

SUBACUTE MASSIVE PULMONARY THROMBOEMBOLISM IN YOUNG PATIENTS: A COMPARATIVE PRESENTATION

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Abstract: Introduction: Subacute massive pulmonary embolism is a potentially fatal condition that can manifest in various clinical ways in a young patient, from mild and nonspecific to lethal. The incidence of pulmonary embolism in the younger population should not be overlooked, whether it involves individuals with certain risk factors, either genetic or acquired, or individuals with unidentified risk factors.

Case Presentation: We are presenting two young patients, aged 35 and 37, who had a protracted course of disease and clinical manifestations at least 15 days before admission. The first patient had nonspecific pains and sensations in the chest area and coughed up blood on two occasions. The day before admission, he had an intense one-hour swimming workout. The second patient had rapid fatigue and choking, which led to an echocardiogram of the heart and a treadmill test that was terminated at the second level due to poor condition, as stated by the patient himself. He came in due to intense pain in the epigastrium, preceded by a loss of consciousness. In both patients, a diagnosis of massive PTE was made: the first by Multi-Slice Computed Tomography of the pulmonary artery (MSCTPA) and the second by clinical autopsy. The first patient received thrombolytic therapy and was discharged with NO-ACs (Apixaban) after 10 days of hospitalization.

Conclusion: It is always necessary to keep in mind the possibility of PTE, even in younger patients and in cases with subtle clinical presentations, even without identified predisposing factors.

Keywords: pulmonary thromboembolism, subacute, massive, MSCTPA, risk factor, genetic, acquired, unidentified.

INTRODUCTION

Pulmonary Thromboembolism (PTE) is the foremost avoidable cause of mortality in patients admitted

to the hospital (1). Furthermore, it ranks as the third most common cause of cardiovascular-related deaths, following myocardial infarction and cerebrovascular accidents (strokes). Subacute massive PTE is defined as the onset of symptoms for 2-12 weeks and a pulmonary angiogram showing massive pulmonary embolism ($\geq 50\%$ obstruction in the main pulmonary arteries) (2). Idiopathic Venous Thromboembolism (VTE) is defined as “any VTE” in the absence of an identified predisposing factor (3).

The current literature review suggests that the frequency of PE in the younger population should not be overlooked, whether they are individuals with certain risk factors, either genetic or acquired, or individuals with unprovoked factors. A retrospective observational study following pulmonary embolism (PE) in the 18-45 age group across five years in a district general hospital revealed that 17.1% of patients had unprovoked disease (4). Treating unprovoked PE requires consideration for further investigation into potential disease etiology. The current review of the literature suggests that the incidence of PE in the younger population should not be overlooked, whether it involves individuals with certain risk factors, genetic or acquired, or individuals with unprovoked factors. In a 2007 study conducted by Sakuma and colleagues, an analysis of autopsy records revealed that Pulmonary Embolism (PE) was responsible for 2.3% of all fatalities within 20 to 39 years of age (5). Only 20% of PE detected at autopsies was diagnosed during life. The death rate for diagnosed and managed pulmonary embolism fluctuates between 3 and 8%. However, if left untreated, this rate can surge to roughly 30% (6). The wide range of clinical symptoms associated with this condition complicates its diagnosis. Additionally, treatment approaches can differ significantly, and the unpredictability of the outcomes leads to high rates of morbidity and mortality.

This article presents two young patients with distinct clinical manifestations of subacute massive PTE.

CASE REPORT No 1

A 35-year-old patient presented to the Emergency Center of the Clinical Center of Serbia (UCCS) due to nonspecific left-sided chest pain persisting for two weeks and coughing up blood-streaked sputum on two occasions. A chest X-ray conducted at the local Health Center exhibited a slight pathological finding (Figure 1), accompanied by an elevated CRP level of 41.8mg/l (cut-off 5), prompting referral to the UCCS Emergency Center.

The patient was hemodynamically and respiratory stable (blood pressure (BP) 130/70 mmHg, SpO₂ 98% on room air, heart rate 70/min, body mass index (BMI) 27.7 kg/m²), with a normal ECG (Figure 2A), normal heart sounds on auscultation, and reduced breath sounds over the left basis of the lung. A CT pulmonary angiogram was immediately performed, which revealed a massive thrombus at the bifurcation of the pulmonary artery with propagation into both

main, lobar, and segmental branches, along with a left-sided pleural effusion (9 mm thick), a ratio of Ao/pulmonary artery of 0.8 with slight reflux of contrast into the inferior vena cava (IVC) - signs of right heart strain (Figure 3).

The patient was admitted to the coronary intensive care unit, where an echocardiogram indicated severe pulmonary hypertension (with a floating thrombus at the pulmonary artery bifurcation and its right branch, RV diameter: 3.0 cm, AccT: 59 msec). Alteplaza was administered intravenously at 100mg, 50ml/h for 2h, as per protocol.

During hospitalization, laboratory analyses showed elevated D-dimer levels (11.2 mg/l, cut off 0,5) and slightly elevated inflammation parameters. A Doppler ultrasound of the lower extremities was also performed, which did not show thrombotic masses in the lower extremities. After ten days, the patient was discharged with advice for continued home treatment with dual anticoagulant therapy (Apixaban). However, he did not undergo the recommended hematological examination.



Figure 1. *Prominent arch of the pulmonary artery in the cardiac bay. 2. Amputated lower pole of the left hilus shadow 3. Discretely elevated left hemidiaphragm 4. Flattened left KF sinus and posterior left Costo-diaphragmatic angle*

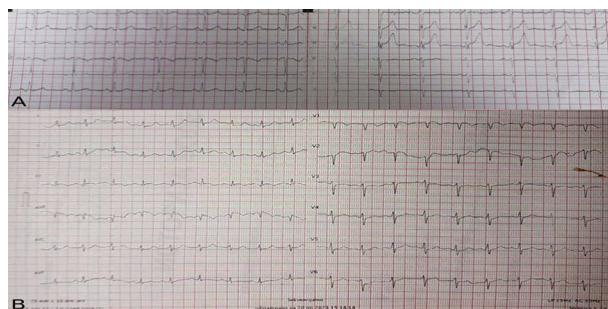


Figure 2. *A) ECG, case 1. sinus rhythm, heart rate 75/min, early repolarization in V1-3, B) ECG, case 2. sinus rhythm, heart rate 108/min, ST depressions up to 1mm in DI, D3, aVL, and precordial leads, aVR minimal ST elevation*

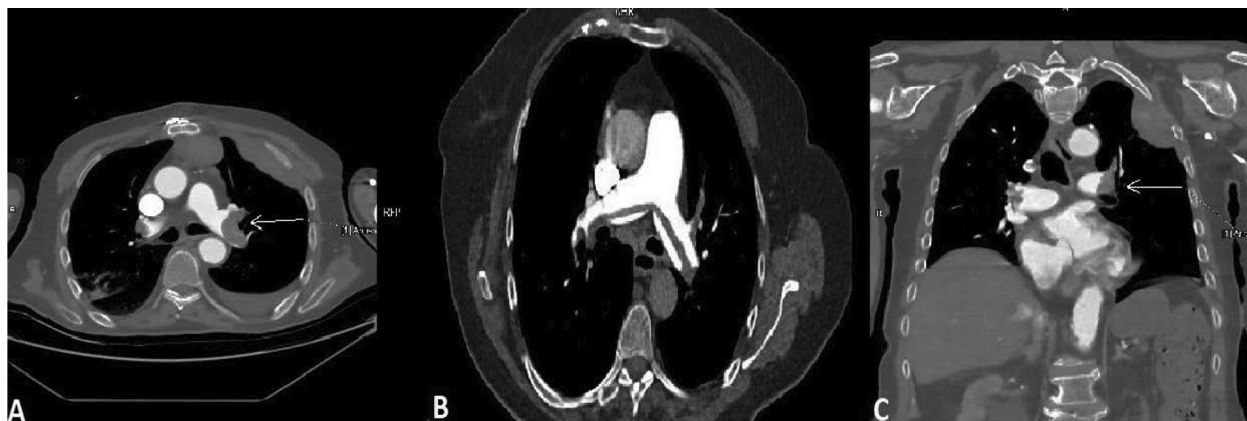


Figure 3. *Massive thrombus at the bifurcation of the pulmonary artery with propagation into both main branches. A) Axial section, PTE in the main branches, B) Axial section, "saddle thrombus", C) Coronal section, PTE in the main branches*

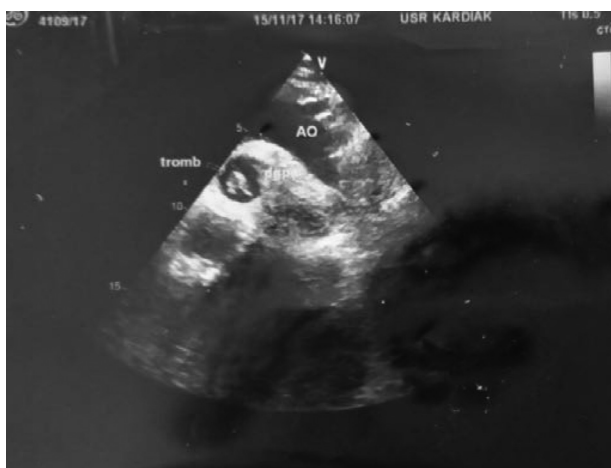


Figure 4. Floating thrombus is at the bifurcation of the pulmonary artery and its right branch

CASE REPORT No 2

A 37-year-old patient was brought to the Emergency Center of the Clinical Center of Serbia (UCCS) due to a fall, following a loss of consciousness preceded by severe epigastric pain. He reported that he had been examined by a cardiologist due to chest pain and rapid fatigue that had lasted for 15 days, an echocardiographic examination had been performed which was normal, and an exercise stress test was stopped at the second stage (due to poor physical condition, as he was been told). Additionally, the patient had a known medical history of hypertension and insulin resistance.

Upon admission to the Emergency Center, the patient was conscious, pale, hypotensive (BP 80/55 mmHg), tachycardic (108/min), normal-saturated on room air (SpO₂ 95%), with a BMI 30.9 kg/m². Physical examination revealed a laceration-contusion wound at the root of the nose and epigastric tenderness on light touch. Auscultation showed normal heart and lung sounds. The ECG indicated sinus rhythm, a heart rate of 108/min, ST depressions of up to 1mm in D3, aVL, and precordial leads, and minimal ST elevation in aVR (Figure 2B).

Immediately upon admission, an abdominal ultrasound was performed, which did not indicate acute pathological events. Due to severe epigastric pain, a CT scan of the abdomen and pelvis was indicated, during which the patient experienced a disturbance of consciousness and cardiac arrest. Despite resuscitation efforts, cardiac activity was not re-established, resulting in a lethal outcome. A clinical autopsy was requested, which confirmed the presence of massive pulmonary thromboembolism. Subsequent laboratory analyses revealed a D-dimer level of 25.56 mg/l (cut-off 0.5), with other parameters within the reference range.

Verbal and signed consent was obtained for the publication of this case report. All procedures conducted adhered to the principles outlined in the 1964 Helsinki Declaration and its subsequent amendments.

DISCUSSION

We have presented two young men who had subacute massive PTE and who reported to the Emergency Center of the UCCS about 15 days after the onset of their symptoms. The contributing factors for subacute pulmonary embolism are often unidentified (7) and could lead to repeated embolisms. There's a noticeable lack of studies focusing on risk factors in younger demographics (8, 9). Both patients had a nonspecific, protracted course of the disease, which had a similar duration and in which symptoms sometimes lessened and sometimes intensified. Those who undergo a subacute progression of the illness face a higher death rate and a greater occurrence of thromboembolic hypertension compared to patients with an acute onset of the disease (2).

The first patient had nonspecific pain and coughed up blood on two occasions, so the diagnostic algorithm started from laboratory analyses, with slightly elevated CRP and X-ray of the heart and lungs, which showed a discrete pathological finding. For an experienced radiologist, the alarm was pleural effusion and mild elevation of the hemidiaphragm in an otherwise healthy individual. Since there were no signs of heart failure and signs of malignancy, the next serious differential diagnosis was PTE.

The second patient had difficulty breathing and fatigue that lasted at least 15 days, which led to a transthoracic echocardiogram and a physical stress test, which was interrupted at the second stage due to poor condition, as it was interpreted at the time. Troponin, a biomarker of cardiac necrosis, was also performed, which was within the reference range. The protracted and insidious symptoms led to a delay in diagnosis and treatment, which was fatal in the case of this young man.

A retrospective observational analysis of a younger demographic (age ≤ 45 years) revealed that the predominant clinical manifestations were dyspnea, thoracic discomfort, and cough (10). In a review of 61 instances of lethal pulmonary thromboembolism, the primary clinical presentations observed were dyspnea, syncope, lower extremity discomfort, and chest pain (11).

The term "massive PTE," refers not to the embolism's size but to its hemodynamic consequences, with individuals experiencing hemodynamically unstable pulmonary embolism being at an elevated risk of succumbing to obstructive shock, as a result of acute pressure overload inducing severe right ventricular in-

sufficiency (12). Right ventricular dysfunction, which can be evaluated via echocardiography or MSCT PA, has been linked to elevated mortality rates. However, it is posited that echocardiography provides a more dependable diagnostic approach compared to MSCT.

A meta-analysis of seven studies involving 3395 normotensive and hypotensive patients with PE reported that right ventricular dysfunction is associated with a doubling of hospital mortality from PE (13). Nonetheless, a subset analysis of normotensive patients indicated a weak correlation between right ventricular dysfunction, as detected via echocardiography or MSCT, and mortality. This suggests that it's the symptomatic manifestation of right ventricular dysfunction that serves as a predictor for mortality.

In our normotensive patient, asymptomatic right ventricular dysfunction was observed, and the prognosis appeared favorable. Elevated BNP, NT-proBNP, and troponin in hemodynamically stable patients do not reliably predict fatal outcomes. However, when these markers fall within normal or low ranges, they consistently indicate a benign clinical trajectory (14).

Upon arrival at the emergency department, the first patient was in good general condition. Over 95% of patients with acute PE are (or appear to be) hemodynamically stable at the time of presentation, so they are not considered to be at high risk (15). The second patient suffered severe epigastric pain, after a previous loss of consciousness. In literature, abdominal pain is also described as a rare and atypical manifestation of PE (16), the mechanism of which is still not sufficiently researched. It is believed that it most likely occurs due to liver congestion and consequent distension of Glisson's capsule, as well as due to pleuritis resulting from lung infarction at the base of the lung.

The first patient underwent MSCT PA due to high clinical suspicion, revealing a saddle thrombus. Unfortunately, the second patient died during the diagnostic process before a conclusive CT diagnosis was reached. MSCTPA remains the preferred diagnostic method for suspected PTE, boasting a sensitivity of 83% and specificity of 96% according to PIOPED (Prospective Investigation on Pulmonary Embolism Diagnosis) (17).

The Pulmonary Embolism Rule-out Criteria (PERC) is particularly valuable in risk stratification, especially in younger patients, aiming to prevent unnecessary MSCT PA imaging. PERC allows healthcare professionals to identify patients at low risk of PTE, eliminating the need for further testing, including D-dimer assays. Criteria include age under 50 years, heart rate below 100 beats per minute, oxygen saturation (SpO₂) equal to or above 95%, no hemoptysis, no estrogen use, no history of surgery or trauma requiring hospitalization in the last four weeks, absence

of prior venous thromboembolism (VTE), and no unilateral leg swelling. The effectiveness of this rule was substantiated in a prospective study conducted from 2003 to 2006, where the false-negative rate for PTE was found to be 1.2% (18).

In cases of subacute, massive PE where there is no hemodynamic instability, the decision to initiate fibrinolysis primarily relies on MSCT PA findings. There is a tendency for subacute PE to show a less robust response to thrombolytic therapy compared to acute PE, likely because an older thrombus has less plasminogen compared to a more recent one (7).

Thrombolytic therapy has demonstrated a quicker alleviation of pulmonary obstruction, with a significant associated reduction in the risk of circulatory collapse. However, this comes with an increased risk of severe extracranial and intracranial hemorrhage (19). The International Cooperative Pulmonary Embolism Registry has reported a notably high incidence of intracranial bleeding - 3% among patients with PE who were treated with thrombolytic therapy (20). Early thrombus withdrawal early recovery of right ventricular function and reduction of PAH were seen in our patient who received Alteplase. In a randomized trial, Goldhaber (21) found an improvement in right ventricular function after 24 hours in 16/18 patients with thrombolysis compared to 8/18 treated with heparin.

Both of our patients had an elevated BMI, in the category of overweight to obesity. It remains an open question whether studying potentially causal mechanisms (chronic inflammation, adipokines, decreased fibrinolytic activity, procoagulant microparticles, polycythemia) (22) can reduce the percentage of idiopathic VTE in young patients.

CONCLUSION

Subacute massive PTE requires a good understanding of a wide range of clinical presentations, from very mild and inconspicuous to typical and pronounced. It requires connecting clinical manifestations over a prolonged period into one unit and category. Finally, it requires efficient and appropriate treatment and the search for unknown predisposing factors for young people, as a requirement for future multicenter investigations.

Abbreviation

BMI – body mass index

BP – blood pressure

IVC – inferior vena cava

MSCT – Multi-slice Computed Tomography

MSCT PA – Multi-Slice Computed Tomography of the Pulmonary Artery

PE – pulmonary embolism
PTE – pulmonary thromboembolism
RV – right ventriculus
UCCS – University Clinical Centre of Serbia
VTE – venous thromboembolism

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Sažetak

SUBAKUTNA MASIVNA PLUĆNA TROMBOEMBOLIJA (PTE) - KOMPARATIVNI PRIKAZ

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Uvod: Subakutna masivna plućna tromboembolija je životno ugrožavajuće stanje koje može imati kod mladog pacijenta različite načine kliničkog ispoljavanja, od blagog i nespecifičnog do letalnog. Učestalost PE u mlađoj populaciji ne treba zanemariti, bilo da su u pitanju pojedinci sa određenim faktorima rizika, genetskim ili stečenim, bilo da su u pitanju pojedinci sa neidentifikovanim faktorima rizika.

Prikaz slučaja: Prikazujemo 2 mlada pacijenta, starosti 35 i 37 godina, koji su imali protrahovan tok bolesti i klinička ispoljavanja najmanje 15 dana pre prijema. Prvi pacijent je imao nespecifične bolove i senzacije u predelu grudnog koša i u dva navrata iskašljao sukrvicu. Dan pred prijem imao je intenzivan jednočasovni plivački trening. Drugi pacijent je imao brzo zamaranje i gušenje, zbog čega je rađena

ehokardiografija srca i test fizičkog opterećenja koji je prekinut na drugom stepenu (zbog loše kondicije, kako mu je rečeno). Došao zbog intenzivnog bola u epigastrijumu, sa posledičnim gubitkom svesti. Kod oba pacijenta dijagnostikovana je masivna plućna tromboembolija, kod prvog na multislajsnom skeneru plućne arterije, a kod drugog na kliničkoj obdukciji. Prvi pacijent je dobio trombolitičku terapiju i otpušten iz bolnice posle 10 dana.

Zaključak: Potrebno je uvek imati na umu plućnu tromboemboliju, i kod mlađih pacijenata, i kod neupadljive kliničke slike, i bez identifikovanih predisponirajućih faktora.

Ključne reči: plućna tromboembolija, subakutna, masivna, multislajсни skener plućne arterije, faktor rizika, genetski, stečeni, neidentifikovani.

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