



Diagnostic Dilemma of ANA-negative Pediatric Systemic Lupus Erythematosus in a South Asian Female

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ABSTRACT

BACKGROUND: Systemic lupus erythematosus (SLE) is an autoimmune disorder affecting multiple organs with different degrees of severity. SLE is typically diagnosed based on the presence of antinuclear antibodies (ANA) in the serum. However, seronegative SLE is rare and is diagnosed by clinicians when the patient's ANA is negative but fulfills other diagnostic criteria.

CASE REPORT: We report a case of a 15-year-old South Asian female with SLE who had negative antinuclear antibodies yet displayed the typical clinical presentations of photosensitive maculopapular rash, joint pain, alopecia, anemia, and thrombocytopenia. Clinical evaluations in conjunction with lab results were used to establish a diagnosis of ANA-negative SLE.

CONCLUSION: ANA positivity is an entry criterion for SLE; rarely, cases of ANA-negative SLE may present. A typical clinical presentation may help determine the diagnosis in such a scenario. However, still, the physician should rule out immunodeficiency and other systemic illnesses before reaching a diagnosis of ANA-negative pediatric SLE.

KEYWORDS: Systemic lupus erythematosus, antinuclear antibodies, autoimmune, ACR criteria

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Introduction

Pediatric systemic lupus erythematosus (SLE) is a multisystemic autoimmune condition mainly affecting children below the age of 18 years.¹ The incidences of pSLE range from 0.36 and 2.5 per 100 000 children, with a prevalence of 1.89 to 34.1 per 100 000.² Pediatric SLE is an aggressive condition and has increased morbidity and mortality as compared to adult-onset SLE. The most prevalent causes of increased morbidity and mortality are known to be the longer duration of the disease in children and immunosuppressive medication overburden.³ Overall pediatric SLE has a grimmer prognosis, but it has been improved recently and the 10-year survival rate ranges from 80% to 90%.⁴

Anti-nucleosome antibodies (ANA) are associated with various immunological conditions including SLE. The presence of ANA in the serum of a patient with other supporting laboratory values and clinical features favors the diagnosis of SLE. The clinical feature of SLE includes malar rash, fever, malaise, arthralgias, myalgias, headache, anemia, pericarditis, oral ulcers, petechiae, and loss of appetite and weight.⁵ Seronegative SLE is a condition in which the patient's clinical features and laboratory values are consistent with SLE, but serology is negative for ANA. Both seropositive and seronegative SLE presents similarly and the diagnosis of

seronegative SLE is challenging due to the concomitant signs and symptoms with seropositive SLE.

Different diagnostic criteria are being used for the diagnosis of SLE, some require serology positivity while others only rely on clinical features and laboratory values. Other conditions associated with ANA include ANA-associated rheumatic diseases (AARD), such as systemic sclerosis, mixed connective tissue disease, and Sjogren's syndrome, which are characterized by the presence of autoantibodies against nuclear autoantigens and other intracellular autoantigens. Relying solely on ANA as a marker for SLE (or any of the AARDs) increases the risk of underdiagnosing ANA-negative lupus, which can delay diagnosis and treatment. If the patient fulfills the criteria for SLE despite seronegative, the diagnosis should not be delayed.^{6,7} We herein, report a case of a 15-year-old female diagnosed with systemic lupus erythematosus due to its rare occurrence in the pediatric age group.

Case Report

A 15-year-old female patient presented to the outpatient department of tertiary care hospital with an erythematous rash on the face, easy fatigability, and joint pain for 2 months. The rash began over her face and spread to bilateral upper extremities and was photosensitive and pruritic. On further inquiry,



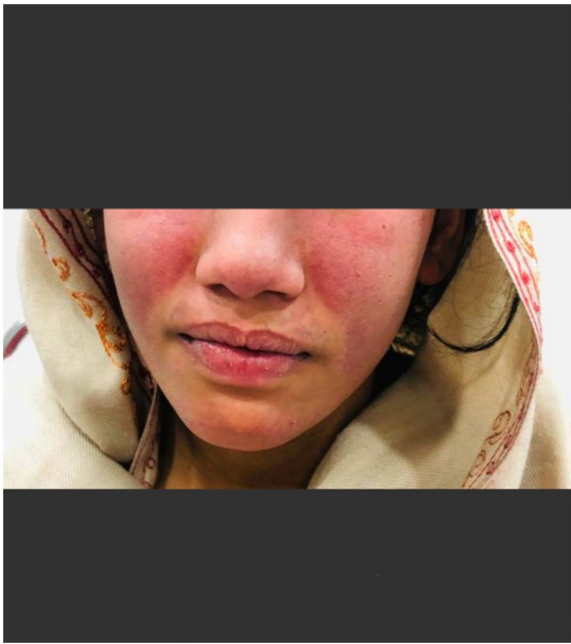


Figure 1. An erythematous rash involving the forehead, nasal bridge, and bilateral cheeks with sparing of nasolabial folds.

the patient also has pain in the small joints of her both hands that are associated with joint stiffness more prominent at night and remained for less than 20 minutes. There was no associated fever, weight loss, and no proximal muscle weakness. The patient was an 8th-grade high school student with no significant past medical history. Family history was unremarkable for malignancies or rheumatologic disorders. She had regular menses with normal flow and has been taking a balanced diet. The patient used oral non-steroid anti-inflammatory drugs (NSAIDs) for joint pain. On examination, the patient was vitally stable with the vital signs of blood pressure of 120/80 mm Hg, a pulse rate of 88 beats per minute, a respiratory rate of 17 breaths, and a temperature of 37°C. There was an erythematous maculopapular malar rash on the face involving the forehead, nasal bridge, and bilateral cheeks with sparing of nasolabial folds (Figure 1).

Palmar erythema and an erythematous violaceous, slightly scaling, densely set confluent papules with sparing of the articular regions were also noted on fingers, dorsum of the hand, and ventral and dorsal surfaces of both forearms (Figure 2).



Figure 2. (A) Palmar Erythema of both hands, (B) erythematous violaceous, slightly scaling, densely set confluent papules with sparing of the articular regions on the dorsum of hands, (C) ventral surface of the forearm, and (D) dorsal surface of the forearm.

Joint examinations revealed mild swelling of the dorsal and palmar aspects of the fingers affecting the metacarpophalangeal joints with sparing the interphalangeal joints. Periungual swelling was observed, and hyperpigmented patches were present on her knee joints with no Gottron's papules. Upon examination there was no lymphadenopathy or visceromegaly. The rest of the systemic examination was unremarkable. Laboratory evaluation revealed normocytic anemia, thrombocytopenia, and elevated erythrocyte sedimentation rate (ESR). Her immunological tests including ANA and other antibodies related to SLE were negative (Table 1).

Peripheral blood smear showed normocytic normochromic anemia and urine analysis was unremarkable for hematuria, pyuria, proteinuria, and/or cellular casts, and her echocardiography revealed preserved left ventricular function with no valvular abnormalities. Skin biopsy was not performed due to lack of affordability. Liver and renal function tests and urinalysis were within normal limits. Chest X-ray and electrocardiography revealed no abnormality. Blood culture was negative for bacterial infection. Ophthalmologic examinations were also normal. Coombs test was negative. The patient was diagnosed with a case of ANA-negative SLE in accordance with ACR criteria 1997.

Table 1. Laboratory evaluation.

INVESTIGATION	RESULT	UNITS	REFERENCE RANGE
White blood cells	8.1	$\times 10^3/\mu\text{L}$	4-11
Hemoglobin	10.7	g/dL	11.5-17.5
HCT	30.4	%	36-54
MCV	84.6	fL	76-96
MCH	33	pg	27-33
Platelet	119	$\times 10^3/\mu\text{L}$	150-450
ESR	67	mm/1st hr	0-20
Blood Urea	18.4	mg/dL	10-50
Total bilirubin	0.42	mg/dL	0.1-1.0
ALT/GTP	32.5	U/L	10-50
Alkaline phosphatase	127	U/L	<187
Ferritin	113	ng/dL	7-140
Creatinine	0.35	mg/dL	0.3-0.9
Calcium	7.3	mg/dL	10.0-10.7
Vitamin D	15	ng/dL	20-40
Glucose	110	mg/dL	90-130
Potassium	4.4	mEq/L	3.4-4.7
Sodium	138	mEq/L	135-145
HDL	48	mg/dL	<45
LDL	78.6	mg/dl	<110
LDH	123	IU/L	105-333
CRP	11.2	mg l-1	0.2-9.8
PT	12.4	seconds	11-13.5
APTT	30	seconds	25-35
INR	0.9	—	0.8-1.1
C3	110	mg/dL	88-201
C4	20	mg/dL	15-45
Anti-Nuclear Antibodies	Negative	—	—
Anti Histone	Negative	—	—
Anti dsDNA	Negative	—	—
Anti ribosome	Negative	—	—
Anti Sm	Negative	—	—
Anti PCNA	Negative	—	—
Rheumatoid factor	Negative	—	—
Anti-phospholipid antibodies	Negative	—	—

(Continued)

Table 1. (Continued)

INVESTIGATION	RESULT	UNITS	REFERENCE RANGE
Anti-platelet autoantibodies	Negative		
CMV antibodies	Negative		
Parvovirus B19 IgM	Negative		
Brucella titre	Negative		
Anti-HIV	Negative	—	—
Anti-HCV	Negative	—	—

Abbreviations: μ L, microliter; ALT/GTP, alanine aminotransferase/glutamic-pyruvic Transaminase; aPTT, Activated Partial Thromboplastin Clotting Time; CMV, cytomegalovirus; CRP, C-reactive protein; dsDNA, double stranded deoxy ribonucleic acid; EBV, Epstein-Barr virus; ESR, erythrocyte sedimentation rate; fL, femtoliter; g/dL, gram/deciliter; HCT, hematocrit; HCV, hepatitis C virus; HDL, high density lipoprotein; HIV, human immunodeficiency virus; INR, international normalized ratio; IU/L, international units per liter; LDL, low density lipoprotein; LDH, lactate dehydrogenase; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; mEq/L, milliequivalents per liter; mg l⁻¹, milligrams per litre; mg/dL, milligram/deciliter; ng/dL, nanograms per deciliter; PCNA, proliferating cell nuclear antigen; pg, picogram; PT, Prothrombin time; Sm, smith; U/L, units per liter.

Patient fulfilled 4 out of 11 characteristics, that is, malar rash, photosensitivity, arthritis and anemia. ACR criteria includes 11 features for diagnosis of SLE, that is, includes malar rash, discoid rash, photosensitivity, oral ulcer, arthritis, serositis, renal disease, neurologic disorder, hematologic disorders (anemia, leukopenia, thrombocytopenia, lymphopenia), immunologic disorder and ANA test positive. Four of the 11 features listed are necessary for a diagnosis.¹¹ She was given a tablet of prednisolone 5 mg two tablets TDS for one-month, topical fluticasone ointment (appropriate 10g) twice daily for one month, a tablet of calcium and vitamin D for one month, a tablet of hydroxychloroquine 200 mg one tablet twice daily, tablet Naproxen 250 mg one tablet twice daily and capsule pantoprazole 40 mg once daily for one morning. At 4 week follow up the patient described marked improvement in the joint pain and photosensitivity the oral steroid therapy was tapered, and topical steroids, naproxen, and pantoprazole were stopped and she was continued with hydroxychloroquine. At 8 weeks the patient's rash decreased in severity and he was continued with hydroxychloroquine for 6 months.

Discussion

Pediatric SLE is one of the most common autoimmune conditions affecting children with the peak incidence at the age of 12 years. The disease incidence before the age of 10 years is rare, and the condition is more common in female children as compared to males. The prognosis of pediatric SLE is not favorable in comparison to adult-onset SLE because of the prolonged course of the disease in children, early involvement of the multi-systems, and the side effects of systemic therapy.⁸

Common laboratory findings in children with SLE include anemia and thrombocytopenia, decreased vitamin D level, and elevated Erythrocyte sedimentation rate (ESR). In addition, autoantibodies such as antinuclear antibodies (ANAs), double-stranded DNA (dsDNA) antibodies, antibodies to the extractable nuclear antigens (ENAs), and antiphospholipid antibodies (aPLs) are expected to present in the serum of children with SLE.⁸

In most series, 100 percent of children with SLE are ANA positive. Occasional cases of "ANA-negative" SLE are described, although the concept is controversial, and an ANA-negative child should be vigorously evaluated for alternative diagnoses.^{8,9} Studies have suggested that a positive ANA may disappear in some SLE patients over time, with sensitivity dropping to 76% and positivity dropping from 98% to 71% in patients with established SLE. ANAs have a sensitivity of 33.6%, while anti-dsDNA has a sensitivity of 57.1%, indicating that a significant portion of SLE cases may be missed based on these markers alone. Sero-negativity in lupus patients may be due to technical failure or entrapment of ANA in circulating immune complexes yet patients exemplify similar clinical presentations to their ANA-positive counterparts.⁹ Additionally, autoantibodies such as anti-dsDNA and anti-Smith (anti-Sm) help to confirm the diagnosis of SLE but are not uniformly present. All these antibodies may also be found in children who do not fulfill the classification criteria for SLE. Some of these children will go on to develop SLE, others will develop other rheumatic diseases, and some will remain asymptomatic.¹⁰

SLE typically presents with a variety of complications, such as vascular, cardiac, nervous system, pulmonary, and renal involvement, as well as positive ANA and or patients with seronegative ANA tests have a higher prevalence of positive Ro factor antibody. However, there were no further systemic symptoms or the presence of these antibodies in our patient. Also, the lack of a biopsy made the diagnosis more challenging, although the patient still exhibited the typical clinical signs of SLE, including photosensitive maculopapular rash, arthralgia, joint pain, and scaly pruritic plaques over limbs. The diagnosis of SLE in our patient was made based on the ACR criteria. Our patient fulfilled 4 of 11 ANA-negative criteria. These include Malar rash, photosensitivity, arthralgia, and hematological evidence of anemia and thrombocytopenia.

Differential diagnosis of pediatric SLE includes infectious causes such as CMV, Brucella and parvovirus B19. These are characterized by disease specific clinical features as well as disease specific antibodies. Other differential diagnosis such as hematological malignancy

Table 2. Reported cases of ANA-negative SLE in the pediatric group.

CITATION	PRESENTATION	IMMUNOLOGY/ HISTOPATHOLOGY I	TREATMENT	OUTCOMES
Caltik et al ¹²	A young boy who developed nephrotic syndrome with acute kidney injury. She was diagnosed with a case of SLE nephritis.	Diffuse proliferative glomerulonephritis, suggesting Class IV B Lupus Nephritis. Full-house pattern, including IgG, IgM, IgA, C3, and C1q depositions. The activity and chronicity index were 12/24 and 1/12. C3 and C4 were low. ANA, antidsDNA pANCA, cANCA were negative.	V MP monthly for 6 mo, dipyridamole (5 mg/kg), and PO CYP (2 mg/kg for 3 mo) followed by PO AZA and PO prednisolone.	Remained in remission during follow-up, 3 y from onset.
Baskin et al ¹³	A young girl presented with recurrent abdominal pain on further workup, she was diagnosed as a case of SLE nephritis.	Class III lupus nephritis with full house staining on immunofluorescence. Presence of tubulovesicular inclusions under electron microscopic examinations. C3 and C4 were within normal range. ANA, anti-dsDNA pANCA, cANCA were negative.	IV-MP and IV CYP monthly	At 12 mo of follow-up, ANA remained negative. However, the patient progressed from CKD3 to 4 (from 60.9 to 17.9 ml/min/1.73m ²) after 17 mo from initial presentation.
Bharati et al ¹⁴	15-y-old boy. Presented with fever for 3 wk, progressive swelling of the body for 2 wk and reduced urine output for 1 wk.	C3 and C4 were both low. ANA was negative. Biopsy was suggestive of proliferative glomerulonephritis with cellular crescents and some interstitial fibrosis tubular atrophy. IgG (3+), IgA (2+), kappa (3+), lambda (3+), C3 (2+) and C1q (2+)	PO prednisolone at a dose of 1 mg/kg/d	ANA positivity after 4 wk from onset.
Kim et al ¹⁵	6-y-old, girl. Presented with interstitial vasculitis and new-onset proteinuria.	Mild mesangial expansion with focal segmental mesangial cell proliferation and segmental collapse were seen. Immunofluorescent staining showed strong IgG deposits, mild IgA, C3 and fibrinogen deposits and minimal C1q deposits. C3 and C4 were within normal range. ANA, antidsDNA pANCA, cANCA were negative.	IV-MP and IV CYP monthly	At 24 mo of follow-up, ANA remained negative. The child was reported to have persistent low-grade proteinuria.

(leukemia, lymphoma) and other autoimmune conditions such as Juvenile idiopathic arthritis (JIA) and juvenile dermatomyositis (JDM) are characterized by specific CBC profile and clinical features such as leukocytosis, positive Anti SM antibodies, antiphospholipid antibodies, and positive Ro factor, grotton's papules and heliotrope rash with progressive muscle weakness. However none of these were present in our patient.

The diagnosis of SLE can be made by combining clinical and laboratory findings but there is no criterion available now for early identification of the disease. ACR published the first, preliminary, criteria for SLE in 1971, which were revised in 1982 and later validated. The second revision from 1997 (ACR-97), although

unvalidated, has been the most widely used criteria set to date. The 1997 American College of Rheumatology (ACR) criteria and its complementary criteria; the 2012 systemic lupus international collaborating clinic (SLICC) criteria are designed for the classification of SLE but not for the diagnosis.¹¹ Children who fulfill the American College of Rheumatology (ACR) criteria, Systemic Lupus International Collaborating Clinics (SLICC) criteria, or 2019 European Alliance of Associations for Rheumatology (EULAR; formerly known as European League Against Rheumatism)/ACR criteria, are considered to have definite SLE.⁸

There are several cases of juvenile seronegative SLE reported previously (Table 2)

It appears that ANA negative SLE is a subgroup of sle that has not received enough attention. Clinicians need to be aware that certain patients may have ANA test results that are consistently negative.

Conclusion

Seronegative pediatric SLE is a rare condition that manifests similarly to seropositive SLE. In the case of ANA-negative SLE, the typical clinical features may serve as diagnostic clues for the disease by the application of the ACR-97 criteria of SLE classification. If the patient fulfills the criteria for SLE despite seronegativity, the diagnosis should not be delayed. Early diagnosis, management, and screening for complications can improve the outcomes of the patient.

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Author's Contributions

Qaisar Ali Khan and Tehmina Khan conceived the idea of the case report. Qaisar Ali Khan was responsible for data collection and acquisition of data. Parsa Abdi, Christopher Farkouh, Michelle Anthony, and Faiza Amatul performed the literature review and wrote the manuscript. Sumaira Iram, Qaisar Ali Khan, and Tehmina Khan reviewed and critically revised the manuscript. All authors have approved the final manuscript.

Informed Consent

Written informed consent was obtained from the patient's father to publish this case report and any accompanying images.

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