Thrombosis Journal

REVIEW

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The well-defined antiphospholipid syndrome induced by COVID-19: a rare case report and review of the literature

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Abstract

COVID-19 may induce a state of hypercoagulability, particularly in critically ill patients, for reasons that remain unknown. Numerous studies have identified the presence of antiphospholipid antibodies in patients with COVID-19; however, the definitive diagnosis of antiphospholipid syndrome continues to pose challenges. Here, we present the case of a patient infected with SARS-CoV-2 who developed life-threatening severe thrombocytopenia, profound anaemia, acute pulmonary hypertension, right ventricular failure, and renal insufficiency. Laboratory investigations revealed significantly elevated levels of antiphospholipid antibodies. We conducted a one-year follow-up study with blood sampling performed every 12 weeks. The patient exhibited persistent high titres of antiphospholipid antibodies and ongoing renal dysfunction necessitating daily oral warfarin antithrombotic therapy. Antiphospholipid syndrome is a complex clinical condition that poses challenges for clinicians, particularly in critically ill patients, and is often associated with delayed and inaccurate diagnosis and treatment. Therefore, we extensively reviewed the literature and international guidelines to conduct a comprehensive analysis of the aetiology, pathogenesis, and treatment strategies of APS. We hope this work will provide a valuable reference for health care professionals.

Keywords COVID-19, Antiphospholipid syndrome (APS), Thrombocytopenia, Anaemia

Introduction

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by thrombosis and/or pregnancy morbidity in patients with persistent antiphospholipid antibodies (aPLs) [1, 2]. In the presence of Systemic Lupus Erythematosus(SLE),it is referred to as secondary antiphospholipid syndrome, otherwise it is classified as primary APS,There are many other secondary causes of APS, including HIV infection, malignancy and other autoimmune diseases (such as Sjogren's syndrome).

Since the outbreak of the COVID-19 pandemic, numerous studies have identified the presence of antiphospholipid antibodies in patients with COVID-19 [3–5]. However, the titres of antiphospholipid antibodies reported in the literature are relatively low, and studies with continuous antiphospholipid antibody monitoring are lacking, suggesting that aPL positivity could be a transient manifestation of COVID-19 [6–8]. The association between antiphospholipid antibody positivity and COVID-19 remains insufficiently established, posing challenges for the accurate diagnosis of antiphospholipid syndrome [4, 9]. In this report, we present the case of a patient in whom high titres of antiphospholipid

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antibodies following SARS-CoV-2 infection were detected, accompanied by life-threatening severe thrombocytopenia and severe anaemia. We followed up this patient for one year and collected blood samples every 12 weeks to assess antiphospholipid antibody levels. The results showed persistent high titres of these antibodies necessitating daily oral warfarin administration for thrombosis prevention. Therefore, we propose that SARS-CoV-2 infection may induce antiphospholipid syndrome characterized by sustained elevation in antiphospholipid antibody levels. Antiphospholipid syndrome is a complex clinical condition characterized by a wide range of manifestations. To gain a comprehensive understanding, we conducted an extensive review of the aetiology, potential pathogenesis, and novel therapeutic approaches for this syndrome.

Case report

A 64-year-old man with a medical history of hypertension and diabetes presented to the Emergency Department (ED) with complaints of fever, cough, and productive sputum. These symptoms had been present for 3–5 days prior to his visit to the ED. The nucleic acid amplification test for SARS-CoV-2 yielded a positive result. The lymphocyte count was decreased, whereas the platelet count; haemoglobin, creatinine, and urea nitrogen levels; and other parameters remained within the normal reference ranges. Tests for the antinuclear antibody spectrum, antineutrophil cytoplasmic antibody spectrum, rheumatoid factor, lupus anticoagulant (LA), and antiphospholipid antibodies yielded negative results. Chest computed tomography (CT) revealed bilateral pulmonary exudation, which subsequently resolved after a 5-day treatment regimen involving Paxlovid and methylprednisolone. Follow-up CT demonstrated lesion resolution. The medication regimen was subsequently discontinued, and the patient was discharged. However, on the second day postdischarge, the patient presented with symptoms of low back pain, fatigue, and dyspnoea, necessitating admission to the intensive care unit (ICU).

The physical examination revealed an acute illness presentation, orthopnoea, diffuse petechiae all over the body, and a significant increase in blood pressure. The laboratory findings revealed a platelet count of 16×10^9/L, a haemoglobin level of 58 g/L, a creatinine level of 293 μmol/L, a urea nitrogen level of 8.3 mmol/L, and a significantly elevated pro-brain natriuretic peptide (pro-BNP) level. The patient exhibited a significantly decreased platelet count, an elevated D-dimer level, and prolonged prothrombin time, but without any apparent signs of bleeding. The International Society on Thrombosis and Haemostasis (ISTH) score was less than 5, and the activity of coagulation factors in a whole-blood sample was within the normal range, ruling out a diagnosis of disseminated intravascular coagulation (DIC). The results are summarized in Tables 1 and 2. Blood pressure elevation was effectively managed, and heart failure was appropriately treated. The patient received a packed red blood cells transfusion and human recombinant thrombopoietin injection. On the second day of hospitalization, the platelet count and haemoglobin level had decreased to 5×10^9/L and 50 g/L, respectively, and an ongoing

Table 1 Antiphospholipid antibody values

Variable&Reference Range	One week before admission Other hospital	At admission	Day 2	One Week	Two Week	Twelve Week	Half a year	thirty-six week	One year
Overall anti-cardiolipin antibody (0-16AU/ml)	1.03	210	> 300	> 300	> 300	> 300	> 300	268	235
Overall anti-β2GPI antibody (0-16AU/ml)	0.72	182	> 300	> 300	> 300	> 300	> 300	196	289
anti-β2GPI IgA (0-16AU/ml)	0.04	ND	165.0	81.7	19. 9	21.2	47.2	36.4	42.3
anti-β2GPI IgM (0-16AU/ml)	0.34	ND	12.9	9.0	7.1	6.3	11	14	13
anti-β2GPI IgG (0-16AU/ml)	0.06	ND	> 200	> 200	> 200	> 200	> 200	> 200	> 200
Anticardiolipin IgM (0-8MPLU/ml)	0.86	ND	5.32	4.34	3.81	4.7	6.4	7.2	6.4
Anticardiolipin IgG (0-8MPLU/ml)	1.02	ND	> 120	> 120	> 120	> 120	> 120	> 120	> 120
Anticardiolipin IgA (0-8MPLU/ml)	0.75	ND	61.6	61.6	18.58	31.24	19.8	21.4	23.6

ND Not Determined, the tests were conducted via enzyme-linked immunoassay (ELISA)

Table 2 Laboratory data

Variable&Reference Range	At admission	Day two	One Week	Two Week	Twelve Week	Half a year	thirty-six week	One year
Hemoglobin (130-175 g/L)	58	62	78	101	98	102	114	125
Platelet count (120–350*10^9 /L)	16	18	34	73	127	136	112	98
D-dimer (0–0.5ug/ml)	2.47	2.7	2.32	1.6	1.46	1.32	ND	ND
Fibrin degradation products (0-5ug/ml)	7.9	8.5	ND	ND	4.2	3.8	ND	ND
Prothrombin time (11-14 s)	16.3	13.0	13.4	13.3	11.6	13.4	ND	ND
Activated partial-thromboplastin time (28-44 s)	49.6	45.1	40.3	39.8	38	35	ND	ND
Antithrombin III (80–120%)	83	76	88	88	96	102	ND	ND
Von Willebrand factor (50–160%)	246	270	ND	ND	189	168	ND	ND
Creatinine (53-106umol/L)	293	138	200	228	286	275	ND	ND
Blood urea nitrogen (3.6–9.5 mmol/L)	8.3	3.1	12.7	12.3	15.2	14.3	ND	ND
COOMbs(DAT)	Positive	Positive	Positive	Positive	Negative	ND	ND	ND
Peripheral blood film	Positive	Positive	Negative	Negative	Negative	ND	ND	ND
Factor V activity (70–120%)	116							
Factor X activity (70–120%)	104.5							
Factor VII activity (70–120%)	98.5							
Factor II activity (70–120%)	80.2							
Factor XI activity (70–120%)	126.4							
Factor XII activity (70–150%)	37.5							
Factor IX activity (70–120%)	152.2							
Factor VIII activity (70–150%)	270							

ND Not Determined

increase in creatinine and urea nitrogen levels, accompanied by the absence of urine output, was observed. Although the transfusions of packed red blood cells and apheresis platelet products continued, they proved to be ineffective. Blood tests revealed significant increases in D-dimer, IgG anticardiolipin, anti-β2 glycoprotein 1 immunoglobulin G (β2GP1 IgG), and lupus anticoagulant (LA) (LA1 and LA2) levels. In addition, the Coombs test yielded positive results, and a peripheral blood smear showed the presence of red blood cell fragments. Conversely, tests for the platelet-related antibodies PAIgA, PAIgG, PAIgD, and PAIgM yielded negative results. Heparin-induced thrombocytopenia-related IgG antibodies were not detected. The activity level of ADAMTS13, a vWF-cleaving protease, was measured to be 120% (reference value: > 42.16%). The results are summarized in Tables 1, 2, 3 and 4. Cardiac ultrasound revealed the presence of pulmonary arterial hypertension. However, owing to acute renal failure, the patient was unable to undergo pulmonary angiography. Renal perfusion scintiscan revealed diminished perfusion in both kidneys. Head CT revealed multiple cerebral infarctions. The patient underwent comprehensive evaluations conducted by a multidisciplinary team of rheumatologists, neurologists, and cardiologists who collectively deliberated the potential diagnosis of antiphospholipid syndrome.

The patient presented with life-threatening thrombocytopenia and severe anaemia, leading to the immediate administration of glucocorticoids and immunoglobulins. An initial dose of 80 mg of glucocorticoids was administered intravenously every day, and the dose was subsequently tapered after 9 days. Upon transfer from the ICU, a small oral dose of methylprednisolone tablet was prescribed as an alternative. The initial dose of immunoglobulin administered via intravenous infusion was 30 mg/d. After a period of 3 days, the dose was subsequently reduced to 20 mg, and immunoglobulin was eventually discontinued upon platelet count stabilization. The haemoglobin level also gradually returned to normal levels following immunoglobulin treatment. Blood pressure was effectively controlled, and heart failure was successfully corrected; however, renal insufficiency persisted, necessitating long-term intermittent dialysis. Unfortunately, the antiphospholipid antibody titre remained persistently elevated. We followed up the patient for one year, collecting blood samples every 12 weeks, and we consistently observed positive results for antiphospholipid antibodies. Given the definitive diagnosis of novel coronavirus-induced antiphospholipid syndrome, long-term oral warfarin anticoagulation therapy was strongly recommended.

Table 3 Other autoantibodies during hospitalization

Variable&Reference Range	Day 2	Day 7
HIT IgG (< 0.4)	0.2	0.32
PAIgA(0–10%)	3.10	2.89
PAIgG(0–10%)	0.80	0.78
PAIgD(0–10%)	0.80	0.80
PAIgM(0–10%)	1.20	1.76
ADAaMTS-13 (42–126%)	120	128

HIT Heprin-induced thrombocytopenia, *PA* Platelet-associated antibody

ADAMTS-13: a disintegrin and metalloprotease with thrombospondin type 1 repeats, member 13

Discussion and review

Aetiology and pathogenesis

Similar to other autoimmune diseases, the aetiology of antiphospholipid syndrome (APS) remains unclear. Furthermore, even individuals without autoimmune disorders may harbour memory B cells capable of producing antiphospholipid antibodies [10]. Study findings have indicated the presence of antiphospholipid antibodies in patients with thrombosis following varicella, hepatitis C,

Table 4 The spectrum of anti-nuclear antibodie and lupus anticoagulant

Variable	One week before admission Other hospital	At admission	One week	Twelve Week	One year
Antinuclear antibody (ANA,0-48Au/ml)	3.26	4.25	3.74	4.65	3.92
Lupus anticoagulant (LA,30–38 s)	32	40.4	32.5	30.1	30.3
Anti-double-stranded DNA(dsDNA) antibodies	—	—	—	—	—
Anti-Smith (Sm) antibody	—	—	—	—	—
Anti-ribosome RNP (rRNP) antibody	—	—	—	—	—
Anti-SSA (Ro) antibody	—	—	—	—	—
Anti-SSB (La) antibody	—	—	—	—	—
Anti-U1 ribonucleoprotein (U1RNP) antibody	—	—	—	—	—
Lupus anticoagulant(LA)	—	—	—	—	—

"—"means negative and the test method was western blot

and cytomegalovirus infections [2, 11, 12]. Notably, over 40% of HIV patients exhibit antiphospholipid antibodies, with 18% displaying anticardiolipin antibodies and 30% showing anti-β2GPI antibodies [13].

Interestingly, since the COVID-19 pandemic, antiphospholipid antibody positivity after SARS-CoV-2 infection has been consistently observed in numerous studies. However, the pathogenicity of these antibodies and their relevance to COVID-19 remain uncertain. In April 2020, Zhang et al. first reported the presence of aPLs associated with thrombotic events in three patients with COVID-19 [14]. Gerard Espinosa et al. conducted a prospective study including 158 consecutive hospitalized COVID-19 patients. Sixteen (28.6%) patients were positive for the criteria APS (both had aCL IgG), but aPL positivity was not related to thrombosis, ICU admission or severe respiratory failure [15]. Another prospective study conducted at a single centre included 74 patients with COVID-19 who required continuous mechanical ventilation. The results showed that antiphospholipid antibodies, namely, LA and/or elevated anticardiolipin IgG/IgM and/or elevated anti-β2-glycoprotein-I IgG, were present in 88% of the patients, but positivity for these antibodies was not associated with thrombotic complications [16]. In conclusion, the prevalence of aPLs in COVID-19 patients is highly variable and depends on the severity of COVID-19 (severe vs. nonsevere). A strong association between thrombosis and the presence of aPLs in critically ill patients with COVID-19 was suggested but not demonstrated.

The possible pathogenesis of APS in patients with COVID-19 is as follows: I) the anti-β2GPI-β2GPI complex disrupts the antithrombotic barrier between endothelial cells and annexin A5; II) the anti-β2GPI-β2GPI complex increases signal transduction; III) the anti-β2GPI-β2GPI complex interferes with fibrinolysis and endogenous antithrombotic formation; and IV) the anti-β2GPI-β2GPI complex triggers platelet activation (summarized in Fig. 1).

Destruction of the endothelial cell surface and the annexin A5 anticoagulant barrier

Annexin A5 is a potent anticoagulant that has a high affinity for negatively charged phospholipids, particularly phosphatidylserine. Annexin A5 is widely distributed across various cell types, including platelets, the placenta, the myocardium, and endothelial cells. This protein forms two-dimensional structures on the surface of the phospholipid bilayer to inhibit clotting factor binding [17, 18]. Recent evidence suggests that the antigen–antibody complex associated with antiphospholipid syndrome (aPL) disrupts the crystal structure of annexin A5 and displaces it from the phospholipid membrane [19]. IgG isolated from patients with APS has been shown to downregulate annexin A5 expression on cultured placental trophoblast cells and endothelial cells while promoting the adhesion of plasma coagulation factors to these cellular surfaces [20].

Binding to surface receptors on vascular endothelial cells increases cellular signal transduction

The binding of anti-β2GPI antibodies to the endothelial cell surface annex A2, a receptor for β2GPI, initiates Toll-like receptor activation primarily involving TLR4 within the innate immune system. This direct interaction stimulates tumour necrosis factor-related factor VI (TRAF6) and myeloid differentiation factor 88 (MYD88), facilitating downstream signal transduction to expedite the P38MAPK and NF-κB signalling cascades. Consequently, tissue factors (TFs) are expressed, and an inflammatory response is initiated [21–23]. Furthermore, the formation of the anti-β2GPI-β2GPI complex results in its association with apolipoprotein E receptor 2 (apoER2) on endothelial cell surfaces via PI3k/Akt pathway induction, increasing the expression levels of both tissue factors (TFs) and adhesion molecules [22–27].

Interference with fibrinolysis and endogenous antithrombotic effects

The antibody titre of annexin A2, a coreceptor of tissue plasminogen activator (t-PA) and plasminase on the surface of endothelial cells, was found to be elevated in patients with antiphospholipid syndrome (APS) [28, 29]. Antibodies against annexin A2 may interfere with the binding of plasminogen and t-PA, reducing plasminogen formation and fibrinolysis [30]. The monoclonal antiphospholipid antibodies of APS patients can directly inhibit the activity of plasminase. β_2GPI is a cofactor of t-PA-mediated plasminogen activation and can interfere with this activity. In addition, APS patients have significantly elevated levels of plasminogen activator inhibitor-1 (PAI-1), suggesting impaired fibrinolysis [31, 32]. aPL antibodies can also modulate the activation of protein C and the activity of APC via thrombomodulin, thereby safeguarding activated V and VIII from inactivation by APC [33].

Antiphospholipid antibodies activate platelets

In vivo imaging of experimental animal models suggests that aPL-induced thrombosis is a consequence of platelet activation, subsequently promoting vascular endothelial cell activation and fibrin formation. aPL antibodies can induce platelet aggregation and potentially facilitate signal transduction via apolipoprotein E receptor 2 (ApoER2) [19, 34]. Platelet ApoER2 binds to the V region of β2GPI. As mentioned earlier, β2GPI inhibits platelet

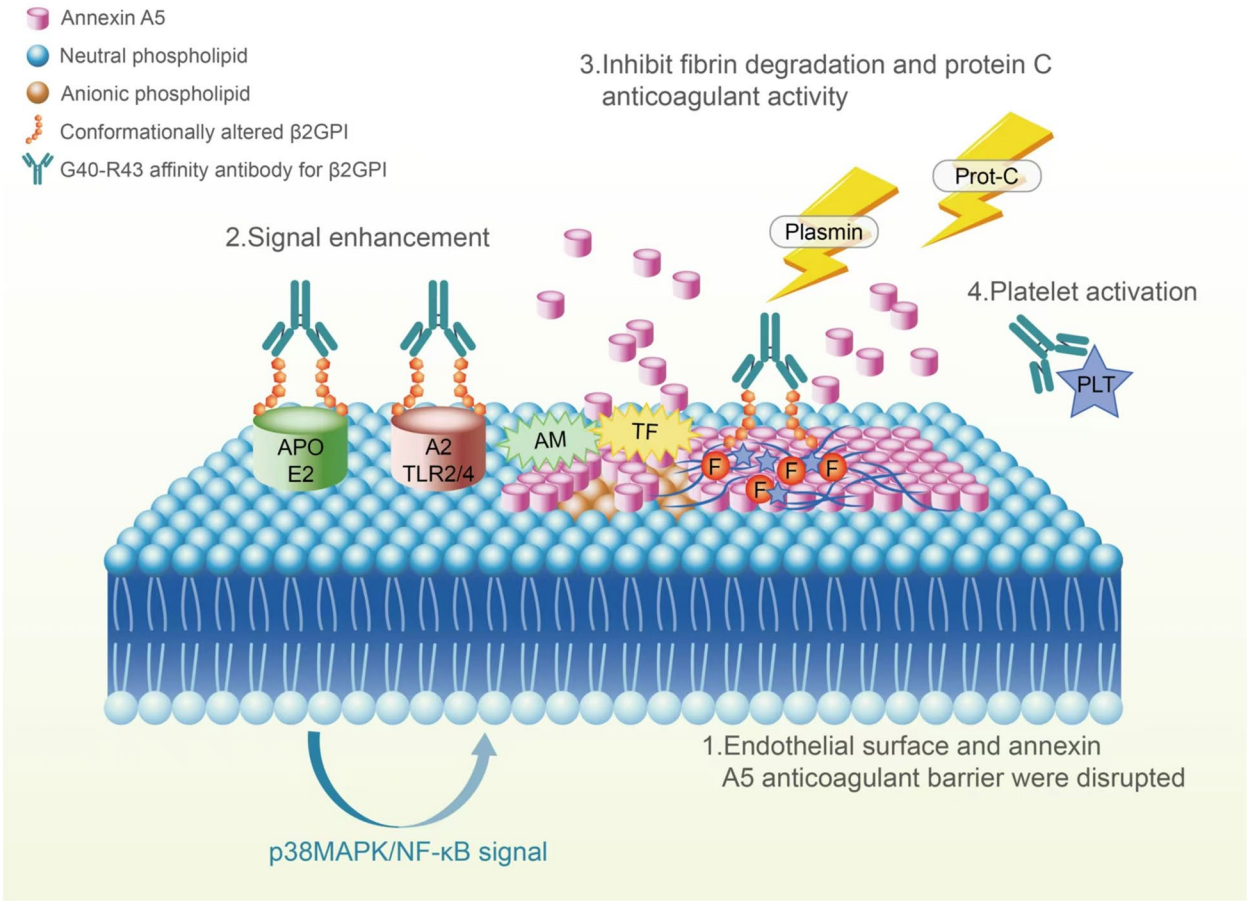

Fig. 1 The pathogenesis of antiphospholipid syndrome. The possible pathogenesis of APS: 1. The anti-β2GPI-β2GPI complex binds to anionic coagulation-promoting surfaces, such as heparan acetylates, via the V-region cation of β2GPI upon damage to the endothelial surface; 2. The anti-β2GPI-β2 GPI complex triggers the activation of annexin A2, ApoE2, TLR4, and other receptors on endothelial cells, thereby promoting downstream signalling pathways involving protein kinase (p38MAPK) and nuclear κB factor (NF-κB). This leads to increases in the levels of tissue factor (TF), adhesion molecule (AM), and proinflammatory coagulation; 3. The anti-β2GPI-β2GPI complex hinders fibrinolysis and anticoagulation by suppressing the activity of fibrinolytic enzymes, the anticoagulant annexin A5, and the protein C (Prot C) pathway. 4. The anti-β2GPI-β2GPI complex directly binds to activated platelets and facilitates platelet aggregation

adhesion by interfering with the binding between platelets and von Willebrand factor (vWF), whereas the β2GPI antibody disrupts this inhibition, leading to increased platelet adhesion in the fluid state [35].

Treatment

Anticoagulant therapy

A multitude of randomized controlled trials have consistently demonstrated that patients with antiphospholipid syndrome (APS) and thrombosis should receive long-term warfarin therapy, maintaining an international normalized ratio (INR) between 2.0 and 3.0 [36]. Furthermore, intense anticoagulation therapy may be required for individuals with arterial thrombosis. Although retrospective studies suggest the necessity of high-intensity treatment (INR > 3.0), a consensus has not yet been reached on this matter [37–39]. The optimal antithrombotic approach for APS-related stroke remains a controversial matter in the current literature. In cases where lupus anticoagulant (LA) interferes with activated partial thromboplastin time (APTT) monitoring during conventional heparin administration, it is advisable to employ an LA-insensitive APTT reagent or consider switching to low-molecular-weight heparin (LMWH) [37, 40]. The use of novel oral anticoagulants (NOACs), including direct factor Xa or thrombin inhibitors, in patients with APS has not been comprehensively evaluated.

Emerging treatments

Hydroxychloroquine has demonstrated potential in reducing the risk of thrombosis in patients with antiphospholipid syndrome (APS) and systemic lupus erythematosus (SLE). Furthermore, animal model studies have also

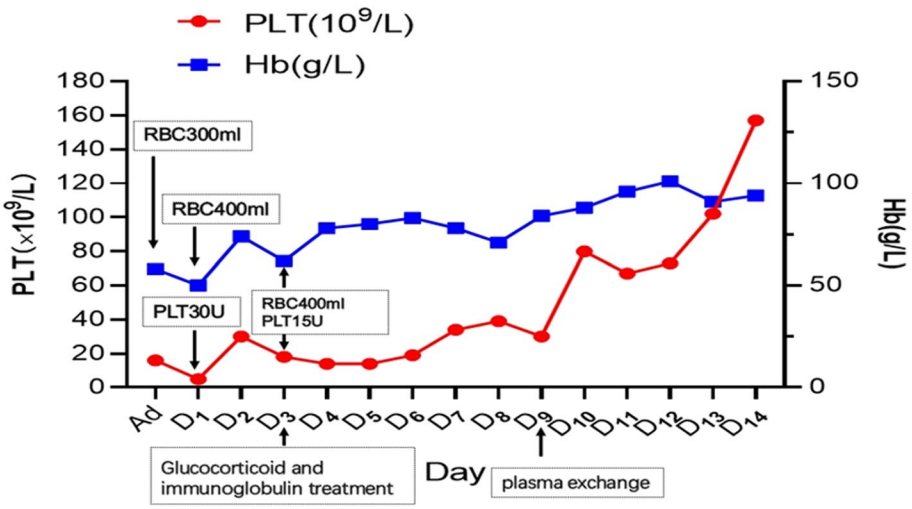

Fig. 2 The changes of Hb and PLT during hospitalization. RBC: Packed red blood cells

shown the therapeutic efficacy of hydroxychloroquine in APL-induced thrombosis [41, 42]. Recent investigations have revealed that hydroxychloroquine directly disrupts aPL IgG and β2GPI complexes while also reversing aPL antibody-mediated annexin A5 binding to phospholipid bilayers and human placental syncytial trophoblasts [43]. The current body of evidence from numerous animal experiments and clinical studies consistently demonstrates the potential of hydroxychloroquine in mitigating organ dysfunction and improving the outcomes of COVID-19 patients [44].

Statins possess immunomodulatory, anti-inflammatory, and antithrombotic properties. Recent studies have demonstrated that APS patients treated with statins exhibit a downregulation of tissue factors and reduced levels of proinflammatory/thrombotic markers such as interleukin-1β (IL-1β), vascular endothelial growth factor, and tumour necrosis factor α (TNF-α) [45, 46].

Alternative therapeutic interventions

Corticosteroids or intravenous immunoglobulins should be considered as secondary treatment options only for patients who have failed anticoagulant therapy, who exhibit severe immune thrombocytopenia, or who have heparin therapy contraindications [2, 39].

For the patient whose case we reported here, glucocorticoid and immunoglobulin therapy were initiated upon high suspicion of antiphospholipid syndrome. Following treatment, there was no longer a sharp decline in the platelet count or haemoglobin level; however, the antiphospholipid antibody titre remained elevated. After plasma exchange, significant improvements in the aforementioned indices were subsequently observed. Anticoagulant and antiplatelet therapy was not administered during the early stage of severe thrombocytopenia and anaemia but was initiated once anaemia was ameliorated and platelet counts significantly increased. Haemoglobin (Hb) level and platelet count alterations throughout the course of treatment are summarized in Fig. 2.

Conclusion

Antiphospholipid syndrome is an acquired thrombophilia involving vascular endothelial injury, complement activation, platelet activation, and dysfunction of the anticoagulation and fibrinolytic systems. The typical clinical manifestations include recurrent arterial or venous thromboembolism. The presence of antiphospholipid antibodies in COVID-19 patients has been previously documented in the literature; however, the diagnosis of antiphospholipid syndrome remains uncertain without continuous monitoring, as nearly all observed changes are transient. The patient whose case is described in this report experienced a sudden onset of life-threatening severe thrombocytopenia and severe anaemia following the remission of COVID-19. Although there were no apparent manifestations of thromboembolism in major blood vessels, the patient'xs D-dimer level remained elevated, accompanied by unexplained pulmonary hypertension, acute right heart failure, renal failure and a significant reduction in renal blood flow, suggesting the possibility of thromboembolism occurring in small vessels or microvessels. The patient was monitored over an extended period, with blood samples collected at 12-week intervals for the detection of antiphospholipid antibodies for up to one year. The findings showed persistent high titres of antiphospholipid antibodies. Currently, our understanding of COVID-19 is still limited. This case implies that patients with COVID-19 exhibit profound

haematological alterations and multiorgan dysfunction that cannot be attributed solely to infection, and clinicians should remain vigilant for concurrent antiphospholipid syndrome. However, a definitive diagnosis necessitates long-term follow-up monitoring.

Authors' contributions

All the authors cited in the manuscript actively participated in the provision of medical care to the patient or the execution of the work, refined and scrutinized laboratory test findings through interpretation and analysis, drafted or revised the manuscript and read and approved the final version of the paper. Zong-fang Ren and Zhi-feng Liu conceptualized the manuscript. Zong-fang Ren conducted extensive literature research and composed the literature reviews with support from Zhi-feng Liu. Ri-cheng Xiong, Ling-ling Wang, Rui-Chen and Zhi-huang Chen made the precise diagnoses and administered effective treatments to the patient with support from Zhi-feng Liu. All authors contributed equally to critical revision of the manuscript and approved the final version. Ethics approval and consent to participate: The publication of this case has been authorized by the Scientific Research Ethics Committee of the General Hospital of the Southern Theatre Command of the Chinese People's Liberation Army (approval number: NZLLKZ2024069). Declaration of competing interests: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. Zong-fang Ren and Zhi-feng Liu conceptualized the manuscript. Zong-fang Ren conducted extensive literature research and composed the literature reviews with support from Zhi-feng Liu. Ri-cheng Xiong, Ling-ling Wang, Rui-Chen and Zhi-huang Chen made the precise diagnoses and administered effective treatments to the patient with support from Zhi-feng Liu. All authors contributed equally to critical revision of the manuscript and approved the final version.

Declaration of generative AI and AI-assisted technologies in the writing process

I hereby affirm that I did not employ generative AI or AI-assisted technology during the manuscript composition and figure creation processes, and I possess a language service certificate from SNAS.

Funding

This work was supported by grants from the Basic Research Project of the Science and Technology Department of Yunnan Province (No. 202201AT070244 to ZF Ren) and the Basic Research Program of the Science and Technology Department of Yunnan Province (No. 202401AY070001-226 to ZF Ren).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The publication of this case has been authorized by the Scientific Research Ethics Committee of the General Hospital of the Southern Theatre Command of the Chinese People's Liberation Army (approval number: NZLLKZ2024069).

Competing interests

The authors declare no competing interests.

Received: 15 July 2024 Accepted: 31 October 2024
Published online: 08 November 2024

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