IgG Seroconversion Coincided with Eruptions, Deep Vein Thrombosis, and Pulmonary Embolism in the Clinical Course of a Mild COVID-19 Case

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Case Report

IgG Seroconversion Coincided with Eruptions, Deep Vein Thrombosis, and Pulmonary Embolism in the Clinical Course of a Mild COVID-19 Case

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Abstract

The currently pandemic coronavirus (SARS-Coronavirus-2 : SARS-CoV-2) is known to have delayed exacerbation of symptoms and emergence of complications, with the mechanisms possibly immune-mediated. Here, we report a mild Coronavirus disease 2019 (COVID-19) case complicated with pulmonary embolism (PE) and deep vein thrombosis (DVT). The 38-year-old male patient had fever, cough, and dyspnea on day 1 and was diagnosed with COVID-19 because specific SARS-CoV-2 RNA was positive in a nasopharyngeal swab taken on day 2. Symptoms resolved without oxygenation or specific treatment, but eruptions on his limbs appeared on day 9 and right calf pain began on day 10. Computed tomography revealed PE and DVT. The eruptions disappeared naturally, and the calf pain improved after administration of rivaroxaban. Specific SARS-CoV-2 RNA was negative on days 13 and 15. IgG and IgM measured using residual serum showed that the emergence of complications coincided with viral clearance and IgG seroconversion. The clinical course of our patient supports the theory that some COVID-19 complications are induced by host immunity.

Key words : COVID-19, SARS-CoV-2, IgG seroconversion, pulmonary embolism, deep vein thrombosis

Introduction

The first cluster of the currently pandemic coronavirus, now called Coronavirus disease 2019 (COVID-19) by the World Health Organization, was reported in late 2019 in Wuhan, China.

COVID-19 presents with various clinical manifestations, including fever, respiratory symptoms and dermatologic findings, which can lead to serious complications, such as acute respiratory distress syndrome (ARDS), pulmonary embolism (PE), and acute stroke[1)2)]. The mechanisms of these complications have as yet not been fully elucidated, but several theories suggest immune-mediation[3)~6)].

We experienced a case of mild COVID-19 that was complicated by eruptions, deep vein thrombosis (DVT), and PE that began several days after the onset of the initial symptoms. Our research found that the appearance of these complications coincided with viral clearance and IgG seroconversion. The clinical course of this patient

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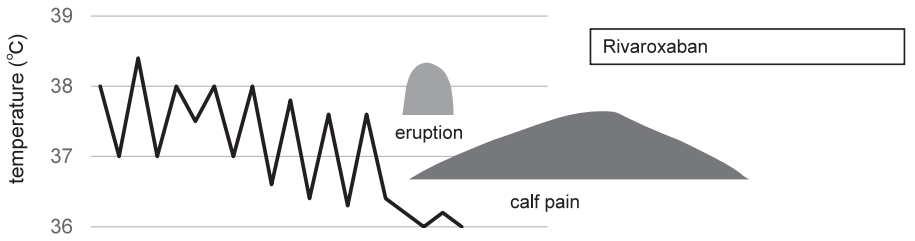

Days after onset	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	・・・	41
SARS-CoV-2 PCR		+										+	−		−										
IgM			−			±					+			±			−			−					−
IgG			−/0.05			−/1.01					+/8.93			+/9.55			+/9.79			+/9.78					+/9.52
CRP (mg/dL)	0.25					5.18					15.09			2.58			1.13			0.33					0.07
D-dimer (μg/mL)	NT					NT					NT			NT			10.8			6.1					0.8
WBC (*10^3/μL)	5.7					4.0					7.3			4.3			8.3			7.6					5.8
Ly (%)	22.8					22.9					22.9			23.8			22.2			26.8					31.5
Platlet (10^4/μL)	17.4					14.1					22.2			31.9			31.5			28.2					24.2

NT; not tested

Fig. 1 Clinical course, symptoms, treatment, and laboratory data. IgG seroconversion and viral clearance coincided with eruptions and calf pain. The results of IgG indicate qualitative measure / quantitative measure (cut-off index values greater than or equal to 1.4 are considered positive). Abbreviations ; NT : not tested.

supports host immune system involvement in these complications in COVID-19 patients.

Case report

A 35-year-old, overweight, male patient (176.0cm, 90.0kg, body mass index 29.1), a nonsmoker with no medical history, developed fever, cough, and dyspnea. Three of his colleagues had been diagnosed with COVID-19 several days before. Real time reverse transcription-polymerase chain reaction (RT-PCR) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nucleic acid obtained from a nasopharyngeal swab specimen was positive on the day after symptom onset. He was admitted to the hospital on day 4.

On admission, vital signs demonstrated no consciousness disorder, blood pressure 147/103 mmHg, heart rate 64 beats per minute, respiratory rate 16 breaths per minute, and oxygen saturation 97% under room air. Laboratory data showed little inflammation response (WBC, 5,700/μl ; Neu, 70.0% ; Ly, 22.8% ; CRP, 0.26 mg/dl) and no other obvious abnormality. Non-enhanced chest computed tomography (CT) revealed a ground-glass opacity typical of COVID-19 in the right upper lobe of the lung.

Because of the good respiratory condition and only mild pneumonia, no specific treatment was given, such as anti-viral, immunosuppressive, or anticoagulation therapy. He had no exercise limitations and could walk to the restroom, and we did not perform any thromboprophylaxis, such as prophylaxis anticoagulation or compression stockings. Fever resolved on day 9, but on the same day eruptions with itching sensation appeared on all four limbs. On the next day, he felt strong pain in his right calf on motion. The eruptions had disappeared by day 12. Although the calf pain continued, he was mobile. SARS-CoV-2 RT-PCR from nasopharyngeal swab specimen tested negative twice, on days 13 and 15. He was discharged from the hospital on day 15 (Fig. 1).

The severe right calf pain continued, and he consulted a doctor two days after discharge. Vital signs showed blood pressure 100/61 mmHg, heart rate 100 beats per minute, respiratory rate 18 breaths per minute, and oxygen saturation 98%

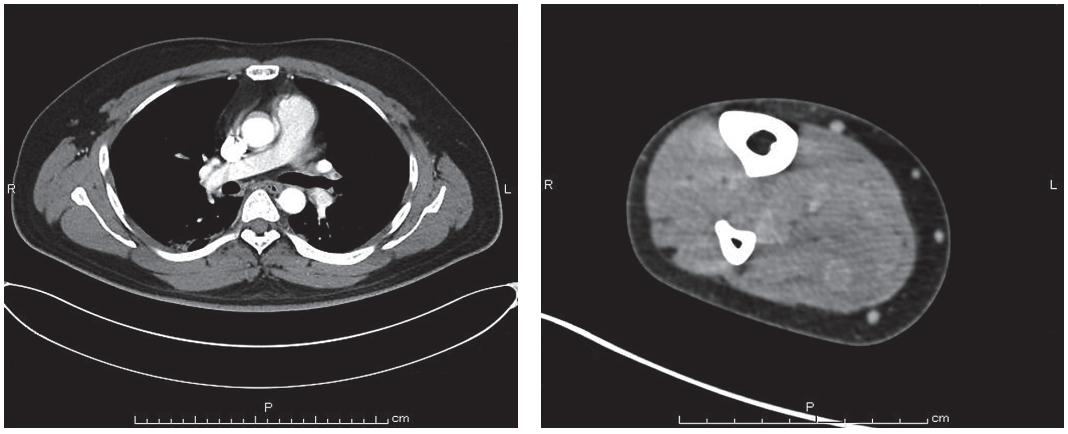

Fig. 2 Contrast-enhanced computed tomography on day 16. It revealed pulmonary embolism and deep vein thrombosis in the right lower limb with perivascular inflammation.

under room air. Laboratory data showed normal platelet count ($31.5 \times 10^4/\mu l$), prothrombin time (12.0s), and activated partial thromboplastin time (28.5s), but increased D-dimer (10.8μg/ml), fibrin degradation products (20.7 μg/ml), and fibrinogen (437.0 mg/dl) (Fig. 1). Lupus anticoagulant was within the normal upper limit (LA, dilute Russell's viper venom time, 1.32). The patient exhibited normal protein S activity (PS, 100%) and protein C activity (PC, 137%). There was no swelling or redness on his lower limbs at rest, but they became slightly red after exercise. He complained of right calf pain on motion and on palpation, but had no chest pain or dyspnea. Contrast-enhanced CT revealed deep vein thrombosis (DVT) in his right lower leg with perivascular inflammation and PE in the inferior lingular segment of the left lung (Fig. 2). Hemodynamics and respiratory condition were stable, we administered rivaroxaban for non-massive PE at 15mg twice per day for two weeks, then 15mg once a day for ten more weeks. After starting the treatment, his calf pain improved and CT revealed no DVT or PE on day 41.

Complement and antibody measurement was done using residual serum. Antibodies were measured qualitatively using a SARS-CoV-2 IgM/IgG antibody kit (2019-nCoV IgG/IgM Rapid Test Cassette, Hangzhou Alltest Biotech Co. Ltd., China) and quantitatively using a SARS-CoV-2 IgG assay (ARCHITECT SARS-CoV-2 IgG, Abbott, USA), that detect the nucleocapsid protein antibody. Complement on day 11, the day after the appearance of calf pain, had elevated to C3 218 mg/dl, C4 48 mg/dl, and CH50 63.0 U/ml. IgM became positive on day 7, followed by IgG on day 11. IgM became negative on day 17. IgG maintained positivity after seroconversion, at least until day 41 (Fig. 1). The results of IgG were consistent between both procedures.

Discussion

The present case is that of a patient with mild COVID-19 who experienced eruptions and lower extremity pain associated with DVT that appeared immediately after fever resolution, viral clearance, and IgG seroconversion. There were no findings of secondary thrombosis other than COVID-19. The patient had no family history of thromboembolism, surgery, or strict immobility during hospitalization. The patient had normal LA, PS, and PC. Notably, the timing of complications in the clinical course coinciding with IgG seroconversion and viral clearance suggests that host immunity may have been the cause of these complications.

In some COVID-19 patients, dyspnea, ARDS, and thromboembolic complications develop several days after the initial onset of symptoms. The mechanisms of the time deviation between the

initial symptoms and exacerbation of symptoms or the appearance of complications has been reported to be due to immune response to SARS-CoV-2. When SARS-CoV-2 infects host cells using angiotensin converting enzyme 2, which is mainly expressed on the surface of lung epithelial cells, type I interferon shows antiviral activities that cause apoptosis of the infected cells and promote antibody production by enhancing the antigen-presenting ability of the infected cells and activating adaptive immunity. However, uncontrolled and over-activated adaptive immunity can cause a cytokine storm that can trigger a second wave of inflammation that causes various complications of COVID-19[5].

Thromboembolism is a very common complication for COVID-19 patients. A large study that surveyed 3,334 hospitalized patients reported that 6.2% of the patients were complicated with venous thrombosis (3.2% PE and 3.9% DVT). Among intensive care unit patients, the complication rate was 13.6% (PE in 6.2% and DVT in 9.4%), despite having performed prophylaxis anticoagulation for most patients[7]. The mechanisms of thromboembolism have been reported to be the result of hypercoagulability caused by a cytokine storm, activation of complement pathways, endothelial injury, and thrombotic inflammation[1)4)8)9)]. These mechanisms are consistent with the CT imaging in our case, which showed strong perivascular inflammation around the thrombosis in the lower limb (Fig. 2).

Although the mechanisms of cutaneous manifestations of COVID-19 is not yet well documented, some theories suggest a relation to host immunity. Viral particles present in the cutaneous blood cause vasculitis, and the immune response leads to Langerhans cell activation, which results in a state of vasodilation and spongiosis that causes cutaneous disturbances[6]. A pathological study revealed colocalization of SARS-CoV-2-specific spike proteins with complements in the lung and skin tissue[4].

There are two limitations to our confirmation of this hypothesis. First, the detection of SARS-CoV-2 IgM and IgG in the present case was of antibodies to the nucleocapsid protein, which may not be a direct cause of the complications. Second, we evaluated nasopharynx viral clearance using RT-PCR for SARS-CoV-2, which may have a weaker influence on host immunity compared to lower respiratory tract infection or viremia. However, the clinical course, in which the complications appeared several days after the initial symptom onset and that coincided with IgG seroconversion and viral clearance supports the proposition that cutaneous manifestations and thrombosis would be caused by hyperimmunization.

Ethical approval

Informed consent to publish this paper was obtained from the patient and his family.

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Conflicts of interest

The authors declare no conflicts of interest.

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（和文抄録）

IgG 陽転化の時期と一致して皮疹，深部静脈血栓症，肺塞栓症を合併した，新型コロナウイルス感染症の軽症例

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新型コロナウイルス感染症（COVID-19）は，症状増悪や合併症が発症から遅れて出現することが知られており，そのメカニズムは自己免疫が介在している可能性が報告されている．ここに，軽症の COVID-19 に肺塞栓症（PE）と深部静脈血栓症（DVT）を合併した症例を報告する．38 歳の生来健康な男性患者が，day 1 に発熱，咳嗽，呼吸困難を呈し，day 2 に採取した鼻咽頭スワブによる PCR で新型コロナウイルス（SARS-CoV-2）RNA が陽性であったため，COVID-19 と診断された．酸素投与や特異的治療を要することなく自然解熱したものの，day 9 に四肢に発疹が出現し，day 10 に右腓腹部の疼痛を認めた．造影 CT にて PE と DVT が確認された．発疹は自然消失し，腓腹部痛は rivaroxaban 投与後に改善した．day 13，15 に PCR 陰性化を確認した．残存血清を用いて血清 IgG と IgM を測定したところ，合併症の出現時期はウイルスクリアランスと IgG seroconversion と一致した．本患者の臨床経過は，COVID-19 の合併症の中には宿主免疫によって引き起こされるものがあるという仮説を支持するものであった．

キーワード：COVID-19，SARS-CoV-2，IgG セロコンバージョン，肺塞栓症，深部静脈血栓症