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A Rare Case Report on ANA Negative SLE with Lupus Nephritis with B/L Lower Lobe Bronchiectasis

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Abstract
Systemic Lupus Erythromatous (SLE) is an autoimmune disease in which the body's immune system attacks the healthy tissues or organ by mistake and is characterized by various autoantibodies to nuclear and cytoplasmic antigens. It can affect any part/organ (s) of the body and can detiorate their normal functioning. SLE is confirmed by an anti-nuclear antibody (ANA) test. The presence of ANA antibodies is usually the decisive indication of SLE, but sometimes in a few subset of population, ANA negative results yield the presence of SLE, which is the condition in this patient.

Keywords
SLE, ANA negative test, Pyelonephritis, Organ damage, bronchiectasis.

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INTRODUCTION:
Systemic lupus erythematosus (SLE) is a complex disease that is characterized by an autoantibody response to nuclear and cytoplasmic antigens. The autoantibody response is associated with the inflammatory cascades and end-organ damage in the kidney, skin, brain and other organs. Immune-complex deposits of autoantibodies have been implicated as major pathogenic mediators, mainly in the kidney. [1] There are a few types of lupus that just affect the skin – such as discoid lupus erythematosus and subacute cutaneous lupus erythematosus. However, the term 'lupus' is most often used to describe a more severe form of the condition called systemic lupus erythematosus (SLE), which can affect many parts of the body, including the skin, joints and internal organs. [2]
Normal variations (polymorphisms) in many genes can increase the risk of developing SLE, and in most cases multiple genetic factors are thought to be involved in the causative patterns of the disease. In rare cases, SLE is caused by mutations in single genes. Most of the genes associated with SLE are involved in immune system function, and variations in these genes likely affect proper targeting and control of the immune response. A wide variety of environmental factors including viral infections, diet, stress, chemical exposures, and sunlight are also thought to play a role in triggering this complex disorder in various proportions of contributions. Sex hormones can also contribute to the disorder. About 10 percent of SLE cases are thought to be triggered by drug exposure, and more than 80 drugs that may be involved have been identified. In people with SLE, cells that have undergone self-destruction (apoptosis) because they are damaged or no longer needed. Although the relationship of this loss of function to the cause or features of SLE is unclear,

researchers suggest that these dead cells may release substances that cause the immune system to react inappropriately and attack the body's tissues, resulting in the signs and symptoms of SLE. [3] It has been speculated that the development of antinuclear antibodies (ANAs) or anti–double-stranded DNA (anti-dsDNA) antibodies increases the risk of SLE. The presence of rheumatoid factor (RF) correlates with active inflammatory arthritis in SLE. Subacute cutaneous lupus erythematosus, photosensitivity, and leukopenia are all associated with anti-Ro antibodies, and anti-Ro has been observed in patients with SLE who have skin disorders.

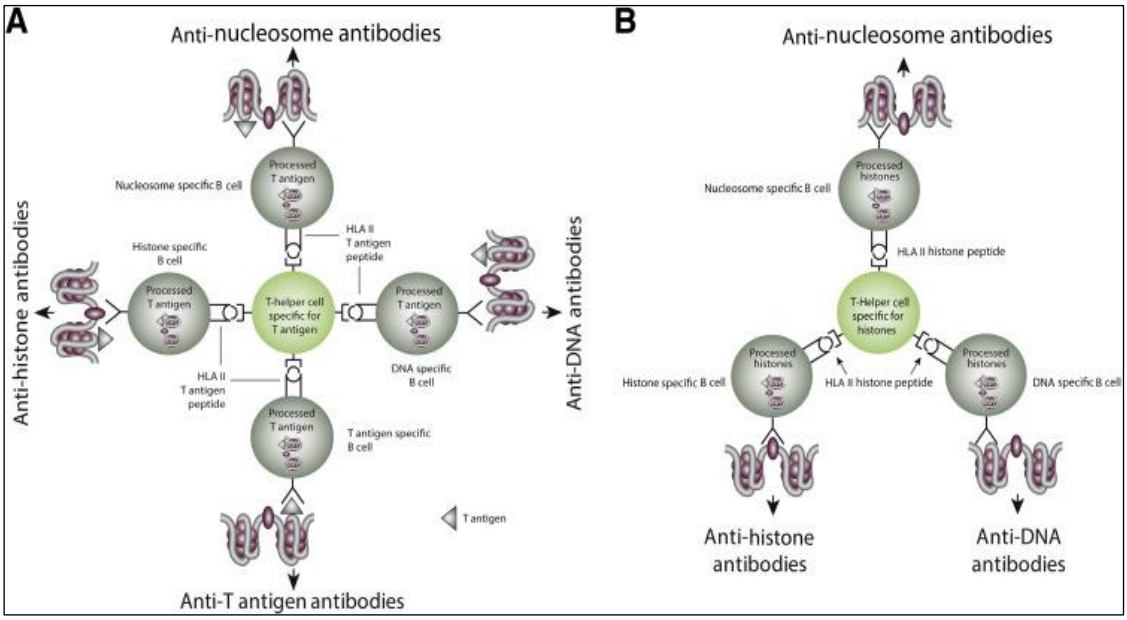
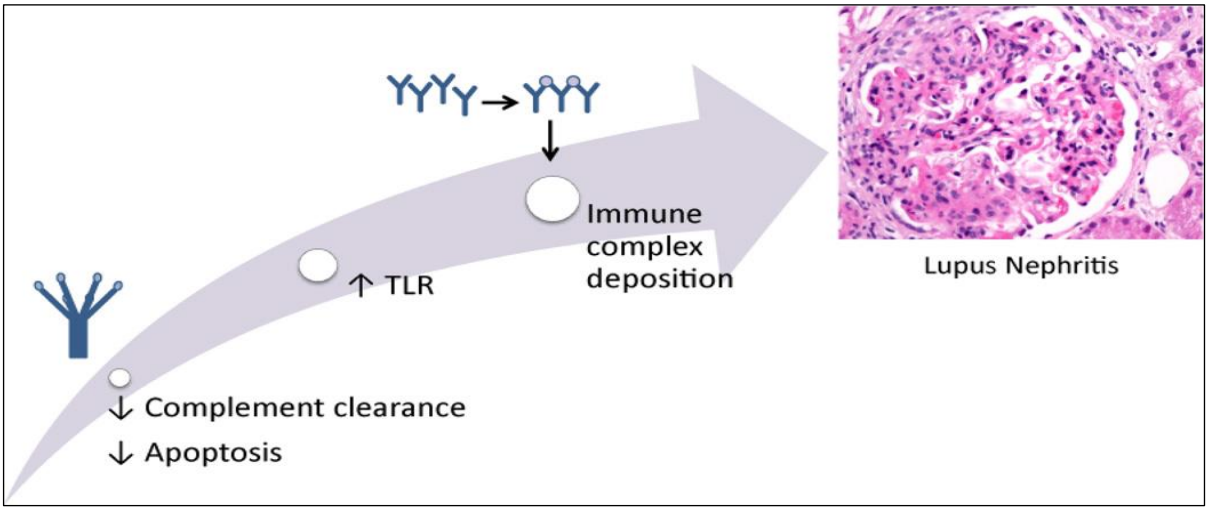


Figure 1: Cognate interaction of nucleosome-specific B cells and infectious-derived (A) or autoimmune-derived (B) peptide-specific T cells. The figure presents classic hapten-carrier–like models to explain linked production of chromatin-reactive antibodies. **A:** Here, chromatin plays the role as a hapten, whereas heterologous peptides play the role as carrier protein. This model describes two features typical for systemic lupus erythematosus (SLE), production of affinity-maturated anti-dsDNA antibodies and linked production of antibodies to dsDNA, histones, and nonhistone chromatin-associated proteins. **B:** A hapten-carrier–like model is presented where chromatin represent the hapten, whereas chromatin-derived peptides represent the carrier protein. [4]

Lupus nephritis has been associated with several autoantibodies including anti-dsDNA, anti-C1q, and anti–ribosomal P antibodies and higher anti-dsDNA titers have been associated with nephritis. Furthermore, anti-dsDNA can be observed in affected kidneys of patients with SLE. Anti-C1q antibodies are also found in immune complex depositions in kidney samples from those detected with SLE, and these autoantibodies contribute to tissue inflammation, resulting in the impairment of kidney functioning. [5] Lupus nephritis is a type of kidney disease caused by systemic lupus erythematosus (SLE or lupus). Lupus is an autoimmune disease —a disorder in which the body's immune system attacks the body's own cells and organs. Kidney disease caused by lupus may get worse over time and lead to kidney failure. The symptoms include foamy urine and edema, high blood pressure, joint pain or swelling, muscle pain, fever with no known cause, a red rash, often on the face, across the nose and cheeks, sometimes called a butterfly rash because of its shape. [6]

Lupus nephritis is characterized by renal deposition of immune complexes. IgG antinuclear autoantibodies against components such as DNA and nucleoprotein are commonly found in the glomeruli and serum of individuals with lupus nephritis. Lupus nephritis is characterized by renal deposition of immune complexes. IgG antinuclear autoantibodies against components such as DNA and nucleoprotein are commonly found in the glomeruli and serum of individuals with lupus nephritis. Circulating immune complex antibodies have been shown to more readily bind DNA but not glomerular basement membrane antigens whereas IgG from the glomeruli of SLE patients readily bound DNA, glomerular basement membrane antigen, proteoglycan, and heparan sulfate. [7]

Figure 2: Proposed mechanism of Lupus Nephritis



Bronchiectasis is an irreversible lung condition that results from dialation of the bronchioles that causes a persistent cough and excess phlegm, or sputum. This leads to recurrent lung infections and lung damage. Air passages in the respiratory system make it possible for oxygen to enter the lungs and for carbon dioxide to leave the body. In healthy lungs, the bronchial tubes narrow smoothly towards the edges of each lung, but in bronchiectasis, they widen and become collapsible and scarred. The cilia, the hair-like structures that sweep mucus out of the lungs, no longer function and are ineffective, so the mucus builds up. This increased mucus provides a place for bacteria to grow. Ongoing infections increase inflammation, and this leads to worsening lung damage. [8] [9]

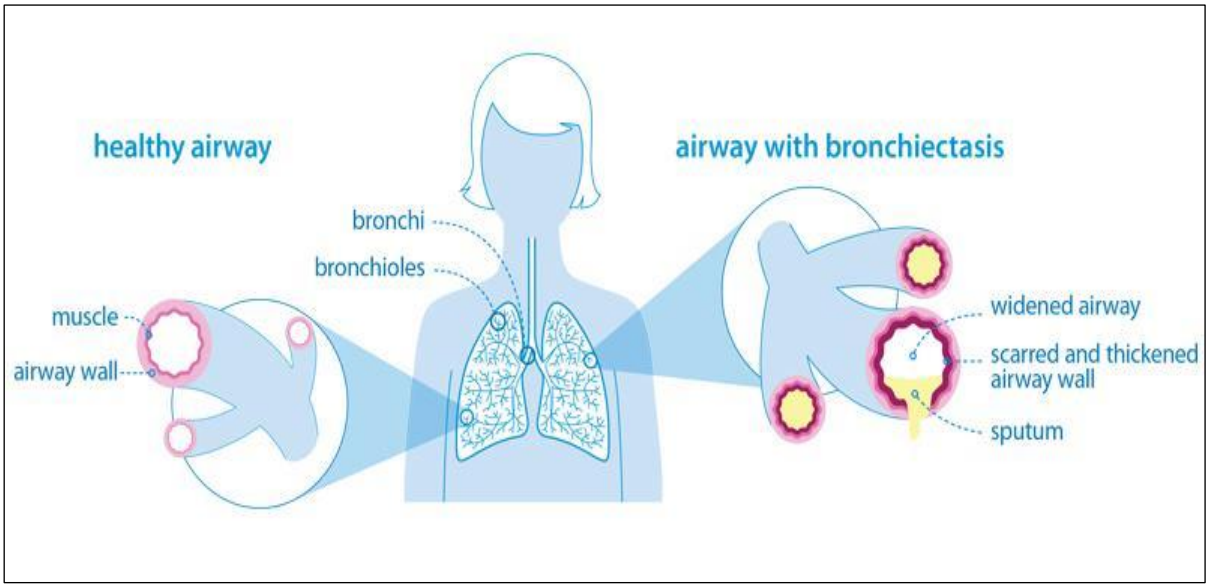


Figure 3: Difference between a healthy airway and an airway with bronchiectasis

Case Presentation:

A 40-year-old female, was admitted in the General Medicine Department of a tertiary care hospital with chief complaints of easy fatigability (since 1 month), pedal edema (since 15 days), abdominal distension (since 15 days) and facial puffiness (since 15 days). She had a H/O pain in the groin region (since 3 months).

On examination, patient was conscious/coherent, BP-120/90mmHg, PR-92/min, P/A-soft, CVS- S1S2+,

R/S-BAE+, CNS-NFND and she was found to be pallor in appearance and pedal edema+.

Laboratory Investigations:

Table 1: Abnormalities listed in the Complete Blood Picture (CBP):

S.NO	BLOOD PARAMETERS	ON DAY 1	ON DAY 9	REFERENCE RANGE
1.	Hemoglobin (gm/dl)	4.5	6.5	12-15.5
2.	RBC (milli/cumm)	1.36	2.4	3.8-4.8
3.	HCT (vol %)	15.2	19.75	37-48
4.	Platelets	1,06,000	75,000	1,50,000-4,50,5000
5.	Peripheral Smear	→ RBC- Moderate Anisopoikilocytosis with normocytic, macrocytes → WBC-Normal ***Impression:*** Pancytopenia	→ RBC-Anisopoikilocytosis with hypochromia, microcytes → WBC-Leucopenia → PLT-Thrombocytopenia ***Impression:*** Pancytopenia	

Her Spot urine protein was 134mg/dl (0-20mg/dl), spot urine creatinine was 40mg/dl (40-300mg/dl) and Pro/Cre ratio was 3.3% (<0.16%). In biochemistry, her TSB and TSH levels were found to be normal. Her serum electrolytes, serum creatinine and blood urea were found to be normal on all the three days of testing.

Table 2: Abnormalities listed in the additional biochemical tests that were carried out:

S.NO	BIOCHEMISTRY	ON DAY 2	ON DAY 9	ONN DAY 16	REFERENCE RANGE
1.	S. Protein (g/dl)	4.7	4.99	4.93	6-8
2.	S. Albumin (g/dl)	1.11	2.11	2.15	3.5-5.5
3.	Direct Bilirubin (µmol/L)	-	14.20	-	Less than 5.1
4.	Alkaline Phosphatase (IU/L)	0.3	84.3	-	44-147
5.	S. Thyroxine (T4) (ug/dl)	2.7	-	-	4.6-12

Her **24-hour urine protein** test revealed:
- → 24 hours urine (total): 400ml
- → 24 hours urine (protein): 0.4mg (less than 80mg/24 hours)

Her **Ultrasound abdomen** revealed the following:
- → Liver-Normal in size, increased echotexture (grade 2)
- → Gall Bladder-Distended wall oedematous

Impression: 1. Small Left Kidney with echogenic parenchymal with? Pyelonephritis
2. Chronic cystitis

Her **CT KUB (plain)** revealed the following:
- → Right kidney: 10.7 x 4.4 cms, normal in size and normal attenuation. Pelvicalyceal system is normal. No calculi. No focal lesions.
- → Left kidney: 5.6 x 2.2 cms, relatively small in size. Gross dilation of pelvicalyceal system. Cortex thinned out. No calculi.
- → Urinary bladder: Empty, thickened wall measuring 9mm? Chronic cystitis
- → Lungs: Patchy consolidation with ground glass opacities noted in basal segment of left lower lobe. Tubular bronchiectasis is noted

in B/L lower lobe. Nodular and tree in bud opacities noted in right middle lobe and right lower lobe.

Her **Bone Marrow report** was as follows:

→ Bone marrow aspirated from: Right posterior superior iliac spline
→ Cellularity: Hypo cellular
→ Megakaryocytes and Platelets: Normal with mature and immature forms
→ Erythropoiesis: Increased with megaloblastic, micronormoblastic maturation
→ Erythroid myeloid ratio: 1.5:1
→ Granulopoiesis: Normal with orderly maturation
→ Abnormality of granulocytes: Nil
→ Lymphocytes, Plasma cells, Reticulo endothelial cells: Normal
→ Haemoparasites: No haemoparasites

Impression: Erythroid hyperplasia with megaloblastic and micronormoblastic Maturation-Dual Deficiency anemia

Her **Complement-3 (C3) level** was found to be 23.3mg/dl (90-180mg/dl) and her **Complement-4 (C4) level** was found to be <7.22mg/dl (10-40mg/dl).

Her **Anti-Nuclear Antibodies (IF)-ANA (Hep 2 Cells)** test revealed the following:

→ Nucleoplasm: Granular
→ Nuclear membrane: Negative
→ Nuclear dots: Negative
→ Nucleoli: Accentuation
→ Cytoplasm: Negative
→ Intensity: Positive

Impression: Borderline positive

Her **ANA Profile** revealed the following:

RNP/Sm: Borderline (+)
Sm Antibody
SS-A (Ro-60)
RO-52
SS-B (La)
Scl-70
PM-Scl 100
Jo1
CENP-B
PCNA
Ds-DNA
Nucleosomes
Histone
Ribosomal-P-Protein
AMA-M2
DFS 70

NEGATIVE

Provisional Diagnosis: Chronic Kidney Disease with Anemia

Conformational Diagnosis: ANA Negative SLE with Lupus Nephritis with B/L lower lobe Bronchiectasis

Treatment: During the course of her stay in the hospital, she was administered with the following medications: -

S. NO	BRAND NAME	GENERIC NAME	DOSE	FREQUENCY
1	Inj. Lasix	Furosemide	20mg	1-0-1
2.	T. IFA	Iron+Folic Acid	100mg+500mcg	0-1-0
3.	Inj. Iron Sucrose	Iron Sucrose	50 mg in 100ml NS	1-0-0
4.	T. Enam	Enalapril	5mg	1-0-0
5.	T. BC	B complex	1 tab	0-1-0
6.	T. Sporolac DS	Lactic acid Bacillus	120 million spores	1-0-1
7.	Inj. Monocef	Ceftriaxone	1gm	1-0-1
8.	T. Pan	Pantoprazole	40mg	1-0-0
9.	Inj. H Albumin	Albumin (Human)	20% (100ml)	1-0-0
10.	Inj. Piptaz	Piperacillin+Tazobactum	2.25gm	1-1-1
11.	Inj. Rantac	Ranitidine Hydrocloride	50mg	1-0-1
12.	T. Levoflox	Levofloxacin	750mg	1-0-0
13.	Inj. Metrogyl	Metronidazole	100ml	1-1-1
14.	Inj. Celepid	Gylcerol+ Soyabean oil+ fat+ lecithin	2.25gm+ 20gm+ 20%w/v+ 1.2gm	Alternate days
15.	T. Dytor plus	Spironolactone	½ tab	1-0-0
16.	Inj. Ranerve plus	Pyridoxine Hydrochloride+ Mecobalamin+ Nicotinamide	100mg+1000mcg+100mg	1-0-0
17.	T. PCM	Acetaminophen	500mg	1-1-1

18.	Syp. Ascoril	Bromhexine+Guaifenesin+ Turbutaline + Menthol	10ml	1-1-1
19.	Inj. Celemin	10% Amino acids+ Electrolytes	200/500ml	1-0-0
20.	T. Prednisolone	Prednisolone	40mg	1-0-0
21.	T. Ca/Vit D3	Calcium+ Vitamin D3	1 tab	0-1-0

DISCUSSION:

Systemic lupus erythematosus is a chronic inflammatory autoimmune disease that involves many different organ systems, and this illness exhibits a wide spectrum of clinical manifestations. The diagnosis is individualized to a specific patient's clinical and laboratory abnormalities. Various kinds of autoantibodies are present in the sera of SLE patients, and ANA is a diagnostic hallmark for SLE, having a frequency of 95% or greater in SLE patients. However, cases have surfaced where a small groups of patients with the clinical features of SLE have negative tests for ANA. These patients appear to represent 1-5% of the SLE population. A possible cause of ANA-negative findings is that:

1. ANA is present, but it is bound in the form of immune complexes. It has been observed that patients with lupus nephritis whose ANAs, which were primarily reactive with DNA, were not detected in the serum by indirect immunofluorescence until the ANAs were dissociated from circulating immune complexes.
2. Loss of ANA through the kidney due to profuse proteinuria is also another possibility. [10]

In this case the patient was admitted for complaints of facial puffiness, pedal edema, abdominal distention and easy fatigability. Her investigations revealed abnormality in the anatomical and physiological nature of her kidneys and her lung functioning which ultimately led to the deterioration of their functioning. The abnormalities in her CBP, Bone marrow, KUB and Ultrasound abdomen are contributing factors to establish a basis on which her body is likely to be attacking its own healthy tissues and causing damage to various components of blood or mediators immune response. Her Anti-nuclear antibody and ANA Profile indicate negative for autoimmune disorders, yet she was confirmed with SLE. Although, the tests might provide sufficient evidence to rule out the presence or absence of anti-nuclear antibody indulgence in the pathophysiology of lupus nephritis and bronchiectasis, one cannot completely rely on the tests carried out by the process of immune florescence. The tests could very well be inaccurate, owing to one of these possible reasons:

1. Inter-method standardization of immunofluorescence-antinuclear antibody substrates and anti-Ig conjugates is still difficult.
2. There is no standard protocol for reference ranges in the background of variable prevalence of weakly positive antinuclear antibody results in healthy persons. [11]

As the tests carried out in the patient yielded sufficient information to conclude the most probable etiology in the patient's condition, the treatment listed above had been initiated and although slowly, a progressive improvement in the condition of the patient was observed and the patient was discharged after a time period. Time gap reduction for recovery can be achieved if further tests with more accurate sensitivity and/or protocols can be carried out for the ultimate confirmation to avoid hindering of the best possible therapeutical approaches for a given patient with similar results. Early detection of the condition could have led to a reversible lung damage rather than the irreversible bronchiectasis that had become habitant of the lungs of the patient. The regular ANA tests do yield results sufficient to come near to a conclusion, but may tend to prolong the treatment period. Nevertheless, one cannot deny that factors such as a patient's cooperation, a patient's preexisting clinical conditions, social habits, availability of the testing apparatus and appropriate time schedules may sometimes tend to pose a restriction, in investigating the condition to the furthest possible endpoint and until the highest (most accurate) possible test is done.

CONCLUSION:

ANA negative SLE is a rare disorder where the Anti-nuclear antibodies indicate negative in the development of SLE. Such patients should be carefully monitored over a sufficient time period to ensure that additional organs aren't at risk due to the autoimmune attacks that the body carries out. The depletion in the levels of certain nutrition levels can be carried out by IV parenteral nutrition supplements. Blood transfusions and antibiotics can help improve the blood parameters and eradicate infection respectively, over a period of time. Also, accurate testing and early diagnosis of SLE can prove

to be beneficial in terms of preserving functionality of most organs so that irreversible organ damage does turn fatal. The need to initiate therapy prophylactically at the early stages is achieved and recognized with an early detection of SLE.

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