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Case Report

Clinical complications seen in patients after recovery from coronavirus disease 2019: Experience from a COVID care center



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ARTICLE INFO

Article history:

Received 7 October 2020

Accepted 2 February 2021

Keywords:

COVID-19

Thromboembolic complications

Anticoagulation

SARS-CoV-2

ABSTRACT

We have had recent experience that patients who have recovered from coronavirus disease 2019 (COVID-19) infection are being readmitted with thromboembolic complications, and some have had sudden cardiac death. There is paucity of literature on such presentations after clinical and microbiological recovery. In the present case series, we present five such patients recently managed at our COVID-19 care facility. All the patients described were elderly (mean age: 66 years) with multiple comorbidities (mean Charlson Comorbidity Index score: 3.5). Two were initially managed at another COVID care facility and discharged. They were admitted at our center within one week of discharge. One patient who was managed at our center was discharged and then readmitted. The other two had recovered from their illness and were planned for discharge (mean duration of hospital stay in initial admission: 14.4 days). All presented within one week of clinical and microbiological recovery (mean: 4.2 days). All were on adequate anticoagulation during initial presentation. All these patients had raised D-dimer levels (three suffered sudden cardiac arrest, one had a confirmed pulmonary thromboembolism, and one had acute ST-elevation myocardial infarction). Thromboembolic complications should be considered an important differential diagnosis in all patients who present with any complication in the immediate follow-up period of recovery from COVID-19 disease. Repeat analysis of D-dimer levels at follow-up may be considered in those who recovered from severe disease. Extended period of anticoagulation and close follow-up may be considered in all patients with COVID-19 who are at high risk of developing thromboembolic complications.

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<https://doi.org/10.1016/j.mjafi.2021.02.002>

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Introduction

The occurrence of the coronavirus disease 2019 (COVID-19) pandemic is an unprecedented public health emergency in recent human history. It is caused by a novel betacoronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease can have varied presentation. Flu-like symptoms are the most common presenting features. In a subset of patients, the disease can have a particularly stormy course characterized by inflammatory cytokine response and multi-organ failure and may be potentially fatal.¹

While respiratory complications predominate, several complications involving other organ systems are being increasingly reported. Cardiovascular complications such as myocarditis, myocardial injury, cardiac arrhythmias, and cardiac shock;² neurological complications such as abnormalities of the peripheral nervous system or central nervous system, skeletal muscle injuries, myopathy, or myositis;³ acute kidney injury; liver impairment; and biliary duct injury have all been reported in the medical literature.⁴ The mechanisms leading to these complications are increasingly being studied. Invasion of the endothelial surface by SARS-CoV-2 may lead to thrombotic complications.⁵ However, there is paucity of data about the disease course once the patient has had clinical and microbiological recovery. In the present case series, we present five such patients who presented with clinical complications after having recovered from COVID-19 infection.

Case 1

A 62-year-old male patient, with underlying type 2 diabetes mellitus (DM), hypertension, and coronary artery disease (CAD), on medical management, was diagnosed with COVID-19 on evaluation for fever, dry cough, and anosmia. He was admitted, managed, and discharged after clinical and microbiological recovery after 15 days. His follow-up reverse transcriptase polymerase chain reaction (RT-PCR) result was negative for COVID-19. One week later, the gentleman presented with right-sided pleuritic chest pain, progressive dyspnea, and streaky hemoptysis, warranting an emergency hospital visit. On evaluation, he was found to have pulmonary thromboembolism (PTE) along with radiological sequelae of viral pneumonia. High-resolution computed tomography (HRCT) of the chest with CT pulmonary angiography (CTPA) showed evidence of PTE (filling defect in the distal right pulmonary artery and distal left pulmonary artery with patchy consolidation, ground-glass opacities around areas of consolidation in both lung fields). He was managed with anticoagulation, antibiotics, and supplemental oxygen, with satisfactory clinical response.

Case 2

A 70-year-old female patient with underlying CAD, status post primary coronary intervention to the right coronary artery, was found to be COVID-19 positive when she presented with fever and cough of three-day duration. Her initial chest radiograph showed changes suggestive of viral pneumonia. She was managed as per institutional protocol

including anticoagulation, and during her hospital stay, she became asymptomatic. She was discharged after three weeks. (At discharge, the repeat RT-PCR result was negative for COVID-19.) Four days after discharge, she was readmitted with progressive breathlessness (Modified Medical Research Council scale: 4), hypotension, central and peripheral cyanosis, and bilateral infrascapular and interscapular crepitations. She suffered a cardiac arrest. She was revived initially. Her two-dimensional echocardiography (2D Echo) showed left ventricular ejection fraction (LVEF; 50%), with no evidence of regional wall motion abnormality (RWMA)/clots/vegetation. She expired one week later.

Case 3

A 64-year-old male patient with underlying type 2 DM, hypertension, and CAD, status post coronary artery bypass graft, tested positive for COVID-19 when he presented with fever and non-productive cough of three-day duration. During his hospital stay, he developed features of acute respiratory distress syndrome (ARDS) requiring non-invasive ventilatory (NIV) support. He was subsequently discharged after clinical improvement and microbiological recovery. The gentleman was readmitted with progressive breathlessness three days later. Repeat RT-PCR result was negative. Investigations showed neutrophilic leukocytosis. The level of lactate dehydrogenase (LDH) was 897 IU/L (85–227), procalcitonin was <0.17 ng/ml, D-dimer was >10,000 ng/ml, and ferritin was 214.93 ng/ml, and analysis of presence of C-reactive protein (CRP) showed positive results. His 2D Echo showed LVEF of 55%, grade I diastolic dysfunction, and concentric left ventricular hypertrophy. Contrast-enhanced computed tomography (CECT) of the chest with CTPA showed bilateral lung consolidation with ground-glass opacity, bilateral minimal pleural effusion, and normal study of pulmonary vessels. In view of worsening clinical condition, the patient required mechanical ventilatory support besides empirical antibiotics and intravenous steroids. The patient suffered sudden cardiac arrest despite initial clinical improvement.

Case 4

A 78-year-old male patient with history of after stroke and another, after (right middle cerebral artery infarct) was found of stroke (right middle cerebral artery infarct) was found to be COVID-19 positive when he was evaluated for fever and poor oral intake of two-day duration. Over the course of next three days, he developed features of ARDS requiring NIV support. He received two doses of convalescent plasma therapy. His clinical condition improved over next one week. He was weaned off ventilatory support, and follow-up RT-PCR analysis showed negative results. Before his planned discharge, he again developed progressive breathlessness, requiring invasive ventilatory support. Investigations showed neutrophilic leukocytosis. The level of LDH was 853 IU/L (85–227), serum procalcitonin was 0.25, D-dimer was >10000 ng/ml, and ferritin was 1190 ng/ml, and analysis of presence of CRP showed positive results. His 2D Echo showed normal LVEF and no RWMA. The patient had a sudden cardiac arrest within a few hours.

Case 5

A 55-year-old male patient, with hypertension, developed COVID pneumonia. He was managed at a COVID care facility as per protocol. He was readmitted to our facility three days later with ST-elevation anterior wall myocardial infarction. Repeat RT-PCR analysis for COVID-19 performed at readmission showed negative results. The patient was managed conservatively and he is presently stable.

Discussion

Thromboembolic manifestations of COVID-19 were first highlighted when increased incidence of PTE, deep vein thrombosis, and arterial thrombosis were documented in patients suffering from severe COVID infection.⁶ Increased risk of disseminated intravascular coagulation has also been documented in these patients.⁷ At times, arterial and venous complications may remain unrecognized during the disease course.⁸ The clinical diagnosis has been corroborated with postmortem findings of thrombotic microangiopathy, pulmonary capillary congestion, fibrin deposition, and diffuse alveolar hemorrhage. These findings have been demonstrated even in patients who were on anticoagulation.⁹ It has been observed that there exists a positive correlation between increased D-dimer values, risk of thrombosis, and poor outcomes in patients with COVID-19. This forms the basis of prescribing anticoagulation therapy in patients with COVID-19 with elevated D-dimer values.

The mechanisms that activate the coagulation cascade in patients with COVID-19 are poorly understood. It has been proposed that besides the procoagulant effects of systemic inflammation and cytokine storm, viremia itself may have a role.¹⁰ Invasion of the endothelial surface by SARS-CoV-2 via angiotensin-converting enzyme 2 may lead to thrombotic complications. Use of anticoagulation therapy in patients with high risk of Venous Thromboembolism (VTE) and raised D-dimer levels is being routinely practiced in those with severe COVID-19 infection. Other agents under investigation that deserve special mention are antiplatelets and nebulized fibrinolytic agents. These are being actively investigated as potential treatment options in patients with severe COVID-19.⁵ While all these complications in acute illness have been well documented in the medical literature, we have recently had experience of managing patients who suffered complications after they had clinical and microbiological recovery. All the patients described were elderly (mean age: 66 years) with multiple comorbidities. Two were initially managed at another COVID care facility and discharged. They were admitted to our center within one week of discharge. One patient who was managed at our center was discharged and then readmitted. The other two had recovered from their illness and were planned for discharge (mean duration of initial hospital stay: 14.4 days). All presented within one week of clinical and microbiological recovery (mean: 4.2 days). The details have been summarized in Table 1. All patients were managed as per institutional protocol for severe COVID-19 infection (empirical antibiotics, low-molecular-weight heparin, favipiravir [antiviral], supplemental oxygen, dexamethasone injection

Table 1 – Profile of patients presenting with complications after initial recovery from COVID-19.

S. no.	Age	Sex	Duration of initial hospitalization	Charlson Comorbidity index	Duration between microbiological recovery and complication (days)	Baseline D-dimer levels (ng/mL) (normal <500)	D-dimer levels during second presentation (ng/mL) (normal < 500)	Whether on anticoagulation during initial presentation	Duration of second hospitalization	Outcome
1	62	M	15	04	07	NA	>10,000	Yes	07	Discharged
2	70	F	21	04	04	634	>10,000	Yes	07	Death
3	64	M	12	04	03	>10,000	>10,000	Yes	03	Death
4	78	M	14	04	04	371.49	>10,000	Yes	11	Death
5	55	M	10	02	03	NA		Yes	07	Discharged

COVID-19, coronavirus disease 2019.

± convalescent plasma/remdesivir injection/tocilizumab injection, depending upon their clinical condition). At readmission/presentation with complication, all these patients had raised D-dimer levels (three suffered sudden cardiac arrest, one had confirmed PTE, one had an acute coronary event [acute ST-elevation myocardial infarction (STEMI)]).

At present, we do not have follow-up studies especially for those who have recovered from severe illness. As described in the aforementioned case series, an underlying thromboembolic state was either unrecognized in the initial presentation or manifested once anticoagulation therapy was discontinued. We thus propose prolonged anticoagulation and close follow-up with repeat D-dimer levels on follow-up, for patients with COVID-19 who have high probability of having thromboembolic complications (elderly patients, those with multiple comorbidities, those with raised D-dimer levels in initial presentation, and those with previous history of thromboembolic phenomena).

Disclosure of competing interest

The authors have none to declare.

Acknowledgments

The authors would like to thank the following people: Rajiv Pakhetra, HoD, Internal Medicine CH (SC), Pune, Sushil Jha, Deputy Commandant CH (SC), Pune, MS Tevatia, HoD, Pathology, CH (SC), Pune and S. Hasnain, Commandant, CH (SC), Pune.

REFERENCES

1. Stawicki SP, Jeanmonod R, Miller AC, et al. The 2019–2020 novel coronavirus (severe acute respiratory syndrome coronavirus 2) pandemic: a joint american college of academic international medicine-world academic council of emergency medicine multidisciplinary COVID-19 working group consensus paper. *J Global Infect Dis.* 2020 Apr-Jun;12(2):47–93. https://doi.org/10.4103/jgid.jgid_86_20. PMID: 32773996.
2. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet Lond Engl.* 2020;395(10223):497–506. [https://doi.org/10.1016/S0140-6736\(20\)30183-5](https://doi.org/10.1016/S0140-6736(20)30183-5). PMID: 31986264.
3. Sharifian-Dorche M, Huot P, Oshero M, et al. Neurological complications of coronavirus infection; a comparative review and lessons learned during the COVID-19 pandemic. *J Neurol Sci.* 2020 Oct 15;417:117085. <https://doi.org/10.1016/j.jns.2020.117085>. PMID: 32871412.
4. Jamwal S, Gautam A, Elsworth J, et al. An updated insight into the molecular pathogenesis, secondary complications and potential therapeutics of COVID-19 pandemic. *Life Sci.* 2020 Sep 15;257:118105. <https://doi.org/10.1016/j.lfs.2020.118105>. PMID: 32687917.
5. McFadyen James D, Stevens Hannah, Peter Karlheinz. The emerging threat of (Micro)Thrombosis in COVID-19 and its therapeutic implications. *Circ Res.* 2020 Jul 31;127(4):571–587. <https://doi.org/10.1161/CIRCRESAHA.120.317447>, 2020.
6. Lodigiani C, Iapichino G, Carenzo L, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thromb Res.* 2020 Jul;191:9–14. <https://doi.org/10.1016/j.thromres.2020.04.024>. PMID: 32353746.
7. *Disseminated intravascular coagulation in COVID-19—insights from the front lines.* AACC.org; Jun 4 2020.
8. Levi M, Thachil J, Iba T, et al. Coagulation abnormalities and thrombosis in patients with COVID-19. *Lancet Haematol.* 2020 Jun 1;7(6):e438–e440. [https://doi.org/10.1016/S2352-3026\(20\)30145-9](https://doi.org/10.1016/S2352-3026(20)30145-9).
9. Deshpande Charuhas. Thromboembolic findings in COVID-19 autopsies: pulmonary thrombosis or embolism? *Ann Intern Med.* 2020 Sep 1;173(5):394–395. <https://doi.org/10.7326/M20-3255>. PMID: 32422061.
10. Oudkerk M, Büller HR, Kuijpers D, et al. Diagnosis, prevention, and treatment of thromboembolic complications in COVID-19: report of the national institute for public health of The Netherlands. *Radiology.* 2020 Apr 23:201629. <https://doi.org/10.1148/radiol.2020201629>. PMID: 32324101.