

Asthma-Like Symptoms as a Presentation of Antiphospholipid Syndrome

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Summary. We herein report a case of antiphospholipid syndrome (APS) primarily presenting with asthma-like symptoms that had been misdiagnosed as severe asthma. Patients presenting with severe asthma symptoms along with systemic thrombosis should be systematically evaluated for APS. *Pediatr Pulmonol.* © 2014 Wiley Periodicals, Inc.

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INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways, affecting approximately 10% of childhood worldwide.¹ It is characterized by recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, occurring mostly at night or early in the morning along with variable airflow obstruction which is often reversible either spontaneously or with treatment.² Whereas most children with mild to moderate asthma can be controlled by low-dose inhaled corticosteroids, a subset of children with severe asthma (less than 5% of cases) remain highly symptomatic despite treatment with high-dose inhaled corticosteroids, or even with systemic corticosteroids.^{3,4} These children are predisposed to greater morbidity and require higher healthcare support.⁵ Despite the fact that several clusters of severe asthma in children have been described, one has to be certain that other causes of lung diseases mimic asthma has been excluded.^{6,7} Antiphospholipid syndrome (APS) is a prothrombotic disorder which can affect both venous and arterial circulations of the multiple organ systems.⁸ Pulmonary manifestations are less common findings of APS and limited data are available on the association between asthma and APS, particularly in children.⁹ Herein, we report a case of APS who presented with severe asthma-like symptoms with poor response to conventional asthma treatment. After a proper diagnosis was made, a more specific treatment for APS led to an improved asthma control.

CASE REPORT

A 13-year-old Thai boy was referred to Siriraj Hospital with severe asthma in 2012. At the age of 4, he developed

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generalized vitiligo, anemia, and thrombocytopenia, and was diagnosed as having Evans syndrome (autoimmune hemolytic anemia and immune thrombocytopenia). He was then placed on continuous prednisolone (1 mg/kg/day). At the age of 6, he developed recurrent wheezing and was diagnosed as a case of asthma. He was then put on salmeterol/fluticasone combination (50 µg/250 µg twice daily) and montelukast. His asthma, however, remained uncontrolled needing periodic step-up of asthma treatments. Between age 6 and 13 years, he frequently needed hospitalizations for asthmatic attacks, two of which required intensive care admission for endotracheal intubation and mechanical ventilation. These attacks occurred despite regular use of budesonide nebulization at a dosage of 2,000 µg/day, doxophylline, and montelukast. His serum-specific IgE to aeroallergens were all negative. A body plethysmography revealed a reversible obstructive lung pattern (FEV₁ 63.1%, FVC 63.1%, FEV₁/FVC 69.0%, with 13% improvement in FEV₁ after bronchodilator, total lung capacity 80.0%, residual volume 167.0%, DLCO 80.0%, DLCO/VA 6.21 ml/mmHg/min/L). A methacholine challenge test revealed severe airway hyperresponsiveness (PC₂₀ = 0.125 mg/ml). A flexible bronchoscopy demonstrated normal anatomy of the bronchial tree with no endobronchial lesion. Bronchoalveolar lavage analysis showed total cell count 705 cells/mm³ (neutrophils 75%, lymphocytes 10%, eosinophils 4%, alveolar macrophage 11%). A high resolution computerized tomography (CT) of the chest (HRCT) revealed mild bilateral peribronchial thickening, focal ground glass opacity resulting from respiratory motion artifact at dependent part of right lower lobe. No evidence of interstitial lung disease and airway compression was demonstrated (Fig. 1). CT pulmonary angiography revealed no pulmonary embolism. Perfusion and ventilation lung scan revealed no evidence of perfusion/ventilation defect.

At the age of 13, his Evans syndrome flared with swelling of both legs (possibly due to thrombosis of veins draining lower extremities). He also had a cutaneous ulcer over the dorsum of left foot for 2 weeks. In addition, diabetes mellitus and hypertension were documented. His laboratory revealed hemoglobin 5 g/dl, hematocrit 17.3%, white blood cell count 26,060/mm³ (neutrophils 68%, lymphocytes 25%, monocytes 5%, basophils 2%), platelet count 72,000/mm³, a strongly positive direct Coombs' test, an elevated serum lactic dehydrogenase (2,276 U/L), a reduced plasma haptoglobin (<10 mg/dl), an elevated D-dimer (2,159 µg/L) and a reduced fibrinogen (180 mg/dl). Antinuclear antibody, anti-DNA antibody, ANCA, and lupus anticoagulant tests were negative. Two sets of anticardiolipin immunoglobulins (IgG) and anti-β₂ glycoprotein I antibodies (IgM) were measured at least 12 weeks apart. All levels were elevated above normal (anticardiolipin immunoglobulins-IgG: 8.35 and

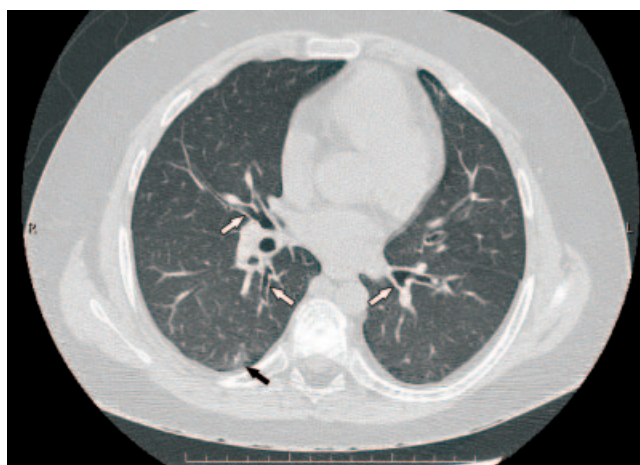


Fig. 1. A high resolution CT of the chest shows mild bilateral peribronchial thickening (white arrow), focal ground glass opacity resulting from respiratory motion artifact at dependent part of right lower lobe (black arrow). No evidence of interstitial lung disease and airway compression is demonstrated.

9.03 GPL U/ml [normal < 6.5 GPL U/ml] and anti-β₂ glycoprotein I antibodies-IgM: 41.26 and 97.28 RU/ml [normal < 20 RU/ml]). A CT venography revealed chronic deep vein thrombosis in hepatic inferior vena cava (IVC) and infrahepatic IVC, bilateral renal vein thrombosis, bilateral common iliac vein thrombosis and bilateral common femoral vein thrombosis. Skin biopsy was performed to determine the nature of a cutaneous ulcer over the dorsum of left foot, which revealed vasculopathy of medium- and small-sized vessels with luminal occlusion by thrombotic materials associated with marked epidermal necrosis and eccrine duct necrosis. No evidence of vasculitis was detected. He was diagnosed as having APS with Evans syndrome, and was treated with pulse methylprednisolone 30 mg/kg/day, followed by prednisolone, azathioprine, and hydroxychloroquine. Also, he has been treated with enoxaparin 40 mg subcutaneously every 12 hr until present (anti-factor Xa 0.6–1 U/ml).

Since he continued to have exacerbations of asthma with active APS, an open-lung biopsy was performed to further characterize the nature of his lung disease. The histopathology displayed chronic pulmonary thromboembolic occlusion (Fig. 2). Small arteries and arterioles contained variable stages of thromboemboli, which included condensed fibrin, organizing thromboemboli, and recanalized thromboemboli. The arteriolar walls did not have significant inflammation. Bronchiolar walls showed only mild chronic lymphocytic inflammation without significant number of eosinophilic infiltrate, goblet cell metaplasia, smooth muscle hyperplasia, or mucus plugging of the bronchioles.

With all the work-up data, we concluded that the patient's recurrent wheezing episodes were asthma-like

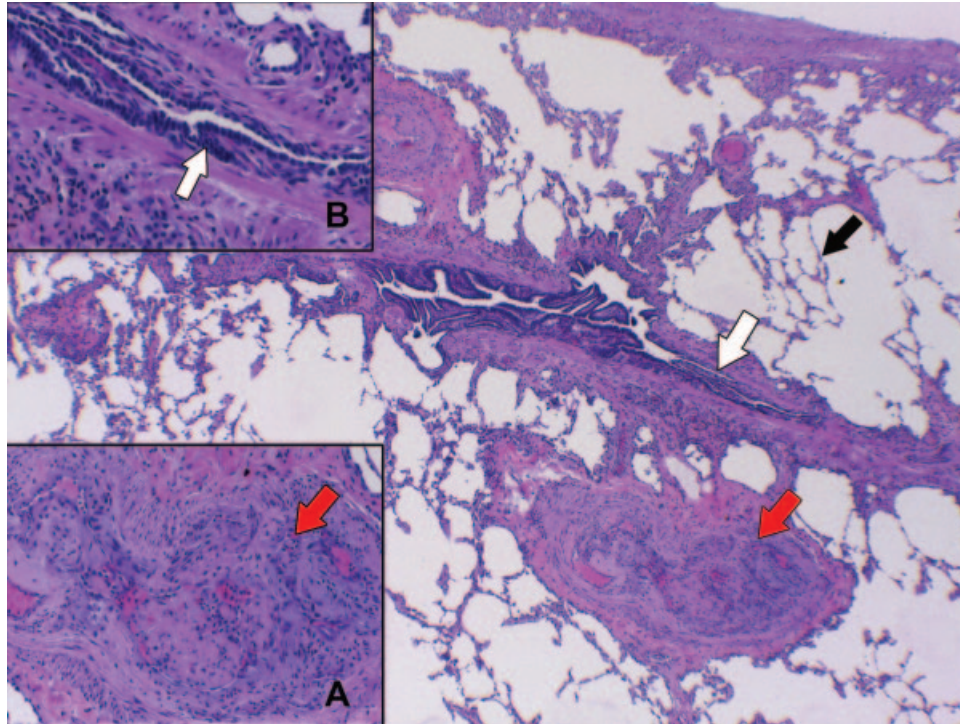


Fig. 2. Low magnification of H&E staining of lung tissue ($\times 40$). A thrombosed pulmonary arteriole with organization and recanalization is noted (red arrow and inset A [$\times 400$]). No inflammation of the arteriolar wall is detected. An accompanying bronchiole is tangentially cut resulting in mucosal infolding (white arrow). The mucosa is lined by low cuboidal, non-ciliated bronchiolar epithelium (inset B [$\times 400$]). Neither goblet cell metaplasia nor thickened basement membrane is seen. Mild degree of airway wall inflammation is present. Pulmonary alveoli are thin and normally aerated (black arrow).

symptoms due to APS. After the initiation of hydroxychloroquine which directly inhibits the binding of anti- β_2 glycoprotein I antibody complexes to phospholipid surfaces,^{10,11} he had a good clinical response and with fewer and milder recurrent wheezing episodes. Prednisolone and asthma medications were decreased gradually.

DISCUSSION

Severe asthma is characterized by persistent asthma symptoms, abnormal lung function test, and high health-care utilization despite complex medication regimens, including high doses of inhaled or oral corticosteroids.^{4,12,13} Severe asthma is a heterogeneous disorder depending on its contributing factors and underlying pathology.^{12,13} The management of children with severe asthma requires a systemic approach including reassessment for the diagnosis of asthma, adequate management of asthma, improving compliance, identification of exacerbating factors, and exclusion of other diagnoses.^{14,15} Our patient was initially diagnosed as a case of severe asthma, based on his recurrent wheezing episodes and response to bronchodilators. A reversible obstructive lung pattern from body plethysmography with positive

methacholine challenge test confirmed the diagnosis of asthma. However, he continued to have asthma exacerbations along with active APS. We therefore decided to proceed on with an open-lung biopsy to further characterize the nature of his lung disease. Indeed, the lung histopathology revealed chronic pulmonary thromboembolic occlusion with subtle changes of small airways. The thromboembolic phenomenon from lung histopathology and the improvement of his asthma after the initiation of hydroxychloroquine suggested that the pathogenesis of his APS and asthma may be interrelated. In fact, the decrease of inhaled corticosteroids and asthma medication requirements coincided with an improvement of his clinical manifestations of APS.

APS is a prothrombotic disorder which can affect both venous and arterial circulations.⁸ The prevalence of pediatric APS is rare in children (more frequent in girls than boys).¹⁶ The most common clinical manifestation of pediatric APS is venous thromboembolism particularly deep vein thrombosis in the lower extremities. Other clinical manifestations are arterial thrombosis, thrombocytopenia, autoimmune hemolytic anemia, livedo reticularis, Raynaud's phenomenon and migraine.^{10,16} Pulmonary manifestations, including pulmonary

thromboembolism, pulmonary hypertension, alveolar hemorrhage, are less common findings compared to other clinical manifestations.⁹ The persistence (for >12 weeks) of high titers of antiphospholipid autoantibodies are an essential component for the diagnosis.⁸ Antiphospholipid autoantibodies promote activation of endothelial cells, monocytes, platelets, complement cascade, and overproduction of tissue factor and thromboxane A₂.¹¹ These effects potentiate thrombus formation and play a key role in the pathogenesis of APS. Additionally, thromboxane A₂ is a potent bronchoconstrictor by direct activation of thromboxane prostanoid receptors on airway smooth muscle cells.^{17,18} Overproduction of thromboxane A₂ may contribute to bronchoconstriction and airway hyperresponsiveness in APS patients.

In conclusion, patients presenting with severe asthma symptoms should be systematically evaluated for other diagnoses which mimic asthma. Such work ups are essential for cases not responding to conventional asthma management.

REFERENCES

1. Asher MI, Montefort S, Bjorksten B, Lai CK, Strachan DP, Weiland SK, Williams H. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;368:733–743.
2. Global Initiative for Asthma Committee. Global strategy for asthma management and prevention updated 2012 [Internet]. c2012 [updated December 2012; cited 2013 September 1]. Available from: http://www.ginasthma.org/local/uploads/files/GINA_Report_March13.pdf
3. Fitzpatrick AM, Teague WG. Severe asthma in children: insights from the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. *Pediatr Allergy Immunol Pulmonol* 2010;23:131–138.
4. American Thoracic Society. Proceedings of the ATS workshop on refractory asthma: current understanding, recommendations, and unanswered questions. *Am J Respir Crit Care Med* 2000;162:2341–2351.
5. Moore WC, Bleecker ER, Curran-Everett D, Erzurum SC, Ameredes BT, Bacharier L, Calhoun WJ, Castro M, Chung KF, Clark MP, Dweik RA, Fitzpatrick AM, Gaston B, Hew M, Hussain I, Jarjour NN, Israel E, Levy BD, Murphy JR, Peters SP, Teague WG, Meyers DA, Busse WW, Wenzel SE. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. *J Allergy Clin Immunol* 2007;119:405–413.
6. Ranganathan SC, Payne DN, Jaffe A, McKenzie SA. Difficult asthma: defining the problems. *Pediatr Pulmonol* 2001;31:114–120.
7. Bousquet J, Mantzouranis E, Cruz AA, Ait-Khaled N, Baena-Cagnani CE, Bleecker ER, Brightling CE, Burney P, Bush A, Busse WW, Casale TB, Chan-Yeung M, Chen R, Chowdhury B, Chung KF, Dahl R, Drazen JM, Fabbri LM, Holgate ST, Kauffmann F, Haahtela T, Khaltaev N, Kiley JP, Masjedi MR, Mohammad Y, O'Byrne P, Partridge MR, Rabe KF, Togias A, van Weel C, Wenzel S, Zhong N, Zuberbier T. Uniform definition of asthma severity, control, and exacerbations: document presented for the World Health Organization Consultation on Severe Asthma. *J Allergy Clin Immunol* 2010;126:926–938.
8. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, Derksen RH, DE Groot PG, Koike T, Meroni PL, Reber G, Shoenfeld Y, Tincani A, Vlachoyiannopoulos PG, Krilis SA. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006;4:295–306.
9. Ford HJ, Roubey RA. Pulmonary manifestations of the antiphospholipid antibody syndrome. *Clin Chest Med* 2010;31:537–545.
10. Ruiz-Irastorza G, Crowther M, Branch W, Khamashta MA. Antiphospholipid syndrome. *Lancet* 2010;376:1498–1509.
11. Giannakopoulos B, Krilis SA. The pathogenesis of the antiphospholipid syndrome. *N Engl J Med* 2013;368:1033–1044.
12. Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, D'Agostino R Jr, Castro M, Curran-Everett D, Fitzpatrick AM, Gaston B, Jarjour NN, Sorkness R, Calhoun WJ, Chung KF, Comhair SA, Dweik RA, Israel E, Peters SP, Busse WW, Erzurum SC, Bleecker ER. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med* 2010;181:315–323.
13. Fitzpatrick AM, Teague WG, Meyers DA, Peters SP, Li X, Li H, Wenzel SE, Aujla S, Castro M, Bacharier LB, Gaston BM, Bleecker ER, Moore WC. Heterogeneity of severe asthma in childhood: confirmation by cluster analysis of children in the National Institutes of Health/National Heart, Lung, and Blood Institute Severe Asthma Research Program. *J Allergy Clin Immunol* 2011;127:382–389.
14. Bush A, Saglani S. Management of severe asthma in children. *Lancet* 2010;376:814–825.
15. Bel EH, Sousa A, Fleming L, Bush A, Chung KF, Versnel J, Wagener AH, Wagers SS, Sterk PJ, Compton CH. Diagnosis and definition of severe refractory asthma: an international consensus statement from the Innovative Medicine Initiative (IMI). *Thorax* 2011;66:910–917.
16. Avcin T, Cimaz R, Silverman ED, Cervera R, Gattorno M, Garay S, Berkun Y, Sztajnbock FR, Silva CA, Campos LM, Saad-Magalhaes C, Rigante D, Ravelli A, Martini A, Rozman B, Meroni PL. Pediatric antiphospholipid syndrome: clinical and immunologic features of 121 patients in an international registry. *Pediatrics* 2008;122:1100–1107.
17. Devillier P, Bessard G. Thromboxane A₂ and related prostaglandins in airways. *Fundam Clin Pharmacol* 1997;11:2–18.
18. Fujimura M, Nakatsumi Y, Nishi K, Kasahara K, Matsuda T. Involvement of thromboxane A₂ in bronchial hyperresponsiveness of asthma. Kanazawa Asthma Research Group. *Pulm Pharmacol* 1995;8:251–257.