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Antinuclear Antibodies in Systemic Lupus Erythematous – Their Complex Role and Clinical Significance in Diagnosis

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ABSTRACT

Antinuclear antibodies (ANA) are a wide group of proteins directed against autologous cellular components, primarily nucleic acids and histones. Their levels are assessed using immunofluorescence on Hep-2 cells or a solid-phase ANA screening immunoassay to subsequently obtain titer value with positive cut-point of ≥1:80. Studies show that ANA can be found in 13% of general population, but typically they are associated with autoimmune conditions and inflammatory connective tissue diseases for example: systemic lupus erythematosus (SLE), sjögren's syndrome, rheumatoid arthritis, mixed connective tissue disease, juvenile idiopathic arthritis, systemic sclerosis, inflammatory myopathies.

ANA detection is especially important for SLE, where 2 antibody types - anti-Sm and anti-dsDNA - serve as an entry diagnostic criterion. With increasing patient screening for those antibodies, it is important to determine that alone, positive ANA assays cannot confirm nor deny any disease and to classify their presence as a marker of a disease it is required to satisfy

additional additive criteria approved in 2019 by European League Against Rheumatism/American College of Rheumatology. SLE diagnosis can be made when patient collects 10 points from clinical or immunologic domains described by EULAR/ACR, which makes SLE diagnosis challenging and therefore, describing the guidelines is vital to remain cautious about overestimation of the position positive ANA values hold in clinical practice.

In conclusion the positive ANA test may be a basis for diagnosis, when additional symptoms occur, but alone does not hold any diagnostic significance and may lead to unnecessary stress for patient.

Keywords: SLE, Antinuclear antibodies, Lupus, Rheumatic diseases, Dermatology, Antibodies.

I Introduction

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease where the body's immune system mistakenly attacks its own healthy tissues. This disease can impact various parts of the body, leading to a wide range of clinical manifestations and organ involvement. The organs commonly affected include the skin, joints, kidneys, brain, and other vital systems, making SLE a highly heterogeneous condition in terms of symptoms and severity [28].

The exact cause of SLE is not fully understood, but it is believed to result from a complex interplay of genetic, environmental, and hormonal factors. Women of childbearing age are predominantly affected by SLE, highlighting the potential role of hormonal influences in the disease's development [6]. Genetic predisposition also plays a significant role, as SLE tends to run in families, and certain genetic markers have been associated with an increased risk of developing the disease. Environmental factors, such as exposure to ultraviolet light, infections, and certain medications, may trigger the onset or exacerbate the symptoms of SLE in genetically susceptible individuals [4].

A hallmark of SLE is the production of a wide spectrum of autoantibodies directed against various nuclear and cellular components [29]. These autoantibodies are not only central to the pathogenesis of the disease but also serve as crucial diagnostic markers. Among these, antinuclear antibodies (ANAs) are particularly significant. ANAs target structures within the cell nucleus and are found in nearly all individuals with SLE. However, the presence of ANAs

is not exclusive to SLE and can be observed in other autoimmune diseases and even in some healthy individuals.

Diagnosing SLE can be particularly challenging due to its diverse symptoms that often mimic those of other conditions. Therefore, detecting different types of ANAs and other specific autoantibodies is a critical component of the diagnostic process [26]. Despite being known for over 60 years, the precise roles of these autoantibodies in the pathogenesis, diagnosis, and prognosis of SLE remain an active area of research [5]. The great number of ANAs variants furthermore complicates the diagnostic process [21]. Significant efforts continue to be made to better understand the specificity of these antobodies and mechanisms by which they contribute to disease development and progression, as well as their potential utility in predicting disease flares and outcomes.

II State of knowledge

Pathophysiology of antibody formation

The formation of antinuclear antibodies (ANAs) in Systemic Lupus Erythematosus (SLE) is driven by genetic susceptibility, environmental triggers, and immune dysregulation. These factors collectively lead to the breakdown of immune tolerance and the production of autoantibodies targeting nuclear components [2]. Genetic factors, including specific alleles of the Human Leukocyte Antigen (HLA) system such as HLA-DR2 and HLA-DR3, increase the risk of developing ANAs and SLE [4]. Additionally, non-HLA genes involved in immune regulation contribute to susceptibility. Environmental factors like UV radiation, which induces apoptosis in skin cells, and infections caused by certain viruses and bacteria, can trigger autoimmunity through molecular mimicry and exposure of nuclear components [22].

In SLE, the immune system's ability to distinguish between self and non-self is compromised, leading to an autoimmune response against self-antigens. Defective apoptosis and clearance mechanisms result in the accumulation of cellular debris, including nuclear antigens. These antigens are then taken up by dendritic cells, which process and present them to T cells, leading to the activation of autoreactive T cells. These T cells, in turn, provide help to B cells that have

internalized nuclear antigens, promoting B cell activation, proliferation, and differentiation into plasma cells that produce ANAs [25].

The dysregulated expression of B cells primarily drives the formation of antibodies subsequent immune complex development [25]. Among these antibodies, IgG antibodies are particularly pathogenic due to structural features such as arginine residues in the complementarity-determining region 3 (CDR3), which enhance their binding capacity [4]. Based on the trigger for antibody formation we can distinguish two main types: transient antibodies associated with viral infection and sustained antibodies triggered by autoimmune T_H cells [26]. The origin of these antibodies—whether induced by viral infections or autoimmune processes—dictates their duration and persistence.

Once produced, antibodies form complexes can deposit in various tissues, leading to inflammation and organ damage characteristic of SLE [20]. These immune complexes, when deposited, particularly in the kidneys, activate the complement system and incite inflammation. This inflammatory response results in the clinical manifestations of lupus nephritis, characterized by kidney damage and impaired renal function [22]. The deposition of immune complexes and subsequent complement activation also occur in other organs, such as the skin, joints, heart, and brain, contributing to the diverse clinical symptoms of SLE, including rashes, arthritis, carditis, and neuropsychiatric manifestations [10].

Antibody testing

Testing for autoantibodies in Systemic Lupus Erythematosus (SLE) involves a range of laboratory methods crucial for diagnosing, prognosing, and managing the disease. Anti-DNA antibodies, for instance, can be detected in serum up to 2 years before the clinical diagnosis of SLE, and a significant increase in their levels often predicts a severe flare-up of the disease within the next 6 months [3].

The most commonly employed assays include Radioimmunoassay (RIA), Indirect Immunofluorescence (IIF) using Crithidia luciliae, and Enzyme-Linked Immunosorbent Assay (ELISA) [7]. RIA and IIF are well-established methods for their diagnostic and prognostic

value, particularly in detecting various autoantibodies associated with SLE. Meanwhile, ELISA is highly valuable in clinical laboratories for quantifying high-avidity anti-dsDNA antibodies, which are closely linked to disease activity in SLE [3].

Each specific antibody detected in these assays is assessed based on a particular titer, which determines its clinical significance [12].

Overall, these antibody tests are pivotal in the comprehensive management of SLE.

Antibody Classification

Among the ANAs, certain autoantibodies are particularly significant for the diagnosis and management of SLE [7]. Anti-double-stranded DNA (anti-dsDNA) and Anti-Smith (anti-Sm) antibodies are specific markers for SLE, used in diagnosis at titer of ≥1:80 [5]. Other antibodies that can be present include anti-nucleosome, anti-snRNP, anti-SSA/Ro and anti-SSB/La, anti-phospholipid, anti-β2 glycoprotein I (anti-β2GP1), anti-C1q, anti-ribosomal P protein, anti-NMDAR (N-methyl-D-aspartate receptor) and anti-PCNA (proliferating cell nuclear antigen) [29]. While these autoantibodies are not essential for diagnosing SLE, their presence can be associated with specific clinical manifestations and complications [20]. Therefore, testing for a broad spectrum of autoantibodies is important in managing SLE, as it helps in predicting disease course, monitoring organ involvement, and tailoring treatment strategies.

Anti-DNA antibodies

The most prominent group of antibodies in Systemic Lupus Erythematosus (SLE) are anti-DNA (anti-DNA) antibodies, known for their high specificity in SLE, estimated at around 95-97% [5]. These antibodies are crucial for monitoring disease activity due to their positive correlation with clinical manifestations [18]. They target various structures including linker B-DNA, higher order bent structures in nucleosomes, phosphodeoxyribose backbones, and the immunogenic Z-DNA structure [18].

The main pathogenic effect of anti-DNA antibodies primarily affects the kidneys, a major site of internal damage in SLE patients, leading to lupus nephritis [30]. Glomerular cells, unlike most body cells, can be permeable to immunoglobulins, making them susceptible targets. This process occurs in two phases: initially, chromatin fragments exposed on the glomerular basement membrane trigger inflammation through complement activation, facilitated by immune complexes [11]. In a subsequent phase, anti-DNA antibodies cross-react with components of the glomerular basement membrane, such as laminin, α-actinin, and entactin [30]. This deposition of immunoglobulin complexes on the glomerulus leads to ongoing damage and exposure of more chromatin fragments, perpetuating the cycle.

Clinically, this mechanism manifests as various forms of nephritis including lupus nephritis, glomerulonephritis, mesangial nephritis, and nephropathy, often presenting with symptoms like hematuria and proteinuria [10].

Beyond kidney involvement, anti-DNA antibodies also impact the skin [29]. They exhibit high affinity for dermo-epidermal laminin and collagen, a process exacerbated by ultraviolet light exposure, which promotes keratinocyte apoptosis through antibody-dependent and cell-mediated cytotoxicity [11]. This contributes to hallmark cutaneous manifestations of lupus, such as the malar rash (butterfly rash), as well as discoid rash, photosensitivity reactions, and alopecia [15].

Overall, anti-dsDNA antibodies are intimately connected to the most common clinical findings in lupus making their detection and monitoring play a crucial role in SLE [8].

Anti-Sm Antibodies

The second most prominent group of antibodies used in diagnosing Systemic Lupus Erythematosus (SLE) are anti-Sm antibodies, targeting the Smith antigen, a nuclear ribonucleoprotein complex crucial for RNA splicing [17]. These antibodies are detected in approximately 20% of Caucasian patients and in higher proportions (30-40%) among patients of other ethnicities, particularly African Americans [1]. While anti-Sm antibodies exhibit low

sensitivity, they are highly specific to SLE, distinguishing it from related autoimmune diseases [9].

Contrary to anti-double-stranded DNA (anti-dsDNA) antibodies, anti-Sm antibody titers do not correlate with disease activity over the course of SLE [9]. However, their presence is associated with serious complications, notably lupus nephritis, where they serve as biomarkers for renal involvement [17]. Additionally, anti-Sm antibodies are linked to other lupus manifestations such as hemolytic anemia, leukopenia, vasculitis, pulmonary arterial hypertension, neurological complications (including cognitive dysfunction and seizures), Raynaud's phenomenon, lupus arthritis, and serositis [1].

In clinical practice, the detection of anti-Sm antibodies plays a crucial role in confirming the diagnosis of SLE, particularly when combined with other diagnostic criteria [23]. Their specificity for SLE underscores their utility in distinguishing it from other autoimmune conditions. Despite their diagnostic significance, further research is needed to fully understand their role in disease pathogenesis and their implications for clinical outcomes in SLE patients.

Other types

In Systemic Lupus Erythematosus (SLE), while the primary diagnostic focus revolves around two main groups of antibodies—anti-double-stranded DNA (anti-dsDNA) and anti-Smith (anti-Sm) antibodies—a diverse array of additional autoantibodies correlates with distinct clinical manifestations and lupus subtypes [13]. These antibodies encompass a spectrum of specificities against various nuclear and cellular components, reflecting the intricate and multifaceted pathogenesis of SLE. Below some of the most important clinically subtypes will be presented.

- Anti-SSA/Ro and anti-SSB/La antibodies are detected earlier in the course of Systemic Lupus Erythematosus (SLE) compared to other SLE-related autoantibodies, often appearing approximately 6.6 years before a formal diagnosis of SLE is made. These antibodies are believed to play a pathogenetic role in initiating tissue damage, particularly in cases of photosensitive SLE.

One significant aspect of anti-SSA/Ro and anti-SSB/La antibodies is their ability to cross the placenta during pregnancy, potentially leading to neonatal lupus erythematosus (NLE) in newborns. This condition can manifest with various clinical features, with the most serious complication being isolated complete atrioventricular block (CHB) due to their affinity for heart conduction tissue. CHB poses a critical risk to affected infants and requires close monitoring and potentially early intervention.

- Another notable group of antibodies in Systemic Lupus Erythematosus (SLE) is anti-histone antibodies, which target all classes of histones: H1, H2A, H2B, H3, and H4 [19]. These antibodies exhibit a wide range of specificity, ranging from approximately 17% to 95% [19]. They are particularly prevalent in patients with idiopathic and drug-induced forms of SLE, the former most commonly triggered by penicillamine, isoniazid, and methyldopa [20].
- The last common group of antibodies found in Systemic Lupus Erythematosus (SLE) are anti-phospholipid antibodies [23]. While they are not specific to SLE, their presence is clinically significant due to their association with important complications. These antibodies contribute to vascular thrombosis, increasing the risk of conditions such as deep vein thrombosis and stroke. In pregnant individuals, anti-phospholipid antibodies can lead to pregnancy-related complications including miscarriages, stillbirths, and pre-eclampsia, collectively termed as pregnancy morbidity [25]. Additionally, they are associated with other hematologic manifestations such as thrombocytopenia and hemolytic anemia. Detection of anti-phospholipid antibodies in SLE patients is crucial for assessing thrombotic risk and managing pregnancy outcomes, highlighting their role in guiding clinical care and therapeutic strategies.

III Limitations

Limitations in reviewing the role of antibodies include their common presence in healthy individuals. According to a study conducted in the United States, the prevalence of antinuclear antibodies (ANA) in healthy individuals above 12 years old can reach 13.8% [24]. This prevalence is also higher in females, who are more prone to autoimmune diseases [24]. This may contribute to overdiagnosis and unnecessary stress related to false-positive test results [14].

Although anti-DNA and anti-Sm antibodies are used as diagnostic criteria in SLE, their evaluation must be carefully interpreted in the context of clinical manifestations [16].

Furthermore, despite the pathogenesis described above, the formation of immune complexes that damage cell structures requires a combination of factors including genetics and environmental triggers [13]. At the same time appearance of skin-specific autoantibodies may indicate that early events in the break of tolerance take place in cutaneous structures, so further research is needed to review the potential of those antibodies [14]. Looking ahead, advancements in blood profiling for expressed autoantibodies and genetic markers hold promise for identifying individuals at risk for developing autoimmune diseases, including lupus [12]. This approach may enable early intervention and personalized management strategies, potentially improving outcomes for patients with SLE and other autoimmune conditions [27].

IV Summary

In conclusion, antinuclear antibodies play a crucial yet intricate role in the diagnosis of Systemic Lupus Erythematosus. They are important biomarkers that aid in identifying and confirming the presence of autoimmune processes in affected individuals and have a potential to forecast the course of the disease. However, their detection in clinical practice presents challenges due to their prevalence in healthy populations and their association with various autoimmune and rheumatic conditions beyond SLE.

The clinical importance of ANAs lies not only in their diagnostic utility but also in their potential to predict disease severity and guide treatment decisions. Specific antibodies such as anti-double-stranded DNA, anti-Smith are particularly valuable in distinguishing SLE from other diseases whereas some other like anti-SSA/Ro, and anti-SSB/La antibodies are invaluable in terms of stratifying lupus subtypes and forecasting clinical manifestations.

Despite their diagnostic value, ANAs must be interpreted alongside clinical findings and other laboratory tests to minimize false positives and ensure accurate diagnoses. Ongoing research into the pathogenic mechanisms of ANAs, including their role in tissue damage and immune dysregulation, is essential for advancing our understanding of SLE and improving patient outcomes.

Looking forward, advancements in technology and personalized medicine hold promise for refining the use of ANAs in clinical practice. This could enable earlier detection, better prognostication, and more targeted therapies for individuals with SLE and related autoimmune disorders. Continued collaboration between clinicians, researchers, and patients will be crucial in harnessing the full potential of ANAs to enhance the management and care of those affected by SLE.

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