



## CASE REPORT

# REVISED Case Report: Successful revascularization in massive pulmonary embolism with a large protruding thrombus and dilated cardiomyopathy [version 3; peer review: 2 approved]

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## Abstract

Pulmonary embolism is a potentially life-threatening condition. Despite advances in diagnostics, lack of consensus and delays in determining the diagnosis of pulmonary embolism are still important problems. We report the diagnosis and management of a 37-year-old man suffering from massive pulmonary embolism, a large protruding thrombus, and dilated cardiomyopathy. Echocardiography showed dilatation of all cardiac chambers, a large protruding thrombus in the right atrium to the inferior vena cava, impaired left and right ventricular systolic function, and global hypokinetic of the left ventricle with eccentric left ventricular hypertrophy. A thoracic computerized tomography scan showed pulmonary embolism with infarction. The patient's blood pressure was 60/40 mmHg and heart rate was 110 bpm. The patient was diagnosed with high-risk acute pulmonary embolism. We gave him hemodynamic support and reperfusion therapy with a loading dose of 250,000 units of Streptokinase followed by 100,000 units/hour for 24 hours. After revascularization, the patient's hemodynamic condition improved. The diagnosis of acute pulmonary embolism is based on clinical symptoms, hemodynamic changes, or radiological examination. Unstable hemodynamic underlies high-risk stratification. Hypotension or shock results from obstruction of the pulmonary artery which causes increased right ventricular afterload and acute right ventricular dysfunction. Reperfusion with thrombolysis therapy could provide good outcomes in this patient. Prolonged anticoagulation should be given to prevent the recurrence of venous thromboembolism.

## Keywords

Massive pulmonary embolism, large protruding thrombus, unstable hemodynamic, reperfusion

## Open Peer Review

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1

2

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### version 2

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report




report




report

### version 1

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**REVISED Amendments from Version 2**

We have repaired the grammatical errors in the manuscript, corrected [Figure 3](#) and [Figure 4](#), and added the explanation of the abbreviations in the figures.

**Any further responses from the reviewers can be found at the end of the article**

**Introduction**

Venous thromboembolism, a clinical presentation of deep vein thrombosis (DVT) or pulmonary embolism, is the third most commonly found acute cardiovascular syndrome after myocardial infarction and stroke<sup>1</sup>. Pulmonary embolism is a potentially life-threatening condition. Most patients die from pulmonary embolism within the first few hours of the event. Despite advances in diagnostics, delay in determining pulmonary embolism diagnosis is still a significant problem<sup>2</sup>.

Pulmonary embolism contributes to approximately 300,000 deaths per year in the United States<sup>3</sup>. This makes pulmonary embolism one of the high-rank causes of cardiovascular death. In six European countries, over one million venous thromboembolism events or deaths per annum occurred in 2004. Of these patients, 34% died suddenly or within a few hours of the acute event, before therapy could be administered<sup>4</sup>. Clinicians should be able to better recognize the signs and symptoms of acute pulmonary embolism; thus, diagnosis and management can be determined quickly and accurately to reduce patient's mortality. We present a rare case of protruded thrombus in the right atrium passing through the tricuspid valve which position moving from the inferior vena cava towards the right atrium, causing a massive pulmonary embolism and dilated cardiomyopathy. We successfully performed revascularization in such case.

**Case presentation**

A 37-year-old Indonesian man was referred to the emergency department of Dr. Soetomo General Hospital, Indonesia, in June 2019, with complaints of shortness of breath and swollen legs. His occupation was a farmer. Two months earlier, the patient went to the public health center for a prolonged cough ( $\pm$  five months), which was sometimes accompanied by shortness of breath. In the public health center, acid-fast bacillus (AFB) testing was performed with a negative result. Based on a chest radiograph, the doctor decided to give group 1 anti-tuberculosis drugs through the public health center. The treatment prescribed was fixed-dose combination, four tablets daily taken orally, with the composition of each tablet as follows: Rifampicin 150 mg, Isoniazid 75 mg, Pirazinamide 400 mg, and Ethambutol HCl 75 mg. Thus, in the emergency department, he was referred to the pulmonology department with a diagnosis of pulmonary tuberculosis.

In addition, the patient also had a history of proximal bilateral femoral deep vein thrombosis (DVT) of the left inferior limb proven by ultrasonography examination; the patient had

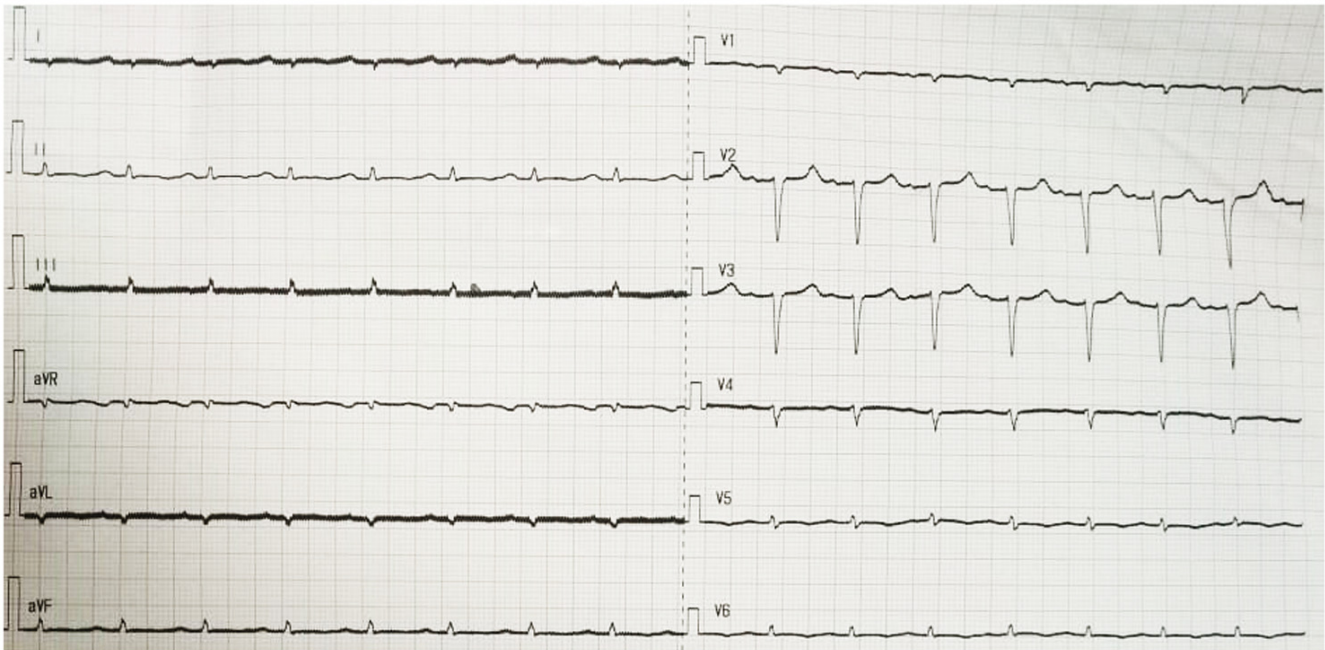
undergone a thrombectomy a month before his referral to the hospital. The complaints of swollen leg were slightly reduced at that time; however, had recurred again, accompanied by swelling on his right limb.

The patient had been diagnosed with uncontrolled diabetes mellitus and heart failure one month before admission. He received subcutaneous injection 8 units of insulin aspart three times a day before meals, captopril 6.25 mg every eight hours orally, spironolactone 25 mg once daily orally, digoxin 0.25 mg once daily orally, codeine 10mg every eight hours orally, and rivaroxaban 15 mg every twelve hours orally.

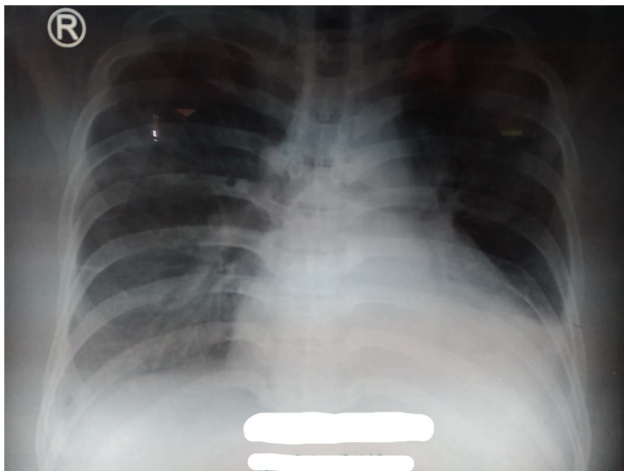
When admitted to the pulmonary ward, the patient complained of shortness of breath, accompanied by pain and swelling in both legs. His blood pressure was 120/80 mmHg, pulse 128 beats per minute, respiratory rate 26 breaths per minute, and 3 liters per minute oxygen via nasal cannula. Physical examination revealed jugular venous distention, bilateral basal rales, hepatomegaly, and pitting edema in lower extremities.

In laboratory findings, serum electrolytes revealed hypokalemia (K: 3.3 mmol/L; normal range 3.5–5.1 mmol/L), serum protein showed hypoalbuminemia (albumin: 3.1g/dL; normal range 3.4–5.0 g/dL), while other parameters were between normal limits. An electrocardiogram (ECG) showed sinus tachycardia rhythm 125 beats per minute, right-sided frontal axis, horizontal axis clockwise rotation, and slow progression of R waves at V1–V4 ([Figure 1](#)). A chest X-ray showed cardiomegaly, pulmonary congestion, and minimal bilateral pleural effusion ([Figure 2](#)). Echocardiographic examination revealed moderate mitral regurgitation (dilated mitral annulus), dilatation of all cardiac chambers (Left ventricular internal diastolic diameter 5.8 cm), visible thrombus in inferior vena cava to right atrium, decreased left and right ventricular systolic function (EF teich 35%, TAPSE 1.3 cm), and global hypokinetic of the left ventricle with eccentric left ventricular hypertrophy. The scans from a transthoracic echocardiogram (TTE) showing thrombus is shown in [Figure 3](#) and [Figure 4](#).

A chest CT scan ([Figure 5](#)) showed right pulmonary artery embolism at  $\pm$  5.9 cm from bifurcation on the anterior side of the intermediate right bronchus; emboli on the left pulmonary artery bifurcation and the left pulmonary artery basal part; multiple right intraatrial hypodense lesions not showing contrast enhancement leading to a visualization of the right intraatrial thrombus; pulmonary infarction in the lateral-posterior segment of the base of the inferior lobe of the right lung, the lateral-posterior segment of the base of the inferior lobe of the left lung, and the anterior segment of the superior lobe of the left lung; and superior vena cava thrombus at VTH level 1-5. [Figure 6](#) shows the protruded thrombus in the right atrium passing through the tricuspid valve. TTE also showed the position of the thrombus moving from the inferior vena cava towards the right atrium ([Figure 7](#)). The movement of the large protruding thrombus can be seen in the supplementary video files 1–3<sup>5-7</sup>.



**Figure 1.** Electrocardiogram (ECG) of the patient.



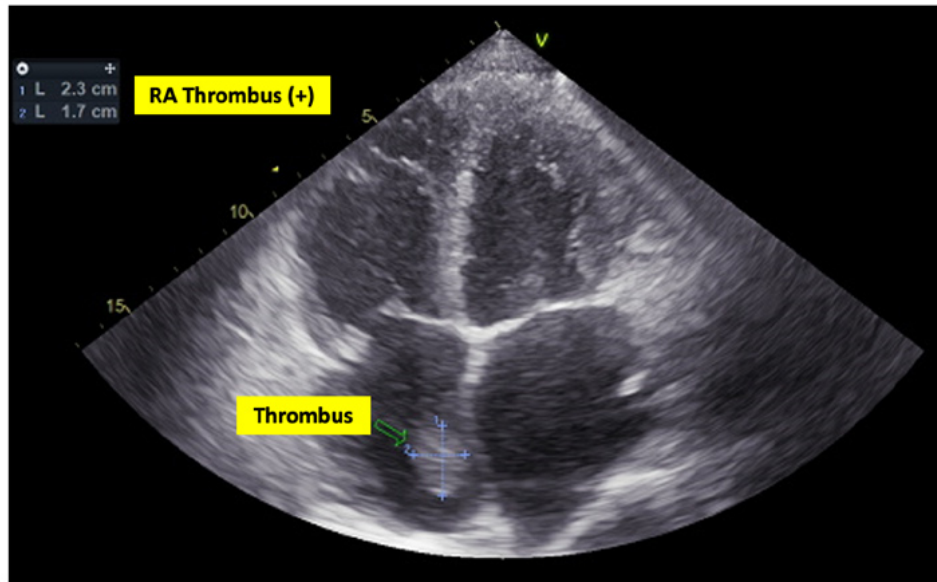
**Figure 2.** Chest X-ray of the patient.

In the course of the assessments, no clinical, laboratory, or radiological signs of pulmonary tuberculosis were found. Eventually, the patient was transferred to the cardiology ward with the assessment of dilated cardiomyopathy + acute decompensated heart failure + deep vein thrombosis of the right and left inferior limbs + right atrial thrombus + pulmonary embolism + type II diabetes mellitus. During three days of treatment, the patient received Spironolactone 50 mg, Ramipril 5 mg, and low-dose Bisoprolol started at 1.25 mg each once daily orally, 20 mg of Furosemide by the intravenous injection every

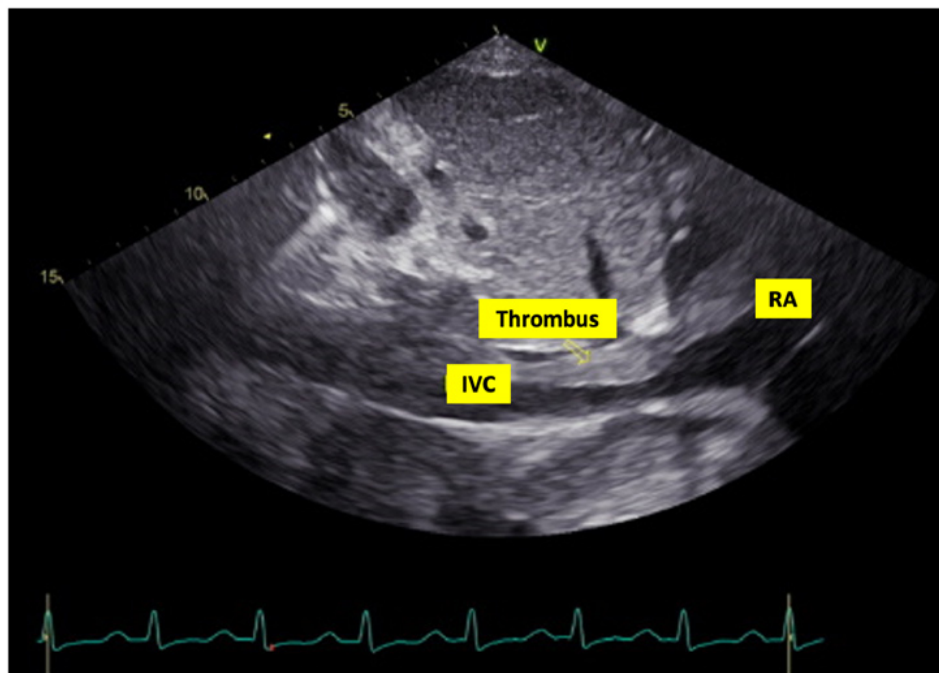
eight hours, subcutaneous injection of Enoxaparin 60 mg every twelve hours, and subcutaneous injection 6 units of insulin aspart three times daily before meals. However, in the course of this treatment in the cardiology ward, the patient suddenly complained of shortness of breath accompanied by chest pain and cold sweat. His blood pressure became 60/40 mmHg, pulse 110 beats per minute, and respiratory rate 28–30 breaths per minute, thus showing hemodynamic instability and shock. Therefore, he was reassessed as having high risk acute pulmonary embolism, and the patient was transferred to the cardiovascular care unit (CVCU) for observation and reperfusion therapy.

In the CVCU, we gave the patient hemodynamic support with Norepinephrine starting at 50 nanograms/kg/minute by titration. Reperfusion was carried out by giving a loading dose of 250,000 units of Streptokinase intravenously for 30 minutes, followed by 100,000 units of Streptokinase per hour for 24 hours with continuous intravenous pump. After revascularization, the patient's hemodynamic condition improved until vasopressors/inotropic drugs could be tapered off. TTE also showed the disappearance of the large protruding thrombus (supplementary video files 4–5)<sup>8,9</sup>. After the patient's condition was stable, he was transferred to the cardiology ward until the patient was discharged after one week of thrombolytic treatment. In his discharge, rivaroxaban was prescribed at a daily dose of 20 mg as an oral anticoagulant for at least three months. The diabetes mellitus was well-controlled with subcutaneous injection 6 units of insulin aspart three times daily before meals.





**Figure 3.** Transthoracic echocardiogram (TTE) showing thrombus in the right atrium. RA = right atrium.



**Figure 4.** Transthoracic echocardiogram (TTE) showing thrombus in the inferior vena cava. RA = right atrium; IVC = inferior vena cava.

One week after discharge, the patient made a follow-up visit at the cardiology outpatient clinic. At that time, it was found that the patient's symptoms and exercise tolerance had improved, and his shortness of breath and swollen leg were reduced. The patient's adherence to treatment was good, and there was neither sign of minor nor major bleeding due to

anticoagulants' use. Even though the clinical condition has improved, there was no improvement in the ejection fraction. Therefore, anticoagulant therapy and insulin injection were continued, accompanied by therapy for heart failure according to guideline-directed medical therapy (GDMT) for heart failure with reduced ejection fraction (HFrEF).

## Discussion

Pulmonary embolism is a critical medical emergency. It can lead to rapid deterioration of hemodynamic conditions with high mortality rate<sup>10</sup>. Pulmonary embolism usually arises from thrombus originating from the deep venous system in the inferior limb. After heading to the lungs, a large protruding thrombus can attach to the branching of the main pulmonary artery or lobar branches, causing massive pulmonary embolism and hemodynamic disorders. This case report is unique as it showed massive pulmonary embolism due to a large protruding right-sided heart burden thrombus, which is rarely found

in normal cases. This condition led to hemodynamic instability of the patient. This case also showed how immediate thrombolytic therapy could make the large thrombus disappear and provide a better outcome in such a patient. Pulmonary thromboembolism is not a basic disease in itself; instead, it is a complication of the underlying venous thrombosis<sup>11</sup>. On vascular ultrasound examination in the present case, thrombi were found in the common femoral vein as well as the right and left popliteal veins. From the echocardiographic examination, thrombi in the inferior vena cava and the right atrium was also found. The limitation of this case report was the unexplained etiology of hypercoagulability of this patient.

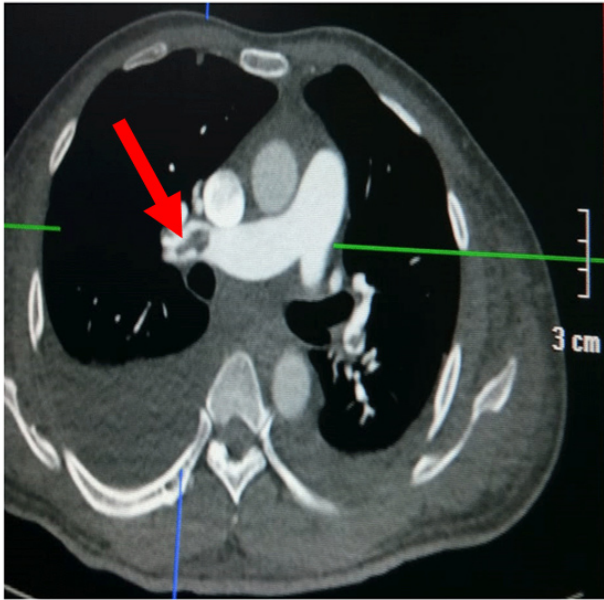
## Clinical symptoms

Pulmonary embolism presentations are pleuritic chest pain, sudden onset, shortness of breath, and hypoxia. However, most patients with pulmonary embolism have no apparent symptoms. Conversely, symptoms can vary from sudden hemodynamic collapse to progressive shortness of breath. A diagnosis of pulmonary embolism should be suspected in patients with respiratory symptoms that cannot be explained by other alternative diagnoses<sup>12</sup>.

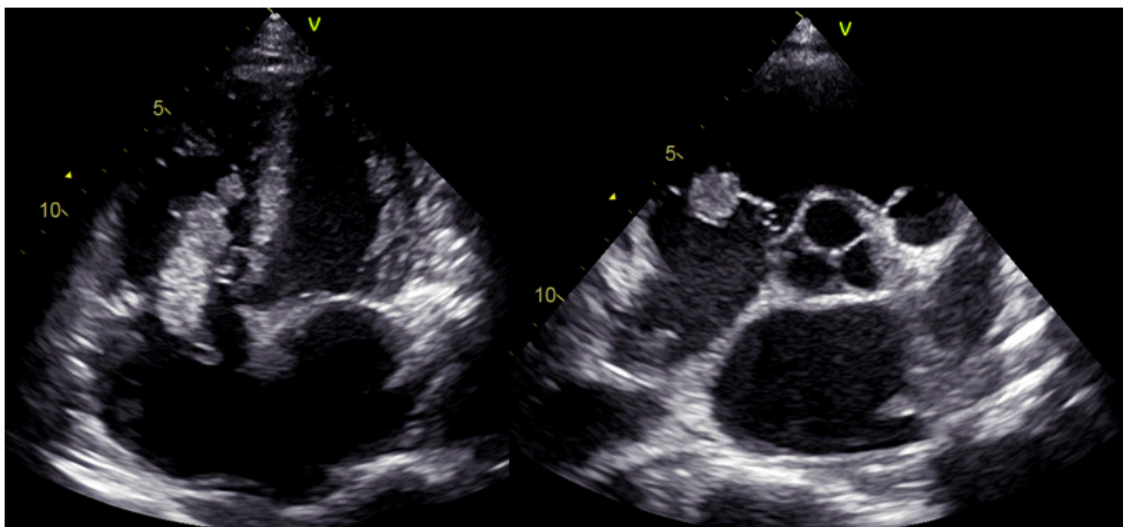
One of these hemodynamic instability manifestations indicates a high-risk acute pulmonary embolism<sup>13</sup>: first is cardiac arrest; second is an obstructive shock; and third is persistent hypotension. In this patient, clinical symptoms included shortness of breath, tachycardia, chest pain, coughing, signs of the inferior extremity DVT, tachypnoea, bilateral basal rhonchi, neck venous distention, minimal bilateral pleural effusion, and hemodynamic disorders. This patient had an obstructive shock; therefore, he was classified into a high-risk acute pulmonary embolism.

## Management

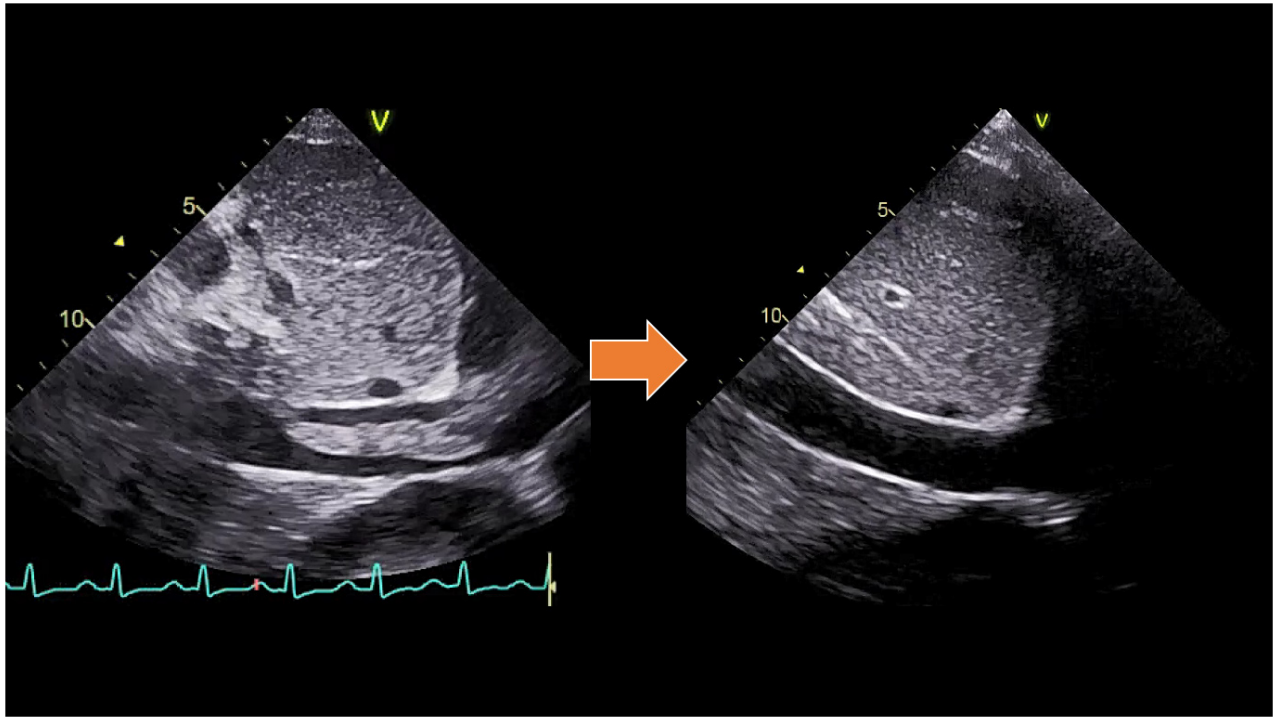
All patients with pulmonary embolism need immediate risk stratification. Thrombolytic therapy should be given to patients with acute pulmonary embolism with clinical hypotension



**Figure 5.** Chest CT scan of the patient. Red arrow showing the location of the thrombus.



**Figure 6.** Transthoracic echocardiogram (TTE) showing protruded thrombus in the right atrium passes through the tricuspid valve.



**Figure 7.** Transthoracic echocardiogram (TTE) comparison showing the position of the thrombus moving from the inferior vena cava towards the right atrium.

(systolic pressure <90 mm HG) who do not have a high risk of bleeding. Thrombolysis in these patients should not be delayed because of the potential for irreversible cardiogenic shock. Thrombolytic therapy is recommended in certain patients with acute pulmonary embolism indicating a high risk of hypotension at initial clinical presentation or after starting anticoagulants. Assessing the severity of pulmonary embolism, prognosis, and bleeding risk determines whether thrombolytic therapy can be given. Thrombolytic therapy is not recommended for most patients with acute pulmonary embolism that is not associated with hypotension<sup>14</sup>. Primary reperfusion therapy - in most cases systemic thrombolysis - is the treatment of choice for patients with high-risk pulmonary embolism (with hemodynamic instability). Surgical pulmonary embolectomy or percutaneous catheter-directed treatment is an alternative reperfusion option in patients with contraindications to thrombolysis<sup>13</sup>.

Before conducting thrombolysis therapy, several absolute and relative contraindications must be considered. Absolute contraindications for thrombolysis are<sup>13</sup>: the history of hemorrhagic stroke or stroke of unknown cause; ischemic stroke during the last six months; neoplasms of the central nervous system; major trauma, surgery or head injury in the past three weeks; bleeding diathesis; and active bleeding. While relative contraindications are: transient ischemic attacks in the last six months; the use of oral anticoagulants; pregnancy or the first week postpartum; non-compressible puncture sites; traumatic resuscitation; traumatic hypertension (systolic blood pressure > 180 mmHg);

severe/advanced liver disease; infectious endocarditis; and active peptic ulcer.

Acute right heart failure with low cardiac output is the leading cause of death in patients with high-risk acute pulmonary embolism. Long-term anticoagulation is very important for preventing the recurrence of DVT or pulmonary embolism, as even if a patient has been administered anticoagulants, DVT and pulmonary embolism still often recur. Apixaban, dabigatran, rivaroxaban, and edoxaban are alternatives to warfarin as the prophylaxis and treatment of pulmonary embolism. Apixaban, edoxaban, and rivaroxaban inhibit factor Xa, while dabigatran is a direct inhibitor of thrombin<sup>15</sup>.

All patients with pulmonary embolism must be given anticoagulants for more than three months. The use of novel oral anticoagulants (NOAC) is considered to have a lower risk of bleeding than vitamin K antagonists. However, treatment with NOAC still has risks. Phase III clinical trials in venous thromboembolic patients with extended therapy show that major bleeding rates are around 1% and clinically relevant non-major bleeding is around 6%<sup>16,17</sup>.

In our patient, after the diagnosis of acute pulmonary embolism had been established, thrombolysis was the first choice. Reperfusion was carried out by giving a loading dose of 250,000 units of Streptokinase intravenously for 30 minutes, then followed by 100,000 units of Streptokinase per hour for

24 hours. Hemodynamic support was performed by giving Norepinephrine from 50 nanograms/kg/minute by titration.

## Conclusion

We reported the case of a 37-year-old man with a massive pulmonary embolism. The distinctiveness of this case was the presence of a large protruded thrombus in the right atrium passing through the tricuspid valve which position moving from the inferior vena cava towards the right atrium, causing the condition of massive pulmonary embolism and dilated cardiomyopathy in the patient. The diagnosis of acute pulmonary embolism was based on clinical symptoms, hemodynamic changes, echocardiographic examination, and a chest CT scan. Unstable hemodynamic conditions classified this patient in the high-risk stratification. Hypotension or shock resulted from acute right ventricular dysfunction due to the obstruction of the pulmonary artery embolus, which caused an increase in right ventricular afterload. Inotropic agents or vasopressors with Norepinephrine were needed to improve the hemodynamic profile. Successful revascularization was performed by thrombolysis with Streptokinase, which gave good outcomes in this patient. In conclusion, early diagnosis, risk assessment, and prompt treatment are important to treat patients with massive pulmonary embolism due to a large protruding thrombus. Hemodynamic deterioration, such as hypotension and shock, should be monitored in patients with massive pulmonary embolism to reduce mortality. Reperfusion therapy should be administered soon for patients with high-risk pulmonary embolism after assessing indication and contraindication for thrombolytic treatment. The problem with the current management of pulmonary embolism is when to start reperfusion therapy in patients with intermediate-high risk. Further research is needed to determine the proper management and immediate prompt treatment in such patients.

## Data availability

All data underlying the results are available as part of the article and no additional source data are required.

## Videos

### Video 1. Movement of the large protruding thrombus (1)

1 Data File

<https://dx.doi.org/10.6084/m9.figshare.13475550.v1<sup>5</sup>>

### Video 2. Movement of the large protruding thrombus (2)

1 Data File

<https://dx.doi.org/10.6084/m9.figshare.13475721.v1<sup>6</sup>>

### Video 3. Movement of the large protruding thrombus (3)

1 Data File

<https://dx.doi.org/10.6084/m9.figshare.13475760.v1<sup>7</sup>>

### Video 4. Disappearance of large protruding thrombus after revascularization (4)

1 Data File

<https://dx.doi.org/10.6084/m9.figshare.13475799.v1<sup>8</sup>>

### Video 5. Disappearance of large protruding thrombus after revascularization (5)

1 Data File

<https://dx.doi.org/10.6084/m9.figshare.13475844.v1<sup>9</sup>>

## Consent

Written informed consent for publication of their clinical details and clinical images were obtained from the patient.

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# Open Peer Review

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The case reports submitted by the authors were fascinating and provided additional knowledge for clinicians. In terms of case descriptions and discussions that are presented, it is quite clear. However, the authors still lack detail in submitting their case reports. The figures included do not provide the reader with information. Likewise, writing words and sentences are sometimes confusing and mistyped. Even though this article only requires a minor revision, it is quite important to note. The following are proposed minor revisions to this article:

- The word "**occured**" in "...over one million VTE events or deaths per annum **occured** in 2004..." should be "**occurred**".
- "**We presents** a rare case of protruded thrombus in the right atrium passing through..." - It appears that the subject pronoun "**We**" and the verb "**presents**" are not in agreement. Consider changing the verb, which should be "**We present...**".
- "...passing through the tricuspid valve, which **position** moving from the inferior vena cava towards the right atrium..." - The plural verb "**position**" does not appear to agree with the singular subject "**the tricuspid valve**". Consider changing the verb form for the subject-verb agreement that should be "**positions**".
- "...for a prolonged cough ( $\pm$  **5** months)..." - The numeral "**5**" is used instead of the word spelled out. Consider spelling out the number.
- It appears that "**anti tuberculosis**" is missing a hyphen. Consider adding the hyphen(s).
- It appears that the "**fixed dose**" is missing a hyphen. Consider adding the hyphen(s).
- "...**4** tablets daily taken orally..." - The numeral "**4**" is used instead of the word spelled out.

Consider spelling out the number.

- "...with **composition** of each tablet as follows:..." - The noun phrase "**composition**" seems to be missing a determiner before it. Consider adding an article, "**the composition**".
- The word "**admitted**" in "When **admitted** to the pulmonary ward..." should be "**admitted**".
- "...**pulse 128 bpm, respiratory rate 26/minute, and 3 liter per minutes** oxygen via nasal cannula", should be "**pulse 128 beats per minute, respiratory rate 26 breaths per minute, and 3 liters per minute**". The singular noun "**liter**" follows a number other than *one*. Consider changing the noun to the plural form. It seems that "**minutes**" may not agree in number with other words in this phrase.
- "...**hepatomegaly, and pitting edema in both lower extremities**". It appears that "**both**" may be unnecessary in this sentence. Consider removing it.
- The noun phrase "**supplementary video**" seems to be missing a determiner before it. Consider adding an article so that it reads, "**the supplementary video**".
- The noun phrase "**intravenous injection**" seems to be missing a determiner before it. Consider adding an article. "**the intravenous injection**".
- "...**Spironolactone 50 mg once daily orally, Ramipril 5 mg once daily orally, low-dose Bisoprolol started at 1.25 mg once daily orally...**" - It looks like your sentence contains a redundancy. Consider simplifying them.
- "His blood pressure became 60/40 mmHg, heart rate 110 bpm, and respiratory rate 28-30/minute..." - That should be "**heart rate 110 beats per minute, and respiratory rate 28-30 breaths per minute**".
- There is an inconsistency in using the word "**pulse**" or "**heart rate**". We recommend using one word that is uniform and consistent.
- "...followed by 100,000 units of Streptokinase per hour for 24 hours with intravenous continuous pump..." - It appears that the modifiers in the noun phrase "**intravenous continuous pump**" are in the wrong order. Consider changing the word order to "**continuous intravenous pump**".
- "The diabetes mellitus was well-**controlled** with subcutaneous injection of 6 units insulin aspart three times daily before meals." - The word "**controlled**" should be "**controlled**" and "**6 units insulin**" seems that preposition use may be incorrect here and should be "**6 units of insulin**".
- The phrase "**the use of anticoagulants**" may be wordy. Consider changing the wording to be "**anticoagulants' use**".
- The word "**Eventhough**" should be "**Even though**".

- *"It can lead to rapid deterioration of hemodynamic **condition** with high..."* - It seems that "**condition**" may not agree in number with other words in this phrase. It should be "**conditions**".
- *"From the echocardiographic examination, **the presence of thrombi** in the inferior vena cava and the right atrium was also found."* - It appears that "**the presence of**" may be unnecessary in this sentence. Consider removing it.
- The phrase "**presentations of pulmonary embolism**" may be wordy. Consider changing the wording to "**pulmonary embolism presentations**".
- The noun phrase "**obstructive shock**" seems to be missing a determiner before it. Consider adding an article so that it reads, "**an obstructive shock**".
- *"...chest pain, coughing, signs of **inferior extremity**..."* - The noun phrase "**inferior extremity**" seems to be missing a determiner before it. Consider adding an article so that it reads, "**the inferior extremity**".
- *"This patient had an obstructive shock, **therefore**, he was classified into..."* - This sentence appears to consist of two independent clauses. Consider using a semicolon or period before "**therefore**".
- *"...**history** of hemorrhagic stroke or stroke of unknown cause"* - The noun phrase "**history**" seems to be missing a determiner before it. Consider adding an article so that it reads, "**the history**".
- *"Reperfusion was carried out by giving a loading dose of 250,000 units of Streptokinase **intravenously** for 30 minutes..."* - It should be "**intravenously**".
- *"We reported the case of a 37-year-old man with **massive** pulmonary embolism"*. It seems that article use may be incorrect here. It should be "**a massive**".
- *"The distinctiveness of this case was the **present** of a large protruded thrombus..."* - The word "**present**" doesn't seem to fit this context. Consider replacing it with a different one. It should be "**presence**".
- *"Further research is needed to determine the **right** management and immediate prompt treatment in such patients"* - It appears that the noun "**management**" might combine better with an adjective other than "**right**". Consider rewriting this word pair or choosing a synonym for "**right**". It should be "**proper**".
- *"Written informed consent for publication of their clinical details and clinical images **was** obtained from the patient"* - It seems that the verb **did** not agree with the subject. Consider changing the verb form. It should be "**were**".
- It is best if all the abbreviations are written as their meanings (VTE, LVIDd, RA, IVC, LVH).
- Please clarify and tidy up the electrocardiogram image.



- Please write a description below the figures about the explanation of an abbreviation that has been written in the figure.
- Please correct the word "**trombus**" to "**thrombus**" in figure 3 and figure 4.

**Is the background of the case's history and progression described in sufficient detail?**

Yes

**Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?**

Yes

**Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?**

Yes

**Is the case presented with sufficient detail to be useful for other practitioners?**

Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Clinical cardiology, cardiovascular prevention and rehabilitation.

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

Author Response 17 Mar 2021

**Citrawati Wungu**, Airlangga University, Surabaya, Indonesia

We have repaired the grammatical errors, written the abbreviations as their meaning, corrected the word "thrombus" in the figures, and added the explanation of the abbreviations in the figures as suggested.

**Competing Interests:** We declare that we have no competing interest regarding this

Reviewer Report 15 February 2021

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**Henry Sutanto** 

Department of Cardiology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht, The Netherlands

Thanks for addressing my previous comments. I have no other questions or remarks, only that the manuscript writing and case reporting could still be improved.

**Is the background of the case's history and progression described in sufficient detail?**

Yes

**Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?**

Yes

**Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?**

Yes

**Is the case presented with sufficient detail to be useful for other practitioners?**

Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Cardiovascular disease, cardiogenetics, cardiac arrhythmias, arrhythmogenesis, inherited arrhythmia syndromes, computational modeling and bioinformatics.

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

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**Version 1**

Reviewer Report 12 January 2021

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**Henry Sutanto** 

Department of Cardiology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht, The Netherlands

In this case report, Dr. Susilo and colleagues reported a case of a man with pulmonary embolism (PE), right atrial (RA) thrombus and dilated cardiomyopathy (DCM). In general, the manuscript

showed nicely the rapidly progressing PE into hemodynamic instability, which was immediately corrected following the administration of thrombolytic agent. However, I have some major and minor comments to be addressed by the authors, including the completeness of data.

- **Overall, the authors need to highlight the distinctiveness of this case, which is not well-defined in the current version of the manuscript.** It is currently unclear why this case is different than the other PE cases? The fact that one of the thrombi is located in the RA does help to stress the importance of this case report.
- **I would suggest the authors to arrange and discuss the data more systematically, and provide complete history and supporting data in the manuscript.** For example, the patient was diagnosed with diabetes mellitus and heart disease 1-month before admission. Which heart disease? What about the glycemic status prior to and after admission? Was the diabetes controllable?
- **The time course of clinical and laboratory parameters is lacking.** For example, it is currently unclear about the ejection fraction after discharge and during the follow-up visit? What about the hypercoagulable state and so on? These values are important to report in this manuscript.
- Here, the authors explicitly mentioned three observed phenomena in the title: 1) PE; 2) RA thrombus and 3) DCM. However, **the manuscript mainly focused on the PE and RA thrombus with a very limited discussion regarding DCM and its correlation with the other observed pathologies.** Please clarify the reason and adapt the discussion accordingly elaborating the potential interactions between those pathologies.
- In addition to the clinical presentations, please include the ECG recordings and other data justifying the diagnosis of acute PE during the shock event.
- The authors are requested to speculate on the origin of the RA thrombus. Is it primarily from the RA or is it a migrating thrombus? Was there any evidence of situations facilitating thrombus formation, such as hypercoagulability, atrial fibrillation, tricuspid valve disease, and so on prior to the incident? Provide some supporting data (e.g., lab results, etc.).
- The authors mentioned that the etiology of hypercoagulability in this patient is unknown. However, laboratory results showing hypercoagulability were not reported. Please add them into the study. What about the link between diabetes and hypercoagulable state, which has been discussed by many other publications? Please discuss this.
- Was left ventricular (LV) noncompaction observed in this patient? Elaborate your arguments.
- The rationale of DCM diagnosis in this patient is unclear. The authors need to provide a table containing checklist of clinical, imaging, and genetic data supporting this diagnosis. The authors can benefit from the paper by Mestroni et al. (Eur Heart J. 1999)<sup>1</sup> or Mathew et al. (Echo Res Pract. 2017)<sup>2</sup>.
- Please confirm the nature of DCM in this patient? Familial or acquired? Include the family pedigree if there is an evidence of inherited DCM.

- Patients with DCM have a high risk of sudden cardiac death. Please explain the reason why in this patient, implantable cardioverter defibrillator (ICD) was not (planned to be) implanted? Moreover, the patient was hypokalemic, which poses to a bigger risk for life-threatening cardiac arrhythmias. Please also clarify the approach has been done to fix this problem.
- The authors mentioned in the abstract that echocardiography showed dilation of all cardiac chambers. However, no quantitative assessment of the atrial diameter provided. Please add.
- I am still not sure why anti-tuberculosis drugs were prescribed while AFB test was negative? Is there any involvement of these drugs on the clinical presentation of the patient?
- What is the rationale of administering rivaroxaban in the patient prior to the hospital admission? Was that due to the DVT? Please speculate on the reason why thrombi still persisted after rivaroxaban therapy (perhaps could also be supported by patient's lab results)?
- In Figure 5, please add some details / labels on the abnormalities observed in the CT scan, including the location of thrombi in the pulmonary artery.
- Avoid using numbers 1), 2), 3) in the text. Convert them into words: first, second, etc. if necessary.
- In the abstract: *"We gave him ..."* please change into passive sentence similar to the rest of the manuscript.
- In the abstract: please add the administration route of streptokinase.
- Please convert the incidence of PE in six EU countries in the introduction into 1 in XXX. The way the authors reported the epidemiological data is not common.
- *"be better able to"* should be *"be able to better ..."*
- *"... determined quickly and accurately to reduce **patients'** mortality"*
- *"the patient had **undergone** a thrombectomy a month before ..."*
- *"SpO2 99% with 3 lpm nasal cannula"* should be *"3 liter per minutes oxygen via nasal cannula"*.
- *"morality"* should be *"mortality"*

## References

1. Mestroni L, Maisch B, McKenna WJ, Schwartz K, et al.: Guidelines for the study of familial dilated cardiomyopathies. Collaborative Research Group of the European Human and Capital Mobility Project on Familial Dilated Cardiomyopathy. *Eur Heart J*. 1999; **20** (2): 93-102 [PubMed Abstract](#) | [Publisher Full Text](#)



2. Mathew T, Williams L, Navaratnam G, Rana B, et al.: Diagnosis and assessment of dilated cardiomyopathy: a guideline protocol from the British Society of Echocardiography. *Echo Res Pract.* 2017; **4** (2): G1-G13 [PubMed Abstract](#) | [Publisher Full Text](#)

**Is the background of the case's history and progression described in sufficient detail?**

Partly

**Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?**

Partly

**Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?**

Partly

**Is the case presented with sufficient detail to be useful for other practitioners?**

Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Cardiovascular disease, cardiogenetics, cardiac arrhythmias, arrhythmogenesis, inherited arrhythmia syndromes, computational modeling and bioinformatics.

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Author Response 27 Jan 2021

**Citrawati Wungu**, Airlangga University, Surabaya, Indonesia

Thank you for your review. We have made revision according to your suggestions. These are our explanations regarding the comments:

1. We have added the distinctiveness of this case, that this was a rare case of protruded thrombus in the right atrium passing through the tricuspid valve which position moving from the inferior vena cava towards the right atrium, causing a massive pulmonary embolism and dilated cardiomyopathy.
2. We have added the history and supporting data as suggested.
3. We have added the explanation of the ejection fraction which had not improved at the follow-up visit. Ejection fraction was not an indicator for discharge in such patient. We have stated in the last paragraph of discussion section that the limitation of this case report was the unexplained etiology of hypercoagulability of this patient.
4. In this case report we did not focus on the DCM. However, DCM increases the risk of intracardiac thrombus which causes hypokinetic condition (venous stasis), a part of

Virchow's triad.

5. ECG in PE is less specific. The most common ECG finding in the setting of a pulmonary embolism is sinus tachycardia. S1Q3T3 is a specific pattern in PE, however, this pattern only occurs in about 10% of people with pulmonary embolisms and is similar to the ECG findings of a **left posterior fascicular block, or LPFB** (Mohammed and Elsayed, 2020).
6. It was a migrating thrombus from proximal femoral vein. The patient had a history of proximal bilateral femoral deep vein thrombosis (DVT) of the left inferior limb proven by ultrasonography examination and the patient had had a thrombectomy a month before his referral to the hospital. The complaints of swollen leg were slightly reduced at that time; however, had recurred again, accompanied by swelling on his right limb. He had no atrial fibrillation or tricuspid valve disease.
7. Endothelial abnormalities undoubtedly play a role in the enhanced activation of platelets and clotting factors seen in diabetes. Coagulation activation markers, such as prothrombin activation fragment 1+2 and thrombin-anti-thrombin complexes, are elevated in diabetes. The plasma levels of many clotting factors including fibrinogen, factor VII, factor VIII, factor XI, factor XII, kallikrein, and von Willebrand factor are elevated in diabetes. Conversely, the level of the anticoagulant protein C (PC) is decreased. The fibrinolytic system, the primary means of removing clots, is relatively inhibited in diabetes due to abnormal clot structures that are more resistant to degradation and an increase in plasminogen activator inhibitor type 1 (PAI-1). Increased circulating platelet aggregates, increased platelet aggregation in response to platelet agonists, increased platelet contractile force (PCF), and the presence of higher plasma levels of platelet release products, such as beta-thromboglobulin, platelet factor 4, and thromboxane B(2), demonstrate platelet hyperactivity in diabetes (Carr, 2001). However, our opinion is that the extensive thrombosis condition in this patient was not solely due to his diabetes. Hypercoagulability conditions can be related to genetic disorders, for example: Factor V Leiden (the most common), Prothrombin gene mutation, deficiencies of natural proteins that prevent clotting (such as antithrombin, protein C and protein S), elevated levels of homocysteine, elevated levels of fibrinogen or dysfunctional fibrinogen (dysfibrinogenemia), elevated levels of factor VIII (still being investigated as an inherited condition) and other factors including factor IX and XI, abnormal fibrinolytic system, including hypoplasminogenemia, dysplasminogenemia, and elevation in levels of plasminogen activator inhibitor (PAI-1) (Khan and Dickerman, 2006; Jan, 2020). However, we acknowledge that the weakness of this case report was that we did not have data for any genetic abnormalities.
8. There were no signs of LV noncompaction in this patient. No family history data was obtained. The Echo result did not show any trabeculations.
9. No genetic data available. DCM was diagnosed based on clinical and structural abnormalities by echocardiography. We found large ventricular enlargement with global hypokinetic and reduced ejection fraction.

10. ICD is indicated in heart failure patients with reduced EF (EF < 35) and no improvements with optimal medical treatment based on GDMT (Ponikowski *et al.*, 2016). In this patient we found high burden intracardiac thrombus, thus it will be so dangerous for us to perform ICD. It can make the thrombus escape and migrate, thus we focus on the emergency and gave GDMT as the optimal treatment.
11. We have added atrial diameter as follows: LA mayor 6.4 cm, LA minor 4.7 cm; RA mayor 5.5 cm, RA minor 4.5 cm, RVDB 3.2 cm.
12. In the public health center, the doctor diagnosed the patient with clinical TB with negative AFB, however, in the course of the assessments in the hospital, no clinical, laboratory, or radiological signs of pulmonary tuberculosis were found, thus the patient was transferred to the cardiology ward.
13. Rivaroxaban was prescribed as a DVT therapy that has been known before by the referring doctor. Persistent thrombus may be due to the patient's hypercoagulability condition. However, we cannot give more specific conclusions regarding this matter due to limited data and laboratory examination results.
14. We have inserted the arrow to the figure. In manuscript we have stated that the CT scan showed right pulmonary artery embolism at  $\pm$  5.9 cm from bifurcation on the anterior side of the intermediate right bronchus.
15. We have made changes to the formatting as suggested.

**References:**

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**Competing Interests:** No competing interests were disclosed.

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