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Recurrent pulmonary embolism in a boy with antiphospholipid syndrome

Christian Müller[1*], Christian Willaschek[1], Mathias Borst[2], Reiner Buchhorn[1]

[1]Department of Pediatrics, Caritas Krankenhaus, Bad Mergentheim, Germany; [*]Corresponding Author: muellisin@googlemail.com
[2]Department of Medicine, Caritas Krankenhaus, Bad Mergentheim, Germany

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ABSTRACT

We report a 14-year-old patient with recurrent pulmonary embolism due to catastrophic antiphospholipid syndrome (APS) with severe pulmonary inflammation. We considered elevated antibodies against cardiolipin and anti-beta2-glycoprotein-1, but no clinical nor laboratory manifestations of systemic lupus erythematosus (SLE). Pulmonary embolism had been the first manifestation of catastrophic APS in this patient. We prescribed warfarin and systemic corticosteroids. A second embolism appeared during anticoagulation with warfarin. This event led to a marked decrease of his physical performance due to his obstructive and restrictive lung disease. Anticoagulation was changed from enteral warfarin to subcutaneous enoxaparine. We also prescribed inhaled corticosteroid which led to an improvement of his respiratory symptoms and overall poor physical condition.

Keywords: Pulmonary Embolism; Antiphospholipid Syndrome; APS; Inhaled Corticosteroid

1. INTRODUCTION

APS is a rare disease, especially in children [1]. As opposed to the secondary form of APS occurring in patients with autoimmune disorders, predominately SLE. APS is said to be primary if there are no features of SLE or other autoimmune disorders [1,2].

Clinical manifestations of primary APS are variable [3]: one feature is pulmonary embolism [4] which in one case study occurred in 2.1% of patients with APS [5].

Especially in children, pulmonary embolism associated with APS is rare [6], but may be its first manifestation [2].

Chronic thromboembolic pulmonary hypertension (CTEPH) due to APS is a severe disease with high morbidity and mortality [2,7]. Histopathologically, there may be signs of catastrophic APS such as alveolar hemorrhage, microvascular thrombosis and pulmonary capillaritis, which is the most severe course of high mortality due to multiple vascular occlusive events [8]. Pulmonary embolism in APS associated with fever and elevated autoantibodies are usually caused by SLE. Diagnosis of SLE is based on clinical and laboratory features according to the classification criteria [9-12]. Because there was no evidence of autoimmune disorders the present case was classified to primary APS.

2. CASE REPORT

We report a 14-year-old male in good overall physical condition (BMI: 19.6 kg/m^2) with no history of severe diseases. He did not consume any medication, nicotine, alcohol, or other drugs. The familial history was unremarkable. He presented with acute chest pain and fever up to 40˚C having lasted for one week. There was no trauma recalled by the patient or his family. He presented with pain, which was located in the right hemithorax and increased in intensity when in supine position. During physical examination a reduced respiratory sound over his right lower pulmonary lobe was found.

Chest x-ray showed a consolidation in the right lower pulmonary lobe. C-reactive protein (CRP) was elevated to 9.37 mg/dL. An initial diagnosis of pneumonia was made and antibiotic therapy (Cefuroxim, Doxycycline, Gentamicin) was initiated.

Five days later there was no clinical improvement. A computed tomography (CT) scan of the thorax (**Figure 1**) showed signs of past pulmonary embolism in the right lower lobe. We started effective anticoagulation with intravenous heparin and enhanced the antibiotic therapy (Cefuroxim, Doxycycline, Gentamicin and Vancomycin). An ultrasound examination showed a deep venous thrombosis of the left lower extremity. The patient's clinical

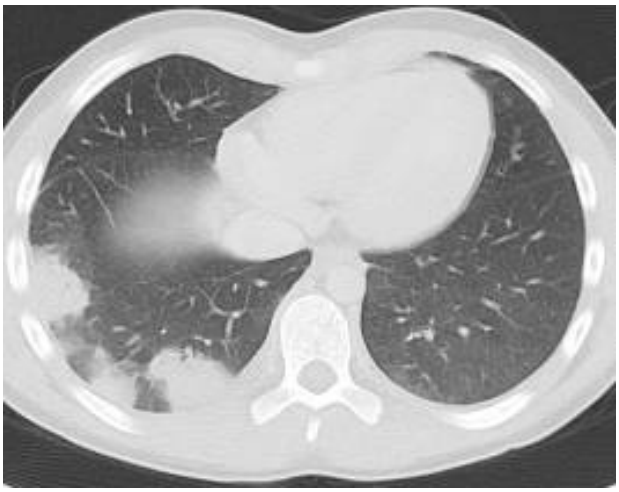

Figure 1. Primary thoracic computerized tomography.

conditions deteriorated and because of respiratory failure with tachypnea he needed supplemental oxygen.

A CT-guided lung biopsy demonstrated changes suggesting a hemorrhagic pulmonary infarct. Moreover, features of catastrophic APS such as capillary inflammation, microvascular thrombosis and alveolar haemorrhage were found [4,13]. A malignant transformation was excluded by means of a bone marrow biopsy.

Laboratory analyses demonstrated elevated autoantibodies directed against cardiolipin and anti-beta$_2$-glycoprotein-1 on several occasions. Antinuclear antibodies, dsDNA-antibodies, anti-SM-antigen and SSA-antigen were negative. Based on the laboratory results and the histological findings the diagnosis of catastrophic APS was made.

Intravenous glucocorticosteroid therapy (methyl prednisolone 150 mg/d) was begun. Body temperature decreased from 39.8˚C to 37.0˚C within twelve hours and the clinical condition improved. Anticoagulation therapy was changed from heparin to warfarin [14,15] with a target INR of 2.0 - 3.0. The patient was equipped with an INR home monitoring system. Compression stockings were prescribed.

Two weeks later the patient suddenly felt acute chest pain in the left hemithorax, consistent with pleuritic pain. He reported shortness of breath and dyspnea. His body temperature was normal. The INR was 2.18. A second CT scan of the thorax showed a new pulmonary embolism in the left lower lobe.

Therapeutic options such as thrombolysis, embolectomy, and plasmapheresis were discussed.

Finally we decided to change the anticoagulation to subcutaneous enoxaparine (2 × 60 mg/d). Warfarin and corticosteroid therapy was tapered.

Six weeks later during an outpatient visit the boy complained about generalized malaise. He felt that he was unable to attend school. Cardiopulmonary exercise (CPX) testing showed an impressive reduce of peak oxygen uptake with predominant pulmonary limitation (**Table 1**). Pulmonary hypertension was excluded by echocardiography. Also congestive heart failure appeared very unlikely as NT-Pro-BNP levels were normal (**Table 2**). However, heart rate variability was reduced as determined by Holter ECG.

We decided to treat the suspected pulmonary inflammation with inhaled corticosteroids (fluticasone). A reapeted CPX test and Holter ECG showed an impressive improvement of exercise capacity and heart rate variability (**Table 1**). Nearly 5 months later the patient complained of erythema and urtication after injection of subcutaneous enoxaparine. We changed his anticoagulation therapy from subcutaneous enoxaparine to moderate-intensity warfarin and low dose acetylsalicylic acid (ASS) [16]. As before, target INR was 2.0 - 3.0. Laboratory analyses showed a progressive improvement of CRP and D-Dimer values (**Table 2**).

3. DISCUSSION

Pulmonary embolism in our patient was the first manifestation of primary APS [2]. The diagnostic criteria of SLE [9] were not met because no organ manifestations other than deep vein thrombosis with pulmonary embolism were present and specific laboratory features were negative. However, septic fever unresponsive to antibiotics and the impressive clinical improvement after the first dose of corticosteroids clearly indicate the inflammatory origin of our patient's disease. Systemic corticosteroid therapy could be terminated after 5 weeks.

Despite an evidence based anticoagulation with warfarin [14,15] the patient developed a second pulmonary embolism two weeks after discharge from hospital. In this situation he was at risk for the development of CTEPH that usually has a fatal outcome in APS patients [4]. Together with the patient and his parents, we decided against plasmapheresis [17] or local therapies like thrombolysis [18-20] or vena cava filter [21,22].

After a therapeutic switch to subcutaneous enoxaparine and thereafter to warfarin and low dose ASS [23] a progressive decrease of D-Dimer values were observed (**Table 2**).

We had no evidence for heart failure indicated by normal pro-BNP values or for pulmonary hypertension indicated by normal tricuspid regurgitation velocity (**Table 2**). However, for complete clinical recovery and restitution of his exercise capacity the patient depended on inhaled corticosteroid therapy (**Table 1**), upon our hypothesis of persistent pulmonary inflammation.

4. CONCLUSION

In summary, this case shows that pulmonary inflam-

Table 1. Monitoring by spirometry and Holter ECG before and after inhaled corticosteroid.

	Before fluticasone	After fluticasone	Reference values
Spirometry			
Vital capacity [L]	2.57	3.09	4.3
FEV_1 [L]	1.35	2.76	3.6
FEV_1/VC [% pred.]	52.4	107.2	>75
Spiroergometry			
VO_2 peak [L/min/m^2]	21.1	31.0	>25
V_E peak [L/min]	51	86	104
Breathing reserve [%]	0	11	28
RQ	0.97	1.06	>1
Heart rate max [1/min]	173	175	187
Holter ECG			
Mean heart rate [1/min]	99	88	85
Triangle index	16	33	22 - 52
pNN50 [%]	1,68	7,58	5 - 47
SDNN [ms]	70	119	102 - 180
RMSSD [ms]	23	36	15 - 39

FEV_1: forced exspiratory volume in one second; W: Watts; V_E: minute ventilation; RQ: respiratory quotient; VO_2: oxygen uptake. Holter ECG: electrocardiography 24 h; pNN50: number of pairs of adjacent NN intervals differing by more than 50 ms divided by the total number of all NN intervals; SDNN: standard deviation of all NN intervals; RMSSD: the square root of the mean of the square of differences between adjacent NN intervals.

Table 2. Laboratory values and echocardiographic parameters during the whole treatment.

	1. embolism acute	1. embolism subacute	2. embolism	Discharge	2 months later	4 months later	Reference values
Therapy	Antibiotics	Corticoid aspirine heparine	Corticoid warfarin	Enoxaparine	Enoxaparine fluticasone	Warfarin ASS fluticasone	
Laboratory							
CRP [mg/dl]	6.3	0.4	1.36	1.78	0.18	0.34	0 - 1
INR	1.23	0.99	2.18	1.02	1.1	2.27	0.8 - 1.25
PTT [s]	103.6	76.4	55.3	114.4	104.5	67.3	28 - 40
D-Dimers [µg/l]	7620	2980	900	1730	230	50	0 - 500
NT-proBNP [pg/ml]	64.1			<5	19.6		0 - 85
Cardiolipin IgG	66			14		52	<10
Cardiolipin IgM	<5.0			<5.0		<5.0	<7
β-2-Glykoprotein IgG	69			13		40	<10
β-2-Glykoprotein IgM	7			21		3	<12
LVEDD [mm]	42	43	40	44	43	43	35 - 51
FS [%]	42	36	36	45	46	35	>30
TI [m/s]	2.4	2.2		2.2	2.4	2.5	<2.5
(PASP [mmHg])	(28)	(25)		(25)	(28)	(30)	(20 - 30)

CRP: C-reactive protein; INR: international normalized ratio; PTT: partial thromboplastin time; BNP: N-terminal pro brain natriuretic peptide; LVEDD: left ventriclular enddiastolic diameter; FS: fractional shortening; TI: tricuspidal regurgitation velocity; PASP systolic pulmonary arterial pressure derived from TI; Ig: Immunglobuline.

mation can play an important role in manifestation of primary APS that requires consequent immunosuppressant treatment. Inflammation and anticoagulation have to be monitored by D-Dimer values, CRP values and specific tests that depend upon the regiments.

A critical cardiopulmonary monitoring including echocardiography, ECG, spirometry, CPX and Holter ECG is necessary to recognize pulmonary hypertension and decreased endurance of the patient. Cardiac limitations due to pulmonary hypertension may be treated by endarterectomy or endothelin receptor antagonist, if patients are deemed inoperable.

In patients with only pulmonary limitations like in our case inhaled corticosteroid seems to be a good course of treatment.

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ABBREVIATIONS

APS: antiphosphorlipid syndrome
ASS: acetylsalicylic acid
BMI: body mass index
CPX: cardiopulmonary exercise
CT: computed tomography
CTEPH: chronic thromboembol pulmonary hypertension
ECG: electrocardiography
INR: international normalized ratio
SLE: systemic lupus erythematosus