

Systemic lupus erythematosus presenting with pseudotumor cerebri: a rare association

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We describe a 13-year-old systemic lupus erythematosus (SLE) patient who presented with severe headache. The diagnosis of pseudotumor cerebri (PTC) was confirmed by an increased intracranial pressure and normal neuroimaging studies of the brain, including magnetic resonance (MR) venography. She later developed a Coombs positive anemia, lymphopenia, positive tests for antinuclear antibody (ANA) and anti-dsDNA and a migratory polyarthritis confirming the diagnosis of SLE. IgM type anticardiolipin antibodies were positive in low titer. Since she did not have a demonstrable thromboembolic phenomenon in neuroimaging studies, a diagnosis of antiphospholipid antibody syndrome could not be made and anticoagulant treatment was not given. Treatment with pulse IV methylprednisolone followed by oral treatment along with azathioprine produced a rapid and dramatic resolution of the clinical symptoms. PTC may also be a neurological manifestation of childhood SLE and should be considered in the differential diagnosis. We suggest that pulse steroids and azathioprine is an effective treatment for this feature.

Key words: pseudotumor cerebri, idiopathic intracranial hypertension, systemic lupus erythematosus, corticosteroids, azathioprine, anticardiolipin antibodies.

Systemic lupus erythematosus (SLE) is a disease that may involve different organ systems and manifest a large variety of clinical syndromes. Neuropsychiatric involvement in SLE may range from subtle cognitive or behavioral disorders to coma and death¹. Pseudotumor cerebri (PTC), also known as idiopathic intracranial hypertension (IIH), is a syndrome characterized by the occurrence of raised intracranial pressure in the absence of a mass lesion, hydrocephalus, focal structural abnormalities and biochemical or cytological abnormalities, in alert and oriented patients^{2,3}. PTC is included among the rare neuropsychiatric manifestations of SLE and may present as an unremitting headache^{1,3}. Since the first case of Bettman et al.⁴, there have been sporadic reports of concomitant SLE and PTC in adults and, more rarely, in children⁵⁻⁷.

Here, we describe a 13-year-old girl presenting with PTC as a first manifestation of SLE who showed a dramatic response to pulse steroid treatment and azathioprine.

Case Report

A 13-year-old girl was admitted with a two-month history of headache, fever and malaise. She had no history of preceding drug therapy. She did not describe vomiting, diplopia, or blurred vision. Body temperature was 38.3°C. Her weight was 53 kg, within 50 to 75% of normal. On eye examination, she had visual acuity of 20/20 in both eyes and no afferent pupillary defect. Funduscopic examination revealed bilateral papilledema. The neurologic and physical examinations were otherwise normal. Fluorescein angiography showed increased hyperfluorescence extended beyond the disc margins and confirmed optic disc edema. Laboratory examinations on admission revealed a mild normocytic, hypochromic anemia with a hemoglobin of 9.6 g/dl, mean corpuscular hemoglobin of 24.8 pg, reticulocyte count of 1.9% and ferritin of 117 ng/ml. Direct Coombs test was positive. White blood cell (WBC) count was 3,634 cells/mm³ with 1,360 lymphocytes/mm³ and the platelet count

was 160,000/mm³. Urinalysis was normal. Erythrocyte sedimentation rate was 44 mm/hr. Protein electrophoresis revealed an elevated gammaglobulin fraction of 30.7%. Levels of complement components C3 and C4 were within normal limits. Prothrombin time and activated partial thromboplastin time results were normal. Antinuclear antibody (ANA) titer was 1:40 (speckled pattern) and anti-ds DNA antibody was 44.0 IU/ml (normal, <5). Anti-Sm and anti-RNP antibodies were negative. IgM anticardiolipin antibodies (aCL-ab) were low positive at 17 MPL U/ml (normal, <10) and IgG aCL-ab were negative. Lupus anticoagulants were also negative. Serum cortisol, parathyroid hormone, thyroid-stimulating hormone (TSH), and free T3 and T4 levels were normal.

Contrast enhanced brain computerized tomography (CT), magnetic resonance imaging (MRI), and MR venography were normal with no evidence of cerebral venous thrombosis, mass lesion, or obstruction of the ventricles. A lumbar puncture showed an opening pressure of 270 mm H₂O, glucose concentration of 42 mg/dl, protein concentration of 25 mg/dl and five red blood cells/mm³.

After admission, migratory arthralgia in the knees, wrists and proximal interphalangeal joints were reported. On the fifth day of hospitalization, fusiform swelling and tenderness in the 3rd and 4th proximal interphalangeal (PIP) joints of the right hand, and mild swelling and warmth of the left wrist were noted consecutively. X-ray examination revealed only soft tissue swelling in the relevant joints.

Three pulses of intravenous methylprednisolone (1 g each dose) were given on three consecutive days with a definite diagnosis of SLE presenting PTC as a neurological manifestation. This was followed by oral prednisolone combined with azathioprine (75 mg/d) treatments. Low-dose aspirin treatment was added as a prophylactic regimen. All of the complaints resolved in the first week and papilledema had completely disappeared in the third week of the therapy. Sedimentation rate and anti-ds DNA levels returned to normal after the third week. After one month of high-dose treatment, steroid dose was tapered. At her last follow-up, three months after diagnosis, she was in clinical remission with normal laboratory values of complete blood count, sedimentation rate, ANA, and anti-dsDNA.

Discussion

Our patient fulfilled the modified Dandy criteria² for the diagnosis of PTC with symptoms and signs of increased intracranial pressure (headache and bilateral papilledema); no localized findings on neurological examination; normal neurodiagnostic studies (brain CT, MRI, MR venography) with no evidence of venous obstructive disease; increased intracranial pressure measured by lumbar puncture (270 mm H₂O); normal chemical and hematological compositions of cerebrospinal fluid (CSF); and no abnormality in consciousness level (awake and alert patient).

Case series have reported an association between PTC and a variety of medical conditions, which include endocrinological abnormalities such as hypo- and hyperthyroidism, Cushing's syndrome, and hypoparathyroidism; severe anemia; use of some medications such as vitamin A, antibiotics, oral contraceptives, steroids and indomethacin; and pregnancy⁸⁻¹⁰. ICH in postpubertal children has similar characteristics to the disease in adults, which shows a strong relation to obesity and female sex^{3,8}. Our patient did not have any of these associations that might have predisposed her to PTC, apart from female sex.

According to the revised American College of Rheumatology (ACR) criteria¹¹, this patient was diagnosed with SLE with her arthritis, lymphopenia (<1500 lymphocytes/mm³), Coombs positive anemia, and positive results for ANA and anti-dsDNA. PTC and its clinical symptom, headache, were regarded as central nervous system (CNS) involvement of SLE in the presented case. Up to date, approximately 25 adults and children manifesting PTC in association with SLE have been reported^{1,4-7,12,13}. There have been only a few reported pediatric cases in whom PTC was the initial presenting sign of SLE^{7,14}, as in our patient.

The pathogenetic mechanism of PTC in SLE is not yet clear. Immune-mediated injury within the arachnoid villi and the resultant decrease in CSF absorption and/or thrombotic obliteration of cerebral arteriolar and venous systems due to a hypercoagulable state are among the most probable mechanisms^{5,13,15}. It has been reported that 58% of patients with concomitant PTC and SLE had either recurrent thromboembolic events or a high aCL-ab titer.⁵ aCL-ab, which

are regarded as one of the important causes of recurrent venous and arterial thromboses, can be frequently detected in patients with SLE¹⁶ and also in 8.1 to 42.8% of patients with IICH without SLE¹⁷. However, 3%-5% of healthy people may also have circulating low-titer antiphospholipid antibodies¹⁸. Our patient had low-titer IgM type aCL-ab on admission. IgG type antibodies and lupus anticoagulant were negative. Antiphospholipid antibody syndrome is characterized by persistent, moderate, or high titer IgG or IgM aCL-ab, lupus anticoagulant, or both. Transient or low-titer antibodies are inconclusive for diagnosis or treatment¹⁹. Moreover, she did not have an overt thromboembolic phenomenon. Hence, a diagnosis of antiphospholipid antibody syndrome could not be made in this patient and anticoagulant treatment was not given. The mild elevation of the antiphospholipid antibodies in our patient was regarded to be due to her disease and it might have been associated with PTC. Only low-dose aspirin prophylaxis was started as suggested in the literature²⁰. In our patient, PTC probably was not due to cerebral venous thrombosis given the normal neuroimaging studies (MRI and MR venography) and the nonsignificant rise in aCL-ab levels. Immune-mediated injury of CSF outflow may be a more probable cause of increased intracranial pressure (ICP). Nevertheless, undetected cerebral venous microthrombosis remains a mechanism that could not be ruled out definitely without cerebral angiography.

High-dose oral corticosteroids have been the most widely used treatment modality for SLE-associated PTC^{5,6,12,13,15}. Although most cases showed a good response to this treatment, recurrent PTC^{12,13,15} and a more severe course of SLE⁵ have been reported in patients with concomitant SLE and PTC. Immunosuppressive combination regimens may result in a more favorable outcome in these cases. Pulse steroid treatment has not been reported previously in SLE-associated PTC. We suggest that pulse steroid and azathioprine is also an effective treatment regimen for SLE-associated PTC.

In conclusion, severe unremitting headache may be the first manifestation of PTC associated with SLE in children. An extensive workup for prothrombotic factors and angiographic studies should be performed to better delineate the pathogenesis of this association.

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