JMS 2024; Vol7 (1):171-181
UDC:616.98:578.834]-097
https://doi.org/10.55302/JMS2471171pm

ANTIPHOSPHOLIPID-LIKE SYNDROME INDUCED BY COVID19: A CASE REPORT STUDY

Sanja Petrusevska-Marinkovic[1,4], Ankica Anastasovska[2], Lidija Todorovska[3,4]
[1]University Clinic for Respiratory Diseases in Children Kozle, Skopje, North Macedonia,
[2]University Clinic for Infectious Diseases and Febrile conditions, Skopje, North Macedonia,
[3]University Institute for MEP Physiology with Anthropology, Skopje, North Macedonia,
[4]Faculty of Medicine, Ss Cyril and Methodius University in Skopje, Skopje, North Macedonia

Abstract

Many patients with severe COVID-19 present with coagulation abnormalities associated with severe infections, such as disseminated intravascular coagulation or trombotic mycroangiopathy. That's why is important to pay attention to the differential diagnoses of COVID-19 and other diseases following thrombotic events. Antiphospholipid syndrome is an autoimmune disorder characterized by thrombosis.

The diagnosis criteria for antiphospholipid syndrome are based on the detection of abnormal levels of at least one of the most common antiphospholipid antibodies .

In this study, we discuss the relationship between COVID-19, antiphospholipid syndrome and antiphospholipid syndrome -like phenomenon, and thrombosis that may occur. We present a 60-year-old woman hospitalized for COVID-19 and pneumonia with a moderately severe clinical picture.

During the hospitalization under anticoagulant therapy, she developed coagulation disorders with prolonged active partial thromboplastin time, positive lupus anticoagulant and positive beta-2glycoprotein. The coagulation disorder is in addition to antiphospholipid syndrome, which is associated with the possibility of bleeding in the patient.

Elevated levels of the isotypes of antiphospholipid antibodies in COVId-19 patients create antiphospholipid syndrome-like condition. Considering the high rate of mortality due to coagulation abnormalities and thrombosis among COVID-19 patients, it is important to pay attention to the differential diagnoses of COVID-19 and other diseases following thrombotic events, as well as their implication on the therapeutic approach to patients. Current data recommend the use of prophylactic anticoagulation with low molecular weight heparin in hospitalized patients with COVID-19 **r**egardless of the severity of the clinical picture.

Key words: COVID-19, antiphospholipid syndrome, antiphospholipid antibodies, coagulation disorders, thrombosis, lupus anticoagulant, anti-beta 2 glycoprotein I (anti-b2GPI), immune disorders, antimalarials, anticoagulant therapy, plateled agonists.

Introduction

COVID-19 is an infectious disease, which can occur as a result of an infection with the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Pandemic of coronavirus disease 2019 (COVID-19) created huge havoc among global health care practicioners in terms of identification of primary disease symptomatology, signs, diagnosis and management [1].

Most patients with COVID-19 predominantly have a respiratory tract infection[2].

In general, COVID-19 symptoms are nonspecific, such as dyspnea, fever, cough, and headache. The US Center for Disease Control and Prevention (CDC) subsequently added chills, muscle pain, sore throat, and loss of taste or smell to this list (neurological manifestations) [3].

The severity of the infection may vary from asymptomatic patients to severe cases of pneumonia that can lead to death [2].

A proportion of patients progress to a more severe and systematic disease, acute lung injury with acute respiratory distress syndrome (ARDS), shock, and mulpiple organ dysfunction, associated with substantial mortality [4].

Sars-Cov2 appears to have gained increased capacity for transmission over time, infecting millions of people globally and causing significant morbidity and mortality [5]. This is seen particulary among the olderly and those with comorbid condition, including advanced age, hypertension, diabetes, and obesity [5].

Many patients with severe COVID-19 present with coagulation abnormalities that mimic other systemic coagulatopathie associated with severe infections, such as disseminated intravascular coagulation (DIC) or trombotic mycroangiopathy, but COVID-19 has distinct features [6]. Coagulopathy in patients with COVID-19 is associated with an increased risk of death [7].

The most typical finding in patients with COVID-19 and coagulopathy is an increased D- dimers concentration, a relatively modest decrease in platelet count, and a prolongation of the active partial thromboplastin time (aPTT) [7].

During the COVID-19 disregulated immune state characterized by a hyperinflammatory response and a hypercoagulable state, leading to a pulmonary and systemic micro- and macro- immunothrombosis [5].

Some studies reported increased risk of incident autoimmune disorder among patients with COVID-19 infection, which indicates the viral infection to be a risk factor for the development of autoimmunity [8].

Various autoimmune diseases associated with COVID-19 have been reported as they are: spondyloarthritis [9], rheumatoid arthritis [10], pemphigoid [11], immune mediated thrombocithopenia [12], multiple sclerosis [13], vasulitis [14], osteonecrosis [15]. Antiphospholipid syndrome (APS) occupies a significant place among them [16-18].

Antiphospholipid syndrome (APS) is a multisystemic autoimmune disorder characterized by thrombosis as its main pathological process and symptoms such as arterial and venous thrombosis, recurrent miscarriage in pregnant women, thrombocytopenia, and neurological and cardiac disorders [18,19].

The diagnosis criteria for APS are based on the detection of abnormal levels of at least one of the most common antiphospholipid antibodies, viz. lupus anticoagulant (LA), anticardiolipin antibodies (IgM and IgG isotype in medium-to-high titer), or anti-beta 2 glycoprotein I (anti-b2GPI) antibodies (IgM and IgG isotype), along with thrombotic events in arterial or venous blood flow, thrombosis in tissues and organs, or pregnancy complications [19, 20].

It has been recommended to reexamine the patient at least two times in 12 weeks to confirm this diagnosis [21, 22].

Considering the high rate of mortality due to coagulation abnormalities and thrombosis among COVID-19 patients, it is important to pay attention to the differential diagnoses of COVID-19 and other diseases following thrombotic events. In this study, we discuss the relationship between COVID-19, APS, an APS-like phenomenon, and thrombosis that may occur, as well as their implication on the therapeutic approach to patients.

Case Presentation

The patient was 60- year-old women, by profession specialist in gynecology who works in her own private ambulance, without comorbidities. The patient's main complaints were fever up to 37,8^{0}C, malaise and cough. She was examined by a family doctor. The third day from the onset of symptoms a rapid test for the detection of SARS-CoV-2 was carried out, which was negative. A pneumo-slide was made with positivity for IgM class antibodies for Legionella pneumophila, after which therapy with Tbl. Levofloxacine was carried out for 7 days.

Due to maintaining a subfebrile temperature up to 37.6C, the patient was referred to an infectious disease specialist, where a PCR test for the detection of COVID-19 from a nasopharyngeal swab was recommended and performed, which had a positive result. From the physical examination, apart from a red

throat, the rest of the system findings are within normal limits. From the performed laboratory analyses, the blood test, sedimentation, C-reactive protein (CRP) and coagulation findings with D- dimmers levels, are with normal values. A lung x-ray was with normal findings and the patient was returned to home treatment with a recommendation to take vitamin and symptomatic therapy.

The female patient maintains a subfebrile temperature, with intensification of dry cough and deepening of weakness. She returned again for an examination after 4 days. Except lung posterior-anterior radiograph which sees some insignificant small initial changes,, a lung computed tomography (CT) were performed and areas of ground glass opacities were verified (Figure1/A). Because of COVID-19 and pneumonia, the patient was hospitalised in our covid center with moderate illness. Sp O2 levels of 94-97% in room air. She was receiving antibiotic therapy, ceftriaxone 2 gr per day, during 10 days. The hemostatic findings were at first with normal values, which is why the transfusionist recommended protective anticoagulant therapy with low-molecular weight heparin (LMWH). Anticoagulant protective treatment with Enoxaparin 40 mg sc was prescribed.

But on the fifth day of treatment, it occurs deterioration of pulmonary auscultatory findings with the appearance of crepitations, maintenance of febrile temperature which was up to 38^0C, occurrence of bone and joint pain, and deterioration of laboratory analyzes with the appearance of leukopenia of $3.3x10^9$ L, with lymphopenia of 6,9%, but normal value of CRP, procalcitonin (PCT) and normal value of lactate dehydrogenase (LDH) , troponin and ferritin. Interleukine 6 (IL-6) values rise easily to 7.56 pgr/ml.

The patient also received dexamethason therapy in dose of 6 mg per day during 10 days. Enoxaparin was increased to 2x40 mg subcutaneous (sc). In the patient, after 10 days there was a clinical improvement in the general condition with regression of lung auscultatory findings and calming of the cough. Retraction of the inflammatory process was registered on the CT of the lungs Figure1/B.

However, the temperature was still maintained in the form of subfebrile peaks up to $37.2\text{-}37.3^0$ C which appeared in the afternoon hours. New coagulation tests were performed with changes in coagulation parameters.

Because of coagulation disorders and prolonged active partial thromboplastin time and slightly prolonged prothrombin time a transfusion medicine specialist was consulted and new investigations were recommended and performed (Tabela 1).

Lupus anticoagulant (LA) and /anti b2GPI were positive. Beside antiphospholipied antybodies, three plasma platelet agonists have been analized. At the same time, an examination by a rheumatologist was carried out. The rheumatologist's opinion is that it is an autoimmune reaction after COVId-19 infection with positive antiphospholipid antibodies (apL) and lupus anticoagulans (LA) .

At his suggestion, complement C3 and C4 were taken, which were slightly elevated values. After all these investigation, the patient underwent therapy with Resochin (Chloroquine) a 155 mg 2x1 and it was recommended to continue therapy with Vit. D. According to coagulation findings, in correlation with a transfusiologist, the anticoagulant therapy with LMWH and Sintrom (Acenocoumarol) was overlapped. After that, she was released for home treatment with a recommendation to continue with Resochin (Chloroquine) a 155 mg 2x1 and Sintrom (Acenocoumarol) according to the prescribed scheme.

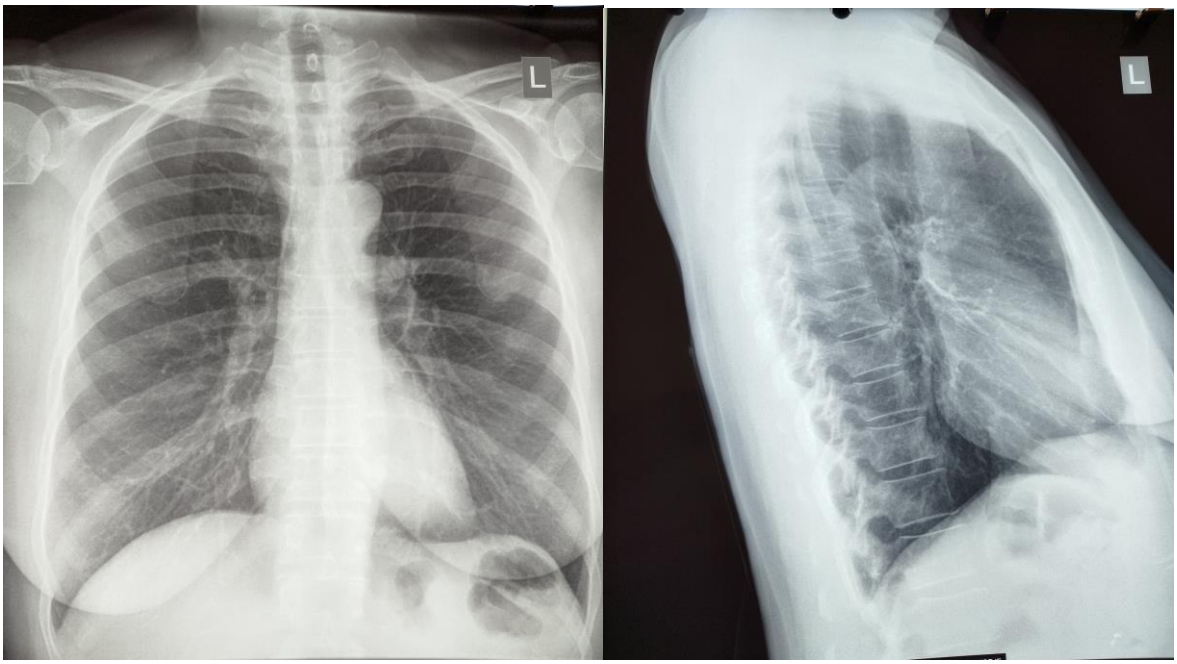
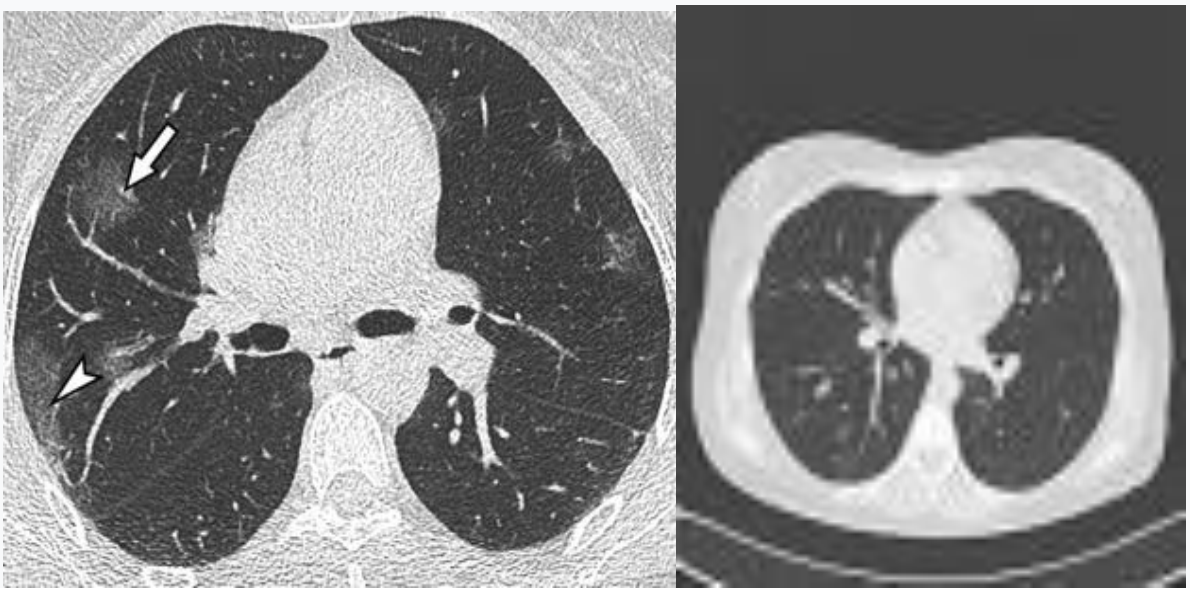


Figure 1. Posterior-anterior radiograph of 60- year-old women patient with initial consolidation



A **B**

Figure 2. A- CT finding with verified pneumonia with areas of ground glass opacities; **B-** CT finding after regression of lung changes

Table 1. Coagulation findings in the female patient during hospitalization

Plateled (**PLT**)10^9L {150-50}	167	219	132	172	275	286
Hematocrit Ht(%) {35-50}	37	36,4	41,3	34,4	37,5	39,6
Protrombine time(PT) sek {9,8(13)14,2}	11,66	12,2	13,8	13,5	**15,2**	14,1
Active partial thromboplastin time(aPTT) sek. {27,9(33)37,7}	32,6	32,3	**43,2**	**51,9**	**42,8**	**41,6**
Thrombin time(TT) sek{16,1(22)24,1}	19,87	17,6	28,5	18,5	18,2	19,7
D-dimers (ngr/ml){0-500}	263,96	242,1	750	434,8	458,8	413
Lupus anticoagulant Screening {25-42}	**72**					
Lupus anticoagulant Konfirmatoren {26-38}GPL	**39**					
Lupus anticoagulant	**positive**					
Screening **antiphospholipid antibodies (apL) anti-beta 2 glycoprotein I (anti-β2GPI) antibodies** (IgM, IgG , IGA isotype (SE):{0-20}:	**positive** **42**					
Adenosine diphosphatase (**ADP**)-optically[%] {69-68}	**45**	**33**	**26**			
Colagen- optically [%] {70-94}	**47**	**29**	**45**			
Ristocetin-optically[%] {87-102}	**59**	**55**	**68**			
Fibrinogen gr/l	3,5	2,19				

Follow up of the patient

According to the previously assigned task, in correlation with transfusiologist and reumathologist we followed the patient for at least 12 weeks. During therapy with Resorchine (Chloroquine) and Sintrom (Acenocoumarol), the female patient was clinically better. The temperature normalized and the coagulation findings gradually improved. After 9 weeks, the therapy was stopped due to the normalization of coagulation findings and lupus anticoagulant and aPL negativization. She had no adverse effects from the medication, nor any bleeding manifestations.

Discussion

The presence of thrombotic events in COVID-19 patients has been described since the beginning of the pandemic. This association has been confirmed in most of the reported studies [8,16-18]. Autopsy reports have shown that most thromboses are located in the lung, although they have also been observed in other organs such as the skin and kidneys [23].

SARS-CoV2 infection induces a generalized prothrombotic condition, which is attributed to a combination of factors such as hypoxia, excess cellular apoptosis, and mainly to overactivation of the immune system [17]. In many cases, these trombotic events occured even if patients receive standard dose of tromboprophylaxis [24].

When a viral infection occurs without prior contact with the immune system, a coordinated response of innate immunity and adaptive immunity develops [25].

In viral infections, as in other infections, the coordinated activity of innate and adaptive immunity is essential to generate an effective response [26]. SARS-CoV-2 infection produces a dysregulation with hyperactivation of adaptive immunity that leads to its exhaustion, which can be evidenced in total lymphocytopenia [1].

This lymphopenia is directly proportional to the clinical severity. After the control of adaptive immunity disappears, an overactivity of innate immunity occurs, leading to the massive release of cytokines of innate immunity (IL-1, IL-6, TNF-alpha), causing tissue damage and a hyperinflammatory condition. The sum of the damage generated by all these factors has fatal consequences at the systemic level [27,28].

Among immune-mediated prothrombotic conditions, antiphospholipid syndrome stands out [18].

The pathogenesis of the occurrence of APS in COVID-19 has not yet been clarified. It is assumed that it is triggered by the injury of the endothelium. The virus itself leads to loss of protective antioxidant pathways resulting in activation of the coagulation cascade [29].

APS is a systematic autoimmune disease characterized by the appearance of trombosis or gestational morbidity (clinical criteria) in a patients with persistently high levels of antiphospholipid antibodies (aPL) [17].

There are two review papers that talk about the association of APS and COVID-19, as well as pathogenesis of APS, such as papers reported from Serrano et all and Tung et all [17,18].

However, there is a small number of published papers with own experiences indicating the incidence of APS or APS-like conditions in patients with COVID-19. First Xiao et all in 2020, provide a brief report on the prevalence and characteristics of aPL in 66 critically ill patients with COVID-19. The conclusion is that aPLs are more common in critically ill patients and that COVID-19 triggers the development of an autoimmune condition similar to APS or APS- like syndrome. The tests they have done, demonstrate medium to high titers of aPL that help in identifying patients who are at risk of developing cerebral infarction [30].

In our study, in a 60-year-old female patient, moderately elevated values of aPL were also detected, however, she did not develop a severe clinical picture. Perhaps the timely initiation of corticosteroid therapy as well as prompt monitoring of the patient lead to the avoidance of the development of a severe clinical picture and complications. Various trials have recorded the beneficial outcome of corticosteroids in decreasing the mortality and morbidity of COVID-19 [1, 2,15].

The other case report refers COVID-19 associated catastrophic antiphospholipid syndrome successfully treated with Eculizumab [20].

In that report Chidharla et all describe a 64-year-old woman with a history of tipe 2 diabetes melitus and triple positive APS who had multiple thrombotic and bleeding episodes after being found to have a COVID-19 infection. This female patient was with Catastrophic APS (CAPS) that is a severe manifestation of APS [20]. But this patient also has a severe clinical picture.

The article reported by Bahramnezhad et all is also significant. They presents a case of COVID-19 and APS syndrome in the 56-year-old Iranian man with trombosis in the brachial artery and massive pneumonia with two subsequently negative, and the third positive PCR test [16].

The patient had positive aPL and this created a condition similar to APS, which in the absence of reliable COVID-19 testing, can lead to misdiagnosis and consequently delayed or improper treatment [16]. In contrast to the mentioned cases, in the case of the patient that we presents in our study was promptly diagnosed with the help of PCR testing, which is more specific and sensitive than the rapid tests for COVID-19 [31].

PCR testing is considered as a "gold standard" in SARS-CoV-2 detection. While the rapid test can get you results very quickly, the results may not always be accurate. The time when the nasopharyngeal swab is taken for testing is also significant [31].

In the patient who is the subject of our study, control coagulation tests were performed, after worsening of clinical condition. Prolonged APTT was noted in addition to an increased possibility of bleeding. Coagulation disorders occurred even though the patient was under adequate therapy with LMWH and her activity was monitored with Anti.X a which was within therapeutic limits. The anti-Xa assay can also be used to guide the determination of therapeutic APTT ranges in the clinical management of unfractionated heparin [32].

Therapeutic ranges of heparin are: LMWH: 0.5-1.2 IU/mL [32].

According to the recommendation of a transfusiologist, three plasma platelet agonists have been developed, adenosine diphosphatase (ADP), ristocetin and collagen which were of reduced values and that indicated platelet hypoaggregability. Plateled aggregation at site of vascular injury is essential for the formation of the primary haemostatic plag [33]. Platelet aggregation agonists reduce the possibility of this [33].

From the existing antiphospholipid antibodies, in our study we made beta 2 glycoprotein (b2GPI), which was twice elevated compared to normal values, and lupus anticoagulant, which was also positive. The disadvantage is that we did not have the opportunity to make anti-cardiolipin antibodies which were not available to us at that time. Lupus anticoagulans (LA) were so- named because they were first found among the patients with lupus, but LA testing is not used to diagnose the autoimmune disorder and LA are frequently absent in people with lupus [30, 34].

LA are autoantibodies produced by the immune system that mistakenly attack phospholipids that are found in the other –most layer of cells (cells membranes). These autoantibodies interfere with the blood clotting process in a way that is not fully understood and increase a person's risk of developing a blood clot [16-18,22].

It's known that b2GPI is a unique protein capable of regulating both complement and coagulation cascades and maintaining or altering haemostasis. The presence of a b2GPI antibodies in APS could modify these interactions contributing to the pathogenesis of thrombosis [34, 35].

Presence of these aPLs, such as LA and b2GPI leads to thrombophilia [16-18, 34]. Therefore, anticoagulant therapy is recommended for our patient.

The rheumatologist also prescribed an antimalarial medication that is used in addition to the treatment of malaria and they are used as well for treatment of autoimmune diseases like antiphospholipid antibody syndrome (APS).

The patient's temperature normalized after the first week of antimalarial therapy. However, in the era of modern immunosuppressive drugs and biological therapy, the significant therapeutic potential of this medication may be underestimated [36].

Our patient was followed for more than 12 weeks and it was noted that the antiphospholipid antibodies were neutralized 8 weeks after discharge from the hospital.

Conclusion

Elevated levels of the isotypes of antiphospholipide antibodies in COVId-19 patients create condition similar to antiphospholipid syndrome or antiphospholipid-like syndrome.

Of course, this is only a presentation of one case in which complications occurred and it was not a critically ill patient and without comorbidities.

However, the early recognition of such developments and immune reactions in the patient leads to adequate therapy, especially anticoagulant, which leads to a better prognosis for these patients, prevention of complications such as brain bleeding or bleeding in other organs and tissues. Current data recommend the use of prophylactic anticoagulation with LMWH in hospitalized patients with COVID-19 **r**egardless of the severity of the clinical picture.

Considering the high rate of mortality due to coagulation abnormalities and thrombosis among COVID-19 patients, it is important to pay attention to the differential diagnoses of COVID-19 and other diseases following thrombotic events.

References

1. Harapan H, Itoh N, Yufika A, et all Coronavirus disease 2019 (COVID-19): A literature review. J Infect Public Health. 2020 May;13(5):667-673. doi: 10.1016/j.jiph.2020.03.019. Epub 2020 Apr 8. PMID: 32340833; PMCID: PMC714268
2. da Rosa Mesquita R, Francelino Silva Junior LC, Santos Santana FM, Farias de Oliveira T, Campos Alcântara R, Monteiro Arnozo G, Rodrigues da Silva Filho E, Galdino Dos Santos AG, Oliveira da Cunha EJ, Salgueiro de Aquino SH, Freire de Souza CD. Clinical manifestations of COVID-19 in the general population: systematic review. Wien Klin Wochenschr. 2021 Apr;133(7-8):377-382. doi: 10.1007/s00508-020-01760-4. Epub 2020 Nov 26. PMID: 33242148; PMCID: PMC7689634.
3. Center for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19). https://www.cdc.gov/ coronavirus/2019-ncov/symptoms-testing/symptoms. html. Accessed 27May 2020
4. Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, Greninger AL, Pipavath S, Wurfel MM, Evans L, Kritek PA, West TE, Luks A, Gerbino A, Dale CR, Goldman JD, O'Mahony S, Mikacenic C. Covid-19 in Critically Ill Patients in the Seattle Region - Case Series. N Engl J Med. 2020 May 21;382(21):2012-2022. doi: 10.1056/NEJMoa2004500. Epub 2020 Mar 30. PMID: 32227758; PMCID: PMC7143164.
5. Datta PK, Liu F, Fischer T, Rappaport J, Qin X. SARS-CoV-2 pandemic and research gaps: Understanding SARS-CoV-2 interaction with the ACE2 receptor and implications for therapy. Theranostics. 2020 Jun 12;10(16):7448-7464. doi: 10.7150/thno.48076. PMID: 32642005; PMCID: PMC7330865.
6. Levi M, Scully M. How I treat disseminated intravascular coagulation. Blood. 2018 Feb 22;131(8):845-854. doi: 10.1182/blood-2017-10-804096. Epub 2017 Dec 18. PMID: 29255070.
7. Levi M, Thachil J, Iba T, Levy JH. Coagulation abnormalities and thrombosis in patients with COVID-19. Lancet Haematol. 2020 Jun;7(6):e438-e440. doi: 10.1016/S2352-3026(20)30145-9. Epub 2020 May 11. PMID: 32407672; PMCID: PMC7213964.

8. Peng K, Li X, Yang D, Chan SCW, Zhou J, Wan EYF, Chui CSL, Lai FTT, Wong CKH, Chan EWY, Leung WK, Lau CS, Wong ICK. Risk of autoimmune diseases following COVID-19 and the potential protective effect from vaccination: a population-based cohort study. EClinicalMedicine. 2023 Aug 16;63:102154. doi: 10.1016/j.eclinm.2023.102154. PMID: 37637754; PMCID: PMC10458663
9. El Hasbani G, Jawad A, Uthman I. Axial and peripheral spondyloarthritis triggered by sars-cov-2 infection: a report of two cases. Reumatismo. 2021 Apr 19;73(1):59-63. doi: 10.4081/reumatismo.2021.1374. PMID: 33874649.
10. Derksen VFAM, Kissel T, Lamers-Karnebeek FBG, van der Bijl AE, Venhuizen AC, Huizinga TWJ, Toes REM, Roukens AHE, van der Woude D. Onset of rheumatoid arthritis after COVID-19: coincidence or connected? Ann Rheum Dis. 2021 Aug;80(8):1096-1098. doi: 10.1136/annrheumdis-2021-219859. Epub 2021 Mar 1. PMID: 33648960.
11. Olson N, Eckhardt D, Delano A. New-Onset Bullous Pemphigoid in a COVID-19 Patient. Case Rep Dermatol Med. 2021 Jun 7;2021:5575111. doi: 10.1155/2021/5575111. PMID: 34211788; PMCID: PMC8187076.
12. Deruelle E, Ben Hadj Salem O, Sep Hieng S, Pichereau C, Outin H, Jamme M. Immune thrombocytopenia in a patient with COVID-19. Int J Hematol. 2020 Dec;112(6):883-888. doi: 10.1007/s12185-020-02943-5. Epub 2020 Jul 16. PMID: 32677007; PMCID: PMC7365304.
13. Palao M, Fernández-Díaz E, Gracia-Gil J, Romero-Sánchez CM, Díaz-Maroto I, Segura T. Multiple sclerosis following SARS-CoV-2 infection. Mult Scler Relat Disord. 2020 Oct;45:102377. doi: 10.1016/j.msard.2020.102377. Epub 2020 Jul 7. PMID: 32698095; PMCID: PMC7340057.
14. Reiff DD, Meyer CG, Marlin B, Mannion ML. New onset ANCA-associated vasculitis in an adolescent during an acute COVID-19 infection: a case report. BMC Pediatr. 2021 Aug 5;21(1):333. doi: 10.1186/s12887-021-02812-y. PMID: 34353302; PMCID: PMC8338201.
15. Agarwala SR, Vijayvargiya M, Pandey P. Avascular necrosis as a part of 'long COVID-19'. BMJ Case Rep. 2021 Jul 2;14(7):e242101. doi: 10.1136/bcr-2021-242101. PMID: 34215639; PMCID: PMC8256728
16. Bahramnezhad F, Ghorbani B, Ghaedrahamt M, Jamaati H. Coronavirus-disease-2019-induced antiphospholipid-like syndrome: a case report. J Med Case Rep. 2021 Jul 29;15(1):408. doi: 10.1186/s13256-021-02966-4. PMID: 34321077; PMCID: PMC8318629.
17. Serrano M, Espinosa G, Cervera R, Serrano A. COVID-19 coagulopathy and antiphospholipid syndrome. Revista Colombiana de Reumatología. 2022 Jun;29:S25–34. doi: 10.1016/j.rcreu.2021.02.013. Epub 2021 Aug 27. PMCID: PMC8390358.
18. Tung ML, Tan B, Cherian R, Chandra B. Anti-phospholipid syndrome and COVID-19 thrombosis: connecting the dots. Rheumatol Adv Pract. 2021 Feb 4;5(1):rkaa081. doi: 10.1093/rap/rkaa081. PMID: 33615129; PMCID: PMC7882149.
19. Bustamante JG, Goyal A, Singhal M. Antiphospholipid Syndrome. 2023 Feb 7. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 28613698.
20. Chidharla A, Syed SB, Chatterjee T, Tarantino MD. A Case Report of COVID-Associated Catastrophic Antiphospholipid Syndrome Successfully Treated with Eculizumab. J Blood Med. 2021 Oct 30;12:929-933. doi: 10.2147/JBM.S324873. PMID: 34744467; PMCID: PMC8566005.
21. Del Ross T, Ruffatti A, Cuffaro S, Tonello M, Calligaro A, Favaro M, Facchinetti M, Hoxha A, Punzi L. The clinical relevance of the IgM isotype of antiphospholipid antibodies in the vascular antiphospholipid syndrome. Thromb Res. 2015 Nov;136(5):883-6. doi: 10.1016/j.thromres.2015.08.019. Epub 2015 Sep 5. PMID: 26410418.
22. Kravvariti E, Koutsogianni A, Samoli E, Sfikakis PP, Tektonidou MG. The effect of hydroxychloroquine on thrombosis prevention and antiphospholipid antibody levels in primary

antiphospholipid syndrome: A pilot open label randomized prospective study. Autoimmun Rev. 2020 Apr;19(4):102491. doi: 10.1016/j.autrev.2020.102491. Epub 2020 Feb 19. PMID: 32084592
23. Hanley B, Naresh KN, Roufosse C, Nicholson AG, Weir J, Cooke GS, Thursz M, Manousou P, Corbett R, Goldin R, Al-Sarraj S, Abdolrasouli A, Swann OC, Baillon L, Penn R, Barclay WS, Viola P, Osborn M. Histopathological findings and viral tropism in UK patients with severe fatal COVID-19: a post-mortem study. Lancet Microbe. 2020 Oct;1(6):e245-e253. doi: 10.1016/S2666-5247(20)30115-4. Epub 2020 Aug 20. PMID: 32844161; PMCID: PMC7440861.
24. Jovanoski M, Boshev M, Marinkovikj Petrusevska S, Srceva Jovanovski M, Georgiev A, Damjanovska Lj. Pulmonary embolism in a patient with COVID-19 pneumonia despite satisfying anticoagulation status Macedonian Journal of Anaes thesia, Dec 2022,3(6):60-69;
25. Germain R.N. The cellular determinants of adaptive immunity. N Engl J Med. 2019;381:1083–1085. doi: 10.1056/NEJMcibr1909387.
26. Berry R, Watson GM, Jonjic S, Degli-Esposti MA, Rossjohn J. Modulation of innate and adaptive immunity by cytomegaloviruses. Nat Rev Immunol. 2020 Feb;20(2):113-127. doi: 10.1038/s41577-019-0225-5. Epub 2019 Oct 30. PMID: 31666730.
27. Norbury CC, Malide D, Gibbs JS, Bennink JR, Yewdell JW. Visualizing priming of virus-specific CD8+ T cells by infected dendritic cells in vivo. Nat Immunol. 2002 Mar;3(3):265-71. doi: 10.1038/ni762. Epub 2002 Feb 4. PMID: 11828323
28. James JA, Robertson JM. Lupus and Epstein-Barr. Curr Opin Rheumatol. 2012 Jul;24(4):383-8. doi: 10.1097/BOR.0b013e3283535801. PMID: 22504579; PMCID: PMC3562348.
29. Delgado-Roche L, Mesta F. Oxidative Stress as Key Player in Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) Infection. Arch Med Res. 2020 Jul;51(5):384-387. doi: 10.1016/j.arcmed.2020.04.019. Epub 2020 Apr 30. PMID: 32402576; PMCID: PMC7190501.
30. Xiao M, Zhang Y, Zhang S, Qin X, Xia P, Cao W, Jiang W, Chen H, Ding X, Zhao H, Zhang H, Wang C, Zhao J, Sun X, Tian R, Wu W, Wu D, Ma J, Chen Y, Zhang D, Xie J, Yan X, Zhou X, Liu Z, Wang J, Du B, Qin Y, Gao P, Lu M, Hou X, Wu X, Zhu H, Xu Y, Zhang W, Li T, Zhang F, Zhao Y, Li Y, Zhang S. Antiphospholipid Antibodies in Critically Ill Patients With COVID-19. Arthritis Rheumatol. 2020 Dec;72(12):1998-2004. doi: 10.1002/art.41425. Epub 2020 Oct 7. PMID: 32602200; PMCID: PMC7361932.
31. Hernández-Pérez JM, Martín-González E, Pino-Yanes M. Strengths and weaknesses of the diagnostic tests for SARS-CoV-2 infection. Med Clin (Engl Ed). 2020 Nov 27;155(10):464-465. doi: 10.1016/j.medcle.2020.05.025. Epub 2020 Oct 30. PMID: 33521299; PMCID: PMC7836751.
32. Newall F. Anti-factor Xa (anti-Xa) assay. Methods Mol Biol. 2013;992:265-72. doi: 10.1007/978-1-62703-339-8_19. PMID: 23546719
33. Ramasamy I.Inherited bleeding disorders: disorders of platelet adhesion and aggregation, Critical Rev in Oncol./Hematol, 2004,49(1),1-35,ISSN 1040-8428,https://doi.org/10.1016/S1040-8428(03)00117-3.
34. Stelzer M, Henes J, Saur S. The Role of Antiphospholipid Antibodies in COVID-19. Curr Rheumatol Rep. 2021 Jul 14;23(9):72. doi: 10.1007/s11926-021-01041-7. PMID: 34259944; PMCID: PMC8278370.
35. McDonnell T, Wincup C, Buchholz I, Pericleous C, Giles I, Ripoll V, Cohen H, Delcea M, Rahman A. The role of beta-2-glycoprotein I in health and disease associating structure with function: More than just APS. Blood Rev. 2020 Jan;39:100610. doi: 10.1016/j.blre.2019.100610. Epub 2019 Aug 16. PMID: 31471128; PMCID: PMC7014586.
36. Haładyj E, Sikora M, Felis-Giemza A, Olesińska M. Antimalarials - are they effective and safe in rheumatic diseases? Reumatologia. 2018;56(3):164-173. doi: 10.5114/reum.2018.76904. Epub 2018 Jun 30. PMID: 30042604; PMCID: PMC6052376.

Abbreviated terms

- *antiphospholipid syndrome (APS)*
- *antiphospholipid like- syndrome*
- *(APS-like syndrome)*
- *antiphospholipide antibodies (aPL)*
- *acute respiratory distress syndrome (ARDS)*
- *active partial thromboplastin time (aPTT)*
- *anti-beta 2 glycoprotein I (anti-b2GPI)*
- *disseminated intravascular coagulation (DIC)*
- *C-reactive protein (CRP)*
- *computed tomography (CT)*
- *Interleukine 6 (IL-6)*
- *Interleukine 1(IL1)*
- *lactate dehydrogenase (LDH) ,*
- *lupus anticoagulant (LA)*
- *low-molecular weight heparin (LMWH).*
- *procalcitonin (PCT)*
- *severe acute respirathory syndrome*
- *coronavirus 2.....(SARS Cov-2)*
- *polymerase chain reaction(PCR)*
- *Tumor necrosis factor alpha(TNF-alp*ha)