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Autoimmune polyendocrine syndrome type 4 with systemic lupus erythematosus and anti-phospholipid syndrome

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A 50-year-old Chinese woman who experienced intermittent fever with xerostomia and xerophthalmia for 24 years, paroxysmal loss of consciousness for 11 years, aggravation for 1 year was admitted to the Peking University First Hospital in 2019. She started to have intermittent fever (38–39°C) every 2 to 3 months 24 years before first rheumatological evaluation, and the temperature can return to normal without intervention. After she had an episode of epilepsy with abdominal pain 23 years ago, she had severe weight loss, fatigue, weakness, skin pigmentation, and low blood pressure (80/45 mmHg). Laboratory test showed normal potassium, hyponatremia 133 mmol/L (normal range 135–145 mmol/L), low serum cortisol concentration in the early morning 0.56 μg/mL (normal range 4.40–9.20 μg/dL), low 24-h urine-free cortisol 259.6 μg/d (normal range 370.0–639.0 μg/d) and high adreno-cortico-tropic-hormone (ACTH) 128.37 pg/mL (normal range 7.20–63.30 pg/mL). She also had anemia with hemoglobin 77 g/L, thrombocytopenia with platelet 70×10^9/L to 90×10^9/L and dramatically prolonged activated partial thromboplastin time (APTT) 105.1 s (normal range 22.7–31.8 s). Serum creatinine was elevated from 110 to 135 μmol/L (normal range 44–133 μmol/L). Both blood cultures and purified protein derivative test were negative. With prednisolone 30 mg daily along with supportive therapy, the patient's blood pressure was back to normal with no more fever, and serum creatinine decreased to 120 μmol/L. Meanwhile, the patient's fatigue and skin pigmentation were also alleviated, but her armpit and pubic hairs shed. Further autoimmune tests showed positive anti-nuclear antibodies (ANA) 1:1000 and anti-SSA antibody; however, normal serum complements levels. Since she was diagnosed as autoimmune adrenal insufficiency (AI), prednisone replacement therapy (5 mg 8 AM and 5 mg 4 PM each day) has been maintained for more than 20 years.

Eleven years ago, the patient had episodes of loss of consciousness with limb twitch, usually lasting 3 min. Although levetiracetam 1 g per day has been used to control her epilepsy for recent 2 years, the episodes became frequent since last year. Brain magnetic resonance imaging (MRI) showed minor lacunar infarction, and electroencephalogram showed focal epilepsy discharge. Increased dosage of levetiracetam to 1 g twice a day did not help. The neurologist referred her to endocrinologist and rheumatologist for opinions. She denied photosensitivity, oral or genital ulceration, arthralgia or Reynaud phenomenon. Both her medical and family histories were not remarkable.

On physical examination, there were no hyperpigmentation of the skin and mucosa. She had multiple decayed teeth and dry mouth mucosa. Results of completed blood count, biochemical analysis, and endocrine hormones examined are listed in Supplementary Table 1, http://links.lww.com/CM9/A184.

In addition, distal renal tubular acidosis was diagnosed as blood gas analysis pH 7.3, PO_2 98 mmHg, PCO_2 33.4 mmHg, HCO_3^- 17.3 mmol/L, urinary titratable acid decreased to 8.4 mmol/L (normal range >10.5 mmol/L) with normal anion gap. All her thyroid related antibodies, including anti-thyroglobulin, anti-thyroperoxidase, and anti-thyrotropin receptor antibodies were negative. Coomb test was negative. She also had positive ANA, anti-SSA, anti-SSB, and anti-histone antibodies, with negative anti-double strained DNA. Anti-cardiolipin antibody (IgG) was 36.07 U/mL (normal range <12.00 U/mL), anti-β-2-glycoprotein-1 antibody (IgM) was 26.06 U/mL (normal range <20.00 U/mL), and positive lupus anticoagulant 2.0 (normal range 0.8–1.2). Her APTT was 52.8 s (normal range 27.0–37.6 s). She had low complement 3 (C3) level of 0.547 g/L (normal range 0.6–1.5 g/L), and normal C4. Immunoglobulins and IgG4 level were normal. Her Schirmer test was less than 5 mm of both eyes. Lumbar puncture showed elevated cerebrospinal fluid pressure, cell count, protein, cerebrospinal fluid IgG index, with positive oligoclonal banding. Ultrasound revealed normal thyroid. Atrophy of bilateral adrenal glands was found by computed tomography. MRI showed normal pituitary body and some increased signals in the white matter on T2 weighted images.

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The diagnosis of autoimmune polyendocrine syndrome type 4 was established as she had Addison disease (low body temperature, low blood pressure, hyponatremia, low cortisol, and high ACTH), and gonadal failure. After long term prednisone replacement therapy, she had tertiary of secondary AI. No elevated thyroid stimulating hormone to low thyroxine (T4) may be due to autoimmnune hypophysitis. She was also diagnosed as systemic lupus erythematosus (SLE), Sjogren syndrome and anti-phospholipid syndrome. With the therapy of prednisone 60 mg daily, hydroxychloroquine, aspirin, and sodium bicarbonate, she was dramatically improved. During 6 month follow up, she had no symptoms of seizures or loss of consciousness, then stopped anti-epileptics. Prednisone was tapered to 10 mg daily, with hydroxychloroquine, aspirin, and sodium bicarbonate. She remained stable.

We report a case of SLE with type 4 autoimmune poly-endocrine syndrome. Autoimmune poly-endocrine syndromes comprise of several different conditions, mostly with multiple endocrine disorders listed in Supplementary Table 2, http://links.lww.com/CM9/A184. Addison disease is a prominent component of type 1, 2, 4; however, may be with non-endocrine autoimmune disease.[1]

Besides endocrine organs involvement, she also had fever, SICCA symptom, low platelet count, renal tubular acidosis, and chronic progress renal disease without glomerulonephritis. Together with positive ANA and anti-SSA/SSB antibody, she was diagnosed as primary Sjogren syndrome by fulfilling 2016 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria[2] in her first phase of disease.

After the patient had refractory epilepsy, the laboratory tests and imaging was re-evaluated. Then the diagnosis of SLE was established by fulfilling 2019 EULAR/ACR Classification Criteria (positive ANA, fever, thrombocytopenia, seizure, positive anti-phospholipid antibodies, and low C3).[3] In new classification system, positive ANA >1:80 is an entry criterion, and inclusion of fever assists with the classification of early SLE. The structure and weighting system were designed to reflect current thinking about SLE especially in neuropsychiatric manifestations.

Although she had no clinical manifestations of thrombosis or pregnancy complications, she satisfied non-criteria manifestations of anti-phospholipid syndrome reviewed by 14th International Congress on Anti-phospholipid Antibodies Technical Task Force Report.[4]

AI is her major severe clinical manifestations. At onset, she was presented as Addison disease, usually resulting from autoimmune adrenalitis in about 80% to 90% of patients. Although clinical features of SLE are heterogeneous, AI secondary to SLE is rare, with only a few reported cases until now.[5] Common autoimmune mechanisms or vasculitis may provoke AI in SLE patients.

Anti-phospholipid syndrome is an autoimmune disease characterized by presence of anti-phospholipid antibodies and recurrent thrombosis or fetal losses. Endocrine abnormalities involving adrenal, thyroid, pituitary, ovaries are uncommon. An anti-phospholipid syndrome case with involvement of multiple endocrine glands was never reported. AI was ever reported as the first endocrine manifestation of autoimmune poly-endocrine syndrome. 0.4% of patients with positive anti-phospholipid had AI. The etiology of AI associated with anti-phospholipid syndrome might be explained by thrombosis followed by hemorrhagic infarction of the adrenal gland, being particularly vulnerable to thrombotic events due to a single venous drainage. Cases review disclosed that hemorrhage was the leading cause (38% patients) of AI, followed by infarction, adrenal hematoma, and adrenal atrophy was only in 2% of patients. Mono therapy, mainly steroid, was adopted in 44% patients, and 25% received a combination of steroid and anti-coagulant.

The involvement of central nerve system was probably due to SLE, and/or anti-phospholipid syndrome, nevertheless high dose steroid improved her seizes. Her autoimmune poly-endocrine syndrome is secondary to these connective tissue diseases. Further follow up and research are necessary to decipher the relationship of autoimmunity and endocrine diseases.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Conflicts of interest

None.

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