RHEUMATOLOGY NURSE
PRACTICE

Inside this Issue

ISSUE **6** | VOLUME **3**

- What are the various types of lupus found in the general population, and how are they different?
- What are the known primary risk factors that have been linked to the development of systemic lupus erythematosus (SLE)?
- How does B cell biology, T cell regulation, and cytokine inhibition drive the development of SLE?
- What precautions do patients with SLE need to take to protect themselves from sun exposure?

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THE PATHOPHYSIOLOGY OF SYSTEMIC LUPUS ERYTHEMATOSUS: A NURSING PRIMER

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TARGET AUDIENCE

This activity has been designed to meet the educational needs of nurses and nurse practitioners. Other healthcare providers may also participate.

ACTIVITY DESCRIPTION

In this issue of *Rheumatology Nurse Practice*, we will provide an introductory-level description of the basic immunology and pathophysiology of systemic lupus erythematosus (SLE) that will allow rheumatology nurses and nurse practitioners to better understand and explain key concepts of SLE to their patients.

LEARNING OBJECTIVES

After participating in the activity, learners should be better able to:

- Identify at least three genetic, environmental, and hormonal risk factors that have been tied to an increased risk of developing SLE
- Discuss the primary immunologic events that set in motion the development and progression of SLE
- Differentiate the manifestations of the three types of skin diseases that are specific to SLE
- Develop strategies to appropriately transmit the seriousness of an SLE diagnosis to patients and their families in a manner that promotes adherence and overall cooperation with long-term disease management

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THE PATHOPHYSIOLOGY OF SYSTEMIC LUPUS ERYTHEMATOSUS: A NURSING PRIMER

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Nurses

Rheumatology Nurses Society is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

Rheumatology Nurses Society designates this educational activity for 1.75 contact hours (1.0 pharmacotherapeutic contact hours).

METHOD OF PARTICIPATION

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Systemic lupus erythematosus (SLE), often referred to simply as lupus, is a complex condition that can begin to develop, in some cases, years before it becomes clinically apparent. Dysfunctions in the adaptive and innate immune system are central to the onset of SLE, although the precise timing and causes are currently unclear.

Genetic, environmental, and hormonal factors have all been associated with the cascade of immunologic events that adversely affect several organs in the body and cause SLE, potentially resulting in end-organ damage. As more is known about its etiology, targeted treatments are being developed that may provide much-needed help for the treatment and management of SLE.

SLE Epidemiology

SLE is an autoimmune disease that leads to inflammation and damage of body tissues. It is a systemic disease that affects several organ systems in the body, such as the kidneys, lungs, heart, liver, and brain.[1] SLE develops through multiple steps, with autoantibodies multiplying, in some cases, several years before the onset of clinical symptoms. While the interactions that cause the development of SLE are not entirely clear, SLE is thought to be triggered by a combination of genetic, environmental, and hormonal factors.[2,3]

SLE is the most common, but not only, type of lupus. Other types include the following:[1]

- Discoid lupus erythematosus, which manifests as a skin rash that may wax and wane with treatment
- Cutaneous lupus erythematosus, which can cause skin lesions on body parts exposed to the sun

Drug Names Included Within This Supplement

GENERIC	BRAND
Belimumab	Benlysta
Atacicept	*TBA*
Blisibimod	*TBA*
Anifrolumab	*TBA*
Sifalimumab	*TBA*
Diaminodiphenyl sulfone	Dapsone
Mycophenolate mofetil	CellCept
Rituximab	Rituxan
Oseltamivir phosphate	Tamiflu
Hydroxychloroquine	Plaquenil

- Drug-induced lupus, a lupus-like condition caused by certain prescription drugs such as isoniazid or hydralazine
- Neonatal lupus, a rare condition affecting some infants of women with lupus that puts the newborn at risk for congenital heart block. Neonatal lupus usually resolves within a few months, often with no lasting effects.

Due to the varying definitions of the disease, small study populations, and the complexity of diagnosis, the overall prevalence of SLE is difficult to determine. Recent estimates indicate between 0.05% and 0.1% of the U.S. population has SLE.[4] In other words, there are between 10 to 150 cases of SLE per 100,000 people, depending on geography, race, and gender.[5]

SLE occurs about 10 times more frequently in women than in men and is more common in women of African American, Hispanic, Asian, Caribbean American, and Native American descent than in Caucasian women.[1] SLE usually affects individuals between the ages of 15 and 45, although it can occur in childhood or later in life. About 90% of people with SLE are women, predominantly of childbearing age.[6]

One study that looked at the prevalence and incidence of SLE in a sociodemographically diverse population in Michigan found that the prevalence of SLE was 2.3-fold higher in African Americans than in Caucasians. In that study, the annual incidence (new cases) of SLE among all females was 9.3 per 100,000 persons while the prevalence (total living cases in the population) was 128.7 per 100,000 individuals. African-American patients with SLE were, on average, younger at diagnosis and experienced increased rates of renal disease and progression to end-stage renal disease compared with Caucasians.[4]

Risk Factors

Although the etiology of SLE is not fully known, several potential risk factors have been identified in recent years. These factors are related to personal genetics, environmental exposures (including viruses), and hormonal and reproductive risk factors (see Figure 1).

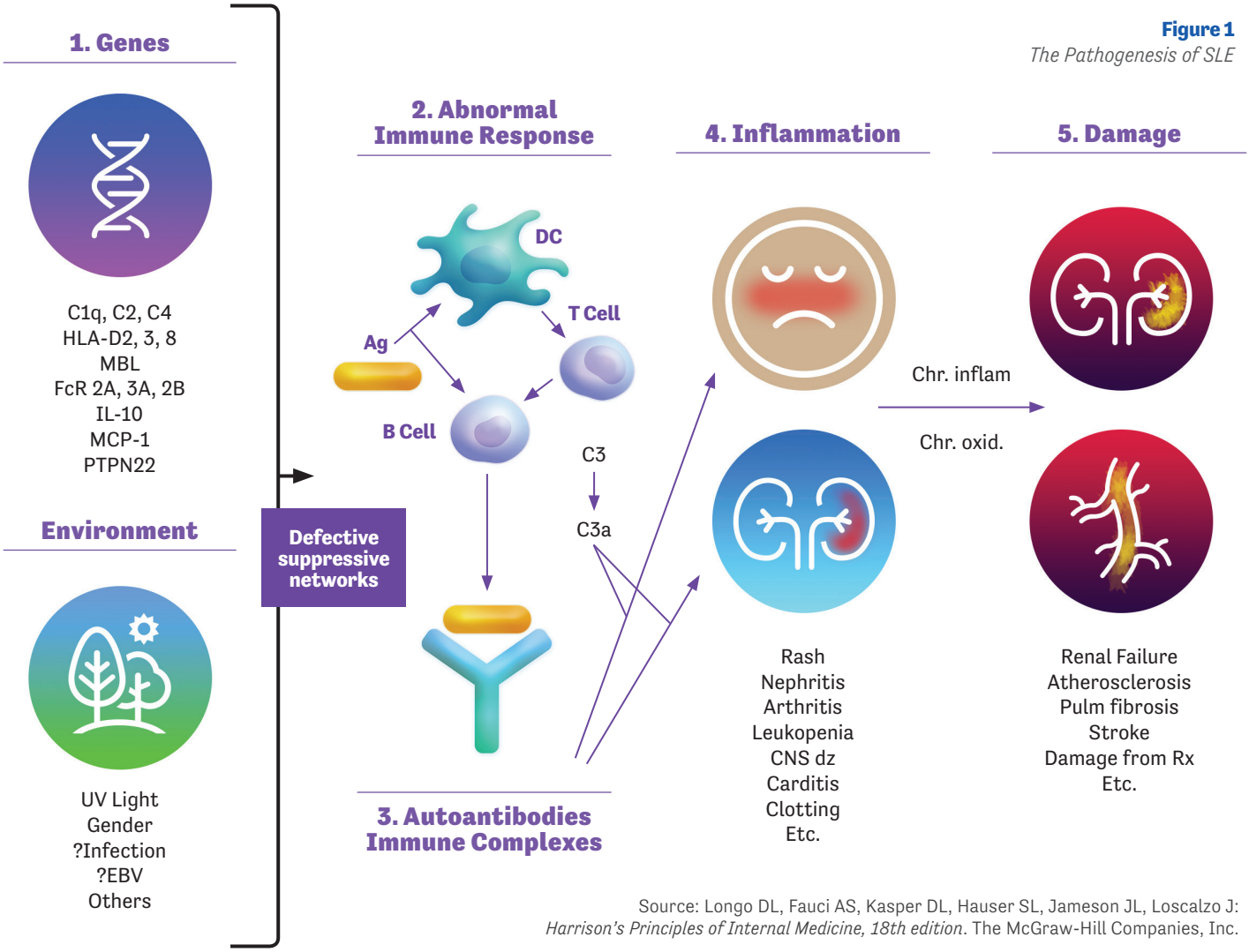
Even though numerous genes and susceptibility loci have been identified that seem to predispose an individual to develop SLE, genetic variation that has been identified so far only explains approximately 8% of genetic SLE risk.[7] Many of the so-called "SLE susceptibility genes" are known to have immune functions.[6] Susceptibility genes in a person's genome not only contribute to the risk of developing SLE but can also influence age of disease onset and clinical manifestations.[2]

Researchers have found that certain sub-phenotypes of SLE—presence of anti-dsDNA autoantibodies, immunological abnormalities, young age at onset, hematological disorders, and absence of oral ulcers—are associated with higher cumulative genetic risk scores. These observations suggest that distinct phenotypes of SLE could be defined by genetics, but, more likely, these phenotypes occur in combination with expanded genetic markers and other immunologic biomarkers.[8]

About 10-12% of patients with SLE have first- or second-degree family members with the disease. Some relatives never develop SLE even though they have disease-specific antibodies. Twin studies have estimated that the rate of SLE concordance in identical twins is 24-35%, whereas the rate is 2-5% in non-identical twins.[6]

Environmental risk factors have also been implicated as triggers for SLE, perhaps through epigenetic mechanisms; in other words, by turning on or off certain genes.[6] Environmental risk factors known to trigger SLE include exposure to silica dust, tobacco smoke, and infectious agents. In 2010, the National Institute of Environmental Health Science Expert Panel determined that occupational exposure to silica was the only exposure that could confidently be classified as a contributor to risk of SLE. Exposure to silica, which includes crystalline silica or quartz, is common among miners and those working in sandblasting, granite cutting, construction work, cement work, and

Figure 1
The Pathogenesis of SLE



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th edition*. The McGraw-Hill Companies, Inc.

In patients who develop SLE, gene-environment interactions result in abnormal immune responses that generate pathogenic autoantibodies and immune complexes that deposit in tissue, activate complement, cause inflammation, and, over time, lead to irreversible organ damage.

Ag, antigen; C1q, complement system; C3, complement component; CNS, central nervous system; DC, dendritic cell; EBV, Epstein-Barr virus; HLA, human leukocyte antigen; FcR, immunoglobulin Fc-binding receptor; IL, interleukin; MCP, monocyte chemotactic protein; PTPN, phosphotyrosine phosphatase; UV, ultraviolet.

brick and tile laying. Cigarette smoking is also a likely contributor in some patients with SLE, the panel determined, and can affect the course of disease among patients with SLE.[2]

Currently, insufficient evidence has been compiled to definitively link other suspected environmental risk factors to SLE, such as exposure to metals, pesticides, persistent organic pollutants, asbestos, solvents, or air pollution. Exposure to the sun and ultraviolet light, however, certainly can trigger development of skin lesions in people with SLE (see sidebar **"Skin Protection Protocols in Lupus Patients"**).[2,9]

Exposure to the Epstein–Barr virus is another potential contributor to the development of SLE. The immunologic response to the Epstein–Barr virus depends on a person's genetic background, with the immune response to the infection playing a significant role in development of early autoantibodies.[2]

Insufficiency of vitamin D, an essential steroid hormone, is recognized for the effects it has on the immune system. Insufficient levels of the vitamin have been noted in patient populations with SLE and have been associated with various comorbidities and complications associated with the disease.[2]

Skin Protection Protocols in Lupus Patients

After the kidney, skin is the second most common organ affected by SLE. Ultraviolet (UV) light, immune cells, cytokines, and immunoglobulin deposition seem to drive the development of skin inflammation and damage among patients with SLE. Specific areas where immunoglobulins have been deposited and where other components of the immune system have accumulated can result in skin lesions when skin is exposed to UV light.[32]

In patients with SLE, exposure to the sun can result in flares that occur soon after exposure. These flares are sometimes transient but they may also, in some instances, persist for weeks to months. In children, these flares can result in renal disease. Some SLE patients report joint pain, weakness, fatigue, or headaches after they have been exposed to the sun.

Sun-induced, skin-related reactions vary among patients with SLE. Some patients describe their reaction as a "stinging/itching sensation" characterized by tiny red bumps or raised patches of skin that occur immediately after sun exposure. These rashes and other skin manifestations can appear on the face or extremities.[33]

The majority of patients with lupus have sensitivity to sunlight and other UV radiation, which can include artificial lighting. For some photosensitive patients, exposure to the sun can result in exaggeration of sunburn-like reactions and skin rashes, and flares can be triggered in other parts of the body.[34] Patients with any of these reactions should avoid sun exposure when possible and use sunscreen and protective clothing when exposed.

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Given the female predominance in SLE, ongoing research continues to look specifically at hormonal and reproductive risk factors for lupus in women. Some studies have found no association between risk of developing SLE and use of hormone replacement therapy or oral contraceptives. However, associations of SLE risk with breast feeding, preeclampsia, and early menopause have been observed in population-based studies, although this association requires additional study. Some studies have found a decrease in the number or severity of disease flares in women with SLE after menopause.[10]

A study of two prospective cohorts with 238,308 women found that early menarche, use of oral contraceptives, and use of postmenopausal hormones were all associated with susceptibility to SLE. Other observations identified a borderline relationship between menstrual irregularity and increased risk of SLE in younger women.[11] As of yet, there is no certainty about the role of these factors on development of disease.

Processes of SLE Development

The development of SLE involves a complicated process that can be difficult for even the most experienced clinicians to fully understand. In this section, we'll provide a high-level explanation of the known immunologic events that set in motion the onset and progression of the clinical manifestations of SLE. These include a breach of tolerance in the adaptive immune system, the amplification of autoimmunity through innate and adaptive immune system dysregulation, and end-organ damage (see Figure 1).[8,12] As the body begins to produce more and more autoantibodies, immune complexes or pathogenic autoantibodies are deposited in the body's tissues.[5]

Adaptive and innate immune mechanisms are associated with the impaired immune response that can result in the development of SLE. The normal adaptive or acquired immune system depends on lymphocytes—the T and B cells—to differentiate foreign molecules such as bacteria, pathogens, and viruses from those that are native to the body so that any new threat can be eradicated. The adaptive immune system produces antibodies and T cells that are highly specific for a particular pathogen or antigen.[13]

Different types of T cells regulate the body's immune response by secreting cytokines and chemokines that stimulate and strengthen the immune response, target and kill infected cells, protect against antigens, and help control the immune response. Helper T cells activate B cells and killer T cells. These helper T cells are initially activated by dendritic cells that recognize and then target and kill a specific pathogen, virus, or infection. In SLE, however, this immune system response does not work as intended (see Figure 2).

Dysfunctions in the immune system

Abnormal B cell activation is strongly implicated in the pathogenesis of SLE. B cells manufacture antibodies, which enable other proteins in the immune system to target antigens. When B cells are hyper-activated, they function as potent antigen-presenting cells and activate autoreactive T cells,[14] which leads to the emergence of autoimmunity.[15] B cells are pivotal in the development of SLE because they not only produce pathogenic autoantibodies but also modulate immune responses through production of cytokines and chemokines.[14]

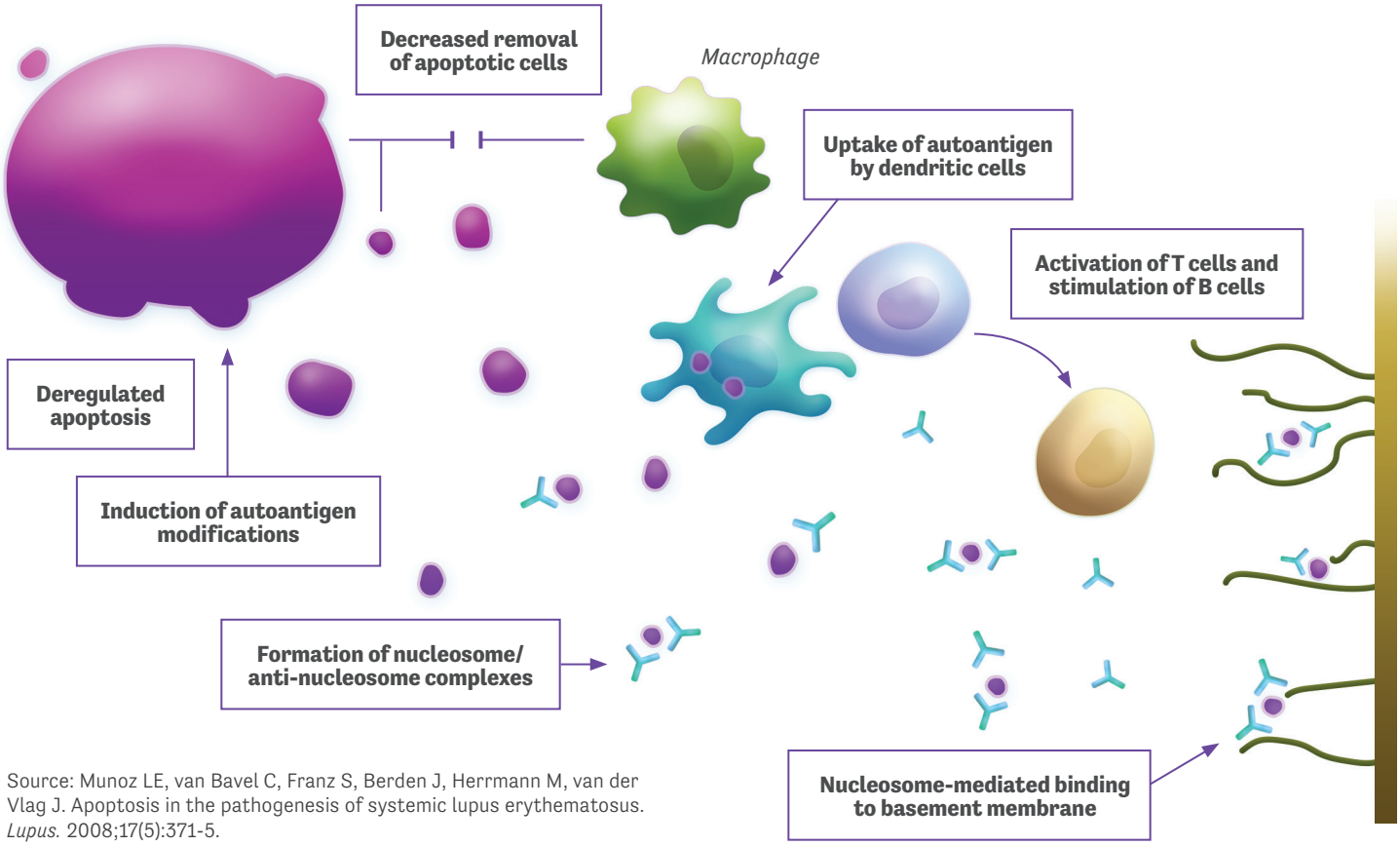
The breakdown of B-cell tolerance, usually at a very early stage,[8] is a defining event in the development of SLE. This breakdown may occur through multiple pathways, including alterations in factors that affect B-cell activation thresholds, B-cell longevity, and apoptotic cell processing. Disturbances in B-cell/T-cell collaboration amplifies autoimmunity in the adaptive immune system, but can also amplify innate immune cell activation through antibody-dependent and antibody-independent mechanisms.[8,16]

Production of high titers of pathogenic autoantibodies against nuclear antigens is considered central to the development of SLE. As SLE emerges, the immune system produces autoantibodies against proteins in the nucleus of the cells, which contributes to the inflammation that characterizes the disease.[17] SLE begins with an autoimmune/preclinical phase marked by production of autoantibodies that are common to other systemic autoimmune diseases, such as subacute cutaneous lupus, before proceeding to a more disease-specific autoimmune phase.[18]

When innate immune responses fail to clear away pathogenic or harmful particles such as modified autoantigens, SLE can develop. These defective responses increase tissue injury by releasing inflammatory cytokines and activating autoreactive T and B cells. Abnormal activation of B cells leads to production of pathogenic autoantibodies and end-organ injury.[17,19]

Figure 2
Systemic Processes in SLE

In patients who develop SLE, deregulated apoptosis and/or insufficient removal of apoptotic cells/blebs leads to the release of (modified) chromatin into the circulation. This leads to the activation of antigen-presenting cells, a T cell–mediated autoimmune response, and the formation of pathogenic immune complexes that incite glomerulonephritis.



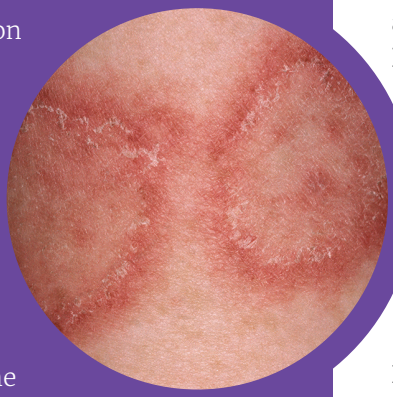
Source: Munoz LE, van Bavel C, Franz S, Berden J, Herrmann M, van der Vlag J. Apoptosis in the pathogenesis of systemic lupus erythematosus. *Lupus.* 2008;17(5):371-5.

"Skin Protection..." continued

There are three types of skin disease that are specific to SLE:

- **Chronic cutaneous lupus erythematosus (CCLE) or discoid lupus erythematosus (DLE)**
- **Subacute cutaneous lupus erythematosus (SCLE)**
- **Acute cutaneous lupus erythematosus (ACLE)**

Some individuals may have lesions related to all three types of these conditions, while others may have only one of the forms of skin disease and not be diagnosed with 'full-blown' SLE. However, if an individual has one of these types of skin disease, they are at increased risk of developing SLE later in life.



If patients develop signs of lupus on the skin, they are usually given a diagnosis of CCLE, which is sometimes called DLE. About 5% of individuals with CCLE will eventually develop SLE. A discoid lesion (see image at right) can be coin-shaped, thick and scaly, and may plug hair follicles and form scars. There can be hair loss when this type of lesion develops on the scalp. People with discoid lupus should avoid exposure to the sun if possible. The lesions, which can be difficult to treat and manage, appear not only on skin exposed to the sun but may also occur on nonexposed areas. If sun exposure is unavoidable, affected patients should wear protective clothing that covers as much skin as possible, including a hat, and use sunscreen.[34,35]

Approximately 50% of individuals with SCLE will also fit the criteria for SLE. Patients with SCLE will commonly have a rash that appears as a red circle or a scaly area that is very sensitive to the sun. SCLE lesions are triggered by exposure to sunlight, generally do not form scars, are not thick, and usually do not itch. Instead, the rashes are small, scaly, and can be described as papular eruptions. Patients with SCLE should wear protective clothing and sunscreen.[34,35]

ACLE, meanwhile, is the most common form of cutaneous lupus associated with SLE. ACLE lesions occur in

Continued on page 10

BAFF (B cell activating factor) and APRIL (a proliferation-inducing ligand) belong to the tumor necrosis factor superfamily and are linked with B-cell maturation and survival. Elevated levels of BAFF and APRIL have been detected in the cerebrospinal fluid in individuals with SLE and correlate to increased levels of autoreactive antibodies.[19]

Monocytes, macrophages, dendritic cells (DCs) and T cells are the primary sources of BAFF. Research has demonstrated that, in patents with SLE, B cells release BAFF/APRIL upon activation, which then initiates a cycle where enhanced levels of BAFF and APRIL lead to systemic activation of the humoral immune system.[19]

With the increased understanding of the role of B cells in SLE, there is a growing body of research focused on the development of new therapies that target B cells. Belimumab, approved by the U.S. Food and Drug Administration for the treatment of adult patients with active, autoantibody-positive SLE who are receiving standard therapy, was the first targeted biological therapy for SLE. Belimumab specifically targets the B lymphyocyte stimulator (BLyS), which is also known as BAFF. BLyS is considered an important target for SLE treatment since it is a costimulator for B-cell survival and function.

Development of a drug that targets BLyS was attractive because it could potentially control the B-cell dysfunction in SLE by decreasing B-cell survival and production of autoantibodies.[17,20]

Atacicept is another targeted therapy under development that targets BLyS and APRIL. Currently in phase IIb/III trials, atacicept neutralizes BLyS and APRIL to prevent them from binding to their receptors on lymphocytes, thereby reducing the number of circulating B cells.[21]

Another investigational agent targeting B cell activity in patients with SLE is blisibimod, a selective inhibitor of BAFF.[21,22]

Although SLE was previously considered a B cell disease, it is now understood that the important role in autoimmunity played by T cells is also severely compromised in patients with SLE. In SLE, T cells enhance the production of autoantibodies by stimulating B cells to differentiate, proliferate, and mature. In other words, many researchers think that SLE could be a T cell-driven condition, because T cells do not appropriately regulate or suppress the immune response in patients with SLE.[23, 24]

There are several ways that T cells are abnormal in patients with SLE. For example, the phenotypic and functional alterations in T cells in people with

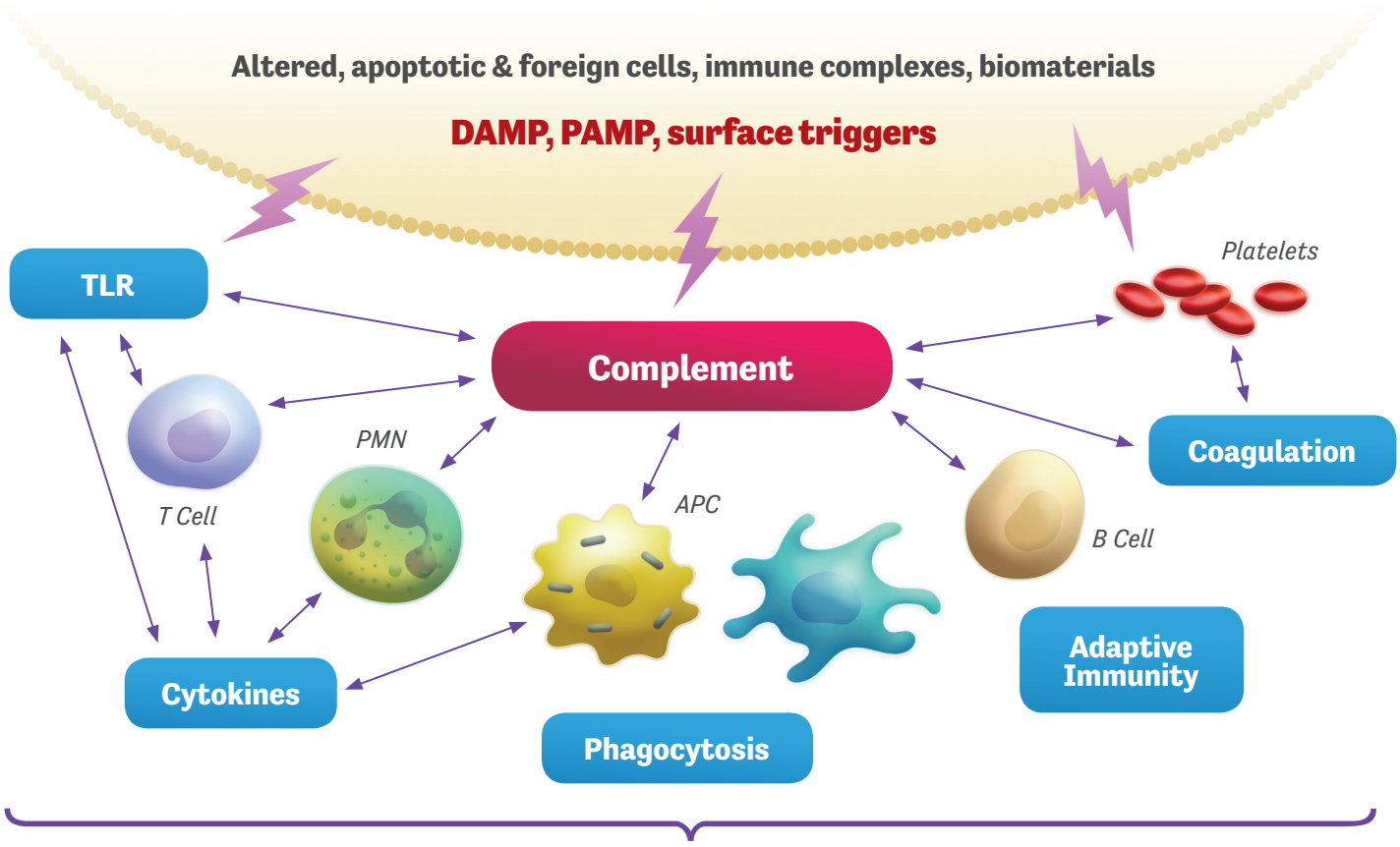


Figure 3
The Hublike Organization of Complement and Its Cell Surface-Directed Action

Triggered directly by foreign and altered surfaces, the complement network resides upstream of most defense and homeostatic systems, thereby acting as an important mediator in physiological and pathophysiological processes.

DAMP, damage-associated molecular patterns; PAMP, pathogen-associated molecular pattern; PMN, polymorphonuclear cells; TLR, toll-like receptor; APC, antigen presenting cell.

Source: Ricklin D, Lambris JD. Complement in immune and inflammatory disorders: pathophysiological mechanisms. *J Immunol*. 2013;190(8):3831-8.

SLE can include expansion of the helper T cell 17 population, a deviation in the way the T-cell receptors (TCRS) function, oxidative stress, and epigenetic changes. Also, the regulatory T lymphocytes CD4+ and CD8+ do not alleviate the proinflammatory milieu that occurs in SLE.[23]

Abatacept is the first drug targeting costimulation between T cells and antigen-presenting cells, and it has been approved for treatment of several autoimmune diseases. Because of its mechanism of action and its efficacy in treating rheumatoid arthritis, clinical trials are evaluating its potential use for treatment of SLE.[22]

Complement System in SLE

The complement system is formed by more than 30 proteins that present in either a soluble form or on the surface of cell membranes. Some of these proteins are sequentially activated by different pathways.[25] The complement system plays a significant and complex role in immune response and SLE, and much remains unknown about how the complement system works. It is known, however, that when autoantibodies form immune complexes with their antigens, as in the pathogenesis of SLE, the resulting immune complexes activate complement. When complement is activated, it then triggers a cascade of inflammatory reactions (see Figure 3).[26]

A deficiency in complement has been observed in patients with SLE.[27] There are two possible explanations for this. The first explanation suggests that, when the disease is active, complement factors are deposited in tissue such as the kidney, causing complement levels in the blood to decrease.

"Skin Protection..." continued

approximately 50% of patients with SLE during the course of their disease. This type of skin disease can manifest as a butterfly rash. The lesions are predominantly located in areas exposed to the sun, are triggered by sunlight, and usually fade over a few weeks without scarring. Usually, this type of rash is found on palmar surfaces of the hands as "red spots" in people who are having an SLE flare; the rash is brought on or worsens with exposure to sunlight. As with the other types of lupus-related skin disease, patients with ACLE should wear protective clothing and apply sunscreen when outdoors.[34,35]

While not everyone with chronic CLE, subacute CLE, or acute CLE is diagnosed with SLE, the presence of any of these forms of lupus-specific skin diseases seems to increase the risk of SLE development later in life.[34]

Regardless of the form of cutaneous lupus, all patients should take the following precautions when exposed to sunlight:[34-36]

- Wear sunscreen
  - Should be SPF 70 or higher sunscreen
  - Should contain Helioplex, which blocks UV-A and UV-B rays
- Avoid the sun during the hours between 10 a.m. and 3 p.m.
- Apply sunscreen everywhere, including skin covered by clothing, every day throughout the year
- Use a UV-blocking shield if a lot of time is spent near windows or riding in a car
- Follow sunscreen application directions and reapply often, particularly after sweating and prolonged sun exposure
- Wear a hat with a wide brim, preferably one that has SPF built into the material
- Avoid antibiotics containing sulfamethoxazole and trimethoprim (ie, Bactrim and Septra), which increase sun sensitivity and lower blood counts
- Wear protective clothing outdoors on sunny days, including a long-sleeved shirt
- Avoid tanning booths or other places with artificial light sources
- Wear sunglasses with UV protection to help prevent the development of cataracts due to UV rays

The second explanations posits that hereditary and inborn abnormalities of the complement system can cause an inability to make certain complement receptors.[27]

Hereditary complement deficiency may cause SLE. The most prevalent and most severe disease is associated with deficiency of the proteins of the complement 1 (C1) complex and with total C4 deficiency. More than 75% of individuals with deficiency of one of these proteins have SLE, and this deficiency is commonly associated with a more severe form of the disease. There is lower prevalence of lupus associated with C2 deficiency, while hereditary C3 deficiency is not commonly associated with SLE.[26]

Another association of complement with SLE is that the disease processes that occur in SLE lead to development of autoantibodies to certain complement proteins. About a third of patients with SLE have anti-C1q, an important autoantibody to a complement protein.[26]

Dendritic cells

Dendritic cells (DCs) are also at work in the pathogenesis of SLE. DCs are antigen-presenting cells that bridge innate and adaptive immunity. DCs contribute to both clearance of dying cells and maintenance of tolerance, and are thought to play a key role in the development of SLE by breaking immunologic tolerance.

One proposed model explaining how DCs contribute to the immunopathogenesis of SLE is that the initial injury is caused by a build-up of dying cells, which results from either dysregulated apoptosis or insufficient clearance of dying cells by DCs or other phagocytes.[5]

DCs produce type 1 interferons (IFNs) in response to a viral infection. In patients with SLE, however, these cells synthesize IFN via toll-like receptors (TLR), which are central to the innate immune system.[28] The TLRs activate multiple inflammatory pathways to defend against invading pathogens. When the TLR pathways are inappropriately activated, an autoimmune response begins or continues, and tissue injury results. Once the immune response is amplified, it becomes self-sustaining.[18]

Type 1 IFNs directly promote B cell activation, antibody production, and T cell survival and expansion. The frequency, composition, and phenotype of DCs in patients with SLE are different compared to individuals without the disease. High levels of type 1 IFNs are found in >70% of patients with SLE.[5] A majority of patients with SLE have

ongoing production of type 1 IFNs and an increased expression of type 1 IFN-regulated genes.

Because activation of the type 1 IFN system is implicated in SLE, researchers have looked at using it as a potential target for therapy. Anifrolumab is a type 1 IFN receptor antagonist in phase III trials that binds to the type 1 IFN receptor known as IFNAR. Investigators are pursuing whether blockade of IFNAR with this agent may reverse some of the immune dysregulation that occurs in patients with SLE.[29]

A second novel therapy targeting IFN-α, sifalimumab, appeared promising in early clinical trials, but further development of the drug was halted pending additional data evaluation.

Cytokines and Autoimmunity

Several cytokines are involved in the pathogenesis of SLE that have numerous effects. Cytokines are secreted by immune cells such as lymphocytes, macrophages, and DCs, and are mostly generated by innate immune cells when they encounter invading pathogens. When certain cytokines are elevated in patients with SLE, they can contribute to hyperactivation of the immune system. A defect or an excess of cytokines can lead to the development of immune-mediated disease.[30]

Cytokines are grouped according to their function—T helper (Th)1, Th2, and Th17. The overproduction of Th2 cytokines promotes B-cell hyperactivity and humoral responses. An excess of Th1 and Th17 cytokines, meanwhile, is generally associated with T cell hyperactivity and inflammation. In patients with SLE, cytokines from each group have been linked to development and progression of the disease.[30]

Among the antiinflammatory cytokines are the isoforms of transforming growth factor β (TGF-β). The most important of these isoforms in patients with SLE is TGF-β1, which is predominantly expressed in the immune system. Patients with new onset of SLE have a decreased concentration of serum TGF-β1.[19]

IL-10 is an anti-inflammatory cytokine produced by almost all leukocytes. The production of IL-10 can be induced by TLR or non-TLR signaling in macrophages and myeloid DCs. Antigen-presenting cells and lymphocytes are the main targets of IL-10 on immune cells. IL-10 may function as a potent B-cell stimulator that enhances activation, proliferation, and differentiation of B cells. It may also promote autoantibody production. Several studies have found that serum IL-10 titers are significantly elevated in patient with lupus and correlate with overall disease activity.[19]

Abnormal levels of IL-6, a proinflammatory cytokine, have also been observed in patients with SLE. Elevated levels of IL-6 correlate with more severe disease activity, and increased levels of serum IL-6 may also be involved in the development of anemia in patients with lupus. IL-6 plays a dominant role in SLE pathogenesis because it accelerates autoantibody production by promoting proliferation of autoreactive B cells.[19]

Conclusion

Increased understanding of SLE pathogenesis by focusing on B-cell biology, T-cell regulation, and cytokine inhibition may provide important and novel treatments for the disease.[8,31] Bringing novel therapies from initial development through the clinical trial process has been slow, given the complexity of SLE, the various ways the disease presents, the involvement of several organ systems, and the many processes involved in the immune system. Yet as the pathogenesis of this complex disease is better understood and as biological drug therapy development continues to advance, promising new therapies are expected to be developed and potentially introduced into clinical care.

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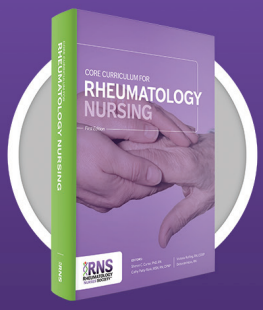

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Don't Let Age Fool You!

by Linda Grinnell-Merrick, MS, NP-BC

AUTHOR PROFILE:

Linda Grinnell-Merrick, MS, NP-BC

Linda Grinnell-Merrick, MS, NP-BC, is a board-certified nurse practitioner at the University of Rochester Medical Center in Rochester, NY, and the President of the Rheumatology Nurses Society.

I work in a university-based rheumatology practice that includes an inpatient team that sees patients on the rheumatology service or consults on patients admitted to other services within our system.

Three years ago, our team was called in for a consult on SJ, a 72-year-old male patient who was newly diagnosed with lupus nephritis. SJ had initially been admitted to the hospital complaining of nausea, fatigue, shortness of breath, and bilateral lower extremity edema. He reported that he was generally in good health, with no known underlying medical conditions.

SJ's symptoms came on quickly. He initially dismissed everything as a "flu bug," but as his symptoms worsened and he became increasingly shorter of breath, SJ sought medical care and was admitted to our emergency department.

Laboratory results showed high levels of creatinine, blood urea nitrogen, and potassium. In addition, SJ's urine test results were abnormal with proteinuria, red cell casts, and red blood cells noted on urinalysis. He was hypertensive and struggling to breathe, and was clearly in acute renal failure of unknown etiology. Treatment was initiated with IV fluids, aggressive diuresis, oxygen, and anti-hypertensive medications.

After an evaluation by our nephrology team, a kidney biopsy was scheduled, which revealed stage V kidney failure (Table 1).[1] This came as a surprise as SJ had no history or prior symptoms suggestive of systemic lupus erythematosus (SLE). He was also older than most newly-diagnosed SLE patients. A rheumatology consult was placed.

Immunologic testing revealed high levels of anti-nuclear antibody and anti-double

Stage	Description	GFR Range (mL/min/1.73 m²)	Clinical Presentations*
	At increased risk	≥60 (without markers of damage)	CKD risk factors
1	Kidney damage with normal or ↑ GFR	≥90	Markers of damage (nephrotic syndrome, nephritic syndrome, tubular syndrome, urinary tract symptoms, asymptomatic urinalysis abnormalities, asymptomatic radiologic abnormalities, hypertension due to kidney disease
2	Kidney damage with mild ↓ GFR	60-89	Mild complications
3	Moderate ↓ GFR	30-59	Moderate complications
4	Severe ↓ GFR	15-29	Severe complications
5	Kidney failure	<15 (or dialysis)	Uremia, cardiovascular disease

Table 1
Stages of Chronic Kidney Disease[1]

Includes presentations from preceding stages. Chronic kidney disease is defined as either kidney damage or GFR <60 mL/min/1.73 m² for ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies

"It remains important to take a comprehensive history, perform a thorough physical exam, and order appropriate laboratory testing regardless of patient age when SLE is suspected"

stranded DNA. There were no apparent physical manifestations of SLE such as rash or mouth ulcers. Following this workup, treatment was initiated with high-dose IV glucocorticoids and IV cyclophosphamide in hopes of preventing chronic renal failure.

I first met SJ a few months after he was discharged from the hospital. At that time, he was still struggling with fluid retention, fatigue, and shortness of breath. His renal function was little improved, and there was talk of initiating hemodialysis, although SJ was reluctant to move forward with this more drastic measure as he had been healthy until a few months ago. SJ's SLE was being managed with mycophenolate mofetil, hydroxychloroquine, and a tapered dose of glucocorticoids. There were still no physical manifestations of SLE. As a former dialysis nurse, I suggested to SJ that hemodialysis would likely make him feel better, and he agreed to give it a try.

Several months later, SJ returned to our office looking and feeling like a new man. He had begun dialysis and was breathing comfortably. The fluid in his legs was gone, and he claimed that he felt great. It has now been close to 2 years from my first meeting with SJ and he continues to do well, remaining on regular dialysis to help forestall the development of additional SLE symptoms.

I think of SJ every time we receive a referral for evaluation of possible SLE, which often comes as a result of a low-titer ANA. Just because a patient is in their 60s or 70s should not forestall the possibility of a new diagnosis of SLE. It remains important to take a comprehensive history, perform a thorough physical exam, and order appropriate laboratory testing regardless of patient age when SLE is suspected.

I have had several older patients who will come to me with printouts from the Internet, claiming that "it says right here that I'm too old to be diagnosed with SLE," but I always remember SJ whenever I need to explain to them, "You never know—we've all been fooled at one time or another!"

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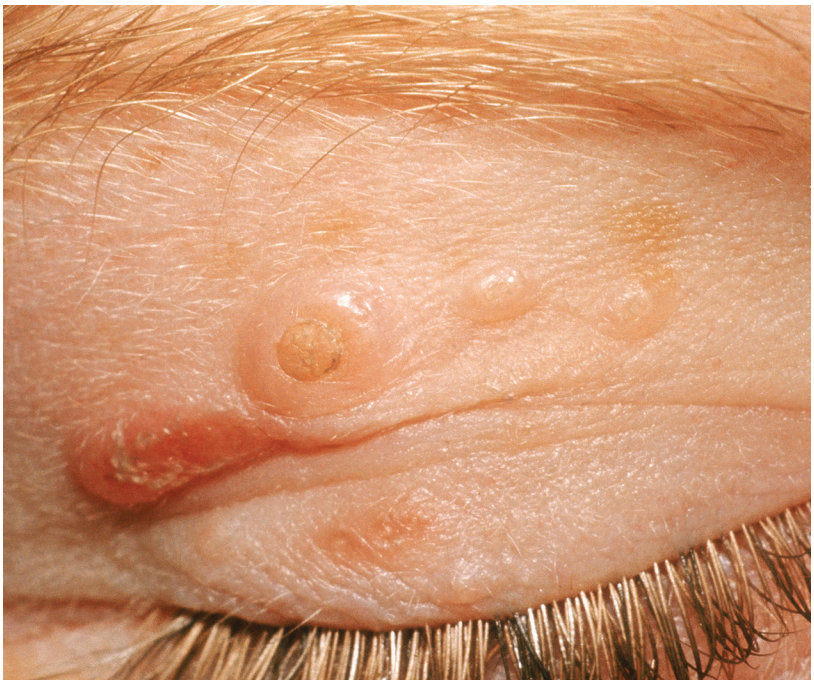
It Takes a Team to Beat "The Beast"

by Monica Richey, NP, MSN, ANP-CP/GNP

When I met JP, she had just turned 22 years old. She had been living with systemic lupus erythematosus (SLE) since the age of 13, suffering through many ups and downs.

As with every other young lupus patient I see, JP had extremely aggressive disease. Since being diagnosed, she had presented at one time or another with almost every major complication of SLE, including bullous lupus. She had tried (and failed) numerous oral medications. Diaminodiphenyl sulfone caused hemolytic anemia and neutropenia. She could not tolerate methotrexate. Azathioprine did not work. She would not take mycophenolate mofetil—the pills were too big.



Molluscum contagiousus is a virus-caused skin condition characterized by the presence of white, umbilicated papules. It is common in immunocompromised patients, especially adolescents.

Being immunosuppressed also caused JP to develop molluscum contagiousus (see image above) over her face. You can imagine how depressed this would make any teenager, and it caused JP to isolate herself from her classmates throughout high school.

Then, at the tender age of 20, JP was given the greatest of all challenges—Class III and IV lupus nephritis.

Even for the most experienced provider, a mix of Class III and IV lupus nephritis is considered a beast with no reins. It can go very badly, very quickly. In hopes of getting even a minimal amount of control over the disease, JP was urged again to try mycophenolate mofetil, although she was honest in telling her providers that she was often noncompliant with the suggested regimen.

During her treatment, JP developed Libman-Sacks endocarditis, a form of nonbacterial endocarditis that is sometimes seen in association with SLE. This required the addition of yet another pill to JP's treatment regimen.

Things became even more complicated when JP became pregnant at the age of 22. That resulted in an immediate transfer from her pediatric rheumatology practice to an adult practice. There was no gradual transition or formal plan in place—once she became pregnant, it was a quick "goodbye." To make matters worse (yes, they became worse), JP had an ectopic pregnancy that required surgical intervention to remove her 8-week old fetus. As JP later told me, "It was whirlwind craziness."

I met JP after the resolution of the ectopic pregnancy. I familiarized myself with JP's medical history prior to our first meeting, and I frankly expected the worst. I was therefore extremely surprised at how cool and calm JP was during our first encounter. As a matter of habit, I try to get to know the person behind the patient when I first meet someone new. I find that it helps in determining treatment decisions to get a sense of a new patient's personality, their risk tolerance, and their likelihood of adhering to certain regimens.

During our initial conversation, it became clear to me that—despite a 9-year history with the disease—JP had absolutely no clue what lupus was or what she was up against. She thought that lupus

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was a disease that eventually would just "go away" and that it made little difference whether or not she took her medications. Her knowledge of her disease process was, at best, poor. She had no idea what Libman-Sacks or lupus nephritis meant. While I was shocked with her lack of knowledge (although it is not uncommon among patients to be this uninformed about their disease), I took the situation as an opportunity to start from the beginning, explaining to JP what lupus is as well as what her serologies were and what they meant.

We then talked about JP's goals and dreams, which included having children and finishing college. Because she needed so much 1-on-1 education about her disease, I scheduled JP for follow-up appointments every 2 weeks. She became an eager learner and often asked what "her numbers" meant. She started to become an advocate for her own care, frequently asking me what she could do to better help control her disease. It was an important step when JP began to understand that I was in her corner and would help her in this difficult fight.

Our conversation about contraception, unfortunately, did not go as well as our initial discussions. Despite the significant danger, JP was adamant that she wanted to become pregnant again "as soon as possible." Her obstinance literally sent a cold chill through my spine, so I tried to negotiate (ie, beg) to come up with a reasonable solution.

I tried my best to explain to JP that a pregnancy at this time would be extremely dangerous, though I tried to remain cool and calm so as not to ratchet up the level of drama. JP is one of my more educated young patients (she is a college student) so I showed her lots of data to hammer home my point. Fortunately, she agreed to stop trying to get pregnant for the time being, although this remains a frequent topic of discussion between us.

We then turned to a discussion of treatment. JP "had had it" with mycophenolate mofetil so I suggested a trial of rituximab, which, while not approved for the treatment of SLE, has shown the ability to decrease disease activity.[1] I also suggested azathioprine at the highest dose possible given JP's stage III and IV kidney disease.

Although, knowing JP's prior issues with nonadherence, I was leery to introduce an additional medication, I also suggested most of our patients' worst nightmare—high-dose prednisone (40 mg). To cement our "team" relationship, I gave JP my cellphone number in case of emergency and emphasized to her that she needed to let me know if she decides to stop any of her medications as soon as possible.

As nurses, one of our primary jobs is to provide our patients with appropriate education so that they understand their disease and gain insight into why we are suggesting specific treatment options. I tend to give out information in small doses. I also provide my patients with a list of reliable online resources and suggest support groups to help them avoid those dreadful blogs that promise "miracle cures" (I once lost a patient because of such a website). In today's information-rich environment, we need to be Internet cops—there are too many unreliable websites that can provide our patients with misleading information.

In treating lupus, we may sometimes need to take creative approaches that require us to think outside the box. But most importantly, we need to get to know our patients and embrace their disease. It takes a team to beat the beast.

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Pulling Back the Curtain on "The Great Imposter"

by Iris Zink, MSN, NP, RN-BC

Systemic lupus erythematous (SLE) has been called "The Great Imposter." A sneaky disease that frequently changes its tactics to target its prey's deepest vulnerabilities, SLE is like a grey wolf lurking at the edge of the woods, waiting patiently to attack an individual's bloodstream when it identifies an opportunity.

Of all the autoimmune diseases, SLE is the most difficult to treat and treat successfully. Its effects can be devastating to a patient's quality of life and potentially life threatening down the road. Developing effective strategies takes patience and persistence.

My personal education about SLE was accelerated early in my career by JD, a 50-year-old Caucasian female who presented to me with SLE that manifested in multiple ways. Despite having lived with SLE for more than 20 years, JD had a wonderful outlook on life and a sharp sense of humor.

Since being diagnosed with SLE in her mid-20s, JD's disease morphed every few years, attacking new systems and causing new problems with each adjustment. JD's medical history was significant and—in addition to the traditional oral sores, nasal sores, hair loss, skin sores, and recurrent fevers—included the following:

- A period of intractable migraines that required several hospitalizations
- Anemia and neutropenia that required multiple blood transfusions
- Vascular inflammation near the optic nerve that caused short-term blindness lasting 7 days
- Cardiac inflammation and pericardial effusions
- Pleurisy and pleural effusions
- Avascular necrosis of the hip due to high doses of steroids

And these are just some of the long list of issues JD had battled over the years. Her SLE just never let up. She started on hydroxychloroquine, switched to mycophenolate mofetil, and then eventually moved on to IV cyclophosphamide after a bout of renal nephritis.

One of the reasons caring for JD was such a valuable personal learning experience was because it occurred early in my professional career, just as I was learning about the insidious nature of autoimmune diseases. At the time I began caring for JD in the mid-1990s, we did not know a lot about how or why SLE developed and progressed. Treating the disease mostly required guesswork. In JD's case, we would try a new approach that seemed to work for a short time, only to watch in disbelief as another organ system came under attack.

The end of my journey with JD came when "the great imposter" attacked her liver. With no apparent cause, JD's liver enzymes shot up to 400 virtually overnight. She was sent to a hepatologist for evaluation, who promptly counseled her about her "obvious alcoholism" and the need to quit drinking immediately. The only problem was that JD did not drink. Her doctor, however, did not believe her and insisted that she must be a closet drinker and a liar, as there was no other possible explanation for her cirrhosis of the liver.

JD returned to our office in tears. We were horrified by the accusations made by JD's doctor, and I reassured her that I believed her and felt that the only logical answer was that her SLE was affecting her liver. A few years later, the literature confirmed our beliefs, showing that approximately 25-50% of patients with SLE may have liver abnormalities, including inflammation and scarring.[1]

Shortly after fibrosis of the liver was diagnosed, JD was hospitalized with pneumonia and eventually developed sepsis. Due to years of steroid exposure, JD was at high risk of infection, so this did not come as a complete surprise. Once sepsis set in, JD's kidneys failed, and her body simply stopped fighting. She looked at her husband and daughter and told them that this was the end. At age 50, JD died due to complications of SLE.

What JD taught me is that we can't fit any of our patients, and especially those with SLE, into a typical "bucket" of symptoms. While SLE has been shown to be most aggressive in non-Caucasians,[2] JD was a Caucasian patient who still developed multiple serious and life-threatening complications. She was a fighter with a "can-do" attitude who tried to—and usually did—overcome every obstacle thrown her way. Her case is not one that any nurse would have read about in a textbook, but has been a valuable lesson in showing me the range of possibilities in patients with SLE.

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The Pitfalls of Fragmented Care

by Cathy Patty-Resk, MSN, RN, CPNP-PC

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Cathy Patty-Resk, MSN, RN, CPNP-PC is a certified pediatric nurse practitioner in the Division of Rheumatology at Children's Hospital of Michigan in Detroit, MI, where she provides medical services to inpatient and outpatient pediatric rheumatology patients.

TK was an 8-year-old female who presented to our pediatric rheumatology clinic about a year ago with a positive antinuclear antibody (ANA) test result (1:320), general fatigue, and a recent preliminary diagnosis of pediatric systemic lupus erythematosus (SLE) that was made after she was hospitalized with pneumonia.

A review of TK's medical history showed hemoglobin S sickle cell disease (SCD), an inherited red blood cell disorder (both of her parents also had the disease), for which she received regular exchange transfusions via an implantable device.

The month prior to her pediatric SLE diagnosis at a local hospital, TK was hospitalized for several days with abdominal pain and joint pain in her wrists, knees, and feet without swelling. Her mother told us that, at the time, TK's urine looked dark brown, but it had returned to normal coloration by the time she was again hospitalized a month later. Her clinicians concluded that the pain was most likely attributable to her SCD, although TK's mother was dubious as she had not experienced joint pain throughout her own personal history of SCD.

TK's lab workup provided to us yielding the following results:

ANA 1:320	Decreased albumin level
Hemoglobin: 9.1, WBCs: 9.1, Platelets: 576	Elevated thyroid stimulation hormone and activated partial thromboplastin time
Negative anti-double stranded DNA test (dsDNA)	Positive lupus anticoagulant (LA)
C3/C4 compliment, creatinine, free thyroxine all within normal limits	ENA negative
Slightly elevated C-reactive protein	No evidence of sarcoidosis
Significantly elevated liver function tests (5x normal)	Urine studies were positive for urine protein and urobilogen

TK's physical exam in our office was completely normal. We therefore interpreted her fatigue to be consistent with a child recovering from a severe case of pneumonia. TK complained of general intolerance to physical activity, though there was no shortness of breath or difficulty breathing.

Uveitis had already been ruled out by an ophthalmologist prior to TK coming to our office, which would otherwise have been a possible explanation for her abnormal ANA result. ANA results can also be abnormal in children who are ill, so we decided to repeat the test, as well as get a urinalysis, now that TK's influenza and pneumonia had passed. Our office is diligent about ordering urine testing in new patients since children are often at high risk of developing autoimmune diseases that affect their kidneys such as lupus nephritis or Wegener's granulomatosis.[1,2] TK's mother chose to have her blood drawn during her next exchange transfusion the following week rather than in our hospital.

It was almost two weeks later that we finally received the results of the repeat ANA and urinalysis. Much to our surprise, TK's ANA result had ballooned to 1:>10,240 and she had protein with 3+ glucose in her urine. We immediately contacted TK's mother to inform her of these abnormal lab results and to urge her to bring TK back to our office as soon as possible for further evaluation.

Our first step was to expand our urine testing to include a urinalysis as well as urine protein and urine creatinine tests so that we could calculate TK's urine protein creatinine (UPC) ratio. UPC results give us an idea of how well a patient's kidneys are working. There are often changes in a patient's UPC that show up before serum creatinine levels rise, making it helpful in identifying children at risk of renal disease.

Our urgency initially alarmed TK's mother. Because we showed no initial reason for urgent intervention during our preliminary workup, her mother asked us to send all lab results to TK's primary care physician (PCP) and hematologist so that they could determine the appropriate next steps. TK's mother told us that her daughter was feeling fine and nothing had changed in her overall health since her last visit to our office. We did our best to explain to her that fluctuations in lab results are not unusual, but that the most recent results we had in hand were alarming and required urgent follow-up. She assured us that she "was on it."

TK saw her PCP the following week to have the additional laboratory tests we had requested performed. Because her mother refused a separate additional blood draw, we had to wait until TK's next exchange transfusion to get the information we needed. We had a strong suspicion that the initial diagnosis of SLE would be confirmed, but we could not rule out other possibilities without the missing lab tests.

Several weeks later, we found out that TK was recently also evaluated by a second pediatric rheumatology practice nearby. At this practice, TK was preliminarily diagnosed with juvenile idiopathic arthritis, although TK's mother eventually told us that she had not provided this practice with any of TK's recent lab results and did not notify them of our alarm related to her high ANA levels.

After our initial consultations, TK popped back up onto our radar screen when our office was called to arrange her transfer from an outside hospital's emergency department (ED) to our ED. She had been hospitalized the previous week with a 104.5-degree fever and because she generally "just was not feeling well." Urine and blood cultures were negative, so TK was eventually discharged with a prescription for oseltamivir phosphate. Her mother had difficulty initially acquiring the medication, so TK didn't start treatment for nearly a week after her discharge. The medication was initially effective, but within a week, TK was again febrile, complaining of a cough and neck pain that prompted a return visit to the outside hospital's ED and, eventually, a transfer to our hospital's ED.

Chest x-rays were performed that showed cardiomegaly and bilateral pleural effusions. Nothing abnormal was seen on ultrasound, although an echocardiogram showed a large global pericardial effusion with tamponade at the location where the right atrium was collapsing during systole.

TK was transferred to pediatric intensive care, where she was intubated and underwent pericardiocentesis

to remove 500 ml of fluid. A drain was left in place. TK also received a 3-day course of high-dose methylprednisone 30 mg/kg before transitioning to hydroxychloroquine after extubation.

We again repeated lab testing and made a definitive diagnosis of SLE based on TK's high ANA levels (1:>10,240), positive dsDNA and LA, positive anticardiolipin antibodies, proteinuria, pleural effusion, pericardial effusion, and arthritis. TK was discharged from the hospital with instructions to take hydroxychloroquine 100 mg po daily and prednisone 40 mg po daily.

We opted against initially starting TK on mycophenolate mofetil due to her non-functional spleen secondary to SCD as well as the risk of infection. Upon further discussion with TK's hematologist, we agreed to start mycophenolate during our steroid taper.

It has now been 6 months since our last major adjustment to TK's treatment. She is doing extremely well with no signs of disease flare. This latest scare seems to have jolted TK's mother into action as she is now one of my "prize mothers," following our every instruction, getting her daughter's labs drawn on schedule, and engaging with our team in fruitful discussions about TK's disease. She now realizes the "lion" this disease can be after seeing how close it came to devouring her child.

There are few routine SLE cases in the pediatric world. TK's case was complicated by her young age at presentation (pediatric SLE typically presents between the ages of 12 and 14),[3] her absence of typical flare symptoms, our difficulty obtaining lab results, and irregular follow-up visits to our office. Her initial care was extremely fragmented, with management at three different hospital systems that all prioritized different components to care.

With all of these complications, it's hard to fault TK's mother for being resistant to our initial recommendations. Her daughter appeared largely happy and healthy when we first saw her, and there was naturally some surprise when we urged immediate medical interventions based upon abnormal lab results. Putting myself in TK's mother shoes as a non-healthcare provider, I would likely have been skeptical as well without discussing the matter with a clinician with whom I had some personal history (ie, her pediatrician).

This case serves as a good personal reminder of the need to communicate information in a delicate yet persistent fashion with our patients and their families. We never want to underemphasize the potential impact of a diagnosis like pediatric SLE, but it's also important not to sound the alarm too quickly with a family that is fragile and does not know us well.

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