Case Report

Avascular necrosis of bone with hemiparesis: a rare presentation of primary antiphospholipid antibody syndrome

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ABSTRACT
Vascular complications are well known manifestations of primary antiphospholipid antibody syndrome but the concurrent existence of avascular necrosis of bone and stroke due to vasculitic infarct is a very rare presentation. We report a case of a middle-aged man who presented with right knee pain and left hemiparesis and was subsequently diagnosed to have primary antiphospholipid antibody syndrome.

Keywords: Avascular necrosis of bone, Primary antiphospholipid antibody syndrome

INTRODUCTION
Antiphospholipid syndrome (APS) is primarily considered to be an autoimmune pathological condition that is also referred to as "Hughes syndrome". It is characterized by arterial and/or venous thrombosis and pregnancy pathologies in patients with antiphospholipid antibodies (aPL)- positive sera. aPL comprises three main antibodies: anticardiolipin (aCL), lupus anticoagulant (LA), and anti-b2-glycoprotein-I antibodies (antib2GPI).¹,² APS can occur either as a primary disease or secondary to a connective tissue disorder, most frequently systemic lupus erythematosus (SLE). Damage to the nervous system is one of the most prominent clinical constellations of sequelae in APS and includes:

- Arterial/venous thrombotic events
- Psychiatric features
- Other nonthrombotic neurological syndromes.

Musculoskeletal involvement also have been reported in many cases, further affecting the quality of life in APS patients. In this organ system, avascular necrosis of bone is a chief manifestation of APS, among several other complications. The simultaneous co-existence of both these manifestations has rarely been reported.

CASE REPORT
A 38-year-old male with no significant past history presented with history of fever associated pain and swelling in the right knee for 2 weeks and weakness on the left side of the body since 4 days prior to admission. Clinical examination revealed that the patient was normotensive, febrile and the right knee joint was swollen and tender with restricted range of movements. The left upper and lower limbs had spasticity, decreased power and brisk deep tendon reflexes. The patient had reduced sensations of touch, pain and temperature over the left half of the body. There was no bruit over the carotids, the peripheral pulses were felt equally and the fundus was normal. The examination of cardiovascular, respiratory and gastro-intestinal systems was normal. Laboratory investigations revealed: Haemoglobin 10.0gm%, TLC-7,800/mm³; DLC- P70 L26 M3 E1 B0; Platelet count-2,33,000/mm³. All other investigations, i.e. liver function...
tests, renal function tests, lipid profile, roentgenogram chest and ultrasound of abdomen were normal. Patient was also tested negative for HIV, Hepatitis B and C. MRI scan of the brain showed multiple acute/subacute infarcts in the right thalamus, capsular region, right periventricular region, right frontal and parietal lobes (Figure 1).

MRI scan of the right knee shows diffuse altered marrow signal intensity in tibia and patchy areas of altered signal intensity in lower femur suggesting osteomyelitis with bony infarcts (Figure 2). Colour Doppler of the carotids, 2D echocardiography and serum homocysteine levels were normal. Autoimmune markers like ANA and anti-ds DNA were negative. The anticardiolipin (aCL) antibodies were positive and the lupus anticoagulant (LA) and anti-b2-glycoprotein-1 antibodies (anti2GPI) were negative during admission. Patient was put on antibiotics and was started on Acenocoumarol 2mg and was discharged after the INR reached therapeutic range of 2.5-3.5. The patient was again tested positive for anticardiolipin antibodies at the end of 12 weeks when he had come for follow up.

DISCUSSION

APS is mainly considered an autoimmune disorder where a vascular thrombosis and/or recurrent pregnancy pathologies are observed in patients with laboratory evidence for antibodies against phospholipids or phospholipid-binding protein cofactors (Table 1).

### Table 1: Revised criteria for APS (2006).

| Revised criteria for APS (2006) |
|--------------------------------|
| **APS is present if at least one of the clinical criteria and one of the laboratory criteria that follow are met:** |
| **Clinical** |
| 1. **Vascular thrombosis** |
| One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ. Thrombosis must be confirmed by objective validated criteria (i.e. unequivocal findings of appropriate imaging studies or histopathology). 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 foetus at or beyond the 10th week of gestation, with normal foetal morphology documented by ultrasound or by direct examination of the foetus, or defined according to standard definitions. |
| (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 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 (LA) 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 Las/phospholipid dependent antibodies). |
| 2. Anticardiolipin (aCL) antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (i.e. >40 GPL or MPL, or >99th percentile), on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA. |
| 3. Anti-b2 glycoprotein-1 antibody of IgG and/or IgM isotype in serum or plasma (in titer >99th percentile), present on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA, according to recommended procedures. |
As mentioned in Table 2, the clinical manifestations of the syndrome include venous and arterial thromboses and embolisms, disseminated large and small vessel thromboses with accompanying multi-organ ischemia and infarction, stroke, premature coronary artery disease, and spontaneous pregnancy losses. The aetiology of APS is multifactorial, and an exact, single cause cannot always be determined. Pathophysiology includes the activation of endothelium, oxidized LDL mediated vascular injury, heparin induced thrombocytopenia and molecular mimicry.

Table 2: Clinical manifestations of APS.

| **Neurological manifestations of APS** |  |
|--------------------------------------|--|
| Cerebro-vascular disease             |  |
| Transient ischemic attacks           |  |
| Ischemic strokes                     |  |
| Acute ischemic encephalopathy        |  |
| Cerebral venous thrombosis           |  |
| Epilepsy                             |  |
| Headache                             |  |
| Chorea                               |  |
| Multiple sclerosis                   |  |
| Transverse myelitis                  |  |
| Idiopathic intracranial hypertension |  |
| Other neurological syndromes         |  |
| Sensori-neural hearing loss          |  |
| Guillain-Barré syndrome              |  |
| Transient global amnesia             |  |
| Ocular syndromes                     |  |
| Dystonia parkinsonism                |  |
| Cognitive dysfunction                |  |
| Dementia                             |  |
| Other psychiatric disorders          |  |
| Depression                           |  |
| Psychosis                            |  |

| **Musculoskeletal manifestations of APS** |  |
|------------------------------------------|--|
| Arthralgia/arthritis                     |  |
| Avascular necrosis of bone               |  |
| Bone marrow necrosis                     |  |
| Complex regional pain syndrome type-1 (reflex sympathetic dystrophy) |  |
| Muscle infarction                        |  |
| Non-traumatic fractures                  |  |
| Osteoporosis                             |  |

According to the largest survey of APS patients to date, deep vein thrombosis, sometimes accompanied by pulmonary embolism, is the most frequently reported manifestation of this syndrome (38.9%). Conversely, cerebrovascular accidents, either stroke (19.8%) or transient ischemic attacks (11.1%), are the most common arterial thrombotic manifestations. In addition, several other clinical features are present in these patients, i.e. thrombocytopenia (29.6%), livedo reticularis (24.1%), heart valve lesions (11.6%), hemolytic anemia (9.7%), epilepsy (7%), myocardial infarction (5.5%), leg ulcers (5.5%), amaurosis fugax (5.4%) and avascular necrosis of bone (2.4%).

The osteoarticular manifestations of APS include arthralgia, arthritis and avascular necrosis of bone. It has been suggested that the avascular necrosis (AVN) of bone in SLE patients is probably multifactorial. A possible link between AVN and aPLs has been postulated, but the relationship is still unproven; the lack of other risk factors points to a suspected etiological role of antiphospholipid antibodies in AVN syndrome.

Strokes and transient ischemic attack (TIA) are considered the second most common clinical manifestations of APS after venous thrombosis. The cerebral ischemia, which is mainly focal, can be transient or permanent. Recurrent disease often leads to multifocal deficits. The risk for recurrent stroke appears to be increased in APS patients. Generally, the territory of the middle cerebral artery is more commonly affected.

Although not very frequent, cardiac emboli may be another cause of cerebral ischemia in aPL positive patients (cerebral emboli from Libman-Sacks endocarditis in SLE patients 128 or from the heart chambers or the internal carotid artery). Brain MRI in ischemic stroke shows cortical abnormalities consistent with large vessel occlusion in aPL positive patients. Often, small foci of high signals in the white matter of the brain are seen on MRI. Larger sizes and atypical topographic distributions of these lesions may also be consistent with demyelination and are sometimes difficult to differentiate from MRI pictures seen in multiple sclerosis.

Recurrent ischemic events in aPL-positive patients are related to aCL at the time of the initial stroke. In consecutive patients with aPLs and focal cerebral ischaemia, cerebral infarctions within the first follow-up year supported the data that IgG aCL represented a risk factor for recurrent stroke. In a later study this was confirmed, and the subsequent thrombo-occlusive events were associated with IgG aCL (most frequently in patients with aCL 40 GPL), thus confirming the role of aCL as a risk factor for recurrent stroke.

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