Evolving phenotype of systemic lupus erythematosus patients and correlation with antibody against C1q: A review article

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Abstract

Background: Systemic lupus erythematosus (SLE) is a persistent illness that results in inflammation of connective tissues, including cartilage and the lining of blood vessels, which give structures throughout the body their flexibility and strength. A multi-system autoimmune illness, SLE affects several organ systems. There are several phenotypes of the illness, and clinical symptoms in individuals may range from modest mucocutaneous signs to severe central nervous system involvement affecting multiple organs. SLE is an illness that develops along many immune-pathogenic pathways.

Aim: To explore various phenotypes of SLE and possible role of anti-C1q antibodies in SLE

Conclusion: Anti-C1q antibodies were strongly associated with lupus disease activity in SLE patients, suggesting that it may be a reliable, sensitive, and non-invasive serological marker for SLE patients with active SLE disease.

Keywords: Anti-C1q; Systemic lupus erythematosus; Lupus nephritis; Complement; Proteinuria.

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1. Introduction
SLE is a persistent illness that results in inflammation of connective tissues, including cartilage and the lining of blood vessels, which give structures throughout the body their flexibility and strength. SLE symptoms vary from person to person and may impact a wide range of organs and systems (Marin et al., 2014).

The illness known as SLE is one of several autoimmune disorders, which are brought on when the body's own tissues and organs are attacked by the immune system (Alarcón et al., 2010). "Butterfly rash," a flat red rash across the cheeks and bridge of the nose, which is more noticeable when exposed to sunlight, is a distinguishing feature (Isenberg et al., 2008). Calcinosis, cutaneous vasculitis, and little red patches known as petechiae are other skin conditions that may develop in SLE. Additionally, those who are impacted may develop alopecia, mouth, nose, or, less often, genital ulcerations (Ahmadpoor et al., 2014).

Kidney illness affects around one-third of individuals with SLE (nephritis). Pericarditis and faulty heart valves, which regulate blood flow in the heart, are just two more cardiac issues that may manifest in SLE patients. Even more patients with SLE than the general population get atherosclerosis-related heart disease. SLE-related inflammation may harm the neural system and cause seizures, strokes, and problems with information processing, learning, and memory. It can also cause peripheral neuropathy, which causes altered feelings and weakness in the limbs (cognitive impairment). In SLE, anxiety, and sadness are also prevalent (Amoura et al., 2004).

Because many SLE symptoms and indicators are similar to those of other conditions, it may be difficult to pinpoint the precise prevalence. Some people with the disorder may never get a diagnosis, or it may take years to do so. SLE affects women around nine times more often than it does men. Although it is more frequent in younger women, especially during the reproductive years, 20% of SLE cases affect persons over 50. Immune cells generate the cationic glycoprotein known as complement C1q, which is the first element to be discovered in the established mechanism for complement activation. It has been shown that it is increased in various autoimmune illnesses, namely urticarial vasculitis (Alarcon et al., 2012).

The most common age range for SLE diagnosis is between 15 and 45. It has a significant influence on health and is physiologically and clinically varied. Combining inflammatory responses in the target organs with side effects of the medication, particularly those brought on by glucocorticoids, is what causes this. These elements raise the risk of permanent organ damage, comorbidity buildup, and early death. The 10-year mortality rate for SLE patients is still over 10%, with organ failure, infection, heart disorders, and cancer being the more common reasons for death. SLE patients also have a considerably worse quality of life in terms of their health than both the general population and those with other persistent diseases (Kiani et al., 2013).
genetic, immunological, endocrine, and environmental variables (Amarnani et al., 2021)

Although there is no clear pattern of inheritance, family segregation and high correlation ratios in identical twins point to a significant genetic component in SLE. According to some reports, identical twin concordance rates may reach 50%. More than 50 genes or chromosomal loci have been linked to SLE, the majority of which encode proteins involved in immune system function. These genes are linked to self-antigen production, innate and adaptive immune system activation, and immune system responses to external antigens. Rare but extremely high-risk gene variants for SLE development include deficits of early complement components C1q, C1r, and C1s (>90% risk), C4 (>50% risk), C2 (20% risk), and TREX1.

HLA-DRB1, HLA-DR2, HLA-DR3, HLA-DRX, TNFAIP3, STAT-4, STAT-1, TLR-7, IRAK1/MECP2, IRF5-TNPO3, ITGAM, and other genes are also linked to this condition. SLE risk is 10 times higher for women than for males, and it is 14 times higher in those with Klinefelter syndrome (47, XXY). This shows a relationship with X-chromosome genes, although, despite several types of research, the precise genes involved have not been discovered (Chi et al., 2014).

SLE is significantly influenced by female sex and hormonal influences. Prolactin and estrogens control lymphocyte and plasmacytoid dendritic cells this, and molecular mimicry is likely to be the fundamental mechanism. Compared to the general population, children and adults with SLE have higher rates of Epstein-Barr virus (EBV) antibodies. Smoking is also considered to have a risk that is dose-responsive. Silica exposure, other viral infections, a lack of vitamin D, alfalfa sprouts, and foods that contain canavanine are other possible risk factors (Fraser et al., 2009).

3. Epidemiology

SLE prevalence and occurrence rates have been observed to vary, with variations mostly attributed to demographic variations. In largely Caucasian and African-American populations, the lupus registries in Georgia and Michigan revealed prevalence rates of 72.1 to 74.4 per 100,000 people and prevalence rates of 5.6 per 100,000 person-years. The greatest rates are among African-Americans, while rates among Asian and Hispanic groups are greater than among Caucasians. African-Americans tend to experience the illness more
severely and at an earlier age of beginning. Among women of reproductive age, SLE affects them more often than males (9 to 1). However, following menopause, the risk for women diminishes, even though it is still twice as high as for males. Studies have shown that while it's uncommon, lupus in males often has a worse prognosis (Bansal et al., 2021).

The prevalence of the multi-system autoimmune disease SLE ranges from 4.3 to 45.3 per 100,000 people. About 90% of those afflicted are female, and SLE is one of the top 10 killers of young women. In non-Caucasian people, such as Asians and Indigenous Australians, the condition is 2-4 times more prevalent and frequently more serious (Yen and Singh, 2018).

4. Pathophysiology

SLE has complicated pathophysiology, and our knowledge of this pathogenesis is continually changing. When exposed to environmental variables, a genetically sensitive person's tolerance breaks down, which activates their autoimmune system. The immune system is exposed to self-antigens as a result of cell damage brought on by infectious agents and other environmental variables. This nephritis or cutaneous lupus, even though the majority of patients have multi-system involvement. The most prevalent illness characteristics are various mucocutaneous signs (such as cytopenias, serositis, glomerulonephritis, inflammatory polyarthritis, and constitutional symptoms), inflammatory polyarthritis, photosensitivity, alopecia, and mouth ulcers. Although less common, vascular disease, neurological, cardiovascular, respiratory, gastrointestinal, and ophthalmic activation of T and B cells causes an ongoing, self-directed immunological response. Organ damage results from cytokine release complement activation, and the generation of autoantibodies (Pan et al., 2015).

5. Histopathology

The pathology of tissue SLE may show a range of abnormal immunologic pathways, such as immune complex formation, the production of autoantibodies, and tissue harm caused by the immune system. A defining feature of SLE pathology is the LE body or hematoxylin body. Hematoxylin stains the nuclear material, which is a uniform spherical mass, bluish-purple. It may be seen in the lymph nodes, heart, lungs, kidneys, spleen, serous, and synovial membranes. They include DNA and immunoglobulins, and when phagocytes engulf an LE body, the traditional LE cell is created (Gergianaki and Bertias, 2018).

6. Clinical presentation

There is a wide range of possible SLE symptoms, ranging in severity from moderate to organ or life-threatening, and they may first emerge in almost any organ system. However, certain people may have single-organ dominant illnesses, such as isolated lupus symptoms are all well-known (Gavand et al., 2019).

Patients with SLE often exhibit symptoms including tiredness, myalgia, mood swings, and cognitive impairment in addition to those directly linked to immune-mediated inflammation. These symptoms often don't react well to immunosuppressive and don't always correspond with inflammatory activity in other organ systems, but they may have a crippling effect on a patient's quality of life (Cantsilieris et al., 2019).

7. Disease course
The precise course of an SLE patient’s condition may differ substantially. While sudden flare-ups are often represented as a feature of relapsing-remitting sickness, some people endure continuous clinical symptoms, while others go through remissions of different depths and duration. New illness activation is often more common in the years just the following identification and may be less probable in instances with long-standing sickness, but there are numerous exceptions. Relapses may be identified by a flare-up in previously damaged organs, the formation of new organ systems, or a combination of the two. As a result, it is very difficult to predict the course of any specific patient (Gladman et al., 2009).

8. Clinical manifestations
Principal clinical characteristics and organ involvement
8.1. Constitutionalsymptoms: throughout the illness, the majority of SLE patients have constitutional symptoms such as tiredness, fever, and weight loss (Chi et al., 2015).
8.2. Fatigue: the most frequent complaint, which affects 80 to 100 percent of patients, is fatigue, which may sometimes be incapacitating. Its existence is more usually linked to depression, sleep issues, and concurrent fibromyalgia, and its correlation with other indicators of disease activity is unclear (Laboni et al., 2006).
8.3. Fever: Over 50% of SLE patients have a fever, which might be a sign of an active illness. Consideration should be given to serious infections in all immunocompromised SLE patients who have fever since they are a significant source of morbidity for patients (Bock et al., 2015).
8.4. Myalgia: Patients with SLE often get myalgia as well, although significant muscular weakness or myositis is rather rare. We go into greater information about myalgia and muscular weakness individually (Ferdian et al., 2019).

8.5. Weight change: Patients with SLE often have weight fluctuations, which may be caused by the condition or its treatment (Chi et al., 2014).

9. Investigations
Both general and organ-specific tests are performed on patients whose diagnosis of SLE is under consideration. SLE-related antibodies and inflammation-related biomarkers are included in general assays. Blood and urine tests, imaging studies, and histology are some examples of organ-specific testing that may be used to determine which systems are impacted. When clinical examination indicates involvement; such as echocardiography for probable myopericarditis, or when significant involvement may be asymptomatic organ-specific tests are required (e.g. evaluation of the urine for lupus nephritis), therefore, to determine the proper sequencing of investigations, a complete physical examination, a detailed history, and a systems assessment including frequently afflicted organs are essential. Depicts methods for prescribing investigations for individuals with suspected SLE, Alternative differential diagnoses should be taken into account since SLE often resembles a variety of other rheumatological and non-rheumatological illnesses (Connelly et al., 2021).

10. Management
In SLE, remission and avoiding organ damage are the two main therapy objectives. The organ system(s) or systems involved and the degree of the engagement determine the therapy option, which might vary from basic treatment (NSAIDs, antimalarials) to
rigorous treatment (Corticosteroids, cytotoxic drugs) (Binello et al., 2018).

The management of SLE places a strong emphasis on patient education, lifestyle and physical modification, and emotional support. Patients with SLE should get a thorough education on the disease's pathophysiology, any probable organ involvement, the significance of therapy, and compliance monitoring. Exercise, excellent sleep hygiene, stress management strategies, and the usage of emotional support are all suggested. Smoking may make SLE symptoms worse, thus patients should be made aware of the value of quitting. Alfalfa sprouts and echinacea should be avoided, and a diet high in vitamin D should be included, according to dietary guidelines. Photoprotection is essential, and all SLE patients must avoid direct exposure to the sun by planning their activities wisely, dressing in light-weight, loose-fitting darkish clothes that cover the majority of their bodies, and applying sunscreen that gives both waves that cause prevention (Honda et al., 2018).

It was assumed that any protein with this property would likely have a structural function in the extracellular matrix rather than be engaged in the stimulation of the serum complement system until it was formally shown that collagen triple helical coils were existent in the C1q molecule. By the end of the 1980s, it was understood that several serum proteins, including subcomponent C1q, also included sections that were similar to collagen and were probably implicated in innate immune response systems. These included lung surfactant protein D, and bovine serum lectin (CL-43) are three more lectins that are now known to belong to a vast family of proteins that have collagen-like sections and are associated with immunological resistance. By interacting with a range of immunological targets and cell surface receptors through their globular head regions and collagen-like triple-helical sections, these proteins serve as a bridge between innate and adapted immunity. As a result of the significant achievement of producing point mutation variations, the correlation between structural and functional concerning the numerous bindings and triggering properties shown by C1q should now be able to be even more thoroughly explored. C1q is a complex protein structure made up of three different polypeptide chains (Ancelet et al., 2013).

11. Collagen-Like Region of C1q's Structural Model, Its Interaction with C1r2-C1s2, and Potential Role in Activation of the C1 Complex

Every known protein structure data as well as electron microscopy demonstrate that the 460 kDa C1q molecule has a bouquet-like structure. Six heterotrimeric triple helices, or "stalks," each ending in a heterotrimeric globular domain, are arranged in a fibril-like form at their N-termini. The stalks then divide at a bend, or "kink," halfway down the collagen-like area. Other serum proteins; such as (MBLs and Ficolins) which have a general shape with C1q, also connect with similar proteases through collagen-like sites. The lysine residue in the conserved sequence of amino acids (-Hyp-Gly-Lys-Xaa-Gly-Pro-), which existent in various chains of C1q, MBL, and Ficolin from...
various species, was shown to be the key residue involved in interaction with its related protease, MASP, by site-directed mutagens of Ficolin A. The most probable main binding position for C1r2-C1s2 on the stalks of C1q was predicted to be this conserved location, which is six Gly-Xaa-Yaa triplets C-terminal to the link area of C1q and is also found in each of the three chains of C1q (Dodds et al., 2007).

12. Antibody against Complement Component C1q in SLE

The archetypal case of a systemic autoimmune illness is SLE, although the complex pathogenic pathways causing organ damage and inflammation remain poorly understood. Both intrinsic (genetic) and extrinsic (environmental) variables are thought to contribute to SLE. Multiple genetic variables are often believed to be implicated, and the risk of getting SLE may change due to differences in several genes that are heavily engaged in the control and operation of the immune system. The strongest genetic disease susceptibility factor for human SLE was discovered to be homozygous complement C1q deficiency, showing that complementing C1q plays a crucial part in the progress of SLE. The recognition and starting molecule of the complement system's traditional route is called C1q. It is an 18-polypeptide chain, 460 kDa glycoprotein with an N-terminal domain that resembles collagen (Tsokos, 2020).

The six triple helices created by these chains come together to form a structure like a bouquet of tulips, with the collagen-like areas acting as the stalks and the C-terminal portions as the globular head regions, which serve as the primary receptors for C1q. The so-called "waste disposal theory" offered an extensive (but not exclusive) justification for C1q's involvement in SLE. According to this theory, systemic autoimmunity in SLE is brought on by the ineffective removal of apoptotic cells, which may later develop into antigenic substances and trigger an autoimmune reaction. The surface of apoptotic cells contains typical autoantigens that are targeted in SLE, such as Antigens related to phospholipids and nuclear antigens (Bock et al., 2015).

In more recent research employing a mouse model of autoimmunity, it was shown that C1q modifies the mitochondrial metabolism of CD8+ T cells, which may themselves spread autoimmunity, to regulate the immune responses to self-antigens (Binello et al., 2018). These findings give an alternate (or extra) explanation for how C1q prevents lupus in addition to suggesting a connection between C1q and CD8+ T-cell metabolism. The discovery may also have consequences for how viral infections contribute to the persistence of autoimmunity. It will be intriguing to investigate if anti-C1q also has a function in this theory.

The research of (Chi. et al., 2015) showed that the link between anti-C1q antibodies and renal flares in 95 SLE patients. Additionally, anti-C1q antibodies demonstrated a stronger link with renal dysfunction activity in SLE patients than anti-dsDNA antibodies and a decline in C3 and C4 in terms of diagnosing specificity. Importantly, the ability to identify SLE patients with ongoing illnesses and LN is more specific but less sensitive when anti-C1q and anti-dsDNA antibodies, complements C3 and C4 serum levels, or combinations of these factors are present. The fact that only 95 SLE samples were examined, that follow-up information
was insufficient, and that the LN activity in renal biopsies was mostly assessed by laboratory measures and clinical symptoms rather than by pathogenic analysis are all limitations of this research (Pan et al., 2015).

Table 1. The role of anti-C1q in the assessment of disease activity and its correlation with lupus nephritis and lupus cerebritis other phenotypes

<table>
<thead>
<tr>
<th>Anti C1q</th>
<th>Effect</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>Systemic lupus activity</td>
<td>anti-C1q antibodies correlate with overall disease activity (Csorba et al., 2019)</td>
<td></td>
</tr>
<tr>
<td>Lupus nephritis</td>
<td>Occurrence of severe lupus nephritis making them an important diagnostic marker. (Bock et al., 2015)</td>
<td></td>
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<tr>
<td>Diseases Course</td>
<td>Anti-C1q has the potential to accelerate the course (Mahler et al., 2013)</td>
<td></td>
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<tr>
<td>Neuropsychiatric lupus</td>
<td>Levels of anti-C1q antibodies were higher in patients with neuropsychiatric lupus than in SLE only (Magro-Checa et al., 2016)</td>
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</table>

Conclusion

SLE is a chronic, multisystem autoimmune illness that has a high morbidity and death rate. Loss of immunological tolerance to self-antigens results in the development of pathogenic autoantibodies, which harm tissue through a variety of mechanisms. This process is influenced by genetic, immunological, endocrine, and environmental variables.

Regarding the relation between lupus activity and anti-C1q antibody; a multisystem autoimmune illness, SLE affects several organ systems. There are several phenotypes of the illness, and clinical symptoms in individuals may range from modest mucocutaneous signs to severe central nervous system involvement affecting multiple organs. SLE is an illness that develops along many immune-pathogenic pathways.

Since then many pathogenic autoantibodies have been discovered. The precise etiology of SLE is still unknown, despite recent breakthroughs in technology and our knowledge of the pathological underpinnings and risk factors for the disease. SLE diagnosis may be difficult, and while many categorization criteria have been proposed, their applicability in the clinical environment is still up for discussion.

Organ system involvement determines how SLE should be managed. Despite various medications that are effective in treating SLE, the illness still has a high risk of morbidity and death for its victims.

Since the discovery of these autoantibodies, much work has been done to comprehend the importance of their etiologic, clinical, and prognosis aspects. The abnormal production of a wide diverse set of autoantibodies is a serological signature in SLE. A clinical significance assessment of the autoantibody profile and illness characteristics will assist in the early detection of SLE patients at risk for certain problems, allowing doctors to begin an effective treatment approach...
that may lower morbidity and death for SLE patients.

Anti-dsDNA antibodies in particular showed a pathogenic significance in LN; increased autoantibodies towards nucleosome and dsDNA (anti-dsDNA) and lower complements were observed to connect with disease severity and production of renal inflammation in SLE. However, a sizable number of non-LN patients and medically inactive SLE patients also had dsDNA antibodies and a decrease in complements.

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