

Massive Pulmonary Embolism in a Chinese Adolescent Boy

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Abstract

This is a case report of massive pulmonary embolism, an uncommon condition in the paediatric population, in a boy who presented with acute onset shortness of breath. The use of tissue plasminogen activator, a form of thrombolytic therapy not commonly used in children, reversed the critical condition of our patient who eventually made a good recovery. Literature review of the disease was performed and the epidemiology, clinical features, investigation tools and strategies and management are discussed.

Key words

Adolescent medicine; Pulmonary embolism; Thromboembolic disease; Tissue plasminogen activator

Introduction

Pulmonary embolism (PE) is not a common disease in children and often occurs in patients with underlying predisposing factors such as presence of central venous catheter, malignancy or hyperviscosity state. Massive PE, defined by acute pulmonary embolism with hypotension, has a very high mortality rate and only accounts for 4.2% of the adult PE cases. We reported a case of massive PE in a Chinese Adolescent boy who presented with right heart failure. He was treated with thrombolytic therapy (tissue plasminogen activator) with full recovery. The case was presented with discussion on epidemiology, presentation, diagnostic tools and treatment and the use of different diagnostic tools on pulmonary embolism.

Case Report

A 15-year-old boy was admitted to the hospital in April 2009 for one week history of shortness of breath. He was first seen in 2007 for fever with cough and chest radiograph show in left pleural effusion. Blood tests at that time showed normal white cell count, and C-reactive protein was elevated to 41 units (normal range <8). Cold agglutinin rose to 128 but the anti-mycoplasma IgM was negative. Antibiotics including clarithromycin were given. Computed tomography (CT) of the thorax with contrast showed left lower lobe consolidation and left pleural effusion. Thoracocentesis by ultrasound guided pigtail insertion was performed for the persistent pleural effusion, which turned out to be exudative with negative culture and did not re-accumulate after drainage.

There was an incidental finding of abnormal coagulation before thoracocentesis with APTT 64 second (normal range 24-35 sec), PT 15.4 second (10-13 sec), INR 1.2, D-dimer 3385 ng/ml FEU (normal <500) and platelet count $122 \times 10^9/L$. Further blood tests showed anti-cardiolipin antibody IgG isotypes (aPL) >80 GPL units, lupus anticoagulant positive, but anti-nuclear antibody, rheumatoid factor, ESR, C3 and clotting factors including factor VIII, IX, XI and XII were normal.

He was followed up regularly after discharge and was asymptomatic until current admission, when he complained of sudden onset of progressive shortness of breath for one week. There was mild chest discomfort with no fever or flu

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symptoms. He had no palpitation, orthopnoea, paroxysmal nocturnal dyspnoea, recent trauma, cigarette or other illicit drug use. He was not on medications or herbs. Family history was unremarkable and there was no history of travel on plane or prolonged immobilisation. Physical examination on admission showed that his blood pressure was 125/80 mmHg and the heart rate was 100/min. The pulse was regular with normal volume. The apex was not displaced but there was a mild right ventricular impulse. Heart sounds were normal with no murmur. He was not in respiratory distress but mild crepitation was noted over the right lower lobe. Abdominal examination was unremarkable.

Chest radiograph showed mild peri-hilar haziness with pleural thickening at left lower lobe and no cardiomegaly. Blood test showed APTT of 82 second and the platelet count dropped to $32 \times 10^9/L$. WBC was $6.4 \times 10^9/L$ and the CRP and ESR were normal. He was treated as pneumonia with antibiotics.

His blood pressure dropped suddenly to 78/43 mmHg 24 hours after admission with increased dyspnoea and chest discomfort. The saturation dropped to 90% in room air and the heart rate rose to 150/min. There was profuse sweating and hand tremor. Cardiovascular examination showed a forceful apex beat with strong right ventricular impulse. There was a grade 3/6 ejection systolic murmur over left sternal border. Liver was palpable 2 cm below the right costal margin and there was no calf tenderness.

Electrocardiography showed right ventricular strain with right bundle branch block (RBBB) and S1Q3T3 pattern (Figure 1). Chest radiograph showed cardiomegaly with right lower lobe haziness. Platelet count further dropped to $11 \times 10^9/L$ and troponin I raised to 1.75 ug/L (normal <0.5 ug/L) with D-dimer up to 8302 ng/ml FEU. Blood gas showed pH 7.35 with pCO_2 3.64 kPa. The creatinine level rose to 114 umol/L (normal <103). Echocardiography showed dilation of right atrium, right ventricle and main pulmonary artery with compressed left ventricle. There was severe tricuspid regurgitation and pulmonary regurgitation and the estimated systolic pulmonary pressure was 60 mmHg. CT thorax with contrast showed large luminal filling defects in both right and left pulmonary arteries with extension into the lobar arteries in both lungs indicative of extensive pulmonary embolism (Figures 2 & 3). A 2.5 cm peripheral consolidation was seen in right lower lobe compatible with pulmonary infarction. Subsequent lung perfusion scan showed multiple large segmental mismatched perfusion defects highly suggestive of pulmonary embolism. With all these findings, the diagnosis of massive pulmonary embolism in the background of antiphospholipid syndrome was established.

Patient was treated in intensive care unit with fluid resuscitation, oxygen and low molecular weight heparin (LMWH). His dyspnoea and hypotension persisted despite dobutamine infusion of 5 mcg/kg/min so one dose of recombinant tissue plasminogen activator, Alteplase

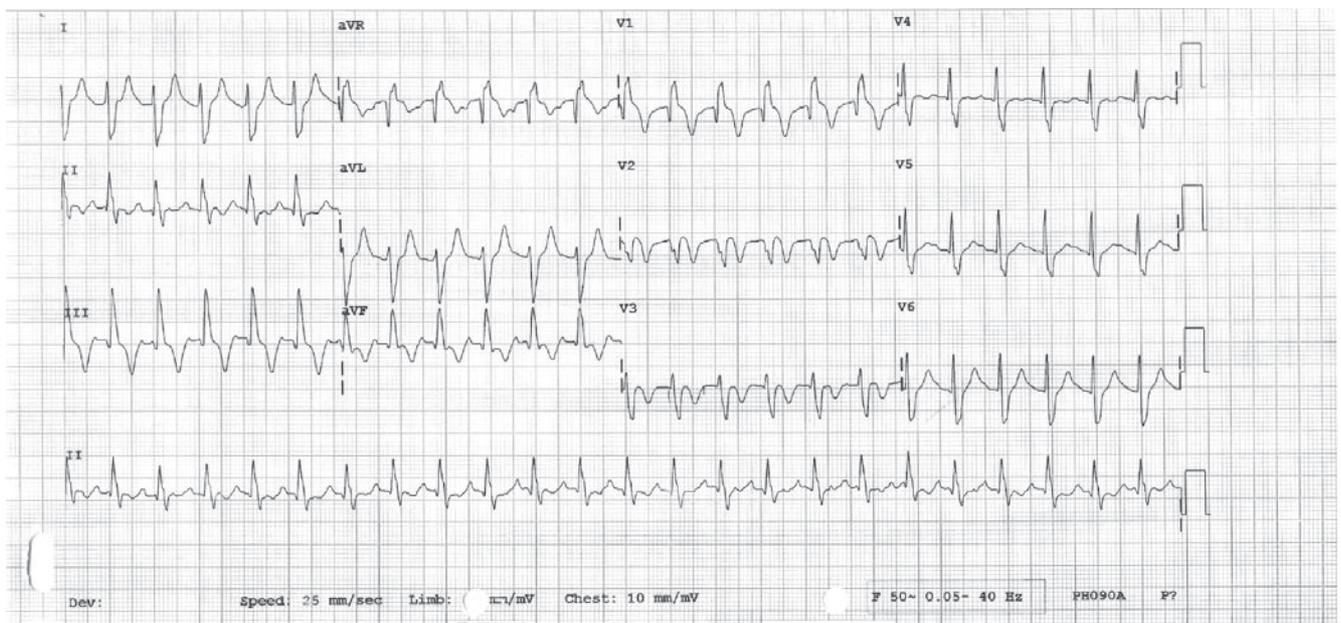


Figure 1 ECG during the attack of massive pulmonary embolism.



Figure 2 CT thorax showing thrombi in the left main pulmonary artery.

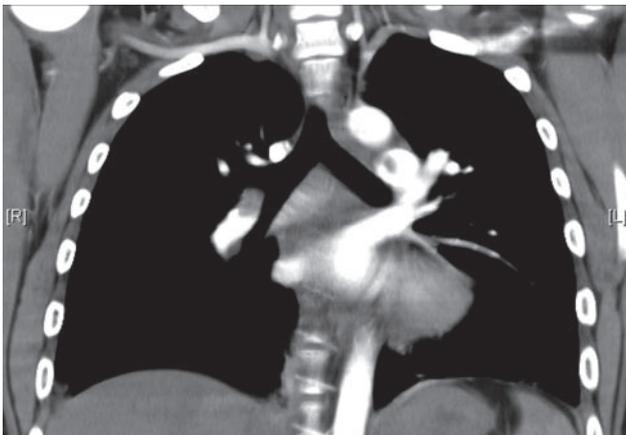


Figure 3 CT scan showing thrombi in the left main pulmonary artery.

100 mg, was given after platelet transfusion. His condition improved rapidly in the next 12 hours. Inotropic support and oxygen was stopped 20 hours later with creatinine and troponin I level returning to normal. LMWH was changed to warfarin and serial electrocardiogram and echocardiogram showed normalisation of right heart function.

Doppler ultrasound of both lower limbs was normal. Blood tests for other prothrombotic disorders including the protein C, protein S and antithrombin III level were normal. He was discharged with long term anticoagulant therapy (warfarin with target INR 2-2.5) and follow up CT thorax 4 weeks later showing disappearance of the thrombus.

Discussions

Antiphospholipid syndrome (APS), the underlying disease causing the massive pulmonary embolism in our patient, is an acquired autoimmune disease characterised by persistent presence of aPLs and thrombosis and/or pregnancy morbidity. The 2006 revised version of the APS Sapporo Criteria is a more stringent diagnostic criteria for the diagnosis of this heterogeneous group of patients and only 59% of those meeting the Sapporo criteria met the new criteria for the diagnosis of APS.¹ Cerebrovascular disease including sinus vein thrombosis and ischaemic stroke was present in 32% of patients in the Ped-APS registry, which is significantly higher than reported in adults (16-21%). Common nonthrombotic events include haematological manifestation (39%), skin disorders (25%) and nonthrombotic neurological disease (16%). Those APS associated with underlying autoimmune disease showed a significantly higher frequency of haematological and skin disease than primary APS and the most common associated underlying condition is systemic lupus erythematosus (SLE).²

The incidence of venous thromboembolism (VTE) in Chinese population was not as high as those in Caucasian^{3,4} but it was increasing,³ probably because of the shifting to the western diet of the Chinese people nowadays and most of the cases of PE presented as mortality cases in the past. In children, the establishment of the central registry in both Canada and Netherlands had provided data on the incidence of PE in children, which was reported as 0.14 per 100,000 children in the Canadian registry each year.^{5,6} It was probably an underestimation because of the high mortality rate, the clinically silent PE and probably some presented with symptoms that could be explained by the primary disease. There is insufficient data for the incidence of massive PE. In adult, 4.2% of the PE cases were massive PE cases.⁷

About the etiologies and risk factors of pulmonary embolism, the Canadian registry showed that risk factors were present in 96% of all patients with deep vein thromboembolism / PE and 90% had 2 or more. Of the 69 reported pulmonary emboli, 39 were associated with central venous catheters. The top 5 predisposing factors were central venous catheter (60%), malignancy (25%), cardiac surgery (19%), other major surgery (15%) and infection (12%). The Netherland study showed similar results but the most prevalent risk factor was infection (46%) in their study. Other factors include congenital prothrombotic disorder, acquired prothrombotic disorder e.g. nephrotic

syndrome leading to antithrombin III deficiency, oral contraceptive pills.⁸ Antiphospholipid syndrome only accounted for a minority of the cases in the Registry.

Different risk stratification protocol had been developed in the adult population as a diagnostic aid to the clinicians e.g. the Revised Geneva Score,⁹ the Wells score and different guidelines e.g. the British Thoracic Society guidelines for the management of suspected PE.¹⁰ Patients were classified into low, intermediate and high probability groups in adults with suspected PE and different recommendations were made for each group respectively.

Such stratification was needed due to the non-specific presentation, the variable availability of CT scan in different parts of the world, the relatively high radiation exposure of the CT pulmonary angiography and the high mortality rate of the disease. The average whole body radiation dose of the MDCT range from 2-19 mSv and it causes significant breast radiation of at least 20 mGy. The Biological Effects of Ionizing Radiation, seventh report (BEEIR VII) estimates that the lifetime attributable risk for breast cancer from a dose of 20 mGy is approximately 1 in 1200 for women aged 20, and 1 in 3500 for a woman aged 40.⁹ CT angiography is not without risk.

In paediatric population, these risk stratification protocols had not yet been validated and the predisposing factors to PE in children were different from those in adults. And suspected PE cases in children were much less common than in adult and these protocols should only be applied cautiously in the paediatric population.

The most common presentation of PE in children was sudden death. Apart from that, dyspnoea and hypoxemia were present in 7 out of the 8 cases reported by Baird et al.⁵ Pleuritic chest pain appeared to be the most common presenting complaint, mentioned in 84% of patients⁶ apart from dyspnoea (58%), cough (47%) and haemoptysis (32%).

The attack of shortness of breath of our patient in 2009 is a classical presentation of massive PE although not commonly seen in children. The pleural effusion that occurred in 2007 was diagnosed as parapneumonic pleural effusion because of the raised cold agglutinin but there was a possibility that it was a false positive result. Unfortunately, mycoplasma PCR test was not available in our hospital in 2007 and the pleural effusion subsided after thoracentesis. With raised D-dimer, slighted decreased platelet count and the presence of anti-cardiolipin antibody and lupus anticoagulant, it could well be the result of a milder pulmonary embolism, which resolved with supportive

treatment. If PE was confirmed during that episode and Antiphospholipid syndrome was diagnosed, anticoagulant like warfarin could have prevented the latter life-threatening massive PE.

D-dimer had always been one of the diagnostic tools in thromboembolic diseases. But the specificity of an increased D-dimer level was reduced in patients with cancer, pregnant women and elderly patients.¹¹ And its use is limited in patients with a high clinical probability of pulmonary embolism. Troponin-I was commonly used as a risk stratification tool for haemodynamically stable suspected PE cases and helped to identify the subgroup of PE patients who had a particularly high risk for adverse outcome. PE patients with elevated troponin level had an increased risk of death from PE by a factor of 9.4.¹¹

Pleural fluid secondary to pulmonary embolism could be transudate or exudate and the concept had been challenged by some studies.¹² It had been reported that the PE related pleural effusion were more likely exudative in nature probably related to increased permeability of the capillaries in the lung due to the release of cytokines or inflammatory mediators (e.g. vascular endothelial growth factor) from the platelet-rich thrombi. The excessive interstitial lung fluid traversed the visceral pleura and accumulated into the pleural space.¹² Clinicians should have a high level of alertness and consider the diagnosis of pulmonary embolism especially in patients with small unilateral exudative pleural effusion with no identifiable infective cause.¹²

Pulmonary embolism is one of the common causes of pleural effusion, which occurs in 20-50% of patients with pulmonary embolism. Worsley et al reviewed the chest radiographs of 383 patients in the PIOPED I study with angiographically proven pulmonary emboli and reported that 36% had pleural effusion.¹³ Porcel et al found that in 230 PE patients, pleural effusion secondary to PE was usually unilateral and small (occupied less than 1/3 of the hemi thorax) and only 11% of them were found to be bilateral.¹² Loculated pleural effusion was also reported in pleural effusion secondary to PE.

CT thorax pulmonary angiography (CTPA) was regarded as the single first line test in the diagnosis of PE because of its high diagnostic accuracy and ability to provide alternate diagnosis for disease of the lung parenchyma and other surrounding structures.¹⁴ Multidetector CT (MDCT) had several advantages over single detector CT (SDCT) in the diagnosis of PE, which included improved z-axis resolution (allow rapid acquisition of large volumetric datasets over a

greater craniocaudal distance than SDCT), shorter scan times (meaning less artifact related to breathing motion) and reduction in volume of contrast and the ability to do a combined CTPA/CT venography examination at the same setting with a single bolus of contrast.¹⁴ It was recommended as the first line investigation in different guideline for patients with suspected PE.

In cases in which MDCT was not available or in patients with renal failure or contrast allergy, ventilation-perfusion scan (VQ scan) was an alternative. A normal VQ scan essentially ruled out pulmonary embolism with a negative predictive value of 97%¹⁵ while a scan with findings that suggested a high probability of PE had a positive predictive value of 85-90%. However, VQ scan was diagnostic only in 30-50% of suspected PE cases.

Echocardiography was another useful tool to look for the presence of right ventricular dysfunction and transesophageal echocardiography might confirm the diagnosis by showing emboli in the main pulmonary arteries. For those that transport was unsafe, thrombolytic therapy should be considered if there are unequivocal signs of right ventricular overload on echocardiography.³

In the PIOPED III trial, magnetic resonance angiography was recently shown to have insufficient sensitivity and a high rate of technically inadequate images when used for the diagnosis of PE and was not recommended.¹⁶

Low molecular weight heparin had been proven to have a similar efficacy and safety profile to the unfractionated heparin.¹⁷ And apart from anticoagulation, thrombolysis and embolectomy were the recommended therapy for massive PE cases. A dose of alteplase, the recombinant tissue plasminogen activator (tPA) was given to our patient when there was no improvement after heparinisation. The US Drug and Food Administration recommended a dosage of 100 mg given intravenously over 2 hours for patients with massive PE. Our patient demonstrated favorable outcome and was free from any bleeding complications. Unlike streptokinase, alteplase did not cause hypotension and its adverse effect included cardiac dysrhythmia, reperfusion injury, cholesterol embolus syndrome, and gastrointestinal or intracranial haemorrhage. The risk of intracranial haemorrhage was reported to be 1-2% while other reported bleeding complications were as high as 40% of those treated with tPa. Wang et al was able to demonstrate in their randomised multicenter controlled trial in China that half dose of alteplase i.e. 50 mg over 2 hours was as effective as the 100 mg dose regimen and perhaps a better safety profile in the recipients, especially those with lower body weight.

Dose reduction could be a safer way to give life-saving tPA to many patients.¹⁸ If cardiac arrest occur while patient was in hospital and massive PE was strongly suspected clinically, an immediate intravenous bolus of 50 mg alteplase during cardiopulmonary resuscitation might be life saving.¹⁰

Conclusion

We reported an uncommon case of massive pulmonary embolism in a Chinese boy who survived without major complications. The use of aggressive thrombolytic therapy, although not free from complications, could be life saving in massive PE patients. The incidence of PE or massive PE would be increasing in the Chinese population in view of the rapid modernisation of the society and clinicians should be aware of this rare possibility when treating patients with sudden onset of dyspnoea and chest discomfort.

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