Clot-in-transit cardio-pulmonary thrombosis during convalescent phase of COVID-19

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Running title: Clot-in-transit COVID-19 thrombosis

Keywords: Clot-in-transit, COVID-19, convalescent, cardiac, echocardiography, thrombosis

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Previous presentation in conferences; not applicable

Acknowlegdements: not applicable

Funding statement: not applicable

Conflicts of interest: The authors declare no competing interests

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Sir,

Acute pulmonary thromboembolism (PTE) is a known complication in patients with respiratory symptoms of coronavirus disease 2019 (COVID-19) infection [1]. However, acute PTE is rarely reported as late sequelae in asymptomatic or minimally symptomatic cases of COVID-19 infection [1–3]. We herein present a case of asymptomatic nasopharyngeal reverse transcriptase–polymerase chain reaction (RT-PCR) swab positive COVID-19 patient developing massive acute PTE during the convalescent phase of SARS-CoV-2 infection, nearly 4 weeks after two consecutive negative nasal swab results.

A 41-year-old man (weight, 99 kg; height, 177 cm), was diagnosed with asymptomatic COVID-19 disease based on the positive nasopharyngeal SARS-CoV-2 RT-PCR swab result and household contact with a proven COVID-19 case. He had no prior comorbidities, except a history of lower limb cellulitis induced deep vein thrombosis 5 years earlier, for which he received anticoagulation therapy for 6 months duration and had completely recovered. He was managed on home isolation for 16 days until the two consecutive nasal swabs done on day 11 and day 15 of the disease were negative. During this period, he remained ambulatory and received 4 weeks of low-dose enoxaparin prophylaxis. Nearly 42 days following the disease onset, he presented with dyspnea, hypoxemia (room-air oxygen saturation of 91%), and hypotension. D-dimer (>35200 ng/ml), C-reactive protein (94.8 mg/L) and Troponin-T (1.196 mcg/L) were elevated. His repeat RT-PCR swab was negative. Transthoracic
echocardiography showed large freely mobile right atrial (RA) thrombus 5 cm x 0.8 cm attached to the posteroinferior wall, normal left ventricle, dilated right ventricle (RV), severe pulmonary hypertension (systolic pressure 60 mmHg), and moderate tricuspid regurgitation. CT chest did not show pulmonary consolidation. CT pulmonary angiogram (CTPA) showed extensive right and left pulmonary artery thrombosis, enlarged RA and RV with filling defects. In the first 24 hours, he was treated with intravenous fluids, inotropes and tissue plasminogen activator (t-PA) thrombolytic therapy that resulted in improvements in his vital signs to blood pressure 110/75 mmHg, heart rate 76 beats / min and oxygen saturation 96% on 2 L/min nasal oxygen. Subsequently, he was started on therapeutic dose subcutaneous enoxaparin and transesophageal echocardiography (TEE) was performed to delineate the extent and burden of cardiac thrombosis. 2D and 3D TEE showed a large right atrial thrombus attached to Chiari network, a strangulated thrombus 1.1 cm x 0.3 cm in transit crossing the patent foramen ovale, thrombus of both branches of main pulmonary artery, right ventricular dilatation with mild dysfunction and minimal tricuspid regurgitation (Fig. 1). Later, due to significant hemodynamic instability, an emergency pulmonary thrombectomy under cardiopulmonary bypass was performed. Immediate post bypass TEE showed complete resolution of pulmonary thrombus burden but with severe RV dysfunction. However, he was weaned off mechanical ventilation the next day and inotropes after 3 days. Follow-up echocardiography a week later showed no residual thrombus and normal RV function.

While, thromboembolic complications seem to be an important issue in patients with severe COVID-19 disease, with an incidence as high as 20 to 30% [1], there exist only a few reports describing such complications following recovery from symptomatic COVID-19 disease [1,2]. A single-center report of 163 patients without post-discharge thromboprophylaxis suggested a 2.5% cumulative incidence of thrombosis at 30 days following discharge, including segmental pulmonary embolism, intracardiac
thrombus, thrombosed arteriovenous fistula and ischemic stroke [4]. In a recent case-series, Tu et al. reported 10 cases of acute ischemic stroke in adults 50 years or younger in the convalescent phase of asymptomatic COVID-19 infection. The median (range) time from a positive serological test result to acute ischemic stroke was 54.5 (0-130) days [5]. However, none of these patients were on thromboprophylaxis. Thus, the present case is unique as the patient developed massive acute pulmonary embolism nearly 42 days post-asymptomatic COVID-19 infection despite thromboprophylaxis.

Further, the present case highlights the possibility of prolonged COVID-19-associated coagulopathy (CAC) following asymptomatic SARS-CoV-2 infection resulting in massive cardiopulmonary thrombosis in the convalescent phase. Pow et al. reported a similar case of submassive pulmonary embolism during the convalescent phase in a patient with minimally symptomatic SARS-CoV-2 infection [2]. However, as their patient had a positive nasal swab result on readmission, it raised the possibility of reinfection resulting in hypercoagulable state instead of prolonged CAC as a cause of submassive pulmonary embolism. Probable mechanisms of CAC and thrombosis in post-acute COVID-19 syndrome include dysregulated renin-angiotensin system activity, endothelial dysfunction, cytokine induced inflammation, complement and platelets activation, platelet-leukocyte interaction, neutrophil extracellular traps, anti-lupus anticoagulants, up-regulation of tissue factor, thrombin and fibrin with down-regulation of fibrinolytic and anticoagulant mechanisms [1,2,4]. The risk of thrombotic complications in the post-acute COVID-19 phase is probably linked to the duration and severity of a hyperinflammatory state, although how long this persists is unknown [4].

Given the increase in thrombotic complications post-acute COVID-19 infection, Nalbandian et al. argued that extended post-hospital discharge (up to 6 weeks) and prolonged primary
thromboprophylaxis (up to 45 days) in those managed as outpatients may have a more favorable risk–benefit ratio [4]. However, individual patient-level considerations for risk versus benefit should dictate recommendations at this time. The elevated D-dimer levels, in addition to comorbidities such as cancer and immobility, may help to risk-stratify patients at the highest risk of post-acute thrombosis [4]. Notably, increased D-dimer levels (>500 ng/ml) were observed in 25.3% of patients up to 4 months post-SARS-CoV-2 infection [3]. Thus, elevated D-dimer levels and history of deep vein thrombosis (even though not associated with hypercoagulable disorders) might have placed our patient at high risk of thrombotic complications despite thromboprophylaxis and ambulation. Furthermore, as optimal therapy is not defined for COVID-19 associated thrombosis, this might have resulted in an unsuccessful outcome with the thrombolytic therapy in our patient. In conclusion, we highlight the possibility of late-onset acute COVID-19 associated thrombosis even in asymptomatic infections, the lack of understanding of the appropriate dose and duration of thromboprophylaxis, and risk of failure of thrombolytic therapy; all warrants close follow up of the patients in the convalescent phase of COVID-19 infection.
References


Fig. 1. 2D TEE images showing large right atrial thrombus (T) in 4-chamber view (A), right ventricular inflow-outflow view (B), 3D TEE (C) with thrombus-in-transit through patent foramen ovale (P) and CT pulmonary angiography (D) with bilateral pulmonary thrombi.