ABSTRACT

Objective: To review diagnosis and treatment of systemic lupus erythematosus (SLE).

Methods: Review of the literature in the context of a clinical case.

Results: SLE is an autoimmune disorder affecting multiple organ systems. There is no cure, and the disease course is variable with unpredictable outcomes. Despite significant progress in early detection and advancements in treatment, frequent unpredictable flares and complications related to both SLE and treatment require careful monitoring and management. Lifestyle modifications, including sun avoidance, rest, and exercise, are important for managing disease. Antimalarial therapy using hydroxychloroquine is first-line immunomodulatory therapy for mild disease, as studies have shown that it decreases both the likelihood of mild flares and development of new damage from SLE. Corticosteroids are also frequently used, as they provide immediate and effective immunosuppression, but chronic use is limited by the adverse side-effect profile. In more severe cases, immunomodulators and biologic agents are often used as steroid-sparing agents.

Conclusion: Although significant progress has been made in the detection and treatment of patients with SLE, there is still significant morbidity and mortality associated with the disease. Careful monitoring and management of disease activity is recommended to improve patient outcomes.

Systemic lupus erythematosus (SLE) is an autoimmune disorder affecting multiple organ systems. Circulating autoantibodies directed against cell nuclear components lead to wide-spread inflammation, vasculitis, and immune-complex deposition. There is no cure and the disease course is variable with unpredictable outcome. The estimated world-wide prevalence is between 20 to 70 per 100,000 persons [1], with reported prevalence of 52 per 100,000 in the United States [2]. The etiology is unknown, with a complex interplay between gender, genetic, ethnic, hormonal, and environmental factors. Despite significant progress in early detection and advancements in treatment, there is still significant early mortality associated with infections and organ-specific disease progression [3]. Ten-year survival is greater than 90% [4], but frequent unpredictable flares and complications related to both SLE and treatment require careful monitoring and management of disease activity.

CASE STUDY

Initial Presentation

A 28-year-old Hispanic woman presents to her primary care physician with a 1-month history of fatigue, facial rash, and joint pains.

History

The patient’s symptoms began during a tropical vacation 1 month ago when she noticed a red, nonpruritic rash on her face, initially attributed to sunburn. She endorses progressive fatigue and joint pains in bilateral wrists and hands, which is worse in the morning and associated with at least 45 minutes of stiffness. She reports history of fatigue and muscle aches over the past 4 months accompanied by 10-lb weight loss and diffuse hair thinning. She denies any fever, chills, chest pain, preceding illness, or insect bites. The patient is of Mexican ancestry and was born and raised in Texas. Her past medical history is unremarkable, and family history is significant for rheumatoid arthritis and hypothyroidism in her mother and no history of other rheumatologic diseases including lupus. Her only medication is oral contraceptive pills and she denies history of tobacco, alcohol, or drug use. She works as an office assistant, lives with her husband, and denies any menstrual irregularities or prior pregnancies.

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Physical Examination
The patient is a thin young woman with a temperature 37.8°C, pulse 80 bpm, blood pressure 118/72 mm Hg, and respiration 16 breaths/minute. There is a well-demarcated, erythematous, mildly scaly rash on bilateral cheeks over the malar eminences, across the nasal bridge, and on the chin with sparing of the nasolabial folds. Diffuse alopecia without scarring is present. There are no oral or nasal ulcers and no conjunctival pallor. The neck is supple without lymphadenopathy. The lungs are clear, and there are no cardiac rubs or murmurs. The abdomen is soft and nontender without organomegaly. Examination of the extremities reveals tender, swollen metacarpophalangeal (MCP) and wrist joints bilaterally with mild effusions and intact range of motion. There are no deformities and the remainder of the musculoskeletal exam is unremarkable with normal muscle strength and non-focal neurological examination.

Workup
Laboratory testing reveals the following:

- White blood cell count 5800/mm³ with 45% lymphocytes
- Hemoglobin 11.2 g/dL with mean corpuscular volume 87 fL
- Platelet count 128,000/μL
- Serum electrolytes normal
- Serum creatinine 1.1 mg/dL
- Urine positive for 1+ proteinuria, 3 red blood cells (RBCs)/high-powered field (HPF), without casts
- Erythrocyte sedimentation rate 34 mm/hr
- C-reactive protein 1.2 mg/dL
- Anti-nuclear antibody (ANA) positive at 1:640
- dsDNA antibody by ELISA 535 IU/mL

A plain radiograph of the chest and electrocardiogram (ECG) are unremarkable.

What are risk factors for developing SLE?
The strongest risk factor for developing SLE is gender, with a 9:1 female-to-male ratio in adults with peak incidence during the reproductive years, ages 15 to 44 [1,2]. SLE occurs with more frequency and severity in non-Caucasian ethnic groups such as African Americans, Hispanics, and Asians, and has an association with lower socioeconomic status [1,5]. These factors are also known to be associated with worse disease outcome and higher mortality rates [6–8]. Most cases of SLE are sporadic, but family history of lupus or other autoimmune diseases poses an increased risk [9], and several genetic polymorphisms have been linked to SLE susceptibility [10]. UV-light exposure can be a triggering factor by its role in DNA and cellular damage and release of lupus-specific antigens. The role of female hormones in SLE is poorly understood, but pregnancy can lead to devastating exacerbations and organ damage, and should be carefully planned during periods of well-controlled disease [11]. Studies in SLE patients without antiphospholipid antibodies have shown no increase in flares with combined oral contraceptives containing low-dose estrogen [12,13], but the use of estrogen in oral contraceptives and hormone replacement therapy in SLE patients remains controversial.

What is the initial presentation of SLE and how is it diagnosed?

Clinical Presentation and Diagnosis
Initial presentation of SLE is variable with both systemic and organ-specific findings. Systemic complaints such as fever, fatigue, and weight loss are nonspecific but may raise suspicion to look for further diagnostic findings. For the past 15 years, diagnosis has been made in patients fulfilling at least 4 of 11 of the 1997 revised American College of Rheumatology (ACR) criteria for classification of SLE (Table 1) [14]. Classification of SLE still remains a challenge, however, as the 1997 ACR criteria have known weaknesses, including the lack of emphasis on the presence of autoantibodies as a key criterion [15].

To address the weaknesses, the Systemic Lupus Collaborating Clinics (SLICC) recently published a new set of criteria (Table 2) which has higher sensitivity (94% vs. 86%) and similar specificity (92% vs. 93%) for SLE classification compared with the 1997 ACR criteria [16]. Like the ACR guidelines, the criteria are cumulative and may be present at different points in time. The SLICC classification expands the cutaneous manifestations of SLE, includes more organ-specific disease manifestations.
and serologic markers, and divides the criteria into clinical and immunologic features. The diagnosis is made by either fulfilling 4 of the 17 criteria with at least 1 clinical AND 1 immunologic criterion, OR by having the presence of either ANA or dsDNA antibodies in a patient with biopsy-proven lupus nephritis.

The most common clinical findings in SLE are mucocutaneous and musculoskeletal manifestations, which are present in 80% to 90% and 76% to 100% of patients, respectively [17]. The classic cutaneous lesion is the malar rash, which is an acute-onset, photosensitive, erythematous, edematous, and occasionally scaly rash that mimics the shape of a butterfly, with its body over the nasal bridge and wings distributed over the malar eminences. The malar rash spares the nasolabial folds, which can help distinguish it from other causes of facial erythema. Other
photosensitive rashes are seen on sun-exposed areas including forehead, chin, neck, upper chest, shoulders, and extensor surfaces of the arms. Although the presence of malar rash and photosensitivity represent 2 separate ACR criteria, they fall under a single criterion in the SLICC acute cutaneous category, which also includes other skin findings such as subacute cutaneous disease. As such, patients who fulfill multiple criteria under the ACR classification would lose a criterion and fulfill a single SLICC acute cutaneous skin criterion.

Other cutaneous findings include discoid lupus rash, which is a form of chronic disease. It presents as erythematous plaque lesions with scaly plugs in hair follicles. Although less common compared to the acute rashes, discoid lesions can lead to disfiguring and atrophic scars. Patients may also have diffuse or patchy alopecia, which is often reversible but can be permanent and scarring when associated with discoid lesions affecting the follicles. Other findings to look for are oral ulcerations, which are usually painless and most commonly seen on the hard palate. However, the buccal mucosa and tongue should also be carefully inspected and a speculum examination should be performed for nasal ulcers, which are often bilateral and found on the lower nasal septum.

Musculoskeletal complaints are among the most common initial symptoms. Patients present with a range of symptoms, from arthralgias and myalgias to arthritis and myositis. Typically there is symmetric inflammatory
involvement of at least 2 joints, usually proximal interphalangeals (PIPs), MCPs, wrists, and knees, accompanied by effusions and morning stiffness. Physical findings include swelling, tenderness, erythema, increased warmth, and decreased range of motion. Joint involvement is usually nonerosive and nondeforming, but pararticular involvement of the joint capsule, ligaments and tendons may result in reducible, hypermobile, Jaccoud-like arthropathy.

Serositis presenting as pleuritis or pericarditis is the most common cardiopulmonary symptom included in the classification criteria, with a frequency of 41% to 56% and 9% to 54%, respectively [18]. Pleuritis presents as chest pain that worsens with inspiration and may also present with exudative effusions. Although pleuritis is the most common pulmonary finding, worsening dyspnea and chest pain should prompt clinicians to evaluate for other pathologies seen in SLE such as pulmonary embolism, pneumonitis, intra-alveolar pulmonary hemorrhage, pulmonary hypertension, or shrinking lung syndrome. Pericarditis presents as substernal chest pain, classically described as worse with inspiration and when in the supine position and improved with sitting up and leaning forward. Patients may have a cardiac rub or ECG findings, but echocardiogram is the most sensitive diagnostic test. Progression to cardiac tamponade is rare, but other cardiac pathology such as myocarditis and Libman-Sacks fibrinous endocarditis should be considered, as complications of valvular insufficiency, arrhythmias, and embolism can occur. In addition, coronary artery disease should be considered in any SLE patient with worsening chest pain, even in younger patients who would not typically be considered high-risk based on age and gender, as the risk of cardiovascular events is significantly increased in SLE patients. In one study, SLE patients in the 35- to 44-year-old age-group had up to a 50-fold increased risk of myocardial infarction compared to age- and gender-matched controls [19].

SLE may induce various central and peripheral neurologic deficits either due to vascular or thrombogenic complications, or antibody-mediated neuron toxicity [20]. The SLICC classification criteria include a more thorough list of neuropsychiatric manifestations in addition to seizures and psychosis, which are the only symptoms in the ACR criteria. Symptoms include cognitive deficits in the areas of memory, concentration and attention, severe headaches, mood disorders, and anxiety. As these are nonspecific findings, other etiologies such as infections, drug effects, metabolic imbalance, stress, and psychosocial factors must be ruled out and appropriately treated before attributing the symptoms to SLE.

Renal involvement affects approximately 50% to 60% of patients and is a poor prognostic factor [21]. It is more common in non-Caucasian patients and is a major cause of mortality in the first decade of disease [3]. Clinicians should perform urine dipstick and 24-hour protein quantification with initial diagnosis and continue surveillance for new-onset renal involvement. A 3+ dipstick, urine protein/creatinine ratio or 24-hour proteinuria greater than 0.5 g, or the presence of cellular casts are part of the classification criteria. However, even a 1+ dipstick proteinuria should prompt further quantification. Classification of lupus nephritis is done by histologic grading of renal biopsy according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) [22], which has implications for prognosis and prompt treatment. Active proliferative disease such as diffuse proliferative nephritis (Class IV) and progressive forms of focal proliferative nephritis (Class III-A) have worse prognosis than membranous (Class V) and can present with nephrotic syndrome, hypertension, microscopic hematuria and RBC casts. Recently published ACR guidelines for lupus nephritis can guide treatment plans for patients with an established diagnosis of lupus nephritis [23].

**What additional laboratory tests are indicated?**

In addition to urine protein and creatinine quantification, complete blood count should be assessed for anemia, thrombocytopenia, and leuko-/lymphopenia, which each constitute separate hematological criteria under the SLICC classification. These hematologic findings are initially due to peripheral destruction initiated by autoantibodies, but medication-induced bone marrow suppression and anemia of chronic disease are additional causes in long-standing disease. Hemolytic anemia may be associated with positive Coombs test or microangiopathic hemolytic anemia. However, Coombs positivity can also be present without active hemolysis and represents a separate immunologic criterion in the SLICC classification. In some patients, thrombocytopenia is the initial finding in SLE and can precede symptoms and diagnosis by years [24]. Marked thrombocytopenia may present with petechiae and fulfills the criterion.
when platelets fall below 100,000/mm³ with no other attributable causes such as drug effects. Lymphopenia is the most common form of leukopenia in SLE patients, and SLICC classification criteria requires one occurrence of either lymphocyte count < 1000/mm³ or leukopenia < 4000/mm³. Inflammatory markers such as erythrocyte sedimentation rate or C-reactive protein can be elevated, especially with infection, but are nonspecific in both diagnosis and disease progression.

Once clinical suspicion for SLE is present, initial serologic testing includes the highly sensitive (98%) ANA, which is present in most SLE patients [25]. However, ANA antibodies are found in other connective tissue diseases such as Sjögren’s, rheumatoid arthritis, and scleroderma. A positive ANA antibody test has low specificity and is found in up to 32% of the general population at 1:40 titer [26]. Higher titers increase specificity for autoimmune disease, with positivity at 1:320 found in only 3.3% of normal subjects [26]. However, autoantibodies are often present years prior to symptoms and may be a preceding sign of future disease [27,28].

Serologic workup includes testing for anti-dsDNA, anti-smith or antiphospholipid antibodies, which each constitute separate SLICC classification immunologic criteria. Anti-dsDNA antibody titers often fluctuate with disease activity [29]. Compared to ANA, anti-dsDNA antibody has a specificity of 95% when detected at titers greater than 1:10, but its sensitivity is lower at 60% to 70% [25]. Anti-Sm is also highly specific but its sensitivity is lower at 30% to 40% [25]. Lupus anticoagulant, false-positive RPR, anticardiolipin and anti-β₂ glycoprotein antibodies fulfill the antiphospholipid antibody criterion and are associated with coagulopathic states, increased risk of thrombotic events, and placental insufficiency [17]. Complement system activation results in low C3 and C4, which are followed along with anti-dsDNA antibody titers during acute flares [30–33].

Other antibodies that are not included in the classification or used to follow disease activity have important clinical correlations. SS-A/Ro and SS-B/La antibodies are found in 30% to 40% and 10% of SLE patients, respectively [25], and are associated with sicca syndrome, subacute cutaneous lupus erythematosus, photosensitivity, and a higher risk of neonatal lupus during pregnancy [17]. Anti-nuclear antibodies are associated with increased incidence of neuropsychiatric manifestations, and anti-RNP antibodies are associated with presence of musculoskeletal symptoms and Raynaud’s phenomenon [17].

Case Continued

The patient is referred to a rheumatologist and found to have anti-Sm and anti-RNP antibodies in addition to ANA and anti-dsDNA antibodies. She is negative for antiphospholipid, anti-SSA/Ro, anti-SSB/La, and antiribosomal P antibodies. Serum C3 and C4 levels are low and direct Coombs test is positive. A spot urine protein/creatinine is 0.2. Lifestyle modification is advised and patient is started on naproxen, prednisone 20 mg and hydroxychloroquine 200 mg daily. Over the course of 6 weeks, hydroxychloroquine is increased to 400 mg and prednisone is tapered to maintenance dose of 5 mg daily.

• What is the first-line treatment for mild to moderate forms of disease?

Lifestyle Modification

Patient education regarding avoidance of known triggers and lifestyle modifications is a key component in prevention and treatment of flares and in decreasing associated morbidity. Photosensitive patients should limit UV-light exposure by avoiding sunlight and applying sunscreen. Limiting daily stress has been shown to decrease flares and treatment with steroids [34]. A balanced lifestyle consisting of rest and exercise improves fatigue and muscle mass and decreases cardiovascular and osteoporosis risk. Patients who smoke should be counseled for smoking cessation. In addition to increased risk of various malignancies, cigarettes are associated with more active disease and blunted response to treatment with antiinflammatory agents in patients with cutaneous disease [35].

SLE patients are at increased risk of vitamin D deficiency and should be monitored closely by laboratory measurement and supplementation [36,37]. This is partly due to decreased sunlight exposure, but renal failure and use of chronic steroids also raise the need for osteoporosis surveillance and appropriate treatment with calcium, vitamin D, and bisphosphonates [37]. SLE is associated with increased risk of lymphoma (especially non-Hodgkin lymphoma), lung, and cervical malignancies. Patients should undergo annual cervical cancer screening in addition to age-appropriate cancer screening recommended for the general population [38,39]. Influenza and pneumococcal vaccinations are also important preventative measures given the increased risk of infections secondary to underlying immune system dysfunction and
immunosuppressive medications. Sulfur antibiotics are known to trigger disease activity and should be avoided, particularly in patients with allergies [40].

NSAIDs

NSAIDs are first-line treatment for musculoskeletal pain, mild forms of serositis, and headaches. Both non-selective and selective COX inhibitors (Celecoxib) are frequently prescribed with variable efficacy. Long-term use or polypharmacy with aspirin and glucocorticoids should be undertaken with caution and co-administered with proton-pump inhibitors to avoid gastrointestinal side effects. NSAIDs are used with caution in SLE patients to minimize kidney injury and can provoke hypertension. They are contraindicated in renal failure and should be avoided in patients with nephritis and in pregnancy. Other side effects include reversible transaminitis and rare neurologic manifestations of cognitive dysfunction, confusion, and aseptic meningitis which can mimic SLE disease involvement [41].

Steroids

Steroids provide immediate and effective immunosuppression, but chronic use is limited by the risk of infection and adverse effects such as Cushingoid body habitus, hypertension, dyslipidemia, osteoporosis, osteonecrosis, cataracts, glaucoma, and diabetes mellitus. Disease flares limited to mucocutaneous manifestation should be managed with topical corticosteroids alone. Low-potency steroids should be used first and highly potent and fluorinated forms should be avoided on facial lesions to avoid atrophy, pigmentation changes, and telangiectasia. Highly potent agents such as clobetasol can be used to treat alopecia and severe eruptions on the trunk and extremities. Long-term or continuous use should be limited due to risk of tachyphylaxis and adrenal suppression, and can be substituted with second-line topical agents such as tacrolimus, pimecrolimus, and topical retinoids [42].

Severe disease affecting the kidneys, central nervous system (CNS), lungs, and vessels can be treated with high-dose prednisone 1–2 mg/kg/day in IV or oral equivalents, or pulse intravenous methylprednisolone 1 g for 3 days. Less severe disease with limited organ involvement can be treated with prednisone 5–30 mg daily. Systemic steroids are often co-administered with other immunomodulators such as antimalarials that may take months to take effect after initiation. Systemic steroid administration is minimized to avoid the side effects of chronic use, and is tapered down to a maintenance dose of < 5 mg daily or alternate day dosing once adequate response to the alternate agent is achieved.

Antimalarials

Antimalarial therapy using hydroxychloroquine is the first-line immunomodulatory therapy for mild disease and is dosed starting at 200 mg/day and up to 400 mg/day, with maximal dose of 6.5 mg/kg/day [42]. Other antimalarials also used alone or in combination with hydroxychloroquine are chloroquine and quinacrine. Continued treatment with antimalarials has been shown to decrease both the likelihood of mild flares and development of new damage from SLE [43,44]. Furthermore, antimalarials have been shown to have a protective effect on survival and thrombosis [45–47].

Antimalarials are generally well tolerated. The most common side effect is gastrointestinal, which usually resolves and can be managed by lowering the dose. Other potential adverse effects are hemolytic anemia in G6PD-deficient patients, nail and cutaneous changes, hypoglycemia, and cardiotoxicity. Retinopathy is a rare (approximated at 0.5% [48,49]) but serious side effect that is potentially irreversible if not detected early. A baseline ophthalmologic examination is advised for patients starting antimalarial drugs. Patients should begin annual screening after 5 years of use, and earlier in the presence of other risk factors such as higher dosing, renal or hepatic dysfunction, known ocular disease, or older age [50]. Patients with longer duration of therapy are at increased risk and should be followed at more frequent intervals [49].

Immunomodulators

Evidence demonstrating efficacy of immunomodulators in non-renal SLE disease is limited but they are often used as steroid-sparing agents. Methotrexate, which is used to treat rheumatoid arthritis, has been shown to decrease the use of steroids and treat cutaneous and joint disease activity when given at 15–20 mg weekly doses for a duration of 6 months [51]. Leflunomide, which decreases T and B cell proliferation, is another rheumatoid arthritis drug that was effective and safe in mild to moderate severity SLE disease in a small randomized controlled trial [52]. Compared with methotrexate, it is less nephrotoxic and can be used in patients with renal failure. Purine synthesis inhibitors azathioprine (AZA) and mycophenolate mofetil (MMF) have been studied
SYSTEMIC LUPUS ERYTHEMATOSUS

more extensively in treatment of lupus nephritis, with only limited studies demonstrating efficacy in extra-renal disease, but favorable efficacy and reduction in steroid usage have been demonstrated with MMF use [53].

Belimumab (Benlysta) is the newest FDA-approved drug to control disease activity in active, autoantibody-positive SLE patients who are undergoing standard treatment. It decreases B cell survival and differentiation by inhibiting the B-lymphocyte stimulator cytokine (BlyS). Two large international studies in antibody-positive patients with active disease receiving standard treatment regimens (prednisone, antimalarial and immunosuppressive agents) had statistically significant improvement in disease activity compared with placebo at 52 weeks when given belimumab at 10 mg/kg [54,55]. The difference was not significant in results of continued therapy at 72 weeks despite a greater response rate [54]. Notably, there was a reduction in dsDNA antibody titers and increases in C3 and C4 levels. The results from the trials are promising but the financial burden of the therapy is significant, with an estimated annual cost of $35,000 for weight-based dosing [56]. Side effects include infections, infusion reactions, and gastrointestinal disturbances. Of note, patients with severe lupus nephritis, severe CNS disease, or undergoing treatment with IV cyclophosphamide and other biologic agents were excluded from the trials. Due to this limitation, belimumab is not currently recommended for treatment of lupus nephritis or CNS disease due to unknown safety and efficacy.

Case Continued

The patient responds well to initial treatment with hydroxychloroquine, prednisone, and naproxen PRN. She has no visual complaints on hydroxychloroquine and undergoes regular ophthalmologic evaluations, which are normal. However, episodes of noncompliance and attempts to wean off the medication lead to frequent flares. Over the next 6 years, her flares become more frequent, marked by recurrence of initial symptoms and development of new pleural effusions with shortness of breath and poor exercise tolerance. She also develops chronic gastritis, hypertension, and borderline diabetes due to frequent high-dose steroids. On a routine visit, 24-hour urine protein is elevated at 2.8 g with RBC casts, and creatinine is 1.7 mg/dL. All NSAIDs are discontinued, and the patient undergoes a kidney biopsy, which shows ISN/RPS Class IV diffuse lupus nephritis.

• What is the treatment for lupus nephritis?

Immunomodulators

For years the traditional treatment regimen for severe lupus nephritis was the NIH IV cyclophosphamide induction therapy at 0.5–1 g/m² dose for 6 months with methylprednisolone, followed by maintenance pulse therapy every 3 months for 2 years [57]. However, cyclophosphamide carries a significant risk of infection due to bone marrow suppression. It can lead to premature ovarian failure and is contraindicated in pregnancy and lactation, rendering it a difficult treatment option for women of reproductive age desiring conception. Other side effects include nausea and vomiting, alopecia, cervical dysplasia and hemorrhagic cystitis, which can be minimized with mesna.

A shorter course of cyclophosphamide with lower dose (3 g over 3 months) of induction treatment with AZA maintenance in the Euro-Lupus regimen has been shown to be as effective as high-dose cyclophosphamide in primarily Caucasian patients for up to 10 years [58,59]. Additionally, MMF has been compared to cyclophosphamide in studies with ethnically diverse populations, with higher remission rates at 24 weeks in one US-based study [60], and similar decrease in proteinuria and serum creatinine levels between the 2 induction agents in the ALMS study [61]. In black and Hispanic populations, MMF demonstrated superior efficacy compared to cyclophosphamide in the subset analysis of the ALMS study [61]. MMF is also preferred for minimizing ovarian toxicity, although it is contraindicated in pregnancy and lactation. It is administered at a starting dose of 0.5 g twice daily and titrated up 0.5 g/week to a maximum of 3 g/day. Infections are reported to be less frequent than with cyclophosphamide, although gastrointestinal symptoms are higher [60]. In patients with severe lupus nephritis with crescents, the ACR guidelines recommend induction with either cyclophosphamide or MMF with the caveat that there is no prospective, international, or North American data supporting MMF usage in this setting [23]. Both induction agents should be co-administered with either oral prednisone or IV methylprednisolone pulse with tapering down to maintenance doses as described above.

Once partial or complete remission is achieved with induction therapy, maintenance therapy with either MMF
or AZA should be continued for at least 2 years to prevent relapse [62–64]. Both MMF and AZA maintenance therapies were shown to be superior to cyclophosphamide in event-free survival, relapse rates at 6-year follow-up, and side effect profile (ALMS trial) [62]. Furthermore, MMF at 2 g/day has been shown to be superior to AZA in preventing relapses in a mixed population study [63]. The MAINTAIN study comparing AZA and MMF in a primarily Caucasian population showed no significant difference in flares, proteinuria, and serum creatinine levels but a higher incidence of AZA-induced cytopenia [64]. However, due to teratogenicity of MMF, AZA dosed at 2 mg/kg/day [64] is an alternative maintenance therapy in stable patients attempting pregnancy.

Other Therapies, Including Biologic Agents
Lupus nephritis resistant to cyclophosphamide or MMF treatment may benefit from biologic therapy using rituximab. Although B-cell depletion with rituximab is not FDA-approved for SLE therapy with conflicting research trials, therapeutic responses with favorable side effect profiles have been observed in case reports and observational studies [65,66]. T-cell directed therapy using calcineurin inhibitors such as tacrolimus has been shown induce remission in membranous forms of lupus nephritis (Class V), or mixed proliferative and membranous lupus nephritis (Class IV and V), although data demonstrating long-term benefit is limited [67,68]. High-dose intravenous immunoglobulin, plasmapheresis, and stem cell transplant with immunoablation therapy can be considered in treatment-resistant, life-threatening disease. In patients with evidence of thrombotic microangiopathy, the primary course of treatment should include plasma exchange therapy.

Case Conclusion
The patient undergoes induction therapy for lupus nephritis with 1 g MMF twice daily with prednisone 60 mg. MMF is increased to 1.5 mg twice daily over the next several weeks, with decrease in serum creatinine to 1.3 mg/dL, and proteinuria down to 0.2 g/day. Her prednisone is tapered down to 2.5 mg/day and she is placed on maintenance therapy with MMF 1 g twice daily for the next 2 years.

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