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Systemic lupus erythematosus and immunodeficiency

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Abstract

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease caused by a combination of genetic, epigenetic, and environmental factors. Recent advances in genetic analysis coupled with better understanding of different immune regulatory and signaling pathways have revealed the complex relationship between autoimmunity, including SLE, and immunodeficiency. Furthermore, the expanding therapeutic armamentarium has led to the increasing awareness of secondary immunodeficiency in these patients. This article serves to update the current understanding of SLE and immunodeficiency by discussing the shared genetic factors and immunobiology. We also summarize the effects of immunosuppressive therapies with a focus on secondary antibody deficiency (SAD) after B-cell targeted therapies.

Introduction

Systemic lupus erythematosus (SLE) is a complex systemic autoimmune disease characterized by immune dysregulation and loss of immune tolerance to autoantigens, leading to autoantibody production, immune complex deposition, and secondary inflammatory damage. Advances in genetics and molecular biology have led to a better understanding of different diseases, including immunodeficiency and autoimmune conditions. Autoimmunity and immunodeficiency were previously considered to be distinct entities. The concept has evolved over time, however, and autoimmunity and immunodeficiency are now regarded as two sides of the same coin.[1] Autoimmune manifestations are common in patients with primary immunodeficiency (PID),[2] and patients with autoimmune diseases are prone to develop severe infections. There is considerable overlap in the clinical presentations, pathophysiology, and genetic factors between the two entities. In the case of SLE, causative genes in monogenic lupus and susceptibility genes identified by genome-wide association studies (GWAS) have been shown to overlap with genes responsible for PID.

Lupus-like diseases, rather than definite SLE, may also occur in certain PIDs.

Another important cause of immunodeficiency in SLE is the use of immunosuppressive therapies. The growing armamentarium of immunosuppressants and biological therapies have led to better lupus disease control and a great improvement in the prognosis of SLE over the years. However, infection remains an important cause of morbidity and mortality. The burden of serious infection has increased over the past decades and is a major cause of mortality.[3, 4] Understanding the mechanisms underpinning the susceptibility to infections and recognizing immunodeficiency in patients with SLE are therefore important. Clinical awareness, appropriate assessment, and management are essential to minimize infective complications.

This article serves to update the current understanding of SLE and immunodeficiency by discussing the shared genetic factors and immunobiology. We also summarize the

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effects of immunosuppressive therapies with a focus on secondary antibody deficiency (SAD) after B-cell targeted therapies.

Autoimmunity and Immunodeficiency: Immune Tolerance and Immune Regulation

The development of autoimmunity is characterized by a breach of immune tolerance, where the body fails to recognize self-antigens and initiates an inappropriate immune response. Different immune mechanisms are involved in the maintenance of central and peripheral tolerance. In addition, various regulatory pathways are essential to prevent uncon¬trolled inflammation secondary to immune activation. PID with defects involving major steps responsible for immune tolerance and immune regulation can give rise to autoimmune manifestations.

Central tolerance involves the elimination of autoreactive lymphocytes during lymphocyte development. T-cell development occurs in the thymus. The process involves several important steps such as T-cell receptor (TCR) rearrangement, thymic education, and selection. VDJ (variable, diversity, joining) recombination allows diversity of the TCR repertoire. After TCR rearrangement, MHC-peptide complexes carrying self-antigens are presented to developing T cells by medullary thymic epithelial cells (mTEC). The degree of affinity between TCR and self-antigens determines the fate of the developing T cells. Positive selection occurs to ensure the major histocompatibility complex (MHC) restriction of T cells, and negative selection occurs to eliminate autoreactive T cells.[5] B-cell development differs as the process occurs in the bone marrow, but shares some similarities. VDJ recombination also occurs in the development of B-cell receptor (BCR). Autoreactive B cells undergo receptor editing or apoptosis.[6] Peripheral tolerance ensures that self-reactive lymphocytes that escape central tolerance do not cause autoimmunity. Regulatory T cells (Tregs) and B cell activating factor (BAFF) homeostasis are key components for peripheral tolerance.[7]

PID with defects in pathways responsible for immune tolerance can therefore be associated with autoimmunity. Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) is caused by mutation in the autoimmune regulator (AIRE) gene.[8] AIRE is a transcription factor expressed by mTEC, which are responsible for negative selection in the thymus. Patients with APECED develop autoimmune manifestations in their endocrine glands and a proportion of patients suffer from chronic mucocutaneous candidiasis. Similarly, thymic T-cell development is impaired in patients with DiGeorge syndrome and patients with partial DiGeorge syndrome may manifest autoimmune features due to a lack of deletion of autoreactive cells. Immune tolerance may also be breached as a consequence of recombination-activating

gene (RAG) defects. RAG are proteins important for VDJ recombination. Defects of RAG proteins are associated with restricted T- and B-cell repertoire, aberrant thymus architecture, reduced AIRE expression, lymphopenia, reduced Treg, and increased level of BAFF.[9] RAG deficiency causes severe combined immunodeficiency, whereas hypomorphic RAG mutations are associated with Omenn syndrome. Patients with Omenn syndrome present with lymphadenopathy, hepatosplenomegaly, eosinophilia, T-cell infiltration in multiple organs, and severe hypogammaglobinaemia. Immune dysregulation, polyendocrinopathy, enteropathy, and X-linked (IPEX) syndrome are caused by mutation of Forkhead box protein P3 (FOXP3), a Treg transcription factor. Patients with IPEX syndrome develop systemic autoimmunity, typically beginning in the first year of life. These diseases illustrate how defects affecting key components of immune tolerance can give rise to both immunodeficiency and autoimmunity.

Furthermore, the immune system is tightly regulated by multiple pathways to limit uncontrolled inflammation and immune activation. PID with defects in these mechanisms are also associated with autoimmunity. For example, mutations in the T-cell costimulatory pathway and intracellular signaling may result in T-cell overactivation. Cytotoxic T-lymphocyte associated protein 4 (CTLA4) is a co-receptor on T cells and mediates peripheral tolerance by inhibiting co-stimulatory signals between antigen-presenting cells and T cells. It is constitutively expressed on Treg cells and upregulated on activated T cells. LPS-responsive beige-like anchor (LRBA) prevents the degradation of CTLA4. CTLA4 insufficiency and LRBA deficiency result in similar manifestations, with uncontrolled T-cell activation, autoimmune cytopenia, hypogammaglobinaemia, lymphoproliferation, viral infections, and infiltration of organs by activated T cells.[10] The knowledge from PID also leads to a better understanding about different therapeutic strategies. Abatacept, a CTLA-4-immunoglobulin (Ig) fusion protein, is licensed for the treatment of rheumatoid arthritis and has been explored for the treatment of other rheumatological diseases. Abatacept is also a potential treatment option for patients with CTLA/LBRA deficiency.[11, 12] In contrast, anti-CTLA-4 therapies lead to T-cell activation and are used as immunotherapies for the treatment of different malignancies, and are commonly associated with autoimmune side effects.

Lymphocyte function is dependent on intracellular signaling pathways. Phosphatidylinositol 3'-kinse (PI3K)/protein kinase B (Akt)/mechanistic target of rapamycin kinase (mTOR) is an intracellular transduction pathway in response to extracellular signals. Gain-of-function mutations in the genes encoding PIK3CD and PIK3R1 lead to activated PI3K-delta syndrome (APDS). APDS is combined immunodeficiency characterized by constitutive T-cell activation, a substantial deficiency in naïve T cells, and an over-representation of senescent effector T cells. Patients with APDS develop recurrent bacterial and viral infections, lymphoproliferation, and/or

autoimmune diseases. Increasing understanding of the underlying mechanism of APDS enlightens us on the role of T cells in autoimmunity. It also uncovers a therapeutic potential of targeted treatment with selective PI3K-delta inhibitor and mTOR inhibitor by Sirolimus in patients with APDS and rheumatic diseases.[13, 14]

PID with defects in other immune regulatory pathways may also give rise to autoimmune manifestations. This includes the complement pathways, defective apoptosis, and interferon signaling. Patients with these conditions may present with lupus-like manifestations and are discussed in detail in the following section.

SLE and Immunodeficiency: Shared Genetic and Pathogenic Pathways

SLE is characterized by a loss of immune tolerance to nuclear self-antigens, resulting in autoantibody production and immune complex deposition. Several immune dysregulations are thought to be central to the pathogenesis of SLE. These include defective apoptosis, impaired immune complex clearance, and increased type I interferon. PID with defects in these pathways are associated with lupus-like diseases and monogenic lupus.

The imbalance between apoptosis and removal of apoptotic debris is believed to be an important pathway for SLE pathogenesis. The increased exposure of modified nuclear autoantigens to the immune system results in the generation of nucleic acid autoantibody. The fas cell surface death receptor (Fas) is a protein in the tumor necrosis factor (TNF) receptor superfamily and plays a key role in regulating apoptosis. Defective Fas-mediated apoptosis results in disrupted lymphocyte homeostasis and leads to autoimmune lymphoproliferative syndrome (ALPS). ALPS is a disease characterized by lymphadenopathy, hepatosplenomegaly, increased risk of malignancy, and systemic autoimmunity, including SLE. Lymphoproliferation is the predominant clinical manifestation, followed by autoimmunity. Immune-mediated cytopenia is the most common autoimmune manifestation, but other organ manifestations can also be present such as nephritis, hepatitis, pulmonary fibrosis, colitis, and neurological manifestations.[15] The multisystem involvement gives rise to a lupus-like picture. Diagnosis is based on a combination of clinical features, laboratory findings (increased double-negative T cells, and defective Fas-mediated apoptosis in vitro), and genetic mutations.[16]

The immune system is essential for the clearance of self-antigens. Complement deficiencies are the first described form of monogenic lupus characterized by early disease onset and recurrent infections. Complement is a group of circulating proteins (some are membrane-bound) that form a part of the innate immune system. In addition to its important role in host defense, it is essential for the clearance of apoptotic cells and immune complexes. Furthermore, C1q also acts as a negative regulator of type I interferon, a cytokine important for the pathogenesis of SLE. As a result, deficiencies in early components of the classical pathway are associated with SLE.[17] Around 90% of patients with C1q deficiency develop SLE. Deficiencies of C1r and C1s are rare and are present predominantly with recurrent severe infections. Only half of these patients develop lupus-like disease. C2 deficiency is the most common complement deficiency, but SLE manifests only in 10% of these patients with disease phenotype similar to the general SLE population.[18] The risk of SLE in patients with C4 deficiencies is variable and depends on the number of C4 gene copies.[19] The importance of the complement pathway in SLE pathogenesis extends beyond monogenic lupus. For example, anti-C1q autoantibodies were found more frequently in patients with SLE compared with healthy controls.[20] Some studies also showed its association with lupus nephritis (LN) and overall disease activity.[21]

Chronic granulomatous disease (CGD) is a PID characterized by a defect in nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex, which is responsible for the production of reactive oxygen species and intracellular killing by phagocytes.[22] Patients with CGD are at increased risk of recurrent infections and granuloma formation. Inflammatory and autoimmune complications are increasingly important as life expectancy improves with the introduction of antimicrobial prophylaxis.[23] Registry data have shown that patients with CGD have a higher frequency of SLE and discoid lupus.[24, 25] Abnormal apoptosis and impaired clearance of apoptotic cells in patients with CGD have been proposed to account for the occurrence of lupus-like diseases in these patients.[26]

The abovementioned examples of PID and monogenic lupus are not exhaustive, but serve to illustrate the concept that autoimmunity and immunodeficiency are intricately linked with overlaps in genetic and immunobiology. Although most SLE cases are not caused by single-gene defects, the contribution of genetic susceptibility is well demonstrated and reinforces the immunobiological predisposition of disease development in these patients. From GWAS analyses, >100 susceptibility loci have been identified in the human leukocyte antigen (HLA) and non-HLA regions involving coding and non-coding variants suggesting disease complexity.[27] Pathways related to lymphocyte activation, immune response regulation, and immune cell proliferation have been implicated from GWAS data.[28] Other genetic studies have demonstrated that mutations in genes implicated in monogenic lupus are also found in a proportion of patients with SLE, including three prime repair exonuclease 1 (TREX1) and acid phosphatase 5, tartrate resistant (ACP5) genes, which are implicated in type I interferon regulations.[29, 30] Better knowledge of the genetic and immunobiological bases of

autoimmune diseases may translate into clinical advances in biomarkers and therapeutics discoveries.

SLE and Infection Risk: Clinical Factors and Immunosuppressive Therapies

Infection remains an important cause of morbidity and mortality in patients with SLE. Disease activity, nephritis, high anti-dsDNA (double-stranded DNA) antibody, and leukopenia have been found to be risk factors for infections.[31] Protein-losing state (such as proteinuria and protein-losing enteropathy), concomitant infections, or malignancies may also contribute to secondary immunodeficiency and confer infection risk. Another important contribution to infection risk is pharmacological interventions and use of immunosuppressive agents.

Glucocorticoids (GC) are commonly used in patients with SLE. GC have multiple anti-inflammatory and immunosuppressive effects. They inhibit macrophage differentiation and cytokine production and suppress their microbicidal activities.[32] They also affect neutrophil function and adhesion, and impair dendritic cell maturation and function.[33, 34] GC can cause lymphopenia affecting all lymphocyte subpopulations and inhibit T-cell activation by inhibiting cytokines, including interleukins 2.[32] GC also inhibit B-cell proliferation and Ig production.[35] Both the dose and duration of GC therapy are associated with infections in patients with SLE. One study showed that an average daily dose of steroid equivalent to prednisolone 10 mg or above is associated with a 10-fold increase in the risk of infections. Prolonged medium- to high-dose GC (defined as prednisolone 20 mg daily equivalent or above for >30 days) is also a risk factor for infection. Studies in rheumatoid arthritis have shown that even "low-dose" steroids may pose an increased risk of infections.[36] Pulse methylprednisolone is useful for controlling life-threatening manifestations and reducing cumulative steroid dose.[37] Low-dose pulse methylprednisolone has equivalent effectiveness in controlling disease activity and is associated with significantly fewer infections compared with the high-dose regimen.[38]

Cyclophosphamide (CYC) is a powerful agent in treating organ-threatening diseases and is a useful rescue therapy in refractory cases.[39] CYC is an alkylating agent that exerts its action through DNA damage and therefore selectively affects rapidly replicating cells. Infections are common in SLE patients undergoing CYC treatment. Leukopenia and sequential intravenous and oral therapy are associated with infection risk.[40] Low-dose intravenous CYC is associated with a lower risk of infections compared with the high-dose regimen as shown in the Euro-Lupus Nephritis Trial, even though the difference did not reach statistical significance.[41]

Mycophenolate mofetil (MMF) is a prodrug of mycophenolic acid, an inhibitor of inosine-5-monophosphate dehydrogenase. It preferentially inhibits T- and B-lymphocytes proliferation and lymphocyte recruitment into sites of inflammation.[42] Azathioprine (AZA) is a prodrug of 6-mercaptopurine which inhibits purine synthesis and DNA replication. MMF is a useful drug in the management of moderate to severe lupus, whereas AZA is useful for mild to moderate disease.[39] There is growing preference of MMF for induction therapy for proliferative LN due to the its reduced gonadal toxicity and oncogenicity compared with CYC. However, it should be noted that MMF is not necessarily less toxic than CYC. The results from meta-analysis showed no significant difference in infection risk between patients receiving CYC and MMF for LN induction therapy.[43, 44] A study was conducted to compare the cellular changes in a small group of SLE patients on CYC, MMF, and no immunosuppressants. The study showed that although the rate of hypogammaglobinaemia was comparable between MMF and CYC, MMF use was associated with a more enduring reduction of markers of B-cell activation, including plasmablasts and plasma cells compared with CYC.[45] Studies comparing MMF and AZA as maintenance therapy in patients with LN showed no significant differences in infection risk between the two agents.[46, 47] In a nationwide study, it was shown that the risk of infection did not differ among new users of CYC, MMF, and AZA after matching of other risk factors using propensity score.[48]

Hydroxychloroquine (HCQ) and chloroquine (CQ) are antimalarials widely used in patients with SLE and associated with a myriad of benefits, including protection against infections.[49] Several pathways have been proposed to account for their immunomodulatory effects and have been summarized by a previous review.[50] They interfere with lysosomal activities and inhibit MHC class II expression and antigen presentation. Production of various of pro-inflammatory cytokines is also inhibited by these drugs. HCQ and CQ also interfere toll-like receptor 7 (TLR7), TLR 9, and cyclic GMP-AMP synthetase (cGAS) activity. Aside from their immunomodulatory effects, both HCQ and HCQ have antimicrobial effects, especially antiparasitic activity. Data from the Lupus Cruces cohort demonstrated a strong protective effect of antimalarials (Odd Ratio 0.06, $P < 0.05$) in protecting SLE patients against major infections.[49]

Biologic Therapies and Secondary Immunodeficiency

Over the recent decades, biologic therapies have emerged as important therapeutic options in the treatment of rheumatological diseases, including SLE. These drugs have the advantages of targeting specific components in the immune pathway involved in the pathogenesis of diseases. Despite their specificity, biologic therapies are also associated with different side effects and can cause secondary immunodeficiency. Among the different biologics investigated, B-cell-targeted therapies are at the forefront of SLE therapies.[51]

Belimumab is a B-lymphocyte stimulator (BLyS) inhibitor. BLyS is a B-cell survival factor with important roles in the differentiation of immature to mature B cells, Ig class switching, and production. It is the first biologic approved for the treatment of SLE and a recent study also demonstrated its efficacy in LN.[39, 52] Belimumab treatment is associated with a reduced median level of cluster of differentiation (CD) 20 B cells while preserving memory B cells and T-cell population.[53] Hypogammaglobinaemia is infrequent and occurs in around 2% of patients only.[54] Data from clinical trials showed no significant increase in infection risk associated with Belimumab.[55]

Rituximab is a chimeric monoclonal antibody against CD20. CD20 is a B-cell-specific marker expressed on B cells from pre-B to mature B cells. Rituximab achieves depletion of peripheral B cells via complement-mediated and antibody-dependent cell-mediated cytotoxicity. Since autoreactive B cells are one of the key immune cells implicated in the pathogenesis of SLE, peripheral B cell depletion appears as an attractive treatment strategy in SLE. Despite its negative results in randomized controlled trials,[56, 57] subsequent meta-analysis has demonstrated its usefulness in the management of refractory lupus.[58] Rituximab is currently used off-label in patients with severe renal or extrarenal disease refractory to other immunosuppressants.[39] Since stem cells, pro-B cells, and plasma cells do not express CD20, they are spared in anti-CD20 therapies and play a role in B-cell recovery subsequent to treatment. Levels of peripheral CD20-expressing B-cells remain low or undetectable for 2–6 months before returning to pretreatment levels, generally within 12 months.[59] It is increasingly recognized that hypogammaglobinaemia may occur in patients after treatment with Rituximab. The occurrence of hypogammaglobinaemia is believed to be caused by the depletion of short-lived plasma cells resulted from prolonged B-cell depletion.[60] A study involving 243 patients with multisystem autoimmune disease showed that 26% patients developed hypogammaglobinaemia (IgG <5 g/L) following Rituximab treatment. A subgroup of patients had recovery of IgG, but some required Ig replacement.[61] Hypogammaglobinaemia continues to occur over time post-Rituximab with median time to moderate hypogammaglobinaemia (IgG <5 g/L) being 22.5 months and severe hypogammaglobinaemia (IgG <3 g/L) being 24.5 months as shown in one study.[62] Long-term monitoring after Rituximab is therefore important.

The intricate relationship between autoimmunity and immunodeficiency was shown by a recent study of patients with rheumatic diseases with secondary hypogammaglobinaemia after immunomodulatory treatments.[63] Using next-generation sequencing, a high frequency of variants in genes associated with PID were found in those who developed secondary hypogammaglobinaemia. Based on their data, the authors proposed the concept of a shared genetic background between primary and secondary hypogammaglobinaemia. It also highlighted the fact that patients with PID can present with a predominant autoimmune phenotype, and immunodeficiency may be unmasked by the use of immunosuppressants. The study suggested that PID and autoimmune rheumatic diseases are not mutually exclusive, but represent different manifestations of a shared dysregulated immunobiology.

Clinical Approach to Secondary Antibody Deficiency

Antibody deficiencies or hypogammaglobinaemia are characterized by reduced number or function of circulating Ig resulting in the susceptibility to infections. SAD can be due to many different causes, including infection, malignancies, protein-losing states, and use of immunosuppressive therapies. With the increasing availability of biologics therapy, iatrogenic cause of SAD is becoming more important, especially after Rituximab treatment. Early identification of SAD and personalized management is key to avoiding morbidity and mortality.

In the absence of guidelines on SAD in rheumatological patients, our group has previously reviewed this topic and proposed recommendations regarding screening and factors to consider when deciding for Ig replacements.[64] In general, we recommend that serum Ig levels should be routinely monitored, especially in symptomatic and high-risk patients. Screening for hypogammaglobinaemia before the commencement of immunosuppressive therapies and every 3–6 months afterwards should be performed. Hypogammaglobinaemia should also be considered in the presence of infections with unusual severity or frequency or a lack of response to antimicrobial therapy. Infections involving characteristic pathogens such as encapsulated bacteria (e.g., *Streptococcus pneumoniae*, *Haemophilus influenzae*), parasites (e.g., *Giardia lamblia*, *Cryptosporidium*), or persistent/severe viral infections (e.g., chronic norovirus or enteroviruses) should prompt the consideration of antibody deficiency. A careful review of drugs, protein-losing states, and possible concurrent infections or malignancies should be performed. Further workup including lymphocyte subsets, IgG subsets, vaccine response, and immunologist referral should be considered.

The management of SAD includes the identification of causative factors (and reverse the underlying cause if possible), prophylactic vaccination, and individualized assessment for antibiotics prophylaxis and Ig replacement therapy. Non-live vaccine against influenza and *S. pneumoniae* are recommended as some helpful protection via T-cell immunity and residual antibody response may still be achieved. Prophylactic antibiotics and Ig replacement therapy are considered based on a combination of factors, including recurrent and/or severe infection, hypogammaglobulinemia, and vaccination responses. The European Medicines Agency

(EMA) has recommended that intravenous Ig replacement therapy can be used in patients with SAD who suffer from severe or recurrent infections, ineffective antimicrobial treatment, and either proven specific antibody (e.g., vaccine response) or serum IgG level of <4 g/L. When administered, the recommend dose of Ig replacement therapy is 0.2–0.4 g/kg/month followed by titration based on clinical response and trough Ig level. The route of Ig replacement should also be discussed based on local resources and patient's preference. Ongoing review is needed, including clinical response, adequacy of replacement, changes in primary disease conditions and medications, and possible recovery of antibody function.

Conclusion

Autoimmunity and immunodeficiency are interrelated with overlapping genetic factors and immunobiology. The knowledge from PID generates a better understanding of mechanisms underpinning immune tolerance and immune regulations, which offer insights into the pathogenesis of autoimmune diseases. Immunosuppressive therapies are important causes of secondary immunodeficiency. Clinical awareness, regular monitoring, and individualized management are important.

Conflict of Interest

Funding

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