







Systemic thrombolysis and anticoagulation improved biomarker measurements in massive-like pulmonary embolism and severe COVID-19 pneumonia: a case report

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Background

From asymptomatic patients to severe acute respiratory distress syndrome, COVID-19 has a wide range of clinical presentations, and venous thromboembolism has emerged as a critical and frequent complication.

Case summary

We present a case of a 69-year-old man with a clinical presentation of massive-like pulmonary embolism (PE) overlapping with severe COVID-19 pneumonia. The diagnosis was made based on hypotension, severe oxygen desaturation (33%), and right ventricular dysfunction (RVD). We used alteplase and low-molecular-weight heparin, obtaining immediate clinical improvement. Also, we identified an extremely elevated D-dimer (31.2 mcg/mL), and computed tomography pulmonary angiography (CTPA) revealed an unexpected low thrombus burden and a crazy-paving pattern. Considering this, we decided to discontinue the alteplase. Therefore, the mechanisms of pulmonary hypertension and RVD could be multifactorial. Despite the patient's respiratory status worsening and ongoing mechanical ventilation, biomarkers kept lowering to normal ranges. It appears a favourable outcome was related to early PE diagnosis and a multimodal therapeutic approach.

Discussion

Physicians in the ER should be warned about extremely high D-dimer measurements and severe oxygen desaturation as possible markers of severe COVID-19 pneumonia in patients with high-clinical suspicion of PE. Although ESC guidelines recommend immediate reperfusion in cardiogenic shock secondary to PE, we suggest initial CTPA in patients with high-clinical suspicion of severe COVID-19.

Keywords

Case report • COVID-19 • SARS-CoV-2 • Pulmonary embolism • Thrombolysis

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Learning points

- Overlapping severe COVID-19 pneumonia and pulmonary embolism (PE) is a challenge, extremely D-dimer measurements and severe oxygen desaturation are possible markers of severity.
- Bedside echocardiogram and biomarker measurements are critical elements in the assessment of COVID-19 and PE patients.
- Although ESC guidelines recommend the same thrombolytic regimes for COVID-19 patients, the ideal regime remains unknown.

Primary Specialties involved other than cardiology

Cardiology, Pneumology and Critical Care Medicine, Infectology

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was discovered in Wuhan, China, in late 2019, and coronavirus disease 2019 (COVID-19), the disease caused by SARS-CoV-2, rapidly evolved into a global pandemic. COVID-19 is characterized by high mortality predominantly in male patients secondary to severe acute respiratory distress syndrome.¹ However, among common complications observed in deceased patients with COVID-19 disease, venous thromboembolism has emerged as a critical and frequent complication. Currently, most of the data regarding this clinical association has been derived from hospitalized patients. Data on the clinical presentation, therapeutic approach, and biomarkers behaviour in outpatients are scarce.² Here we present the case of a 69-year-old man with a clinical presentation of massive-like pulmonary embolism (PE) overlapped with severe COVID-19 pneumonia in whom we observed immediate clinical improvement using a reduced alteplase dose. Additionally, we identified an unusual D-dimer (DD) measurement, multifactorial mechanisms of pulmonary hypertension, and upon admission, despite severe right ventricular dysfunction, a borderline B-type natriuretic peptide (BNP) value.

Timeline

Time	Events
Medical history	Hypertension, chronic obstructive pulmonary disease (COPD), obstructive sleep apnoea, arthritis, morbid obesity
27 days prior to admission	Contact with SARS-CoV-2 (+) son
Initial presentation	
On arrival to the ER	Clinical instability, oxygen desaturation (33%) Electrocardiogram: sinus tachycardia, S1Q3T3, qR, ST-elevation in V1 and aVR Chest X-ray: bilateral ground-glass opacity Transthoracic echocardiogram: severe right ventricular dysfunction Biomarkers: D-dimer 31.2 mcg/mL, B-type natriuretic peptide (BNP) 101 pg/mL, hs-cTnI 49.7 mcg/L

Continued

Continued

Time	Events
Day 1	Computed tomography pulmonary angiography: interlobar and segmental thrombi; extensive bilateral ground-glass opacity Recombinant tissue plasminogen activator 10 mg and enoxaparin 80 mg BID Influenza A and B negative Isolated intensive critical care (ICU) with telepresence robot for interaction Hydroxychloroquine, azithromycin, lopinavir/ritonavir
Day 2	Hemodynamic stability Hs-cTnI and BNP increased, D-dimer decreased Real-time reverse transcription-polymerase chain reaction (rRT-PCR): SARS-CoV-2 (+)
Day 3	Invasive mechanical ventilation due to respiratory failure Paradoxical improvement of biomarkers Hydroxychloroquine suspended (prolonged QTc) Tocilizumab is started
Day 5–8	Daily dose of hyperimmune plasma Improved ventilatory support
Day 9	Azythromycin discontinued
Day 14	Lopinavir/ritonavir discontinued
Day 20	Weaned off from mechanical ventilation Hospital-acquired pneumonia Negative antiphospholipid antibodies Switched enoxaparin 80 mg BID to rivaroxaban 20 mg QD
Day 29	rRT-PCR: SARS-CoV-2 (-) Discharged with rivaroxaban 20 mg QD
Follow-up	
At 15 days by telemedicine	Asymptomatic and undergoing physical rehabilitation

Case presentation

A 69-year-old man presented to the Emergency room (ER) with a 2-h history of stabbing pain in the right lower limb, associated with sudden dyspnoea, plus severe chest pain 6/10, presyncope, and profuse diaphoresis. His past medical history included former smoking, hypertension

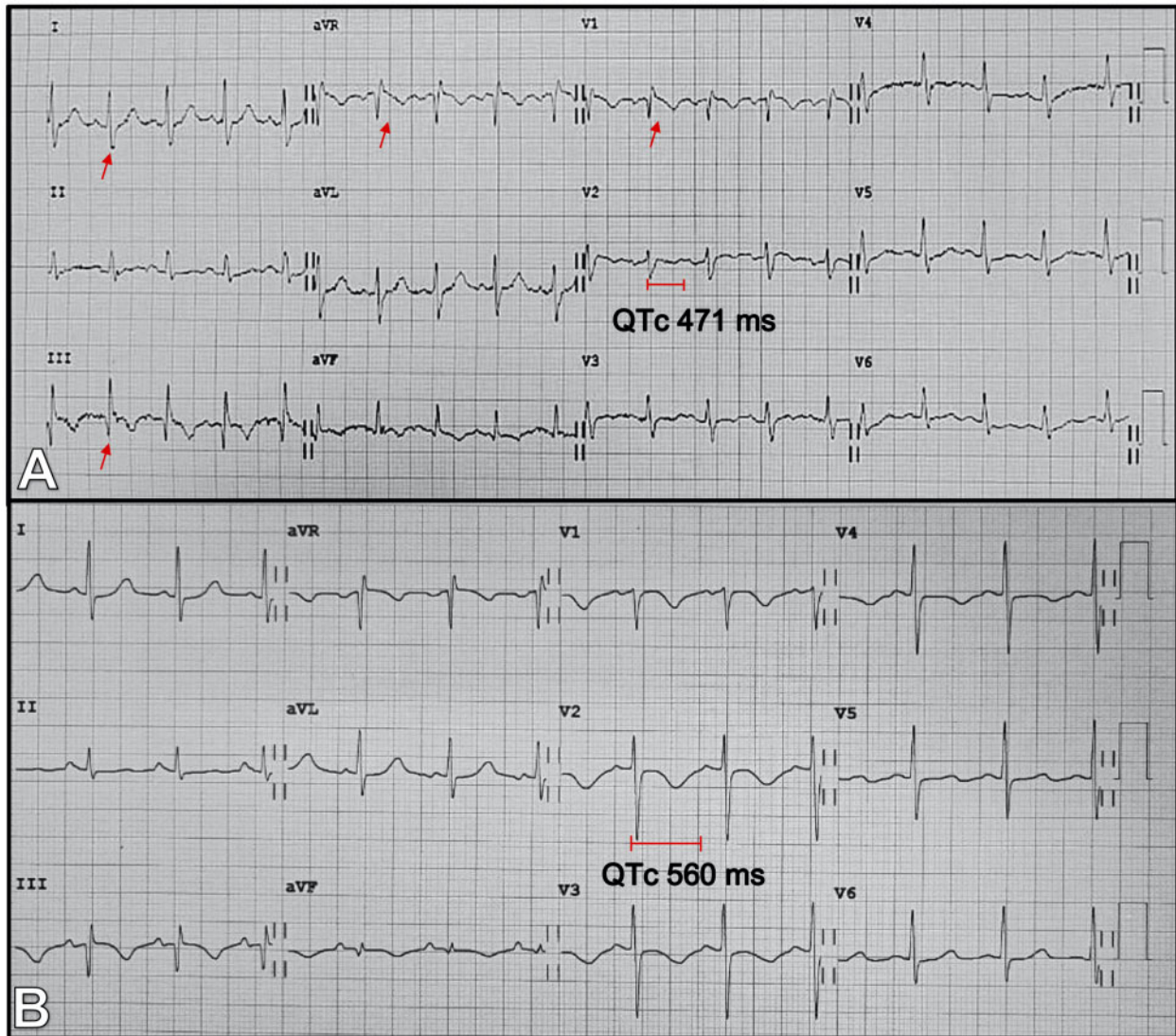


Figure 1 (A) Initial electrocardiogram with sinus tachycardia (110 b.p.m.), right axis deviation, QTc 471 ms, S1Q3T3 pattern, presence of qR, ST-elevation in V1 and aVR, inferior pseudonecrosis, and right ventricular systolic overload. (B) Follow-up electrocardiogram on Day 3, with prolonged QTc 560 ms. There is improvement of RV ischaemia and systolic overload.

(valsartan, hydrochlorothiazide, and atenolol), chronic obstructive pulmonary disease (non-specified treatment), obstructive sleep apnoea syndrome treated with continuous positive airway pressure (CPAP), undifferentiated arthritis (sulfasalazine and acetaminophen), and morbid obesity. Additionally, his son had been recently diagnosed with severe COVID-19 after a recent trip to Vail, Colorado, 31 days ago, and they had contact in Mexico City 27 days before his admission. On arrival at the ER, the patient was afebrile, with clinical instability, hypotension (80/50 mmHg), tachycardia (140 b.p.m.), respiratory failure (30 b.p.m.), and severe oxygen desaturation (33%). The physical examination revealed a stuporous patient with pallor, diaphoresis, loud S2, bilateral lung crackles, swollen feet, and a body mass index (BMI) of 42.1 kg/m². We started oxygen with a reservoir mask at 10 L/min, improving consciousness state, oxygen saturation (73%), and heart rate (HR) (110 b.p.m.).

The initial electrocardiogram (ECG) showed sinus tachycardia at 110 b.p.m., right axis deviation, QTc 471 ms, S1Q3T3, qR, ST-elevation in aVR and V1, and right ventricular overload (Figure 1A). A chest X-ray showed bilateral ground-glass opacity, and pulmonary infiltrates (Figure 2). A transthoracic echocardiogram revealed severe right ventricular dysfunction and hypokinesis, left ventricular ejection fraction (LVEF) of 80% by the Teicholz method, tricuspid annular plane systolic excursion (TAPSE) 9 mm, tricuspid regurgitation gradient of 28 mmHg, and pulmonary artery systolic pressure (PASP) of 48 mmHg (Video 1). Blood tests showed haemoglobin 14.6 g/dL (13.2–18.0 g/dL), $11.6 \times 10^3/\mu\text{L}$ leucocytosis ($4.5\text{--}11.0 \times 10^3/\mu\text{L}$), lymphocytes 700 per mm³ ($1000\text{--}4000$ per mm³), platelets $323 \times 10^3/\mu\text{L}$ ($150\text{--}420 \times 10^3/\mu\text{L}$), glucose 242 mg/dL (60–100 mg/dL), creatinine 1.3 mg/dL (0.7–1.3 mg/dL), hypoalbuminaemia 2.6 g/dL

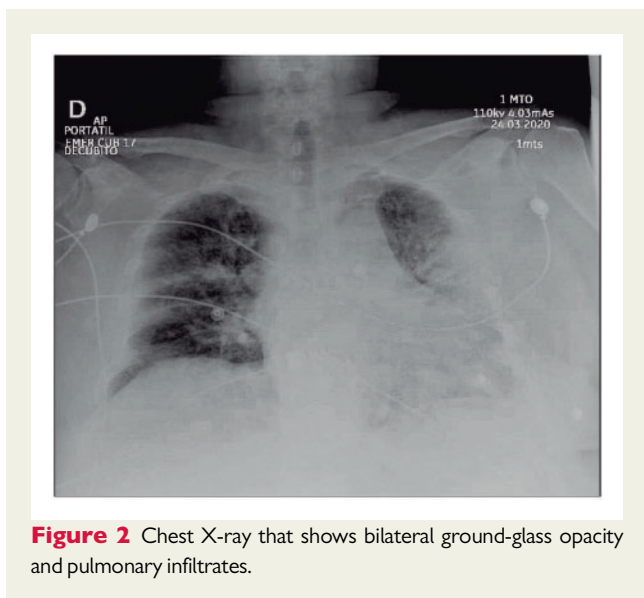
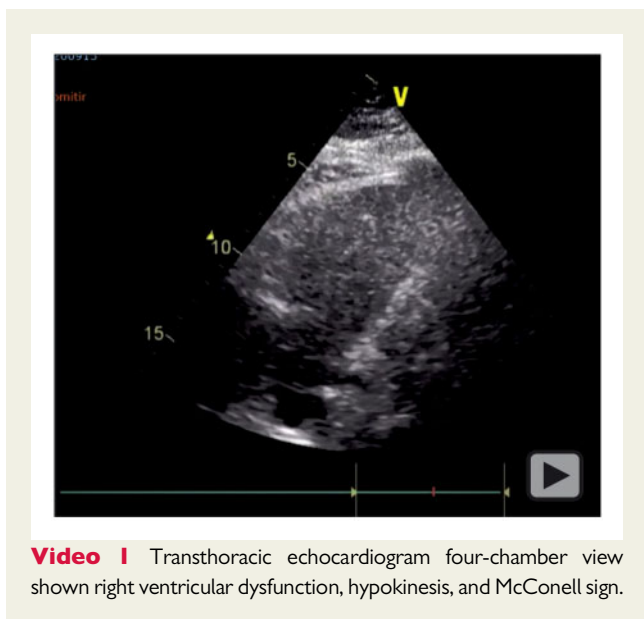


Figure 2 Chest X-ray that shows bilateral ground-glass opacity and pulmonary infiltrates.



Video 1 Transthoracic echocardiogram four-chamber view shown right ventricular dysfunction, hypokinesis, and McConnell sign.

(3.5–5 g/dL), lactate dehydrogenase (LDH) 528 U/L (125–243 U/L), sodium 139 mEq/L (136–145 mEq/L), potassium 3.7 mEq/L (3.5–5.1 mEq/L), chloride 98.2 mEq/L (98–107 mEq/L), and fibrinogen 551 mg/dL (238–498 mg/dL).

Biomarkers revealed a DD of 31.2 mcg/mL (<0.5 mcg/mL), BNP 101 pg/mL (<100 pg/mL), high-sensitivity troponin I (hs-cTnI) 49.7 ng/L (<2 ng/L) (Figure 5), high-sensitivity protein C 22.68 mg/dl (0.00–0.50 mg/dL), ferritin 304 ng/mL (20–250 ng/mL), and procalcitonin 0.55 ng/mL (<0.5 ng/mL). Based on risk factors, clinical presentation, a very high-risk pulmonary embolism severity index (PESI) score (239 points), and high-risk sPESI score (3 points), chest X-ray, biomarkers, and echocardiographic findings, we established a high-clinical suspicion of massive PE and community-acquired pneumonia.

We decided to commence treatment using alteplase with a 10 mg bolus, followed by 40 mg in 2 h and enoxaparin 80 mg BID. The computed tomography pulmonary angiography (CTPA) revealed a dilated main pulmonary artery (34 mm) and the presence of thrombus located in the right interlobar artery and the segmental branches of the superior left lobe and inferior left and right lobes (Figure 3). Unexpectedly, the lung parenchyma revealed a crazy-paving pattern, highly suggestive of severe COVID-19 pneumonia (Figure 4). Immediately after the 10 mg alteplase bolus, consciousness state, blood pressure (120/85 mmHg), HR (100 b.p.m.), and respiratory rate (25 b.p.m.) improved. Severe oxygen desaturation remained low (75%) despite using a reservoir oxygen mask at 10 l/min. Considering the thrombus burden and severe pneumonia, we decided to discontinue the 40 mg alteplase infusion and transfer the patient to the COVID-19 isolated ICU. To protect the patients and healthcare workers, we used a telepresence robot for daily interaction. The rapid nucleic acid amplification test for influenza A and B was negative. We collected samples following Center for Disease Control and Prevention (CDC) guidance (serum, and nasopharyngeal and oropharyngeal swab specimens). The patient received enoxaparin 80 mg BID, oral hydroxychloroquine 200 mg thrice in a day (TID), azithromycin 500 mg QD, IV ceftaroline 1 g QD, oral lopinavir/ritonavir 200/50 mg BID, and IV paracetamol 1 g TID.

On Day 2, the patient remained mostly stable. Upon follow-up examination, hs-cTnI and BNP increased, and D-dimer decreased (Figure 5). A chest X-ray reported a slight improvement of bilateral ground-glass opacity and pulmonary infiltrates. The nasopharyngeal and oropharyngeal swabs tested positive for SARS-CoV-2 by real-time reverse transcription-polymerase chain reaction (rRT-PCR) assay.

On Day 3, due to respiratory failure and diagnosis of acute respiratory distress syndrome (ARDS) we started invasive mechanical ventilation (FiO₂ 70%, PEEP 16, and Kirby index of 105). The patient had hypotension as a side effect of sedation, which required transient inotropic support (norepinephrine). For the mechanical ventilation, we used A/C mode, with lung-protective ventilation using tidal volumes of 6 mL/kg predicted body weight and inspiratory pressure of 12 cmH₂O. We maintained an initial respiratory rate (RR) 16 b.p.m., I:E relation of 1:1.5, and a constant PEEP of 16 cmH₂O with decremental titration. We provided prone ventilation, and we did not use recruitment manoeuvres. Despite clinical worsening, the biomarkers continued to improve (Figure 5). We stopped hydroxychloroquine due to abnormal QTc (up to 560 ms) on follow-up ECG (Figure 1B). We administered three doses of tocilizumab 800 mg TID and continued full anticoagulation with enoxaparin. We maintained the norepinephrine support intermittently for nine days.

On Days 5 through 8, due to clinical worsening and the high viral load, we administered three doses of hyperimmune plasma each day, with improvement in ventilatory support (Kirby index of 187). On Day 9, we discontinued azithromycin, and after 14 days lopinavir/ritonavir.

On Day 15, the patient had a fever, and we suspected a ventilator-associated pneumonia. We obtained a tracheal aspirate culture, which showed *Klebsiella pneumoniae*, and we started meropenem for 7 days. After 20 days, clinical, ventilatory, and laboratory parameters

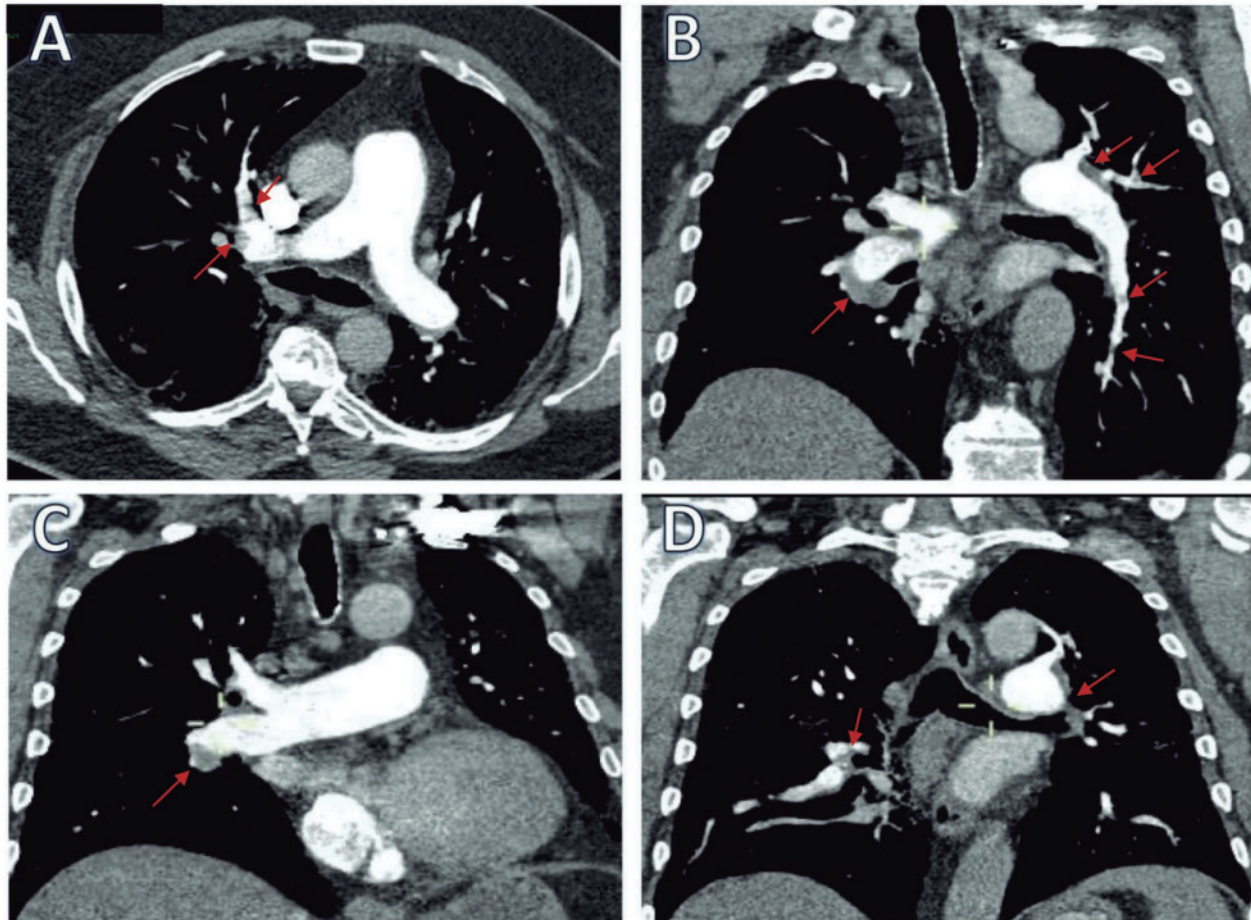
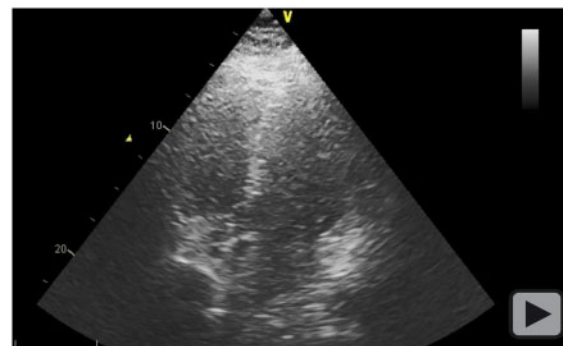


Figure 3 Computed tomography pulmonary angiogram. (A) An axial view with main pulmonary artery dilation with a diameter of 34 mm and the presence of thrombus located in the right interlobar artery. (B) A coronal view with thrombus in the segmental branches of the superior and inferior left lobe. (C, D) A coronal view with thrombus in the right interlobar artery and thrombus in segmental branches of the inferior right lobe, respectively.

improved (Figure 5), and we successfully removed the patient from mechanical ventilation.

The patient remained in hospital with episodes of delirium and intermittent dry cough, with oxygen saturation of 98% and ongoing enoxaparin 80 mg BID. A repeat rt-PCR swab was negative for SARS-CoV-2 and negative anti-cardiolipin IgM, IgG, Beta-2-glycoprotein antibodies, and phosphatidylserine IgA, IgM, and IgG were reported. We did not perform lower limb ultrasound and further CTPA due to critical illness.

After 29 days, the patient was discharged with propranolol 10 mg TID, losartan 50 mg BID, amlodipine 5 mg QD, and rivaroxaban 20 mg QD. In a telemedicine follow-up office visit 15 days later, the patient remained asymptomatic and was undergoing physical rehabilitation. A follow-up echocardiogram performed four months after initial presentation showed improvement in right ventricular size and function, with a TAPSE of 23 mm (Video 2).



Video 2 Transthoracic echocardiogram follow-up shown normal right ventricular function.

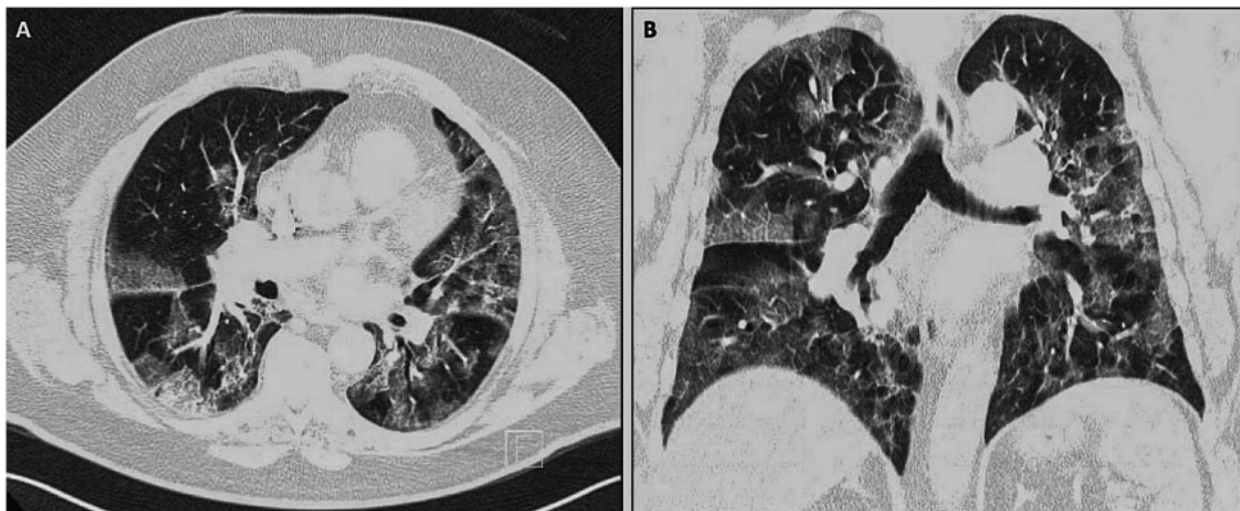


Figure 4 Chest computed tomography. (A) A classic crazy-paving pattern, with extensive bilateral ground-glass opacities in middle and lower lobes. Upper lobes extension of the aforementioned opacities is depicted in (B).

Discussion

The main observations of this case were as follows: firstly, after thrombolysis and anticoagulation, DD measurements improved. Secondly, upon admission BNP was discordantly low despite severe right ventricular dysfunction, likely related to a short time between the onset of symptoms and admission to hospital; in the next 24 h BNP correlated with the presence and degree of right ventricular dysfunction and higher hs-cTnI measurements, suggesting type 2 myocardial infarction³ (Figure 5). Thirdly, this case was a clinical challenge because acute PE and COVID-19 pneumonia overlapped. Finally, this case represents—to our knowledge—the first description of biomarkers (DD, BNP, hs-cTnI) in scenarios involving COVID-19 pneumonia and PE.

Since the first clinical description,⁴ abnormal DD measurements and age have been related to increased mortality and a high prevalence of thrombotic events in COVID-19.^{5,6} Patients with severe COVID-19 disease are at high-risk of thromboinflammation since they have proinflammatory risk factors and cardiopulmonary comorbidities related to inflammation.⁷ The SARS-CoV-2 infection leads to a cytokine storm, inducing endothelial activation, cell damage, increased platelet aggregation, thrombi sensitivity, arterial inflammation, as well as disruption of vulnerable plaques.^{8,9} Interleukin-6 (IL-6) induces the expression of several prothrombotic factors and dysregulation of antithrombin III, protein S, and thrombomodulin.^{9,10} Additionally, it could activate immunothrombosis, another thrombosis mechanism.¹⁰ All these mechanisms can induce diffuse microangiopathy with micro and macro thrombosis.¹¹ Also, SARS-CoV-2 may predispose to both venous and arterial thrombosis secondary to antiphospholipid antibodies,^{12,13} hypoxia, immobilization, and diffuse intravascular coagulation.¹⁴

Among the common complications observed in deceased patients with severe COVID-19,⁷ venous thromboembolism (VTE) has emerged as a critical and frequent complication.⁹ Currently, we do not have strong evidence of the overall incidence and recommendations for in-hospital anticoagulation in patients with PE.^{9,11,15} However, the available evidence suggests a frequency of 25% to 27% in ICU patients^{14,16} and imaging has demonstrated both unilateral and bilateral thrombus (small branches, segmental, lobar, and main pulmonary artery).^{5,17,18} DD measurements seem to be an available test to identify high-risk groups of VTE^{14,18} and patients that need different doses of enoxaparin [low (0.6 mg/kg/12 h)¹⁸ or standard treatment¹⁷].

In this complicated case with overlapping severe COVID-19 pneumonia and PE, the clinical presentation suggesting massive PE drove the decision to use systemic thrombolysis. We supported the high-clinical suspicion of massive PE based on sudden dyspnoea, chest pain, presyncope, a fall in blood pressure, ECG changes, echocardiographic findings, as well as signs of deep venous thrombosis. We decided to interrupt the alteplase infusion based on thrombus burden, which was lower than expected considering the clinical presentation of massive PE, a high rate of bleeding (16%) in populations with respiratory failure¹⁵ and lacking recommendations in severe COVID-19 disease.^{9,15} A relevant observation is that after the alteplase bolus, an immediate significant clinical improvement suggesting reperfusion appeared. This result could represent the effectiveness and safety of 10 mg or 5 mg alteplase bolus to initiate fibrinolysis in ST-elevation myocardial infarction¹⁹ and left atrial thrombus, respectively.²⁰ Also, another low dose of alteplase (30 mg) was safe and effective in submassive PE patients,²¹ and an alteplase bolus of 10 mg followed by a 2-h 40 mg infusion in ARDS²² and pulmonary vascular phenotype COVID-19 patients.²³

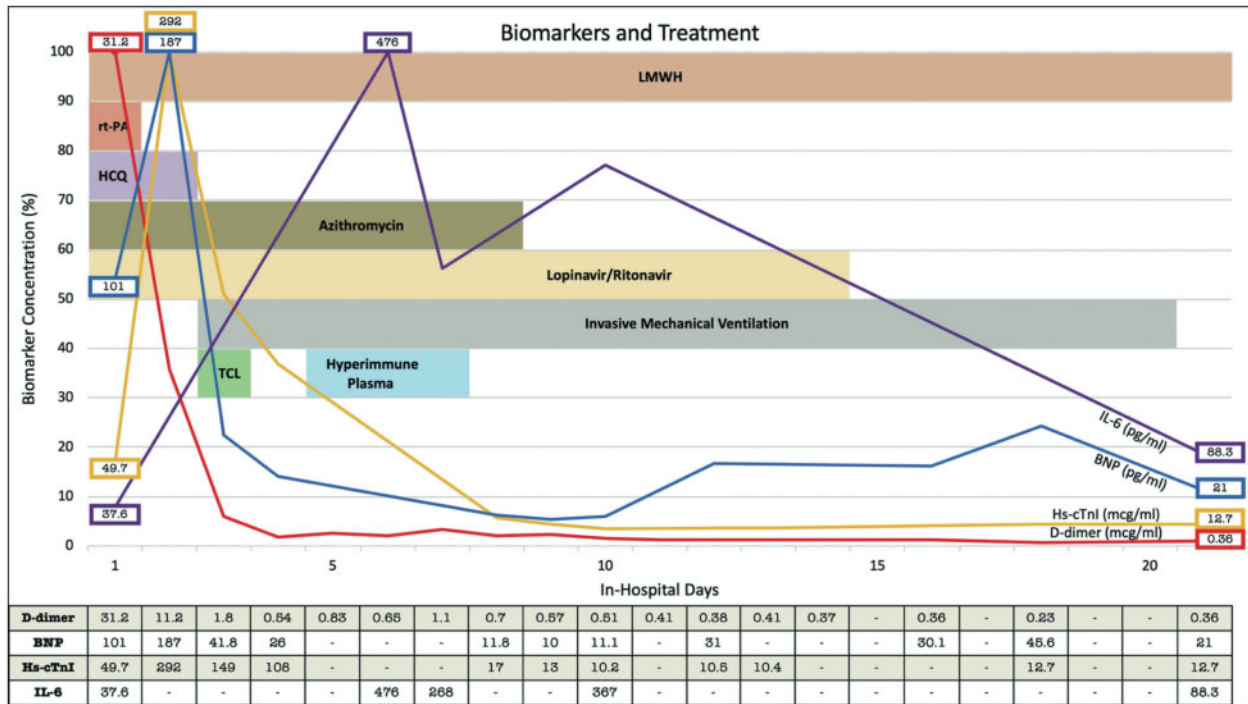


Figure 5 Biomarker values on admission and their immediate reduction following anticoagulation and thrombolytic treatment. We also demonstrate biomarkers in-hospital follow-up, the IL-6 behaviour, and the therapeutic approach during the in-hospital stay. D-dimer red line, B-type natriuretic peptide blue line, Hs-cTnI yellow line, and IL-6 purple line. HCQ, hydroxychloroquine; LMWH, low-molecular-weight heparin; rtPA, recombinant tissue plasminogen activator; TCL, tocilizumab.

After thrombolysis, in the first 96 h, enoxaparin achieved a significant decrease in DD measurements (Figure 5). Considering the clinical condition, the evidence suggesting prophylactic anticoagulation failure,²⁴ and the high risk of recurrence (individual, COVID-19, ICU, and hospital stay), we sustained the subcutaneous therapeutic anticoagulation without bleeding complications during the in-hospital stay. At admission, the exceptionally high DD levels observed suggested hyper-inflammation, hypercoagulability, and an actual thrombotic disease, possibly induced by cellular activation triggered by the virus,²⁵ and resemble the extremely high values encountered in COVID-19 related acute or pulmonal,²⁶ as well as thrombotic events in cerebral²⁷ and coronary circulation.²⁸ Additionally, we should never ignore abnormal or extremely elevated DD levels²⁹ in COVID-19, since it is the expression of the coagulation system and fibrinolysis activity, suggesting high-risk of acute thrombosis.²⁹ Although, in our case, the extremely elevated DD levels could be explained by the association of severe COVID-19 and VTE, we cannot exclude the possibility of subclinical cancer.³⁰ After anticoagulation therapy, reduced DD levels suggest anticoagulation effectiveness¹⁶ (Figure 5). Preliminary evidence suggests mortality benefit from anticoagulation in severe COVID-19 disease,³¹ including anti-inflammatory mechanisms.³² Upon admission, the measurement of hs-cTnI suggested myocardial injury with a subsequent increase (likely due to type 2 myocardial infarction) still detectable until 96 h later³³ (Figure 5), similar to the behaviour observed in PE patients.³³ The initial therapeutic approach decreased the expression of hs-cTnI, which is historically

related to poor in-hospital outcomes in COVID-19¹⁵ and non-COVID-19 patients.³ Another interesting finding was the initial borderline BNP measurements despite severe RVD. B-type natriuretic peptide concentration might seem discordantly low in flash pulmonary oedema (1 h), acute pulmonary oedema secondary to acute mitral regurgitation, immunologic myopericarditis with predominantly right ventricular involvement³⁴ and submassive PE.³⁵ In these settings, BNP gene expression may have had insufficient time between the initial trigger of increased ventricular wall stress and the measurement of BNP concentrations, since the half-life of BNP is 23 min and 2 h are required for its full expression.³⁵ The mechanism of massive PE and initial almost normal BNP value was the immediate patient presentation after symptom onset.³⁵ This case identifies another clinical condition characterized by severe ventricular dysfunction and discordantly low BNP. BNP measurements in the next 24 h correlated with the right ventricular dysfunction stage and reperfusion,³⁶ and serial measurements were useful in assessing the success of thrombolysis and anticoagulation.³⁶ Despite worsening respiratory effects and mechanical ventilation, BNP remained below 50 pg/mL until discharge (Figure 5).

Non-COVID-19 pneumonia and PE have a frequent association (65.6%) that increases mortality.³⁷ This patient with risk factors for PE and risk factors for severe COVID-19 disease had both acute events at home. Current evidence regarding COVID-19 pneumonia and PE comes from in-hospital series and case reports.^{5,14,17,18,26,38-40} Therefore, the clinical presentation of an acute PE in the setting of

severe COVID-19 pneumonia in an outpatient is not clear. Recently, in a case series of PE patients with risk factors, the clinical presentation was characterized by persistence or worsening of respiratory symptoms with increasing oxygen requirements. Besides, DD levels were several-fold higher than the normal upper threshold.² Recently, systemic thrombolysis in one massive PE patient with COVID-19 induced bleeding complications as the cause of mortality;² however, the thrombolytic regimen and the bleeding complication were not described. Initial clinical behaviour in this case was similar to that observed in non-COVID-19 submassive and massive PE patients.^{41,42} Considering CTPA findings, the mechanisms of pulmonary hypertension and right ventricular dysfunction could be multifactorial, including pulmonary thrombi, hypoxic pulmonary vasoconstriction,⁴³ and possible pulmonary microthrombi.^{23,44} Also, SARS-CoV-2 direct down-regulation of ACE2 may result in unopposed angiotensin II accumulation and local renin-angiotensin-aldosterone system (RAAS) activation, increasing pulmonary vasoconstriction.⁴⁵ Finally, the favourable outcome was related to early PE diagnosis and a multimodal therapeutic approach, including respiratory support, fibrinolysis activation, coagulation system inhibition, antivirals, antibiotics, a monoclonal antibody, and hyperimmune plasma (Figure 5). We also need current and robust evidence to identify if we need a different thrombolytic regimen to those currently recommended.^{26,46}

Conclusion

Physicians in the ER should be warned about high or extremely elevated DD measurements and severe oxygen desaturation, as possible risk markers of severe COVID-19 pneumonia in patients with high-clinical suspicion of PE. Also, they should be aware of this 2-h lag period before the onset of BNP increase to avoid underdiagnosing right ventricular dysfunction.³⁵ Finally, we suggest CTPA before starting immediate reperfusion in a severe COVID-19 patient with high-clinical suspicion of massive PE.⁴⁶

Lead author biography



Héctor Betancourt del Campo is a Cardiology Fellow in training and has an Internal Medicine PhD. He actually practices echocardiography, heart failure, haemodynamics, and electrophysiology in Zambrano Hellion Hospital, TecSalud of Tecnológico de Monterrey. He is interested in becoming an Electrophysiology Fellow next year.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidelines.

Conflict of interest: none declared.

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References 21 to 46 are available in [Supplementary material online](#).