had familial protein S deficiency, improved on anticoagulants and supportive care, however, it was not explicitly mentioned to develop PAH.

The cause of pulmonary hypertension in our patient appears unlikely because of any condition other than pulmonary thromboembolism due to protein S deficiency, though, conditions like WG and LCH can have respiratory manifestations and cystic lesions in the lungs, pulmonary arterial thrombosis with low protein S level have never been described to coexist. Moreover, lack of response to corticosteroid in this patient further weakens the possibility of interstitial lung diseases, WG or LCH [18].

Protein S circulates in plasma in two forms. Approximately 60% is bound non-covalently to complement component C4b binding protein β chain (C4BP), whereas the remaining 40% is free (functional form) [19]. Three subtypes of protein S deficiency have been recognized based on the levels of total protein S antigen, free protein S antigen, protein S activity in plasma. Functional assay of protein S activity could detect all types of protein S deficiency, which was also performed in this case; however, for further characterization of subtype, protein S antigen assay (free & total) needs to be done. Acquired causes of protein S deficiency are seen in liver disease, disseminated intravascular coagulation, severe bacterial and viral infection, and therapy with Lasapaginase and coumarin etc [20]. The markedly low level of protein S in the index case cannot be attributed to any of the acquired causes as these conditions were nonexistent, and the test was performed twice, two & four wks after discontinuation of heparin infusion and before initiating warfarin therapy. Percutaneous catheter-based embolectomy has been found successful to remove pulmonary thrombus in neonate presenting as pulmonary hypertension due pulmonary artery thrombosis [14]. We decided to perform surgical embolectomy in this patient, but parents denied for the procedure. Thromboembolic PAH considered nowadays as a dual pulmonary vascular disorder with major vascular remodeling of thrombus organization, combined with a small vessel pulmonary arteriopathy that is a target for vasodilator treatment [21]. Long term therapy with Bosentan has been used widely in children with
pulmonary arterial hypertension. In a study comprising of 42 children with idiopathic pulmonary arterial hypertension (IPAH), 39% of all children started on bosentan alone needed additional sildenafil or epoprostenol, or both. 65% of children with IPAH remained event free at 1 yr and 38% at 2 yrs [22]. The present patient was put on bosentan and sildenafil along with warfarin and failed to treatment after about 15 months; however, our patient had PAH due to different etiology, remained hypoxemic (oxygen dependent) which might have augmented the PAH; and it seems that embolectomy, if performed at earlier stage would have given a better chance for survival. In conclusion, pulmonary arterial hypertension should be suspected in any child presenting with pulmonary insufficiency and easy tiredness when there is no evidence of cardiac or pulmonary disease; and investigative workup should include search for thromboembolism and thrombophilia. However, optimal treatment for this condition remains unclear.

8. Learning Points/Take Home Messages

Protein S deficiency may present in young children despite being non-familial.
- Thromboembolic pulmonary hypertension may be the only presentation of Protein S deficiency, it needs to be evaluated in children presenting with unexplained respiratory insufficiencies.
- Without thrombolytic therapy or embolectomy, resolution of thrombus can be misleading because of ongoing/recurrent embolization, especially in absence of significant and sustained clinical response.
- Without embolectomy, long term treatment with warfarin, bosentan and sildenafil may not be appropriate for the management of thromboembolic pulmonary artery hypertension due to protein S deficiency.

References