Ischemic Stroke in a Patient with Lupus Following Influenza Vaccination: A Questionable Association

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Central nervous system involvement in systemic lupus erythematosus encompasses a wide range of syndromes collectively referred to as neuropsychiatric lupus. Approximately 60% of patients with SLE experience one of a wide variety of neuropsychiatric syndromes during the course of their disease. According to the American College of Rheumatology, the most common manifestations are cognitive impairment, which occurs in 50% of the patients, followed by headaches (25%), mood disorders, ischemic strokes (10%), seizures, anxiety and psychosis [1].

Ischemic strokes in SLE patients derive from several pathologies. The most common is atherosclerotic disease causing thrombotic or embolic occlusion of a major blood vessel. The presence of antibodies to phospholipids leads to endothelial damage causing *in situ* occlusion. Endothelial damage secondary to vasculitis may also result in compromised blood flow and ischemia. Embolic strokes might be associated with non-infectious endocarditis (Libman-Sachs endocarditis). Other conditions mimicking ischemia are lupus cerebritis and an adverse affect of drugs, such as corticosteroids. All these should be considered in the differential diagnosis.

SLE = systemic lupus erythematosus

PATIENT DESCRIPTION

A 55 year old Caucasian woman was admitted to our hospital with an acute confusional state lasting 2 days, accompanied by erratic behavior and severe headaches. Her past medical history was significant for osteoporosis and non-erosive knee arthritis for which she had been treated with short courses of low dose prednisone. She received no other medications prior to her admission, except for an influenza vaccination 4 days prior to the hospitalization.

On admission the patient was restless and had no fever. Her blood pressure was 134/81 mmHg, the heart rate was 70 beats per minute, and oxygen saturation level was 98%. A mildly enlarged spleen was noticed. The rest of the physical examination was unremarkable. Laboratory evaluation revealed white blood cell count of 6.3 x 10^3/ml, hemoglobin 12.6 mg/dl, platelet count 88,000/ml, sodium 133 mEq/L, potassium 3.8 mEq/L, and calcium 9.8 mg/dl. C-reactive protein level was normal. The toxicological urine screen assay was negative. The initial evaluation also included a brain computed tomography scan that was normal. Cerebrospinal fluid analysis, comprising glucose and protein level, cell counts, gram stain, and microbial cultures, was negative. Further investigations included an electroencephalography study that showed low voltage and mild generalized slowing. Echocardiography was normal. A chest radiograph and an ophthalmologic examination were both unremarkable.

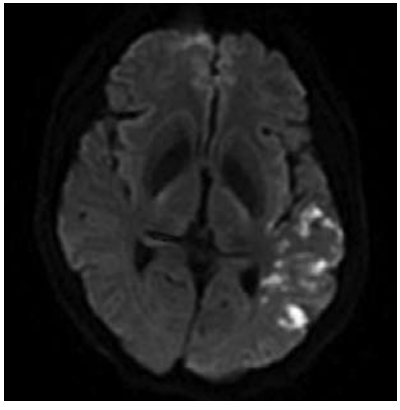
At that point the differential diagnosis included ischemic stroke, cerebritis or vasculitis. Brain magnetic resonance imaging revealed acute left middle cerebral artery infarcts with significant periventricular white matter changes [Figure]. Other changes compatible with chronic ischemia were seen in the white matter of the right hemisphere. In order to establish the diagnosis, further laboratory evaluation revealed antinuclear antibody titer > 1:500 and anti-double stranded DNA antibodies of 0.026 units. Anti-Smith, -Ro, and -La antibodies were negative. C3 and C4 levels were normal. Positive immunoglobulin G (98 GPL U/ml) anticardiolipin antibodies were observed. Lupus anticoagulant test demonstrated prolonged clotting time that was not corrected after mixing.

The diagnosis of SLE with secondary antiphospholipd antibody syndrome was confirmed and treatment with warfarin and hydroxychloroquine was initiated. The patient's confusional state significantly improved, and she was referred to a rehabilitation center. In a follow-up visit 3 months after her discharge the patient was without neurological deficits.

COMMENT

Our patient presented with acute confusional state. She was diagnosed with SLE based on the following findings: inflammatory arthritis, thrombocytopenia, positive test for antinuclear and dsDNA antibodies. In addition she was diagnosed with secondary antiphospholipid syndrome due to the presence of aCL, positive lupus anticoagulant test, throm-

aCL = anticardiolipin antibodies



Coronal MRI view of the patient's brain showing extensive ischemic stroke in the territory of the left middle cerebral artery

bocytopenia and clinical/radiographic evidence for acute thrombotic event.

Neurological syndromes in SLE patients are best classified according to the nature of the symptoms. Diffuse symptoms such as confusion, seizures, coma and psychosis are usually secondary to central nervous system lupus. These manifestations appear to be primarily caused by autoantibodies directed to neuronal cells or their products (e.g., cerebritis). The autoantibodies are hypothesized to affect neuronal function in a generalized manner. Increased levels of cytokines may also contribute. Focal symptoms such as tremor, hemiplegia or blindness are most likely related to intravascular occlusion. Atherosclerosis and antiphospholipid syndrome are the main causes. Other, less common reasons for neurological deficits in patients with SLE are brain vasculitis, cardiac emboli, infection, and adverse effects of steroids.

Our case is unique since the patient presented with diffuse symptoms that were attributed to localized blood flow occlusion. Thrombotic blood flow occlusion and the resulting stroke are very challenging to diagnose because lupus cerebritis might appear identical. The diagnosis of cerebritis remains difficult and no single imaging modality can accurately diagnose it. CT scan has low sensitivity for this entity while MRI is not specific, making these diagnostic tools impractical to differentiate between SLE-derived pathologies and non-SLE-related pathologies [2]. Demonstrating this statement, the patient presented here had a normal CT scan parallel to a pathological MRI scan.

Our patient presented with ischemic stroke 4 days after the influenza vaccination. The association between influenza vaccine and the patient's symptoms is intriguing. Abu-Shakra et al. [3] studied 24 patients with SLE who received an influenza vaccine, after which 25% of them developed aCL. A possible mechanism underlying the generation of these antibodies is molecular mimicry [4,5]. aCL antibodies were not documented in our patient prior to the admission. Whether the existence of these antibodies in our patient was associated with the vaccine and whether they actually caused the stroke is still a matter of debate.

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