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Review article

Catastrophic antiphospholipid syndrome during pregnancy

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ABSTRACT

Catastrophic antiphospholipid syndrome (CAPS) is an uncommon and the most severe form of antiphospholipid syndrome (APS). A 33-week pregnant patient with Klippel-Trenaunay syndrome, past SARS-CoV-2 infection and type I fetal growth restriction with shortening of the fetal long bone was diagnosed in our center with a probable CAPS. Cesarean section was performed four days after the diagnosis due to the torpid evolution of the patient. Clinical improvement was noted a few days later and the mother and baby were discharged within a week. We review the current literature on CAPS during pregnancy and provide an updated view.

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Introduction

Antiphospholipid syndrome (APS) is an autoantibody-mediated acquired thrombophilia that is characterized by recurrent vascular thrombosis, thrombocytopenia and recurrent fetal loss, as well as the presence of three main antiphospholipid antibodies (anticardiolipin, lupus anticoagulant and antbeta2-glycoprotein) [2,5].

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Catastrophic antiphospholipid syndrome (CAPS, Ronald Asherson syndrome) is the most severe form of antiphospholipid syndrome (APS) that results in a widespread coagulopathy and high titers of antiphospholipid antibodies (aPL). CAPS mainly affects the small vessels supplying organs, resulting in multiorgan failure. Ronald Asherson described it for the first time in 1992 as a potentially life-threatening variant of APS.

This condition is rare, accounting for less than 1% of antiphospholipid syndrome cases, and is possibly triggered by pregnancy.

Although CAPS develops in a very small number of patients with APS, mortality rates in affected patients are as high as one-

third, so a proper diagnosis and emergency treatment are essential [1,3,4].

Case report

A 20-year-old woman, gravida 1, arrived at 33 + 2 weeks gestation, complaining of pain in the fifth toe of her right foot and presented associated thrombocytopenia.

Her pregnancy had been controlled by our High Risk Obstetrics Unit for a known history of antiphospholipid syndrome with high titers of the three antiphospholipid antibodies and 4 episodes of deep venous thrombosis, as well as a rare congenital syndrome called Klippel-Trenaunay syndrome (KTS).

KTS is a complex congenital disorder historically defined as the triad of capillary malformation, venous malformation, and limb overgrowth, of unknown prevalence and incidence. In our patient this syndrome presented with agenesis of the infrarenal inferior vena cava, agenesis of the left iliac venous sector and lymphatic malformation in the lower limbs. Therefore, and due to her high thrombotic risk, she had been controlled and treated with warfarin until she got pregnant.

In the first trimester of her pregnancy she suffered from SARS-CoV-2 infection and was diagnosed with type I fetal growth restriction at 26 weeks of pregnancy, in association with shortening of the fetal long bones (normal amniocentesis and negative immune serology with Rubella, Varicella, CMV, Parvovirus and Toxoplasma). Due to a history of non-pregnancy related thrombosis, Hematology modified her previous treatment from warfarin to tinzaparin 10,000 IU and aspirin 150 mg from the beginning of pregnancy.

The examination revealed two very painful violaceous lesions on the 5th toe of the right foot as well as erythematous-violaceous plaques that disappeared on acupressure on the malar region, conserving the nasal dorsum.

Blood test showed low platelets (78.000/microliter) and increased inflammatory parameters (ESR and CRP). Her renal function was deteriorated (estimated glomerular filtration rate dropping from 95 to 78 mL/min) with a protein/creatinine ratio <0.3, elevated liver enzymes (ALT 45 U/L; AST 54 U/L; GGT 41 U/L) and an increased activated partial thromboplastin time (APTT) ratio of 3.9 (possibly justified by the underlying antiphospholipid syndrome and the use of heparin).

On account of the symptoms of pain and erythema in the fifth toe (without involvement of other toes) and a foot X-Ray that ruled out osteomyelitis, broad-spectrum antibiotic treatment was instated.

A follow-up obstetric ultrasound was also performed, which revealed a breech presentation of a fetus with type I fetal growth restriction, a pathological mean uterine artery pulsatility index, and cerebro-placental index <p5; Long bones were short for gestational age, with normal morphology of the fetus and nodular and dyshomogeneous placenta, probably related to placental infarcts.

Given the complexity of the case, the patient was reevaluated by the Rheumatology, Hematology, Internal Medicine and Gynecology services, and the suspicion of a possible ischemic origin of the foot lesions was established.

A diagnosis of probable CAPS was made on the basis of involvement of 3 or more organs (skin, kidney, liver), development of the

symptoms in less than a week, and laboratory confirmation of elevated titers of antiphospholipid antibodies. Despite a lack of histological evidence, obstetric ultrasound was highly suspicious of placental infarctions.

The patient received treatment with methylprednisolone 500 mg IV/day for 3 days followed by prednisone 60 mg/day, enoxaparin 80 mg/24 h and plasmapheresis.

Previous fetal lung maturation, caesarean section was performed due to breech presentation and probable CAPS. A premature female was born at 33 + 4 weeks, weight 1560 gr. and Apgar score 8/10.

On the first day postpartum, the patient presented high blood pressure levels that required oral treatment with calcium antagonists and labetalol, in addition to oliguria and elevated creatinine after surgical procedure. Clinical improvement was noted within a few days. Both the patient and newborn were discharged within a week and she is currently being treated with warfarin therapy.

The newborn presented moderate patent ductus arteriosus without hemodynamic impact. Amniotic fluid tests were negative for aneuploidies in 21, 18, 13 and sexual chromosomes. The pathological study of the placenta revealed several areas of necrosis and vascular congestion, all compatible with placental infarcts.

Literature review

Approximately 4–6% of CAPS occur during the third trimester of pregnancy or during puerperium, and half of the patients had a history of APS [10]. In addition, and according to Hoayek et al [3], CAPS in pregnancy or puerperium is associated with earlier age of onset and fewer previous clinical manifestations, compared to the general population with CAPS. Validated classification criteria for definitive CAPS were established in 2002 and are shown in Table 1.

Given that CAPS only occurs in 1% of patients with APS, recommendations are based on case reports and expert opinions and there are no randomized clinical trials to guide the treatment of CAPS [1,9].

CAPS remains a diagnostic challenge as its broad range of clinical signs, symptoms, and laboratory findings, as seen in our case, often overlap with other obstetric complications.

Using the data recorded by Collicet et al, Table 1 summarizes the clinical manifestations, treatment given and maternal and fetal outcomes of each CAPS case from 1994 until 2020, chronologically ordered (Table 2).

Discussion

Catastrophic antiphospholipid syndrome continues to be a diagnostic challenge due to its low prevalence and the non-specificity of its clinical and analytical presentation.

Maternal clinical manifestations can range from abdominal pain, general malaise, altered mental status, seizure, chest pain, hypertension, proteinuria, dyspnea, or pulmonary embolism among others. Fetal morbidities are directly associated with placental insufficiency leading to preterm birth, growth restriction or death [3,4].

Despite the criteria, CAPS symptoms and laboratory findings often overlap with other obstetric complications such as HELLP

Table 1
Validated classification criteria for definitive CAPS.

1. Evidence of involvement of 3 or more organs.
2. Development of manifestations simultaneously or within less than a week.
3. Confirmation by histopathology of small vessel occlusion.
4. Laboratory confirmation of the presence of elevated titres of antiphospholipid antibodies (>12 weeks). Probable CAPS if only three out of the four criteria above are met.

Table 2
Eighteen cases of CAPS in pregnancy.

Author	Maternal age	Gestational age	CAPS features	Treatment	Maternal outcome	Fetal outcome
Khizroeva <i>et al</i>	n/a	28 weeks of gestation	Multiorgan failure	n/a	n/a	n/a
Hanouna <i>et al</i> (case 3)	26 years	25 weeks of gestation	Cardiac, renal, hepatic, cutaneous, hemolytic anemia and thrombocytopenia	Heparin, aspirin, glucocorticoids, IVIG, plasma exchange and dialysis	n/a	Fetal death
Hanouna <i>et al</i> (case 6)	33 years	36 + 5 weeks of gestation on the day of the delivery	Adrenal, cutaneous, hepatic, thrombocytopenia and hemolytic anemia	Heparin and glucocorticoids	Adrenal insufficiency	Healthy child
Hanouna <i>et al</i> (case 11)	32 years	17 weeks of gestation on the day of the delivery	Cutaneous, hepatic, renal, adrenal thrombocytopenia and gallbladder	Heparin, glucocorticoids, plasma exchange and dialysis	Renal insufficiency with proteinuria	Fetal death at 17 weeks
Hanouna <i>et al</i> (case 12)	27 years	13 weeks of gestation on the day of the delivery	Cardiac, cutaneous, hepatic, placenta and thrombocytopenia	Heparin, glucocorticoids and IVIG	n/a	Fetal death at 13 weeks
Hanouna <i>et al</i> (case 13)	23 years	31 weeks of gestation	Cardiac, renal, cutaneous, thrombocytopenia and hemolytic anemia	Heparin, aspirin, glucocorticoids and plasma exchange	Sudden death at 2.5 years	Child with developmental delay
Derks <i>et al</i> (case 1)	32 years	n/a	Multiple infarcts in liver and placenta	Intensive medical treatment including anticoagulation	Died of massive PE	n/a
Derks <i>et al</i> (case 2)	27 years	n/a	Thrombocytopenia, disturbances in hepatic function and epigastric pain	Glucocorticoids	n/a	Fetal death
Derks <i>et al</i> (case 3)	36 years	n/a	Hepatic infarcts and petechiae	Glucocorticoids, IVIG and plasmapheresis	n/a	Healthy child
Marson <i>et al</i>	33 years	23 weeks of gestation	HELLP, thrombocytopenia, anemia, acalculous cholecystitis and cutaneous.	Therapeutic plasma exchange	Recovery	Intrauterine death at 23 weeks
Bendon <i>et al</i>	22 years	30 weeks of gestation	Placental infarctions, myocardium, renal, gastrointestinal and myometrium TMA		Death	Intrauterine fetal death
Kitchens <i>et al</i>	38 years	38 weeks of gestation	HELLP, portal vein, inferior vena cava, mesenteric vein thrombosis	Anticoagulation	Recovery	
Wisłowska <i>et al</i>	26 years	25 weeks of gestation	ARDS, encephalopathy, nephritis, skin ulcers	LMWH, glucocorticoids, cyclophosphamide	Recovery	Miscarriage
Asherson <i>et al</i>	22 years	20 weeks of gestation	HELLP, ARDS, cerebral infarcts	Glucocorticoids, intravenous heparin, cyclophosphamide	Recovery	Death
Koenig <i>et al</i>	19 years	17 weeks of gestation	HELLP, hepatic infarctions, bone necrosis	LMWH, fresh frozen plasma	Recovery	Death
Gomez-Puerta <i>et al</i> (case 1)	29 years	28 weeks of gestation	HELLP, bone marrow hypoplasia, renal failure, DVT, respiratory failure, livedo reticularis	Glucocorticoids, LMWH	Death	Prematurity
Elchalal <i>et al</i>	37 years	16 weeks of gestation	Thrombocytopenia, bilateral pleural effusions	LMWH, IVIG, glucocorticoids	Recovery	Fetal death
Collic M <i>et al</i>	31 years	28 + 5 weeks of gestation	Severe PE, bilateral exudative retinal detachment, renal, acalculous cholecystitis, pulmonary and abdominal sepsis, liver, cardiac, placental infarction and multiorgan thrombosis (lung, brain, spleen)	Broad-spectrum antibiotics, glucocorticoids, LMWH, aspirin	Recovery	Healthy premature child

ARDS, acute respiratory distress syndrome; CAPS, catastrophic antiphospholipid syndrome; DVT, deep venous thrombosis; HELLP, hemolysis, elevated liver enzymes, low platelet count; IVIG, intravenous immunoglobulin; LMWH, low molecular weight heparin; n/a, not available; PE, pulmonary embolism.

syndrome, thrombotic thrombocytopenic purpura (TTP), or acute fatty liver of pregnancy (AFLP), leading to a delayed diagnosis and treatment [6,7].

Given that CAPS is a thrombophilic disorder with characteristic extensive microvasculopathy, anticoagulant therapy is required.

Pregnant patients with CAPS usually receive combined therapy with anticoagulants, corticosteroids, plasmapheresis or intravenous immunoglobulins (triple therapy) [4,6,9].

Plasmapheresis may help to remove pathologic antibodies and other proinflammatory and prothrombotic mediators. The usual protocol is to remove 2–3 L of plasma daily for 3–5 days.

In cases of refractory CAPS, other immunosuppressive therapies should be considered. Given its relative safety, it is reasonable to consider hydroxychloroquine because of its numerous immuno-

suppressive properties. Rituximab has been reported to be useful in improving CAPS in 75%, as proposed by Silver [1]. Another monoclonal antibody, Eculizumab, represents a valid addition to the current treatment regimen. It can prevent the rapid deterioration of clinical conditions in CAPS during pregnancy, as Rovere-Querini *et al* and A. Gustavsen mentioned in both of their articles [9,11].

Among the studies that focus on new treatments, the one by Mineo C *et al*. shows that 1N11, a fully human antibody that disrupts aPL recognition of β 2-GPI, may afford another opportunity to develop an anti- β 2-GPI monoclonal antibody as a therapy [8].

Rapid deterioration can occur at any time in CAPS, leading to detrimental outcomes to both mother and fetus. A proper management is therefore crucial in these patients, as early diagnosis and

aggressive treatment remain key factors for a favorable mother and fetal outcome and survival.

Conclusions

Catastrophic antiphospholipid syndrome (CAPS) is a severe form of antiphospholipid syndrome (APS) rarely seen in pregnancy, making early recognition difficult.

The suspicion should be high in any pregnant woman who presents multi-organ thrombosis, thrombocytopenia as well as positive antiphospholipid antibodies.

Early intervention before microvascular thrombosis and organ failure should be a fundamental goal in pregnant patients. Therefore, a proper management is required with the triple therapy (anticoagulants, corticosteroids and fresh frozen plasma replacement therapy or intravenous immunoglobulins), if necessary combined with immunosuppressive therapies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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