

Misdiagnosis of pulmonary embolism in patients with allergic reaction – the importance of prior probability of disease

Karin Janata¹, Mathias Prokop², Cornelia Schaefer-Prokop², and Anton N. Laggner¹

¹Department of Emergency Medicine and ²Department of Radiology, Vienna General Hospital, University of Vienna, Vienna, Austria

Fehldiagnose einer Pulmonalembolie bei Patienten mit allergischer Reaktion – die Wichtigkeit der klinischen Vortestwahrscheinlichkeit

Zusammenfassung. Die akute Pulmonalembolie ist eine Erkrankung mit hoher Mortalität, jedoch auch ihre Behandlungsmethoden sind mit erheblichen Risiken behaftet, eine eindeutige Diagnose ist daher entscheidend. Wir berichten von 2 Patienten mit allergischer Reaktion bei welchen Routine-EKG und D-Dimer den Verdacht auf Pulmonalembolie aufkommen ließen, der schließlich durch ein Spiral-CT erhärtet wurde. Die Patienten wurden heparinisiert und eine Langzeitantikoagulation in Erwägung gezogen. Da sich in der Anamnese der Patienten keine prädisponierenden Faktoren für eine Pulmonalembolie fanden, wurden die Krankengeschichten mit folgenden Ergebnissen reevaluiert: das erhöhte D-Dimer wurde nun auf die allergische Reaktion zurückgeführt, das EKG als konstitutionell pathologisch und die ursprünglichen Hinweise auf Pulmonalembolie im Spiral-CT als Atemartefakte und Partialvolumeneffekte interpretiert. Die ursprüngliche Diagnose eine Pulmonalembolie wurde widerrufen und die Antikoagulation ohne weitere Folgen abgesetzt.

Der Verlauf dieser Fälle zeigt die Bedeutung der Festlegung der klinischen Wahrscheinlichkeit für das Vorliegen einer Pulmonalembolie vor weiteren diagnostischen Tests, sowie der Notwendigkeit einer kritischen Interpretation von Befunden in Bezug auf die erhobene klinischen Vortestwahrscheinlichkeit.

Schlüsselwörter: Pulmonalembolie, allergische Reaktion, Vortestwahrscheinlichkeit, D-Dimer, Spiral-CT.

Summary. Because pulmonary embolism (PE) and its treatment carry substantial risk of morbidity and mortality, accurate diagnosis is essential. We report two cases with allergic reactions, in which PE was suggested by routine ECG and D-dimer elevation and strengthened by spiral CT. Therapy with low-molecular-weight heparin was initiated and long-term anticoagulation was considered. As their histories did not reveal any predisposing factor to PE, the cases were re-evaluated. Elevation of D-dimer was now attributed to allergic reaction, ECG abnormali-

ties were considered as constitutional, and findings from spiral CT attributed to breathing artifacts and partial-volume effects. The diagnosis of PE was therefore rejected and anticoagulant treatment discontinued without sequelae. These cases show the importance of determining clinical probability before ordering further diagnostic tests and critical interpretation of test results suggestive of PE, based on prior probability of the disease.

Key words: Pulmonary embolism, allergic reaction, pretest probability, D-dimer, spiral CT.

Introduction

Both pulmonary embolism (PE) and its treatment carry substantial risk of morbidity and mortality, therefore a consistent approach to evaluation is desirable [1]. Recently proposed diagnostic algorithms for PE include clinical evaluation, D-dimer determination, and spiral CT [1–3].

We report two patients with allergic reactions, in whom the suspicion of PE was generated by a positive D-dimer test and electrocardiographic signs of right ventricular strain. Despite the fact that the patients' history made the diagnosis of PE unlikely, spiral CT investigation was prompted. Findings from spiral CT strengthened the diagnosis of PE and the patients were put on anticoagulants.

Case 1

A 62-year-old woman was transferred to our emergency department (ED) by the local EMS helicopter because of an allergic reaction due to a bumble bee sting to her right shoulder. She complained of nausea, vomiting and paresthesia in both arms. The emergency physician administered epinephrine, H1-blockers, methyl-prednisolone, and Ringers lactate.

On admission the patient was already free from subjective symptoms and stable (pulse 96/min, non-invasive oscillometric blood pressure 140/80 mmHg, respiratory rate 15/min, pulse oximetry 96%). The skin of the face and upper thorax was flushed. Clinical examination revealed no other abnormalities. History of this patient was uneventful despite insulin-dependent diabetes for the last three years and known allergies to penicillin and insect stings.

Laboratory examinations were normal except for elevated D-dimer values (20.80 µg/dl, normal <0.5 µg/dl, Data-Fi Dimer

Test Latex Assay, American Dade, Miami, FL, USA). ECG showed sinus rhythm, a heart rate of 101/min, PR time 0.16 s and a complete right bundle branch block with S in lead I and Q in III. Electrocardiographic signs of right ventricular overload together with the D-dimer values raised the suspicion of PE and a spiral CT was ordered.

Spiral CT was performed on a standard single-slice spiral CT scanner (Philips Tomoscan AV-E; Philips Medical Systems, Best, NL) with 1 s tube rotation. We used 3 mm slice collimation, a table feed of 5 mm per rotation, and a 2 mm image reconstruction interval. Nonionic contrast material (140 ml) was injected at a flow rate of 3 ml/s and a fixed start delay of 20 s between the beginning of contrast injection and the beginning of the spiral scan. Spiral CT findings indicated PE in the left main pulmonary artery and left upper-lobe main artery (Fig. 1a). Anticoagulant treatment was initiated and long-term anticoagulation was considered.

As the history of the patient revealed no predisposing factor and made the probability of PE unlikely, the reliability of the diagnostic tests was re-evaluated. This time, elevation of D-dimer was attributed to the allergic reaction, and ECG findings were considered to be constitutional, as transthoracic echocardiography was normal. Re-evaluation of spiral CT (by M.P.) revealed that diagnosis of PE was falsely positive. The suspected emboli had been simulated by partial volume averaging between contrast-enhanced vessels and adjacent lung parenchyma and a bronchopulmonary lymph node (Fig. 1b).

Diagnosis of PE was rejected and anticoagulant therapy discontinued. The patient was discharged without sequelae.

Case 2

A 43-year-old woman attended our ED complaining of respiratory distress, pruritus and generalized urticaria. Five days previously she had chills, dyspnea, diarrhea and rhinitis. Four days ago urticaria developed and the family physician prescribed corticosteroids and H1-blockers, which did not lead to complete remission.

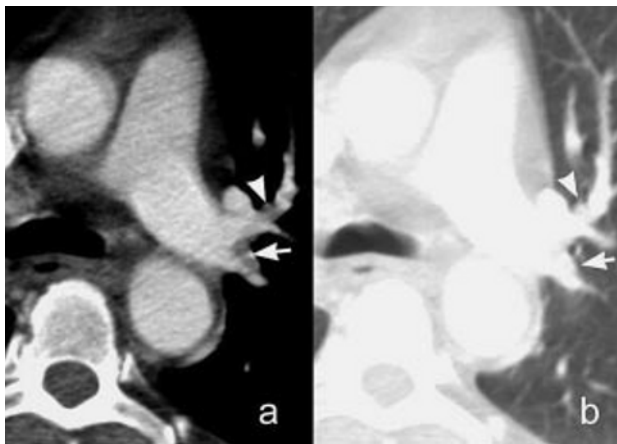


Fig. 1. Emboli were suspected in the anterior segment (arrowhead) and in the posterioapical segment (arrow) of the left upper lobe (a). In the lung window setting (b), the vessels can be seen to decrease in density because they take a curved course, partially leaving the scan plane, and are thus subject to partial volume effects (arrowheads). In addition there is an indentation identifying the suspected embolus in the posterioapical segment as a bronchopulmonary lymph node (arrow)

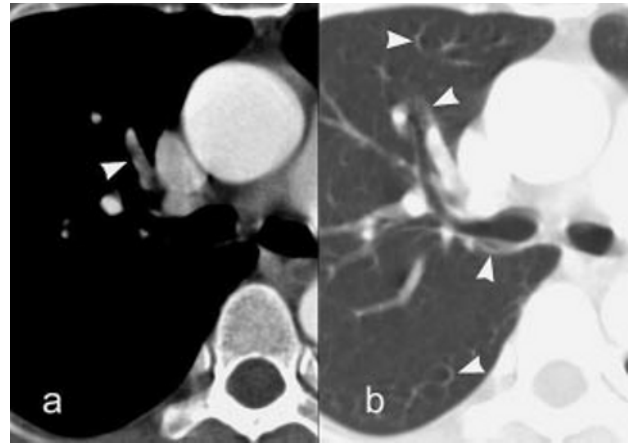


Fig. 2. An embolus was suspected in the anterior segment of the right upper lobe (arrowhead, a). In the lung window setting, the decrease in intraluminal density could be attributed to typical breathing artifacts that are characterized by double contours, blurring of vessel interfaces and hypodense areas close to peripheral vessels (arrowheads, b)

On admission the patient was stable (pulse 91/min, non-invasive oscillometric blood pressure 135/80 mmHg, respiratory rate 14/min, pulse oximetry 97%). The skin was covered with generalized urticaria. Clinical examination revealed no other abnormalities. History of the patient was uneventful despite a known allergy to nickel. Laboratory examination revealed elevated values of leucocytes (20.5 G/l), C-reactive protein (1.2 mg/dl), and D-dimer (15.10 µg/dl, method as in case 1). ECG showed a sinus rhythm with a heart rate of 79/min, PR time 0.16 s and a slight right axis deviation. Respiratory symptoms, ECG changes, and elevated D-dimer raised suspicion of PE, and a spiral CT was performed using the same technique as above.

In this second patient also, spiral CT demonstrated PE in the right upper and lower-lobe pulmonary arteries (Fig. 2a). Anticoagulant treatment was initiated and long-term anticoagulation was planned.

Predisposing factors to PE were absent, therefore the diagnosis was reconsidered by a different consultant. This time, respiratory symptoms and elevation of D-dimer were attributed to the allergic reaction. As transthoracic echocardiography did not demonstrate signs of right ventricular strain, ECG findings were interpreted as constitutional. Finally, re-evaluation of spiral CT (by M.P.) now rejected the diagnosis of PE. The suspected embolus had been caused by breathing artifacts that could be identified on lung window settings (Fig. 2b).

The initial diagnosis of PE was rejected in this patient also, and anticoagulant treatment stopped. The patient was discharged without any further event.

Discussion

PE has a wide range of clinical presentation, and a reasonable level of clinical suspicion is required to avoid missing the diagnosis [3]. Clinical assessment remains the cornerstone of diagnostic management of PE. Although almost one in two cases of PE occur in the absence of any classic predisposing factor, the history of the patient with respect to primary and secondary risk factors of PE is

essential [3]. For diagnosis of PE, individual clinical signs (e.g. tachypnea, tachycardia, swollen legs, fever and cyanosis) and symptoms (such as dyspnea, chest pain, cough, hemoptysis and syncope) are not very helpful as they are neither sensitive nor specific [3]. However, using a validated clinical score, the combination of risk factors and clinical signs and symptoms can be used to classify outpatients with suspected PE into three groups of clinical probability of the disease [4]. In our two patients, neither risk factors nor individual clinical signs were highly suggestive of PE, a fact that finally led to re-evaluation of the cases by a second physician. However, these patients presented with ECG and D-dimer findings that made diagnosis of PE possible.

ECG signs of right ventricular strain (S1Q3 pattern, inversion of T-waves in V1-V3, right bundle block, right axis deviation) are suggestive of PE. Usually these changes are associated with massive PE [5], but they may also occur constitutionally without any underlying cardiac disease. As echocardiography did not show any evidence of right ventricular strain, we had to interpret ECG abnormalities in these patients as constitutional.

D-dimer determination has a high negative predictive value and is therefore recommended for use in emergency wards mainly to rule out thromboembolic disease [1, 3]; the test may be used in primary screening or in combination with objective diagnostic imaging [6, 7]. However, a positive D-dimer test is not diagnostic for PE as a wide variety of conditions such as cancer, inflammation, infection, necrosis, and even in allergic reactions may test positive [3, 8–10]. It is not surprising that our patients, who presented with allergic reactions, had considerably elevated D-dimer values. Recent data suggest that simple clinical criteria can permit safe D-dimer testing in the majority of ED patients with suspected PE [11].

Spiral CT is widely accepted and often used, as it offers a non-invasive accurate diagnosis of PE. Although the negative predictive value of Spiral CT is still under debate, recently published literature indicates that we use it in most of our patients to confirm the diagnosis of PE [12, 13]. False positive findings are infrequent, resulting in a specificity ranging between 78% and 97% [2].

Various diagnostic pitfalls that can lead to false positive interpretation of CT scans have been identified [14, 15]. In particular, if a suspected embolus is only visible on a single section, the possibility of a partial volume or breathing artifact has to be taken into account, because most emboli are longer than 2mm and thus should appear on more than one image. Breathing during the scan alters the position of vessels and thus may lead to errors in the calculated CT numbers, which again may simulate the appearance of emboli. Although these pseudoemboli may look quite realistic (Fig. 2a) they can be distinguished from real emboli by close scrutiny of the same section using a lung window setting (Fig. 2b) and identifying the typical blurring and double contours associated with breathing. These artifacts are easy to identify but may still lead to erroneous interpretation. In our two patients, re-evaluation by an experienced radiologist led to identification of these artifacts and to rejection of the diagnosis of PE.

These two cases again underline the importance of clinical assessment and estimation of likelihood of PE.

Clinicians should not forget that the prior probability greatly influences the posterior probability that PE is present. A positive CT scan, coupled with a low pretest probability of PE, does not rule in the disease; a negative CT scan with a moderate-to-high prior probability does not rule it out [16]. In such cases of discrepancy between clinical likelihood and objective tests we should always consider further diagnostic procedures to guarantee safe therapeutic management.

Conclusion

Accurate diagnosis of PE is essential, as both missing the diagnosis and instituting inappropriate therapy are associated with increased morbidity and mortality. However, diagnosis of pulmonary embolism is still a challenge because many diagnostic tools are highly sensitive but lack specificity. Our cases reinforce the importance of estimating clinical likelihood before ordering further diagnostic tests in patients with suspected PE. In order to safely rule PE in or out, 'objective' tests have to be interpreted carefully in the context of clinical probability of the disease. As both false positive and false negative test results are common, clinicians should not forget their capability of accurately estimating the prior probability, the first and decisive step in the diagnostic algorithm of PE.

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Correspondence: Anton N. Laggner, Department of Emergency Medicine, Vienna General Hospital, University of Vienna, Währinger Gürtel 18–20, A-1090 Vienna, Austria,
E-mail: Anton.Laggner@AKH-Wien.ac.at

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