Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editors-in-Chief

Arterial and venous thromboembolic disease in a patient with COVID-19: A case report

Dear Editors,

We read with great interest the study of Klok et al. [1], about the sky-high (31%) incidence of thrombotic complications despite thromboprophylaxis in ICU patients with COVID-19, and the letter by Rotzinger et al. [2], about their plea to perform a CT pulmonary angiography (CTPA) instead of a non-contrast chest CT in patients with respiratory deterioration or elevated D-dimer levels. While both articles are interesting and further generate hypotheses about the causal role of pulmonary embolism (PE) in clinical worsening of patients with COVID-19, we would like to take a moment to reflect on their papers, with an intriguing case presentation that highlights and further substantiates several key points.

We describe a patient with COVID-19 who consecutively developed an arterial (ischemic stroke) and venous thromboembolic event (PE) despite thromboprophylaxis with low molecular weight heparin (LMWH), following treatment for ischemic stroke with intravenous rt-PA (alteplase) and clopidogrel. On top of that PE was diagnosed after two previously performed CTPA imaging studies were negative.

1. Case presentation

A 57-year-old male with a history of peripheral arterial disease (PAD) presented to the emergency department with progressive cough, dyspnea, thoracic pain, headache and fever for 5 days. Vital signs revealed hypertension (150/70 mmHg), tachycardia (110 bpm), hypoxia (SpO2 of 87% at ambient air, respiratory rate: 16/min), and fever (40 °C). Laboratory results were notable for d-dimer (908 μg/L), lactate dehydrogenase (585 U/L) and C-reactive protein (78 mg/L). Because of thoracic pain, tachycardia and an elevated d-dimer level, CTPA, instead of a non-contrast chest CT, was performed, revealing pulmonary abnormalities consistent with COVID-19 pneumonia (Fig. 1a), while pulmonary embolism (PE) was ruled out (Fig. 1b). Oxygen via nasal cannula (3 L), amoxicillin, chloroquine and prophylactic LMWH (nadroparin 3800 IU sc daily) were started upon admission.

On day 2, COVID-19 was confirmed by reverse transcriptase-polymerase chain reaction assay of SARS-CoV2-mRNA with a Ct value of 23. The patient deteriorated rapidly and was transferred to the medium care unit (MCU) for intensified oxygen therapy via a non-rebreathing mask (15 L, FiO2 80%). A new CTPA was performed, showing severe progression of ground glass opacities and crazy paving patterns (Fig. 1c) and PE was again ruled out (Fig. 1d).

On day 5, the patient developed dysarthria, left-sided weakness and neglect. CT-imaging of the brain (including CT-angiography and CT-perfusion) showed no brain haemorrhage (Fig. 2a) or arterial occlusion, yet a defect right frontal with large mismatch between perfusion and vascular volume recordings, indicative of right frontal lobe infarction, was seen (Fig. 2b). No atrial fibrillation (AF) was observed in the MCU. He received intravenous rt-PA and after 24 h clopidogrel was initiated for secondary stroke prevention. Pragmatically, thromboprophylaxis was also increased to intermediate dose (nadroparin 5700 IU sc daily).

On day 7, further respiratory deterioration occurred. PE was deemed unlikely because of the recently administered rt-PA, intermediate-dose thromboprophylaxis, clopidogrel and two recent negative CTPAs. Nevertheless, a third CTPA was performed after a chest x-ray had excluded pleural effusion and pneumothorax, and repeated d-dimers were > 10,000 μg/L. Remarkably, the COVID19-associated lung damage seemed to be improving (Fig. 1e), but multiple PE in the right pulmonary artery (Fig. 1f) and bilateral (sub)segmental PE were found. Therapeutic LMWH (tinzaparin 18,000 IU sc daily) was initiated. The patient is still recovering in the MCU, but is soon to be discharged to a regular nursing ward. Of note, family history for (VTE) and antiphospholipid antibodies (lupus anticoagulant, IgG and IgM for anticardiolipin and IgG for anti-β2-glycoprotein I) were negative.

2. Discussion

COVID-19 appears to be associated with a strong thrombotic tendency, due to thrombo-inflammation, probably driven by distinct mechanisms that still require exploration [3]. This case provides vital clues why the COVID-19-pandemic leads to very poor outcome in some individuals [4].

First, it reveals an unusually high burden of consecutive thromboembolic events in both the arterial and venous vascular beds, despite thromboprophylaxis and several other anticoagulant treatments, and in the absence of additional risk factors including atrial fibrillation, family history for VTE, or antiphospolipid antibodies. An additional risk factor for stroke that was not excluded was patent foramen ovale. Although, transthoracic echocardiography showed a structurally normal heart, no 'bubble-contrast' study was performed. However, according to young stroke guidelines [5] combined with patient's age, calcifications at the level of the carotid bifurcation, and history of PAD, there was no strict indication to perform such a contrast study.

Second, it also shows the diagnostic challenges in patients with COVID-19, and in particular those who deteriorate rapidly. The impossibility to differentiate between respiratory failure due to progression of lung-tissue related abnormalities such as ground glass opacities or ARDS on the one hand and PE on the other hand is unprecedented. Where normally an alternative diagnosis is rather reassuring and actually reduces the risk of concurrent PE, in patients with COVID-19 this is at least questionable. In fact, our case shows that both, progression of COVID-related abnormalities and PE, can occur simultaneously or in a very short time frame. Eventually, repeated d-dimer (> 10.000 μg/L) was decisive to perform CTPA a third time. A report of the National Institute of Public Health for the Netherlands (RIVM) suggests that the combination of d-dimer levels increasing progressively and clinical worsening is suggestive for PE [6]. D-dimer elevations also have already been associated with poor

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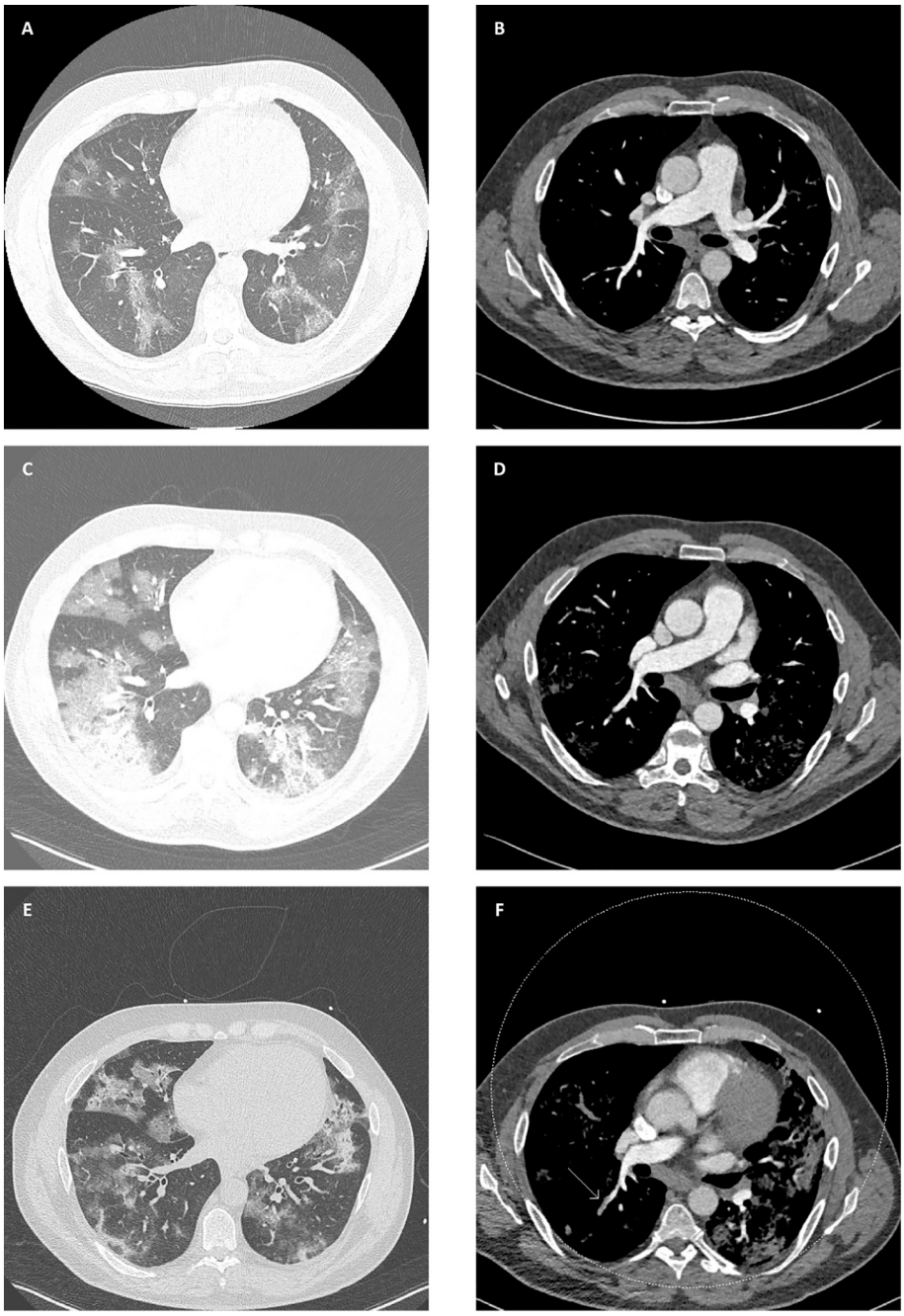

Fig. 1. CT scans of the chest.
(A) High resolution chest CT scan performed at admission, showing ground-glass abnormalities with and without reticulation ("crazy paving") with a predominantly peripheral distribution, consistent with COVID-19-related pneumonia.
(B) CTPA performed at admission that did not reveal signs of pulmonary emboli.
(C) High resolution chest CT scan performed on day 2, showing a marked increase in COVID-19-related pulmonary involvement and new areas of consolidation.
(D) CTPA performed on day 2, again showing no signs of pulmonary embolism.
(E) High resolution chest CT scan performed on day 7, showing improvement of COVID-19-related pulmonary changes with less extensive abnormalities and signs compatible with organising pneumonia.
(F) CTPA performed on day 7, showing lobar (arrow) and subsegmental (not shown) pulmonary emboli.

prognosis [7]. Therefore, we believe that CTPA should be considered at a low threshold in patients with unexplained respiratory deterioration, certainly when d-dimer levels have increased progressively. In retrospect, we could have performed compression ultrasonography of the legs (CUS) before proceeding to the second or third CTPA [8]. If CUS would have been positive, an indication for anticoagulant therapy would be present already and another CTPA could have been avoided. It also would have helped in fully understanding the course of events, although deep vein thrombosis is lacking in the majority of patients [9].

In summary, this case highlights hypercoagulability as a major contributor to COVID-19 related complications and suggests that commonly used diagnostic and therapeutic approaches may be insufficient to ameliorate the risk of thromboembolic events, underscoring the need to remain vigilant for the occurrence of these events in patients with COVID-19.

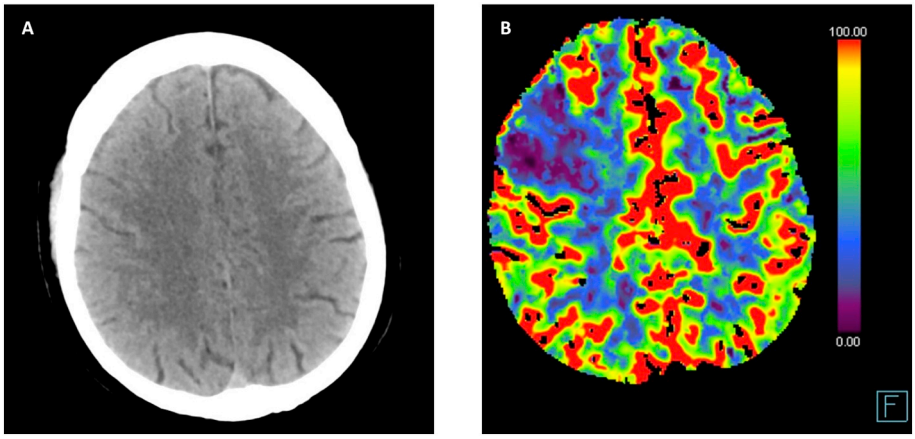

Fig. 2. CT imaging of the brain.
(A) CT excluding brain haemorrhage.
(B) CT-perfusion showing a defect right frontal with large mismatch between perfusion and vascular volume recordings, indicative of right frontal lobe infarction.

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Declaration of competing interest

The authors have declared no conflicts of interest.

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