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Chapter

COVID-19 and Catastrophic Antiphospholipid Syndrome

Hisyovi Cardenas Suri, David Jimomila Bening and Benjamín Demah Nuertey

Abstract

One year after the beginning of the epidemic, mortality continues to be high despite several different protocols being tried. Critical patients with Covid 19 in some degree of organ failure and thrombotic events meet the diagnostic criteria of a complete or incomplete catastrophic antiphospholipid syndrome (CAPS) or at least we may need to consider a partial form of it. The findings of autopsies and the involvement of different organs and systems are similar to those of CAPS. Currently the only therapy that has been shown to reduce mortality include steroids, anticoagulation and an antinuclear antibody. The same therapy has been shown to be effective for CAPS.

Keywords: COVID-19, multiorgan failure, thrombosis, antiphospholipid antibodies, catastrophic antiphospholipid antibodies syndrome

1. Introduction

After the COVID-19 outbreak in December 2019, a clinical picture was identified in most critical patients that was diagnosed as a cytokine storm associated with high mortality. Hypoxemia was also justified in those patients with severe ARDS who did not respond to the usual ventilation maneuvers such as a reflex of pulmonary hypoxic vasoconstriction, which subsequently lost value or there were no more reports in this regard when thrombosis of pulmonary microvasculature was demonstrated.

After more than a year the medical community has been fighting COVID-19 and having published a number of articles perhaps like never before talking about the same subject in such a short time. We continue with almost the same mortality and with many unanswered questions about the fatal presentation with other systemic manifestations of the disease in patients who develop a serious clinical picture [1].

Obesity, hypertension, diabetes mellitus, cancer, and other chronic diseases have been clearly identified as risk factors for developing severe disease with complications. Just as after large studies it has been shown that the use of steroids, anticoagulation and antinuclear antibodies considerably reduce mortality, being the only recommended treatment in critical patients. Antiviral treatment has been shown to help in 'converting' SAR-COV-2 virus positive patient into having a negative PCR result but has not been shown to modify mortality from the disease [2].

Severe and critical cases of COVID-19 generally present with multi-organ failure, evidence of thrombosis, marked elevation of ferritin, cytokine storm, some

patients with DIC but this is generally not a frequent event in the final stages of the disease.

Since March 2020, upon seeing this clinical presentation that appeared suddenly with high mortality, we began to raise the possibility initially in The Lancet rheumatologic, later in Expert Review of Respiratory Medicine about the possibility of taking into account the diagnosis of Catastrophic Antiphospholipid Antibody Syndrome (CAPS). However despite several studies having been carried out, especially relating to the presence or absence of antinuclear antibodies in patients with COVID-19, we have not found any that has made this diagnosis even after meeting the criteria, much less has it been treated as such. However, drugs have been used in COVID-19 that have been shown to reduce mortality in that are part of the CAPS therapeutic arsenal, even in children with multisystemic inflammatory syndrome, immunoglobulins have been used with good results [3].

The presence of antiphospholipid antibodies have been reported in patients with COVID-19 with a percentage that ranges from 9–96% depending on severity of condition and the presence of thrombosis. Overall figures are around 54%, however, in few studies its presence is associated with failure of more than three organs, thrombosis, and even elevated ferritin which meets the criteria for making a diagnosis of CAPS [4].

Catastrophic Antiphospholipid Antibody Syndrome or Asherson's syndrome to honor Ronald A. Asherson for his impressive work on this condition was named in 1992 when catastrophic was added to define an accelerated form of the antiphospholipid syndrome (APS). CAPS is a rare phenomenon, according to the CAPS registry, it occurs in around 1% of all antiphospholipid syndromes, however, since it is a little-studied entity and at the same time little known by doctors, we infer that it is underdiagnosed [5].

2. Precipitating factors in CAPS

Infections
Postpartum or recent fetal loss
Minor surgical procedures or surgery
Other: malignancy, medication, anticoagulation withdrawal, and SLE exacerbation.

Although the pathogenesis of CAPS continues to be insufficiently understood, antiphospholipid (aPL) antibodies (Ab) belong to the immunoglobulin (Ig) family and are directed against phospholipid-binding plasma proteins such as Beta2 Glycoprotein1 (B2- GP1), prothrombin, annexin V, PS, PC, etc.

As a consequence of initial damage, anionic phospholipids would be exposed on the cell surface B2-GP1. If there are circulating anti-B2-GP1 Ab, they will bind to this complex, inducing cell activation with the release of tissue factor (TF), adhesion molecules, IL-8, C3b, C5a, among others, such as the activation of leukocytes and platelets. This increases their adhesion to the vascular endothelium, promoting microthrombosis and promoting the release of proteases and free radicals. Multiple vascular occlusion triggers necrosis tissue with excessive release of cytokines. A present marker is ferritin, which is elevated in 71% of CAPS patients and according to a recent study could play a role in the pathogenesis of APS and as a follow-up marker in CAPS [6, 7].

Kitchen postulates that vascular occlusion triggers additional thrombosis ("thrombotic storm"), which leads to increased thrombin and decreased fibrinolysis. As her son proposes the theory of "molecular mimic-cry" (molecular imitation), where on one hand the anti-B2-GP1 Ab when bound to the B2-GP1 of

the endothelial cell generate a procoagulant state and on the other hand, certain viruses and bacteria that have an amino acid sequence similar to that of B2-GP1. This therefore favors the synthesis of more Ab. Furthermore, B2-GP1 could activate the immune response through interaction with a membrane receptor TLRs (toll-like) and from this a series of signals are generated, which increase the production of proinflammatory cytokines (TNF, IL-1B, IL-6, IL.8) and FT, PAI-1, PAF, etc. leading to multi-organ failure [8].

3. The criteria for the classification of catastrophic antiphospholipid antibody syndrome

1. Evidence of involvement of three or more organs, systems, or tissues.

2. Development of manifestations simultaneously or in less than a week.

3. Confirmation by histopathology of small-vessel occlusion in at least one organ or tissue.

4. Laboratory confirmation of the presence of antiphospholipid antibodies (lupus anticoagulant or anticardiolipin antibodies) [5].

4. Probable catastrophic antiphospholipid antibody syndrome

1. All four criteria, except only two organs, systems, or tissues are involved

2. All four criteria, except for the absence of laboratory confirmation at least 6 weeks apart because of the early death of a patient never previously tested for aPL before the catastrophic event.

3. Criteria 1, 2, and 4

4. Criteria 1, 3, and 4, and the development of a third event in more than a week, but less than a month, despite anticoagulation.

There are several reports during this pandemic where a high incidence of antiphospholipid antibodies has been demonstrated in patients with COVID-19. In addition, multiorgan failure and the presence of microthrombosis in critical patients have been associated with cytokine storm and the elevated ferritin. From the first reports in Wuhan, elevated ferritin was identified as a marker of severity in critically ill patients with COVID-19. Four well-recognized clinical conditions may be associated with high ferritin levels: the macrophage activation syndrome (MAS), adult-onset Still's disease (AOSD), catastrophic antiphospholipid syndrome (CAPS), and septic shock. The presentation of critical patients with COVID-19 does not meet the criteria to make a diagnosis of any of these diseases, however, they do meet the criteria to make the diagnosis of complete or incomplete CAPS [9, 10].

However a study by the American society of Hematology (ASH) in which they performed an antiphospholipid antibody (aPL) screen in 27 patients with COVID-19. Only four of these patients were positive for lupus anticoagulant. None of these patients were positive for anticardiolipin or anti-β-2 glycoprotein I antibodies. Given the fact that antiphosholipid antibodies may transiently be elevated during acute infections, thrombosis or inflammation, the American Society of Hematology

has strongly recommended against routinely testing for these antibodies (aPL) in COVID-19 patients unless clinically indicated by the history.

It is however important to note that most studies that have been published in this regard do not report findings specific for critical patients with COVID-19. Inclusion criteria have been more generalized targeting patients with COVID-19. This could lead to recording lower positivity rate for aPL antibodies. Also, most of these studies have only tested specifically for lupus anticoagulant which is the least sensitive among the different types of antiphospholipid antibodies which could be positive among this group [11].

This recently led Amezcua-Guerra et al. to test a panel of aPL antibodies in blood specimens from 21 patients hospitalized in the intensive care unit due to severe or critical COVID-19. Anticardiolipin, anti-β2 glycoprotein I, antiprothrombin, antiphosphatidylserine, antiphosphatidylinositol and antiannexin V antibodies were measured, each in IgM and IgG isotypes. Subsequently, demographic and clinical data were obtained from electronic medical records. Samples (sera) collected before the SARS-CoV-2 pandemic from 12 healthy individuals, matched for age and sex, were tested as controls. A total of 19 patients (90%) had dyspneoa while on admission, 57% eventually required mechanical ventilation (invasive) during their stay in the hospital. All of these patients had elevated levels of D-dimer, ferritin and C reactive protein at time of presentation.

Out of the 21 patients with COVID-19, 12 of them tested positive for at least one aPL antibody with only 1 of the 12 controls yielding a positive result. Age and number of comorbidities tended to be lower in patients with aPL antibodies. In contrast, levels of D-dimer, ferritin and C reactive protein were higher both on admission and throughout the hospital stay in the patients. Patients who were positive for aPL demonstrated elevated levels of interleukin-6 (>40 pg./mL) [12].

Interestingly, significant levels of circulating anticardiolipin and anti-β-2glycoprotien I antibodies have recently been described in three severely ill COVID-19 patients with multiple cerebral infarctions by Zhang et al. This is suggestive that coagulopathy associated with COVID-19 could be within or close to the spectrum of antiphospholipid syndrome. A higher-than-expected number of thrombotic episodes have been reported involving both veins and arteries (pulmonary thromboembolism, deep venous thromboses, myocardial infarction and stroke even with the use of anticoagulant therapy or prophylaxis [13].

It is now established that vascular changes are well associated with COVID-19. Formation of fibrin thrombi has been observed in some patients. Many patients with severe illness have shown elevated levels of D-Dimers with other clinically relevant findings suggesting thrombotic microangiopathy such as cutaneous changes in the limbs. Autopsy finding of four out of seven patients with COVID-19 showed that thrombi were consistently present in all pulmonary vessels with a diameter of 1 mm- 2 mm. Also, microthrombi were 9 times more likely to be found in the alveolar capillaries of patients with COVID-19 than in patients with influenza [14].

5. Clinical manifestations of CAPS

Renal (70%): usually accompanied by hypertension and acute renal failure.

Pulmonary (65%): severe dyspnea, frank adult respiratory distress syndrome (ARDS), pulmonary emboli, sometimes multiple pulmonary infarction, interstitial infiltrates, and intraalveolar hemorrhage.

Central nervous system (55%): major cerebral infarctions, cerebral sinus thrombosis, encephalopathy and seizures.

Cardiac (50%): typical myocardial infarction, diffuse myocardial involvement with congestive heart failure or valve lesions.

Gastrointestinal (45%): vascular occlusions of mesenteric, portal and inferior vena cava, arterial occlusions accompanied by gangrene of the bowels and splenic infarctions, hepatic involvement and pancreatitis.

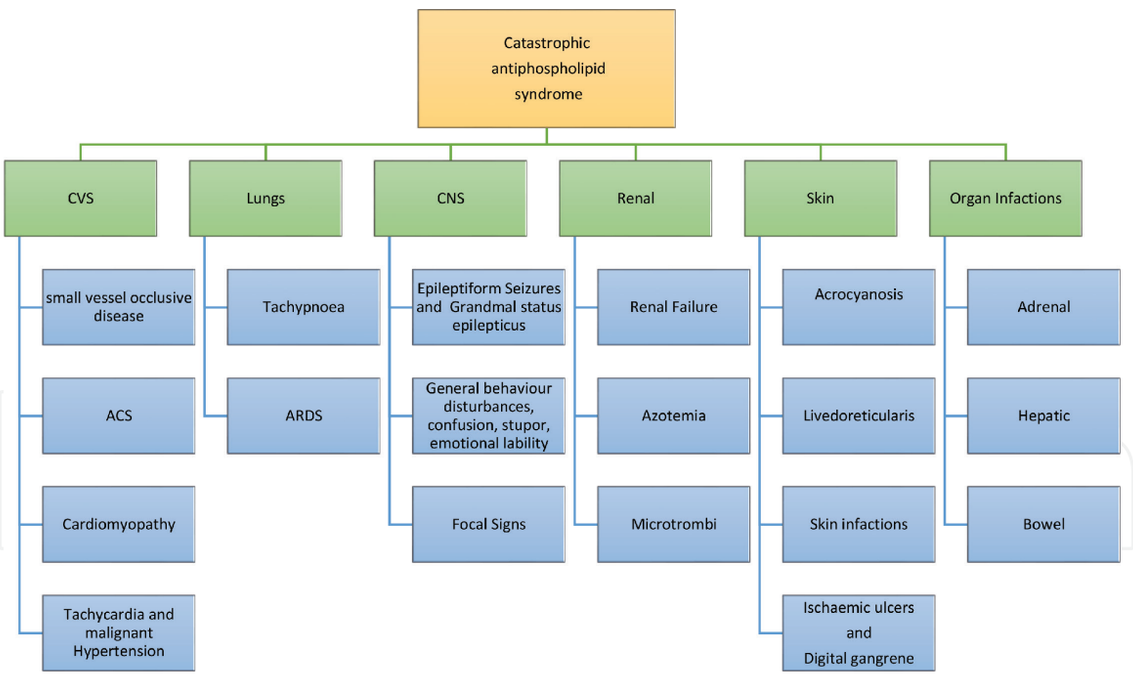
Skin (40–45%): livedo reticularis, ulcerations, gangrene, purpura, acrocyanosis or digital ischemia.

Other manifestations: adrenal thrombosis, testicular infarction, necrosis of the prostate gland [7].

The clinical manifestations are described in multiple reports during the coronavirus pandemic including skin involvement, so we believe, according to the evidence, that a high percentage of critically ill patients meet the diagnostic criteria of this entity.

Coagulation disorders were initially thought to be due to diseminated intravascular coagulopathy (DIC), but with the current evidence from all autopsies it has been shown to be due to a procoagulant phenomenon together with a severe inflammatory state. These findings may explain the events of venous thromboembolism observed in some of these patients and support antithrombotic prophylaxis/treatment. The cumulative incidence of thrombotic complications (mostly PE) is high between 25 and 30%.

The incidence of cerebral thrombosis in two weeks is almost 10 times higher in patients with COVID-19 than in the normal population in patients under 50 years of age. In a report of 3 patients with ischemic stroke the association with antiphosphilipid antibodies was 100% [15, 16].



This multisystem inflammatory syndrome is caused by cytokine activation [7]. Cytokines involved include tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, IL-18 and macrophage-migration inhibitory factor. These cytokines are responsible for acute lung inflammation via increasing neutrophil migration and lung vascular permeability, not only for ARDS but also for the cerebral edema, which may be a factor in the initial confusion and deterioration of consciousness in these patients, as well as myocardial dysfunction encountered.

In 6 autopsies performed in a hospital in France it was found that one patient presented a lymphocytic viral pneumonia that could be considered as type L. For five other patients with a phenotype H, the histologic pattern was an acute fibrinous

and organizing pneumonia (AFOP), characterized by an extensive intra-alveolar fibrin deposition called fibrin "balls", rather than hyaline membranes. AFOP, a rare form of acute lung injury. This pattern differs from the diffuse alveolar damage (DAD) found in the classic ARDS by the fact that organizing intra alveolar fibrin constitutes the dominant histological finding in AFOP, especially in its subacute presentation by contrast to the fulminant presentation, is a cortico-sensitive pathology.

Kidney histopathology was examined in an autopsy series of 26 patients who died of respiratory failure secondary to COVID-19. All patients had evidence of acute tubular injury (of varying severity); a range of other histopathology findings, such as erythrocyte clusters and pigmented casts, were also present [17].

Myocardial involvement has been described since the first reports adding an increase in the incidence of ACS and arrhythmias in these patients. Reports vary 20–30% of myocardial involvement, even higher percentages of troponin elevation have been found as a marker of myocardial damage [18].

The slightly rarer skin manifestations in this entity, especially when it is secondary to an infectious process, have been reported in two articles, even during the autopsy of these patients with purpuric skin rash. The conclusions of this study were severe COVID-19 may define a type of catastrophic microvascular injury syndrome mediated by activation of complement pathways and an associated procoagulant state.

In the CAPS Registry, CAPS as the initial manifestation of antiphospholipid syndrome occurred in 86.6% of children with infections being the triggering factor in 60.9% of the cases. Cardiac involvement was present in 57.4% of children and included cardiac failure, heart valve lesions, lung 63%, skin 37% and gastrointestinal 17.4% [19, 20].

Infections in children are more frequent than adults, which have been shown to play a role in the theory of "molecular mimic-cry" (molecular imitation) where certain viruses and bacteria that have an amino acid sequence similar to that of B2-GP1 result in an immune response producing antiphospholipid antibodies. B2-GP1 could activate the immune response through interaction with a membrane receptor TLRs (toll-like) and from this a series of signals are generated, which increase the production of proinflammatory cytokines. The medical community recognizes the MIS but most do not agree with the diagnosis of kawassaki disease [16].

Given the data made available from the various studies mentioned earlier, we can say that there is some evidence that critically ill patients with COVID-19 are demonstrating a disease form that meets the criteria for making the diagnosis of complete catastrophic antiphospholipid antibodies syndrome, or at least showing a disease form that is within the spectrum of manifestation of this syndrome. CAPS registry was created in 2000. As of 2012 it had been updated with data from over 400 patients. Not much advancement has been made in the area of this poorly understood syndrome after that. This interesting phenomenon observed during this pandemic which has become the largest public health emergency in recent times calls for more research work in the area of Catastrophic antiphospholipid syndrome. More awareness is required in the medical community in this area [21–23].

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