Team Medicine

31#

SLE and Scleroderma

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Systemic Lupus Erythematosus

❖ Definition:

It is a chronic, multisystem inflammatory disease characterized by autoantibodies directed against self- antigens, immune complex formation, and immune dysregulation resulting in damage to essentially any organ.

It is a collection of sign and symptoms behind which is an autoimmune phenomenon.

Lupus = wolf

❖ The eleven criteria to diagnose SLE:

Usually you diagnose lupus if you have 4 or more of these criteria:

1. Malar rash:

Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabialfolds.

2. Discoid rash:

Discoid rash is the only rash that even if it's goes away it leaves scars. (Kaplan)

Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions.

3. Photosensitivity:

Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation.

4. Oral ulcers:

It is usually painless, observed by physician.

5. Arthritis:

Polyarticular symmetrical arthritis. (Kaplan)

Involving two or more peripheral joints, characterized by tenderness, **swelling** or effusion.

6. Serositis:

a) Pleurtits: Pleuritic pain or rubbing heard by a physician or evidence of pleural effusion.

b) Pericarditis: Documented by ECG or rubbing heard by a physician or evidence of pleural effusion.

c) ascites

Pleuritis is the most common pulmonary finding. (Step up 241)

7. Renal disorders: (The most common and most serious)

a) Persistent proteinuria > 0.5 gm per day or > 3 gm if quantitation not performed. b) Cellular casts: Red cells, hemoglobin, granular, tubular or mixed.

About 40 % of lupus patient will have renal involvement. (Kaplan)

8. Neurologic disorders:

Seizures, or psychosis in the absence of offending drugs or known metabolic derangements. Eg. Uremia, ketoacidosis, or electrolyte imbalance.

9. Hemolytic disorders:

Any of the following disorders:

a) Hemolytic anemia with reticulcytosis.

b) Leukopenia< 4,000/mm <>3<> total on 2 or more occasions. And usually due to lymphopenia

c) Lymphopenia< 1,500/mm <>3<> total on 2 or more occasions.

d) Thrombocytopenia< 100, 00/mm <>3<> in the absence of offending drugs.

10. Immunologic disorders:

Any of the following disorders:

a) Positive finding of antiphospholipid antibodies: (Recently we are adopting this tests)

Based on:

1. An abnormal serum level of IgG or IgManticardiolipin antibodies.

2. A positive test result for lupus anticoagulant using a standard method

3. A false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by Treponemapallidum immobilization or fluorescent treponemal antibody absorption test.

b) Anti-DNA.

c) Anti-Sm: antibody to Sm nuclear antigen.

d) False positive selelogic test for syphilis known to be positive for at least 6 months and confirmed by

Treponemapallidum immobilization or fluorescent treponemal antibody absorption test.

11. Antinuclear antibody:

An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome.

In SLE, ANA have to be positive. (Kaplan)

❖ Epidemiology:

Locally: 2 cases of SLE among 10,372 studied (prevalence of 19.28 per 100,000).

Internationally: Denmark (21.7/100,000), Britain (12/100,000), India (3.2/100,000), Sweden (39/100,000).

Women = 90%

❖ Etiology:

Specific cause(s) of SLE is unknown.

Multiple factors are associated include:

❖ Genetic predisposition:

- Multiple of genetic associations suggests a complex genetic predisposition.
- Concordance rate in monozygotic twins is 25-70%.
- If a mother has SLE, her daughter's risk of developing the disease is 1:40, and her son's risk is 1:250. (Male is less because of hormonal affect)
- Relatives have a high prevalence of other autoimmune diseases.
- HLA-DR2 and HLA-DR3 and other HLA genes occur more often in SLE than in the general population.
- Null complement alleles and congenital deficiencies of complement (C4, C2, and other early components) are associated with an increased risk of SLE.
- SLE is NOT inherited

❖ Hormonal factors:

- F: M ratio of prevalence in different age groups:
    - In children, f :m ratio is 3:1.
    - In adults, f:m ratio is 10-15:1
    - In older, the ratio is approximately 8:1.

- Age at onset:
    - 65% have onset between 16 and 55.
    - 20% before age 16.
    - 15%t after age 55.
- Higher prevalence in men with Klinefelter disease. (Because they have an extra X chromosome)
- Exogenous estrogen and exacerbations of SLE.
- Men at all ages have the same risk of disease as women who are prepubertal or postmenopausal.
- Males do not have an age-related peak in incidence.

- SLE IN SAUDI ARABIA KKUH:

Sex	Number	percent
Male	58	9.3
Female	566	90.7
Total	624	100

❖ Racial and geography:

- Higher prevalence (2.5- to 6-fold) in USA African American women than in white women. But, of course infrequently in Blacks in Africa.
- Higher among Asians, Afro-Americans, Afro-Caribbeans, Hispanic Americans, and Asian Indians.
- More common in urban than rural areas.
- Also In New Zealand, 50 per 100,000 Polynesians, but only 14.6 cases per 100,000 in the whites.
- In France, more common among immigrants from Spain, Portugal, North Africa, and Italy.

❖ Environmental:

- Worldwide variability of prevalence the disease. (Black in Africa and US)
- Influence of environmental factors on the course of the disease, e.g.:
  - Ultraviolet light.
  - Viruses.
  - Drugs cause or exacerbate.
  - Silica dust. (Like cosmetic surgeries)
  - Cigarette smoking.
  - Alfa Alfa sprouts.

Ultraviolet light is the only environmental factor known to cause flares. (Kaplan)

❖ Pathophysiology:.

- Lack of intolerance, usually the immune system is tolerant to your skin, your hair, your joints and tolerant to everything. Breakdown of your tolerance makes autoimmune cells attack your body and then you get the infection.
- Disturbances in the immune system:
  - High ratio of CD4+ to CD8+ T cells.
  - Defects in immune cell tolerance leading to production of autoantibodies targeting antigens located in nuclei, cytoplasm, on cell surfaces, and in plasma proteins.
  - Autoantibodies lead to mostly immune complex formation (e.g. kidney) and direct antibody-mediated cytotoxicity (hemolytic anemia, thrombocytopenia).
  - Cell-mediated autoimmunity also plays part.
  - Tissue damage follows.

❖ **Organ involvement in SLE: (Foreign study results)**

Joints	90%
Skin: - Rashes - Discoid lesion - Alopecia	 70% 30% 40%
Pleuropericardium	60%
Kidney	50%
Raynaud's	20%
Mucous membranes	15%
CNS (psychosis\ convulsions)	15%

❖ **SLE – Presenting and Prevalent Symptoms: In Saudi Arabia**

ARA Criteria	+ve at presentation n (%)	+ve on * followup n (%)	Total prevalent n (%)
Malar rash	265 (42.5)	34 (5.4)	299 (47.9)
Discoid rash	99 (15.9)	11 (1.8)	110 (17.6)
Photo sensitivity	165 (26.4)	26 (4.2)	191 (30.6)
Oral ulcer	223 (35.7)	21 (3.4)	244 (39.1)
Arthritis	454 (72.8)	7 (1.1)	461 (73.9)
Serositis	82 (13.1)	89 (14.3)	171 (27.6)
Renal disorder	281 (45)	18 (2.9)	299 (47.9)
Neurological disorder	98 (15.8)	20 (3.2)	172 (27.6)
Hematological disorder	505 (80.9)	31 (4.9)	536 (85.9)
Immunological disorder	470 (75.3)	30 (4.8)	500 (80.9)
ANA	622 (99.7)	0	622 (99.7)

❖ Other presenting symptoms

Fever	30.6	Splenomegaly	2.6
Wight loss	23.1	Hepatosplenomegaly	6.1
Fatigue	42.5	Genetic ulcer	1.4
Arthralgia	86.9	HTN	28.4
Raynaud's phenomenon	8.7	Myalogia	6.6
Alopecia	47.6	Pancytopenia	12.2
Lymphadenopathy	20	Pleuritis	15.8
DVT	7.4	Pericarditis	20.7
Ascites	8.9	Pulmonary symptoms	28
Hepatomegaly	3.2	Gastrointestinal symptoms	38.6

❖ Neurologic Signs or Symptoms:

- Meninges: **Headache**and Meningismus.
- Cerebellum: Ataxia.
- Spine: Paraparesis and multiple sclerosis-like disorders.
- Cerebrum: Dementia, strokes, subarachnoid hemorrhages, migraines, other headaches.
- Cranial and peripheral sensory, motor neuropathies: Mononeuritis multiplex, myasthenia gravis, seizures, Guillain-Barre syndrome, Chorea, rigidity, tremor, SIADH.(Psychiatric manifestations are common.)

❖ Special considerations:

- **Drug-induced lupus:** (consider before diagnosing native lupus)
  - Sex ratios are nearly equal.
  - Nephritis and CNS not common. (Not as serious as native SLE)
  - No anti-native DNA or hypocomplementemia.
  - Resolution on discontinuation of drug.

Drugs associated with lupus erythematosus:

- **Definite association**

Chlorpromazine	Procainamide
Methyldopa	Isoniazid
Hydralazine	Quinidine

- **Possible Association**

Betablockers	Methimazole
Captopril	Nitrofurantoin
Carbamazepine	Penicillamine
Cimetidine	Phenytoin
Ethosuximide	Propylthiouracil
Hydrazines	Sulfasalazine
Levodopa	Sulfonamides
Lithium	Trimethadione

- **Unlikely Association:**

Allopurinol	Griseofulvin
Penicillin	Streptomycin
Chlorthalidone	Methysergide
Phenylbutazone	Tetracyclines
Gold salts.	Oral contraceptive.
Reserpine	

❖ Treatment:

▪ General considerations:

- Prevention: (You can't prevent the disease but you can prevent symptoms)
  - Avoid UV light and sun. (Sunsceening)
  - Antimalarial (e.g. hydroxychloroquine) to prevent relapses.
  - Treat hypertension and dyslipidemias.
- Treat depending on the organ system(s) involved:
  - Skin, musculoskeletal, and serositis: NSAIDs, HCC, and local corticosteroids.
  - More serious organ involvement. (CNS, renal)
- Immunosuppression with high-dose steroids, AZA and/or cyclophosphamide, mycophenolate, and
- Tacrolimus.
- Targeted therapy (biological): rituximab.
- Other treatments
  - Plasma exchange for TTP or diffuse alveolar hemorrhage
  - Intravenous immunoglobulin for severe steroid-nonresponsive thrombocytopenia.

Steroids are the best treatment for SLE patients with acute flare. (step up, quick hit 244)

❖ Prognosis:

- **Poor prognostic factors for survival in SLE include:**
  - Renal disease. (especially diffuse proliferative glomerulonephritis)
  - Hypertension.
  - Renal and central nervous system disease.
  - Less education because of poor compliance.
  - Poor socioeconomic status because of inadequate access to medical care.
  - Black race because of their low socioeconomic status.
  - Presence of antiphospholipid antibodies.
  - High overall disease activity.

  - **Male sex**
    - Men similar frequency of renal, skin, arthritis, and CNS as women.
    - Less photosensitivity.
    - More serositis.
    - An older age at diagnosis.
    - A higher one-year mortality.

  - **Young age**
    - SLE in children more severe, higher malar rashes, nephritis, pericarditis, hepatosplenomegaly, and hematologic abnormalities. (Why more sever? It is because the longer you live the more damage you get with the disease)

❖ Remission:

- After appropriate therapy, many patients go into a clinical remission requiring no treatment.
  - **A long-term follow-up of 667 patients noted:**
    - ≈25 % had at least one treatment-free clinical remission lasting for at least one year.
    - The mean duration of remission was 4.6 years. (Underestimated since one-half of the patients were still in remission at the end of follow-up)
    - A long history of SLE or the presence of renal or neuropsychiatric disease did not preclude remission.

  - We get 95–96% survival (10 years survival) in our patient . 25% of them may go even without any medication or period more than 1 year to 5 years. Others may use hydroxychloroquine for even longer years. And hydroxychloroquine we do not usually give daily, we may skip a day of two, a week or two.

Scleroderma

❖ Definition:

Scleroderma is a chronic multisystem disease characterized clinically by thickening of the skin caused by accumulation of connective tissue and by involvement of visceral organs (GI, lungs and kidneys) (Kaplan)

❖ Pathophysiology :

Cytokines stimulate fibroblasts, causing an abnormal amount of collagen deposition. It is the high quantity of collagen that cause the problems associated with this disease. (Composition of the collagen is normal)(step up 244).

❖ Classification of scleroderma:

1. Localized:

Sub-classifications:

Morphea, plaque like, guttate, and generalized linear scleroderma.

2. Generalized:

With diffuse visceral involvement.

CREST syndrome. (Calcinosis, Raynaud's syndrome, esophageal dysmotility, sclerodactyly, telangiectasia) Overlaps with other connective tissue disease.

3. Chemical-induced scleroderma-like conditions:

E.g.: Vinyl chloride disease

4. Diseases with skin changes mimicking scleroderma:

E.g.: Scleredema

5. Eosinophilic fasciitis:

❖ Progressive Systemic Sclerosis: Preliminary Diagnostic Criteria

Patient must have major criterion or 2 minor criteria.

1. **Major criterion:**

Proximal scleroderma

2. **Minor criterion:**

Sclerodactyly

Digital pitting or scars or loss of substance from finger pads

Bibasilar paulmonary fibrosis

❖ Systemic manifestations of scleroderma

- **Pulmonary:** Dyspnea, cough, hemoptysis, pleuritic pain, and clubbing of nails.
- **Gastrointestinal:** Dysphagia, dyspepsia, constipation, diarrhea and malabsorption.
- **Renal:** Proteinuria, azotemia, hypertension, and renal failure.
- **Musculoskeletal:** Polyarthralgia, swelling of joints, and contractures.
- **Cardiovascular:** Arrhythmias myocardial failure.

The patients used to die due to renal problem but nowadays they die due to pulmonary (most) and cardiac (suddenly sometimes)

❖ Secondary Raynaud's phenomenon: classifications and causes:

It is a sudden spasm of the vessels in the extremities.

- **Connective tissue diseases:**
  - Systemic sclerosis,
  - CREST.
  - SLE.
  - Mixed connective tissue disease ,
  - Rheumatoid arthritis ,
  - Dematomyositis/ polymyositis.
- **Miscellaneius:**
  - Reflex sympathetic dystrophy.
  - Hypothyroidism.
  - Pheochromocytoma.
  - Neoplasm.
  - Primary pulmonary hypertension,
  - Variant angina.

❖ Treatment : (step up 247)

- No effect cure.
- Treat symptoms: NSAIDs for musculoskeletal pain. H2 blockers of proton pump inhibitors for esophageal reflex.
- Raynaud's phenomenon: avoid cold and smoking, keep hands warm. If severe, use calcium –channel blockers.
- Treat pulmonary and renal complications if present.

Mixed Connective Tissue Disease

❖ Definition:

A collection of number of diseases (arthritis, scleroderma, Raynaud's pulmonary involvement, esophageal dysfunction, cutaneous manifestation and polymyositis). It is an overlap syndrome.

❖ Clinical and laboratory features of MCTD:

- Polyarthritis.
- Raynaud's phenomenon.
- Swollen hands or sclerodactyly.
- Abnormal esophageal motility.
- Myositis.
- Low incidence of lupus nephritis.
- Hyperglobulinemia.
- Positive ANA (often speckled pattern)
- Antibody to nRNP.

❖ Criteria for the Diagnosis of MCTD:

Positive criterion	Algorithm of	
Serological test	Alarcon-segovia and villareal	Kahn and appelboom
	Anti-(U1-RNP)titer≥1:1600	Anti-(U1-RNP) titer ≥ 1:1200 in a patient with an ANA titer ≥ 1:2560 and a speckled ANA pattern
Clinical faetures	≥3; one of which must be synovitis or myositis, with others	≥3; one of which must be Raynaud's phenomenon, with others
	To include: Swollen hands Raynaud's phenomenon Acrosclerosis	To include: Swollen fingers Synovitis Myositis

❖ Antibodies Associated with Rheumatic Diseases: Percentages of Patients Affected

- Antibodies to native DNA: SLE 50% - 60% of patients.

- Anti-Sm antigen:SLE: 30% patients.

- Antibodies to histones:Drug-induced SLE: 95%, SLE: ≤ 60%, Rheumatoid arthritis: 20% patients.

- Antibodies to SS-A: Sjogren's syndrome: 70%, SLE: 30% - 40%(especially in neonatal SLE and sub-acute cutaneous SLE), scleroderma and mixed connective tissue disease: frequency and titers low.

- Antibodies to SS-B: Sjogren's syndrome: 60%, SLE: 15% patients.

- Antibodies to RNP: Mixed connective tissue disease: 95% - 100%, SLE: 30% at low titers, scleroderma: 10% - 20%

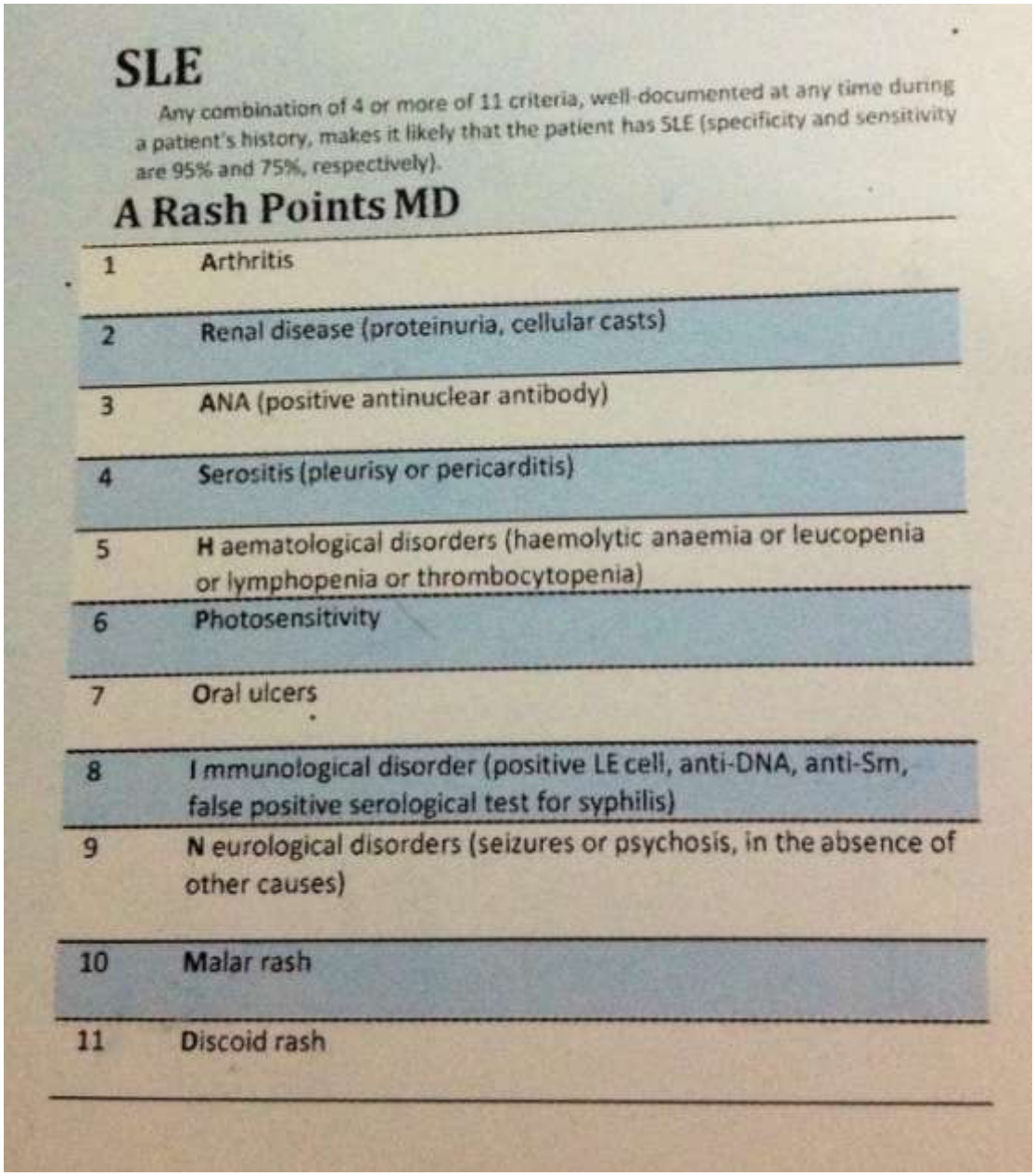
- Antibodies to Scl-70 :scleroderma: 10% - 20%

- Antibodies to nucleolarantigens :Scleroderma: 40% - 50%

- Antibodies to centromere antigens :CREST: 80% - 90%

- Antibodies to PM-1: Polymyositis: 50%, Dermatomyositis: 10%

Summary



SLE

Any combination of 4 or more of 11 criteria, well-documented at any time during a patient's history, makes it likely that the patient has SLE (specificity and sensitivity are 95% and 75%, respectively).

A Rash Points MD

1	Arthritis
2	Renal disease (proteinuria, cellular casts)
3	ANA (positive antinuclear antibody)
4	Serositis (pleurisy or pericarditis)
5	Haematological disorders (haemolytic anaemia or leucopenia or lymphopenia or thrombocytopenia)
6	Photosensitivity
7	Oral ulcers
8	Immunological disorder (positive LE cell, anti-DNA, anti-Sm, false positive serological test for syphilis)
9	Neurological disorders (seizures or psychosis, in the absence of other causes)
10	Malar rash
11	Discoid rash

- SLE : chronic , inflammtory, multisystemic disease in which arthriris is one of myriad of possible symtom and presentation.

- Diagnostic criteria for SLE (SOAP BRAIN MD) : Serositis , Oral ulcer , Arthritis , Photosensitivity, Blood d/o , Renl abnormalities, ANA+ , Immunological phenomenon (anti-Sm, anti-dsDNA), Neurologic sx , Malar rash, Discoid rash.

- The best initial diagnostic test is ANA but is not the most accurate.

- Anti-dsDNA and Anti-Sm test are more specific.

Question

1- A 20-year-old woman has developed low-grade fever, a malar rash, and arthralgias of the hands over several months. High titers of anti-DNA antibodies are noted, and complement levels are low. The patient's white blood cell count is 3000/μL, and platelet count is 90,000/μL. The patient is on no medications and has no signs of active infection. Which of the following statements is correct?

A. If glomerulonephritis, severe thrombocytopenia, or hemolytic anemia develops, high-dose glucocorticoid therapy would be indicated
B. Central nervous system symptoms will occur within 10 years
C. The patient can be expected to develop Raynaud's phenomenon when exposed to cold
D. The patient will have a false-positive test for syphilis
E. The disease process described is an absolute contraindication to pregnancy

2- 28 year old women present with facial rash and joint pain , and tou suspect it is SLE what the initial diagnosis you want to do it ?

A. Anti-sm serology
B. Anti- dsDNA serology
C. ANA test
D. Urinalysis with microscopy

ANSWER:-

1- A The combination of fever,malar rash, and arthritis suggests systemic lupus erythematosus, and thepatient's thrombocytopenia, leukopenia, and positive antibody to native DNA provide more than four criteria for a definitive diagnosis. Other criteria for the diagnosis of lupus include discoid rash, photosensitivity, oralulcers, serositis, renal disorders (proteinuria or cellular casts), and neurologic disorder (seizures). High-dose corticosteroids would be indicated for severe or life-threatening complications of lupus such as described in item a. Patients with SLE have an unpredictable course. Few patients develop all signs or symptoms. Neuropsychiatric disease occurs at some time in about half of all SLE patients and Raynaud's phenomenon in about 25%. Pregnancy is relatively safe in women with SLE who have controlled disease and are on less than 10 mg of prednisone

2- C