Pontine Infarct as Initial Presentation of Catastrophic Antiphospholipid Syndrome in Systemic Lupus Erythematous

*Rathika Rajah[1], Rizna A. Cader[2]**

[1] Department of Medicine, Universiti Kebangsaan Malaysia (UKM) Medical Centre, Cheras, Kuala Lumpur, Malaysia.

[2] Nephrology Unit, Department of Medicine, UKM Medical Centre, Kuala Lumpur, Malaysia

**** Corresponding Author:***

Rizna Abdul Cader, MD. Consultant Nephrologist. Nephrology Unit, Department of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latif, 56000 Cheras, Kuala Lumpur, Malaysia. Email: rizna_c@hotmail.com.

ABSTRACT

Antiphospholipid syndrome (APLS) is an autoimmune condition which commonly manifests as an arterial or venous thrombosis affecting medium to large vessels, with the presence of antiphospholipid antibodies. APLS can be a primary disease by itself, or secondary to other autoimmune diseases, such as Systemic Lupus Erythematosus (SLE). Catastrophic APLS is a rare but a fatal sequelae of APLS, affecting up to three or more organs, and progresses rapidly with a high mortality rate. We report a case of catastrophic APLS in a young woman with underlying SLE who presented to us with multiple cranial nerve palsies due to bilateral pontine infarct, and eventually developed deep vein thrombosis and pulmonary embolism during the course of the illness. She was treated with high dose corticosteroids and intravenous cyclophosphamide with biochemical improvement. In this case report, we would like to highlight the fact that our patient had bilateral pontine infarcts as the initial presentation, with no inciting events and antiphospholipid antibodies were negative during the acute illness.

Keywords: *Antiphospholipid Syndrome, Catastrophic APLS, Infarct, Thrombosis, Cyclophosphamide*

INTRODUCTION

Antiphospholipid syndrome (APLS) was first described in 1983 by Graham Hughes, in which there will be a single arterial or venous thrombosis as a result of an occlusion of the medium to large vessels with the presence of antiphospholipid antibodies.[1] APLS is a hypercoaguable state that predominantly affects females with a mean age of 37 years.[2] It can either stand on its own as primary APLS, or associated with other autoimmune conditions, primarily SLE. Anticardiolipin antibodies (aCL) and Lupus anticoagulant antibodies (LA) are seen in a significant amount in patients with SLE, which then contributes to the formation of APLS.

Catastrophic APLS is a life threatening, rare variant of APLS seen in less than 1% of APLS.[3] It progresses rapidly to cause diffuse small vessel ischemia due to the presence of micro-thromboses, in contrary to APLS. The four most commonly affected organs are renal (71% - 89%), followed by cerebral (62%), lungs (45% - 64%) and cardiac (45% - 51%).[4,5] Diagnosing catastrophic APLS is rather challenging and often be blinded by other differential diagnoses, especially disseminated intravascular coagulopathy (DIVC) and thrombotic thrombocytopenic purpura (TTP). The diagnostic criteria include a history of APLS or persistent positive antibodies in two occasions six weeks apart, with three or more organs affected, symptoms onset within a week and biopsy proven micro-thrombosis. A definite catastrophic APLS requires all four criteria to be

fulfilled, whereas a probable catastrophic APLS requires three out of four criteria.[6]

Many reviews have reported catastrophic APLS to have a mortality rate as high as 44%, and patients usually succumb due to cerebral involvement, cardiac cause and infection. A combination of anticoagulant, corticosteroids and plasma exchange was thought improve outcomes, while the use of intravenous cyclophosphamide was not proven to be beneficial.[3]

CASE ILLUSTRATION

We report a case of a 28-year-old lady, single, nulliparous, who was diagnosed to have SLE with musculoskeletal and hematological involvement at a private hospital in 2017 where she presented with anaemic symptoms and fever. She first presented to our institution in 2018 with relapsed SLE and lupus nephritis (LN). Renal biopsy showed diffuse proliferative lupus nephritis (ISN/RPS LN Class IV). She was then treated with intravenous Methylprednisolone and subsequently induced with Mycophenolate Mofetil (MMF) and Cyclosporin A (CSA). However, she never achieved complete remission (normal renal function and albumin, but persistent proteinuria of 3g/day). Renal biopsy was repeated in June 2019 and showed the presence of focal proliferative lupus nephritis (ISN/RPS LN Class III). She was once again treated with intravenous Methylprednisolone and scheduled for intravenous Cyclophosphamide. Two weeks later, she presented with complaints of left eye ptosis, preceded with three days of fever and cough which had resolved. She denied having any constitutional symptoms, recent trauma or surgery.

Upon examination, she was comfortable, orientated and not septic looking. She was neither hypertensive nor febrile with BP being 140/83. Both pupils were equal and reactive. She had a partial ptosis over the left eye. There was limited adduction of the left eye, whereas on the right eye, the adduction and abduction were both limited. She also had right facial lower motor neuron weakness. Other examinations were unremarkable.

Her full blood count showed normochromic normocytic anaemia, with thrombocytopenia (Hb 9.3 g/dL; Platelet 106 x 10^9/L). Peripheral blood film showed no evidence of haemolysis. The coagulation profile was normal. There were no biochemical or radiological evidence of infection (WBC 4.4 X 10^9/L; CRP 0.95 mg/L; Blood C&S showed no growth; Chest X-ray clear lung fields). Her renal function was normal throughout admission, but had a heavy proteinuria of 6g/day. Serum albumin was 26. Urine full examination and microscopic examination (UFEME) showed protein of 4+ and blood 5+. Her antinuclear antibody (ANA IF) was positive, 1:640 homogenous. But, her antiphospholipid antibodies were tested to be negative (We do not have a prior antiphospholipid antibody tests done). Her serum complement C3 and C4 levels were low. Patient was subjected for contrast enhanced computerized tomography (CT) scan and MRI/MRA brain. Both were suggestive of bilateral pontine infarct, with no meningeal enhancement or dural venous thrombosis.

She was empirically started on intravenous antibiotics. She was also given intravenous Methylprednisolone 250mg once daily for three days, followed by oral prednisolone. We decided to continue the second cycle of intravenous cyclophosphamide during this period for her active lupus nephritis.

During the 5th day of admission, she complained of shortness of breath. Further workup showed the presence of extensive left lower limb deep vein thrombosis and bilateral acute pulmonary embolism. With regards to her rapidly progressing thrombotic symptoms involving three major organs (brain, renal and lungs), she was deemed to have probable catastrophic APLS. Patient was started with low molecular weight heparin (LMWH) in ward and switched to warfarin upon discharge.

During her clinic follow up for further Cyclophosphamide doses, we did see a significant biochemical improvement (proteinuria), but remained to have residual neurological symptoms.

DISCUSSION

The hallmark of catastrophic APLS includes the presence of antiphospholipid antibodies, thrombocytopenia, anaemia, and prolonged

clotting time as opposed to the absence of haemolytic picture in the blood film. Thrombotic storm, is an alternative diagnosis that presents in a similar manner, whereby the thrombotic events occur rapidly without a triggering factor diagnosed based on clinical grounds.[7] Both conditions keep physicians on the ball in events of patient progressing into definite catastrophic APLS, requiring aggressive treatment with corticosteroid and immunosuppressants.

The nervous system is the second most commonly affected organ in catastrophic APLS after the renal system. The dual pathology of thrombotic damage and antibodies induced oxidative stress contributes to the formation of infarction. They vary in terms of distribution of lesion (central or peripheral) and phenotype due to genetic predisposition or individual susceptibility. With middle cerebral artery territory being the most common affected site, pontine infarcts are said to be the least commonly affected area involving less than 10% of individuals.[8] Catastrophic APLS can also present with non-thrombotic features such as headache, seizures, neuropsychiatric symptoms and movement disorders.

Asherson et al,[4] reported that almost half of the patients with catastrophic APLS will have a preceding event mainly infection, followed by trauma, surgery, malignancy or obstetric condition, none of which were seen in our case. Epstein Bar virus (EBV) and Cytomegalovirus (CMV) infections are closely linked to catastrophic APLS. Catastrophic APLS leads to immune activation, then systemic inflammatory response syndrome and small vessel thrombosis.

The presence of antiphospholipid antibodies with thrombosis is needed to define APLS and catastrophic APLS, portraying the importance of these antibodies in the pathogenesis of the disease. The most commonly seen antibodies are aCL IgG and LA, 83% and 82% respectively. But, there have been cases reported where the antibodies were only positive two months later. [9,10] It can be explained by the fact that the antibodies can be falsely negative due to the antibody consumption by a larger thrombus size during the acute period and become positive shortly after. It is also postulated that these antibodies are occasionally directed to some other antigens and creating a complex that cannot be tested using the conventional method. Therefore, it is wise to repeat the test later on.[10,11] It is not known to when is the best time to repeat the test.

As mentioned above, catastrophic APLS mostly affects the kidney causing a rise in serum creatinine, proteinuria of more than 6g/day and severe hypertension. Be it definite or probable catastrophic APLS, the standard treatment regime includes anticoagulant plus corticosteroids plus plasma exchange with or without intravenous immunoglobulin.[12] This is to treat the precipitating factor and thrombotic event, thus further suppressing the cytokines released during the acute period. Few reports have suggested that the use of cyclophosphamide during the acute period does not confer a better prognosis.[12] But for some physicians, high dose corticosteroids together with cyclophosphamide had been the preferred initial choice of treatment. On the other hand, Rituximab, an anti-CD20 monoclonal antibody used in hematological malignancies, has been widely studied in catastrophic APLS. Catastrophic APLS and hematological malignancies often have the same blood picture, which is anaemia, thrombocytopenia or thrombotic micro-angiopathies. Hence, the use of Rituximab in catastrophic APLS with haematological involvement has shown to be equally effective. Rituximab has also been proven to be beneficial in patients with renal and cardiac involvement.[13]

Besides being a poor prognostic factor for catastrophic APLS, the co-existence of active SLE and APLS with both pulmonary and renal involvement confers a higher rate of relapse. Age of more than 36 years and the presence of antinuclear antibodies and lupus anticoagulant also have an added value to cause relapse.[14]

With regards to our patient, a normal clotting time and fibrinogen level excludes DIVC, whereas the absence of haemolysis with a background of thrombocytopenia excludes TTP. The onset of symptoms was within days and progressed to involve three major organs (renal,

cerebral and lungs) but the antiphospholipid antibodies were tested to be negative. We regarded her as having probable catastrophic APLS, as any further delay in aggressive treatment could cause a detrimental effect. The decision to continue the cyclophosphamide instead of plasma exchange or giving intravenous immunoglobulin was made as she was having active lupus nephritis which did not respond to MMF. And, as to whether Rituximab can lead to neurological improvement, it is still unknown as there is lack of trials in this aspect. It is imperative for us to follow her up closely to repeat her antiphospholipid antibodies and be watchful for relapse.

CONCLUSION

Catastrophic APLS can have various clinical and biochemical presentations. The diagnosis criteria is a useful guide, but high index of suspicion and early initiation of treatment is needed to prevent any unwanted complications.

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