Case report

Catastrophic antiphospholipid syndrome in pregnancy: a life-threatening condition

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SUMMARY

Catastrophic antiphospholipid syndrome (CAPS) is a rare and potentially life-threatening variant of the antiphospholipid syndrome which is characterised by multiple small vessel thrombosis which can lead to multiorgan failure. CAPS is a clinical emergency which all clinicians need to be aware of because early diagnosis and treatment may improve maternal and fetal outcome. Here, we report a case of CAPS in pregnancy in a 31-year-old female patient who presented at 28 weeks of gestation. A literature review of CAPS in pregnancy and the puerperium is also included.

BACKGROUND

Antiphospholipid syndrome (APS) is a state of hypercoagulation that is characterised by recurrent vascular thrombosis, thrombocytopaenia and recurrent fetal loss.[1] APS is an autoantibody-mediated acquired thrombophilia characterised by the presence of three main antiphospholipid antibodies namely; anticardiolipin, lupus anticoagulant and antibeta2-glycoprotein.[2]

Catastrophic antiphospholipid syndrome (CAPS) was first described in 1992 as a potential life-threatening variant of the APS, characterised by multiple small vessel thrombosis leading to multiorgan failure.[3] CAPS is rare and develops in about 1% of cases of APS.[4] CAPS is defined as multiorgan thrombosis, affecting a minimum of three different organs, requiring histopathological confirmation of small vessel occlusion in at least one organ or tissue and presence of antiphospholipid antibodies on two separate occasions, 6 weeks apart.[4 5]

Here, we report a case of a 31-year-old female patient who developed CAPS during pregnancy.

CASE PRESENTATION

A 31-year-old woman, gravida 3 para 0+2 presented at 28+5 weeks gestation complaining of epigastric pain, worsening bilateral limb oedema and blurred vision. Physical examination revealed high blood pressure of 180/114 mm Hg, bilateral lower limb oedema and brisk reflexes 4+. Blood investigations showed low platelets (67×10^9 L) and high uric acid of 442 µmol/L (normal range 142.8–339.2 µmol/L). The 24-hour urine protein test was more than 6000 mg (normal range 1–150 mg/24 hours) in keeping with severe pre-eclampsia. The patient was started on intravenous labetalol, and magnesium sulfate and was given two doses of 12 mg of dexamethasone intramuscularly. The baby was delivered via an emergency caesarean section at 28+6 weeks gestation and transferred to the neonatal paediatric intensive care unit (NPICU). The patient received one dose of co-amoxiclav intravenous and was started on 40 mg/day of enoxaparin subcutaneously.

Day 3 postpartum, the patient developed severely reduced visual acuity, abdominal pain, headaches and started spiking a temperature up to 39.4°C. On examination, the patient was found to have abdominal tenderness in the right upper quadrant, and Murphy's sign was positive. Review by ophthalmologist showed bilateral exudative retinal detachment. Blood tests showed a white cell count of 13.74×10^9/L, platelet count dropped to less than 50×10^9 L, and haemoglobin level dropped to 8.3 g/dL. Blood picture showed normochromic, anisoctyic erythrocytes. Her renal function also deteriorated (estimated glomerular filtration rate dropping from 107 to 35 mL/min/1.73 m^2), while the activated partial thromboplastin time (APTT) ratio increased to 1.61 and prothrombin time to 14.7 s. Ultrasound abdomen showed acalculous cholecystitis, and CT scan of the abdomen and pelvis showed mild ureterohydronephrosis with enhancing ureteric walls suspicious of bilateral pyelonephritis, bilateral bibasal consolidations and suspected liver abscesses. MR liver showed very small early liver abscesses which were not amenable to drainage. A transthoracic cardiogram revealed a poor left ventricular ejection fraction of 43% and a pericardial effusion, while cardiac MR showed myopericarditis and peripartum cardiomyopathy with global left ventricular wall hypokinesia (figure 1). MR head revealed multiple ischaemic foci in both cerebral hemispheres (figure 2). Urine and blood cultures were negative, but both were taken after the administration of antibiotics.

Broad spectrum antibiotics (intravenous piperacillin/tazobactam 4.5 g three times per day and levofloaxcin 500 mg/day orally) were started to cover pulmonary and abdominal sepsis, enoxaparin dose was reduced from 40 mg to 20 mg/day in view of the low platelets, and the patient was transferred to intensive care for closer monitoring. After 4 days, headaches and abdominal pain improved, fever settled and the blood pressure was controlled by carvedilol 3.125 mg two times per day and nifedipine 20 mg three times per day.

After 7 days of broad-spectrum antibiotics, the patient started spiking a temperature again and reported left-sided pleuritic chest pain. On examination, the patient was found to have a temperature of 38.8°C, pulse rate of 115 beats/min and

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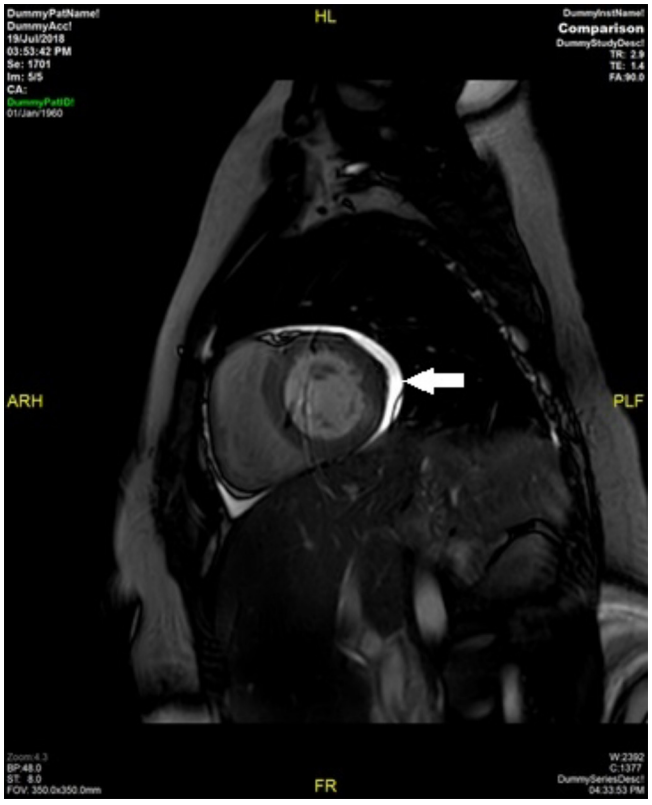

Figure 1 MR cardiac—T2 short axis view through the heart showing small pericardial effusion (arrow).

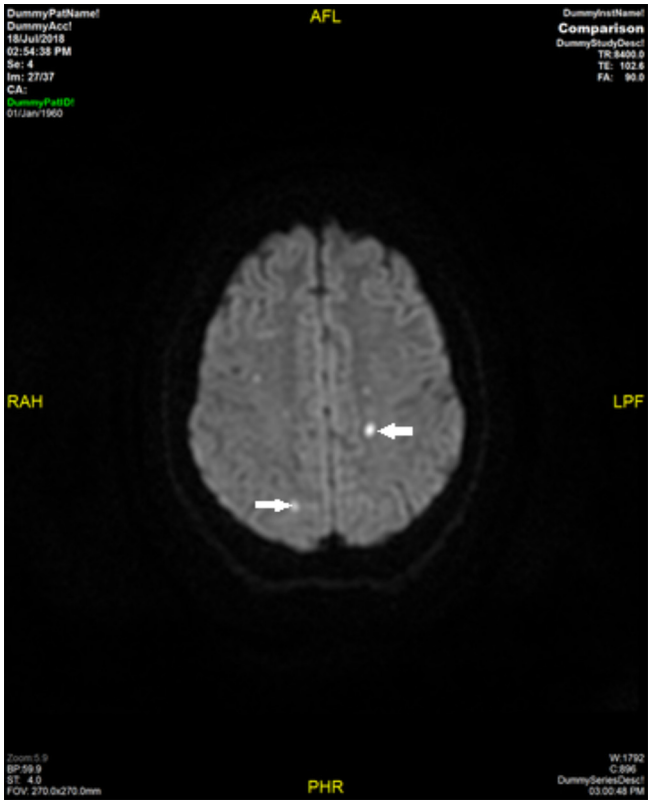

Figure 2 MR brain—diffusion-weighted axial image showing foci of restricted diffusion in periventricular white matter consistent with acute ischaemia (arrows).

oxygen saturation was 93% on room air. No infectious source was identified. CT pulmonary angiogram revealed left lower lobar pulmonary embolism and intrasplenic vessel thrombosis. At this point, the patient was found to have positive anticardiolipin antibodies, positive antibeta2-glycoprotein antibodies and positive lupus anticoagulant. Histology of the placenta showed placental infraction. Antinuclear antibody, extractable nuclear antigen antibody and antidouble-stranded DNA antibody were negative.

A diagnosis of CAPS was made on the basis of positive serology, multiorgan thrombosis (lung, brain, spleen) and histologically proven placental infarction.

TREATMENT

In addition to broad-spectrum antibiotics, the patient was given three pulses of 1 g intravenous methylprednisolone followed by prednisolone 60 mg/day, 4 days of 0.5 g/kg/day of intravenous IGs, 1 mg/kg two times per day enoxaparin and aspirin 75 mg/day. Clinical improvement was noted within a few days. The patient was initiated on long-term warfarin. Prednisolone dose was tapered slowly over 4 months.

OUTCOME AND FOLLOW-UP

The patient was discharged home after 4 weeks. Repeat antiphospholipid antibodies 6 weeks later remained positive. The platelet count and renal function improved to normal levels. Her visual acuity also improved significantly, and funduscopy was essentially normal except for a few areas of retinal pigmentation. An echocardiogram 8 months later showed improved left ventricular systolic function, and the ejection fraction was 55%. The baby was discharged from NPICU after 10 weeks with normal growth and development.

DISCUSSION

CAPS is a life-threatening condition which is rarely seen in pregnancy making early diagnosis difficult. It presents with very non-specific symptoms which may mimic many other conditions such as sepsis, infective endocarditis, vasculitis and other autoinflammatory conditions. Timely diagnosis and aggressive management is critical for a good outcome. Here, we report a 31-year-old previously healthy woman who developed multiple clinical manifestations at 28 weeks of gestation which initially were attributed to pre-eclampsia and sepsis. Partial response to antibiotics and development of multiorgan thrombosis eventually led to the diagnosis of CAPS.

Gómez-Puerta *et al* reported in 2007 that CAPS during pregnancy or puerperium represents only 6% of all cases of CAPS.[6] A PubMed literature search was carried out using the search term 'CAPS', 'CAPS in pregnancy' 'CAPS and puerperium', and 35 different cases were identified from 1994 to 2018 (table 1). Table 1 summarises the clinical manifestations, treatment given and maternal and fetal outcomes of each case. The combination of treatment given is further summarised in table 2.

CAPS in pregnancy presents a complex clinical scenario both in terms of diagnosis as well as treatment. The acute manifestations of CAPS are usually the result of an acute thrombotic microangiopathy. The differential diagnosis of CAPS in pregnancy and puerperium includes: disseminated intravascular coagulation (DIC), thrombotic thrombocytopaenic purpura (TTP), haemolytic-uraemic syndrome (HUS), heparin-induced thrombocytopaenia (HIT)[7] and HELLP (haemolysis, elevated liver enzymes, low platelet count) syndrome, all of which can form part of the manifestations of CAPS. TTP and HUS are both characterised by

Table 1 Thirty-five cases of CAPS in pregnancy and puerperium

Author (reference no.)	Maternal age	Time of onset	CAPS features	Treatment received	Maternal outcome	Fetal outcome
Khizroeva *et al*[14]	n/a	28 weeks of gestation	Multiorgan failure	n/a	n/a	n/a
Hanouna *et al*[15] (Case 1)	30 years	15th day of puerperium	Renal, hepatic, cutaneous, haemolytic anaemia, placenta	Heparin, aspirin, glucocorticoids	n/a	Healthy child
Hanouna *et al*[15] (Case 2)	32 years	Eighth day of puerperium	Cardiac, renal, hepatic, cutaneous, haemolytic anaemia, thrombocytopaenia	Heparin, aspirin, glucocorticoids, IVIG	n/a	Healthy twins
Hanouna *et al*[15] (Case 3)	26 years	25 weeks of gestation	Cardiac, neurological, renal, cutaneous, haemolytic anaemia	Heparin, glucocorticoids, IVIG, plasma exchange, dialysis	n/a	Fetal death
Hanouna *et al*[15] (Case 4)	31 years	Third day of puerperium	Cardiac, renal, splenic, cutaneous, hepatic, thrombocytopaenia, haemolytic anaemia	Heparin, aspirin, glucocorticoids, IVIG, dialysis	n/a	Fetal death
Hanouna *et al*[15] (Case 5)	37 years	Fifth day of puerperium	Neurological, cutaneous, hepatic, thrombocytopaenia, haemolytic anaemia, placenta	Heparin	Venous thrombosis at 2 months, PE at 3 months	Fetal death
Hanouna *et al*[15] (Case 6)	33 years	On the day of the delivery at 36.5 weeks gestation	Adrenal, cutaneous, hepatic, thrombocytopaenia, haemolytic anaemia	Heparin, glucocorticoids	Adrenal insufficiency	Healthy child
Hanouna *et al*[15] (Case 7)	32 years	Fourth week of puerperium	Cardiac, neurological, pulmonary, renal, hepatic, pancreatic, splenic, ocular, thrombocytopaenia	Heparin, glucocorticoids, IVIG, plasma exchange, dialysis	Mild retinal sequelae	Fetal death
Hanouna *et al*[15] (Case 8)	29 years	15th day of puerperium	Cardiac, neurological, renal, cutaneous, hepatic, pancreatic, gastric, ocular, thrombocytopaenia, haemolytic anaemia	Heparin, glucocorticoids, plasma exchange, dialysis	Renal insufficiency, stroke at 4 years, sudden death at 6 years	Fetal death
Hanouna *et al*[15] (Case 9)	32 years	Second day of puerperium	Adrenal, renal, hepatic, thrombocytopaenia	Heparin, aspirin, glucocorticoids	Adrenal insufficiency	Healthy child
Hanouna *et al*[15] (Case 10)	36 years	Third day of puerperium	Cardiac, neurological, renal, hepatic, pancreatic, cutaneous, thrombocytopaenia, haemolytic anaemia	Heparin, glucocorticoids	n/a	Healthy child
Hanouna *et al*[15] (Case 11)	32 years	On the day of the delivery at 17 weeks gestation	Cutaneous, hepatic, renal, adrenal, thrombocytopaenia, gallbladder	Heparin, glucocorticoids, plasma exchange, dialysis	Renal insufficiency with proteinuria	Fetal death at 17 weeks
Hanouna *et al*[15] (Case 12)	27 years	On the day of the delivery at 13 weeks gestation	Cardiac, cutaneous, hepatic, placenta, thrombocytopaenia	Heparin, glucocorticoids, IVIG	n/a	Fetal death at 13 weeks
Hanouna *et al*[15] (Case 13)	23 years	31 weeks of gestation	Cardiac, renal, cutaneous, thrombocytopaenia, haemolytic anaemia	Heparin, aspirin, glucocorticoids, plasma exchange	Sudden death at 2.5 years	Child with developmental delay
Derks *et al*[16] (Case 1)	32 years	n/a	Multiple infarcts in liver and placenta	Intensive medical treatment including anticoagulation	Died of massive PE	n/a
Derks *et al*[16] (Case 2)	27 years	n/a	Thrombocytopaenia, Disturbances in hepatic function, epigastric pain	Glucocorticoids	n/a	Fetal death
Derks *et al*[16] (Case 3)	36 years	n/a	Hepatic infarcts, petechiae	Glucocorticoids, IVIG, plasmapheresis	n/a	Healthy Child
Marson *et al*[17]	33 years	23 weeks of gestation	HELLP, thrombocytopaenia, anaemia, acalculous cholecystitis, Cutaneous	Therapeutic plasma exchange	Recovery	Intrauterine death at 23 weeks
Bendon *et al*[18]	22 years	30 weeks of gestation	Placental infarctions myocardium, renal, gastrointestinal and myometrium TMA		Death	Intrauterine fetal death
Hochfeld *et al*[19]	37 years	Second day after fetal death	Renal failure, cerebral, cardiac, pulmonary, splenic, and adrenal infarcts, cerebral haemorrhage	Glucocorticoids, cyclophosphamide, plasma exchange	Death	Intrauterine fetal death
Kupferminic *et al*[20]	17 years	Fifth day of puerperium	HELLP, ARDS, placental infarcts, renal failure	Glucocorticoids, plasma exchange, dialysis	Recovery	Prematurity
Kitchens[21]	38 years	38 weeks of gestation	HELLP, portal vein, inferior vena cava, mesenteric vein thrombosis	Anticoagulation	Recovery	
Wislowska *et al*[22]	26 years	25 weeks of gestation	ARDs, encephalopathy, nephritis, Skin ulcers	LMWH, glucocorticoids, cyclophosphamide	Recovery	Miscarriage
Sinha *et al*[23]	22 years	25 weeks of gestation	HELLP, placental infarcts, cerebral infarcts, Bone marrow necrosis	Glucocorticoids, plasma exchange, IVIG	Death	Death
Asherson *et al*[24]	22 years	20 weeks of gestation	HELLP, ARDS, cerebral infarcts	Glucocorticoids, intravenous heparin, cyclophosphamide	Recovery	Death

Continued

Table 1 Continued

Asherson *et al*[24]	27 years	Postfetal loss	PE, digital necrosis, hepatic, renal, intestinal, mesenteric thrombosis	Glucocorticoids, anticoagulation	Death	Death
Ortiz at al[25]	32 years	Second day of puerperium	Renal, multiple cerebral infarcts	Glucocorticoids, FFP, LMWH	Recovery	n/a
Koenig *et al*[26]	19 years	17 weeks of gestation	HELLP, hepatic infarctions, bone necrosis	LMWH, FFP	Recovery	Death
Coward *et al*[27]	30 years	Third week of puerperium	TIA, status epilepticus, renal failure, adrenal haemorrhage	Anticoagulants, dialysis	Death	Healthy child
Weiser M[6]	33 years	Fifth day of puerperium	HELLP, ARDS, renal failure, cerebral infarctions and haemorrhage	Glucocorticoids, IVIG, anticoagulation, dialysis	Death	Healthy child
Gomes-Puerta *et al*[6] (case 1)	29 years	28 weeks of gestation	HELLP, bone marrow hypoplasia, renal failure, DVT, respiratory failure, livedo reticularis	Glucocorticoids, LMWH	Death	Prematurity
Gomes-Puerta *et al*[6] (case 2)	26 years	Third day of puerperium	DVT, PE, respiratory failure	LMWH, glucocorticoids, IVIG	Recovery	Healthy child
Gomes-Puerta *et al*[6] (Case 3)	28 years	Sixth day of puerperium	Placental infarctions, Respiratory failure, Renal failure, Encephalopathy	LMWH, plasma exchange	Recovery	Healthy child
Elchalal *et al*[28]	37 years	16 weeks of gestation	Thrombocytopaenia, Bilateral pleural effusions	LMWH, IVIG, Glucocorticoids	Recovery	Fetal death
Ciolkiewicz *et al*[7]	24 years	Postfetal loss	PE, Myocardial infarction, multiorgan failure	n/a	Death	Fetal death

ARDS, acute respiratory distress syndrome; CAPS, catastrophic antiphospholipid syndrome; DVT, deep vein thrombosis; FFP, fresh frozen plasma; HELLP, haemolysis, elevated liver enzymes, low platelet count; IVIG, intravenous immunoglobulin; LMWH, low molecular weight heparin; PE, pulmonary embolism; TMA, thrombotic microangiopathy; n/a, not available.

Table 2 Treatment combinations given to patients with CAPS

Treatment	Number of cases of CAPS
Individual treatment	
Anticoagulation	5
Glucocorticoids	1
Plasma exchange	1
Treatment combinations	
Anticoagulation and glucocorticoids	7
Anticoagulation and plasma exchange	1
Anticoagulation, glucocorticoids and IVIG	5
Anticoagulation, glucocorticoids and plasma exchange	2
Anticoagulation, glucocorticoids and cyclophosphamide	2
Glucocorticoids, plasma exchange and cyclophosphamide	1
Glucocorticoids, IVIG and plasma exchange	3
Anticoagulation, glucocorticoids, IVIG and plasma exchange	3

CAPS, catastrophic antiphospholipid syndrome; IVIG, intravenous immunoglobulin.

thrombocytopaenia, macroangiopathic haemolytic anaemia and ischaemic organ damage. Neurological manifestations and fever dominate the clinical picture in TTP, while patients with HUS tend to suffer more from progressive renal disease.[8] Nevertheless, the differentiation between CAPS and TTP/HUS might be difficult. The thrombocytopaenia and schistocytosis tend to be marked in TTP/HUS and mild in CAPS. In TTP/HUS, APTT is normal. On the other hand, elevated APTT, the presence of antiphospholipid antibodies and lupus anticoagulant support CAPS.[8] DIC is characterised by thrombocytopaenia, prolonged clotting times, reduced plasma fibrinogen levels and elevated fibrin degradation products. It is also known that DIC can complicate CAPS in one-third of patients.[9] HIT is another differential diagnosis of CAPS which is caused by autoantibodies against platelet factor 4-heparin complex.[10] HIT is characterised by thrombocytopaenia and vascular thrombosis, and it usually follows the administration of unfractionated heparin and less commonly the administration of low molecular weight heparin.[10]

The following therapeutic strategy of CAPS during pregnancy and puerperium is proposed. First, it is essential to prevent and treat any triggering factors such as infection. Second, fetal maturation should be evaluated, and the fetus delivered once fetal pulmonary maturation has been optimised. Third, a combination of anticoagulation and immunosuppression is essential despite the increased risk of bleeding in view of low platelet count, elevated APTT ratio and potentially ongoing sepsis. CAPS is a highly thrombotic state despite prolonged bleeding time and low platelets. In those cases with HELLP syndrome or other microangiopathic features, plasma exchange is strongly indicated. High doses of glucocorticoids and intravenous immunoglobulin (IVIG) have been shown to improve survival.[6 11 12] In fact, triple therapy consisting of a combination of anticoagulation, high-dose glucocorticoids, plasma exchange and/or IVIG has been proposed as the gold standard of care.[11] Our patient made an immediate recovery after the administration of anticoagulation, high-dose glucocorticoid therapy and IVIG. Recently, new therapeutic modalities have emerged for the treatment of refractory CAPS including rituximab, defibrotide and eculizumab.[12]

In conclusion, CAPS is a rare life-threatening disease which requires prompt diagnosis, a multidisciplinary approach and immediate aggressive treatment to avoid irreversible complications and decrease mortality. CAPS has a high mortality rate of up to 30% with the main causes of death being reported to be infections, stroke, cardiac failure and multiorgan failure.[13] CAPS

is a clinical emergency which all clinicians need to be aware of because timely diagnosis and treatment may improve both the maternal and fetal outcome.

Patient 's perspective

I would like to ensure that all the medical professionals are aware of this life-threatening syndrome.

Learning points

- Catastrophic antiphospholipid syndrome (CAPS) is a rare but potentially life-threatening form of APS defined as multiorgan thrombosis affecting at least three organs and histological confirmation of small vessel occlusion in at least one organ or tissue.
- CAPS presents with non-specific symptoms which may mimic other conditions such as sepsis, infective endocarditis, vasculitis and other autoinflammatory conditions.
- Triple therapy consisting of anticoagulation, high-dose intravenous glucocorticoids, plasma exchange and/or intravenous IG has been associated with better outcomes.
- Our patient made a very good recovery thanks to the teamwork and contribution of 14 different consultants in different specialities.
- Increased awareness of CAPS is essential for early diagnosis and treatment to improve maternal and fetal outcome.

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