



Original Article

Tactics of Treatment of Catastrophic Anti-Phospholipid Syndrome in Pregnant Woman: Based on a Clinical Case

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ABSTRACT

Objective: The objective of this study is to investigate the occurrence and management of acute thrombotic microangiopathy, a severe complication associated with antiphospholipid syndrome (APS), particularly in the context of catastrophic APS (CAPS) during pregnancy. The study aims to enhance the understanding of CAPS in pregnancy, improve early diagnosis, and evaluate the effectiveness of different treatment modalities.

Materials and methods: The study employed a case report methodology, focusing on a pregnant patient diagnosed with CAPS and experiencing acute thrombotic microangiopathy. The clinical presentation, laboratory findings, diagnostic procedures, and treatment interventions were documented and analysed. The treatment approach included the use of anticoagulants, glucocorticoids, and plasma exchange. The response to treatment, complications, and patient outcomes were assessed.

Results: The study observed a rapid development of liver, central nervous system, and renal lesions within a week, indicating the severity of CAPS in the pregnant patient. Despite the pregnancy termination, the patient's clinical condition did not show improvement, suggesting a lack of response similar to observations in other cases. The patient received standard CAPS treatment, except for intravenous administration of immunoglobulins. Further details were reported regarding the treatment outcomes, laboratory parameters, and imaging findings.

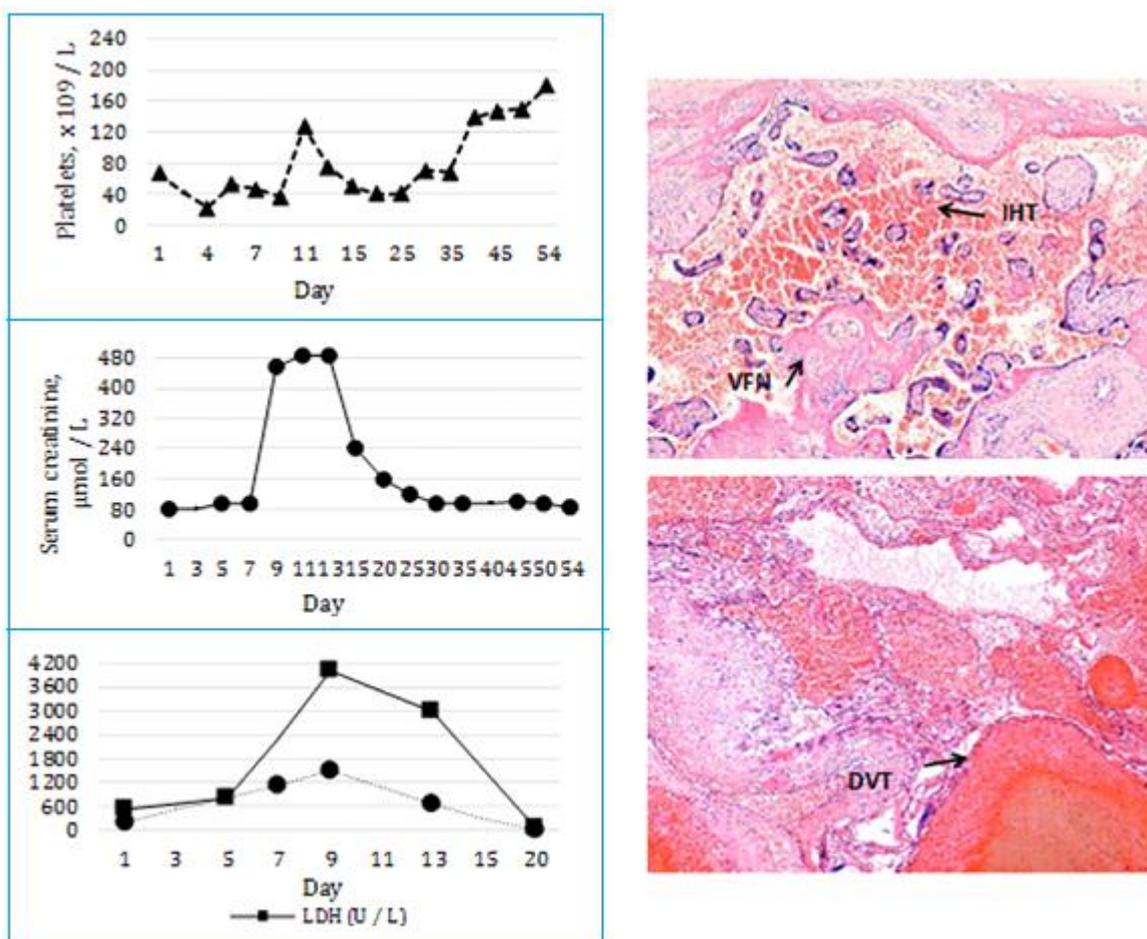
Conclusion: This study highlights the challenges associated with diagnosing and managing CAPS during pregnancy, specifically focusing on acute thrombotic microangiopathy. Early diagnosis, aggressive treatment with anticoagulants and glucocorticoids, and the use of plasma exchange or intravenous immunoglobulin are crucial in achieving positive outcomes. The study suggests the consideration of alternative interventions, such as immunosuppressive therapy or targeted biologic agents, in refractory cases of CAPS. Further research is needed to elucidate the optimal treatment strategies and long-term outcomes in pregnant patients with CAPS.

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GRAPHICAL ABSTRACT



Introduction

Antiphospholipid syndrome (APS) is a multifaceted autoimmune condition characterized by connective tissue impairment, particularly affecting the endothelial lining of microvascular vessels. The underlying cause of APS is the production of autoimmune antibodies against phospholipids (FL) present in cell membranes. These antibodies include lupus anticoagulant (VA), antibodies to cardiolipin (CL), and antibodies to related glycoproteins [1].

The presence of anti-phospholipid antibodies in APS is associated with a range of adverse pregnancy complications. These complications can have a significant impact on both the mother and the developing fetus. Some of the pregnancy-related complications associated with APS include preterm labour, recurrent miscarriage, preeclampsia (a condition characterized by high blood pressure and organ damage), fetal growth restriction, and fetal demise.

The mechanisms by which antiphospholipid antibodies contribute to these complications are complex and not fully understood yet. It is believed that these antibodies can disrupt normal placental function and impair blood flow to the developing fetus. This can lead to inadequate oxygen and nutrient supply, resulting in fetal growth restriction or even fetal demise. In addition, the presence of anti-phospholipid antibodies can increase the risk of blood clot formation, leading to placental infarction (tissue death) and subsequent pregnancy loss. The impact of APS on pregnancy highlights the importance of the early detection and appropriate management of the condition in pregnant individuals. Close monitoring, including regular prenatal visits and specialized testing, is crucial to identify and address potential complications promptly.

The most severe manifestation of anti-phospholipid syndrome is known as catastrophic anti-phospholipid syndrome (CAPS).

CAPS is classified as a distinct clinical entity characterized by the occurrence of thrombotic microangiopathy and thrombotic vasculopathy, affecting blood vessels of various sizes and locations [2]. In CAPS, there is a rapid and widespread formation of blood clots (thrombosis) within the microvasculature throughout the body. This extensive thrombosis can lead to impaired blood flow and damage to vital organs, ultimately resulting in multiple organ failure. The organs commonly affected include the kidneys, lungs, brain, heart, and skin. CAPS is typically associated with high levels of antiphospholipid antibodies (aPL), which contribute to the hypercoagulable state observed in this condition. These antibodies interact with phospholipids in the cell membranes, triggering abnormal clotting mechanisms and promoting thrombosis [3].

In addition, in some cases of CAPS, tissue necrosis (death of cells or tissue) may occur. The combination of widespread thrombosis, organ damage, and tissue necrosis makes CAPS a life-threatening condition that requires immediate intervention and treatment. The clinical manifestations of CAPS can develop rapidly over a short period, often within a week. The condition is characterized by a rapid deterioration in organ function and prompt diagnosis and intervention are crucial to prevent further complications and improve outcomes.

Based on statistical data, antiphospholipid syndrome (APS) affects approximately 5% of the population, with a higher prevalence among women (2:1 ratio), and within all APS cases, catastrophic antiphospholipid syndrome (CAPS) accounts for approximately 1% [4]. Despite the availability of advanced therapies, the mortality rate in CAPS patients is notably high, ranging from 36% to 50%, often attributed to complications such as cardiopulmonary and the most devastating events. Pregnancy can act as a trigger for CAPS, further emphasizing the urgency and accuracy of APS diagnosis as a crucial factor for effective treatment [5]. Pregnant women with CAPS face a mortality rate of around one-third [6, 7]. This study provides a clinical case report highlighting the management of catastrophic antiphospholipid syndrome in a pregnant patient.

Martials and Methods

The case of a pregnant woman with a history of multiple venous thromboembolism and antiphospholipid syndrome at 23 weeks of gestation was presented. During pregnancy, the woman developed catastrophic antiphospholipid syndrome (CAPS) characterized by symptoms such as pain in the right upper quadrant, thrombus formation in the small intrahepatic vessels, thrombocytopenia, multifocal bilateral brain lesions with areas of secondary hemorrhages, elevated creatinine levels, and increased liver enzymes. The International CAPS Registry (CAPS Registry), established by the European APS Forum in 2000, serves as a resource for analysing cases and formulating current recommendations for the CAPS management [8].

Results and Discussion

A 33-year-old pregnant woman, who had not given birth before, arrived at the Vinnytsia Regional Perinatal Center when she was 23 weeks and 2 days pregnant. The patient reported experiencing pain in the epigastric region and the right hypochondrium area. The initial symptoms of catastrophic antiphospholipid syndrome (CAPS) manifested at 22+6 weeks of gestation (day 0, [Figure 1](#)).

Based on the laboratory analysis, the following results were obtained: The hemoglobin level was 10.3 g/dl, new-onset thrombocytopenia (a low platelet count $67 \times 10^9/l$), slightly increased fibrinogen and WBC, absence of the proteinuria, APTT was increased to 56 sec. (the norm is 28-38 sec.), the level of bloodstream creatinine was 81 $\mu\text{mol}/\text{L}$, the level of alanine aminotransferase (ALAT) was elevated to 95 U/ L (ref 0-35), the level of serum amylase was 32 U/ L, the level of aspartate aminotransferase (ASAT) was increased to 202.9 U/ L (ref 0-35), the level of C-reactive protein was 20.7 mg/ L (ref. <10), the level of alkaline phosphatase (AP) was increased to 195.6 U/L (ref 30-120), the level of lactate dehydrogenase (LDH) was increased to 539.3 U/ L (ref 120-246), and the level of procalcitonin was 0.10 $\mu\text{g}/\text{L}$ (ref <1.0).

Based on the conducted laboratory analysis of SARS-CoV-2 by the PCR method, a negative result was obtained. The test results for antiphospholipid antibodies (aPL) were as follows: aCL > 100 U/ml (reference <10), ab2GPI > 160 U/ml (reference <20), and LA-2.5887 (reference range 0.8-1.2) on day 7. During the admission, an ultrasound examination (US) of the abdominal cavity was performed, revealing certain findings. The ultrasound (US) examination revealed thickening of the walls with augmented blood flow, slight bilateral pyelectasis (enlarged renal pelvis), and lumen congestion in the gallbladder (Figure 2).

The pregnant woman experienced a significant decline in her overall condition at 23+6 weeks of gestation, characterized by a sudden decrease in the level of consciousness to 9 points on the Glasgow Coma Scale. Furthermore, the right-sided hemiparesis was observed on day 7 (Figure 1).

As part of the diagnostic evaluation, a magnetic resonance imaging (MRI) scan of the patient's brain was performed. The results showed the presence of multifocal lesions in both hemispheres, predominantly in the posterior and parietal regions, accompanied by areas of secondary haemorrhages (Figure 3).

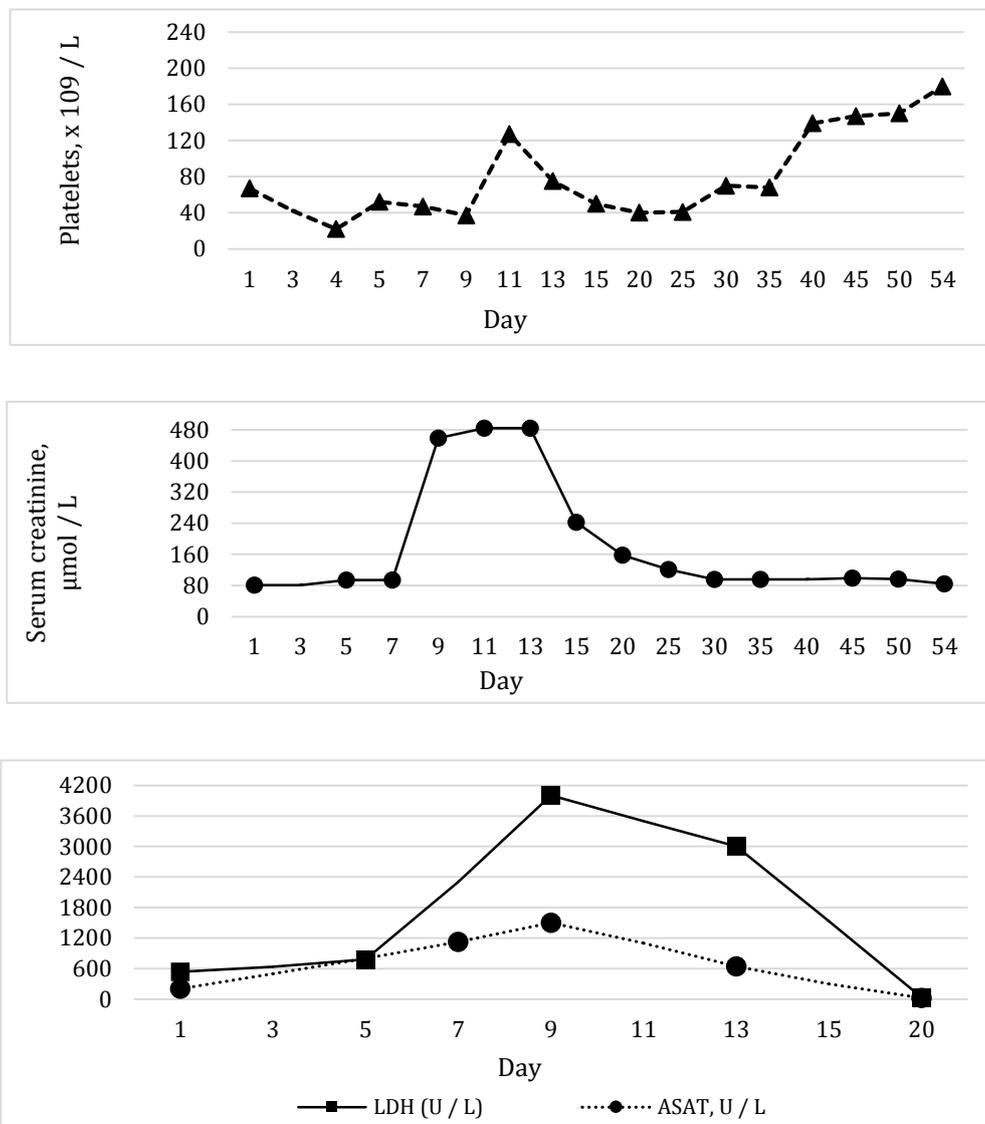


Figure 1: Trajectory of laboratory parameters over time (*LDH: lactic dehydrogenase and SAT: aspartateaminotransferase)



Figure 2: The abdominal cavity was subjected to ultrasound examination upon admission

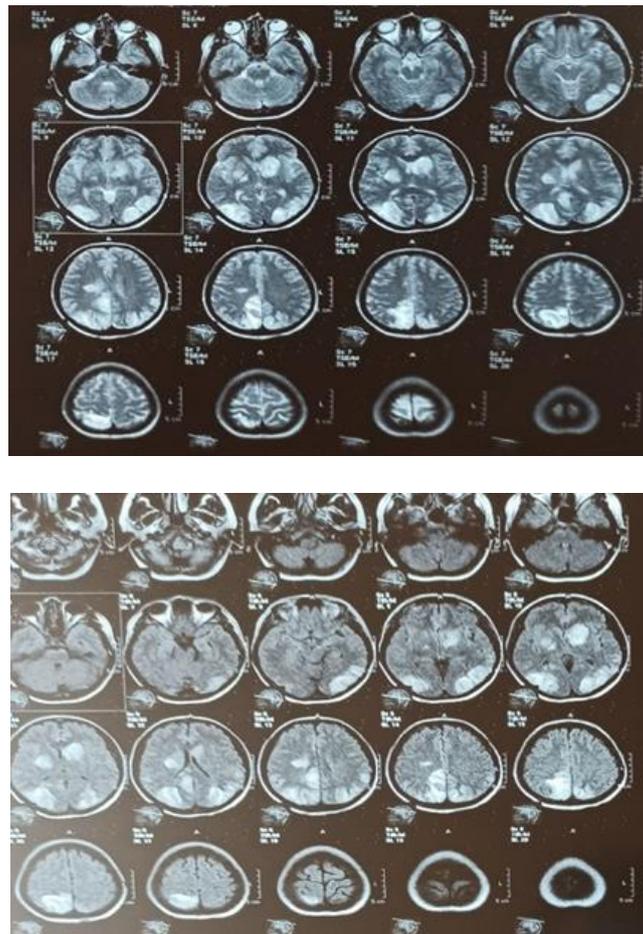


Figure 3: Brain Magnetic Resonance: (A) T2-weighted fluid-attenuated inversion recovery (FLAIR) mode (the left-hand image) and (B) Weighted/Turbo Spin Echo imaging (the right-hand image)

The use of multispiral computed tomography (MSCT) with intravenous contrast and fetal protection revealed evidence of an acute cerebrovascular accident. The MSCT scan depicted multiple foci exhibiting a mixed ischemic-haemorrhagic nature in the basal ganglia of both hemispheres, accompanied by cerebral edema (Figure 4A).

The MSCT of the chest exposed localized pulmonary fibrotic changes within the lung tissue, as depicted in Figure 4B. Furthermore, the abdominal MSCT scan revealed hepatomegaly and the presence of pathological volumetric regions exhibiting decreased density in both the right and left lobes of the liver, suggestive of infarction. Thrombotic lesions were observed in the small branches of the portal vein. Moreover, minor ascites, chronic cholecystitis, and right-sided pyeloectasia were detected (Figure 4B).

Based on the conducted investigations, the pregnant woman was diagnosed with the following conditions:

1. First pregnancy at 24 weeks.
2. Catastrophic antiphospholipid syndrome (CAPS).
3. Acute ischemic-type cerebral circulatory disorder with secondary haemorrhagic infiltration.
4. Anaemia.
5. Brain edema.
6. Intrauterine growth restriction.
7. Intrahepatic thrombosis affecting small hepatic vessels.
8. Placental dysfunction.
9. Post thrombotic syndrome.
10. Post-COVID sequelae characterized by the development of pulmonary fibrosis in the lung tissue.

Syndrome of multiple organ failure (cerebral, respiratory, renal, and hepatic).

Due to a rapid deterioration in the pregnant woman's clinical condition at 24+1 weeks of gestation, a premature delivery was performed

through the natural birth canal on day 9 (Figure 1). Unfortunately, the pregnant woman gave birth to a stillborn fetus (intranatal death). Subsequent autopsy of the fetus revealed the presence of disseminated intravascular coagulation syndrome, characterized by internal organ congestion, microcirculatory vessel thrombosis, and focal haemorrhages in internal organs. Additionally, the fetus exhibited developmental delay. The placental histological assessment exhibited indications of placental insufficiency, presenting with irregularly dilated vessels, erythrocytosis, vascular thrombosis, and the occurrence of extensive ischemic and hemorrhagic infarctions. The histological depiction of placental infarction exhibited heterogeneity, displaying differentiated time intervals of villous necrosis, or the appearance of an ischemic focus on the periphery of intervillous haemorrhage and thrombosis (Figure 5).

Due to the worsening condition of the pregnant woman, a plasma exchange procedure was conducted, replacing 50% of the patient's isolated plasma with fresh frozen donor plasma, and the remaining 50% with balanced crystalloid solutions (the 11th day, Figure 1). Likewise, cyclophosphamide was administered at a dosage of 500 mg via a 2-hour intravenous infusion (the 13th day, Figure 1).

During the subsequent 7-day period, there was a notable improvement in the condition of the pregnant woman, characterized by a gradual regression of neurological symptoms, improvement in speech and movements, and normalization of liver marker levels (the 20th day). By the 25th day of treatment, renal function had stabilized, with serum creatinine levels at 121 $\mu\text{mol/l}$ and diuresis returning to the normal range following the polyuric stage. On the 54th day since the onset of CAPS, the platelet count was the only parameter that had normalized. After a total of 56 days, the patient was discharged in a satisfactory condition.

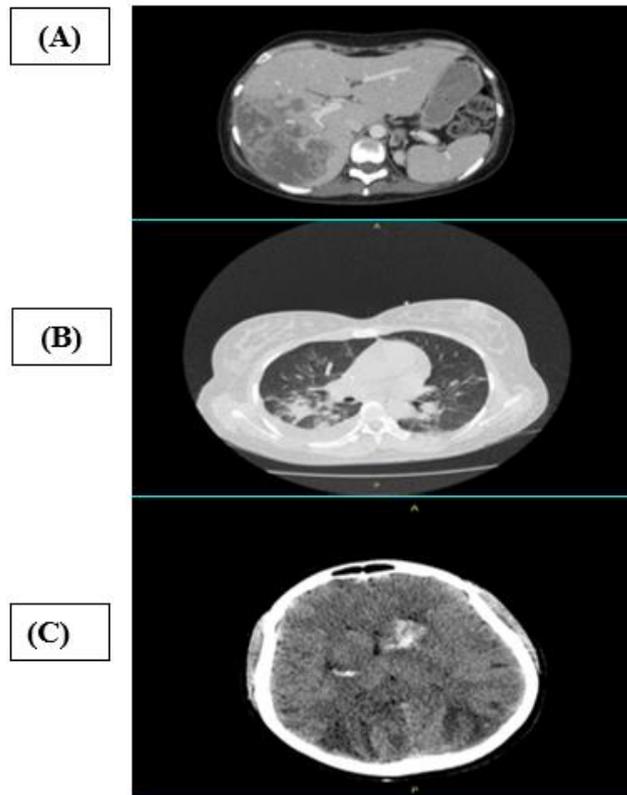


Figure 4: MSCT with IV contrast and fetal protection: (A) chest, (B) abdominal organs, and (C) brain

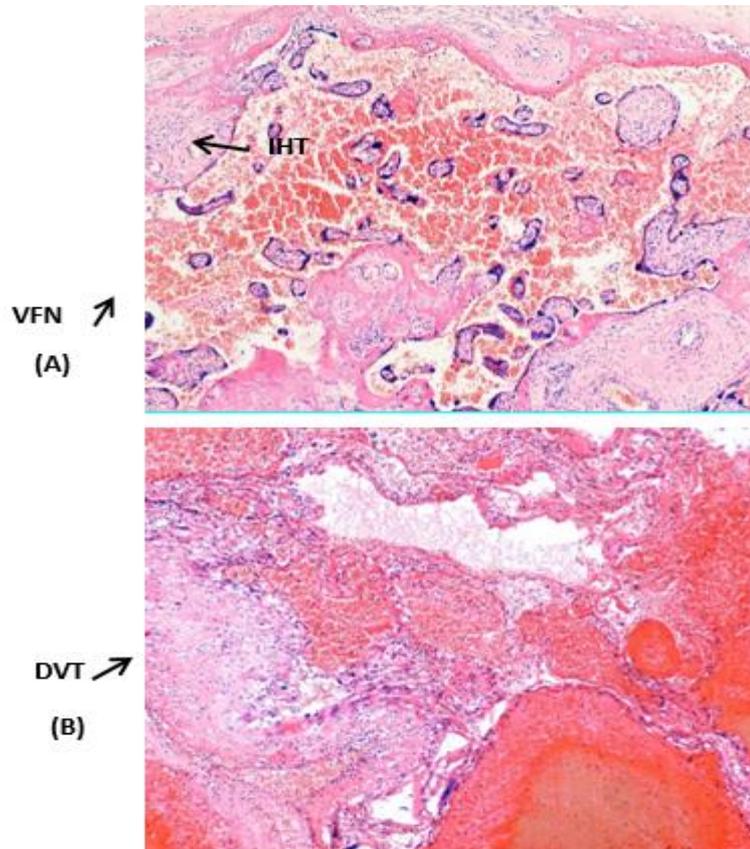


Figure 5: Placental Histology. Hematoxylin-eosin Staining (A and B, objective magnification 10x)* *IHT: Intervillous Hemorrhage and Thrombosis, VFN: Villous Fibrinoid Necrosis, and DVT: Decidual Vessel Thrombosis: (A) Placental villus and (B) Decidual plate

The findings of the conducted study highlight the importance of timely identification and management of catastrophic antiphospholipid syndrome (CAPS) to effectively mitigate the risk of fatal outcomes in patients. The study provides evidence supporting the notion that prompt intervention and treatment can significantly improve patient outcomes and reduce mortality rates associated with CAPS [9, 10]. Early recognition of CAPS is crucial to initiate appropriate therapeutic interventions promptly. This includes the administration of anticoagulant medications to prevent further thrombotic events and the use of immunosuppressive therapies to suppress the autoimmune response. In addition, supportive measures such as organ-specific interventions and intensive care management may be necessary to address organ failure and complications arising from CAPS.

By emphasizing the importance of timely identification, the study underscores the need for healthcare providers to have a high index of suspicion for CAPS in patients presenting with compatible clinical features and risk factors. This includes individuals with a known history of antiphospholipid antibodies, previous thrombotic events, or those experiencing a sudden and rapid decline in organ function. Likewise, the findings of the study underscore the importance of multidisciplinary collaboration in the CAPS management. Given the potentially life-threatening nature of the condition, a coordinated approach involving rheumatologists, haematologists, obstetricians, critical care specialists, and other relevant healthcare professionals is essential. Such collaboration allows for a comprehensive assessment of the patient's condition, prompt diagnosis, and timely implementation of appropriate treatment strategies.

Furthermore, the study highlights the need for ongoing research and advancements in the understanding of CAPS. Improved diagnostic tools, risk stratification models, and targeted therapies specific to CAPS can further enhance patient outcomes and reduce mortality rates. Continued efforts to enhance awareness among healthcare providers and improve patient education are also necessary to ensure timely

recognition of CAPS symptoms and early medical intervention. The disease occurrence in the pregnant woman aligns with the CAPS characteristics, also known as Asherson syndrome, as the patient satisfied all four criteria for the classification of catastrophic antiphospholipid syndrome (CAPS) [11]: The presence of widespread thrombosis resulting in multiorgan dysfunction, affecting the central nervous system, the placenta, kidneys, and liver. The patient exhibited high levels of antiphospholipid antibodies, with aCL levels exceeding 100 U/ml, ab2GPI levels surpassing 160 U/ml, and LA measuring 2.5887. Histological examination of the placenta revealed signs of blood vessel and intervillous space thrombosis (Figure 5).

The case presented in the study described the rapid development of liver, central nervous system, and renal lesions within a week in a patient with catastrophic anti-phospholipid syndrome (CAPS). It is worth noting that unlike HELLP syndrome, a condition that shares some similarities with CAPS, the patient's clinical condition did not show improvement following the pregnancy termination, which is consistent with observations from other cases [9]. The current approach to managing patients with CAPS involves a combination of therapies, including the administration of anticoagulants, corticosteroids, and either plasma exchange or intravenous immunoglobulin therapy [6, 12]. In this particular case, the patient received all recommended treatment methods for CAPS, except for intravenous administration of immunoglobulins. Due to the rapid deterioration of the pregnant woman's clinical condition, premature delivery was performed [13].

In refractory cases of CAPS, additional therapeutic options such as rituximab and eculizumab should be considered [14]. These medications target specific components of the immune system and can help modulate the autoimmune response associated with CAPS. Their use in refractory cases aims to improve outcomes and prevent further organ damage. The CAPS management requires a comprehensive and individualized approach, taking into account the severity of the patient's condition, organ

involvement, and response to initial treatments. The multidisciplinary team involved in the patient's care should closely monitor the response to therapy and adjust the treatment plan accordingly. It is important to continue conducting research and clinical studies to further advance our understanding of CAPS and improve the management strategies. By expanding our knowledge of the underlying mechanisms and identifying potential biomarkers, it may be possible to develop more targeted and effective therapies for CAPS.

Therefore, the case discussed in the study underscores the rapid progression and severity of catastrophic antiphospholipid syndrome (CAPS), highlighting the need for prompt and aggressive management. The current approach involves a combination of anticoagulants, corticosteroids, and either plasma exchange or intravenous immunoglobulin therapy. In refractory cases, additional medications such as rituximab and eculizumab should be considered. Further research and advancements are necessary to optimize the CAPS management and improve patient outcomes.

Conclusion

Thorough evaluation is essential when encountering a pregnant woman who presents with multiorgan thrombosis, abnormal laboratory findings, and a positive antiphospholipid antibody (aPL) test, as these may indicate the presence of catastrophic antiphospholipid syndrome (CAPS). Early diagnosis and prompt treatment are crucial for achieving a positive outcome in CAPS. The current standard treatment approach for CAPS typically involves the administration of glucocorticoids (such as prednisone) to suppress the immune response and reduce inflammation. Anticoagulation therapy is also employed to prevent further thrombotic events by inhibiting blood clot formation. In addition, plasma exchange or intravenous immunoglobulin therapy may be employed to modulate the immune response and remove harmful antibodies from circulation.

In cases where initial treatment fails to adequately control the disease, further

interventions may be necessary. Cyclophosphamide, an immunosuppressive medication, can be considered to target the underlying autoimmune response in refractory CAPS. Monoclonal antibodies, such as rituximab or eculizumab, may also be utilized to specifically target components of the immune system involved in the CAPS pathogenesis. The choice of treatment should be individualized based on the patient's specific condition, disease severity, and response to the initial therapies. Close monitoring of the patient's clinical and laboratory parameters is crucial to assess treatment efficacy and adjust the management plan accordingly. To sum up, when faced with a pregnant woman presenting with multiorgan thrombosis, abnormal laboratory findings, and a positive antiphospholipid antibody (aPL) test, thorough evaluation is necessary to consider the possibility of catastrophic anti-phospholipid syndrome (CAPS). Early diagnosis and timely treatment are keys to achieving favourable outcomes. Treatment strategies typically involve glucocorticoids, anticoagulation therapy, and either plasma exchange or intravenous immunoglobulin. In refractory cases, cyclophosphamide or monoclonal antibodies like rituximab or eculizumab may be considered. Close monitoring of the patient's response to treatment is essential for optimal management.

The study provides a comprehensive and detailed case report of a pregnant patient with catastrophic anti-phospholipid syndrome (CAPS), highlighting the challenges and management strategies associated with this condition. This allows for a thorough understanding of the clinical presentation and treatment approaches in a real-world scenario. Furthermore, the study emphasizes the critical role of early diagnosis and timely treatment in achieving positive outcomes in CAPS. This serves as a reminder to healthcare professionals to be vigilant when evaluating pregnant women presenting with multiorgan thrombosis and positive anti-phospholipid antibodies. The weaknesses of the study include lack of long-term follow-up; the study does not provide long-term follow-up data on the patient's outcomes and recovery. The long-term data would be valuable in assessing the prognosis of

CAPS in pregnancy and evaluating the effectiveness of treatment strategies employed. Further research in the field of catastrophic antiphospholipid syndrome (CAPS) could focus on the identifying reliable and predictive biomarkers for the early diagnosis, prognosis, and monitoring of CAPS. This could involve exploring novel laboratory markers, imaging techniques, and genetic factors associated with the disease.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work

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