Systemic Lupus Erythematosus

728-655
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Learning Objectives

- Discuss the role of nonpharmacologic therapy, nonsteroidal anti-inflammatory drugs, corticosteroids, antimalarial agents, and cytotoxic agents in the treatment of systemic lupus erythematosus.
- Recognize and manage drug-induced lupus associated with commonly implicated drugs
- Understand the rationale for using immunosuppressive agents to treat autoimmune diseases

Reading Assignment

Pharmacotherapy. A Pathophysiologic Approach, 11th edition. Chapter 103 Systemic Lupus Erythematosus. pp 1453-1470.

Reading guide

The chapter's key concepts can be an initial roadmap for the chapter.
Use the learning objectives to guide your reading. The learning objectives have been chosen because of their relevance to systemic lupus erythematosus pharmacotherapy and are the source of the exam questions.
Systemic lupus erythematosus is a prevalent disease and pharmacotherapy intensive. Focus on figure 103-2, 3 and tables 103-2, 3.

Study Questions

1. Which Th phenotype do you think predominates in the pathophysiology of SLE?

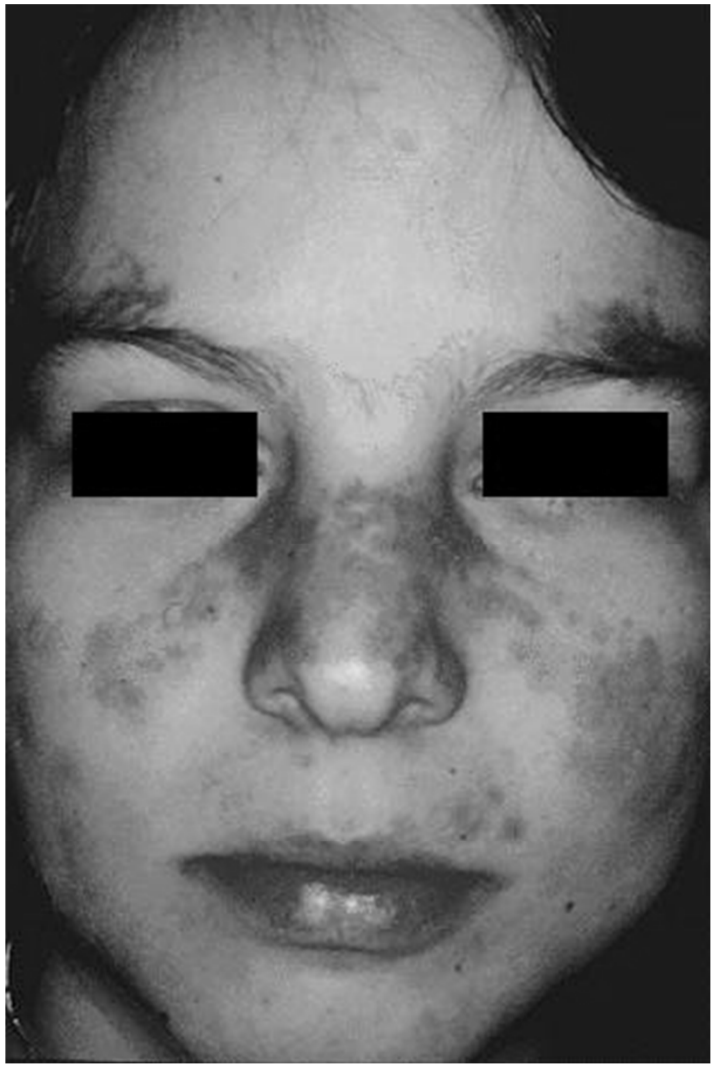
2. Differentiate systemic lupus erythematosus from drug-induced lupus. Consider epidemiology, laboratory findings, symptoms, prognosis, and treatment.

Collagen Vascular Diseases

- Involve musculoskeletal system, integument, blood vessels
- Etiology unknown
- Immune system involved
- Pharmacotherapy involves anti-inflammatory and immunosuppressive agents

Systemic Lupus Erythematosus

- Incidence: 1-10/100,000/year
- Prevalence: 20-70/100,000
- 10:1 female:male
- Usual age range for diagnosis 15-45 years
- Less prevalent in whites than blacks, Hispanics, Native Americans, Asians



SLE Etiology

- Unknown
- Theory: genetic predisposition + trigger
- Many genes implicated
- Environmental agents
- Hormone influence

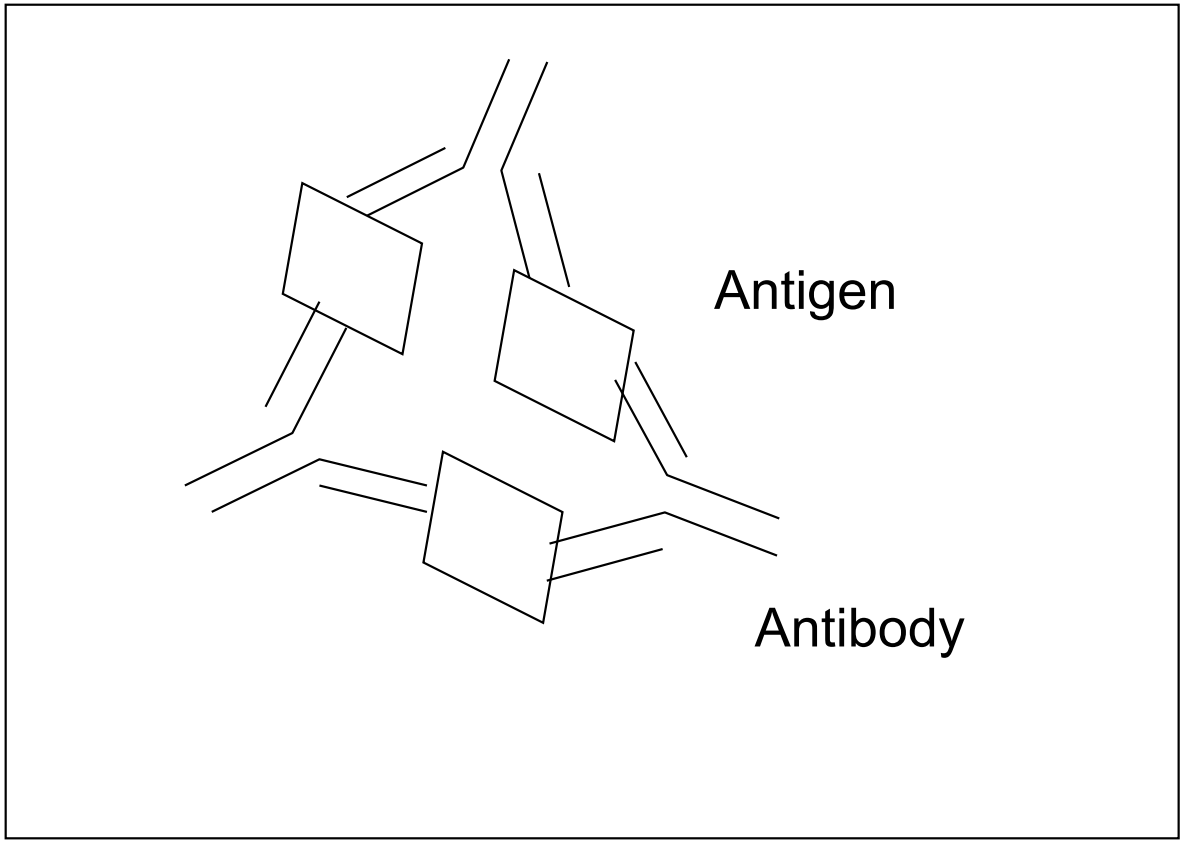
Prognosis

- 5 year survival 95%
- 10 year survival about 92%
  - Lower in those with lupus nephritis
  - Probably lower in males
- CAD and infection leading causes of death

SLE Pathophysiology

- Excessive, abnormal formation of autoantibodies
- Antibodies to cells of multiple organ systems
- Hyperactive B and Th lymphocytes
  - B lymphocyte stimulator (BLyS) high
  - ↓ IL-2; ↑IL-17
- Antinuclear antibodies present

Type III Hypersensitivity
Immune Complexes



Diagnosis

- Clinical criteria and immunologic criteria must be present
- See Table 103-1

Serologic Diagnosis

- Antinuclear antibodies
  - Almost always present in SLE
  - Present in other diseases
- Antibodies to native DNA (dsDNA) and Sm antigen (Smith antigen) specific for SLE

Organ Involvement

- Nonspecific constitutional signs
    - fatigue, fever, anorexia, weight loss
- Musculoskeletal involvement
- Skin and mucous membrane involvement
    - butterfly rash
    - photosensitivity

Multi-organ involvement

- Respiratory
- Nervous system
- Gastrointestinal

Cardiac Manifestation

- Increasing frequency of CAD in SLE patients
- CAD risk factors commonly present
    - Hypertension
    - Hyperlipidemia
    - CAD out of proportion to risks
- Corticosteroid use and renal disease
- Consider importance of inflammation in accelerated atherosclerosis
- Improved disease control may prevent CAD

Organ Involvement

- Lupus nephritis
    - rising serum creatinine, proteinuria
    - variable progression to endstage renal disease
    - major cause of morbidity and mortality in SLE

Hematologic Manifestations

- Antiphospholipid antibodies
  - directed at prothrombin activator complex
  - thrombosis
  - thrombocytopenia (usually mild)
  - fetal loss

Treatment

- Nonpharmacologic
- NSAIDS
- Antimalarial drugs
- Corticosteroids
- Cytotoxic agents

Nonpharmacologic Therapy

- Education and psychosocial support
- Balanced diet
- Balanced routine of rest and exercise
- Avoid smoking
- Avoid sunlight; Use sunscreens

Which of the following is useful advice to help a patient with SLE to minimize rash?

a) Avoid make-up
b) Use fragrance-free laundry detergent
c) Get sun exposure in 20 minute intervals three days a week
d) Avoid sun exposure

NSAIDS

- Initial treatment for mild disease
- Choice of NSAID empiric
- Low dose aspirin added in patients with antiphospholipid syndrome
- Renal function decline related to NSAID rather than disease

Antimalarial Drugs

- (Chloroquine), hydroxychloroquine
- Considered standard of care for all SLE patients
- Control exacerbations
- Steroid sparing
- Decreases skin damage, improves survival, decreases hyperlipidemia, reduce diabetes

Mechanism of Action

- Multiple
    - interfere with macrophage processing of antigen
    - inhibition of cytokines, decreased inflammation
    - decreased sensitivity to ultraviolet light
    - antiplatelet and antihyperlipidemic effects

Hydroxychloroquine Adverse Effects

- Gastrointestinal
- Dermatitis
- Pigmentary changes of the skin
- Retinal toxicity (frequent ophthalmologic exams)

Corticosteroids

- Very effective for suppressing clinical disease
- Reserved for serious disease or unresponsive to NSAIDS or antimalarials

Corticosteroids

- Goal to use minimal dose to suppress disease
  - prednisone <1 mg/kg/ day for mild disease or maintenance
  - prednisone 1-2 mg/kg/day with severe disease--hemolytic anemia, cardiac involvement
  - steroid pulse to induce remission
- Adverse effects refer to corticosteroid lecture

Biologics

- Belimumab
  - Monoclonal antibody to BLyS
  - Promotes B cell apotosis
- Little experience with patients with severe lupus nephritis or CNS manifestations
- May be less effective in African Americans
- Administered 10mg/kg IV infusion every 2 weeks for 3 doses, then q 4 weeks
- Use in addition to standard therapies

Biologics

- Rituximab
  - Monoclonal antibody to CD20 found on B lymphocytes
  - Promotes B cell apotosis
- Conflicting results regarding benefit

Immunosuppressants

- Alkylating agents: Cyclophosphamide
- Antimetabolites: Azathioprine, mycophenolate mofetil
- Often used in combination with corticosteroids
- Suppress clinical manifestations of SLE
    - poorly documented in clinical trials
    - best studied in lupus nephritis

Cyclophosphamide

- Renal disease control
- Survival benefit
- May be useful in extrarenal manifestations
- Pulse dose intravenously
    - minimize toxicity
    - induction with follow-up to maintain remission
    - q month then q3 months for 2-3 years

Cyclophosphamide Toxicities

- Hematologic
- Opportunistic infection
- Bladder: hemorrhagic cystitis, cancer
- Sterility
- Teratogenesis

Azathioprine

- Less clinical experience than cyclophosphamide
- Less toxic than cyclophosphamide
  - Can be used as maintenance following cyclophosphamide induction
  - Not useful for induction
- Steroid sparing

Azathioprine Adverse Effects

- Anemia, leukopenia
- Opportunistic infection
- Hepatoxicity
- Pulmonary fibrosis
- Pancreatitis
- Teratogenesis
- Malignancy

Mycophenolate Mofetil (MMF)

- MMF at least as effective as cyclophosphamide in inducing remission of lupus nephritis
    - In combination with steroids
- MMF more favorable safety profile
    - More GI complaints
    - Fewer severe infections
    - Fewer hospitalizations

Treatment Algorithm

- Figures 103-2,3 and Tables 103-2,3
- High dose pulse steroids + cyclophosphamide for severe lupus nephritis

Management of Lupus Nephritis

- Hydroxychloroquine
- ACE for those with proteinuria
- Strict blood pressure control
- Statin to keep LDL <100mg/dL

Which of the following symptoms of SLE can be managed with hydroxychloroquine?

a) Acute flare of lupus nephritis
b) Rash
c) Severe pericarditis
d) Pancreatitis

Pregnancy

- Considered high risk
- Recommend conception when SLE controlled
- Preeclampsia
- Hypertension
- Thrombosis

SLE Drugs in Pregnancy

- Necessary to control SLE symptoms
    - Hydroxychloroquine
    - Azathioprine if needed
    - Corticosteroids, if needed
- Methotrexate, leflunamide, mycophenolate, cyclophosphamide, thalidomide teratogenic

Drug-Induced Lupus

- No consensus on diagnostic criteria
- Consider when
  - no history of idiopathic lupus
  - ANA develop (usually anti-histone)
  - at least one clinical feature of lupus
  - symptoms resolve upon discontinuation of drug

Drug-Induced Lupus

Contrast with SLE

- No consensus diagnostic criteria
- Develop symptoms later in life
- Greater percentage of whites
- Absence of female predominance
- Slow acetylator type

Implicated Drugs

- Procainamide
  - variable time course
- Hydralazine
  - dose related (>100mg/day males and >50mg/day females)
- Numerous other drugs

Clinical Presentation

- Fever, fatigue, weight loss
- Musculoskeletal manifestations most common
- Pleuropulmonary symptoms common
- CNS, renal manifestations rare
- Positive ANA almost universal

Drug Induced Lupus Management

- Discontinue drug
- Clinical manifestations subside in days to weeks
- May take up to a year for complete resolution
- Manage with NSAIDS

Which of the following is a characteristic of drug induced lupus?

a) Caused only by hydralazine or procainamide
b) Rarely ANA +
c) Resolves when offending drug is discontinued
d) Azathioprine is first-line treatment