The role of hydroxychloroquine in catastrophic antiphospholipid syndrome case: Series of two case reports and review of literature

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Abstract
Catastrophic antiphospholipid syndrome is a rare disorder that remains under-recognized causing a high mortality rate even with treatment. Factors such as infections and systemic lupus erythematosus flare play as an inciting event in the thrombotic crisis which underlies catastrophic antiphospholipid syndrome. The use of plasmapheresis has improved the outcome of such cases with a reduction in mortality rate from over 50% to less than 30%, according to some studies. However, the definitive treatment of this disabling and fatal condition remains an area warranting research. Case 1. A case of 32-year-old female with a background of epilepsy and recurrent abortions who presented with difficulty in breathing, dry cough, and bilateral lower limb swelling. The patient initially received treatment with cyclophosphamide and systemic corticosteroids after being diagnosed with systemic lupus erythematosus. She also underwent plasmapheresis for suspected pulmonary hemorrhage as her condition deteriorated rapidly requiring intensive care. The diagnosis was revised as catastrophic antiphospholipid syndrome given the typical multi-organ involvement, namely, cerebritis, Libman–Sacks endocarditis, and nephritis apart from the pulmonary involvement. Eventually, hydroxychloroquine was added to the regimen which led to a remarkable improvement in her condition after a few days. Case 2. A case of 28-year-old female with history of recurrent abortions presented with abdominal pain and was admitted as a case of pancreatitis. The patient received intravenous fluids and analgesics with no significant improvement. Later, she developed multi-organ failure requiring critical care. Given her history and clinical presentation along with the multi-organ involvement in an acute setting, she underwent extensive workup that favored catastrophic antiphospholipid syndrome and she was started on Aspirin initially, and then, hydroxychloroquine was administered. Few days after initiation, her condition improved markedly and with complete resolution of her abdominal symptoms. Hydroxychloroquine’s antithrombotic effect in synergy with other therapies has been observed in our cases. Yet, its role in the early course of catastrophic antiphospholipid syndrome merits further investigation.

Keywords
Antiphospholipid antibodies, hydroxychloroquine, antiphospholipid syndrome

Date received: 26 February 2018; accepted: 21 May 2018

Introduction
Antiphospholipid syndrome (APS) is an autoimmune disorder demonstrated by vascular thrombosis and/or recurrent abortions. It is accompanied by constantly positive antiphospholipid antibodies (aPL-Ab). These antibodies can be detected by testing for lupus anticoagulant (LA) and employing enzyme-linked immunosorbent assay (ELISA) technique to measure antiphospholipid antibody (aCL) and/or anti-β2-glycoprotein-I antibody (Ab; aβ2GPI).1

In a rare event, a small percentage of patients may deteriorate exponentially and develop a fulminant form of APS, a phenomenon called catastrophic antiphospholipid syndrome (CAPS).2-3 It is featured mainly by the rapid onset of widespread thrombosis, which can lead to multi-organ failure. Other aspects of this condition include the association with other thrombotic micro-angiopathies, observed

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systemic inflammatory response syndrome and increasing the risk of unusual organ involvement. Unfortunately, in most cases, despite reaching maximal therapy, this condition carries a high mortality rate.4

The role of hydroxychloroquine (HCQ) is well recognized in medical literature for its antithrombotic effect in APS.5 However, its use in the treatment of Catastrophic APS has previously not been evaluated or reported in our knowledge to date. Therefore, we aim in these cases to highlight the role of HCQ in active CAPS.

Case report

Case 1

A 32-year-old female with a history of Epilepsy and recurrent abortions (not previously investigated) presented to the Emergency Department with 5 days history of gradually progressive dry cough associated with difficulty of breathing on exertion and bilateral lower limb swelling. The patient denied any fever, chest pain or tightness, cough with blood, palpitations, joints pain, mouth ulcers, rash, gastrointestinal, or urinary symptoms. There was no history of any previous similar symptoms.

On admission, the patient was conscious, alert, and oriented only to person. She appeared in mild respiratory distress and was febrile (temperature (max)=38.5°C). The examination was remarkable for a macular erythematous butterfly-like facial rash, pale conjunctiva, grade II systolic murmur best heard at the apex, bi-basilar lung crackles, and bilateral pitting edema on the feet.

Initial labs showed hemoglobin (Hb) of 6 g/dL, mean corpuscular volume (MCV) of 81 fl, platelets of $75 \times 10^3$ µl$^{-1}$. Electrolytes were remarkable for elevated creatinine of 253 µmol and blood urea nitrogen (BUN) of 18.4 mmol/L. Urine analysis (UA) showed proteinuria in the nephrotic range (4.81 g/L). Other investigations showed activated partial thromboplastin time (aPTT) of 66.0 s, D-dimer of 2.96 mg/L fibrinogen equivalent unit (FEU), lactate acid of 0.74 mmol/L, procalcitonin of 0.83 ng/mL, lactate dehydrogenase (LDH) of 351 U/L, and C-reactive protein (CRP) of 30 mg/L. Chest X-ray (CXR) obtained on admission showed bilateral lower zone infiltrates (Figure 1).

The patient was treated mainly for community-acquired pneumonia and acute kidney injury with intravenous (IV) antibiotics, fluid resuscitation and two units of packed red blood cells (PRBC) transfusion for symptomatic profound anemia. The differential diagnoses of thrombotic thrombocytopenia purpura (TTP), hemolytic uremic syndrome (HUS), and systemic lupus erythematosus (SLE) nephritis were all considered with special attention to APS, given her history of recurrent abortions along with high aPTT. Subsequently, peripheral blood smear revealed severe microcytic hypochromic anemia with moderate thrombocytopenia.

Further workup revealed C3 of 23.7 mg/dL, C4 of 2.0 mg/dL, and anti-dsDNA antibodies above 200.0 IU/mL. Considering the high probability of SLE nephritis in this patient with clinical presentation and corroborative lab results, she was started on cyclophosphamide (1 g/month) and IV methylprednisolone (100 mg/once daily). Her other lab works were remarkable for positive anti-SMB, anti-SMD, anti-RNP-A and anti-RNP-C antibodies with anticardiolipin IgM Ab of 100.2 mg/dL and anticardiolipin IgG Ab of 19.30 mg/dL, favoring the diagnosis of antiphospholipid syndrome. Therefore, heparin infusion was started to prevent thrombotic events.

The patient developed new onset hemoptysis and associated worsening of her dyspnea 2 days after admission. Immediate CXR revealed bilateral pulmonary alveolar shadowing (Figure 2), along with a drop of Hb to 7.3 g/dL after initial rise post-transfusion (9.3 g/dL). The patient was moved to intensive care unit (ICU) keeping in view the high probability of pulmonary hemorrhage. At that point, heparin infusion was stopped. The patient received plasmapheresis (one session) for 3 days, which was stopped after bronchoalveolar lavage (BAL) showed no signs of a pulmonary hemorrhage. During her course in ICU, the patient developed two episodes of tonic–clonic seizures with a decrease in level of consciousness warranting intubation and mechanical ventilation.

After stabilizing the patient, computerized tomography (CT) scan of the head was done which ruled out intracranial hemorrhage. Subsequently, the magnetic resonance imaging (MRI) for brain (to rule out any intracranial lesions) was arranged showing bilateral frontal lobes, right periventricular, cortical atrophy, and bilateral tiny cerebellar foci of faint
diffusion restriction suggestive of active lupus vasculitis/cerebritis (Figures 3 and 4). Trans-thoracic echocardiogram revealed moderate pulmonary hypertension with a right ventricular systolic pressure of 52.77 mmHg, ejection fraction of 50%–55%, thickened mitral leaflet valves and moderate mitral regurgitation. Trans-esophageal echo-cardiogram showed two large vegetations on mitral valve suggestive of Libman–Sacks endocarditis. Given the high likelihood of CAPS in this patient, Aspirin (100 mg/once daily) was added to heparin infusion. Hemodialysis was also required initially for acute renal failure. Minimal improvement of her clinical condition was noticed which was not promising.

Finally, working in close liaison with the Rheumatology team, the decision was made to use HCQ (200 mg/once daily). After a few days of its administration, patient’s level of consciousness improved significantly leading to successful extubation and transfer out of intensive care. Her renal parameters markedly improved, not requiring further sessions of hemodialysis. The repeated aPL-Abs were positive (12 weeks after admission) consolidating the initial diagnosis of CAPS. She continues to improve on current treatment and physiotherapy.

**Case 2**

A 28-year-old South East Asian female with background of recurrent abortions (not investigated before) presented to the emergency department with 4 days history of right upper quadrant abdominal pain associated with abdominal distention, nausea and recurrent vomiting. She denied any cough, phlegm production, hemoptysis, joint pain, skin rash, oral ulcers and palpitations. There was no significant history of similar episodes in the past. She denied use of alcohol and was not on any home medication.

On admission, the patient was conscious, alert and oriented. She appeared in mild distress, with respiratory rate of 25 and temperature of 39°C. The examination was remarkable for mild epigastric tenderness and abdominal distention, few bi-basilar lung crackles and normal heart sounds.
Initial labs showed hemoglobin (Hb) of 13 g/dL, platelets of $71 \times 10^3$ µL and WBC of $14 \times 10^3$. Her lipase was $>3300$ U/L and amylase of $960$ U/L. Further investigations showed aPTT of 67.8 s, D-dimer of 2.96 mg/L FEU, alanine transaminase of 14 U/L, aspartate transaminase of 16 U/L, alkaline phosphatase of 48 U/L, total bilirubin of $14 \mu mol/L$, lactic acid of $0.8 \text{mmol/L}$, procalcitonin of $0.8 \text{ng/mL}$, LDH of $794 \text{U/L}$ and CRP of $323 \text{mg/L}$. CT abdomen with contrast showed ill-defined hypodensities in the tail of the pancreas with irregular outlines and fluid in the peripancreatic space (Figure 5). Echocardiography showed normal ejection fraction of 50% with no structural or valve abnormality. The patient was initially treated as case of acute pancreatitis and received IV fluid resuscitation and analgesics.

However, a few days after admission, her condition deteriorated with persistent abdominal pains, continuing fever spikes and worsening dyspnea with desaturation. CXR showed increased left lower zone and retro-cardiac density suggestive of collapse, with left-sided pleural effusion (Figure 6). Repeated echocardiography showed global hypokinesia with drop in her ejection fraction (20%–25%) but no vegetation. Her labs were significant for rise in alanine transaminase to 196 U/L, aspartate transaminase of 194 U/L, alkaline phosphatase of 148 U/L and total bilirubin of $64.5 \mu mol/L$ with direct component of $40 \mu mol/L$; for that she required management in the ICU.

Septic workup showed negative pan cultures, but her viral panel for acute hepatitis came back positive for cytomegalovirus (CMV) with a polymerase chain reaction (PCR) of 5863 copies. She received Ganciclovir for 2 weeks with little clinical improvement upon clearance of CMV viremia. Her abdominal symptoms also showed minimal resolution in contrast to the biochemical improvement in acute pancreatitis. Repeated imaging of the abdomen showed peri-pancreatic inflammation, with heterogeneous enhancement in the right posterior hepatic segments and segmental portal vein thrombosis (Figure 7).

Giving her high aPTT and low platelets with a history of recurrent abortions, there was no clear cause of acute pancreatitis and multi-organ involvement; autoimmune study was sent to rule out CAPS. The results were antinuclear antibody positive (1:160), with speckled pattern; anti-dsDNA (11, equivocal); C3 of $93 \text{mg/dL}$; C4 of $16 \text{mg/dL}$; antinuclear cytoplasmic antibody (negative); anticardiolipin IgM Ab: (negative); anticardiolipin IgG Ab: (positive, $20 \text{mg/dL}$) and anti B2 glycoprotein IgM (positive, $30 \text{mg/dL}$).

She was started on aspirin and heparin infusion. After discussion with the rheumatology team, we decided to start her on HCQ (200 mg/once daily). Several days later, her condition improved with dramatic relief of her abdominal pain and no more difficulty in breathing or spikes of fever.

**Discussion**

Diagnosis of CAPS requires satisfying the following criteria as described by Asherson et al. These include the following:

1. Involvement of three or more organs or tissues.
2. Onset of symptoms in less than 7 days.
3. Tissue biopsy, which features intravascular thrombosis.
Evidence of antiphospholipid antibodies measured twice with 6 week interval. CAPS can also be labeled as a probable diagnosis if less than four criteria are present. Both patients meet the criteria for the diagnosis of probable CAPS supported by the presence of three end-organs affected within 1 week plus simultaneous manifestations in less than a week and confirmed aPL-Ab (which were persistently positive 6 weeks after admission).

Despite on-going research and considerable improvement in mortality, the treatment of CAPS remains challenging with mortality still in the range of 30% with current treatment. Early diagnosis, treatment of concomitant infections, aggressive treatment of thrombosis and supportive measures form the cornerstone of management. Various regimens have been documented in the literature showing varying degrees of efficacy. The most successful remission rates (69%) were achieved in combinations using anticoagulation, corticosteroids, plasmapheresis and/or intravenous immunoglobulin (IVIG).

HCQ is a well-known antimalarial medication with a recognized role in the treatment of autoimmune conditions such as SLE. Furthermore, it has been evident that HCQ has protective mechanisms against vascular thrombosis. In a study published by Rand et al., it was indicated that HCQ has antithrombotic effect by dissociating aPL-beta2-glycoprotein I (β2GPI) complexes. These complexes are formed by the ability of aPL-Ab of identifying a certain epitope on a domain I of (β2GPI), which consequently disables the anticoagulant activity of Annexin A5 leading ultimately to thrombogenesis.

This antithrombotic mechanism of HCQ was observed in only one case report (by Mar et al.) which described the role of HCQ on the patient’s outcome during pregnancy. In this study, the patient had a history of APS. She developed CAPS previously during her pregnancy which led to abortion, although she was receiving antepartum therapeutic doses of aspirin and enoxaparin. She presented again after conceiving at the sixth week of gestation and ultrasound abdomen was consistent with fetal growth restriction which was suggestive of placental thrombosis. She was treated with HCQ and monthly IVIG in addition to her prophylaxis regimen. Eventually, the patient was able to deliver successfully. HCQ was able to prevent CAPS in combination with IVIG, which ultimately led to successful treatment. It was difficult to tell in our cases whether HCQ had solely resulted in the dramatic improvement; nevertheless, its antithrombotic synergy effect with corticosteroids, aspirin, plasmapheresis, anticoagulants and IVIG was undeniably recognized.

Our theory regarding the role of HCQ as an antithrombotic agent is that it has quick onset of action during CAPS, which is not observed and never reported before in the literature, and late action in the stable form of antiphospholipid syndrome. This rapid antithrombotic effect in APS was described by RG Espinola et al. in 2002. Although it was used in conjunction with other immunosuppressants and anticoagulants, its synergistic effect or the hypothesized early onset of action should be considered only during CAPS.

Conclusion
HCQ has been reported to effectively prevent recurrence of CAPS in pregnancy in studies. However, our cases are unique in that HCQ has not previously been reported to be used either alone or in combination for the treatment of CAPS and merits further research.

Acknowledgements
The authors of this paper appreciate the efforts of Dr Ehab Fadel and Dr Yanal Al-Nimer for their support and guidance in preparing of the manuscript.

Declaration of conflicting interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.
Ethical approval
Our institute does not require ethical approval for reporting cases or case series.

Funding
The author(s) received no financial support for the research, authorship and/or publication of this article.

Informed consent
Verbal and written informed consent was obtained from both patients for their anonymized information to be published in this article.

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