Refractory Syndrome of Inappropriate Secretion of Antidiuretic Hormone in Systemic Lupus Erythematosus–associated Hypophysitis

To the Editor:

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) has been reported in diseases involving the central nervous system (CNS). However, SIADH is rarely reported in patients with systemic lupus erythematosus (SLE)[1,2,3,4,5,6].

We present a case of a 34-year-old woman with a history of SLE who was diagnosed with SLE in 2009 with polyarthritis, leukopenia, oral ulcers, alopecia, photosensitive rash, diffuse proliferative glomerulonephritis, positive antinuclear antibody, and elevated dsDNA. Two months prior to presentation, she was transitioned from mycophenolate mofetil (MMF) 500 mg bid to azathioprine (AZA) 50 mg daily because of the desire to attempt conception. One month later, she started having daily fevers, sore throat, photosensitive rash, tender posterior cervical lymphadenopathy, abdominal pain, and leukopenia. Because of the leukopenia, she was switched from AZA back to MMF. Her worsening leukopenia and elevated inflammatory markers were suggestive of an SLE flare and she was given a higher dose of prednisone.

One month later, she developed abdominal pain, nausea, and vomiting. Her medications included hydroxychloroquine 200 mg every other day, MMF 500 mg qAM and 250 mg qPM, and prednisone 20 mg bid. On examination, she was afebrile and vital signs were stable. Physical examination was unremarkable for oral ulcers, rash, or synovitis. Laboratory studies were notable for white blood cell count of 2.47 k/Ul, platelet 136 k/Ul, sodium 117 mmol/l (compared with 139 mmol/l 1 month prior), blood urea nitrogen 9 mg/dl, creatinine 0.36 mg/dl, aspartate aminotransferase 53 U/l (10–50 U/l), and alanine aminotransferase 99 U/l (10–50 U/l). Urinalysis and sediment were normal. Followup studies showed serum osmolality 245 mOsm/kg (280–296 mOsm/kg), urine osmolality 518 mOsm/kg (150–1150 mOsm/kg), and aldosterone 6.2 ng/dl (< 21 ng/dl), consistent with SIADH.

She was admitted to an intensive care unit for severe hyponatremia because of SIADH and started treatment with hypertonic 3% saline, which raised sodium to 124 mmol/l. However, she was unable to maintain her sodium level above 125 mmol/l on sodium bicarbonate tablets and fluid restriction. Daily infusions of hypertonic saline were required to maintain her serum sodium above 125 mmol/l. Noncontrast computed tomography (CT) brain and CT chest with contrast showed no mass lesion. Further laboratory studies showed a complement factor 3 (C3) of 53 mg/dl and C4 of 12 mg/dl, both were at baseline, and dsDNA of 22 IU (0–25 IU). On hospital Day 5, morning cortisol was 8.3 μg/dl (6.2–19.4 μg/dl). Her sodium continued to fluctuate between 123 mmol/l and 128 mmol/l, requiring hypertonic saline and fludrocortisone. Throughout hospitalization, she did not manifest any clinical evidence of SLE activity. Repeat antiphospholipid antibodies including anticardiolipin antibody, β2 glycoprotein, and lupus anticoagulant were also negative.

Magnetic resonance imaging (MRI) of the brain showed evidence of old parenchymal and subarachnoid hemorrhage, and pituitary stalk enhancement and thickening, suggestive of hypophysitis (Figure 1). Neuromyelitis optica (NMO) was considered unlikely because the anti-NMO immunoglobulin G was negative. Based on the MRI finding and lack of response to other conventional interventions including intravenous (IV) methylprednisolone 24 mg bid, we considered her SIADH with persistent hyponatremia to be a manifestation of an SLE flare. On hospital Day 6, she was switched to IV methylprednisolone 120 mg bid. On hospital Day 7, her sodium increased to 133 mmol/l and remained stable without hypertonic saline. She continued treatment with IV methylprednisolone for a total of 3 days and transitioned to oral prednisone 60 mg daily. On hospital discharge, her sodium was 139 mmol/l (Figure 2). Her leukopenia, thrombocytopenia, and transaminitis also improved. After 2 months of therapy, she was asymptomatic with sodium of 142 mmol/l while receiving 5 mg of oral prednisone.

SIADH is characterized by hyponatremia, renal failure, or presence of adrenal and thyroid insufficiency. It has been rarely described in patients with SLE and the pathogenic mechanism leading to oversecretion of antidiuretic hormone in patients with SLE is not well delineated.

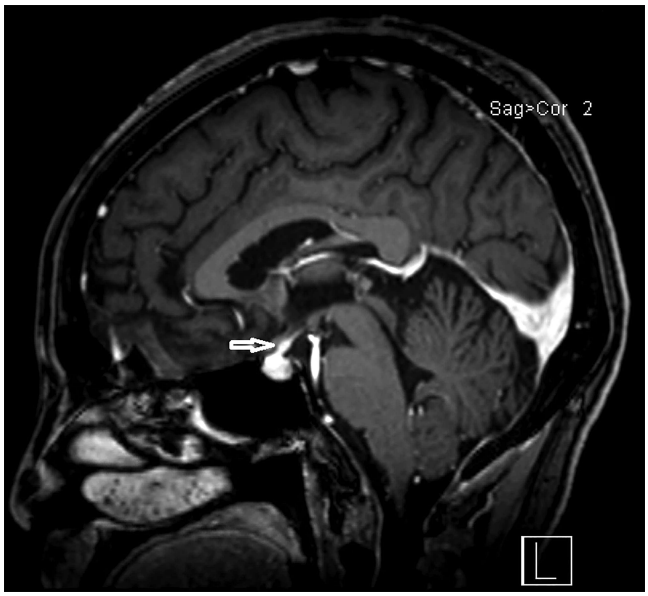

Figure 1. Gadolinium-enhanced magnetic resonance imaging of the brain, sagittal view, showing enhancement and thickening of the pituitary stalk (arrow).

The relationship between CNS involvement of SLE and SIADH has also been controversial. Case reports described SIADH in patients who presented with neuropsychiatric symptoms such as convulsions and psychosis, which were thought to be because of hyponatremia because there was no other evidence of active CNS SLE[1,2,3]. However, patients with active CNS SLE with SIADH have also been reported[4,5,6]. Interestingly, the CNS manifestations disappeared when hyponatremia was corrected and all of the cases required interventions beyond IV fluids.

Our patient presented with hyponatremia without any clinical evidence of SLE activity and required high-dose glucocorticoids to correct the SIADH. The MRI finding of hypophysitis, however, raises the question of whether the SIADH was secondary to SLE or the hypophysitis, because both conditions respond to IV glucocorticoids[7]. Hypophysitis, a rare autoimmune disease, is primarily a condition of pregnancy or puerperium[8,9]. It has been associated with autoimmune diseases such as SLE, but the mechanism of how it may cause SIADH in SLE has not yet been identified. Although SIADH is not a rare medical problem, we need to be mindful of the unusual causes in patients with SLE.

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REFERENCES

1. Ben Hmida M, Bunker D, Baumelou A, Deray G, Bletry O, Jacobs C. Inappropriate secretion of antidiuretic hormone (SIADH) in a patient with systemic lupus erythematosus (SLE): a case report. Clin Nephrol 1992;37:34-5.
2. Elisaf MS, Milionis HJ, Drosos AA. Hyponatremia due to inappropriate secretion of antidiuretic hormone in a patient with

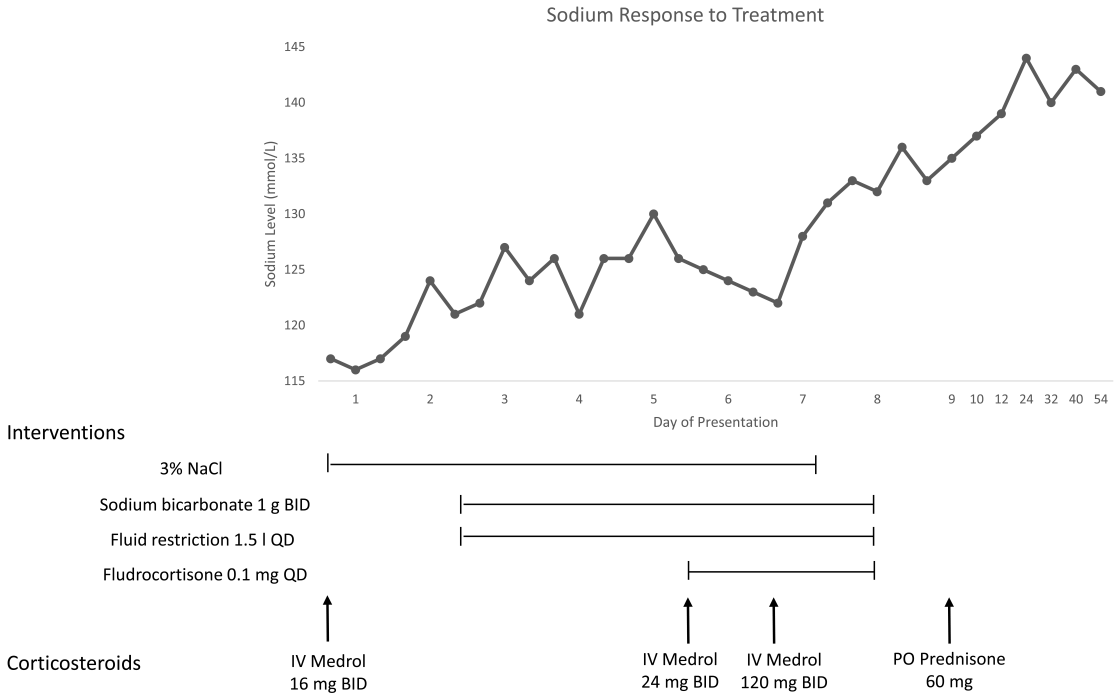

Figure 2. Clinical course of patient showing temporal correlation between sodium level improvement and high-dose methylprednisolone on hospital Day 6. IV: intravenous; Medrol: methylprednisolone.

systemic lupus erythematosus. Clin Exp Rheumatol 1999;17:223-6.

3. Kengne FG, Decaux G. Inappropriate secretion of ADH and central diabetes insipidus are related to antiphospholipid antibodies in SLE—case report and review of the literature. Nephrol Dial Transplant 2006;21:3311-5.
4. Martín Santos JM, Terroba Larumbe MC, Dib B, Armentia Medina A. Systemic lupus erythematosus and the syndrome of inappropriate secretion of antidiuretic hormone [letter]. Clin Exp Rheumatol 1996;14:578-9.
5. Agus B, Nayar S, Patel DJ, McGrath M. Inappropriate secretion of ADH in a patient with systemic lupus erythematosus [letter]. Arthritis Rheum 1983;26:237-8.
6. Mirsattari SM, Power C, Fine A, McGinn GS, Ludwick S, Canvin JM. Neuropsychiatric systemic lupus erythematosus and the syndrome of inappropriate secretion of antidiuretic hormone: a case report with very late onset systemic lupus erythematosus. Br J Rheumatol 1998;37:1132-4.
7. Jennings JE, Sundgren PC, Attwood J, McCune J, Maly P. Value of MRI of the brain in patients with systemic lupus erythematosus and neurologic disturbance. Neuroradiology 2004;46:15-21.
8. Ji JD, Lee SY, Choi SJ, Lee YH, Song GG. Lymphocytic hypophysitis in a patient with systemic lupus erythematosus. Clin Exp Rheumatol 2000;18:78-80.
9. Jennekens FG, Kater L. The central nervous system in systemic lupus erythematosus. Part 1. Clinical syndromes: a literature investigation. Rheumatology 2002;41:605-18.

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