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OVERVIEW OF SYSTEMIC LUPUS ERYTHEMATOSUS RISK FACTORS AND RELATED COMPLICATIONS

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Abstract:
Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease where the immune system attacks the body's cells and tissues, causing inflammation and tissue damage. SLE presents clinically in a diverse manner, impacting various organs such as the heart, joints, skin, lungs, kidneys, and nervous system. The production of autoantibodies, especially antinuclear and anti-DNA antibodies, is linked to SLE and its symptoms may vary among patients, with common signs including rash, arthritis, and fatigue. The disease's development involves genetic, epigenetic, and environmental elements, influencing abnormal B- and T-cell activity.

Keywords: Systemic lupus erythematosus (SLE) – Etiology - Pathophysiology – Flare - Complications

Introduction:

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that impacts various organ systems within the human body, showcasing a complex array of manifestations and symptoms. The condition is distinguished by the immune system launching an assault on the body's cells and tissues, resulting in widespread inflammation and consequential tissue impairment. SLE displays its harmful effects on critical bodily regions such as the heart, joints, skin, lungs, blood vessels, kidneys, and nervous system, portraying the extensive reach of its pathology. The diverse and multifaceted nature of SLE's clinical presentation poses significant challenges in terms of both accurate diagnosis and effective treatment strategies. The underlying mechanisms driving the development and progression of SLE primarily involve the breakdown of immune tolerance mechanisms alongside the dysregulation of B- and T-cell activities, contributing to the chronic inflammatory state observed in affected individuals. Notably, the presence of antinuclear antibodies stands out as a characteristic serological hallmark of SLE, aiding in the diagnostic process. Treatment modalities for SLE typically entail the administration of antimalarial agents,

corticosteroids, and immunosuppressive medications to manage symptoms and mitigate disease activity. Furthermore, the evolving understanding of SLE's pathophysiology has paved the way for targeted biologic therapies, offering promising avenues for more precise and personalized treatment approaches to manage this complex autoimmune disorder (1).

The estimated global prevalence of SLE was determined to be 43.7 cases per 100,000 individuals, a statistic that sheds light on the distribution of this autoimmune disease worldwide (2). It is important to acknowledge that the prevalence of SLE in Saudi Arabia presents variations across different scientific investigations, indicating the need for further exploration of this condition within the region. A specific research endeavor conducted in central Saudi Arabia unveiled a prevalence rate of 19.28 cases per 100,000 individuals, showcasing the localized nature of epidemiological data on SLE within the country (3). In contrast, data from population-based registries in the United States disclosed a prevalence of 72.8 cases per 100,000 person-years for SLE, underlining the varying prevalence rates of this disease in different geographical locations (4). Moreover, a comparative examination between Saudi SLE patients and the general population accentuated a significant susceptibility to major cardiovascular events (MACE) among individuals with SLE, emphasizing the importance of monitoring and managing cardiovascular health in this patient population (5). Specifically, SLE patients were identified to have a heightened risk of MACE when compared to individuals in the general population, signifying the need for targeted interventions to mitigate cardiovascular complications in SLE patients. An insightful retrospective analysis conducted in the southern region of Saudi Arabia revealed that SLE patients constituted a considerable percentage, making up 76% of mucocutaneous manifestations and 57% of musculoskeletal manifestations, underscoring the diverse clinical presentations and impact of SLE on affected individuals within the region (6). This data provides valuable insights into the burden of SLE on patients in Saudi Arabia and highlights the importance of comprehensive management strategies to address the multifaceted manifestations of this complex autoimmune disease.

SLE Etiology:

SLE is a multifaceted autoimmune disorder characterized by a complex interplay of various genetic elements contributing significantly to its etiology. The pivotal role of genetic determinants in the pathogenesis of SLE is underscored by extensive research revealing the implication of more than 100 specific genes in the manifestation of this condition. The mutations exert an influence that spans a broad spectrum of mechanisms involved in the regulation of the immune system, encompassing various abnormalities in processes such as the efficient removal of apoptotic bodies and immune complexes, as well as disturbances in the innate immune responses and the pathways crucial to the functioning of the adaptive immune system. These include but are not limited to intrinsic activation of B cells, eliminating nucleic acids with interferometric properties, and producing autoantibodies. Moreover, dysfunction in mitochondria can also contribute to the pathogenesis of SLE by triggering the release of nucleic acids with interferometric capabilities and activating both innate and adaptive immune cells. The changes in the functioning of T and B cells, which involve the dysregulation of the production of type I interferons, play a significant role in developing autoimmunity in individuals with SLE. Besides, it has come to light that genetic variations within long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) play a notable role in shaping both the susceptibility to SLE and the clinical trajectory of the disease. The perturbation of these non-coding RNA molecules in individuals with SLE offers insights into the condition's pathophysiology. It presents a promising avenue for leveraging them as potential biomarkers to facilitate diagnosis, monitor disease activity, and gauge therapeutic responses (7, 8). In addition, studies have been conducted to pinpoint specific single nucleotide polymorphisms (SNPs) linked to SLE. An illustrative instance is the identification of rs116253043 within the LY6G6D gene, which has been revealed to exhibit a protective function against the development of SLE. Conversely, the presence of the C allele in rs328 located on the LPL gene has been ascertained to act as a predisposing factor for the onset of SLE. The SNP rs1570360 in the VEGFA gene has been correlated with a more favorable clinical prognosis among individuals affected by SLE.

Furthermore, it has been established that genetic variations in the TAP2 gene are intricately linked to the susceptibility of individuals to SLE (9, 10). It has come to light that a mutation within the transcriptional repressor known as BACH1 has been pinpointed as a potential mutation linked to the development of lupus that manifests during childhood. In addition, immune dysregulation has been implicated in the pathogenesis of SLE by alterations in the epigenetic regulation of gene expression, perturbations in T cell function, and dysfunction in the cytosolic DNA sensing pathway. Epigenetic modifications, including changes in DNA methylation patterns and histone post-translational modifications, have been observed in SLE patients, suggesting a potential role in the initiation and progression of the disease.

Immunologically, the disruptions in the process of apoptosis and the release of danger-associated molecular patterns (DAMPs) further exacerbate the development of autoantibodies and inflammation within SLE. The involvement of type I interferon (IFN-I) also emerges as a key player in the pathophysiology of SLE, whereby the formation of immune complexes and the activation of cell-intrinsic pathways instigate the production of IFN-I. These intricate immune-mediated mechanisms culminate in diverse skin manifestations observed in cutaneous lupus erythematosus (CLE), which can manifest solely on the skin or extend to encompass systemic manifestations characteristic of SLE. In essence, it is unequivocal that the immune system assumes a pivotal and indispensable role in shaping the landscape of SLE manifestations through the dysregulation of immune cell activation, cytokine secretion, and identifying self-nucleic acids (11-14). The dysregulation of T cell populations, particularly an imbalance between regulatory T cells (Treg) and pathogenic effector/memory CD4+ T cells, results in the breakdown of immune tolerance and the persistent activation of autoreactive T cells. This dysregulation contributes to the chronic inflammation and tissue damage characteristic of SLE. Additionally, impairment in the cytosolic DNA sensing pathway, specifically involving the cGAS-STING pathway, can lead to sustained activation of the immune system and the loss of self-tolerance, thereby promoting a state of autoinflammation and autoimmunity in individuals with SLE (15). Nevertheless, In patients diagnosed with SLE, a notable reduction is observed in the CD27+IgD+ B cells, characterized as innate-like B cells with significant roles as producers of natural antibodies. It has been documented that these CD27+IgD+ B cells exhibit compromised functionality in producing natural antibody-like Immunoglobulin M (IgM) and Interleukin-10 (IL-10). The dysregulation of pathways such as the B-cell receptor (BCR), toll-like receptor (TLR), and B-cell activating factor receptor (BAFF-R) pathways are identified as contributing factors to the abnormal activation of B cells in SLE. Moreover, a critical pathway involving oxidative phosphorylation (OXPHOS) and mitochondrial dysfunction has been recognized as a key immunological process implicated in SLE, particularly impacting memory B cells. The distinctive OXPHOS signature is linked to the signature of genes related to type I interferon signaling (ISRGs) in memory B cells of SLE patients, and both signatures exhibit correlations with organ damage and specific clinical manifestations of SLE. Exploring pivotal regulatory genes like PRDX6, which govern OXPHOS, presents promising prospects for developing therapeutic interventions targeting SLE. Furthermore, B cells can secrete a wide range of cytokines, including pro-inflammatory and immunosuppressive cytokines, which influence immune responses in autoimmune diseases. Additionally, the significance of immunometabolism in the processes of B-cell activation and differentiation has been emphasized. This includes the intricate involvement of the PI3K-Akt-mTOR signaling pathway, the glycolytic system, and oxidative phosphorylation in facilitating the activation of B cells through immunometabolic mechanisms (16).

Pathophysiology of SLE:

The role of the complement system is of utmost importance in the pathogenesis of SLE. It is well-established that complement activation is pivotal in mediating tissue inflammation and contributing to organ damage in SLE patients. Activation of the complement system can manifest through three distinct pathways, namely the classical pathway (CP), lectin pathway (LP), or alternative pathway (AP), each contributing uniquely to the inflammatory cascade in SLE. In the context of SLE, it is

noteworthy that both CP and LP pathways exhibit activation, with CP activation demonstrating a strong correlation with disease activity. In contrast, LP activation appears to be more closely linked to specific clinical manifestations such as lupus nephritis (LN), a severe renal complication commonly encountered in SLE patients. Traditionally, the assessment of complement activation in SLE has heavily relied on measuring complement levels, particularly C3 and C4, widely used biomarkers in clinical practice. However, it is crucial to acknowledge that these conventional markers lack specificity in distinguishing between the various pathways of complement activation. Recent research endeavors have thus shifted towards exploring novel strategies for evaluating complement activation in a more pathway-specific manner. Notably, there has been a growing interest in quantifying pathway-specific protein complexes, such as C1s/C1-inhibitor for CP-specific activation and MASP-1/C1-inhibitor for LP-specific activation, as potential biomarkers to discern between CP and LP activation in SLE. The emergence of these pathway-specific measurements holds great promise in providing deeper insights into the dynamics of complement activation in SLE, thereby paving the way for more precise disease monitoring strategies and the development of tailored treatment approaches that address the distinct pathophysiological mechanisms underlying CP and LP activation in this complex autoimmune disorder (17).

It is worth noting that individuals with hereditary deficiencies of early complement components within the classical pathway face an increased susceptibility to developing SLE. The dysregulation of the complement system in SLE leads to a cascade of events characterized by uncontrolled inflammation and subsequent organ damage, with a predilection for renal involvement. Complement activation, particularly through the alternative pathway, has been implicated in promoting kidney damage in SLE. In this context, identifying complement split products and cell-bound complement activation products (CB-CAPs) has emerged as a promising avenue for serving as biomarkers in diagnosing, monitoring, and predicting SLE (18).

SLE Triggers:

Environmental triggers linked to the risk of SLE encompass a wide range of factors, including but not limited to infections, alterations in the microbiome, dietary patterns, inhalation of various substances (such as crystalline silica, tobacco smoke, and atmospheric pollutants), presence of organic contaminants, heavy metal exposure, and ultraviolet radiation. It has been observed that exposure to certain environmental elements, such as residing close to agricultural regions, exposure to secondhand smoke, having blood lead levels equal to or exceeding 0.075 mg/L, and prolonged exposure to sunlight, have been significantly correlated with increased risk of developing SLE. Conversely, engaging in physical activities like walking or exercising has been shown to exert a protective influence against the onset of this autoimmune condition (19). In addition, Infections, especially the Epstein-Barr virus (EBV), can serve as initiating factors for developing SLE via intricate processes, including molecular mimicry, epitope spreading, and the polyclonal stimulation of B cells. These infectious agents, like EBV, can induce immune responses that cross-react with self-antigens, thereby contributing to the breakdown of self-tolerance and the onset of autoimmune reactions characteristic of SLE. Air pollution, specifically fine particulate matter (PM2.5) in the atmosphere, has been recognized as a significant risk factor associated with SLE, a chronic autoimmune disease. Numerous studies have established a clear link between exposure to PM2.5 and various negative outcomes in individuals with SLE, including disease exacerbation, higher rates of hospital admissions, increased severity of the condition, and the development of multiple organ dysfunctions. The intricate and multifaceted nature of the etiology of SLE suggests that a combination of genetic predisposition and environmental factors serves as a critical determinant in the initiation and progression of this particular autoimmune disorder. Exposure to ultraviolet (UV) light constitutes a significant environmental factor that plays a crucial role in triggering flares of SLE, characterized by a cascade of biological events such as DNA damage, programmed cell death (apoptosis), exposure of self-antigens leading to autoimmunity, production of signaling molecules known as cytokines, recruitment of inflammatory cells to the affected sites, and the induction of a widespread inflammatory response throughout the body. UV light exposure is a complex

phenomenon that directly damages genetic material and initiates a series of interconnected cellular and molecular processes that ultimately exacerbate SLE symptoms and disease activity (20).

SLE Flare

SLE flares represent acute exacerbations and deterioration in clinical manifestations and laboratory parameters, setting them apart from the usual lupus symptom due to exposure to multiple factors that precipitate the flare, such as smoking, nonadherence to prescribed medications, therapeutic inertia, hormonal influences, insufficient protection from sunlight, overexposure to ultraviolet rays, air pollution, organic pollutants, heavy metals, and reliance on corticosteroids for symptom control. In addition, In the realm of infectious diseases, it has been duly noted that influenza infection, a common viral ailment, has been unequivocally recognized as a significant risk factor contributing to the worsening of SLE flares, thereby leading to the necessitated hospitalization of affected individuals (21-23).

EFFECT OF SLE ON BODY SYSTEMS:

SLE is a complex autoimmune disorder characterized by its ability to impact various organs and systems within the human body. The diverse array of manifestations associated with SLE encompass not only cardiovascular, neurological, hematological, gastrointestinal, and neuritis. (24-26)

Hematological complications encompass a variety of conditions affecting the blood, including anemia. Among the different types of anemia, normocytic normochromic anemia stands out as the most prevalent, followed by microcytic hypochromic anemia. In addition to these common forms, They may experience severe hematological manifestations such as autoimmune thrombocytopenia, hemolytic anemia, thrombotic microangiopathy, and Evans syndrome, an autoimmune disorder characterized by two or more cytopenias. These cytopenias often include autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP), sometimes accompanied by immune neutropenia. Moreover, individuals with SLE face an increased risk of developing hematological malignancies, which are cancers that affect the blood, bone marrow, or lymph nodes. Research has identified older age at the time of SLE diagnosis as a significant risk factor for the development of hematological malignancies. Conversely, being female and receiving treatment with hydroxychloroquine have been shown to have a protective effect on mortality rates among SLE patients with hematological malignancies. These findings underscore the complex interplay between SLE, hematological complications, and the risk of developing malignancies, highlighting the importance of further research in this area. In addition, Thrombocytopenic purpura may manifest before the onset of lupus, either as a persistent complication or suddenly during disease exacerbation, thereby underscoring its significance. The clinical presentation in such individuals might encompass splenomegaly, thrombotic microangiopathy, or even antiphospholipid syndrome. (24, 27)

Symptoms associated with GI involvement in SLE exhibit a wide spectrum of manifestations, spanning from relatively common presentations such as abdominal pain, diarrhea, and nausea to more critical outcomes, including bowel necrosis and perforation. The spectrum of GI complications observed in individuals with SLE encompasses conditions like lupus mesenteric vasculitis (LMV), lupus enteritis (LEn), as well as other clinical presentations such as protein-losing enteropathy, hepatic manifestations including primary biliary cirrhosis and autoimmune hepatitis, and acute pancreatitis. LMV predominantly targets the small intestine, while LEn represents a rare yet notably severe complication that has the potential to progress to intestinal perforation and hemorrhage. (24, 25)

Renal complications, particularly in the form of lupus nephritis, which is characterized by substantial morbidity and an escalated likelihood of developing ESRD and renal impairment, are frequently observed in individuals with SLE along thrombotic microangiopathy (TMA), and antiphospholipid-associated nephropathy (APLN) (24, 25).

Pulmonary manifestations are broad, encompassing benign to life-threatening conditions (28). These manifestations comprise pleural involvement, interstitial lung disease, vasculitis, pulmonary embolism, pulmonary hypertension, large airway pathology, shrinking lung syndrome, and infectious processes. Also, the development of digital gangrene, albeit uncommon, can present as a grave complication of SLE, particularly in instances of late-onset disease. Additionally, pneumomediastinum and pneumopericardium, although infrequent, have been documented as etiologies of respiratory distress in SLE patients. Diffuse alveolar hemorrhage, a critical phenomenon culminating in acute respiratory decompensation, is also linked to SLE and other connective tissue disorders, carrying substantial mortality risks.

In regards to the musculoskeletal manifestations are frequently observed in individuals with SLE, presenting complications such as myositis, arthritis, osteonecrosis, and osteoporosis. Besides, joint abnormalities like subluxation, dislocation, and deformities in various body parts. Additionally, SLE patients can experience inflammatory musculoskeletal alterations, even when asymptomatic, as confirmed by contrasted MRI scans. (25, 29)

Also, Long-term complications linked with the manifestations of SLE encompass severe bacterial infection susceptibility (25). These varied manifestations underscore the importance of a comprehensive approach that considers the involvement of multiple organ systems in the diagnosis and management of Systemic Lupus Erythematosus.

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