HSPI The Open Access Publisher

J C N JOURNAL OF CLINICAL NEPHROLOGY
ISSN 2576-9529

Case Study

An Uncommon Case Report of Hypothyroidism, Type 1 Diabetes Mellitus, and Systemic Lupus Erythematosus with an Immunosuppressive Consequence: A Case Report

Arif Hoda*, Shruti R Shinde, Avinash Chaudhari, Sameer Vyahalkar, Amar Kulkarni, Pooja Binani and Amit Nagrik

Dr. D. Y. Patil Medical College and Hospital, Nerul, Navi Mumbai, Maharashtra, India

More Information

***Address for correspondence:** Arif Hoda, Dr. D. Y. Patil Medical College and Hospital, Nerul, Navi Mumbai, Maharashtra, India, Email: hodaarif@gmail.com

Submitted: December 12, 2023
Approved: August 27, 2024
Published: August 28, 2024

How to cite this article: Hoda A, Shinde SR, Chaudhari A, Vyahalkar S, Kulkarni A, Binani P, et al. An Uncommon Case Report of Hypothyroidism, Type 1 Diabetes Mellitus, and Systemic Lupus Erythematosus with an Immunosuppressive Consequence: A Case Report. J Clini Nephrol. 2024; 8(2): 118-123. Available from: https://dx.doi.org/10.29328/journal.jcn.1001138

Abstract

An autoimmune condition known as Systemic Lupus Erythematosus (SLE) affects several systems and manifests itself in a variety of ways. It is far more common among young women who are fertile.

It has been demonstrated that a mix of environmental and genetic variables may trigger immunological responses, triggering T and B cells, and leading the B cells to overproduce pathogenic autoantibodies and dysregulate cytokines, which ultimately result in harm to many organs and tissues. One feature of SLE is the presence of antibodies against cytoplasmic and nuclear antigens. An autoimmune illness is also type 1 diabetes. β-cell antibodies (Ab) and other antibodies that cause the autoimmune death of the pancreatic β-cells, which make insulin, are part of the multifactorial pathophysiology of type 1 diabetes mellitus (T1DM).

Immunosuppression is the therapy for systemic lupus erythematosus (SLE), and diabetes itself compromises immunity, making infections more opportunistic. We came across an unusual instance of a patient with SLE, T1DM, hypothyroidism on immunosuppression who subsequently acquired pulmonary TB.

Key phrase: Autoimmune diseases such as type 1 diabetes mellitus (T1DM) and Systemic Lupus Erythematosus (SLE).

Overview

The autoimmune illness known as Systemic Lupus Erythematosus (SLE) affects several systems and manifests itself in a variety of ways. It is substantially more prevalent in younger women in the adolescence to adult age range, with roughly 9:1 female to male ratio [1].

The exact origins of this ailment remain mostly unknown. Nonetheless, research has demonstrated that a mix of environmental and genetic triggers can trigger immune responses, triggering T and B cells as well as the overproduction of harmful autoantibodies and dysregulated cytokines by the B cells, which ultimately results in harm to numerous tissues and organs. Anti-cytoplasmic and anti-nuclear antibodies are typically seen in SLE and are indicative of the disease [2].

Numerous correlations have been observed between SLE and other autoimmune disorders, such as the presence of extra autoantibodies in SLE patients example antiphospholipid antibodies, anticardiolipin antibodies, anti-Scl-70 antibodies in systemic sclerosis, and anti-Ro and anti-La antibodies in Sjogren syndrome [3].

Another autoimmune illness is also type 1 diabetes. It is primarily caused by β-cell antibodies (Ab) and other antibodies that cause the pancreatic β-cells, which create insulin, to be destroyed by the immune system [4].

Insulin Autoantibody (IAA), Glutamic Acid Decarboxylase (GAD) Ab, Islet Cell Autoantibody (ICA), and other antibodies are generated against the pancreatic beta cell in patients with T1DM [5,6].

Informed consent was obtained from the patient

before presenting the report. We came across an unusual instance of a patient with SLE, T1DM, hypothyroidism, and immunosuppression who subsequently acquired pulmonary TB.

After being evaluated for two to three months with the main complaint of widespread weakness, an 18-year-old female was found to have hypothyroidism. When taking thyroid medicine for a year, the patient was sent to the hospital when she unexpectedly lost consciousness at home. She was put on insulin treatment after being evaluated and given a T1DM diagnosis with positive islet cell antibodies. After being investigated for her persistent complaints of numerous joint pains, pedal edema, and facial rashes, it was determined that she had SLE based on the results of her anti-DNA and anti-nuclear antibody tests. She was prescribed hydroxychloroquine tablets, corticosteroids along with a 500 mg/day pulse dose of methylprednisolone for 3 days followed by weight-based oral prednisone, and Mycophenolate Mofetil (MMF) at a daily dosage of 2.5 gm. The following is her list of investigations (Table 1).

The patient had been under immunosuppression for six months when fever and cough began. On evaluation, acid fast bacillus sputum was positive, so she was started treatment for tuberculosis with induction phase of HRZE (Isoniazid / Rifampicin/Pyrazinamide/ Ethambutol) for 2 months followed by a maintenance phase of HR (Isoniazid / Rifampicin) for 4 months and immunosuppressive therapy. MMF was reduced to 1 g daily and oral steroids were reduced to half the dose. The patient responded well to the treatment and was well treated. The patient had vitiligo since 2 years of age and had no significant past history. There were no developmental delays in childhood. Her bowel and bladder function were normal and there was no evidence of addiction.

Discussion

T1DM is an autoimmune disease that occurs not only as an autoimmune disease of the beta cell in the pancreas, but also occurs with other glandular and non-glandular structures involved in autoimmune diseases [7]. Autoimmune diseases associated with T1DM include: autoimmune thyroiditis (15% - 30%), type A gastritis (15%), celiac disease of the stomach (3% to 12%), vitiligo of the skin (-1%). 7%, rheumatoid arthritis affecting joints (1.2%), systemic lupus erythematosus (1.15%) and Addison's disease (0.5%) [8-10]. SLE is a chronic autoimmune disease that affects multiple organs. Clinical manifestations range from mild skin lesions to severe damage to multiple organs such as the kidney, heart and lungs. To diagnose SLE, there are several clinical and laboratory findings. The classification criteria used by the European Union Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) [11] are the most advanced and accurate criteria to date.

On hematological and serological investigations, the affected person had anti-dsDNA and anti-Smith antibodies. According to studies, anti-dsDNA antibodies have a specificity of 96% for SLE and is one of the maximum weighted standards in immunological phase of the 2019 EULAR/ACR class. Anti-dsDNA antibodies additionally intently correlate with ailment pastime in SLE. Therefore, its degrees may be undetectable on remedy and growth throughout an SLE flare. As anti-dsDNA antibodies extrude with ailment pastime, their diagnostic sensitivity is low (52% to 70%) [12]. Anti-Smith antibodies (anti-Sm), is likewise one of the maximum weighted standards with inside the immunological phase of the EULAR/ACR 2019 class for SLE. Anti-Sm antibodies are very precise for SLE, with a specificity of 99% [13] According to the 2019 EULAR/ACR criteria, our patient had a core of 30. An autoimmune ailment like SLE and rheumatoid arthritis could be very uncommonly related to T1DM [14]. In 485 patients with SLE and different autoimmune illnesses, T1DM became recognized with SLE in three of the patients [15]. Skin lesions like vitiligo and Alopecia areata were visible in affiliation with autoimmune conditions. Our patient has had vitiligo since the age of two years, which indicates the autoimmune nature of T1D with SLE [16]. Genetic mutations,

Table 1: Showing Investigations of The Patient.

Hemoglobin	8.9 g/dl (13 - 18 g/dl)	Creatinine	0.53 mg/dl (0.5 - 1.5 mg/dl)	pH - Urine	6.5 (4.5 - 8)	fT3	0.45 pg/ml (2.3 - 4.2 pg/ml)
WBC Total Count	1.2/UL (4 - 11/UL)	Blood Urea	34 mg/dl (15 - 42.8 mg/dl)	Specific Gravity	1.015 1.010 - 1.030	fT4	5.7 ng/ml (0.89 - 1.7 ng/ml)
RBC Count	3.07 mill/mm^3 4.2 - 5.4 Mill/mm^3	Blood Urea Nitrogen	15.9 mg/dl (7 - 20 mg/dl)	Glucose Ur	Absent	TSH	21.41 IU/ml 0.35 - 5.5 IU/ml
Platelet Count	55/UL (150 - 450/UL)	Uric Acid	8 mg/dl 8.4 - 10.2 mg/dl	Ketones	Absent	ANA by IF	Positive (Negative)
PCV	22.7% 40 - 54%	Total Proteins	5.3 g/dl 6.3 - 8.2 g/dl	Urinary Proteins	++	Anti ds DNA	Positive (Negative)
MCV	74 fL 82 - 101 fL	Albumin	1.8 g/dl 3.4 - 4.8 g/dl	Blood (Urine)	++	HbA1C	12
ESR	55 mm/hr 0 - 20 mm/hr	Globulin	3.5 g/dl 1.8 - 3.6 g/dl	Bilirubin	Absent	C3	60 mg/dl (90 - 180 mg/dl)
CRP	29 mg/L (0 - 5 mg/L)	24 hours urinary protein		1415 mg/24 hrs <140 mg/24 hrs		C4	9 mg/dl (10 - 40 mg/dl)
		Islet Cell Antibody – Positive					

MCV: Mean Corpuscular Volume; ESR: Erythrocyte Sedimentation Rate; CRP: C Reactive Protein; f. T3: Free T3; f. T4: Free T4; TSH: Thyroid Stimulating Hormone; ANA: Anti - Nuclear Antibody; IF: Immunofluorescence; C3: Complement C3; C4: Complement C4; HbA1C: Glycosylated Hemoglobin; Anti ds DNA: Anti - double stranded DNA

autoimmunity, and viral infections are few of the principle etiopathological elements which can be implicated with the pathogenesis of T1DM. In a study by Kota, et al. three patients of SLE with T1DM had no different co-morbidities [10]. Autoimmune illnesses along with thyroid disorders, adrenal disorders, celiac ailment, myasthenia gravis, and different connective tissue illnesses also can co-exist [17,18]. We had SLE with T1DM and hypothyroidism with vitiligo. Though SLE influences a couple of systems, its course can range in severity, the quantity of flare-ups, organ involvement and remission. Multiple organ involvement—like kidneys, lungs, or heart—can also additionally shorten life expectancy. Our patient had SLE with T1DM, hypothyroidism, and vitiligo, all of which may be connected to autoimmunity. The complicated interplay among external exposures and genome produces an epigenetic alters the expression of many genes specific to SLE and T1DM. Exposure to environmental elements like Ultraviolet B radiation, infections, and pollutants triggers autoimmunity in genetically inclined people and ends in unusual activation of immune cells [2].

Genetic role

More than 90 SLE susceptibility loci have been identified by Genome-Wide Association Studies (GWAS) over the past decade, and many Single Nucleotide Polymorphisms (SNPs). In addition, atypical monogenic forms of SLE have also been documented [19]. Of the 730 SNPs associated with SLE, 484 were found in gene coding regions, 21 caused changes in amino acids, and the remaining variants were intergenic, depicting a significant effect on gene regulation rather than protein sequence. It is suspected that T, B and NK cell dysfunction may play a role in the development of SLE [20]. The role of T cells in autoimmunity in T1DM and SLE. Few studies have shown that T1DM is associated with CD8T autoreactivity to insulin. Islet amyloid polypeptide and glutamic acid decarboxylase are sources of two previously identified epitopes in HLA-A*0201. In islet transplant recipients, autoimmunity is seen in cases where insulin-specific CD8T cell progenitor frequency B10-18 is found in peripheral blood, resulting in T-cell proliferation of CD4T cells, islet autoantibodies, and loss of cell function [21] T cells are important in the pathophysiology of SLE because they secrete proinflammatory cytokines that cause inflammation. It also induces autoantibody production by B cells and perpetuates disease by recruiting autoreactive memory T cells. In people with SLE, T cell numbers and functions are abnormal [22]. Germinal centre induction, proliferation, isotype switching, and somatic mutation all depend on T follicular helper (Tfh) cells. Furthermore, these cells generate the cytokine IL-21, which promotes B cell development into memory B cells and plasma cells that make antibodies. The interaction between Tfh cells and the OX40 ligand, which is expressed on myeloid antigen-presenting cells, drives the pathological growth of Tfh cells in SLE [23]. The induction of OX40 ligand by TLR7 activation from circulating immune complexes leads to pathologic proliferation of the Tfh cell subset, which causes enhanced antibody production and loss of self-tolerance in SLE patients [24]. Regulatory T cells (Treg) are a distinct group of T cells that, in healthy people, decrease autoreactive lymphocytes and inhibit the immune response while upholding self-tolerance. IL2 activity is necessary for the formation of Treg cells. Treg cell production and function in SLE is compromised by an imbalanced T-cell cytokine profile characterized by IL2 depletion [25]. Low levels of activator of transcription factor 1 protein may contribute to reduced expression of IL2 in T cells, which in turn promotes the progression of SLE. The proinflammatory IL17, whose high levels in SLE lead to tissue damage, is another gene regulated by IL2 [26].

There is a significant role of B cells in the autoimmunity of T1DM and SLE. The development of B cells is affected in T1DM. Several studies have shown autoantibodies in diabetic patients and newly diagnosed diabetics. These include anti-insulin antibodies, tyrosine phosphatase IA2, insulin mass-associated protein 2, islet cell antibody 512, and others [27]. B lymphocytes play a role in the pathophysiology of SLE through their production of antibodies in response to antigens. Activation of Toll-Like Receptor (TLR), Beta-Cell Activating Factor (BAAF) and B-cell activating factor (BCR) are mechanisms involved in B-cell activation. Loss of tolerance is promoted by activation of B cells by the TLR pathway [2]. In SLE patients, transitional B cells are sensitive to TLR9 stimulation and produce autoreactive peripheral B cells. Cytokines, especially BAFF, can stimulate B cells, which may impair B cell tolerance. Anti-DNA, anti-histone and anti-cardiolipin antibody levels are higher in SLE patients with high BAFF levels [24]. In addition, the BCR is a critical regulator of positive and negative selection, and in healthy individuals, B cell survival depends on continued BCR expression. Patients with SLE have polymorphisms in the c-Src tyrosine kinase (Csk) gene that have increased B-interacting BCR activation and increased IgM concentrations in the blood [28].

T and B Cell Signaling activation and interaction are regulated by adaptor molecules, kinases, and cytokines, which are encoded by pathognomonic genes involved in abnormal T/B cell signaling in SLE, as the components involved in antigen presentation are encoded by the class II Human Leukocyte Antigen (HLA) gene [29]. This leads to an increase in surface expression, which triggers an overreactive immune response. The HLA-DR2 and HLA-DR3 alleles are associated with autoantibody production in SLE. The effectiveness of both central and peripheral tolerance-inducing pathways is impacted by dysregulated T cell receptor signaling pathway in Type 1 diabetes [30]. Role of the Complement System is hypothesized that complement dysfunction speeds up a number of steps in pathogenesis of SLE, including decreased removal of Immune Complex (IC) and apoptotic debris, elevated autoreactive CD+8 T cell activity, and tissue damage brought on by the inflammatory

cascade being triggered in organs where IC has been deposited [31]. C1q also suppresses the CD8+ T cell's self-reactivity, helping to clear immune complexes and apoptotic debris. Additive proteins increase autoimmune processes that are organ-specific and contribute to the development of T1DM [32]. Our patient was ANA and anti-ds DNA positive, which is 99% specific for SLE with low levels of c3 and c4. Although in the urine protein report the patient had a proteinuria of 1415 mg//24 hours, a kidney biopsy was not performed because the patient refused the biopsy. Vitiligo is also an autoimmune manifestation of melanocytes that occurred in our patient since 2 years of age. More than half of the pathologic SLE genes were found to encode proteins related to the synthesis or response to IFN-I. Overexpression of Toll-like receptor 7 (TLR7) is a known factor in the pathophysiology of SLE and increases IFN-I production [33]. The role of TLRs in the onset of T1DM is only recently discovered. Research in this field has greatly benefited from the discovery of Toll-Like Receptors (TLRs), a critical component of the innate immune system that recognizes microbial infections and initiates antimicrobial defense responses [34]. TLR dysfunction is highly prevalent in SLE. The pathophysiology of the disease is strongly influenced by B-cell lymphocytes involved in TLR mechanical breakdown [35]. Nuclear antigens present in IC or apoptotic debris activate TLRs, which are nucleic acid signaling receptors that trigger an inflammatory response. TLRs are germline-encoded receptors that are specifically activated in response to endocytosed nucleic acids. They are the first line of defense against certain microbes and identify them. When TLRs are activated, two transcription factors - interferon regulatory factor 3 (IRF3) and nuclear factor-κB (NF-κB) are also activated. This leads to the production of type I interferon (IFN), which is crucial for the pathophysiology of the disease [19]. The role of C3 and C4 is important in the pathophysiology of SLE, monitoring the levels of C3 and C4 in the blood of patients has long been a part of laboratory tests. Those with a positive ANA test and low levels of C3 or C4 have a 94.3% chance of developing SLE. On the other hand, patients with a positive ANA test and at the same time low C3 and C4 levels are 97.6% specific for the diagnosis of SLE [36]. Renal System Lupus nephritis is one of the most common clinical manifestations of SLE. About 50 percent of people experience this, and it's one of the first symptoms of SLE [37]. Thrombotic angiopathy and interstitial nephritis are two other renal symptoms associated with increased expression of inflammatory cytokines such as tumor necrosis factor, interleukins (IL-1, IL-6, IL- 17 and IL-18) and Th1 and Th2 cytokines [38].

SLE management is difficult and calls for a multidisciplinary strategy. The organs affected and the severity of the disorders determine the therapy plan. When the patient was started on immunosuppressive therapy with steroids and MMF, she developed tuberculosis after 6 months of therapy, as diabetes itself is an immunocompromised state along with SLE. Immunosuppressive medications like MMF and AZA stop cells from proliferating, which raises the risk of infection while lowering the activity of the disease. In an open-label randomized controlled clinical trial, patients receiving MMF with AZA experienced a notably elevated rate of infection, reaching 48.7% [39,40].

According to a meta-analysis involving 4469 SLE patients, infection accounts for 33.2% of SLE patients' deaths. In a cohort of 470 SLE patients, 30-year long-term follow-up research found a similar outcome of 25.3% mortality from infection [41]. According to Feng, et al. infections were responsible for almost half (46.2%) of the deaths in cases of late-onset elder lupus, with pulmonary infections being the most common kind of infection [42].

Sepsis incidence was shown to be higher in patients with more active illnesses. According to a recent real-world study, the most prevalent pathogens are bacteria, viruses, and fungi, and the most common infection sites are the respiratory system, skin, and urinary system [43]. Our patient had pulmonary tuberculosis. Hence, we needed to be careful while starting immunosuppressive therapy. There is literature suggesting that the highest peak of infection occurs during the first six months of immunosuppressive therapy. Nineteen patients (6.4%) out of a cohort of 282 newly diagnosed SLE patients experienced significant infections in the first year of follow-up. A higher risk of infection was linked to high baseline SLE activity and prednisolone doses greater than 30 mg/day in the first month of treatment [44].

Combined SLE and T1DM is uncommon, and because of the increased risk of renal, peripheral neuropathy, and retinal disease, it is important to be very careful when determining which disease is causing a given clinical feature. This is because T1DM requires better metabolic control, while active SLE requires more immunosuppression [15]. Hence, a very cautious approach needs to be taken while treating a case involving multiple autoimmune diseases at a time.

Conclusion

A careful monitoring is required during the intensive phase of immunosuppression, as most infections develop within 6 months of starting immunosuppressive therapy. Regular follow-up and monitoring of vital signs will lead to an early diagnosis of infection and treatment for the same when other autoimmune diseases co-exist.

References

1. Vaillant AA, Goyal A, Varacallo M. Systemic lupus erythematosus. StatPearls; 2022.
2. Karrar S, Cunninghame Graham DS. Abnormal B cell development in systemic lupus erythematosus: what the genetics tell us. Arthritis Rheumatol. 2018;70(4):496. Available from: https://doi.org/10.1002/art.40396
3. Didier K, Charras A, Daïen CI, Toquet S, Robbins A, Antonicelli F, et al.

Autoantibodies associated with connective tissue diseases: what meaning for clinicians? Front Immunol. 2018;9:541. Available from: https://doi.org/10.3389/fimmu.2018.00541

4. Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. Lancet. 2014;383(9911):69-82. Available from: https://doi.org/10.1016/s0140-6736(13)60591-7
5. Pihoker C, Gilliam LK, Greenbaum CJ, et al. Autoantibodies in diabetes. Diabetes. 2005;54(Suppl 2). Available from: https://doi.org/10.2337/diabetes.54.suppl_2.S52
6. Taplin CE, Barker JM. Autoantibodies in type 1 diabetes. Autoimmunity. 2008;41(1):11-18. Available from: https://doi.org/10.1080/08916930701619169
7. Kahaly GJ, Hansen MP. Type 1 diabetes associated autoimmunity. Autoimmun Rev. 2016;15(7):644-648. Available from: https://doi.org/10.1016/j.autrev.2016.02.017
8. Kahaly GJ, Frommer L, Schuppan D. Celiac disease and glandular autoimmunity. Nutrients. 2018;10(7):814. Available from: https://doi.org/10.3390/nu10070814
9. Barker JM. Type 1 diabetes-associated autoimmunity: natural history, genetic associations, and screening. J Clin Endocrinol Metab. 2006;91(4):1210-1217. Available from: https://doi.org/10.1210/jc.2005-1679
10. Kota SK, Kumar KV, Reddy PV, Kota SK, Modi KD. Clinical profile of coexisting conditions in type 1 diabetes mellitus patients. Diabetes Metab Syndr Clin Res Rev. 2012;6(2):70-76. Available from: https://doi.org/10.1016/j.dsx.2012.08.006
11. Sota S, Umezawa Y, Nakajima A, Insalaco A, Sfriso P, de Vita S, et al. Anakinra drug retention rate and predictive factors of long-term response in systemic juvenile idiopathic arthritis and adult onset still disease. Front Pharmacol. 2019;10:918. Available from: https://doi.org/10.3389%2Ffphar.2019.00918
12. Fu SM, Wang P, Kavanaugh A, et al. Anti-dsDNA antibodies are one of the many autoantibodies in systemic lupus erythematosus. F1000Research. 2015;4(F1000 Faculty Rev). Available from: https://doi.org/10.12688/f1000research.6875.1
13. Flechsig A, Culemann U, Schneider M, Strauss R, Klotsche J, Dähnrich C, et al. What is the clinical significance of anti-Sm antibodies in systemic lupus erythematosus? A comparison with anti-dsDNA antibodies and C3. Clin Exp Rheumatol. 2017;35(4):598-606. Available from: https://pubmed.ncbi.nlm.nih.gov/28281463/
14. Orozco G, Dota M, Muñoz J, Zhernakova S, Roep BO, González-Gay MA, et al. Analysis of a functional BTNL2 polymorphism in type 1 diabetes, rheumatoid arthritis, and systemic lupus erythematosus. Hum Immunol. 2005;66(12):1235-1241. Available from: https://doi.org/10.1016/j.humimm.2006.02.003
15. Cortes S, Salazar-Cardozo C, Jara LJ, Isenberg D. Diabetes mellitus complicating systemic lupus erythematosus–analysis of the UCL lupus cohort and review of the literature. Lupus. 2008;17(11):977-980. Available from: https://doi.org/10.1177/0961203308091539
16. Passeron T, Ortonne JP. Physiopathology and genetics of vitiligo. J Autoimmun. 2005;25:63-68. Available from: https://doi.org/10.1016/j.jaut.2005.10.001
17. Kordonouri O, Hartmann R, Mohnike K, Grüters-Kieslich A, Grabert M, Holl RW. Thyroid autoimmunity in children and adolescents with type 1 diabetes: a multicenter survey. Diabetes Care. 2002;25(8):1346-1350. Available from: https://doi.org/10.2337/diacare.25.8.1346
18. Barera G, Wolf J, Bazzigaluppi E, et al. Occurrence of celiac disease after onset of type 1 diabetes: a 6-year prospective longitudinal study. Pediatrics. 2002;109(5):833-838. Available from: https://doi.org/10.1542/peds.109.5.833
19. Deng Y, Tsao BP. Genetics of human SLE. In: Wallace DJ, Hahn BH, editors. Dubois' Lupus Erythematosus and Related Syndromes. 8th ed. Philadelphia: Elsevier. 2019;54-68.
20. Odendahl M, Mei H, Radbruch A, Feist E, Hiepe F, Burmester GR, et al. Disturbed peripheral B lymphocyte homeostasis in systemic lupus erythematosus. J Immunol. 2000;165(10):5970-5979. Available from: https://doi.org/10.4049/jimmunol.165.10.5970
21. Pinkse GG, Tysma OH, Bergen CA, Kester MG, Ossendorp F, van Veelen PA, et al. Autoreactive CD8 T cells associated with β cell destruction in type 1 diabetes. Proc Natl Acad Sci U S A. 2005;102(51):18425-18430. Available from: https://doi.org/10.1073/pnas.0508621102
22. Suárez-Fueyo A, Bradley SJ, Tsokos GC. T cells in systemic lupus erythematosus. Curr Opin Immunol. 2016;43:32-38. Available from: https://doi.org/10.1016/j.coi.2016.09.001
23. Nakayamada S, Tanaka Y. Clinical relevance of T follicular helper cells in systemic lupus erythematosus. Expert Rev Clin Immunol. 2021;17(10):1143-1150. Available from: https://doi.org/10.1080/1744666x.2021.1976146
24. Tsokos GC, Lo MS, Costa Reis P, Sullivan KE. New insights into the immunopathogenesis of systemic lupus erythematosus. Nat Rev Rheumatol. 2016;12(12):716-730. Available from: https://doi.org/10.1038/nrrheum.2016.186
25. Giang S, La Cava A. Regulatory T cells in SLE: biology and use in treatment. Curr Rheumatol Rep. 2016;18:1-9. Available from: https://doi.org/10.1007/s11926-016-0616-6
26. Mellor-Pita S, Citores MJ, Castejon R, Tutor-Ureta P, Yebra-Bango M, Andreu JL, et al. Decrease of regulatory T cells in patients with systemic lupus erythematosus. Ann Rheum Dis. 2006;65(4):553-554. Available from: https://doi.org/10.1136/ard.2005.044974
27. Wong FS, Wen L, Tang M, Ramanathan M, Visintin I, Daugherty J, et al. Investigation of the role of B-cells in type 1 diabetes in the NOD mouse. Diabetes. 2004;53(10):2581-2587. Available from: https://doi.org/10.2337/diabetes.53.10.2581
28. Jenks SA, Sanz I. Altered B cell receptor signaling in human systemic lupus erythematosus. Autoimmun Rev. 2009;8(3):209-213. Available from: https://doi.org/10.1016/j.autrev.2008.07.047
29. Mak AN, Kow NY. The pathology of T cells in systemic lupus erythematosus. J Immunol Res. 2014;2014:690740. Available from: https://doi.org/10.1155/2014/419029
30. Clark M, Adams S, Collins J, et al. The role of T cell receptor signaling in the development of type 1 diabetes. Front Immunol. 2021;11:615371. Available from: https://doi.org/10.3389%2Ffimmu.2020.615371
31. Cook HT, Botto M. Mechanisms of disease: the complement system and the pathogenesis of systemic lupus erythematosus. Nat Clin Pract Rheumatol. 2006;2(6):330-337. Available from: https://doi.org/10.1038/ncprheum0191
32. Ajjan RA, Schroeder V. Role of complement in diabetes. Mol Immunol. 2019;114:270-277. Available from: https://doi.org/10.1016/j.molimm.2019.07.031
33. Chyuan I-T, Tzeng H-T, Chen J-Y. Signaling pathways of type I and type III interferons and targeted therapies in systemic lupus erythematosus. Cells. 2019;8(9):963. Available from: https://doi.org/10.3390/cells8090963
34. Zipris D. Toll-like receptors and type 1 diabetes. In: Davis S, editor. The Islets of Langerhans. 2010; 585-610. Available from: https://doi.org/10.1007/978-90-481-3271-3_25
35. Fillatreau S, Manfroi B, Dörner T. Toll-like receptor signalling in B cells during systemic lupus erythematosus. Nat Rev Rheumatol. 2021;17(2):98-108. Available from: https://www.nature.com/articles/s41584-020-00544-4
36. Su Y, Jia RL, Han L, Li ZG. Role of anti-nucleosome antibody in the diagnosis of systemic lupus erythematosus. Clin Immunol. 2007;122(1):115-120. Available from: https://doi.org/10.1016/j.clim.2006.10.003
37. Anders HJ, Saxena R, Zhao MH, Parodis I, Salmon JE, Mohan C.. Lupus

nephritis (Primer). Nat Rev Dis Primers. 2020;6(1):7. Available from: https://doi.org/10.1038/s41572-019-0141-9

38. Aringer M, Smolen JS. Cytokine expression in lupus kidneys. Lupus. 2005;14(1):13-18. Available from: https://doi.org/10.1191/0961203305lu2053oa

39. Dooley MA, Jayne D, Ginzler EM, Isenberg D, Olsen NJ, Wofsy D, et al. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. N Engl J Med. 2011;365(20):1886-1895. Available from: https://doi.org/10.1056/nejmoa1014460

40. Mok CC, Ying KY, Yim CW, Siu YP, Tong KH, To CH, et al. Tacrolimus versus mycophenolate mofetil for induction therapy of lupus nephritis: a randomised controlled trial and long-term follow-up. Ann Rheum Dis. 2016;75(1):30-36. Available from: https://doi.org/10.1136/annrheumdis-2014-206456

41. Goldblatt F, Chambers S, Rahman A, Isenberg DA. Serious infections in British patients with systemic lupus erythematosus: hospitalisations and mortality. Lupus. 2009;18(8):682-689. Available from: https://doi.org/10.1177/0961203308101019

42. Feng X, Zou Y, Pan W, Wang X, Wu M, Zhang M, et al. Associations of clinical features and prognosis with age at disease onset in patients with systemic lupus erythematosus. Lupus. 2014;23(3):327-334. Available from: https://doi.org/10.1177/0961203313513508

43. Zhou P, Chen J, He J, Zheng T, Yunis J, Mak V, et al. Low-dose IL-2 therapy invigorates CD8+ T cells for viral control in systemic lupus erythematosus. PLoS Pathog. 2021;17(10). Available from: https://doi.org/10.1371/journal.ppat.1009858

44. González-Echavarri C, Capdevila O, Espinosa G, Suárez S, Marín-Ballvé A, González-León R, et al. Infections in newly diagnosed Spanish patients with systemic lupus erythematosus: data from the RELES cohort. Lupus. 2018;27(14):2253-2261. Available from: https://doi.org/10.1177/0961203318811598