Extrapontine Myelinolysis in a Patient with Systemic Lupus Erythematosus: A Case Report

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Abstract: Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in systemic lupus erythematosus (SLE) is rare and related pathologic changes in brain images have not been reported. We report the case of a 49-year-old woman with SLE who developed extrapontine myelinolysis (EPM) following gradual correction of marked hyponatremia caused by SIADH. EPM was caused by the hyponatremia, which resulted in cerebral hypoxia and brain swelling. SIADH was most likely induced by the occult vasculitis of SLE. After partial correction of hyponatremia, she regained consciousness, but gradually developed parkinsonism including rigidity, bradykinesia, and tremors 1 week later. Magnetic resonance imaging revealed bilateral symmetrical brain lesions at the putamen, globus pallidus, and part of the thalamus. These symptoms improved gradually after administration of levodopa. Mild jerky tremors of both hands persisted 4 months later. The EPM lesions differ from those observed in central pontine myelinolysis (CPM), which is immediately induced by acute correction of hyponatremia. Therefore, hyponatremia in lupus-related SIADH should be carefully corrected to prevent CPM or EPM.

Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) has rarely been described in patients with systemic lupus erythematosus (SLE). Moreover, extrapontine myelinolysis (EPM) caused by hyponatremia secondary to SIADH in SLE has not been reported. The clinical symptoms of EPM may include ataxia, cogwheel rigidity, gait disturbance, and tremor. Herein, we describe a patient with SLE who developed EPM following marked hyponatremia caused by SIADH.

Case Report

A 49-year-old female was admitted to our hospital on January 19, 2001, with a fever and skin rash. The patient had been in good health until September 26, 1998, when she presented with a fever and myalgias. Immunologic evaluation revealed antinuclear antibodies (ANA) at a titer of 1:12,80 with a speckled pattern, and anti-ribonucleoprotein antibodies (anti-RNP) at a level of 56.8 U/mL. A butterfly rash affecting the face was also noted, but she did not meet the criteria of the American College of Rheumatology for SLE. Therefore, unclassified connective tissue disease was diagnosed.

On this admission, oral body temperature was 39.7°C, and multiple patches of skin rash covered the trunk and the face. Laboratory data revealed hemoglobin 10.9 g/dL (normal, 12–16 g/dL), leukocyte count of 5,800/μL (3,500–11,000/μL), total lymphocyte count 406/μL, serum aspartate aminotransaminase 85 U/L (0–34 U/L), alanine aminotransaminase 33 U/L (0–36 U/L), albumin 2.6 g/dL (3.5–5.5 g/dL), globulin 2.2 g/dL (2.8–4.5 g/dL), creatinine (Cr) 0.6 mg/dL (0.4–1.4 mg/dL), sodium (Na) 132 mEq/L (134–148 mEq/L), and potassium (K) 3.3 mEq/L (3.0–4.8 mEq/L). Total urine protein was 0.9 g/day, and anti-double stranded DNA (anti-ds-DNA) antibody was 12 IU/mL (< 40 IU/mL). Chest roentgenography revealed mild left side pleural effusion. Thus, our patient met the criteria for SLE: malar rash, serositis (pleural effusion), renal disorder (proteinuria > 0.5 g/day), twice lymphopenia, and positive ANA [1].

Postprandial vomiting occurred after a meal on January 20. Oral metoclopramide 4 mg three times daily was administered, but postprandial vomiting did not improve.

Thus intravenous (IV) metoclopramide 10 mg every 6 hours was given starting on January 22. Skin biopsy of the facial rash revealed poikilodermatous dermatitis. Metoclopramide was discontinued due to subsidence of vomiting on January 23. However, consciousness disturbance occurred on the same day with a score of E3V2M5 on the Glasgow coma scale (GCS). Neither decreased skin turgor nor pitting edema was noted. Serum biochemical studies revealed serum Na 102 mEq/L and K 1.7 mEq/L. Plasma osmolality was 201 mosmol/kgH$_2$O (normal, 275–295 mosmol/kgH$_2$O) with a simultaneous urine osmolality of 276 mosmol/kgH$_2$O (50–1,400 mosmol/kgH$_2$O). Urine Na was 38 mEq/L (40–220 mEq/L) and Cr was 30.8 mg/dL (800–1,200 mg/dL).

Brain computerized tomography scan displayed no abnormal findings. Ceftizoxime 1.0 g every 12 hours was administered IV due to suspicion of sepsis. Hydrocortisone 100 mg every 6 hours was given for possible central nervous system (CNS) lupus. An IV saline infusion of 3% NaCl 513 mEq/L with KCl at 25 mL/hour for 3 hours was given. Later, 2,000 mL of 0.9% NaCl with KCl daily was administered continuously. The patient regained clear consciousness (GCS: E4V5M6) on January 24. Hydrocortisone was then changed to oral prednisolone 50 mg daily. On January 25, serum Na was 122 mEq/L and serum K was 3.2 mEq/L.

The characteristic features of SIADH are hyponatremia and hypo-osmolar serum with clinical euvolemia and absence of edema, failure of the urine to be appropriately diluted in the presence of hyponatremia, and continuing excretion of sodium in the urine at a concentration greater than 20 mEq/L [2]. Therefore, SIADH was diagnosed in our patient according to her clinical signs and laboratory data.

On February 1, the patient presented symptoms suggestive of extrapyramidal syndrome including expressionless facial features, cogwheel rigidity of bilateral arms, resting tremor of limbs, tongue tremor, and muffled voice.

Over-shooting in finger-nose-finger test and a short-step gait were also noted. Anti-cardiolipin antibody was negative for the immunoglobulin G (IgG) or IgM class, activated partial thromboplastin time (APTT) was 29.0 seconds (normal control, 30.5 sec), and platelet count was 263 x 10^3/μL (150–400 x 10^3/μL). Acute urine retention occurred on the same day and a Foley catheter was placed. On February 8, urodynamic study revealed non-reflexing sphincter, low urethral closing pressure, and complete urinary retention.

Under the impression of SLE complicated with extrapyramidal syndrome, magnetic resonance (MR) imaging was performed on February 21. Symmetrical high signal intensity was noted at bilateral putamina, the head of the caudate nuclei, and part of the bilateral thalami on T2-weighted images (Fig. 1A). However, no abnormal signal intensity was found at the pons (Fig. 1B). Therefore, levodopa 400 mg, trihexyphenidyl-HCl 2 mg, and prednisolone 15 mg daily were given orally. Afterwards, the symptoms improved gradually. A few days before discharge, the Foley catheter was removed. The patient was discharged on March 3, 2001, but required intermittent urine catheterization at home for another 2 to 3 weeks.

At her outpatient department visit on April 6, 2001, she was prescribed prednisolone 15 mg, levodopa 100 mg, and hydroxychloroquine 100 mg daily. Presynaptic dopamine
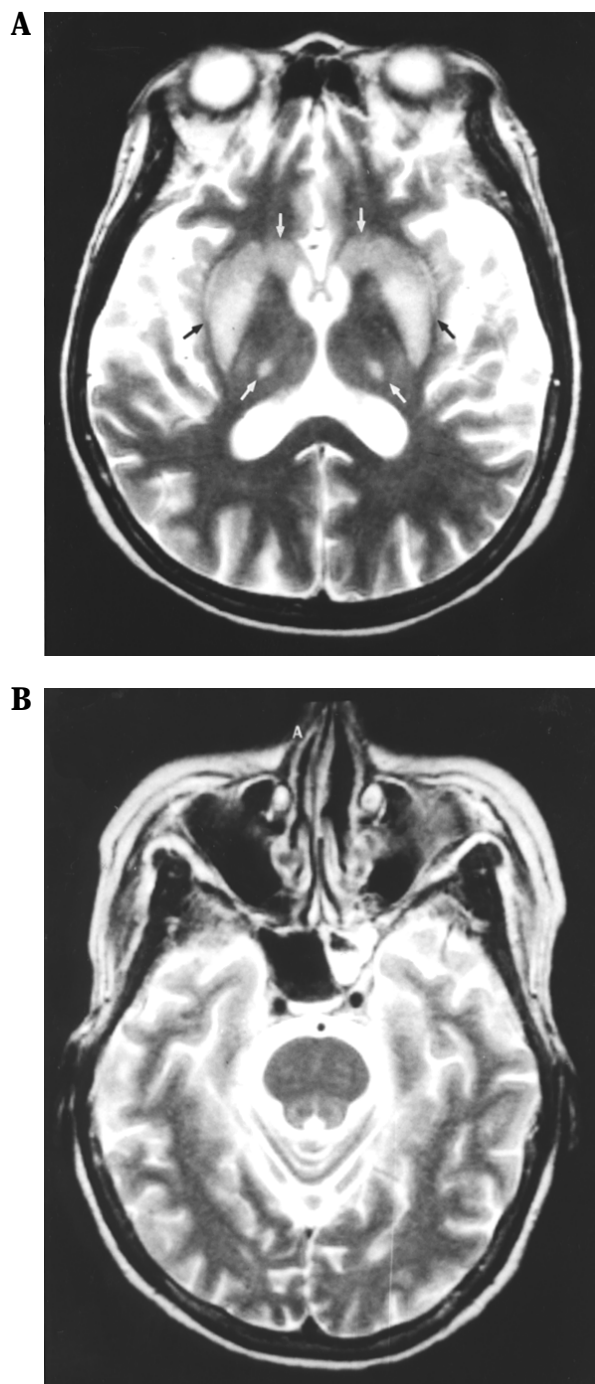
Fig. 1. *T2-weighted brain magnetic resonance image A) at the level of the basal ganglion reveals symmetrical high signal intensity at the bilateral putamina, head of the caudate nuclei, and part of the bilateral thalami (arrows), and B) at the level of the pons shows no abnormal signal intensity.*

transporter was intact as indicated by the normal [99mTc] TRODAT-1 brain scan (Fig. 2) on June 19. At the recall visit on July 27, 2001, the patient had only mild tongue tremor and jerky tremor of hands. Urine routine and anti-ds-DNA antibody were within normal limits. The condition of the patient
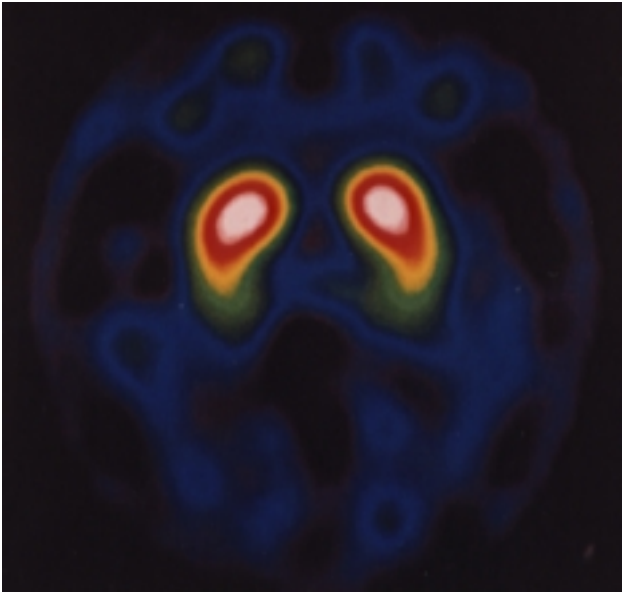
Fig. 2. *[99mTc] TRODAT-1 single photon emission computerized tomography (SPECT) of the brain shows normal striatal uptake bilaterally.*

appeared almost normal at the outpatient department visit on September 28, 2001.

Discussion

Our patient presented with hyponatremia and neurologic abnormality. Plasma osmolality was decreased, while serum glucose and total protein were within the normal range, so pseudohyponatremia could be excluded. There was no evidence of edema, heart failure, or nephrotic syndrome, so hypervolemic hyponatremia was not likely. Vomiting was noted, but there was no massive fluid loss under continuous IV fluid supplementation and no signs of dehydration. Hence, hypovolemic hyponatremia could also be ruled out. Furthermore, if vomiting had been the major cause of sodium loss, the urine sodium concentration would have been less than 20 mEq/L, but in this patient, it was 38 mEq/L. So, vomiting was not the leading cause of hyponatremia, though the potential additive effect of vomiting on hyponatremia should be considered. Thus, normovolemic hyponatremia was most probable. Since urine osmolality was higher than 100 mosm/kg, the cause of hyponatremia was compatible with SIADH [3].

SIADH has been infrequently described in patients with SLE [4]. The pathogenetic mechanisms of inappropriate ADH secretion in such patients are not well

delineated. Despite the negative findings on MR imaging of the pituitary region in our patient (Fig. 1), increased ADH originating from clinically undetectable SLE-induced CNS disease may have been responsible for the decreased serum sodium concentrations [4]. In our patient, there were no major causes of SIADH such as pulmonary disorders, drugs, or major surgery. It is known that severe vomiting induces hypovolemia, which stimulates ADH secretion. However, our patient was normovolemic when consciousness disturbance occurred, so vomiting was not the main cause of SIADH. Moreover, nausea and vomiting are also symptoms of SIADH. It is thus most probable that she had SIADH in association with SLE.

The patient regained consciousness after the serum sodium concentration was increased from 102 to 122 mEq/L within 2 days. Therefore, the consciousness disturbance was attributed to hyponatremia. Following hyponatremia, brain damage may result from brain swelling and increased intracranial pressure, which leads to a decline in cerebral blood flow. Cerebral hypoxia may in turn elicit lesions confined to extrapontine areas, so-called EPM, including the basal ganglia, thalami, cerebral peduncles, and subcortical areas. On the other hand, brain damage after rapid correction of hyponatremia is due to osmotic injury to vascular endothelial cells resulting in a release of myelinotoxic factors or vasogenic edema. This type of myelinolysis usually occurs at the center of the pons, and is diagnosed as central pontine myelinolysis (CPM) [5]. Thus, EPM does not relate to therapy for hyponatremia, and CPM may follow after rapid correction of hyponatremia [6]. The risk of CPM appears to be greatest when the rate of correction is greater than 15 mEq/L/day [7]. Our patient received IV saline infusion at 14.5 mEq/L/day, which is generally acceptable. Moreover, the MR imaging displayed abnormalities only over extrapontine areas (Fig. 1). Therefore, EPM was most probably related to increasing hyponatremia for more than 3 days.

Possible pathologic mechanisms of EPM are as follows. Electrolytes move out of brain cells and into the extracellular space relatively quickly; if hyponatremia persists, other organic osmolytes may enter the extracellular space to help make the brain more iso-osmolar with respect to serum [8]. When the outward movement of these cerebral organic osmolytes is complete, after approximately 7 days, the brain becomes particularly vulnerable to the osmotic demyelination syndrome. The duration of EPM onset following hyponatremia in the patient in this study (around 7 days) is compatible with that reported [8]. Demyelination is an active process, the details of which are just starting to be understood. Activated glial and inflammatory cells participate in the breakdown of myelin

[8]. In a previous investigation, a child with EPM was successfully treated with dopamine [9]. Hence, these authors speculated that extrapontine demyelination of nerve fibers containing dopamine receptors may be involved in the pathogenesis of EPM.

Clinical symptoms of EPM include akinesis, ataxia, catatonia, choreoathetosis, cogwheel rigidity, disorientation, dystonia, extrapyramidal symptoms, emotional lability, gait disturbance, movement disorders, parkinsonism, and tremor [7]. Similar symptoms were displayed by our patient. Furthermore, these symptoms are clearly distinct from CPM. The clinical symptoms of EPM are caused by demyelination of central structures integral to the function of the striatonigral negative feedback loop or its inhibitory autoreceptors, causing elevated concentrations of precursors of dopamine and 5-hydroxytryptophan in the cerebrospinal fluid. This process provides the therapeutic rationale for the use of dopaminergic compounds in the treatment of EPM. Most patients improve markedly within a few days of initiating such treatment [10].

MR image appearances are often unhelpful for diagnosing CNS vasculitis, but may reveal the presence of periventricular white matter lesions, which are probably vascular in origin [11]. T2-weighted MR imaging at the level of the basal ganglion did not show this finding in our patient (Fig. 1). Thus, the probability of EPM directly related to CNS vasculitis (possibly indirectly through hyponatremia) was low. Other secondary parkinsonism could be excluded since the patient had never been exposed to carbon monoxide. The parkinson-like symptoms could not have arisen from lupus itself because, firstly, the symptoms improved with a small increase in the dose of prednisolone, secondly, mild tongue tremor associated with jerky tremor persisted for 4 months, and thirdly, [99mTc] TRODAT-1 brain single photon emission computerized tomography (SPECT) was normal (Fig. 2), indicating the absence of dopamine transporter dysfunction in the striatum. Moreover, this patient suffered from acute urine retention with parkinson-like symptoms. The cause of uncoordinated urinary bladder might have been autonomic nervous system dysfunction resulting from thalamo-hypothalamus involvement, which was compatible with the lesions seen on MR imaging. In contrast, acute urine retention does not occur in patients with CNS lupus with parkinson-like symptoms [12]. Thus, the neurologic disorders observed in our patient were mostly due to EPM.

In summary, in an SLE patient with associated SIADH, urine retention with parkinson-like and imbalance symptoms may occur on prolonged hyponatremia. Therefore, CNS imaging and SIADH studies should be performed in patients with SLE complicated with hyponatremia and parkinsonism.

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