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.

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 10⁹/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. Positive immunoglobulin G (98 GPL U/ml) anticardiolipin antibodies were observed. Lupus anticoagulant test demonstrated prolonged clotting time that was not corrected after mixing.

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 antiphospholipid 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-
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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References

Capsule
A gene for gamma-globin repression may treat anemias

Gamma-globin, a constituent of fetal hemoglobin, is normally expressed during fetal development. After birth, fetal hemoglobin expression is down-regulated when expression of the adult variant, γ-globin, rises. Reliance of the adult on γ-globin is not a problem, unless genetic defects disrupt the structure or function of γ-globin, as is the case with some thalassemias and with sickle cell anemia. In such cases, the fetal variant, γ-globin, could potentially function as a replacement, except the γ-globin gene has usually been turned off by the process of globin gene switching. Sankaran et al. show that the BCL11A gene, which encodes a putative transcription factor implicated in globin gene control, seems to function as a repressor of γ-globin gene expression. Use of small RNAs to knock down BCL11A expression in cultured erythroid cells resulted in increased γ-globin expression. Thus, BCL11A represents a target for interventions to treat sickle cell anemia and some thalassemias.

"It is not how old you are, but how you are old"

Jules Renard (1864-1910), French writer