Coronavirus disease is a highly contagious infection that can be deadly and is caused by the severe acute respiratory syndrome SARS-CoV-2. As pregnancy is a unique condition characterized by prominent physiologic changes as the cardiovascular, respiratory, and immune systems, researchers have questions related to the impact of COVID-19 on pregnant women [2, 3]. The current literature indicates that pregnancy may worsen the course of COVID-19 infection compared to non pregnant women at the same age. On the other hand, the course of severe or critical COVID-19 in hospitalized pregnant women has been shown to be shorter than in non-pregnant population [2, 3]. It has been stated that COVID-19 may cause an increase obstetric complications such as preterm labor and fetal distress [2, 3]. However, international knowledge is still limited on this issue and the experience of large pandemic centers will help to achieve better results.

A 40-year-old woman was referred to our emergency room for persistent cough and dyspnea. She denied fever and reported the occurrence of pretibial edema two days before. She was at 20th week of pregnancy but she didn't undergo any test. The last of the 4 previous pregnancies was complicated by gestational diabetes mellitus and gestational hypertension with the birth of a small for gestational age (SGA) neonate.
At the admission, oxygen saturation (SpO2) was 70%, respiratory rate 35-40 breaths/minute, blood pressure (BP) 240/150 mmHg and heart rate (HR) 140 bpm/min. Nasopharyngeal swabs for COVID-2 was negative. She started therapy with Labetatol ev and MgSo4 ev. High flow oxygen therapy was administered causing a raise of SpO2 to around 80%; nevertheless respiratory function remained severely altered.

A CPAP helmet (PEEP 15 and FiO2 70%) was positioned with rapid improvement of SpO2 up to 100%. BP decreased to 180/130 mmHg and HR to 110 bpm/min. A central venous catheter was placed into the femoral artery. Urinary catheter was inserted as well as the patient remained anuric.

Gynecological evaluation revealed the presence of a fetus with a biometry corresponding to approximately 20 weeks. The placenta was normally implanted. The amniotic fluid appeared regular. The cervix was closed without vaginal bleeding.

Blood tests showed hemoglobin (HB) 6.3 g/dL, white blood count (WBC) 24.100 10^3/mL, platelet count 72.000 10^3/mL, creatinine 10.7 mg/dL, azotemia 192 mg/dL, LDH 1716 IU/L, AST/ALT 63/30 mU/ml, PCR 8.57 mg/dL, D-dimer 5931 ng/mL. Two units of red blood cells were transfused. Chest X-ray revealed diffuse ill-defined area of increased density suggestive of pulmonary edema and bilateral pleural effusion.

In consideration of the worsening clinical conditions, chest CT was performed showing bilateral, multilobar ground glass opacification (GGO) in the lower lobes suggesting SARS-COV-2 infection. Continuous renal replacement therapies (CRRT) with transfusion of plasma was started. Given that differential diagnosis comprised atypical HELLP presentation with progressive reduction of PLT levels versus other thrombotic microangiopathy, after collegial discussion, interruption of pregnancy was carried out. A cesarean section was performed. In consideration of the worsening dyspnea, research of SARS- COV-2 on bronchoalveolar lavage (BAL) fluid was performed with positive result. She started non invasive ventilation (NIV). Complement C3c, C4, IgG, IgA, IgM, indirect coombs test, HBsAg, Anti-HCV, HIV test, ANA, ENA, ANCA, Ab ant-dsDNA, LAC and either IgG/IgM anti-cardiolipin and anti-beta2glicoprotein I antibodies were all negative.

The patient started plasmapheresis. ADAMTS 13 serum activity level of 24% and the lack of anti-ADAMTS 13 antibodies allowed to make the diagnosis of Hemolytic-Uremic Syndrome (HUS). The
patient started therapy with Eculizumab 900 mg that was administered one time every 7 days. The patient resumed spontaneous urination after one day of therapy. Renal failure persisted after 5 days with creatinine levels at 7.9 mg/dL and azotemia at 126 mg/dL. Continuous dialysis was then shifted in intermittent dialysis. Severe anemia persisted after 10 days and two units of red blood cells were trasfused. After 15 days dialysis treatment was stopped. Progressive improvement of platelet count was observed with normalization after 12 days. The patient was discharged 1 month after the start of therapy with normal value of HB, WBC, PLT, creatinine, azotemia, LDH, AST/ALT. She continues antihypertensive therapy with beta blockers, sartan, doxazosin, amlodipine, clonidine. She continued Eculizumab 1200 mg after 14 days from the dimission.

Discussion

Atypical hemolytic uremic syndrome (aHUS) is a complement-mediated disorder, characterized by microangiopathic hemolysis, thrombocytopenia, and renal failure [1]. The incidence of aHUS is estimated at 0.23 per year per million people [2]. Approximately 10–20% of aHUS diagnoses occur in the setting of pregnancy [3]. Excess complement activation is usually mitigated by soluble and membrane-bound regulators of the alternative complement pathway [4]. Recognition of pregnancy-associated aHUS is often delayed owing to misdiagnosis of similar thrombotic microangiopathy disorders, such as hemolysis, elevated liver enzymes, and low platelet count syndrome or thrombotic thrombocytopenic purpura (TTP) [5].

The mechanism by which pregnancy precipitates unopposed complement activation remains unclear. In normal pregnancy the placenta plays an important role in complement activation but is tightly regulated by two specific inhibitory proteins, CD59 and Decay Accelerating Factor, neither of which have been implicated in genetic pathophysiological mechanisms that lead to aHUS [6]. When the placenta is removed and these factors are no longer expressed this balance may be disrupted and unopposed activation triggered, which in part explains the predilection of aHUS to post-partum presentation. The onset during the first time of pregnancy was unusual but may be explained by alternative triggers of complement activation namely the estrogen hyper-stimulation [7].
Like aHUS, TTP is a life-threatening thrombotic microangiopathy disorder, but latter may respond better to plasma exchange as it is usually relies on the presence ADAMTS13 autoantibodies [8]. Thrombotic thrombocytopenic purpura can be easily ruled out with an ADAMTS13 activity level greater than 10% and the absence of autoantibodies. Likewise, complement genetic testing may be performed to support a diagnosis of aHUS, particularly when a pathogenic mutation is discovered. However, ADAMTS13 and complement genetic testing are send-out labs in most institutions, limiting turnaround time. To expedite diagnosis and treatment of aHUS, and to help rule out TTP more quickly, it may be beneficial for clinicians to work with their laboratory medicine department and hospital leadership to review options for ADAMTS13 and complement genetic testing [1].

Over the last decade the treatment of aHUS has been revolutionised by the recognition of the underlying pathophysiology and the availability of the monoclonal anti-complement (C5) antibody, eculizumab. This treatment has improved outcomes for those with aHUS to the extent that return to normal or near normal renal function is a common, if not expected, outcome of treatment [9]. Clinical trials have shown that eculizumab effectively decreases complement-mediated hemolysis, thrombocytopenia, and kidney injury in non pregnant adults with aHUS. Thus, successful treatment of pregnancy-associated aHUS with eculizumab is in line with our understanding of the disease as a complement mediated thrombotic microangiopathy disorder [1].

Eculizumab is the first approved medication for patients with Paroxysmal nocturnal haemoglobinuria (PNH) in 2007 or aHUS in 2011. In patients with PNH, treatment with eculizumab was associated with significant reductions in intravascular haemolysis, thromboembolism, transfusion requirements, anaemia, and fatigue, and improved quality of life. In patients with aHUS, eculizumab inhibited TMA, improved renal function and haematological outcomes, and improved quality of life. Eculizumab therapy has also been associated with improved survival in both clinical settings [7]. Sometimes it may be challenging to distinguish between pregnancy complications like preeclampsia, HELLP syndrome with COVID-19 related to clinical findings and increased rates of pregnancy complications and cesarean section were observed(10-11). Recent studies evidenced higher pregnancy complication rate, erythrocyte sedimentation rate, C-reactive protein, procalcitonin, ferritin, D-dimer, lactate dehydrogenase, IFNγ, and IL-6 values (p < 0.05) in COVID-19 pregnancy. The management
of pregnancies complicated by COVID-19 is challenging for physicians as there is still no consensus on issues such as optimal treatment modality, timing, and route of delivery [12-13-14-15]. However, as pregnancy is a unique process characterized by various immunologic changes and each immunomodulatory event is associated with a specific condition, it is challenging to predict the impact of immune-mediated therapies on pregnant women. Furthermore, additional data about the immunomodulatory changes in COVID-19 patients during pregnancy may reveal pathophysiological events behind this deadly disease. [13].

The experience of major pandemic centers in dealing with a large case load is valuable to improve people’s knowledge on pregnant women with COVID-19 infection.

aHUS represents a rare and even more exceptional disease in the early stages of pregnancy that can put the mother's life at risk and whose timely diagnosis is essential.

all the authors declares that they have no conflicts of interest

References


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Risk factors associated with
