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From pregnancy to SARS Cov II- pandemia. "Like a bridge over troubled waters" COVID 19: a new virus- induced thrombotic microangiopathy model? LDH/AST ratio diagnostic role

Abstract

Several scientific studies have shown that SARS-CoV II infection, responsible for the COVID 19 pandemic, can lead to a state of thrombotic microangiopathy (TM), both thrombotic thrombocytopenic purpura-like (TTP-like) and atypical hemolytic-uremic syndrome-like (aHUS-like), similarly to what occurs in the major thrombotic complications of pregnancy. The differential diagnosis between these disorders is very complex, due to overlapping clinical features, and also because they affect various disciplines. In the context of thrombotic microangiopathies, the test for the evaluation of ADAMTS-13 plays a key role, but in the pending or absence of the ADAMTS-13 test we can use PLASMIC score and /or LDH/AST ratio and these can help in the early stages of the disease. TTP and aHUS have different treatments: plasmapheresis in the TTP and Eculizumab in the aHUS.

Therefore, we propose to the scientific community the LDH / AST score as a diagnostic aid, to help the differential diagnosis between the SARS-CoV II associated-TM and direct towards a more specific and effective therapy, in Covid-19 critical Patients.

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The relationship between pregnancy and sars-Cov II infection: the trombotic microangiopathic state

Recent scientifical studies have reported a high prevalence of thrombotic events in SARS COV II Disease. Coagulation happens in all the organs such as the lung, liver, heart, kidney, bowel, skin, and brain upon in most severe cases of COVID-19.[1]

SARS-CoV-2 is associated with blood clotting such as the prothrombotic stage which is caused by arterial and venous thromboembolism along with the augmented level of the D-Dimer levels. Native COVID-19 is associated with the production of pro-inflammatory cytokines and mediates the activation of mononuclear and endothelial cells with tissue factor expression, leading to the activation of coagulation and generation of thrombosis. The endothelial cell dysfunction mediated by the SARS-CoV-2 infection results in more production of thrombin and stops fibrinolysis which leads to the hypercoagulopathy condition.[2] The COVID-19 patients associated with the hematological changes appear with decreased lymphocyte and platelet count. The host immune system is responded upon interaction with the pathogen, which activates the complement system. Whereas uncontrolled, activation of the complement[3] system leads to inflammation both acute and chronic, intravascular coagulation till to microcirculation and cellular injury furtherly leads to the multi-organ failure.[4]

Therefore we can state that Sars-cov2 infection induces the occurrence of a Trombotic Microangiopathic state

"Thrombotic microangiopathies" (TM)[5] are pathological conditions in which thrombotic occlusion of the microcirculation occurs (capillaries, arterioles) with signs of ischemic suffering affecting various body areas.[6,7]

They include many diseases

Thrombotic thrombocytopenic purpura (TTP) or Moskowitz disease: associated with antibodies to ADAMTS 13, a metallo-protease which processes the von Willebrand Factor (FvW), or constitutional (cTTP), known as Upshaw-Schulman syndrome, more rare and associated with congenital ADAMTS-13 deficiency, Atypical hemolytic-uremic syndrome (aHUS): associated with complement dysregulation and the Typical hemolytic-uremic syndrome (STEC-HUS): associated with Shiga toxin by E. Coli[8]

Pre-eclampsia and eclampsia[9]

HELLP syndrome[10]

Disseminated intravasal coagulation (CID)[11]

Antiphospholipid antibody syndrome[12]

The TM could also be associated with sepsis from various etiological agents including HIV, Herpes Zoster, Cytomegalovirus,

Influenza Virosis, Hepatitis A, B and C, Metapneumonia Virus, Cryptococcus meningitis, E.Coli, Shigella Disentariae, Pneumococcus, Streptococcus Pneumoniae, Mycobacterium Tuberculous, Ehrlich bacterium, Borrelia, Legionella, Bacteroides, Capnocytophaga canimorsus,[13] and with Pulmonary Tumor[14] and Cancer.[15]

Clinically, TM are characterized by the occurrence of thrombocytopenia, non-autoimmune hemolytic anemia and variable organ damage depending on the extent of thrombotic / ischemic tissue damage.[16]

Differential diagnosis, adequate and timely therapy should ensure a better outcome.

From the hematological point of view, at the microvascular level we find[17]:

a. Systemic/renal platelet aggregation: thrombocytopenia (<150,000)

b. Mechanical injury of erythrocytes: schistocytes >1% per 1000 RBC

c. Microangiopathic hemolytic anemia: high LDH levels (largely derived from ischemic or necrotic tissues rather than lysed red blood cells) Reduced levels of haptoglobin.

TM is classified in primary and secondary forms. In primary forms, the disease is defined by the presence of a thrombotic microangiopathy, such as cTTP, due to the deficiency of ADAMTS13, a metalloprotease that cleaves the von Willebrand Factor (FvW), and as aHUS characterized by complement dysregulation.[18] The secondary forms, on the other hand, are events in which TMA arises as a complication of an underlying medical condition: pregnancy is typical but also malignant hypertension, as a complication of a Preeclampsia or HELLP syndrome, drugs, kidney transplantation or bone marrow, systemic lupus erythematosus, tumors and infections like COVID-19.[19]

TM is problematic disorders, due to the imbalance between the coagulation systems, the immune system and the complement system. Pregnancy is associated with physiological changes in the microcirculation and in the hemostatic balance, which can manifest a congenital TM, hitherto silent, or it can be itself the trigger factor of a secondary TM.[20]

In pregnancy there is a framework of hypercoagulation and hypofibrinolysis, with physiological state of latent "CID", mainly due to hormonal state, necessary to protect the mother from bleeding complications during pregnancy, but especially in the period of childbirth and postpartum.[21]

TTP and aHUS are not specific pathologies of pregnancy, but occur more frequently during or in relation to it. The incidence of these in pregnancy is respectively 1/20 pregnancies for Preeclampsia, 1/1000 pregnancies for HELLP syndrome, 1/25000 pregnancies for aHUS[22] and 1/200000 pregnancies for TTP.[23]

From anatomopathological and clinical signs, we can deduce that Sars-cov 2 infection induces a pathological condition characterized by hypercoagulopathy and complement dysregulation, like pregnancy, and can induce an acute episode of TM.

TM differential diagnosis

In the context of thrombotic microangiopathies, the test for the evaluation of ADAMTS-13 plays a key role, facilitating the differential diagnosis of TTP. ADAMTS-13 protease is known to have a marked functional deficit (activity less than 10%) in patients with TTP, while activity is normal or slightly reduced in other thrombotic microangiopathies.[24] However, the application of a seven variable score, called PLASMIC score (Table 1) which, pending/absence of the test, allows to predict a severe ADAMTS-13 deficiency, could help in the early stages of the disease, both in the choice of more appropriate treatments and to focus on more specific diagnostic investigations. Higher values (6 or 7) of the score have been observed to predict severe ADAMTS-13 deficiency. The LDH / AST ratio, introduced by Gupta in 2018,[25] has been also proven useful in the differential diagnosis between TM, with values >10 strongly indicative of aHUS and values <10, indicative of TTP. The differential diagnostic role of the LDH/AST relationship in the context of thrombotic microangiopathies in pregnancy was also confirmed in our recent retrospective study, analyzing the case studies of TM in pregnancy, in the decade 2010-2019, at the Obstetric-Gynecological Department of PISA University-HealthCare System.[26]

Table 1 The PLASMIC score – modified[26]

	Points
Platelet count <30×109/L	1
Hemolysis variables (reticulocyte count elevation; undetectable haptoglobin. or bilirubin - indirect 2.0mg/dL)	1
No active cancer	1
No history of solid-organ or stem-cell transplant	1
MCV <90 fL	1
INR <1.5	1
Creatinine <2.0mg/dL	1

INR: international normalized ratio; MCV: mean corpuscular volume.

The PLASMIC score and the LDH/AST ratio, whereas the functional determination of ADAMTS-13 is not available, (effective diagnostic test) could guide in the differential diagnosis between TTP-like and aHUS-like syndrome, occurring in Covid 19, allowing by a cost-effective and simple test, the timely implementation of specific therapeutic procedures, such as plasma therapy /plasmapheresis in the first case, (possibly associated with steroids and/or Rituximab, in the case of PTT-like TM refractory or partially responsive to plasmapheresis) and anti-complement / antiphlogistic therapy (Eculizumab) in the second case.

Therapy

The natural history of these syndromes has changed significantly since 1996, due to two major discoveries. On one hand, the acquired or constitutional deficiency of ADAMTS 13, (A Disintegrin and Metalloproteinase with a ThromboSpondin type 1 motif, member 13), an enzyme that processes the von Willebrand factor (vW),[27] identified as the main cause of TTP. On the other , the subsequent discovery of mutations in one or more genes, coding for the regulation proteins or activation of the alternative complement pathway, as risk factors of the other microangiopathic thrombotic syndrome, with predominant renal involvement, the Atypical Hemolytic-Uremic Syndrome (aHUS).[28]

In these circumstances, it is essential to "know", in order to "know how" to recognize, to arrive in time and to prevent, if possible.

Survival is linked to the timeliness of the diagnostic suspicion and the consequent start of plasmapheresis treatment in the TTP[29] (possibly associated, in case of inadequate response, with steroid therapy and/or treatment with Rituximab in the acquired form, linked to the presence of autoantibodies) and Eculizumab treatment in the aHUS.[30]

Since COVID 19 induces a procoagulative state like the trombotic microangiopathies disease, why can't we use the same therapies in most severe cases?

Observational studies have found complement markers activation in patients with COVID-19 and various studies have shown that Eculizumab, a monoclonal antibody against a complement factor C5, is able to improve symptoms in critically ill adults with COVID-19.[31]

Conclusion

Moving from the observation that COVID-19 can be considered as a TM and that various scientific studies have highlighted how the use of Eculizumab can improve the inflammatory state given by the Sars-cov2 infection, we suggest to the scientific community the LDH/AST score as a diagnostic aid, to help the differential diagnosis between the Covid-19 associated TM and direct towards a more specific and effective therapy, opting for plasmapheresis in TTP-like forms and for Eculizumab therapy in the aHUS-like forms of Covid 19.

From our specific obstetric perspective, pregnancy and its major thrombotic complications like thrombotic microangiopathies, seem to be "like a bridge over troubled waters ", as Simon and Gairfunkel song in the Sixty, connecting obstetric and infectious medical fields and opening new horizons of treatment in this dramatic pandemia, whereas "the life at the dawn", appears to reach out hand to care and to cure "the life near sunset".

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Conflicts of interest

The authors report no conflicts of interest.

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