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Antiphospholipid Syndrome in Childhood Systemic Lupus Erythematosus

Paudyal B[1]

[1]Department of Medicine,Patan Hospital,Kathmandu, Nepal.

ABSTRACT

Antiphospholipid syndrome is an autoimmune disease that presents with recurrent arteriovenous thrombosis, repeated pregnancy loss and elevated titres of antiphospholipid antibodies in the blood. It is a common cause of acquired thrombosis and can manifest within any part of the vascular tree. Inferior Venacava thrombosis at outset, however, is not a common manifestation of systemic lupus erythematosus associated- antiphospholipid syndrome particularly in children. Here, we present a 14-year old girl who developed antiphospholipid syndrome as a presenting manifestation of systemic lupus erythematosus.

Key words: antiphospholipid syndrome, thrombosis, systemic lupus erythematosus

INTRODUCTION

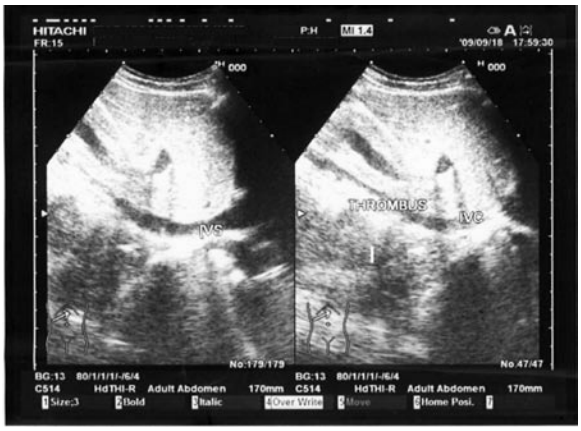
Antiphospholipid syndrome (APS) was initially defined as a noninflammatory autoimmune disorder, consisting of arterial and/ or venous thrombosis, recurrent fetal loss, mild to moderate thrombocytopenia and elevated titres of antiphospholipid (aPL) antibodies namely the lupus anticoagulant (LAC) or/and anticardiolipin antibodies (aCL).[1,2]

The APS can either occur as a free-standing condition (primary APS or PAPS) or be associated with other autoimmune diseases, mainly systemic lupus erythematosus (SLE).[3,4] Common thrombotic presentations in APS include deep vein thromboses of lower extremities, pulmonary embolism, cerebrovascular accidents, and recurrent pregnancy loss. Inferior Venacava (IVC) thrombosis, however, is not a common manifestation of APS particularly in childhood SLE-associated APS. Here we report a case of childhood SLE who had APS as one of the presenting manifestation of the disease.

CASE

A 14 year old girl presented with intermittent fever, photosensitive malar and discoid rashes on face, loss of hair, painful swelling of the multiple joints, and painless oral ulcers. On the following day, she presented to the Emergency Department of another hospital with sudden onset of abdominal pain and leg swelling. Investigations revealed anaemia, thrombocytopenia, neutropenia, positive antinuclear antibodies (ANA), and high titres of anti ds-DNA antibodies (>300, negative being less than 30). Doppler ultrasound of the abdomen revealed intraluminal echogenic linear shadow in the inferior venacava (IVC) wall with narrowing of its lumen suggesting a thrombus in the distal one third of intrahepatic portion of IVC. Further investigations revealed slightly prolonged activated partial thromboplastin time (APTT) at 35 sec (control 30 sec), positive aCL antibodies, IgG 30.5 (negative <12 GPL) & IgM 68.9 (negative <10 MPL). She had slightly elevated liver enzymes: aspartate aminotransferase (AST) 227 and alanine aminotransferase (ALT) 218. The examination of the rest of the liver function, thyroid function, renal function, and urine were normal.

Correspondence: Dr. Buddhi P Paudyal, Department of Medicine, Patan Hospital, Kathmandu, Nepal. Email: buddhipaudyal@yahoo.com , Phone: 5522278.



USG showing Fig. 1. Doppler echogenic thrombus in IVC.

The patient was admitted in hospital for anticoagulation (intravenous heparin followed by warfarin) where she showed gradual recovery. USG of the abdomen one month after the incident revealed complete canalization of the IVC with no intraluminal thrombus. Repeat blood tests revealed normalization of liver enzymes though her APTT was persistently prolonged and aCL were positive in high titres after 3 months of initial investigation. She is currently on hydroxychloroquine, warfarin, and tapering dose of prednisolone, with the good control of her lupus and therapeutic international normalized ratio (INR) between 2 to 3.

DISCUSSION

Following its initial description by Graham Hughes in 1983, APS has become a well characterized clinical entity within a short span of time. A consensus statement on classification criteria for this syndrome has been published in 2006 (Table 1).[3] Venous and arterial thromboembolism in APS patients has been reported in almost any location of the vessel tree, although deep vein thrombosis of the lower limbs, pulmonary embolism, and recurrent pregnancy loss due to placental thrombosis are most frequently occurring events.[6] In fact, APS can affect almost all the organ-systems of body. For this reason some author has proposed it to be named as systemic antiphospholipid syndrome (Table 2).[7] This systemic involvement in APS may be explained because of the ubiquitous existence of the autoantigens i. e., negatively charged phospholipids which are found almost in any cell, tissue, or organ in the body. Moreover there are diverse pathogenic autoantibodies and mechanisms that can explain multiple manifestations.

The American College of Rheumatology (ACR) classification criteria for SLE include the presence of antiphospholipid antibodies (aPLs).[8] The presence of aPL is an important immunological hallmark for the classification and diagnosis of patients with SLE, and aPLs have been detected in samples stored up to 7.6 years prior to the diagnosis of SLE.[9]

Table 1. Summary of the Sydney Consensus Statement on Investigational Classification Criteria for the APS.[13]

Antiphospholipid antibody syndrome (APS) is present if at least one of the clinical criteria and one of the laboratory criteria that follow are met.
Clinical Criteria
Vascular thromboses:
1. One or more documented episodes of arterial, venous, or small vessel thrombosis—other than superficial venous thrombosis— in any tissue or organ. Thrombosis must be confirmed by objective validated criteria. For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.
2. Pregnancy morbidity
(a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or
(b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because of: (i) eclampsia or severe pre-eclampsia defined according to standard definitions, or (ii) recognized features of placental insufficiency, or
(c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.
Laboratory criteria
1. Lupus anticoagulant (LAC) present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis (Scientific Subcommittee on LACs/ phospholipids dependent antibodies).
2. Anticardiolipin antibody (aCL) of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (i.e., > 40 GPL or MPL, or > the 99th percentile), on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA.
3. Anti-β2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma (in titer >the 99th percentile), present on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA, according to recommended procedures.

There is a close relationship between APS and SLE; SLE is a frequent cause of secondary APS, and even primary APS can present with several systemic manifestations (thrombocytopenia, neurological symptoms, haemolytic anaemia, livedo reticularis, renal involvement, arthralgia, etc) that are also shared by SLE. The close relationship between primary APS and SLE is also supported from a biological point of view as primary APS patients frequently display antinuclear and anti- ds DNA antibodies which are typical markers and pathologic mediators of SLE.[10]

Table 2. Organs and systems involved in systemic APS (Hughes' syndrome) [7]

1)	Skin (e.g., livedo reticularis, anetoderma)
2)	Heart (e.g., non-verrucal endocarditis)
3)	Kidney (e.g., renal artery stenosis)
4)	Circulation (e.g., hypertension)
5)	Lung (e.g., pulmonary hypertension)
6)	Brain (e.g., cognitive impairment, epilepsy)
7)	Brain Vasculature (e.g., migraine)
8)	Blood elements (e.g., autoimmine haemolytic anaemia, thrombocytopenia)
9)	Bone (e.g., osteonecrosis)
10)	Adrenals (e.g., apoplexy, catastrophic APS)
11)	Placenta (e.g., insufficiency, foetal death, apoptosis)
12)	Pregnancy (e.g., eclampsia, pregnancy loss)
13)	Coagulation (e.g., hypercoagulable state)
14)	Blood vessels (e.g., accelerated atherosclerosis)
15)	Eyes (e.g., amaurosis fugax, optic neuritis)
16)	Ears (e.g., acute hearing loss)
17)	Gastrointestinal involvement (e.g., spleen, Budd Chiari syndrome)

APS has been estimated to have a population prevalence of 0.3-1% and is recognized to account for 20% of all episodes of deep vein thrombosis (DVT), a third of new strokes in patients less than 50 years of age, and 5-15% of women with recurrent foetal loss.[11] In fact, APS is the commonest cause of acquired venous and arterial thrombosis[12] and the most important treatable cause of recurrent miscarriage.[13]

Whether our patient had preexisting primary APS and on due course developed the features of SLE or this was secondary to SLE from the beginning is not clear. Longterm follow up studies of primary APS revealed that 13 to 21% of paediatric patients with primary APS developed SLE or lupus-like syndrome after an approximate period of 9 years.[14, 4] However, in recent years it has become increasingly clear that this distinction between primary APS and secondary APS is less useful since the clinical and serological features of APS are similar in both groups. In fact, the recently revised criteria for the classification of APS recommended that this distinction be dropped and, instead, any associated disorder be reported, such as SLE-associated APS.[3]

There have been few studies that have evaluated the frequency and behaviour of aPL antibodies in children with lupus. Ravelli and Martini reports that the positivity of APL antibodies varies from 19 to 87% (mean 56%) for aCL antibodies and from 11 to 62% (mean 31%) for LAC. Antiphospholipid syndrome is present in 9 to 24% of the cases.[15] Lately Campos and colleagues observed that the mean positivity of aCL antibodies in SLE was 39%, while LAC could be detected in about 27% of such patients. Despite the high prevalence of APL antibodies among lupus patients, according to the majority of the studies APS is present in only 10-20% of cases.[16] It is important to note that enzyme linked immunoassay (ELISA) is used to identify aCL and B2 glycoprotein I antibodies (IgG and IgM); whereas LACs are detected utilizing various phospholipids dependent tests of coagulation (e.g., APTT, Kaolin Clotting Time [KCT], and dilute Russell Viper Venom time [dRVVT]).[17]

The risk of thromboembolic recurrences in patients positive for APL is often associated with the presence of the lupus anticoagulant (LA) than with anticardiolipin (ACL) antibodies.[18] Patients with secondary forms of APS have been thought to be at higher risk for arterial recurrences, but still unknown is the risk of venous recurrences. Brunner et al[19] reported that a longer duration of anticoagulation with warfarin with a target international normalized ratio (INR) between 3.0 and 4.0 was the most effective among the several tested anti-thrombotic regimens, both one and four years after the first VTE event. Others suggest INR between 2 and 3 for initial episode and higher intensity (INR 3 to 4) for recurrent thromboses.[20] A life-long prophylaxis is suggested to patients with spontaneous and/ or life-threatening thromboembolic events and/ with associated permanent risk factors[6] as well as in patients with SLE.[10]

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