Casual Friday Presents

SLE – Lupus, Part 1

A BIOGENETIX CLINICAL PRESENTATION

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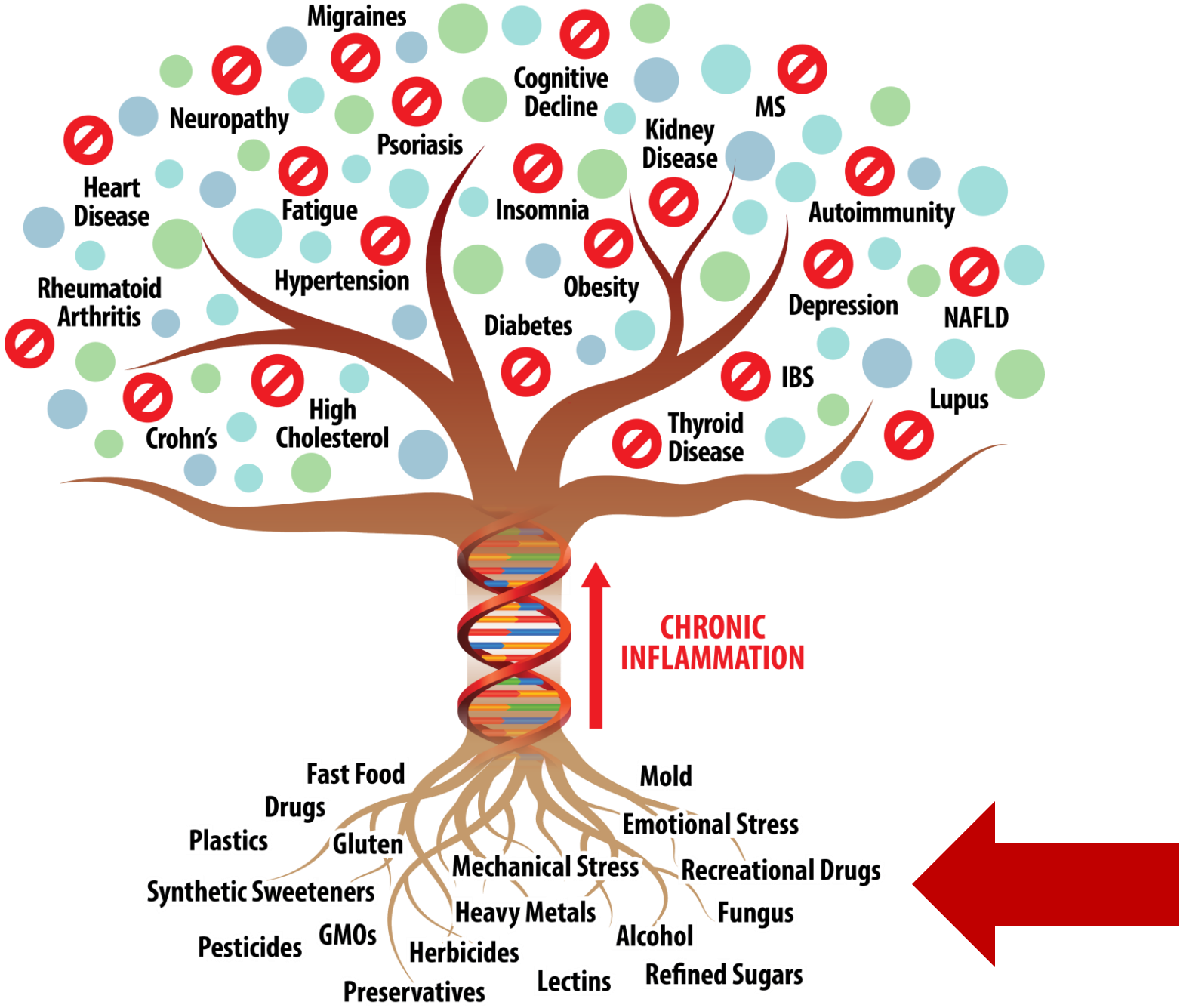
Migraines
Neuropathy
Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Autoimmunity
Rheumatoid Arthritis
Hypertension
Obesity
Depression
NAFLD
Diabetes
IBS
Lupus
Crohn's
High Cholesterol
Thyroid Disease
CHRONIC INFLAMMATION
Fast Food
Drugs
Plastics
Gluten
Synthetic Sweeteners
Pesticides
GMOs
Herbicides
Preservatives
Lectins
Refined Sugars
Heavy Metals
Mechanical Stress
Alcohol
Mold
Emotional Stress
Recreational Drugs
Fungus

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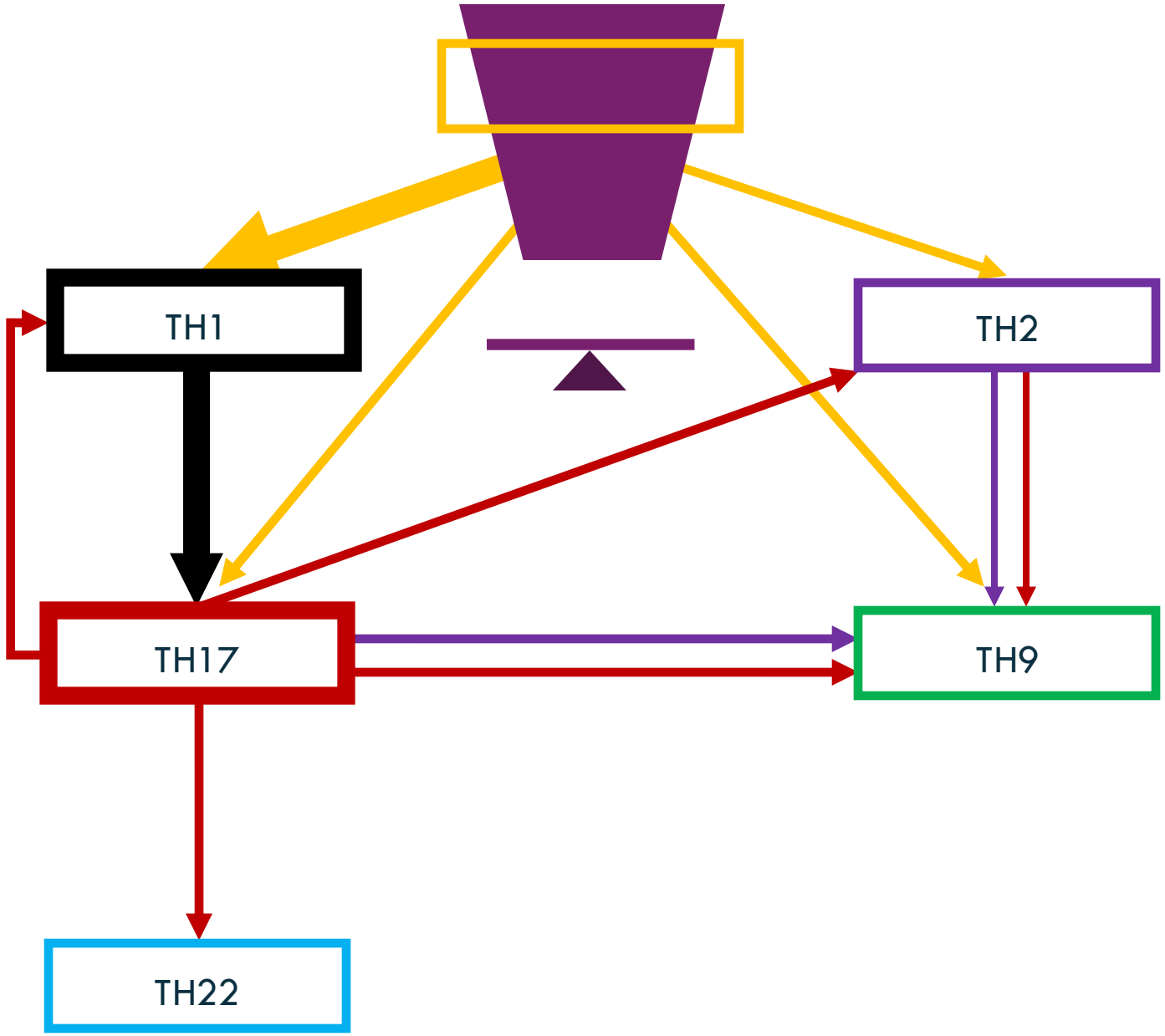

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Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with multisystemic involvement. The condition has several phenotypes, with varying clinical presentations from mild mucocutaneous manifestations to multiorgan and severe central nervous system involvement. Several immunopathogenic pathways play a role in the development of SLE. Hargraves described the lupus erythematosus (LE cell) in 1948. Several pathogenic autoantibodies have since been identified. Despite recent advances in technology and understanding of the pathological basis and risk factors for SLE, the exact pathogenesis is still not well known. Diagnosis of SLE can be challenging, and while several classification criteria have been posed, their utility in the clinical setting is still a matter of debate. Management of SLE is dictated by organ system involvement. Despite several agents shown to be efficacious in treating SLE, the disease still poses significant morbidity and mortality risk in patients.[1]

https://www.ncbi.nlm.nih.gov/books/NBK535405/

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In addition, women are at ten times more risk of developing SLE than men, and the risk of SLE is 14 times more in Klinefelter syndrome (47, XXY). This suggests an association with genes on the X-chromosome. However, despite several studies, the exact genes have not been identified.

Female sex and hormonal influence are significant risk factors for SLE. Estrogen stimulates CD8+ and CD4+ T cells, B cells, macrophages, thymocytes, the release of some specific cytokines (e.g., IL-1), and the expression of HLA and endothelial cell adhesion molecules (VCAM, ICAM). In addition, estrogens and prolactin promote autoimmunity, increase the B-cell activation factor production, and modulate lymphocyte and plasmacytoid dendritic cells (pDC) activation. The use of estrogen-containing contraceptives and postmenopausal hormone replacement therapy can cause flares in patients with SLE and have been associated with a higher incidence of SLE. In addition, elevated levels of prolactin are seen in patients with SLE. Androgens, on the other hand, are immunosuppressive.[3]

Several environmental triggers of SLE have been identified. Several drugs have been implicated in causing a lupus-like phenomenon by causing demethylation of DNA and alteration of self-antigens. While procainamide and hydralazine have the highest incidence of causing drug-induced lupus, more than 100 drugs have been associated with drug-induced lupus. Further, several drugs such as the sulfa-drugs are well known to cause flares in patients with SLE. Ultraviolet rays and sun exposure lead to increased cell apoptosis and are well-known triggers for SLE. Several viral infections have been implicated, and the underlying mechanism is thought to be molecular mimicry. Antibodies against Epstein-Barr virus (EBV) are more prevalent in children and adults with SLE compared to the general population. Smoking is also thought to be a risk, with a dose-response. Other potential risk factors include silica exposure, other viral infections, vitamin D deficiency, alfalfa sprouts, and foods containing canavanine.[4]

Both innate and adaptive immune systems play a role in the pathogenesis of SLE. The innate immune system activation is either Toll-like receptor (TLR) dependent or independent. The cell membrane-bound TLRs (TLR 2, 4, 6) are activated on exposure to the extracellular DNA and RNA from dying cells, which leads to downstream activation of the interferon regulatory family (IRF-3), NF-κB, and MAP-kinases, which serve as transcription factors for the production of proinflammatory mediators such as IFN-b. The endosomal TLRs (TLR 7, 9) are activated by single-stranded RNA and demethylated DNA, leading to interferon-alpha production and RNA binding autoantibodies such as antibodies against Ro La, Sm, and RNP. The TLR-independent pathway is activated by intracytoplasmic RNA sensors (RIG-1, MDA-5) and DNA sensors (IFI16, DAI) and leads to activation of IRF3 and NF-κB. Both self DNA/RNA and foreign DNA/RNA, such as from viruses, can lead to this activation. NETosis has recently gained attention in the pathogenesis of SLE. On activation by various factors such as cytokines, activated platelets, and vascular endothelial cells, neutrophils systematically release their nuclear aggregates in the extracellular environment. These nuclear aggregates can then promote Interferon-alpha production by the dendritic cells, mediate thrombosis and vascular damage and serve as self-antigens for T-lymphocytes.

T-lymphocytes and B-lymphocytes play a significant role in the pathogenesis of SLE. Apoptotic and damaged cell-derived antigens are presented to T-cells by antigen-presenting cells. T-cells in SLE display a distorted gene expression leading to the production of several cytokines. These T-cells produce less IL-2, which leads to altered regulatory T-cell production. Increased IL-6, IL-10, IL-12, and IL-23 increase mononuclear cell production while increased IL-17 and IL-21 lead to increased T-cel production. Increased Interfern-γ leads to defective T-cell production. T-cells lead to the activation of autoreactive B-cells by CD40L and cytokine production, leading to autoantibody production, a hallmark of SLE. Toll-like receptors on interaction with DNA and RNA lead to activation of these B-cells, and the nucleic acid and protein-containing intranuclear complexes are the most prominent antigens leading to B-cel activation. These autoantibodies are pathogenic and cause organ damage by immune complex deposition, complement, and neutrophil activation, altering cell function leading to apoptosis and cytokine production.[4][6]

Pathology from skin lesions in SLE demonstrates immune complex formation leading to tissue damage, vascular and perivascular inflammation, and chronic mononuclear cell infiltration. Acute lesions demonstrate fibrinoid necrosis at the dermo-epidermal junction and the dermis, along with liquefactive degeneration of the epidermis and perivascular inflammatory cell infiltration with a T-cell predominance. Chronic lesions can also demonstrate hyperkeratosis and follicular plugging. In addition, edema and RBC extravasation can be seen in all SLE lesions. Immunofluorescence demonstrates deposition of IgG, IgA, and IgM immunoglobulins and complement components along the dermal-epidermal junction.

Vasculitis is common in SLE, and vascular lesions may demonstrate various pathologies. Immune complex deposition with an inflammatory response is the most common lesion, although it may be seen without a significant inflammatory response. Small and large vessel necrotizing vasculitis with fibrinoid necrosis is less common but can be seen and differentiated from other vasculitides by immune complex deposition in the vessel wall. Thrombotic microangiopathy can present in patients with SLE and antiphospholipid antibody syndrome.[8]

In SLE, central nervous system pathology reveals small intracranial vessel involvement with thrombotic lesions with or without perivascular inflammation and endothelial proliferation. Necrotizing vasculitis is present rarely. Thromboembolism from Libman-Sacks endocarditis has been seen as well.

Cardiac pathology may include valvular involvement leading to Libman-Sacks endocarditis which is sterile verrucous endocarditis. It tends to involve the mitral valve, most commonly with vegetations seen on the forward flow side of the valve. Pathology reveals platelet thrombi, necrotic cell debris, proteinaceous deposits, and mononuclear cells. Pericarditis with fibrinous exudate is common, and pathology reveals mononuclear cells' fibrinoid necrosis and perivascular infiltration. Myocarditis can be seen as well. SLE poses a very high risk for atherosclerotic coronary artery disease, and vasculitis, immune complex deposition in addition to corticosteroid use, and hypertension are thought to be contributory.[9]

Lymphadenopathy is common in SLE, and pathology may reveal follicular hyperplasia with giant cells, plasma cells infiltration of the interfollicular zones, and necrosis of the paracortical T-cell zones. LE bodies may be rarely seen. The necrotic vessel wall shows immunoglobulin and Complement C3 deposition. Splenomegaly is also common in SLE, with pathology showing the classic onionskin lesion with has multiple concentric rings of perivascular collagen. Follicular hyperplasia and periarterial fibrosis are common.

Lupus pneumonitis can be seen in up to 10% of lupus patients. Interstitial pneumonitis, alveolitis, alveolar wall injury, and edema and hemorrhage are commonly seen in these patients. Immunoglobulin and complement deposition is seen in the vessel wall. Chronic interstitial lung disease can occur in up to 50% of these patients and is characterized by interstitial lymphoid aggregates and fibrosis, septal thickening, and type-2 pneumocyte hyperplasia. Medial hypertrophy and intimal fibrosis involving the pulmonary artery branches lead to pulmonary hypertension in SLE. Again, immunoglobulin and complement deposition can be seen in the vessel wall.

Lupus nephritis can involve the glomeruli, interstitium, tubules, and vessels with immune complex deposition in all four compartments. The World Health Organization classification criteria for lupus nephritis describes six classes of lupus nephritis, all with distinct pathological features and significant differences in clinical outcomes. This has led to a different treatment approach for each class and knowing the class of lupus nephritis before initiating treatment is vital.

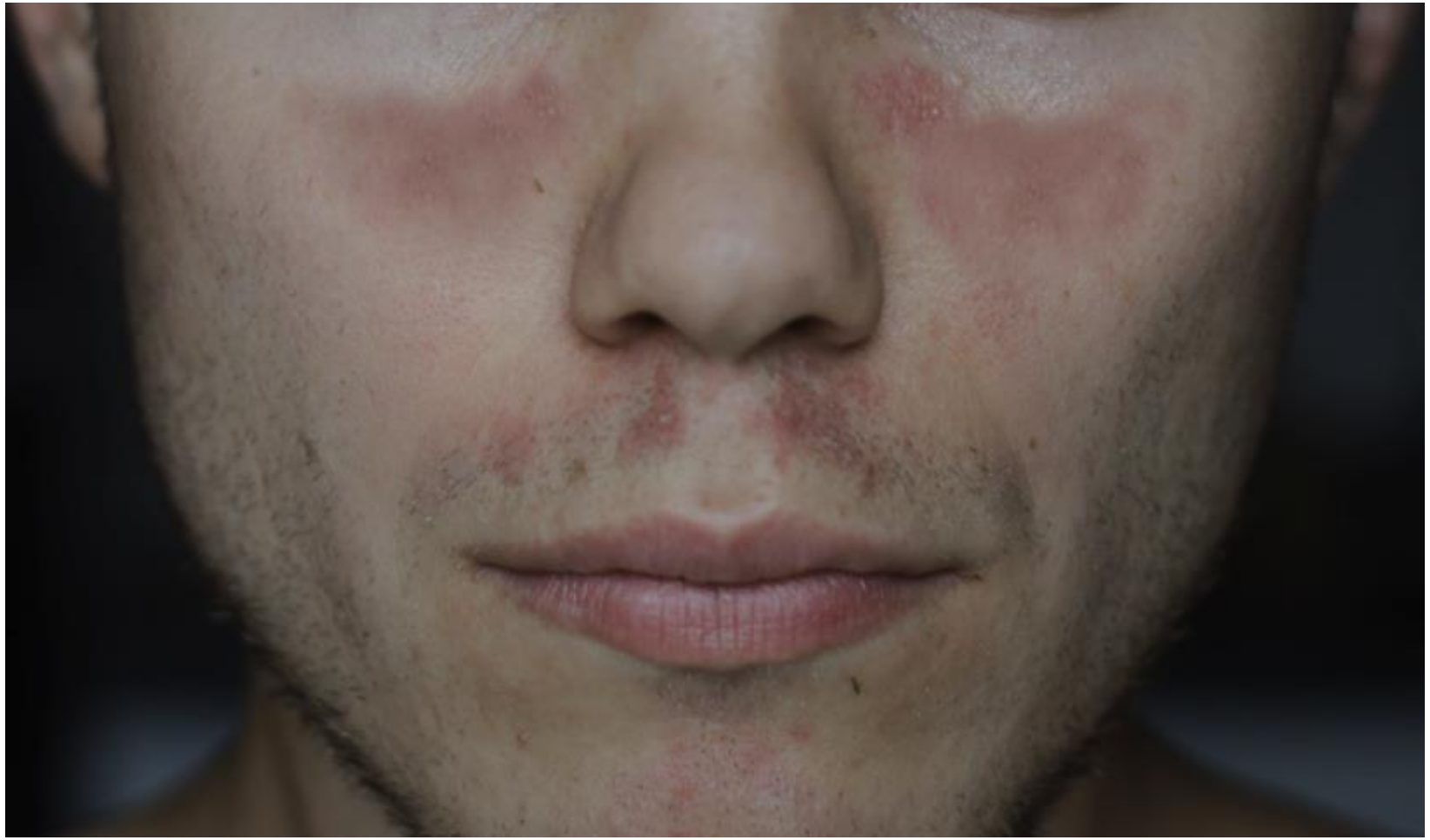
Constitutional symptoms are seen in more than 90% of patients with SLE and are often the initial presenting feature. Fatigue, malaise, fever, anorexia, and weight loss are common. While more than 40% of patients with SLE may have lupus flare as a cause of fever, infections must always be ruled out first, given the immunocompromised state of these patients. Further, SLE is an infrequent cause of fever of unknown origin.[11]

Acute cutaneous lupus erythematosus (ACLE) may be localized or generalized. The hallmark ACLE lesion is the malar rash or the butterfly rash, an erythematous raised pruritic rash involving the cheeks and nasal bridge. The rash may be macular or papular and spares the nasolabial folds (photoprotected).

Subacute cutaneous lupus erythematosus (SCLE) rash is a photosensitive, widespread, nonscarring, nonindurated rash. SCLE may be either papulosquamous resembling psoriasis or an annular/polycystic lesion with central clearing and peripheral scaling.

Discoid lupus erythematosus (DLE) is the most common form of chronic cutaneous lupus erythematosus (CCLE). DLE may occur with or without SLE and can be localized (only head and neck) or generalized (above and below the neck). The lesions are disk-shaped erythematous papules or plaques with adherent scaling and central clearing. DLE heals with scarring and can be associated with permanent alopecia when present on the scalp.

Acute Cutaneous Lupus Erythematosus (ACLE)



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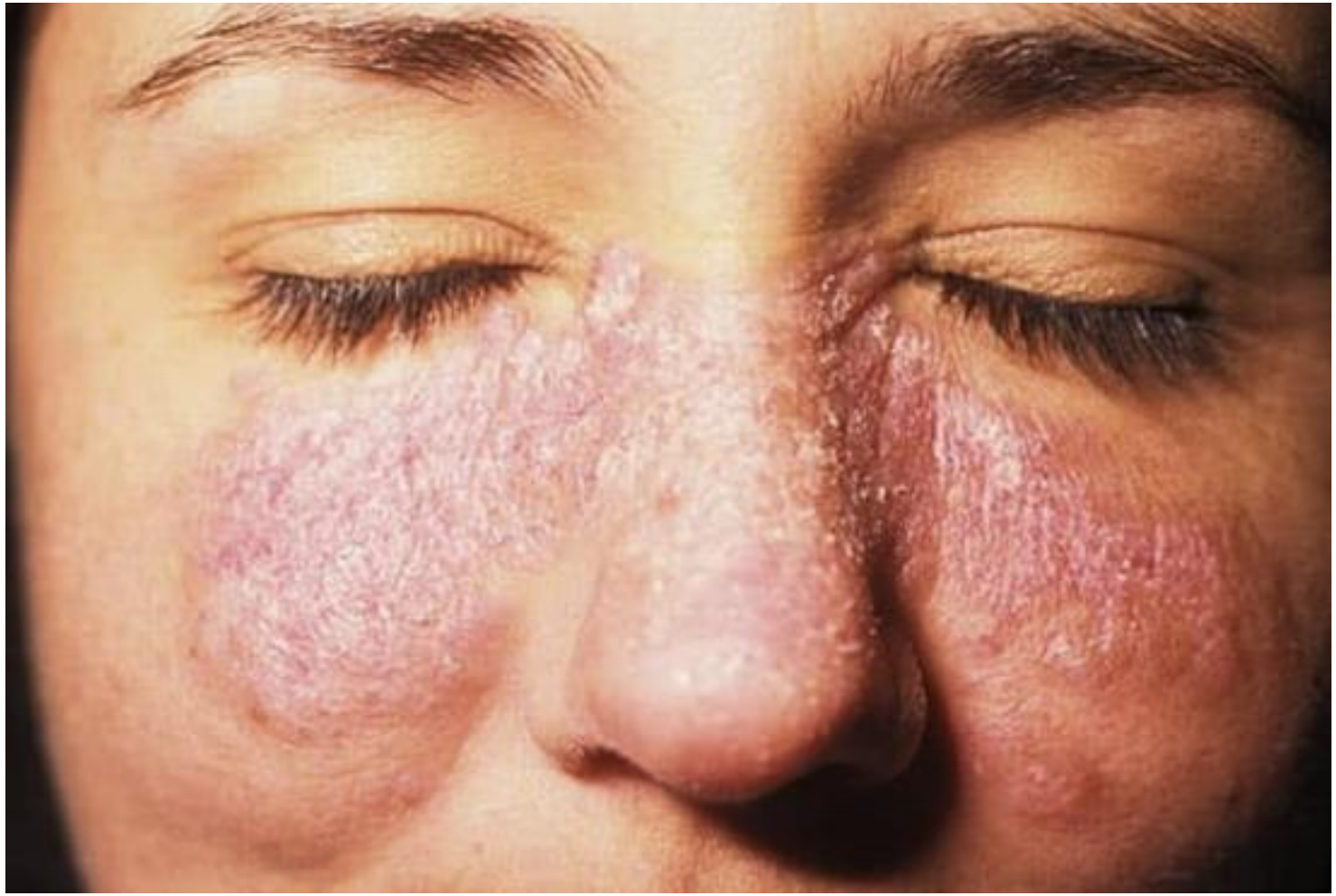
Acute Cutaneous Lupus Erythematosus (ACLE)



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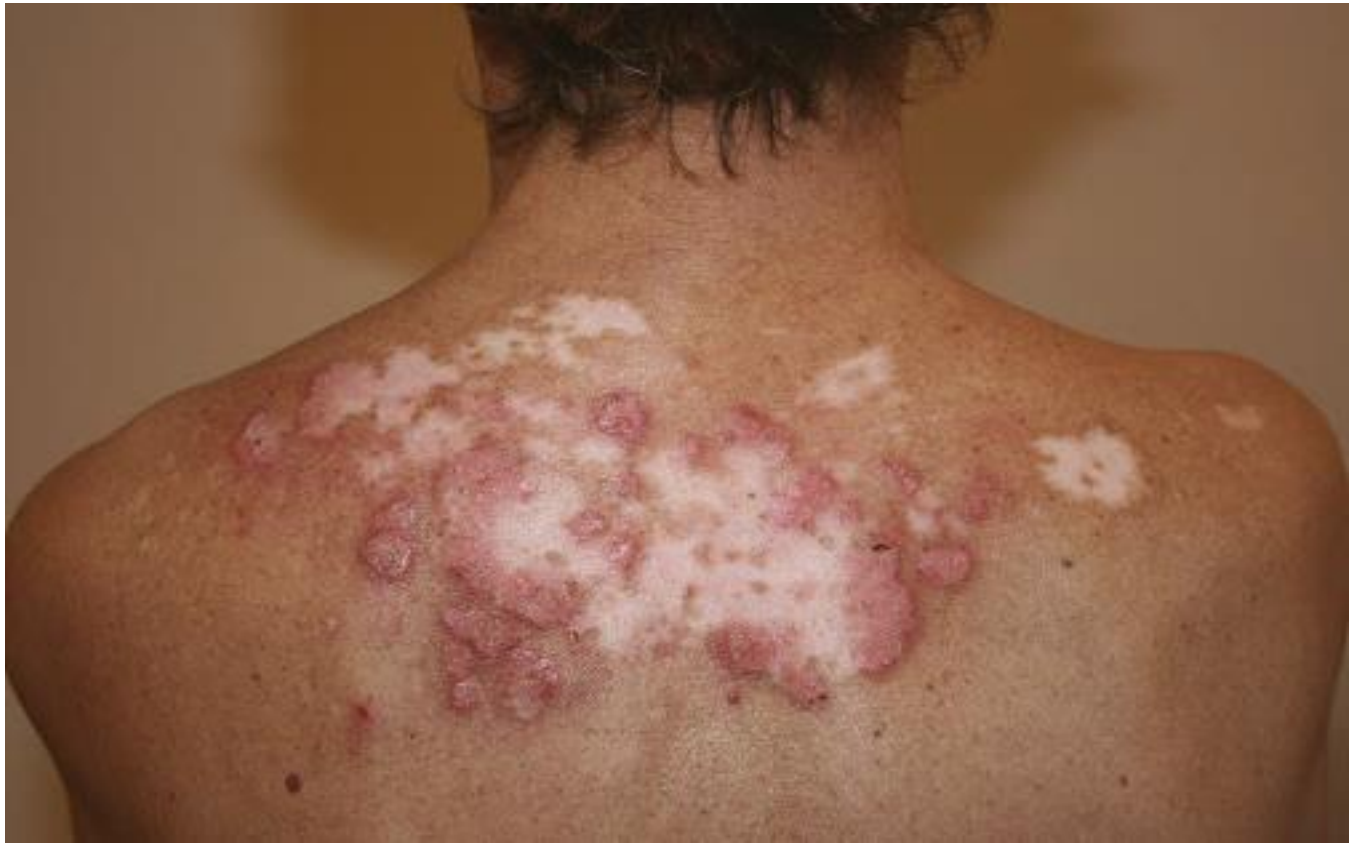
Discoid Lupus Erythematosus (DLE)



https://www.chandigarhayurvedcentre.com/wp-content/uploads/2021/10/Discoid-Lupus-erythematous.jpg

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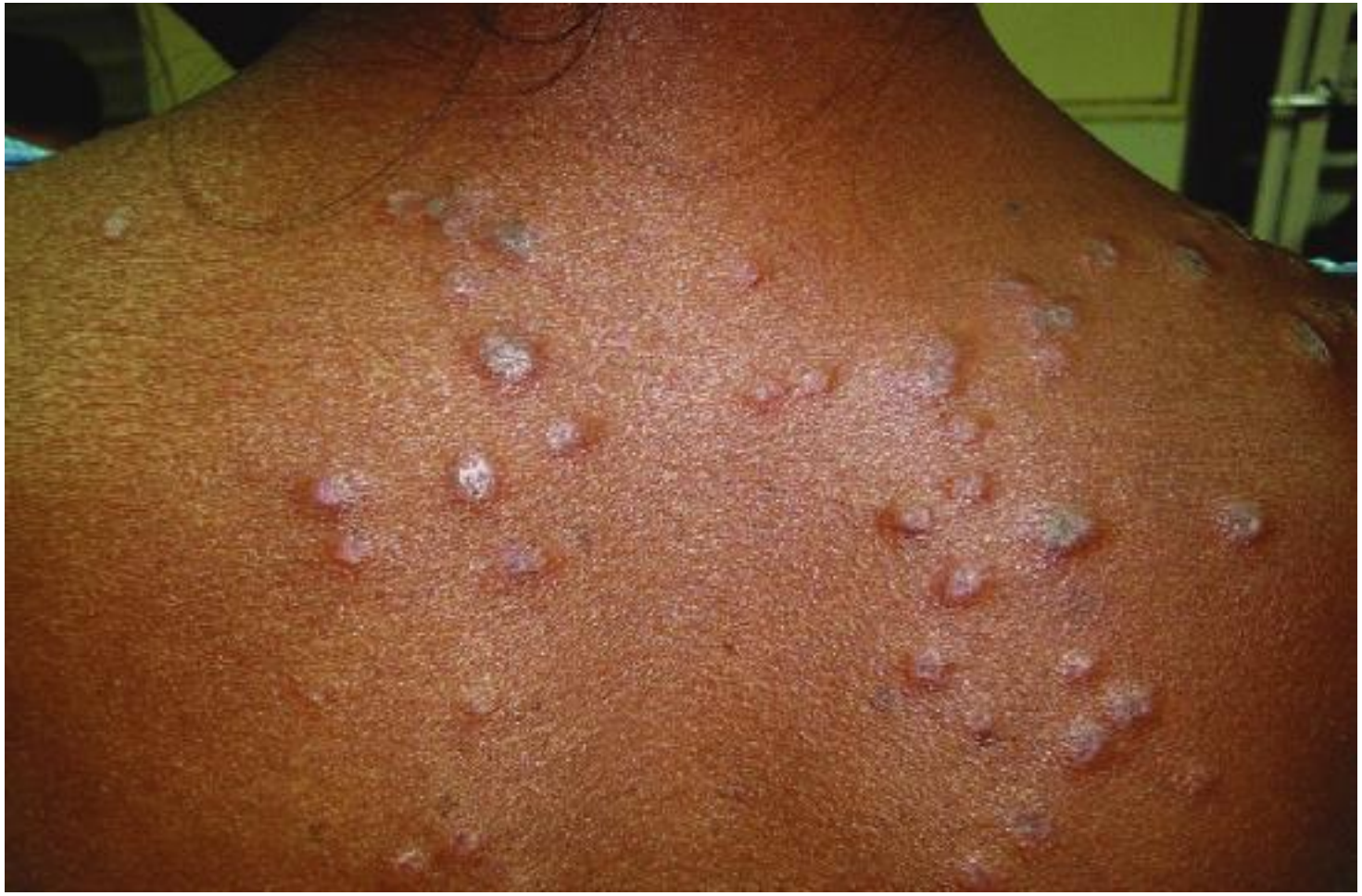
Papulosquamous Rash in SLE



https://www.researchgate.net/publication/338551795/figure/fig3/AS:847136925184001@1578984590229/A-case-of-SLE-with-papulosquamous-rash.png

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Approximately 80 to 90% of patients with SLE suffer from musculoskeletal involvement at some point during their disease course and may range from mild arthralgias to deforming arthritis. Lupus arthritis is typically a non-erosive, symmetrical inflammatory polyarthritis affecting predominantly the small joints of the hands, knees, and wrists, although any joint can be involved. Jaccoud arthropathy results from the joint capsule and ligament laxity, leading to non-erosive deformities of the hands, including ulnar deviation and subluxation of the metacarpophalangeal joints that may mimic rheumatoid arthritis. Usually, these deformities are reducible, although rarely, they may become fixed. Avascular necrosis (with or without steroid use) can occur in up to 10% of patients with SLE and is usually bilateral and involves the hip joints. Inflammatory myopathy with histopathological features similar to but less striking than polymyositis has been seen in less than 10% of SLE cases. Patients with SLE are at high risk for the development of fibromyalgia, with incidences as high as 20% reported. Rheumatoid nodules have been reported in patients with SLE. [13]

https://www.ncbi.nlm.nih.gov/books/NBK535405/

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Antinuclear antibodies (ANA) are the hallmark of the disease and shall be the initial test performed. Immunofluorescence assay is considered the gold standard test for ANA. Although other detection methods such as enzyme-linked immunosorbent assay (ELISA) and multiplex assays are widely available, they lack sensitivity. A positive ANA is seen in more than 97% of cases of SLE. However, it can also be seen in several other disorders and a significant proportion of the healthy population, and have a specificity of only 20%. Hence, a positive ANA does not confirm SLE diagnosis, but a negative ANA makes it significantly less likely. ANA negative SLE has been rarely described, although it is primarily due to methodical error. Those cases have either a positive ANA on immunofluorescence or a positive Anti-Ro (SSA) antibody.

Several patterns of ANAs have been reported, including speckled, homogenous, centromere, cytoplasmic, nucleolar, and dense fine speckled patterns. With the availability of more specific ANAs targeting specific antigens, the staining patterns of ANAs are not considered significant enough by themselves. ANAs with a dense, fine speckled pattern (anti-DFS70) are considered least pathological, and patients with ANAs with this pattern rarely develop systemic autoimmune diseases. The speckled pattern is seen when ANAs are directed against the antigens such as SSA, SSB, Smith, ribonucleoprotein. The homogenous pattern is associated with ANAs targeted at histones, chromatin, and dsDNA, while the centromere pattern is associated with Anti-centromere antibodies seen in limited systemic sclerosis. [17]

Antibodies to deoxyribonucleic acid (DNA) can be primarily divided into two groups: those reactive with denatured, single-stranded (ss)DNA and those identifying native, double-stranded (ds)DNA. Notably, anti-ssDNA antibodies are considered non-specific and may be seen either as a laboratory error or in the healthy population. Anti-double-stranded deoxyribonucleic acid (dsDNA) antibodies have more than 95% specificity for SLE but are found in only about 60% to 70% of SLE patients. Thus a negative anti dsDNA does not rule out the diagnosis of SLE. The Farr radioimmunoassay test is considered the gold standard for detecting anti-dsDNA antibodies, although it is not frequently used. ELISA tests are available, but they have a high risk of giving a false positive test. The immunofluorescence test by using the *Crithidia luciliae* method can confirm the presence of anti-Ds-DNA antibodies. Anti-dsDNA antibodies can also be seen in drug-induced lupus, primarily secondary to anti-TNF agents and interferon-alpha. Rarely low titers of anti-dsDNA antibodies have been reported in rheumatoid arthritis and Sjogren syndrome. In SLE, anti-dsDNA antibodies can correlate with disease activity and the development of lupus nephritis. However, this may not always be true as some patients have elevated anti-dsDNA antibodies in the setting of minimally active or inactive lupus.

Anti-Ro (SSA) and anti-La (SSB) antibodies target ribonucleoprotein particles. Anti-Ro and Anti-La antibodies are seen in up to 90% of cases of Sjogren syndrome but can be seen in SLE as well (anti-Ro in up to 50% and anti-La in up to 20% of the cases). In SLE, they may be associated with secondary Sjogren syndrome and keratoconjunctivitis sicca, subacute cutaneous lupus, photosensitivity, congenital heart block, and neonatal lupus.[18]

Complements C3 and C4 shall be checked in patients with SLE or suspicion of SLE, and low complement levels indicate complement consumption and may correlate with disease activity. Markers of inflammation such as erythrocyte sedimentation rate and C-reactive protein may be elevated. Complete blood counts, liver function tests, and renal function tests, including serum creatinine, urinalysis, and urine protein quantification (24-hour urine protein, or spot urine protein/creatinine ratio), shall be checked to assess organ involvement. Synovial fluid aspiration reveals an inflammatory fluid. Joint radiographs may demonstrate peri-articular osteopenia, deformities, or subluxation but rarely show erosions. Chest imaging with computed tomography (CT) scan, cardiac workup including echocardiography (trans-esophageal when suspecting Libman-Sacks endocarditis), CNS work up with magnetic resonance imaging (MRI), and/or lumbar puncture shall be pursued if specific organ involvement is suspected. Renal biopsy shall always be performed if suspicion of lupus nephritis. Skin biopsies can be considered, especially if atypical presentation.[19]

Test Name	In Range	Out Of Range	Reference Range
THYROID PANEL WITH TSH			
THYROID PANEL			
T3 UPTAKE	29		22-35 %
T4 (THYROXINE), TOTAL	8.4		5.3-11.7 mcg/dL
FREE T4 INDEX (T7)	2.4		1.4-3.8
TSH	1.49		mIU/L
			Reference Range
			1-19 Years 0.50-4.30
			Pregnancy Ranges
			First trimester 0.26-2.66
			Second trimester 0.55-2.73
			Third trimester 0.43-2.91
LIPID PANEL, STANDARD			
CHOLESTEROL, TOTAL	153		<170 mg/dL
HDL CHOLESTEROL	56		>45 mg/dL
TRIGLYCERIDES	87		<90 mg/dL
LDL-CHOLESTEROL	80		<110 mg/dL (calc)
LDL-C is now calculated using the Martin-Hopkins calculation, which is a validated novel method providing better accuracy than the Friedewald equation in the estimation of LDL-C. Martin SS et al. JAMA. 2013;310(19): 2061-2068 (http://education.QuestDiagnostics.com/faq/FAQ164)			
CHOL/HDLC RATIO	2.7		<5.0 (calc)
NON HDL CHOLESTEROL	97		<120 mg/dL (calc)
For patients with diabetes plus 1 major ASCVD risk factor, treating to a non-HDL-C goal of <100 mg/dL (LDL-C of <70 mg/dL) is considered a therapeutic option.			
HS CRP		**3.4 H**	mg/L
Reference Range			
Optimal <1.0			
Jellinger PS et al. Endocr Pract.2017;23(Suppl 2):1-87.			
For ages >17 Years:			
hs-CRP mg/L	Risk According to AHA/CDC Guidelines		
<1.0	Lower relative cardiovascular risk.		
1.0-3.0	Average relative cardiovascular risk.		
3.1-10.0	Higher relative cardiovascular risk. Consider retesting in 1 to 2 weeks to exclude a benign transient elevation in the baseline CRP value secondary to infection or inflammation.		
>10.0	Persistent elevation, upon retesting, may be associated with infection and inflammation.		

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COMPREHENSIVE METABOLIC PANEL		
GLUCOSE	71	65-99 mg/dL Fasting reference interval
UREA NITROGEN (BUN)	18	7-20 mg/dL
CREATININE	0.78	0.50-0.96 mg/dL
EGFR	113	> OR = 60 mL/min/1.73m2
BUN/CREATININE RATIO	SEE NOTE: Not Reported: BUN and Creatinine are within reference range.	6-22 (calc)
SODIUM	139	135-146 mmol/L
POTASSIUM	4.3	3.8-5.1 mmol/L
CHLORIDE	103	98-110 mmol/L
CARBON DIOXIDE	21	20-32 mmol/L
CALCIUM	9.9	8.9-10.4 mg/dL
PROTEIN, TOTAL	8.0	6.3-8.2 g/dL
ALBUMIN	4.7	3.6-5.1 g/dL
GLOBULIN	3.3	2.0-3.8 g/dL (calc)
ALBUMIN/GLOBULIN RATIO	1.4	1.0-2.5 (calc)
BILIRUBIN, TOTAL	0.5	0.2-1.1 mg/dL
ALKALINE PHOSPHATASE	92	36-128 U/L
AST	29	12-32 U/L
ALT	16	5-32 U/L
HEMOGLOBIN A1c	5.5	<5.7 %

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MAGNESIUM	2.0		1.5-2.5 mg/dL
PHOSPHATE (AS PHOSPHORUS)	4.7		3.0-5.1 mg/dL
URIC ACID	4.8		2.4-6.6 mg/dL
LD		**228 H**	100-200 U/L

Results slightly increased due to hemolysis.

GGT	14		6-26 U/L
T4, FREE	1.2		0.8-1.4 ng/dL
T3, FREE	3.3		3.0-4.7 pg/mL
T3, TOTAL	108		86-192 ng/dL
THYROID PEROXIDASE AND THYROGLOBULIN ANTIBODIES			
THYROGLOBULIN ANTIBODIES	<1		< or = 1 IU/mL
THYROID PEROXIDASE ANTIBODIES	1		<9 IU/mL
FIBRINOGEN ACTIVITY, CLAUSS	268		175-425 mg/dL
CBC (INCLUDES DIFF/PLT)			
WHITE BLOOD CELL COUNT	8.9		4.5-13.0 Thousand/uL
RED BLOOD CELL COUNT	4.27		3.80-5.10 Million/uL
HEMOGLOBIN	13.8		11.5-15.3 g/dL
HEMATOCRIT	41.7		34.0-46.0 %
MCV	97.7		78.0-98.0 fL
MCH	32.3		25.0-35.0 pg
MCHC	33.1		31.0-36.0 g/dL

For adults, a slight decrease in the calculated MCHC value (in the range of 30 to 32 g/dL) is most likely not clinically significant; however, it should be interpreted with caution in correlation with other red cell parameters and the patient's clinical condition.

RDW	12.2		11.0-15.0 %
PLATELET COUNT	214		140-400 Thousand/uL
MPV	10.6		7.5-12.5 fL
ABSOLUTE NEUTROPHILS	5429		1800-8000 cells/uL
ABSOLUTE LYMPHOCYTES	2777		1200-5200 cells/uL
ABSOLUTE MONOCYTES	401		200-900 cells/uL
ABSOLUTE EOSINOPHILS	240		15-500 cells/uL
ABSOLUTE BASOPHILS	53		0-200 cells/uL
NEUTROPHILS	61		%
LYMPHOCYTES	31.2		%
MONOCYTES	4.5		%
EOSINOPHILS	2.7		%
BASOPHILS	0.6		%

URINALYSIS MACROSCOPIC				
COLOR	YELLOW		YELLOW	
APPEARANCE		**CLOUDY**	CLEAR	
SPECIFIC GRAVITY	1.020		1.001-1.035	
PH	6.0		5.0-8.0	
GLUCOSE	NEGATIVE		NEGATIVE	
BILIRUBIN	NEGATIVE		NEGATIVE	
KETONES	NEGATIVE		NEGATIVE	
OCCULT BLOOD		**TRACE**	NEGATIVE	
PROTEIN	NEGATIVE		NEGATIVE	

Test Name	In Range	Out Of Range	Reference Range	Lab
NITRITE		**POSITIVE**	NEGATIVE	
LEUKOCYTE ESTERASE		**3+**	NEGATIVE	
IRON AND TOTAL IRON BINDING CAPACITY				CB
IRON, TOTAL	111		27-164 mcg/dL	
IRON BINDING CAPACITY	389		271-448 mcg/dL (calc)	
% SATURATION	29		15-45 % (calc)	
FERRITIN	32		6-67 ng/mL	CB
HEPATITIS B SURFACE ANTIBODY QL	NON-REACTIVE		NON-REACTIVE	CB
HEPATITIS B CORE AB TOTAL	NON-REACTIVE		NON-REACTIVE	CB

For additional information, please refer to
http://education.questdiagnostics.com/faq/FAQ202
(This link is being provided for informational/
educational purposes only.)

C-PEPTIDE	1.63		0.80-3.85 ng/mL	CB
INSULIN	11.4		uIU/mL	CB

Reference Range < or = 18.4

Risk:

Optimal	< or = 18.4
Moderate	NA
High	>18.4

Adult cardiovascular event risk category
cut points (optimal, moderate, high)
are based on Insulin Reference Interval
studies performed at Quest Diagnostics
in 2022.

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Immunology

Test Name	Result	Reference Range	Lab
ANA SCREEN, IFA, W/REFL TITER AND PATTERN			CB
ANA SCREEN, IFA	**POSITIVE**	NEGATIVE	
ANA IFA is a first line screen for detecting the presence of up to approximately 150 autoantibodies in various autoimmune diseases. A positive ANA IFA result is suggestive of autoimmune disease and reflexes to titer and pattern. Further laboratory testing may be considered if clinically indicated. For additional information, please refer to http://education.QuestDiagnostics.com/faq/FAQ177 (This link is being provided for informational/ educational purposes only.)			
ANTINUCLEAR ANTIBODIES TITER AND PATTERN			CB
ANA TITER	**1:80 H**	titer	
A low level ANA titer may be present in pre-clinical autoimmune diseases and normal individuals. Reference Range <1:40 Negative 1:40-1:80 Low Antibody Level >1:80 Elevated Antibody Level			
ANA PATTERN	**Nuclear, Speckled**		
Speckled pattern is associated with mixed connective tissue disease (MCTD), systemic lupus erythematosus (SLE), Sjogren's syndrome, dermatomyositis, and systemic sclerosis/polymyositis overlap. AC-2,4,5,29: Speckled International Consensus on ANA Patterns (https://doi.org/10.1515/cclm-2018-0052)			
Physician Comments:			

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Endocrinology

Test Name	Result	Reference Range	Lab
VITAMIN D,25-OH,TOTAL,IA	64	30-100 ng/mL	CB

Vitamin D Status	25-OH Vitamin D:
Deficiency:	<20 ng/mL
Insufficiency:	20 - 29 ng/mL
Optimal:	> or = 30 ng/mL

For 25-OH Vitamin D testing on patients on D2-supplementation and patients for whom quantitation of D2 and D3 fractions is required, the QuestAssureD(TM) 25-OH VIT D, (D2,D3), LC/MS/MS is recommended: order code 92888 (patients >2yrs).

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Publication | **Article** | January 20, 2016
Pharmacy Times
January 2016 The Aging Population | Volume**82** | Issue **1**

Drug-Induced Autoimmune Diseases

Author(s): Anyssa Garza, PharmD

Ten percent of individuals worldwide are affected by autoimmune diseases, with systemic lupus erythematosus being one of the most common.

Ten percent of individuals worldwide are affected by autoimmune diseases, with systemic lupus erythematosus (SLE) being one of the most common.[1] Drug-induced lupus erythematosus (DILE) was first recognized in 1945 with sulfadiazine as the offending agent.[2] Since then, more than 90 medications from more than 10 drug classes have been implicated in causing lupus.[1,3] DILE is estimated to affect 15,000 to 20,000 individuals each year and accounts for 10% of SLE cases.[1,2] Risk factors for DILE include being a slow acetylator, having certain serologic features (eg, HLA-DR4 and HLADR0301), having complement C4 null allele, and being female.[2]

Drug-Induced Lupus Erythematosus

DILE is similar to idiopathic SLE. However, the prognosis of DILE is promising compared with that of SLE. DILE presents itself after exposure to the offending medication and the symptoms usually resolve within weeks of discontinuing the offending agent.[2] Refer to Table 1[3] for a comparison of DILE and idiopathic SLE.

Patients presenting with DILE may experience fever, arthralgia, arthritis, myalgia, or serositis. In fact, 90% of affected patients present with arthralgia and 50% present with myalgia.[2] After initiation of an offending medication, DILE can develop from 1 month to more than a decade after exposure to it.[2]

DILE can be defined by the following, according to Dipiro and colleagues[4]:

- Exposure to a suspected medication
- No history of idiopathic SLE prior to exposure to an offending medication
- Positive antinuclear antibody (ANA) test result; usually antihistone antibodies
- At least one clinical feature of SLE
- Rapid improvement of symptoms after offending drug is discontinued
- Gradual decline in ANAs after offending drug is discontinued

TABLE 1: DIFFERENCES BETWEEN DRUG-INDUCED LUPUS ERYTHEMATOSUS AND SYSTEMIC LUPUS ERYTHEMATOSUS		
Clinical Features	**Systemic Lupus Erythematosus**	**Drug-Induced Lupus**
Age (years)	20-40	50
Female:Male	9:1	1:1
Onset of symptoms	Gradual	Abrupt
Symptom severity	Mild to severe	Generally mild
Constitutional symptoms	83%	50%
Arthralgia and arthritis	90%	95%
Pleuropericarditis (procainamide)	50%	50%
Hepatomegaly	5%-10%	15%-20%
Cutaneous involvement	54%-70% (malar, discoid rash, oral ulcers)	<5%-25%
Renal disease	32%-53%	Photosensitivity, purpura
Central nervous system disease	20%-32%	5%-10%
Hematologic abnormalities	Common	<5%
Serologic factors		
Antinuclear antibody	>95%	>95%
Antihistone	60%-80%	90%-95%
Anti-double stranded DNA antibodies	50%-70%	<5%
Anti-Smith	20%-30%	Rare
Hypocomplementemia	50%-60%	<5%

Recently, DILE has also been associated with newer medications on the market, which include tumor necrosis factor (TNF) blockers and interferons. There have been several cases of TNF-alpha antagonist—induced lupus syndrome, which is otherwise known as TAILS.[3]

TNF blockers include the following:

- Remicade (infliximab)
- Enbrel (etanercept)
- Humira (adalimumab)
- Cimzia (certolizumab pegol)
- Simponi (golimumab)

According to an article published in *Lupus*, "Most cases of TAILS have been ... due to infliximab because it is the most immunogenic based on its chimeric structure and its ability to reach high tissue concentrations, followed by etanercept and adalimumab, which is a humanized monoclonal antibody. Only one case has been described with certolizumab pegol, and we are unaware of any cases being reported following golimumab therapy."[3]

The interferons that are implicated in DILE include interferons alpha and beta. However, interferon alpha carries the highest incidence of DILE.1,3 Other medications that may be linked to DILE include ticlopidine, various statins, and lisinopril.[2,3]

Causal and associated relationship with SLE

Antihypertensives
Calcium channel blockers
Diltiazem, verapamil, nifedipine
Angiotensin-converting enzyme inhibitors
Thiazide diuretics
Hydrochlorothiazide
Beta blockers
Acebutolol
HMG-CoA reductase inhibitors (statins)
Interferon alpha and beta
Antifungals
Terbinafine, griseofulvin
Antiplatelets
Ticlopidine
Nonsteroidal anti-inflammatory drugs
Piroxicam, naproxen
Antidepressants
Bupropion
Others
Lansoprazole, tamoxifen, leflunomide, docetaxel
Biologicals
Efalizumab, etanercept, infliximab, interferon-beta

- Estrogens, oral contraceptives
- Danazol
- Mesalazine
- Reserpine
- Griseofulvin
- Clonidine
- Hydroxyurea
- Gemfibrozil
- Allopurinol
- Quinine
- Minoxidil
- Calcium channel blockers
- Amiodarone
- Spironolactone
- Clozapine
- Tocainide
- Zafirlukast
- Omeprazole

Although DILE has a more favorable prognosis than SLE, prompt diagnosis and discontinuation of the offending agent are critical. Once mainly associated with cardiovascular drugs, DILE is now associated with more drug classes, including TNF blockers and interferons. Because these agents are used to manage autoimmune disorders, diagnosing DILE can be challenging. The challenge is being able to differentiate a true drug-induced lupus from an exacerbation of preexisting lupus or the unmasking of a second autoimmune disease.[1]

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https://www.pharmacytimes.com/view/drug-induced-autoimmune-diseases

•Chang C, Gershwin ME. Drug-induced lupus erythematosus: incidence, management and prevention. *Drug Saf.* 2011;34:357-374.

•Vasoo Sheila. Drug-induced lupus: an update. *Lupus*. 2006; 15:757-761.

•Araújo-Fernández S, Ahijón-Lana M, Isenberg DA. Drug-induced lupus: Including anti-tumor necrosis factor and interferon induced. *Lupus*. 2014; 23:545-553.

•DiPiro JT, Talbert RL, Yee GC, et al. *Pharmacotherapy: A Pathophysiologic Approach*. 7th ed. United States: The McGraw-Hill Companies, Inc; 2008: 1439-1440.

•Borchers AT, Keen CL, Gershwin ME. Drug-induced lupus. Ann N Y Acad Sci 2007 Jun; 1108; 166-82.

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