

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.  
For more information visit [www.intechopen.com](http://www.intechopen.com)



# Don't Miss Lupus

*Stephen Soloway*

## Abstract

Chapter for Lupus Book Systemic lupus erythematosus is a well-recognized multi-system disease. Hallmarks of the disorder include the prevalence of anti-nuclear antibodies (ANA) and double stranded antibodies (DNA). The disease often presents with lupus rashes and/or arthritis or arthralgias. Lupus is “the great imitator,” as no organ system is excluded, when diagnosing and treating a lupus patient. While lupus remains evasive in novel therapies with true benefit; one issue has been consistent, in that the preponderance of the evidence thus far, leads to B cell dysfunction. More recently Belimumab was indicated for use in lupus patients. This is a BLYS-Specific inhibitor (B lymphocyte stimulator) medication. At this time, I would like to focus on lupus in a manner that you are not used to hearing. Typically, any practitioner who approaches a patient with a plethora of symptoms, would order blood tests, and conclude a diagnosis of lupus. In this chapter, I will point out and focus on the need to think “outside the box” and perhaps consider lupus as simply one of various other scenarios.

**Keywords:** lupus, Sjogren's, Raynaud's, ANA, DNA, DRV VT

## 1. Introduction

### 1.1 Hallmarks of systemic lupus erythematosus

Systemic lupus erythematosus is a well-recognized multi-system disease [1].

Hallmarks of the disorder include the prevalence of antinuclear antibodies (ANA) and double stranded antibodies (DNA). The disease often presents with rashes and/or arthritis or arthralgias. Lupus is “the great imitator,” as no organ system is excluded, when diagnosing and treating a lupus patient.

### 1.2 Most recent development for lupus treatment

While lupus remains evasive in novel therapies with true benefit; one issue has been consistent, in that the preponderance of the evidence thus far, leads to B cell dysfunction. More recently Belimumab was indicated for use in lupus patients, which is an immunomodulator B-Lymphocyte Stimulator (BLYS)-Specific Inhibitor. This drug was approved by the Food and Drug Administration (FDA) for use in lupus patients in 2011 [2]. The majority of patients afflicted with lupus, autoreactive B-cells remain in the body longer than necessary. Belimumab binds to BLYS, causing it to no longer bind to and stimulate the autoreactive B cell.

Information recently discussed at the ACR2020, provides evidence of Belimumab standard therapy ameliorating the outcome for patients with active renal lupus. A combination of Belimumab, with either mycophenolate mofetil or

Azathioprine, was shown to be more effective than either of these therapies alone. While studies are not yet conclusive, a combination of Belimumab with cyclophosphamide, posed no higher risk than cyclophosphamide alone. This combination in a class IV nephritis group exceeded those who received cyclophosphamide alone [3].

Anifrolumab, an interleukin-1 inhibitor, was not shown to be effective in systemic lupus, it did show promise in TULIP-1 and 2 and skin lesions related to lupus. Anifrolumab's effect on non-skin lupus disease activity however, was nominal [4].

## **2. A rheum with a different view**

In this section, lupus will be discussed pragmatically. Most practitioners are unaccustomed to viewing disease features from a rheumatologic standpoint. Typically, the practitioner that approaches a patient with a plethora of symptoms, would order blood tests, and conclude a diagnosis of lupus; however, in this part of the chapter, we will discuss the need to focus "outside the box" and perhaps consider lupus as simply one of various other scenarios.

### **2.1 Finding evidence of lupus**

Features of lupus considered in the differential diagnoses of other conditions include rashes, arthritis, renal disease (glomerular or tubular), Raynaud's phenomenon, sicca syndrome and muscle weakness. The differential diagnoses for these features often include lymphoma, sarcoidosis, phospholipid antibody syndrome, rheumatoid arthritis, inflammatory myopathy, Sjogren's syndrome, IgG4-related disease and scleroderma.

A lupus rash, seen with or without vasculitis, typically small vessel-showing leukocytoclastic vasculitis, is seen at the dermal/epidermal junction with immunofluorescence positive for IgG and complements [5]. Small vessel vasculitis is responsible for much of the severe abdominal pain seen in lupus patients.

Arthritis of lupus is inflammatory but not erosive. Differential diagnoses would include rheumatoid arthritis, gout, or psoriatic arthritis. Rheumatoid arthritis, psoriatic arthritis, scleroderma, sarcoid and gout are all destructive arthritic diseases [6].

Renal pathology is often noted due to blood or protein in the urine. It may be diagnosed by a decrease in renal function, which is differentiated on biopsy. Lupus tends to involve glomerulus with a "full house" pattern on immunofluorescent staining (i.e., presence of glomerular deposits that stain for IgG, IgM, IgA, C3 and C1q). This is the only organ finding to satisfy the SLICC criteria on its own in patients with systemic lupus. IgG and complements would be suggestive of lupus nephritis in a patient with proliferative glomerulonephritis. This may be focal, diffuse or pure membranous nephropathy [7]. A patient with pure membranous disease, high double stranded DNA and low complements often do not apply. Proliferative lesions are often seen in the face of rising double stranded DNA and consumption of complement levels. These levels are not subject to change in Sjogren's, scleroderma, sarcoid, or IgG4-related disease. (IgG4-related disease is unique, as both tubulointerstitial diseases occur simultaneously with glomerular disease). ANCA vasculitis shows pauci-immune deposits [8], while sarcoidosis would show granulomas without positive stain for immunofluorescence. Goodpasture syndrome will show anti-GBM antibodies [9]. Sjogren's syndrome will show renal tubular acidosis, and only rarely, glomerular disease [10]. Most cases of tubulointerstitial nephritis are drug-induced, and may be caused by medications, such as antibiotics medications, NSAIDs, proton pump inhibitors,

and immune-checkpoint inhibitors [11]. Uncommonly, NSAIDs may cause a combination of interstitial nephritis and nephrotic syndrome. Infections (i.e., legionella or *Mycobacterium tuberculosis* infection), may lead to a diagnosis of tubulointerstitial nephritis; however, autoimmune diseases, such as systemic lupus, sarcoidosis, Sjogren's syndrome, and uveitis syndrome, are also proven to cause tubulointerstitial nephritis [12]. Approximately 10–20% of patients diagnosed with lupus nephritis, have isolated lupus membranous nephropathy (class V), with no associated proliferative lesion present [13]. In patients with lupus nephritis, tubulointerstitial interstitial nephritis may accompany glomerular lesions, which is a risk factor for a poor outlook [14]. The IgG4 is a diagnostic differential and reveals tubulointerstitial nephritis, repeatedly associated with hypocomplementemia and hypodense nodular lesions, which can be seen on contrast-enhanced computerized tomography [15]. Tissue eosinophilia and deposits in the tubular basement membrane are often present, in addition to the distinctive pathological features of the disease [16].

Pulmonary renal syndromes can be seen in a very similar fashion, adding that lupus may present with acute glomerulonephritis, proliferative in nature, in addition to concurrent alveolar hemorrhage or diffuse interstitial infiltrates [17]. This pattern of disease seen in ANCA vasculitis is predominantly granulomatous polyangiitis, microscopic polyangiitis, and cryoglobulinemia, which is associated with hepatitis C infection [18].

Oral and ocular dryness, with or without uveitis, are features of lupus [19]. Uveitis is frequently seen in sarcoidosis and described in IgG4-related disease and HLA-B27-related conditions, while corneal-related disease has a differential diagnosis in rheumatoid arthritis, myopathy, and phospholipid antibody syndrome.

Primary muscle weakness while in lupus, [20] is part of a differential diagnoses that includes polymyositis, dermatomyositis, immune mediated necrotizing myopathy, lupus with myopathy, sarcoidosis with myopathy and Crohn's with myopathy. The latter two, show non-caseating granuloma disease on biopsy, while lupus shows diffuse immunofluorescence, mainly immunoglobulins and complements. This could be referred to as a "recurring theme" in lupus deposits of immunoglobulin and complements. Cocaine-laced with levamisole is in the differential diagnosis systemic lupus, myopathy and vasculitis [21].

A rheumatologist should recognize a lupus patient by the malar rash sparing the nasolabial folds, "classic kidney biopsy" and other constellations, such as "non-scarring alopecia" and "discoid lupus". These cases are often straightforward, and do not require biopsy. The classic malar rash sparing the nasolabial folds, is a known hallmark of lupus; although it may be confused with rosacea or polymorphous light eruption. The malar rash with autoantibodies, particularly ANA (almost 100% sensitive), and anti-double stranded DNA (95% specific), will lend themselves to a conclusive diagnosis [22]. Nonetheless, it should be noted that research criteria is not necessary for a diagnosis of lupus. The research criterion is merely a tool, used to randomize patients into homogeneous groups, while in fact physicians are treating a heterogeneous disease. So, in the quest to stratify patients by nonskilled physicians, or those not comfortable diagnosing or treating lupus properly, diagnostic criteria is often helpful, but certainly cannot be the quintessential element of a lupus diagnosis. In reality, actually "labeling" a patient with a lupus diagnosis may require a protracted course. Theoretically, a patient may carry a label of unspecified connective tissue disease (UCTD) for some time, before a conclusive diagnosis can be given. In time, this patient may develop lupus, Sjogren's syndrome, rheumatoid arthritis, scleroderma, myositis, an overlap syndrome, anti-synthetase syndrome, Sjogren's syndrome, IgG4-related disease, or sarcoid.

2.2 Consider evidence of lupus in every disease

Physicians should consider lupus as every disease they see, and work backward from that point. Note the following:

- 1. When a patient presents with hair loss (i.e., a bald spot - non-scarring alopecia); the differential diagnoses are broad and lupus should be investigated, the patient will need to be followed and skin biopsies performed [23].
- 2. Lesions, such as discoid lupus, which are characteristic scaly lesions, discolored, typically hyper-pigmented, and located within the ears, are common

Positive antinuclear antibody (ANA)	97%
Malaise and fatigue	90%
Arthralgia, myalgia	90%
Sun sensitivity, skin changes	70%
Cognitive dysfunction	70%
Low C3 or C4 complement	61%
Fever due to lupus	57%
Antibodies to ds DNA	50%
Arthritis	50%
Leukopenia	46%
Pleuritis	44%
Anemia	42%
Alopecia	40%
Nephritis, proteinuria	40%
Anticardiolipin antibody	35%
Malar rash	35%
Central nervous system	32%
Increased gamma globulin	32%
Weight loss due to lupus	27%
Raynaud’s	25%
Hypertension	25%
Sjogren’s	25%
Oral ulcerations (mouth, nose)	20%
Discoid lesions	20%
Central nervous system vasculitis	15%
Adenopathy	15%
Pleural effusion	12%
Subacute cutaneous lupus	10%
Myositis	10%
Avascular necrosis	10%

**Table 1.**  
*Approximate prevalence (%) of selected symptoms, signs, and laboratory abnormalities of systemic lupus erythematosus during the course of the disease in the United States [29].*



in lupus [24]. Although these lesions may be seen in other conditions, lupus should be considered.

3. Uveitis, typically anterior, is common in lupus [25]. It may occur one time, and may be infectious. Diagnostic possibilities included syphilis, tuberculosis or Lyme disease. If these infections are excluded, then undoubtedly, even if the patient's uveitis is a first-time occurrence, a lupus workup should be initiated.

As with all patients presenting any of the above features, clinicians should initiate confirmatory laboratory workup, including phospholipids, ANA, DNA, ENA, SSA, and SSB, in order to establish a baseline, when a patient exhibits a potential lupus feature at any point. Hypothetically a young patient, between 15 and 20 years of age, may present to a clinic with anterior uveitis. Rather than labeling this as viral, the practitioner should immediately consider a differential diagnosis that includes lupus. Other differential possibilities would include syphilis, tuberculosis, HLA-B27 diseases (including but not limited to psoriatic arthritis), HLA-B27 uveitis, ankylosing spondylitis, reactive arthritis, Crohn's colitis and ulcerative colitis. Regardless of the ultimate diagnosis, the treatment does not change; however, if the patient requires treatment with hydroxychloroquine, early diagnosis may lead to a more favorable outcome. Hydroxychloroquine is paramount. Many clinical trials over decades support its efficacy in prevention of lupus flares, thrombosis in lupus patients, and lipid-lowering potential [26].

In addition to the three presentations listed above, mouth sores also occur in lupus, Crohn's disease, Behcet's disease, phospholipid antibody syndrome, tuberculosis, syphilis, sarcoidosis, Sjogren's syndrome, IgG4-related disease, and viral infections [27]. Viral ulcers tend to be painful. Behcet's ulcers generally reveal large, circumscribed, beefy-red borders. Ulcers associated with Crohn's disease are usually shallow painful ulcers, similar to those seen in sarcoidosis. Lupus ulcers are frequently painless and often noticed surreptitiously [28].

Additionally, isolated lymphadenopathy does not necessarily have to be hilar or mediastinal; it could be epitrochlear, glandular swelling, lacrimal, parotid, or submandibular. However, the finding, incidental or not, with or without dry eyes and dry mouth, may be an indication of lupus (**Table 1**).

### 3. Common presentations of lupus

The following represents selected symptoms and abnormalities in patients diagnosed with lupus within in the United States.

#### 3.1 Arthropathies

Approximately 50% of lupus patients suffer from arthritis [29]. Joint disease, quite often a small joint polyarthritis, typically symmetric, is noted with typical involvement of PIPs, MCPs and wrists, inflammatory in nature; however, this is not erosive, which differentiates it from rheumatoid arthritis [30]. However, the practitioner should keep in mind that the differential diagnosis of IgG4-related disease, lymphomas, Sjogren's, sarcoidosis, or spondyloarthropathies, can also present with a phenotypic appearance of lupus arthritis. The definitive finding of arthritis only seen in lupus would be lupus arthropathy or acute rheumatic fever, which is followed by Jaccoud's arthropathy. Jaccoud's arthropathy is a chronic, non-erosive, reversible (with proper splinting) joint disorder that may occur after repeated bouts of arthritis. This arthropathy is caused by inflammation of the joint capsule and subsequent

fibrotic retraction, causing ulnar deviation of the fingers, through metacarpophalangeal joint subluxation, primarily of the fourth and fifth fingers [31].

The greatest emphasis should be placed on the fact that all joints could be involved in lupus. Arthritis of lupus may be the presenting feature, and therefore, all cases of inflammatory arthritis must be evaluated with x-rays and a thorough history and physical, to exclude other diseases. Treatment would begin with the use of hydroxychloroquine and the addition of methotrexate. If necessary, abatacept (a CTLA4 inhibitor drug), could be added, as well as the newer medication discussed earlier, belimumab. Additionally, low dose steroids are often effective. While some practitioners may view steroids as poison, others feel the patient's quality of life, on Prednisone (5 mg or less), even permanently could be appropriate, if this is necessary for disease control and improvement in the patient's quality of life. The patient should be informed of necessity for vigilance with regard to sleep, lipid and blood pressure monitoring, and the risk of osteoporosis. In the final analysis, the ratio of logic needs to be brought into consideration. As a practicing rheumatologist, with a personal experience of 32 years, experience dictates that 5 mg of Prednisone or less in virtually all the inflammatory patients that cannot be weaned, failed to cause significant steroid side effects. In the minority of patients who do suffer steroid side effects from a 5 mg daily equivalent or less as they begin to age, skin fragility or perhaps early cataracts can be seen; however, this may be difficult to ascertain, unless their ophthalmologist is convinced that any posterior subcapsular cataract is the definite consequence of steroid use. Otherwise, this would be difficult to ascertain [32].

### **3.2 Thrombocytopenia/thrombocytosis**

Approximately 42–46% of patients develop a cytopenia, including leukopenia and anemia [29]. Cytopenias in lupus are typically recognized with anemia, often hemolytic or of chronic disease, thrombocytopenia, or thrombocytosis [33]. Thrombocytosis indicates inflammation, while thrombocytopenia is often autoimmune and antiplatelet antibodies lower platelet counts; however, this should not be taken for granted. As in Sjogren's, the mechanism would be hypersplenism; however, the finding of thrombocytopenia must prompt a probe for lupus. This protocol also stands in the case of a low white blood cell count. A WBC less than 4000 units for all, or lymphocyte of less than 1000, should both prompt an evaluation and workup for lupus. These findings while not specific are quite typical. Please note that one isolated sample needs repeating.

### **3.3 Lupus nephritis**

Approximately 40% of lupus patients are diagnosed with nephritis [29]. The patient presents with blood or protein in the urine [34]. A renal biopsy is performed. A diagnosis is established - Mesangial proliferative, diffuse or focal proliferation, or pure membranous. The treatments for this vary. The current main stay treatment is mycophenolate mofetil. A new medication, which will be available in the near future, is calcineurin inhibitor, Voclasporin [35]. The data regarding this is promising. Rituximab, anecdotally, and in Pureview Data, indicates that it may also be helpful, although it is not the standard of care. Emphasis should be placed on the actuality that "the standard of care" should supersede the Food and Drug Administration's indications for any drug. Approval for a drug by the Food and Drug Administration is solely based on the drug company's actual "indication application" for that particular drug. While it may be used exclusively for its indication, in some cases it should be noted that the drug may prove more effective for off label use. This unfortunately

seems to be a matter of “dollars and cents” where the pharmaceutical companies are concerned when determining the indication, they seek from the FDA.

### **3.4 Central nervous system**

Roughly 32% of lupus patients develop lupus that attacks the central nervous system [29]. Lupus involving the central nervous system is both a confusing and interesting aspect of the disease [36, 37]. Virtually any central nervous system or peripheral nervous system problem including, but not limited to, neuropathy, mononeuritis multiplex, seizures, blindness, loss of hearing, cranial nerve palsy, encephalopathy, psychosis and movement disorders, are not uncommon in the lupus population, and may frequently present as an initial feature of the disease.

To reemphasize, all symptomatology that has been mentioned in this chapter may be an initial feature of lupus; however, the lack of swift rheumatology involvement often ultimately leads to a delay in diagnosis, which is always detrimental to the patient. Therefore, it is important to perform a comprehensive evaluation, including biopsy, angiogram, or other internal organ imaging, as well as complete serologic testing. Additionally, most patients are not willing to take medication for extended periods of time, unless it can be proven to them by their physician that the medication will indeed benefit them by alleviating the symptoms they are experiencing. This will assist in a more accurate diagnosis of lupus versus another disease process. As in every case involving a possible autoimmune process, emphasis should be placed on the importance of swift initiation of workup, as this will facilitate the timely establishment of proper treatment.

If a patient is acutely ill with psychosis, they will typically be treated in a hospital setting, being initially seen by neurology and psychiatry, as other specialists. Unfortunately, this occurs before a rheumatologist is consulted [38]. An immediate MRI of the brain and lumbar puncture should be ordered, along with autoantibodies and cerebrospinal fluid, to assess the ribosomal P antibody, GAD65 antibody and NMO. With these proper evaluations, the likelihood of a CNS lupus diagnosis may be determined.

It is quite typical in that lupus patients, including those with renal and central nervous system involvement, in general, do quite well with medical compliance. Published death rates, transplant rates, and dialysis rates for lupus nephritis are decidedly dependent upon the population type that is investigated. A well-educated compliant group of patients has a very low incidence of end stage renal disease while the noncompliant group almost certainly ultimately develop end stage renal disease [39].

### **3.5 Abdominal pain**

Another presentation would be abdominal pain, rather than splenomegaly. This would account for approximately 27% of lupus symptomatology [29]. A patient with severe abdominal pain, who is known to have lupus, after a proper workup for exclusion of perforated viscus or ischemic disease, the treatment would be steroids for what is mesenteric arteritis or serositis. The prognosis would not change, as they are both treated with moderate high dose steroids, oral or IV. Again, this can be a presenting feature of lupus. To the detriment of the patient, they are often seen by gastroenterologists, who run a plethora of tests, including CTAs and MRIs of various organs, only to ultimately discover a case of hepatosplenomegaly with pain. At that point, to the misfortune of the patient, unnecessary surgery is generally performed for the hepatosplenomegaly, and sadly, the patient passes away as a result. If the patient had been treated properly, their life could have been saved, as they would have been successfully treated with 1 to 2 mg/kg of prednisolone or similar [40].



### **3.6 Pancreatitis and Raynaud's phenomenon**

Pancreatitis is an excellent example of a disease, which is not part of the listed diagnostic criteria for lupus. Raynaud's phenomenon also not listed in the diagnostic criteria, although approximately 25% of lupus patients suffer from this condition [29, 41]. While either of those may be the presenting feature of systemic lupus, neither are listed as diagnostic criteria which is fine; however, the practitioner should perform a thorough workup to determine if a patient who has pancreatitis, as they may well have lupus. It should be noted however, that alcoholism, gallstone disease and pancreatic divisum, without the atypical sausage pancreas of IgG4-related disease, must be ruled out.

With regard to Raynaud's, the reversible spasm of vessels, usually induced by cold or emotional provocation, typically with triple phase color response from 5 to 60 minutes, is a frequent feature in lupus patients and may well be the initial finding of the disease. The practitioner must look past scleroderma, which has a more ominous prognosis than Raynaud's related to lupus. This is often differentiated with a simple in-office nailfold capillaroscopy, which by in large, is a tremendously underutilized tool [42]. For the well-seasoned rheumatologist, this technique is used more often, but it should be used with regularity. In fact, nailfold capillaroscopy should be used as a baseline in all potential cases of autoimmune patients.

### **3.7 Heart and lungs**

Attention to the heart and lungs is essential [43]. A patient with recurrent pneumonias is more likely to have lupus pneumonitis or an autoinflammatory disease, rather than the occurrence of infectious pneumonia every three months. After the onset of a second case of pneumonia, a rheumatologist should be consulted, but commonly, this does not occur. Regrettably, the patient who is suffering from an autoimmune disease has now suffered without a proper diagnosis for an unspecified amount of time. At this point, it would be advantageous to the patient to be seen by a rheumatologist without further delay.

Other common heart and lung manifestations of lupus include pleurisy and/or pericardial effusion [44]. Approximately 12% of lupus patients will develop a pericardial effusion [29]. Alarming, in several medical institutions, the treatment of choice for pericardial effusion is a pericardial window. Unfortunately, as in the case of inappropriate splenectomy with abdominal pain in a case of lupus, as mentioned earlier, a pericardial window is carries equal efficacy in a lupus patient presenting with pericardial effusion. As there is no indication for abdominal surgery for a patient with lupus abdominal pain, there is also virtually no indication for pericardial window in a lupus pericarditis patient. The incidence of tamponade is extraordinarily low. Myxomatosis valvular heart disease or so-called Libman-Sacks endocarditis, with or without phospholipid antibodies, is another finding that should be noted, although this is often woefully overlooked.

### **3.8 Overlooked autoimmunity**

Many lupus patients suffer from autoimmunity that is frequently overlooked and therefore; the percentage of sufferers remains uncalculated [45]. The most common is likely Hashimoto's thyroid disease; however, other conditions include Graves' disease, myasthenia gravis, Addison's disease, primary biliary cirrhosis, and autoimmune hepatitis. Each of these has autoimmune associations that should not be overlooked. Many of the features potentially seen in Sjogren's syndrome, or many lupus-like features such as interstitial lung disease, should never be taken for

granted based on the positive ANA or research criteria, as those patients may well have myositis or scleroderma. As mentioned in Part 2 of this chapter, “A Rheum with a Different View”, lupus should be considered in every disease.

#### **4. The thought process of a rheumatologist**

There are deep gaps between the thought process and treatment plans of a rheumatologist versus that of a general internist, family practitioner, ophthalmologist, or orthopedic surgeon or any other practitioner involved in a patient's care.

Rheumatology remains greatly underutilized. This regrettably adds substantial delay to the diagnosis and treatment of a patient. It bears mentioning again that all organ systems may be involved in lupus. Based on this, the all-purpose criteria is preferable to the new SLICC criteria for diagnosis of lupus, as it was far more practical [46]. It also bears mentioning again that no practitioner may diagnose lupus, or any other disease process, based solely on research criteria. Criteria are to be used merely as a guideline. For example, a patient presents to their physician, stating they are “not feeling well”. Subsequently, blood studies are ordered that reveal an ANA with a very high titer and upon further perusal, a very high DNA is also discovered, yet the physician fails to recognize that this patient has a forme-fruste of lupus. A rheumatologist would have started the patient on Plaquenil and educated them with regard to their diagnosis, and the physical ramifications to expect in the future.

Two of the most interesting, but also difficult to treat diseases, a physician may encounter include pulmonary renal syndrome, presenting with alveolar hemorrhage, and glomerular nephritis with ANA, DNA, successfully treated with cyclophosphamide [47]. Another rare, but not uncommon complication of lupus, would be TTP with or without the ADAMTS13 gene and ocular inflammation and orbital pseudotumor. Consider the case of a patient who presented with true renal failure, visual hallucinations and movement disorder. At that point the patient was treated with IV Cytoxan and pulse steroids. Therefore, the patient did not have fever; however the patient was anemic and had schistocytes with an elevated reticulocyte count. Thus, the patient did not fulfill all of the criteria for TTP; therefore, a clinical diagnosis was made of the same. The patient responded almost immediately to with all features of the disease disappearing with plasma exchange. This is a wonderful case to recall, when a hematologist says to a patient, “It cannot be TTP because there is no fever”, apparently, this hematologist has lost sight of the fact that the high dose steroids likely blunted the fever. They may argue that there are not enough schistocytes [48] to fulfill the bacteria, however when schistocytes should not exist, and anemia cannot be explained, it can only be rationalized that the use of cyclophosphamides and high dose steroids lowered the schistocytes [49, 50]. This is a fantastic example of why research criteria alone, should never be used for diagnostic purposes.

It is very important to understand the mechanism of action for each disease feature, as it will impact a patient's treatment. For the purpose of example, thrombocytopenia will be seen in Sjogren's syndrome and hypersplenism, while in lupus platelet antibodies, both conditions can be present with dry eyes and dry mouth. A salivary gland biopsy may not differentiate, as a positive lymphocyte score of 50 lymphocytes  $4\text{mm}^2$ , may presumably be seen in either condition. This may lead to an overlap diagnosis, or based on the mechanism of thrombocytopenia, it may also sway the diagnosis. Pneumonitis, while common in lupus, is seen in other autoimmune diseases, including sarcoidosis. All conditions mentioned may have a positive rheumatoid factor or positive ANA. Even CCP antibodies can be seen in autoimmune diseases with low values [51].

## 5. Conclusions

Lupus is a great mimicker. This is due in part to a woeful lack of knowledge by most practitioners, as well as the absence of specific treatments. However, based on our available knowledge, with earlier institution of proper rheumatologic assistance, patients would be diagnosed with greater accuracy and proper treatments begun in a timely manner. Also, with patient compliance, education and understanding outcome is better reference. Consulting a rheumatologist promptly, would not only benefit the patient, but also profit the medical system by eradicating useless tests and treatment options that are often unmerited. Unfortunately, in a world of protocol, many are afraid to take an unconventional approach. It is because of this; other physicians often fail to consider a rheumatologic consultation [52].

### Author details

Stephen Soloway<sup>1,2</sup>

1 Arthritis and Rheumatology Associates of South Jersey, P.C., Vineland, NJ, USA

2 Chief of Rheumatology, Inspira Medical Network, Mullica Hill and Vineland, NJ, USA

\*Address all correspondence to: [cdipaola@drsoloway.com](mailto:cdipaola@drsoloway.com)

### IntechOpen

© 2021 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

## References

- [1] Kuhn A, Bonsmann G, Anders HJ, Herzer P, Tenbrock K, Schneider M. The Diagnosis and Treatment of Systemic Lupus Erythematosus. *Dtsch Arztebl Int.* 2015 Jun 19;112(25):423-32. doi: 10.3238/arztebl.2015.0423. PMID: 26179016; PMCID: PMC4558874.
- [2] Wallace, Daniel J. (Daniel Jeffrey), 1949-The lupus book : a guide for patients and their families / Daniel J. Wallace. – 5<sup>th</sup> ed.
- [3] Tunnicliffe DJ, Palmer SC, Henderson L, Masson P, Craig JC, Tong A, Singh-Grewal D, Flanc RS, Roberts MA, Webster AC, Strippoli GF. Immunosuppressive treatment for proliferative lupus nephritis. *Cochrane Database Syst Rev.* 2018 Jun 29;6(6):CD002922. doi: 10.1002/14651858.CD002922.pub4. PMID: 29957821; PMCID: PMC6513226.
- [4] Felten R, Scher F, Sagez F, Chasset F, Arnaud L. Spotlight on anifrolumab and its potential for the treatment of moderate-to-severe systemic lupus erythematosus: evidence to date. *Drug Des Devel Ther.* 2019 May 8;13:1535-1543. doi: 10.2147/DDDT.S170969. PMID: 31190735; PMCID: PMC6514126.
- [5] Baigrie D, Bansal P, Goyal A, Crane JS. Leukocytoclastic Vasculitis. 2020 Aug 11. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. PMID: 29489227.
- [6] Qiao W, Ding H, Zuo Y, Jiang L, Zhou J, Han X, Yu L, Du R, M Hedrich C, Deng GM. Lupus IgG deposition causes arthritis but inhibits bone destruction through competitive occupation of FcγRI and reduced RANKL signalling. *Clin Transl Immunology.* 2020 Sep 6;9(9):e1174. doi: 10.1002/cti2.1174. PMID: 32994999; PMCID: PMC7507387.
- [7] Komolafe OO. Rapidly progressive glomerulonephritis: A wild card manifestation of lupus nephritis. *Saudi J Kidney Dis Transpl.* 2018 Mar-Apr;29(2):443-451. doi: 10.4103/1319-2442.229293. PMID: 29657218.
- [8] Rutgers A, Sanders JS, Stegeman CA, Kallenberg CG. Pauci-immune necrotizing glomerulonephritis. *Rheum Dis Clin North Am.* 2010 Aug;36(3): 559-572. doi: 10.1016/j.rdc.2010.05.002. PMID: 20688250.
- [9] DeVrieze BW, Hurley JA. Good-pasture Syndrome. 2020 Mar 25. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. PMID: 29083697.
- [10] Mustaqeem R, Arif A. Renal Tubular Acidosis. 2020 Aug 16. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. PMID: 30085586.
- [11] Muriithi AK, Leung N, Valeri AM, et al. Biopsy-proven acute interstitial nephritis, 1993-2011: a case series. *Am J Kidney Dis* 2014;64:558-566.
- [12] Cortazar FB, Kibbelaar ZA, Glezerman IG, et al. Clinical features and outcomes of immune checkpoint inhibitor-associated AKI: a multicenter study. *J Am Soc Nephrol* 2020;31: 435-446.
- [13] Huong DL, Papo T, Beaufile H, et al. Renal involvement in systemic lupus erythematosus: a study of 180 patients from a single center. *Medicine (Baltimore)* 1999;78:148-166.
- [14] Yu F, Wu L-H, Tan Y, et al. Tubulointerstitial lesions of patients with lupus nephritis classified by the 2003 International Society of Nephrology and Renal Pathology Society system. *Kidney Int* 2010;77:820-829.
- [15] Cortazar FB, Stone JH. IgG4-related disease and the kidney. *Nat Rev Nephrol* 2015;11:599-609.



- [16] Raissian Y, Nasr SH, Larsen CP, et al. Diagnosis of IgG4-related tubulointerstitial nephritis. *J Am Soc Nephrol* 2011;22:1343-1352.
- [17] McCabe C, Jones Q, Nikolopoulou A, Wathen C, Luqmani R. Pulmonary-renal syndromes: an update for respiratory physicians. *Respir Med*. 2011 Oct;105(10):1413-1421. doi: 10.1016/j.rmed.2011.05.012. PMID: 21684732.
- [18] Jennette JC, Nachman PH. ANCA Glomerulonephritis and Vasculitis. *Clin J Am Soc Nephrol*. 2017 Oct 6;12(10):1680-1691. doi: 10.2215/CJN.02500317. Epub 2017 Aug 25. PMID: 28842398; PMCID: PMC5628710.
- [19] Saccucci M, Di Carlo G, Bossù M, Giovarruscio F, Salucci A, Polimeni A. Autoimmune Diseases and Their Manifestations on Oral Cavity: Diagnosis and Clinical Management. *J Immunol Res*. 2018 May 27;2018:6061825. doi: 10.1155/2018/6061825. PMID: 29977929; PMCID: PMC5994274.
- [20] Andrews JS, Trupin L, Schmajuk G, Barton J, Margaretten M, Yazdany J, Yelin EH, Katz PP. Muscle Strength and Changes in Physical Function in Women With Systemic Lupus Erythematosus. *Arthritis Care Res (Hoboken)*. 2015 Aug;67(8):1070-7. doi: 10.1002/acr.22560. PMID: 25623919; PMCID: PMC4515406.
- [21] Lee KC, Ladizinski B, Federman DG. Complications associated with use of levamisole-contaminated cocaine: an emerging public health challenge. *Mayo Clin Proc*. 2012 Jun;87(6):581-6. doi: 10.1016/j.mayocp.2012.03.010. PMID: 22677078; PMCID: PMC3498128.
- [22] Vasquez-Canizares N, Wahezi D, Putterman C. Diagnostic and prognostic tests in systemic lupus erythematosus. *Best Pract Res Clin Rheumatol*. 2017 Jun;31(3):351-363. doi: 10.1016/j.berh.2017.10.002. Epub 2017 Nov 6. PMID: 29224677; PMCID: PMC5776716.
- [23] Chanprapaph K, Udompanich S, Visessiri Y, Ngamjanyaporn P, Suchonwanit P. Nonscarring alopecia in systemic lupus erythematosus: A cross-sectional study with trichoscopic, histopathologic, and immunopathologic analyses. *J Am Acad Dermatol*. 2019 Dec;81(6):1319-1329. doi: 10.1016/j.jaad.2019.05.053. Epub 2019 May 28. PMID: 31150712.
- [24] Jefferson GD, Aakalu VK, Branietki M. Tumid lupus: An unexpected diagnosis for the otolaryngologist. *Am J Otolaryngol*. 2017 Mar-Apr;38(2):257-259. doi: 10.1016/j.amjoto.2017.01.003. Epub 2017 Jan 17. PMID: 28122678; PMCID: PMC5826658.
- [25] Klímová A, Seidler Štangová P, Svožílková P, Kučera T, Heissigerová J. Klinické projevy experimentální autoimunitní uveitidy [The Clinical Signs of Experimental Autoimmune Uveitis]. *Cesk Slov Oftalmol*. 2016 Feb;72(1):276-82. Czech. PMID: 27041283.
- [26] Tao CY, Shang J, Chen T, Yu D, Jiang YM, Liu D, Cheng GY, Xiao J, Zhao ZZ. Impact of antimalarial (AM) on serum lipids in systemic lupus erythematosus (SLE) patients: A systematic review and meta-analysis. *Medicine (Baltimore)*. 2019 Apr;98(14):e15030. doi: 10.1097/MD.00000000000015030. PMID: 30946340; PMCID: PMC6456110.
- [27] Chi AC, Neville BW, Krayner JW, Gonsalves WC. Oral manifestations of systemic disease. *Am Fam Physician*. 2010 Dec 1;82(11):1381-1388. PMID: 21121523.
- [28] Carubbi F, Alunno A, Gerli R, Giacomelli R. Histopathology of salivary glands. *Reumatismo*. 2018 Oct 3;70(3):146-154. doi: 10.4081/reumatismo.2018.1053. PMID: 30282440.
- [29] Wallace, Daniel J. (Daniel Jeffrey), 1949-The lupus book : a guide for patients and their families / Daniel J. Wallace. – 5<sup>th</sup> ed.

- [30] Ceccarelli F, Perricone C, Cipriano E, Massaro L, Natalucci F, Capalbo G, Leccese I, Bogdanos D, Spinelli FR, Alessandri C, Valesini G, Conti F. Joint involvement in systemic lupus erythematosus: From pathogenesis to clinical assessment. *Semin Arthritis Rheum*. 2017 Aug;47(1):53-64. doi: 10.1016/j.semarthrit.2017.03.022. Epub 2017 Apr 4. PMID: 28465078.
- [31] van Vugt RM, Derksen RH, Kater L, Bijlsma JW. Deforming arthropathy or lupus and rhupus hands in systemic lupus erythematosus. *Ann Rheum Dis*. 1998 Sep;57(9):540-4. doi: 10.1136/ard.57.9.540. PMID: 9849313; PMCID: PMC1752746.
- [32] Kabadi S, Yeaw J, Bacani AK, Tafesse E, Bos K, Karkare S, DeKoven M, Vina ER. Healthcare resource utilization and costs associated with long-term corticosteroid exposure in patients with systemic lupus erythematosus. *Lupus*. 2018 Oct;27(11):1799-1809. doi: 10.1177/0961203318790675. Epub 2018 Aug 1. PMID: 30068254; PMCID: PMC6264911.
- [33] Brierley CK, Pavord S. Autoimmune cytopenias and thrombotic thrombocytopenic purpura. *Clin Med (Lond)*. 2018 Aug;18(4):335-339. doi: 10.7861/clinmedicine.18-4-335. PMID: 30072561; PMCID: PMC6334040.
- [34] Chimenti MS, Di Stefani A, Conigliaro P, Saggini A, Urbani S, Giunta A, Esposito M, Bianchi L, Peris K, Perricone R. Histopathology of the skin in rheumatic diseases. *Reumatismo*. 2018 Oct 3;70(3):187-198. doi: 10.4081/reumatismo.2018.1049. PMID: 30282444.
- [35] Jessop S, Whitelaw DA, Grainge MJ, Jayasekera P. Drugs for discoid lupus erythematosus. *Cochrane Database Syst Rev*. 2017 May 5;5(5):CD002954. doi: 10.1002/14651858.CD002954.pub3. PMID: 28476075; PMCID: PMC6481466.
- [36] Hanly JG, Kozora E, Beyea SD, Birnbaum J. Review: Nervous System Disease in Systemic Lupus Erythematosus: Current Status and Future Directions. *Arthritis Rheumatol*. 2019 Jan;71(1):33-42. doi: 10.1002/art.40591. Epub 2018 Nov 24. PMID: 29927108.
- [37] Kivity S, Agmon-Levin N, Zandman-Goddard G, Chapman J, Shoenfeld Y. Neuropsychiatric lupus: a mosaic of clinical presentations. *BMC Med*. 2015 Mar 4;13:43. doi: 10.1186/s12916-015-0269-8. PMID: 25858312; PMCID: PMC4349748.
- [38] Hanly JG, Li Q, Su L, Urowitz MB, Gordon C, Bae SC, Romero-Diaz J, Sanchez-Guerrero J, Bernatsky S, Clarke AE, Wallace DJ, Isenberg DA, Rahman A, Merrill JT, Fortin PR, Gladman DD, Bruce IN, Petri M, Ginzler EM, Dooley MA, Steinsson K, Ramsey-Goldman R, Zoma AA, Manzi S, Nived O, Jonsen A, Khamashta MA, Alarcón GS, van Vollenhoven RF, Aranow C, Mackay M, Ruiz-Irastorza G, Ramos-Casals M, Lim SS, Inanc M, Kalunian KC, Jacobsen S, Peschken CA, Kamen DL, Askanase A, Theriault C, Farewell V. Psychosis in Systemic Lupus Erythematosus: Results From an International Inception Cohort Study. *Arthritis Rheumatol*. 2019 Feb;71(2):281-289. doi: 10.1002/art.40764. Epub 2019 Jan 18. PMID: 30375754; PMCID: PMC6353684.
- [39] Tesar V, Hruskova Z. Lupus Nephritis: A Different Disease in European Patients? *Kidney Dis (Basel)*. 2015 Sep;1(2):110-8. doi: 10.1159/000438844. Epub 2015 Aug 28. PMID: 27536671; PMCID: PMC4934820.
- [40] Adler BL, Timlin H, Birnbaum J. Lupus intestinal pseudo-obstruction and hydronephrosis: Case report. *Medicine (Baltimore)*. 2019 Jul;98(28):e16178. doi: 10.1097/MD.00000000000016178. PMID: 31305400; PMCID: PMC6641825.
- [41] Hesselstrand R, Iagnocco A, Kayser C, Melsens K, Müller-Ladner U,

- Paolino S, Pizzorni C, Radic M, Riccieri V, Snow M, Stevens W, Sulli A, van Laar JM, Vonk MC, Vanhaecke A, Cutolo M; EULAR Study Group on Microcirculation in Rheumatic Diseases and the Scleroderma Clinical Trials Consortium Group on Capillaroscopy. Standardisation of nailfold capillaroscopy for the assessment of patients with Raynaud's phenomenon and systemic sclerosis. *Autoimmun Rev.* 2020 Mar;19(3):102458. doi: 10.1016/j.autrev.2020.102458. Epub 2020 Jan 10. PMID: 31927087.
- [42] Smith V, Herrick AL, Ingegnoli F, Damjanov N, De Angelis R, Denton CP, Distler O, Espejo K, Foeldvari I, Frech T, Garro B, Gutierrez M, Gyger G, Hachulla E, Hesselstrand R, Iagnocco A, Kayser C, Melsens K, Müller-Ladner U, Paolino S, Pizzorni C, Radic M, Riccieri V, Snow M, Stevens W, Sulli A, van Laar JM, Vonk MC, Vanhaecke A, Cutolo M; EULAR Study Group on Microcirculation in Rheumatic Diseases and the Scleroderma Clinical Trials Consortium Group on Capillaroscopy. Standardisation of nailfold capillaroscopy for the assessment of patients with Raynaud's phenomenon and systemic sclerosis. *Autoimmun Rev.* 2020 Mar;19(3):102458. doi: 10.1016/j.autrev.2020.102458. Epub 2020 Jan 10. PMID: 31927087.
- [43] Signorini V, Elefante E, Zucchi D, Trentin F, Bortoluzzi A, Tani C. One year in review 2020: systemic lupus erythematosus. *Clin Exp Rheumatol.* 2020 Jul-Aug;38(4):592-601. Epub 2020 Jul 10. PMID: 32662410.
- [44] Bezwada P, Quadri A, Shaikh A, Ayala-Rodriguez C, Green S. Myopericarditis and Pericardial Effusion as the Initial Presentation of Systemic Lupus Erythematosus. *Case Rep Med.* 2017;2017:6912020. doi: 10.1155/2017/6912020. Epub 2017 Feb 5. PMID: 28261271; PMCID: PMC5316435.
- [45] Basta F, Fasola F, Triantafyllias K, Schwarting A. Systemic Lupus Erythematosus (SLE) Therapy: The Old and the New. *Rheumatol Ther.* 2020 Sep;7(3):433-446. doi: 10.1007/s40744-020-00212-9. Epub 2020 Jun 2. PMID: 32488652; PMCID: PMC7410873.
- [46] Tiao J, Feng R, Carr K, Okawa J, Werth VP. Using the American College of Rheumatology (ACR) and Systemic Lupus International Collaborating Clinics (SLICC) criteria to determine the diagnosis of systemic lupus erythematosus (SLE) in patients with subacute cutaneous lupus erythematosus (SCLE). *J Am Acad Dermatol.* 2016 May;74(5):862-9. doi: 10.1016/j.jaad.2015.12.029. Epub 2016 Feb 18. PMID: 26897388; PMCID: PMC4879000.
- [47] Nasser M, Cottin V. The Respiratory System in Autoimmune Vascular Diseases. *Respiration.* 2018;96(1):12-28. doi: 10.1159/000486899. Epub 2018 Jul 4. PMID: 29975964.
- [48] Nasser M, Cottin V. The Respiratory System in Autoimmune Vascular Diseases. *Respiration.* 2018;96(1):12-28. doi: 10.1159/000486899. Epub 2018 Jul 4. PMID: 29975964.
- [49] Schapkaitz E, Mezgebe MH. The Clinical Significance of Schistocytes: A Prospective Evaluation of the International Council for Standardization in Hematology Schistocyte Guidelines. *Turk J Haematol.* 2017 Mar 1;34(1):59-63. doi: 10.4274/tjh.2016.0359. Epub 2016 Oct 31. PMID: 27795225; PMCID: PMC5451690.
- [50] Chiasakul T, Cuker A. Clinical and laboratory diagnosis of TTP: an integrated approach. *Hematology Am Soc Hematol Educ Program.* 2018 Nov 30;2018(1):530-538. doi: 10.1182/asheducation-2018.1.530. PMID: 30504354; PMCID: PMC6246034.
- [51] Soloway A. Late-onset Systemic Lupus Erythematosus Presenting with Pneumonitis and Class IV Lupus

Nephritis, 2019 ACP Poster Contest  
Winner NYS

[52] Hoover PJ, Costenbader KH.  
Insights into the epidemiology and  
management of lupus nephritis from  
the US rheumatologist's perspective.  
Kidney Int. 2016 Sep;90(3):487-92.  
doi: 10.1016/j.kint.2016.03.042. Epub  
2016 Jun 22. PMID: 27344205; PMCID:  
PMC5679458.