Tohoku J. Exp. Med., 2019, **248**, 137-141

# Asthma Exacerbation Coincident with Saddle Pulmonary Embolism and Paradoxical Embolism

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Saddle pulmonary embolism (PE) and paradoxical embolism (PDE) are life-threatening disorders carrying a risk of sudden death, and their prompt diagnosis is extremely important. Saddle PE is a radiologic definition and refers to a thrombus that straddles the bifurcation of the pulmonary artery trunk, carrying a risk of sudden hemodynamic collapse. PDE is defined as a systemic arterial embolus due to the passage of a venous thrombus though a right-to-left shunt, such as patent foramen ovale (PFO). We herein present the rare case of asthma exacerbation coincident with saddle PE and PDE. A 69-year-old woman with asthma was suffering from dyspnea, pulse attenuation of the left radial artery and left upper limb pain. An arterial blood gas analysis revealed hypoxemia, and a pulmonary function test demonstrated an obstructive pattern. Enhanced computed tomography (CT) revealed saddle PE, right popliteal venous thrombosis, and left brachial artery occlusion. After the treatment with edoxaban, an anticoagulant, and aspirin, the PE was significantly alleviated, and the brachial artery occlusion was recanalized. Subsequently, the right-to-left shunt through PFO was confirmed, and PDE was suspected of inducting her brachial artery embolism. In the present case, the pulse attenuation of the radial artery and upper limb pain prompted us to consider peripheral vascular disease or coagulation disorders. Physicians should keep in mind that patients with asthma are at considerable risk of PE, and it is important to be aware of possible PFO in patients presenting with the coexistence of PE and systemic arterial embolism.

**Keywords:** anticoagulant therapy; asthma exacerbation; brachial artery embolism; paradoxical embolism; saddle pulmonary embolism

Tohoku J. Exp. Med., 2019 June, **248** (2), 137-141. 

## Introduction

Asthma exacerbation is an acute or subacute episode of progressive worsening of symptoms, including shortness of breath, wheezing, cough, and chest tightness. The symptoms in patients with asthma exacerbation are similar to those with pulmonary embolism (PE). PE may therefore be misdiagnosed as asthma exacerbation in cases with symptoms such as dyspnea or chest pain. Saddle PE is defined as visible thromboembolism straddling the bifurcation of the pulmonary artery trunk, often with extension into both the right and left main pulmonary arteries (Gandara et al. 2011). The accurate diagnosis of saddle PE is critical, because it signals an unstable, large clot burden in the pulmonary artery and the possibility of sudden hemodynamic collapse.

Paradoxical embolism (PDE) is a rare cause of arterial embolism involving the passage of thrombi from the venous circulation into the systemic arterial circulation through a right-to-left cardiac shunt. This disorder is estimated to account for 2% of arterial emboli (Mirarchi et al. 2000) but can have catastrophic outcomes, with a reported early mortality rate of 21% (Aboyans et al. 1998). The clinical presentation is diverse and potentially life-threatening. Although the serious nature and complications of PDE are recognized, the disease entity is still rarely considered and remains under-reported (Windecker et al. 2014).

Patent foramen ovale (PFO) produces the intermittent intra-atrial right-to-left shunt and occurs in approximately 25% of the general population. Although the vast majority of people with PFO are asymptomatic, a few exhibit a variety of clinical manifestations, including systemic embolism, stroke, migraine headache, decompression sickness, high-altitude pulmonary edema, and platypnea-orthodeoxia syndrome (Kedia et al. 2008). Systemic embolism can occur in association with deep vein thrombosis and pulmonary

Received March 26, 2019; revised and accepted June 18, 2019. Published online June 27, 2019; doi: 10.1620/tjem.248.137.

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embolism, if the right atrial pressure rise, subsequently opening up the channel of the PFO (Wilmshurst and de Belder 1994).

We herein report a patient diagnosed with asthma exacerbation accompanied by saddle PE and brachial artery occlusion due to PDE.

## Case Report

A 69-year-old woman with asthma was suffering from dyspnea and left upper limb pain 10 days before admission. The patient had noticed a cough 12 months before admission, and she had been diagnosed with bronchial asthma and started on budesonide/formoterol inhalation treatment three months before admission. She was not receiving any medications other than budesonide/formoterol inhalation. Her adherence to inhalation treatment and control of her symptoms were good. She had a history of hyperlipidemia and had undergone surgery for maxillary sinusitis. She had been using non-steroidal anti-inflammatory drugs (NSAIDs) to relieve transient headache but had not experienced asthma flare. She had no history of thromboembolism, ischemic heart disease, or cerebellar infarction. She was a never-smoker, and her daily routine included 30 minutes of jogging for weight management.

Her height was 145 cm, body weight 56.5 kg, and body mass index 26.9. Her body temperature was 36.8℃, blood pressure 144/96 mmHg, and pulse 84 beats/min. She had no cardiac murmurs, and her lungs were clear on auscultation. The pulse pressure of the radial artery was faint. An arterial blood gas analysis revealed pH of 7.455, partial pressure of arterial oxygen ($PaO_2$) of 68.5 mmHg, and partial pressure of arterial carbon dioxide ($PaCO_2$) of 32 mmHg at room air. The results of laboratory tests showed elevated white blood cell counts (10,010/$\mu$L) and a high level of C-reactive protein (1.02 mg/dL) as well as hyperlipidemia (total cholesterol; 287 mg/dl and triglycerides; 155 mg/dl). Pulmonary function tests showed an obstructive pattern: forced expiratory volume in 1 second ($FEV_1$) of 1.39 L (83.2%), forced vital capacity (FVC) of 2.15 L (103.4% predicted), $FEV_1$/FVC ratio (FEV1%) of 64.7%, and peak flow (PEF) of 3.50 L/sec (52.6% predicted). The fractional concentration of exhaled nitric oxide (FeNO) level was 37 ppb. Her clinical symptoms and results of pulmonary function tests were consistent with asthma exacerbation according to the Global Initiative for Asthma (GINA) guideline; however, her left upper limb pain and faint radial artery pressure were inconsistent with asthma exacerbation. Thus, the comorbidity of peripheral arterial occlusive disease was suspected.

The D-dimer and fibrinogen degradation product levels were increased at 8.47 mg/dL and 21.2 $\mu$g/mL respectively, whereas the prothrombin time and activated partial thromboplastin time were within their respective normal ranges. The value of the tricuspid regurgitation peak gradient (PRPG) on echocardiography was 47 mmHg, which indicated pulmonary hypertension. Although enhanced computed tomography (CT) is not recommended for asthmatic patients, it was performed under corticosteroid prophylaxis. Enhanced high-resolution CT (HRCT) revealed massive PE, including filling defects in the lower lobe pulmonary arteries of both lungs extending into the segmental branches, filling defects in right upper lobe pulmonary arteries, and a saddle embolus. Right popliteal vein thrombosis was found, and the left brachial artery was not delineated (Fig. 1). Perfusion scintigraphy revealed a perfusion defect of the right S8 and the decreased perfusion of the right S3, left lingula, and part of the left S6. Comorbidities of saddle PE, right deep venous thrombosis and left brachial artery occlusion were detected. Thrombotic and vasculopathy work-up revealed negative findings for lupus anticoagulant and anti-cardiolipin IgG antibody. The protein S and protein C activities were within the normal limits.

On admission, repeated short-acting beta agonist inhalation treatment was attempted due to suspected asthmatic exacerbation, but her dyspnea was not improved immediately and the hypoxemia continued for a few days. Intravenous heparin followed by switching to direct oral anticoagulant (30 mg of Edoxaban) was therefore started. The massive emboli located at the bifurcation of the pulmonary artery trunk and both the right and left main pulmonary arteries were disappeared, but the occlusion at part of the segmental pulmonary arteries and the left brachial artery remained on hospital day 17. Subsequently, an antiplatelet agent (100 mg of aspirin) was added. Recanalization of the segmental pulmonary arteries and left brachial artery was observed eight weeks after starting treatment (Fig. 2). Subsequently, transesophageal echocardiography was performed, and the presence of PFO with the right-to-left shunt during the Valsalva maneuver was confirmed. Inhalation treatment was continued after the diagnosis of thromboembolism, and her adherence to the inhalation treatment has been good. The patient is currently asymptomatic.

## Discussion

Asthma exacerbation represents as acute or subacute episodes, characterized by a progressive increase in one or more typical asthma symptoms (dyspnea, coughing, wheezing and tightness of the chest) accompanied by a decrease in the expiratory flow (PEF or $FEV_1$). It is important to make a quick initial assessment and initiate treatment without delay. PE is one of the differential diagnoses, and pulmonary CT angiography has been established as a fast and reliable means of excluding or diagnosing PE. However, patients with asthma are at an increased risk of a moderate to severe anaphylactoid reaction from intravenous contrast media (Lang et al. 1991). In the present case, uncommon symptoms of asthma, such as upper limb pain and faint radial artery pressure suggested comorbidity of peripheral arterial occlusive disease. We decided to perform contrast-enhanced CT for differentiation from vascular diseases, resulting in a diagnosis of saddle PE, right popliteal deep

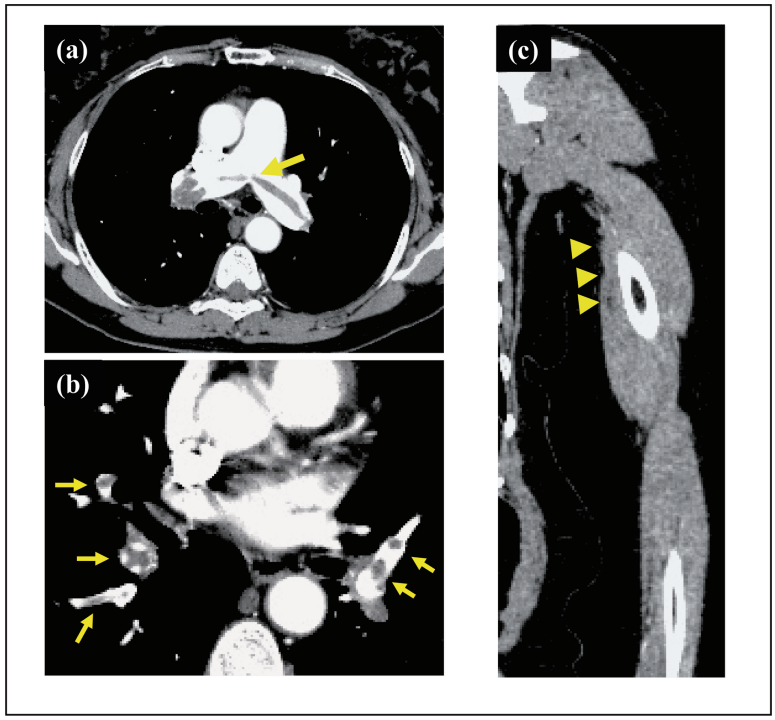


Fig. 1. Findings of enhanced high-resolution computed tomography (HRCT) on admission.
(a) The massive saddle embolus was located at the bifurcation of the main pulmonary artery (arrow). (b) Filling defects were found in the lower-lobe pulmonary arteries of both lungs, extending into the segmental branches (arrow). (c) The left brachial artery was not delineated. The arrowheads indicate the assumed route of the brachial artery.

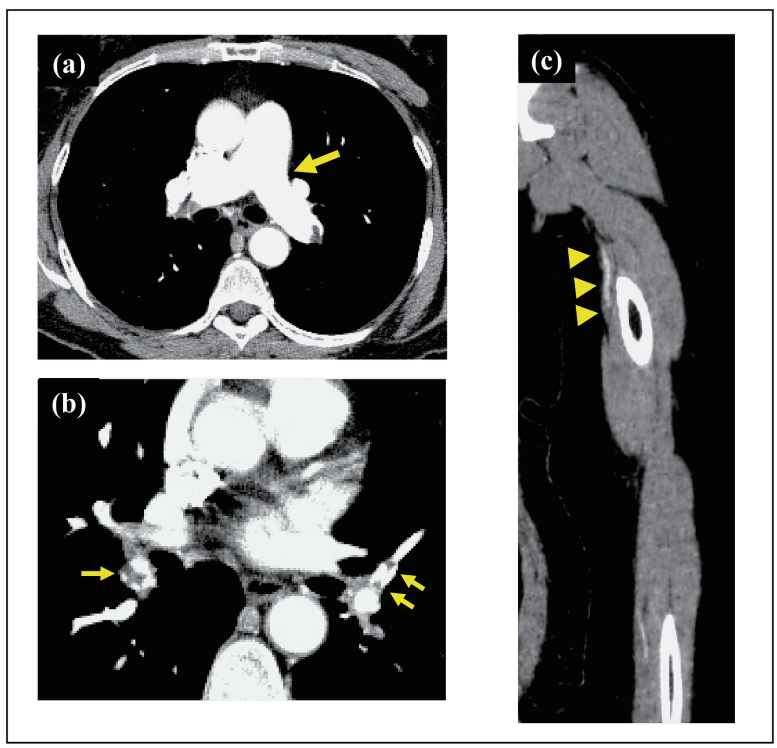


Fig. 2. Findings of enhanced HRCT at eight weeks after starting treatment.
(a) Saddle PE was disappeared (arrow). (b) The emboli in the lower-lobe pulmonary arteries of both lungs were shrunk (arrow). (c) Recanalization of the left brachial artery was noted (arrowhead).

venous thrombosis and left brachial artery occlusion due to PDE. To our knowledge, there have been no reports of patients with asthma exacerbation who had comorbidities of saddle PE and brachial artery embolism due to PDE.

Several reports have shown that the risk of developing PE is significantly increased in asthmatic patients compared to the general population (Majoor et al. 2013; Chung et al. 2014; Zoller et al. 2017). PE has a wide variety of presenting features, ranging from no symptoms to shock or sudden death but the most common symptom is dyspnea followed by chest pain and cough. Furthermore, almost 1 in 10 patients presenting with PE demonstrate wheezing on an examination (Calvo-Romero et al. 2003). It is therefore important to take a patient's history. Important points to address when assessing the history of asthma exacerbation are the extent and duration of exacerbation, recent treatment and steroid use, history of hospitalization and intubation and history of aspirin-exacerbated respiratory disease (AERD) or other complications, including drug allergy, cardiac disease, pneumothorax, and PE (Ichinose et al. 2017). According to PE, the important points of a medical interview are to identify any recent surgery or trauma, and to ascertain a history of congestive heart failure, chronic lung disease, prior venous thromboembolism, or cancer (Kucher and Goldhaber 2005).

Saddle PE is quite rare, accounting for only 2.6%-5.2% of cases of acute PE (Pruszczyk et al. 2003; Ryu et al. 2007). Physicians should be alert for saddle PE, as acute large or multiple PE are more likely than small and peripheral emboli to cause hemodynamic consequences of right ventricular dysfunction, left ventricular failure, and hemodynamic collapse (Weinberg and Jaff 2013) and saddle PE has a 2-week mortality risk of 5.8% (Goldhaber 2002). However, Enzweiler et al. (2002) performed a short-term evaluation of 12 patients with saddle PE, and found that the thromboembolus was resolved in 4 patients and thinning of the embolus at the bifurcation was noted in the remaining 8 patients. In the present case, the massive emboli located at the bifurcation of the pulmonary artery trunk and main pulmonary arteries were disappeared by hospital day 17. Although saddle PE is life-threatening, its early diagnosis and thus the early implementation of anticoagulant therapy can lead to a substantial reduction in subsequent mortality and morbidity.

In patients with hemodynamic stability like the present case, the diagnosis of PE should follow a sequential diagnostic workup consisting of a clinical probability assessment, D-dimer testing, and multidetector CT or ventilation-perfusion scanning (Agnelli and Becattini 2010). Le Gal et al. (2006) found that, if venous ultrasonography of the lower limbs confirms deep-vein thrombosis, lung scanning and multidetector CT can be avoided, and anticoagulant treatment can be started without further testing. However, in patients with underlying disorders, such as chronic pulmonary diseases, heart diseases, and malignancy, the comorbidity of PE can be underestimated due to similarities in clinical episodes among these entities. Circulating levels of D-dimer are a useful diagnostic parameters, but the specificity of an increased D-dimer level is reduced in patients with cancer, pregnant women, and hospitalized and elderly patients (Bruinstroop et al. 2009). A ventilation-perfusion scan is a viable alternative to enhanced CT in patients with renal failure or allergy to contrast dye, but its findings are diagnostic only in 30% to 50% of patients with suspected PE (Anderson et al. 2007). Enhanced-CT, which is associated with a risk of adverse events due to allergies, would be required for confirming the comorbidity with PE during the disease course of bronchial asthma, when either an echocardiogram or a ventilation-perfusion scan does not demonstrate the presence of PE.

Brachial artery occlusion only accounts for approximately 12% of cases of symptomatic upper limb ischemia (Pride et al. 2007). Acute brachial artery occlusion is most often the result of embolism but may result from thrombosis due to trauma or localized arteriosclerosis (Rossi et al. 1965), and atrial fibrillation is thought to cause 80% of cases of arterial embolic occlusion (Haimovici 1982). In contrast, PDE is recognized as the clinical phenomenon of thromboembolism originating in the venous vasculature and traversing through the intracardiac or pulmonary shunt into the systemic circulation (Tompson and Evans 1930). PDE may have an insidious onset with mild symptomatology, which renders it liable to a misdiagnosis. PFO has been demonstrated to be a significant risk factor for PDE (Foster et al. 2003). Konstantinides et al. (1998) showed that the right-to-left shunt through PFO is an independent predictor of an adverse outcome in patients with acute major PE. It is therefore important not to overlook the possibility of PFO in patients presenting with the coexistence of pulmonary and paradoxical systemic arterial embolism (Maffe et al. 2008).

The relationship between bronchial asthma and PE is complex. In patients with asthma with tachypnea and hypoxemia, dehydration of the body may occur, resulting in a likely increase in the development of PE. Furthermore, inflammation due to acute exacerbation may alter the balance between procoagulant and fibrinolytic activities, as inflammation and coagulation stimulate each other (Chung et al. 2014). In patients with acute pulmonary embolism, bronchoconstriction is a common complication, while audible wheezing is uncommon. The local release of various mediators of bronchoconstriction, such as thromboxane, prostaglandins, serotonin and histamine, has been postulated to cause bronchoconstriction, as these mediators are released with platelet aggregation during blood clotting (Braman and Davis 1986). In the present case, it was difficult to determine whether the cause of dyspnea is due to slow-onset asthma exacerbation or underling pulmonary embolism. Both factors may act additively to exacerbate the progression of dyspnea.

In conclusion, saddle PE is a rare but life-threatening entity presenting as a potentially large, unstable clot associ-

ated with hemodynamic collapse. Furthermore, the diagnosis of PDE is often difficult owing to multisystemic involvement, and the condition is associated with a high fatality rate in the absence of specific treatment (Windecker et al. 2014). Physicians should keep in mind that saddle PE can develop during the disease course of bronchial asthma, and it is important to be aware of possible PFO in patients presenting with the coexistence of PE and systemic arterial embolism.

## Conflict of Interest

The authors declare no conflict of interest.

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