CASE REPORT

Antithrombotic effects of hydroxychloroquine in a pregnant patient with Antiphospholipid syndrome and recurrent venous thromboembolism

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SUMMARY

A pregnant woman with antiphospholipid syndrome presented with repeated venous thromboembolism (VTE) in the first and second trimesters of pregnancy despite receiving combination therapy with low-molecular-weight heparin and aspirin. The addition of hydroxychloroquine prevented further VTE recurrence, thus demonstrating its potential antithrombotic effects.

INTRODUCTION

Antiphospholipid syndrome (APS) is an autoimmune condition which is characterised by recurrent vascular thrombosis and/or foetal loss in the presence of antiphospholipid antibodies (aPL). APS occurs either as a primary disorder or associated with an underlying disease, such as systemic lupus erythematosus (SLE). Pregnancy is a state which predisposes women to a higher risk for thromboembolism. This risk is further heightened in pregnant women who have pre-existing APS. For APS patients with a history of thrombosis, life-long anticoagulation is recommended given the risk of recurrence. Low-molecular-weight heparin (LMWH) is the preferred choice of anticoagulant during pregnancy due to its favourable safety profile and predictable anticoagulant response. Despite receiving proven therapeutic dosage of anticoagulation, there were still reported cases of recurrent thromboembolism, thus highlighting the difficulty faced in the management of such patients. Several studies have demonstrated a protective effect of hydroxychloroquine against thrombosis,[2,3] thus suggesting that hydroxychloroquine may be a useful adjunct to anticoagulation. Nonetheless, reports are still lacking on its antithrombotic benefits in pregnant APS patients with a history of thromboembolism. We describe here a case illustrating the potential role of hydroxychloroquine in the prevention of recurrent thromboembolism during pregnancy. Hence we propose the use of hydroxychloroquine in APS patients in combination with anticoagulation during pregnancy.

CASE REPORT

A 24-year-old woman presented to the medical ward with an acute onset of dyspnoea. She was confirmed pregnant at seven weeks gestation.

One year ago, she had presented with unprovoked deep vein thrombosis (DVT) of the right lower limb, which was confirmed on Doppler ultrasonography (US). Activated partial thromboplastin time (APTT) was prolonged at 66.6 seconds. She had positive lupus anticoagulant (LA) and anticardiolipin antibodies (aCL) on two separate occasions which were done 12 weeks apart. LA was analysed using dilute Russel viper venom time (dRVVT). The results showed ratios of 1.58 and 1.53, respectively (ratios above 1.5 was considered positive). Anticardiolipin antibodies IgG were repeatedly positive at 41.36 GPL units and 87.66 GPL units, measured by enzyme-linked immunosorbent assay (Immuno Concepts). Antinuclear antibody (ANA) was positive at a titre of 1:2560. Anti-Ro (SSA) and anti-La (SSB) were also positive, but anti-double stranded DNA (anti-dsDNA) was negative. Complements (C3 and C4) and urinalysis were normal. There were no clinical features to suggest systemic lupus erythematosus. APS was diagnosed and she was anticoagulated with warfarin. Soon after that, she became pregnant. Warfarin was switched to subcutaneous enoxaparin however she suffered a miscarriage two days later, at six weeks of gestation. She resumed warfarin and three months after that, she expressed her wish to conceive. Given the history of a previous miscarriage occurring in early pregnancy, subcutaneous enoxaparin 80 mg bd (at 1 mg/kg/dose) was initiated. Two months later, she became pregnant and aspirin 75 mg daily was added.

Physical examination revealed an obese woman with a body mass index (BMI) of 38 kg/m^2. She was tachycardic with a heart rate of 112 beats per minute. Respiratory rate was 28 breaths per minute. Blood pressure was 120/85 mmHg. There was swelling of the right calf. Examination of the cardiovascular system was normal and auscultation of the lungs revealed good and equal air entry. Arterial blood gas revealed type 1 respiratory failure and electrocardiogram (ECG) showed sinus tachycardia. A ventilation perfusion (V/Q) lung scan demonstrated a mismatched segmental perfusion and ventilation defect at the apical segment of the right upper lobe, consistent with pulmonary embolism. Doppler US of the lower limbs showed thrombosis in the right superficial femoral vein. Anti-factor Xa assay was performed to evaluate LMWH concentrations in the blood given the occurrence of pulmonary embolism despite receiving recommended dosage of LMWH. Anti-factor Xa level was well within the therapeutic range at 1.18 IU/ml (0.7-1.2 IU/ml).

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Nevertheless, the dose of enoxaparin was escalated to 100 mg mane and 80 mg nocte. Her dyspnoea eventually resolved and she was subsequently discharged after one week of hospitalisation.

She remained asymptomatic until her 22nd week of pregnancy when she re-presented with a one-week history of progressive dyspnoea. Clinical examination revealed she was tachycardic and tachypnoea. Blood pressure was normal. Arterial blood gas again showed type 1 respiratory failure. Computed tomography (CT) pulmonary angiogram confirmed evidence of embolism involving the right main pulmonary artery and descending branches of both pulmonary arteries. Anti-factor Xa level was again within the therapeutic range at 0.86 IU/ml. Given the extent of pulmonary embolism, thrombolytic therapy with intravenous recombinant tissue plasminogen activator (r-TPA) at 100 mg was instituted. Further optimisation of therapy was undertaken, with escalation of aspirin to 150 mg daily and introduction of hydroxychloroquine at 400 mg daily. Her symptoms improved and she was asymptomatic upon discharge. She continued to be well throughout the remaining course of her pregnancy with no further episodes of vascular thrombosis. Given the fact that recurrent VTE while fully anticoagulated is a factor that placed her at high risk of maternal mortality, her obstetrician advised for elective Caesarean section at 34 weeks of gestation. She delivered a healthy baby with a birth weight of 1.93kg. The new-born required non-invasive ventilation for one day, and was subsequently discharged in good health conditions at day four of life.

DISCUSSION

Venous thromboembolism (VTE) is one of the leading causes of maternal death. Our patient demonstrated an exceptionally high risk for VTE given the fact that she was pregnant, coupled with an underlying antiphospholipid syndrome and a history of VTE. Despite optimal anticoagulation which was confirmed by therapeutic levels of anti-factor Xa, recurrent VTE still occurred. To the best of our knowledge, this is the first reported case whereby hydroxychloroquine managed to prevent further relapse of VTE in an APS patient during pregnancy. Hydroxychloroquine has been reported to exert antithrombotic properties in patients with SLE and/or APS, and this was discussed in the treatment trends task force in the 14th International Congress on aPL.[1] The task force currently recommends hydroxychloroquine in all aPL-positive SLE patients. Nevertheless, the utility of hydroxychloroquine in the management of APS has not been determined.

A prospective study conducted in France[2] showed that hydroxychloroquine was effective as secondary prophylaxis in primary APS patients. Recurrence of VTE was absent in the group on combination oral anticoagulant and hydroxychloroquine, as opposed to a relapse rate of 30% in the group receiving oral anticoagulant alone despite achieving optimal INR. Besides reducing the risk of VTE relapse, the benefits of hydroxychloroquine in terms of improving pregnancy outcome was also explored. Mekinian et al.[3] reported a significant increase in live born rates among patients with previous refractory obstetrical APS who had additional treatment with hydroxychloroquine, as compared to the group without hydroxychloroquine (81% versus 19%, $p<0.05$). The use of hydroxychloroquine in pregnant women was also deemed safe for the foetus. There was no increase in frequency of congenital malformations in babies who were exposed to hydroxychloroquine.

To date, the exact mechanism of action of hydroxychloroquine in reducing thrombosis recurrence remains unclear. An experimental study by Rand et al.[4] showed that hydroxychloroquine restored the binding of Annexin A5 (AnxA5) from displacement by disruption by aPL on phospholipid bilayers in cultured cells and blood plasma of APS patients, in addition to increasing the AnxA5 anticoagulant activities, thus reducing thrombotic events. Carolis et al.[5] reported a woman with refractory obstetrical APS who achieved favourable pregnancy outcome following addition of hydroxychloroquine. A dramatic drop in levels of aPL was observed and this was considered a mechanism attributed to hydroxychloroquine.

In spite of numerous reports indicating the beneficial role of hydroxychloroquine in reducing thrombosis in APS patients, prospective studies requiring larger number of patients are required to confirm its advantages. Given the encouraging outcome of our patient, we propose for hydroxychloroquine to be seriously considered as an adjunct therapy to anticoagulation in pregnant primary APS patients with a history of thrombosis.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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