A Perplexing Presentation of SLE as Adrenal Insufficiency in a Young Male

Sir,

Systemic lupus erythematosus (SLE) is a chronic multifaceted autoimmune inflammatory disease of unknown etiology that can affect all age groups of both sexes, but have a female preponderance in the child-bearing age and can involve virtually any organ. Organ damage in SLE is predominantly mediated by tissue binding auto-antibodies and immune complexes.[1] SLE can be associated with other autoimmune diseases also, of which, adrenal insufficiency (AI) rarely can be the one. The most common cause of primary AI is acquired, mostly because of autoimmune destruction of the glands, whereas in the Indian subcontinent primary AI due to tuberculous adrenalitis is still overweighed. Primary AI can also be associated with other autoimmune diseases or can

be a part of the autoimmune polyglandular syndrome.[2] Its association with SLE has rarely been reported in the literature.[3]

Case Report

A 35-year-old male presented with a 6-month history of anorexia, fatigue, weight loss, multiple joint pain, generalized abdominal pain, and progressive darkening of the face and hands. He denied having fever, vomiting, blood loss, altered bowel habit, oral ulcers, or lump anywhere in the body. He smoked occasionally and was not suffering from any chronic illness. Physical examination was notable for mild pallor and hyper-pigmentation over the face and limbs. The pulse rate was 88 beats/min, temperature 36.7°C, and blood pressure of 102/68 mmHg while he was seated but dropped to 86/60 mmHg after he stood up. Respiratory and cardiovascular examinations were unremarkable. There was no lymphadenopathy and organomegaly on palpation.

Hematology revealed a hemoglobin of 10.3 g/dL, leukocytes of 2,330 cells/μL, and thrombocytes of 184,000/μL. Peripheral blood smear had normocytic normochromic anemia with normal differential counts and adequate thrombocytes. Kidney function tests, liver function tests, and electrolytes were within normal limits. Spot urine examination revealed 4–5 red blood cells/high power field, casts, and 2+ protein. A 24 urinary protein was 312 mg. Serum iron, total iron-binding capacity, ferritin, and vitamin B12 levels were within normal limits. Direct agglutination test and Mantoux test were negative. Bone marrow aspiration and biopsy showed normal hemopoiesis. Hepatitis B, hepatitis C, human immunodeficiency, and Corona virus disease (COVID-19) viral assays were negative. Blood and urine cultures were sterile. Imaging studies of the abdomen, chest, joints, and heart were all negative for potential etiologies. Hyper-pigmentation and weight loss were evaluated for AI. Serum cortisol at 8 am was 1.92 μg/dL (reference range 5–23 μg/dL) and plasma adrenocorticotropic hormone (ACTH) was 85.7 pg/mL (reference range 0–46 pg/mL). ACTH stimulation with intramuscular injection of 30 IU of Acton Prolongatum showed an inadequate peak cortisol level. Thereafter, he was evaluated for autoimmune disease. ANA by immunofluorescence was +++ with speckled pattern on 1:80 and 160 dilution. Immune panel testing for various antibodies showed the presence of Anti-nucleosome (Anti-NCS) antibodies. Thyroid hormones, parathormone, and anterior pituitary hormones were within the normal range. Low baseline cortisol level at 8 and impaired response after ACTH stimulation test favor the diagnosis of primary AI [Table 1]. Light microscopy and immunofluorescence findings of the renal biopsy were consistent with lupus nephritis class III (revised International Society of Nephrology/Renal Pathology Society [ISN/RPS] 2018), National Institute of Health (NIH) activity score of 8/24 and chronicity 3/12. Based on the clinical examination and lab parameters, he was diagnosed as a case of SLE with anti-NCS antibodies and lupus nephritis in the absence of Anti-double stranded DNA (anti-dsDNA) antibodies, presented with AI. He was managed with hydrocortisone, and other supportive measures, and improved clinically. Prednisolone was tapered after a month, and currently, he is on a low-dose steroid with mycophenolate sodium and hydroxychloroquine.

Discussion

SLE is diagnosed by characteristic clinical features and testing of specific antibodies. ANA is most the sensitive diagnostic test for SLE and is positive in >98% of the patients during the illness. The specific tests for SLE are high titer Immunoglobulin G (IgG) antibodies to dsDNA and antibodies to smith antigen. Various antibodies in SLE differ in sensitivity and specificity for the diagnosis of the disease.[1] Apart from the role of anti-dsDNA antibodies, nucleosome-specific antibodies, and nucleosome-anti-NCS antibody immune complex also play a significant role in the pathogenesis and disease progression.[4,5] Anti-NCS antibodies are more sensitive and specific for SLE than the anti-dsDNA antibodies and strongly correlate with renal damage, especially in patients of SLE lacking anti-dsDNA antibodies.[6] However, autoimmune mechanisms in SLE and AI may be common that could explain the possible coexistence.

In recent days, a nucleosome is identified as a major autoantigen in SLE. It is a basic unit of chromatin and plays an important role in antinuclear antibody response in the pathogenesis of SLE. Anti-NCS antibodies are part of a family of autoantibodies directed against histone epitope exposed in chromatin, which have a higher affinity for intact nucleosome; conformational epitope of the conjugation between dsDNA and the core histone.[4]

The prevalence of anti-NCS antibodies in SLE varies in various studies from 16 to 100%.[4,6-8] Studies which had low prevalence were mainly composed of patients of long disease duration on immune suppressive medications or in an inactive state of disease. On the other hand, higher prevalence studies mainly included patients with either active SLE disease or patients were assessed during major organ involvement like nephritis.[4] A meta-analysis showed that anti-NCS antibodies have equal specificity (94.9% vs. 94.2%), but higher sensitivity (59.9% vs. 52.4%) and prognostic value than anti-dsDNA antibodies in the diagnosis of SLE.[9] A few reports described that anti-NCS antibodies are more sensitive and specific for SLE than the anti-dsDNA antibodies and also have a positive correlation with SLE disease activity index (SLEDAI) and with kidney damage.[8,10] Anti-NCS antibodies had a sensitivity of 100% and specificity of 97% for SLE in a study by Simon and colleagues.[8] Apart from this, an inactive SLE patient having anti-NCS antibodies is also prone to develop renal disease flare, so such patients are required to be continued on immunosuppressive medications.

About 50% of cases of primary AI are acquired, mostly due to autoimmune adrenalitis; the other one-half is genetic. Apart from isolated autoimmune adrenalitis, in 60–70% of cases, it could be a part of an autoimmune polyglandular syndrome.

Table 1: Laboratory investigations

Investigation	Result	Reference range
ANA (IFA)	+++ (Speckled pattern)	
Anti-Nucleosome	++	
Anti-dsDNA	Negative	
Anti-Histone	Negative	
Anti-Sm	Negative	
Anti-Ro/La	Negative	
Scl70	Negative	
U1snRNP	Negative	
C3	1 g/L	0.9-1.8 g/L
C4	0.256 g/L	0.1-0.4 g/L
Rheumatoid factor	Negative	
Anti-beta 2 glycoprotein 1	Negative	
Lupus anticoagulant antibodies		
Anti-CCP	1.71 U/Ml	0.4-5.0 U/Ml
S. Cortisol 8.00 am	1.92 µg/dL	5-23 µg/Dl
4.00 pm	1.44 µg/Dl	3-16 µg/dL
Serum ACTH	85.7 pg/mL	0-46 pg/Ml
S. cortisol at 60 min, after 30 IU of Acton Prolongatum IM injection	4.9 µg/dL	At 60 min Serum cortisol >18 µg/dL
S. Aldosterone	<0.97 ng/dL	2.5 ng/dL-39.2 ng/dL
S. Direct Rennin	47.6 Uiu/mL	Upright posture: 4.4-46.1 Uiu/mL Supine posture: 2.8-39.9 Uiu/mL
24 Urinary Protein	312 mg/day	<140 mg/day
Renal Biopsy	LM & IF: Lupus nephritis class III (ISN/RPS 2018) NIH activity score of 8/24 and chronicity 3/12	

ANA (IFA), Antinuclear antibodies (Indirect immunofluorescence assay); Anti-CCP, Anti-citrullinated peptides; ACTH, adrenocorticotropic hormone; LM, Light microscopy; IF, Immunofluorescence; ISN/RPN, International Society of Nephrology/Renal Pathology Society; NIH, National Institute of Health (NIH)

Other autoimmune diseases can also be associated with primary AI coincidently. Primary AI is commonly present with hyper-pigmentation of skin and mucous membrane, weight loss, craving for salts, and abdominal pain. Other nonspecific symptoms reported in AI are fatigue, anorexia, lack of energy, nausea, vomiting, and arthralgia.[2] The proposed explanation for the association of AI with SLE is multifactorial. The AI in SLE is due to the common autoimmune mechanism or as a complication of SLE vasculitis or due to Anti phospholipid antibodies (APLA) in SLE that leads to acute adrenal hemorrhage, hematoma, or adrenal vessels thrombosis.[11-14] As SLE and AI both can present with hyperpigmentation, weight loss, pain abdomen, and anorexia, hence, we evaluated for associated SLE in this newly diagnosed case of AI. It was a perplexing manifestation of SLE, presented in AI with a specific serological profile and biopsy-proven lupus nephritis.

We conclude that SLE rarely presents with AI. The features of AI can be masked in SLE or vice-versa. Hence, a young male presenting with symptoms of AI should be evaluated for SLE as the cause of AI. Our case was interesting because he presented in AI, and was diagnosed to have anti-dsDNA negative SLE with lupus nephritis having anti-NCS antibodies. Anti-NCS antibody positivity might be responsible for organ involvement in SLE, as our patient had lupus nephritis and AI. It is postulated that AI in the case of SLE could have resulted from a common autoimmune mechanism due to nucleosome anti-NCS antibody complex, or SLE vasculitis. It is worth noting that anti-NCS antibodies could be a good tool for sensitivity, specificity, and multiple organ damage in SLE.

Final diagnosis

Anti-dsDNA negative SLE with lupus nephritis having anti-NCS antibodies presented in AI.

Declaration of patient consent

Consent has been obtained from the patient.

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Conflicts of interest

There are no conflicts of interest.

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