



Thrombotic Complications in SARS CoV-2 IgG Positive Patients with Asymptomatic COVID-19 Infection

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Abstract

Background: Covid-19 disease has potential to result in a wide range of manifestations. Several studies have reported thromboembolic complications of Coronavirus Disease of 2019 (COVID-19). Therefore, we aim to discuss and analyze reported four cases of asymptomatic, positive SARS CoV-2 IgG antibodies Covid-19 infection with various thrombotic complications in the Dr. Hedgewar Hospital.

Methods: We reported and analyzed the clinical, radiographic, and laboratory manifestations, co-morbidity, pathophysiological mechanisms associated with thrombotic complications. Published literatures related to thrombotic complications were also searched in pubmed and embase and reviewed with the case study results.

Case discussion: First case of left sided hemiplegia was diagnosed with right-sided Middle Cerebral Artery (MCA) territory infarct. Second case presented with pulmonary thromboembolism, third case had peripheral vascular disease, and the fourth case had thrombosis involving abdominal aorta and bilateral renal arteries. In all these cases, no significant risk factors were found except rise in inflammatory markers (D-dimer and C reactive protein (CRP)). The results correlate with findings by various studies. Based on evidences, exaggerated state of hyper coagulation was attributed to COVID-19 disease pathogenesis.

Conclusion: The evidence from these cases implies that SARS CoV-2 infection can lead to vascular thrombosis in symptomatic as well as asymptomatic patients.

Keywords: SARS-CoV-2 infection; COVID-19 disease; Thrombotic complications; CORADS.

Introduction

The pandemic of COVID 19 disease caused by SARS-CoV-2 has emerged as a global health crisis and has affected over 69 million population and caused over 1 million deaths worldwide [1]. The clinical manifestations of SARS-CoV-2-infected patients ranged from asymptomatic or mild non-specific symptoms to severe pneumonia with organ function damage. The risk of severe illness is not yet clear. Hospitals in areas with significant community transmission have

experienced a major increase in the number of hospitalized pneumonia patients. The frequency of severe disease in hospitalized patients was approximately 30% [2-4]. The progression from prodromes (usually fever, fatigue, and cough) to severe pneumonia, Acute Respiratory Distress Syndrome (ARDS) requiring oxygen support, mechanical ventilation, or extracorporeal membrane oxygenation and is most commonly seen in the second week following onset of symptoms of a viral infection [2].

Patients suffering from COVID-19 disease report complications including ARDS, shock, acute renal injury, acute cardiac injury, and secondary infection. Several studies have reported thromboembolic complications including venous (pulmonary embolism, deep vein thrombosis) as well as arterial thrombosis, and 90% micro thrombosis was noted in lungs in autopsy of fatal COVID 19 disease. The pathogenesis of disease related to thrombo-inflammation and endothelial injury has been increasingly recognized [5]. Thrombotic complications comprised of 31% of the total complications in patients requiring intensive care unit admission and higher risks were noted in patients on anticoagulation [6-9]. Therefore, we aim to discuss and analyze reported four cases of asymptomatic, positive SARS CoV-2 IgG antibodies Covid-19 infection with various thrombotic complications in the Dr. Hedgewar Hospital.

Methods

We reported and analyzed the clinical, radiographic, and histopathologic manifestations, co-morbidity, pathophysiological mechanisms associated with thrombotic complications. Published literatures related to thrombotic complications were also searched in pubmed and embase and reviewed for correlation analysis with the case study results.

Human rights statements and Data privacy

The present study was conducted as per the ethical principles contained in the current revision of the "Declaration of Helsinki 2013", ICH harmonised guideline integrated addendum to ICH E6 (R1) guidelines for good clinical practice ICH E6 (R2) and following the "Ethical Guidelines for Biomedical Research on Human Subjects" issued by the Indian Council of Medical Research (ICMR) and all other applicable laws and regulations of the country.

Case Discussion

Case study 1

A 61-year-old male with no underlying comorbidities had sudden onset of slurring of speech with weakness of left upper and lower limb. Upon examination, power in left upper and lower limb was reported as Grade 0. His Computerized Tomography (CT) scan of brain result revealed right MCA territory infarct (Figure 1). Subsequently, he was diagnosed with left hemiplegia involving right sided MCA. Laboratory results showed increased level of D Dimer and CRP (Table 1). Due to raised inflammatory markers, COVID-19 infection was suspected. The Reverse Transcriptase (RT), Polymerase Chain Reaction (PCR) test and rapid antigen for SARS-CoV-2 were negative but SARS-CoV-2 Immunoglobulin G (IgG) antibody test was positive. Patient had no prior history suggestive of typical COVID-19 disease. He was managed conservatively.

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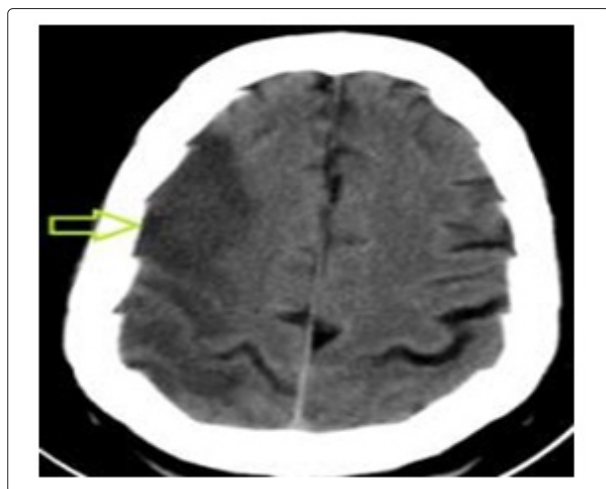


Figure 1: CT brain coronal section showing right MCA (Middle Cerebral Artery) territory infarct (arrow).

Case study number	Case 1	Case 2	Case 3	Case 4	Normal Values
Age (Years)	61	47	58	55	-
Sex	Male	Male	Male	Female	-
Comorbidities	No	No	Type II Diabetes, Essential Hypertension	No	-
SARS-CoV-2 RT-PCR and rapid antigen	Negative	Negative	Negative	Negative	-
SARS-CoV-2 IgG	Positive	Positive	Positive	Positive	-
Hemoglobin (g/dL)	12	14.4	12.4	15.2	12-17 (g/dL)
Total leucocyte count (μ L)	9600	10400	15300	19600	4,000-10,000 / μ L
Neutrophils%	75	67	91	88	55% - 70%
Lymphocytes%	16	27	3	5	20-35%
Platelets (x $10^3/\mu$ L)	379	290	163	220	150-300 x $10^3/\mu$ L
CRP (mg/L)	37		40		0.3-1.0 mg/L
LDH (U/L)	600	749	548	423	100-190 U/L
Ferritin (ng/mL)	890	1500	1036	1189	12-300 ng/mL
D-dimer (μ g/mL)	7.36	5	2.5	5.2	0.05-6.5 μ g/ml
PT (seconds)	16	15	Day 1-16 Day 3-34	14.3	10-13 Seconds
Homocysteine (μ mol/L)	9	9.13	8.2	7.4	<11 μ mol/L
eGFR (ml/min/1.73m ²)	99	77	80	24	90-120
Corads	5	3	5	3	1=Negative 2=Low 3=Moderate 4-5=High

Table 1: Laboratory Test Results. CRP: C-Reactive Protein; eGFR: estimated Glomerular Filtration Rate; IgG: Immunoglobulin G; LDH: Lactate Dehydrogenase; PT: Prothrombin Time; RT-PCR: Reverse Transcriptase-Polymerase Chain Reaction; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; CO-RADS: Coronavirus Disease 2019 (COVID-19) Reporting and Data System.

Case study 2

A 47-year-old male with no history of cardiovascular disease or any other co morbidity, experienced sudden retrosternal chest discomfort and shortness of breath. Upon examination, he was afebrile. His 2-D Echo report revealed dilated right atrium and right ventricle. The high-resolution CT scan showed evidence of thromboembolism in bilateral pulmonary arteries along with patchy ground-glass opacities in superior segment of left lower lobe (CORADS score of 3) (Figure 2). On further evaluation, he was found to have subclinical hypothyroidism and laboratory results showed increase in inflammatory markers are mentioned in table 1. The RT-PCR test and rapid antigen for SARS-CoV-2 were negative however, SARS CoV-2 IgG antibody test was positive shown in table 1 without prior typical symptoms of COVID-19 infection. He underwent thrombolysis with streptokinase. Work up for hyper coagulant status did not reveal any significant disorder.

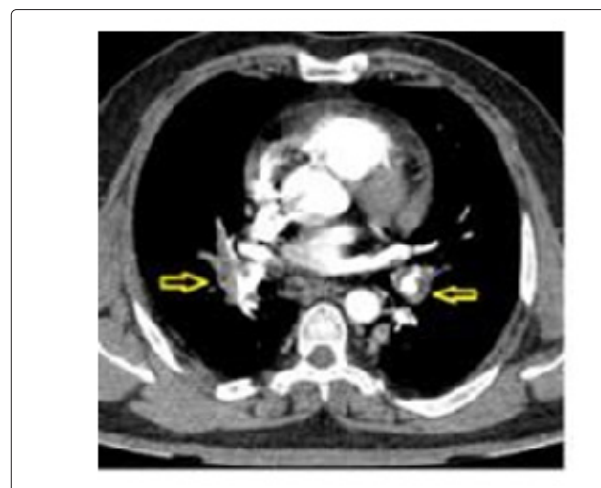


Figure 2: HRCT chest, axial section showing thrombosis of bilateral pulmonary arteries (arrows).

Case study 3

A 58-year-old male with underlying diabetes and hypertension developed blackish discoloration of right lower limb extending from knee to foot and left foot over past 6 days along with progressively increasing claudication. The CT scan of abdomen revealed thrombosis involving suprarenal and infrarenal abdominal aorta, bilateral common and external iliac arteries, right common and superficial femoral to dorsalis pedis artery, and mid left superficial femoral artery (Figure 3). Increase in inflammatory markers was found on further evaluation in table 1. The RT-PCR and rapid antigen tests were negative but SARS-CoV-2 IgG antibody test was positive represented in table 1. His coagulation profile was normal on admission and hence was initiated on low molecular weight heparin. He underwent surgery of above knee amputation. Subsequently, his coagulation profile was deranged. Eventually patient succumbed to death and intracranial bleed was reported as cause of death.



Figure 3: HRCT chest, axial section showing thrombosis of bilateral pulmonary arteries (arrows).

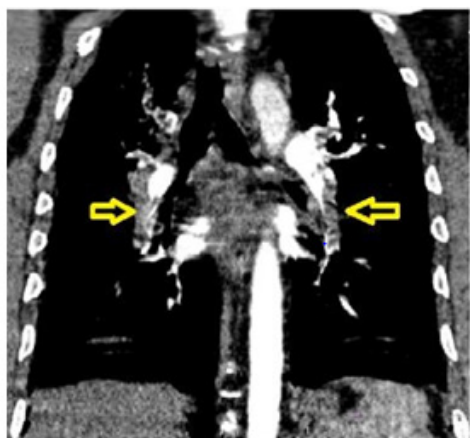


Figure 4: HRCT chest, coronal section showing thrombosis of bilateral pulmonary arteries (arrows).

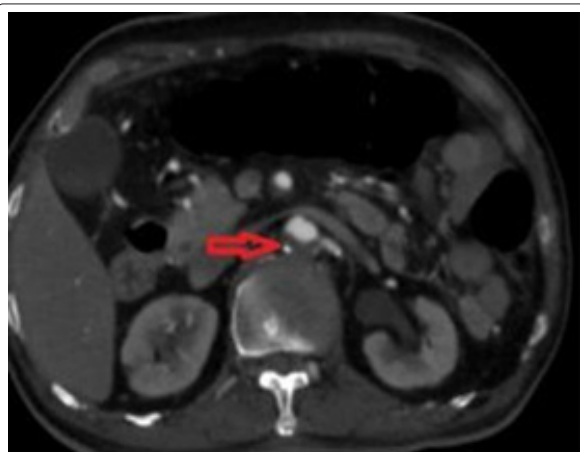


Figure 5: CT abdomen, axial section showing thrombosis in suprarenal aorta (arrow-red).

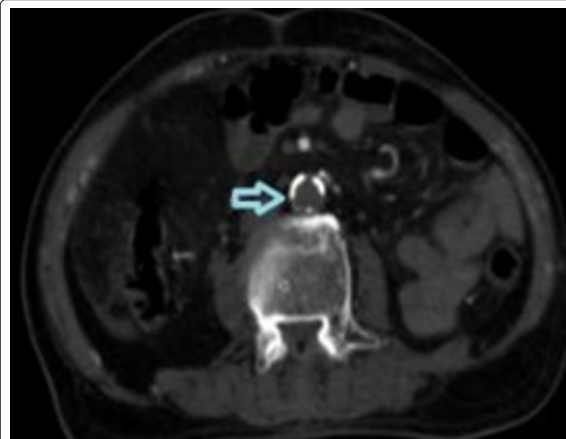


Figure 6: Thrombosis in infrarenal aorta (arrow-blue).

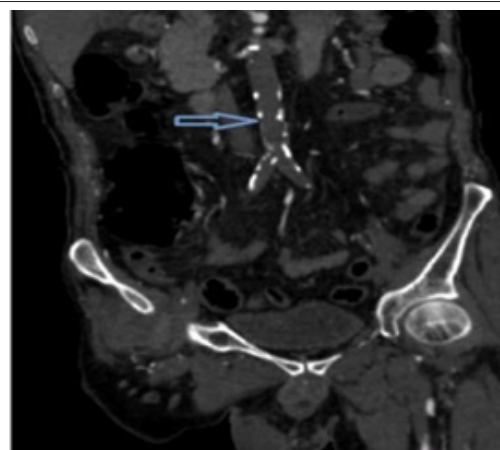


Figure 7: CT scan of abdomen, coronal section showing complete occlusion of infrarenal abdominal aorta and bilateral common and external iliac arteries.



Figure 8: CECT abdomen coronal section showing X: Partial thrombosis of left renal artery, Y: Partial aortic thrombus and thrombosis of right renal artery.

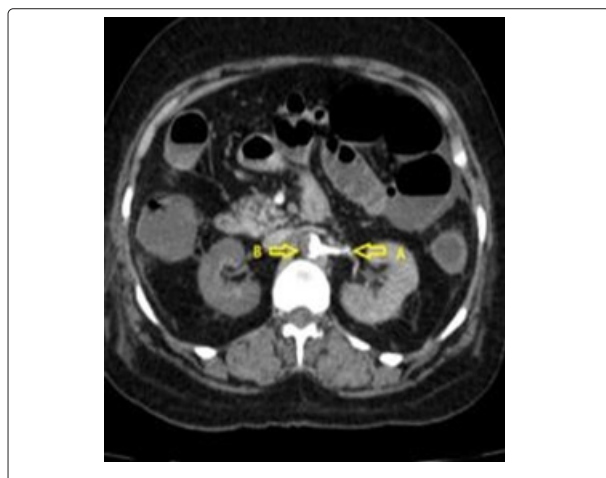


Figure 9: CECT abdomen axial section showing. A: Partial thrombosis of left renal artery, B: Partial Aortic thrombus.

Case study 4

A 55-year-old female experienced pain in abdomen associated with vomiting for last 3 days. She was hemodynamically stabilized. Laboratory results revealed increase in inflammatory markers (Table 1). The RT-PCR and rapid antigen tests were negative but SARS CoV-2 IgG antibody test was positive (Table 1). Plain CT scan of abdomen showed appendicitis. It was confirmed by histopathology after appendectomy. Despite surgery, she had persistent pain in abdomen which was not relieved by analgesic medications. Contrast enhanced CT scan of abdomen and pelvis revealed an extensive thrombus from abdominal aorta involving both renal arteries. She eventually developed multi organ dysfunction and sepsis.

Discussion

Based on the case study results, all patients presented with various thromboembolic complications, of which one of them had recent onset diabetes and hypertension and remaining without any underlying co-morbidities and were tested positive for SARS-CoV-2 IgG antibodies in the absence of usual course of infection. First case of left sided hemiplegia was diagnosed with right-sided MCA territory infarct. Second case presented with pulmonary thromboembolism, third case had peripheral vascular disease, and the fourth case had thrombosis involving abdominal aorta and bilateral renal arteries. In all these cases, no significant risk factors were found except rise in inflammatory markers (D-dimer and CRP). Further evaluation of this pro inflammatory and pro coagulant state was done (protein C and S, anti-thrombin, factor -V Leiden) and no serological abnormalities were detected. These results correlate with findings by various studies which revealed increased level of dimer levels and fibrinogen in COVID-19 patients indicating the disease severity in addition to thrombotic risk [10-12]. A recent study by Bikdeli et al. attributes post COVID-19 infection sequel to excessive inflammation, platelet activation, endothelial dysfunction, and stasis [13]. Study by Spiezia et al. has suggested that formation and polymerization of fibrin are responsible for this hypercoagulability [14]. The SARS CoV-2 IgG antibody test was positive but antigen and RT PCR tests were

negative. According to United States Food and Drug Administration, the sensitivity and specificity for SARS CoV-2 IgG is estimated at 99% and 100%, respectively [15]. Considering these evidences, we attribute this exaggerated state of hyper coagulation to COVID-19 pathogenesis [16]. In all these patients, there were no significant viral prodromal symptoms and hence the primary episode went unnoticed. Their HRCT chest scan reported CORADS (Coronavirus Disease 2019 (COVID-19) Reporting and Data System) score varying from very low (CO-RADS category 1) to very high (CO-RADS category 5), which demonstrated underlying pulmonary pathology.

Conclusion

The case study results conclude that SARS CoV-2 infection can lead to vascular thrombosis in symptomatic as well as asymptomatic patients. Routine monitoring and evaluation of COVID-19 patients by clinical, laboratory and/or radiological assessment will be beneficial for early diagnosis and mitigate the thrombotic risks through various treatment strategies. There is a need for a large-scale prospective study to evaluate the thrombotic complications associated with COVID-19 disease.

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