

AUTOIMMUNE DISEASES - III

INFLAMMATORY MUSCLE DISEASE

(Polymyositis, Dermatomyositis, and Inclusion Body Myositis)

POLYMYOSITIS/DERMATOMYOSITIS (PM/DM)

- I. INTRODUCTION-A member of the connective tissue disease family characterized by chronic inflammation of striated muscle (polymyositis) and sometimes the skin (dermatomyositis) leading to painless proximal muscle weakness with or without a rash. Other organ systems may be affected and an association with malignancy in elderly patients is recognized.
- II. EPIDEMIOLOGY
 - A. Annual incidence-2-10 new cases per million.
 - B. Bimodal peak incidence-children and adults >40 y.o.; paucity of patients with onset in adolescence or young adulthood.
 - C. Overall sex ratio-2.5:1 female to male
 - D. Ethnic association-3-4:1 black to white
 - E. Environmental factors-No striking associations
- III. GENETIC PREDISPOSITION
 - A. Positive genetic predisposition-increased incidence in monozygotic twins and first degree relatives.
 - B. Close relatives tend to suffer from other autoimmune diseases
 - C. Reported associations of certain HLA types with clinical subsets of disease are weak.
- IV. ETIOLOGY
 - A. The host must be genetically predisposed to develop PM/DM in response to the etiologic trigger.
 - B. Only circumstantial evidence points to certain infectious triggers
 - C. D-Penicillamine known to trigger a disease clinically and histologically indistinguishable from PM or DM.
- V. PATHOGENESIS
 - A. Both humoral and cell-mediated immunologic mechanisms are postulated which appear to differ between dermatomyositis and polymyositis
 - B. Dermatomyositis-potential role of humoral immunity
 1. early damage to and obliteration of muscle capillaries may lead to muscle damage.
 2. localization of immunoglobulin and complement membrane attack complex (C5-9) to muscle vascular endothelium.
 3. increased proportion of activated B cells peripherally and in the target tissue.
 - C. Polymyositis-potential role of cell-mediated immunity
 1. activated CD8⁺ T cells and macrophages surround myocytes.

2. B cells are not abundant in the target lesions

VI. MYOSITIS-SPECIFIC AUTOANTIBODIES (MSA's)

A. General characteristics of MSA'S

1. presence of specific MSA'S associated with distinct clinical manifestations (see VI. B, C, and D).
2. MSA'S directed at proteins and ribonucleoproteins common to every cell
3. MSA target autoantigens are intracytoplasmic (not nuclear)
4. MSA target autoantigens are part of the protein synthetic machinery
5. MSA'S are present at time of clinical presentation
6. MSA target autoantigens are unlikely to be the primary pathogenetic agents of muscle damage; likely are footprints of another event.

B. Anti-Jo-1

1. autoantigen-histidyl tRNA synthetase
2. prevalence-15-40% of patients
3. clinical associations-"antisynthetase syndrome"
 - a. interstitial lung disease
 - b. arthritis
 - c. mechanic's hands (roughened surface of index fingers)
 - d. fever

C. Anti-SRP

1. autoantigen-proteins
2. prevalence-<5%
3. clinical associations
 - a. acute severe polymyositis
 - b. cardiac involvement
 - c. myalgias

D. Anti-Mi-2

1. autoantigen-unidentified protein
2. prevalence-<10%
3. clinical associations
 - a. classic dermatomyositis
 - b. V-sign rash
 - c. shawl-sign rash
 - d. cuticular overgrowth

VII. CLINICOPATHOLOGIC FEATURES

A. Adult polymyositis

1. presentation
 - a. insidious development of symmetric, diffuse, proximal muscle weakness of upper and lower extremities.
 - b. dysphagia may develop but facial muscle weakness is uncommon
 - c. 2:1 female to male
2. muscle biopsy
 - a. should be performed in all cases to confirm diagnosis.
 - b. patchy infiltration of mostly chronic inflammatory cells (lymphocytes, some plasma cells, and macrophages) in perivascular areas and between myocytes (80% of cases).
 - c. degeneration and necrosis of myofibrils, phagocytosis of necrotic cells, and myofibril regeneration.
3. muscle enzymes

- a. elevated serum creatine kinase (CK), released from injured myocytes, most reliable enzyme finding
 - b. CK elevated in 95% at some time during disease course
 - c. serum CK levels indicator of extent and acuteness of muscle injury.
4. electromyography
- a. characteristic findings; positive in 90% cases
 - b. useful in following disease activity
 - c. helpful in selection of muscle for biopsy

B. Adult dermatomyositis

- 1. females slightly outnumber males
- 2. classic rash + polymyositis
 - a. classic rash is violaceous discoloration of upper eyelids with periorbital edema.
 - b. in addition, skin manifestations may include scaling erythematous eruption or dusky red patches over multiple sites
- 3. skin biopsy
 - a. dermal mononuclear infiltrates similar to SLE
 - b. immunofluorescence shows patchy deposits of Ig and complement as opposed to "lupus band."
 - c. presence of mucin (strongly suggests DM)

C. PM/DM with neoplasia

- 1. carcinomas-develops in 5-15% of all patients (lung, ovary, breast, and stomach)
- 2. no increase risk in childhood PM/DM
- 3. neoplasia-adult PM(2-3%); adult DM (15-20%)
- 4. myositis preceding evidence of malignancy most common association.

D. PM/DM of childhood

- 1. vasculitis of arterioles, capillaries, and venules (skin and GI tract)
- 2. calcinosis
 - a. overlying ulceration with superimposed bacterial infection.
 - b. predilection for sites of repeated microtrauma (elbows, knees, fingers, buttocks).

E. PM/DM associated with connective tissue disease

- 1. PM more common than DM
- 2. female to male 9:1
- 3. most common-systemic sclerosis, but also see rheumatoid arthritis and SLE.

VIII. OTHER CLINICAL FEATURES

A. Joints-polyarthritis of small joints ("rheumatoid-like" distribution), if present, occurs early and tends to be mild.

B. Respiratory

- 1. diffuse alveolitis with rapid progression of dyspnea
- 2. interstitial fibrosis

C. Cardiac

- 1. arrhythmia most frequent abnormality
- 2. myocarditis or myocardial fibrosis leading to congestive heart failure.

D. GI tract-cervical (pharyngeal) dysphagia; when severe can lead to aspiration.

E. Raynaud's-a frequent accompanying complaint especially with dermatomyositis; digital tip ulceration is unusual.

IX. DIFFERENTIAL DIAGNOSIS

- A. Myasthenia gravis
- B. Amyotrophic lateral sclerosis
- C. Muscular dystrophy
- D. Infectious myositis

X. THERAPY AND PROGNOSIS

- A. Untreated, up to 50% of patients die of complications
- B. Clear benefit of corticosteroids for treatment of muscle weakness.
- C. Current expected survival with treatment->90% survival at 5 years after initial diagnosis (excluding those associated with malignancy).

XI. INCLUSION BODY MYOSITIS

- A. Insidious, yet progressive proximal and distal myositis with atrophy and weakness.
- B. Affects predominantly elderly male population.
- C. Rare or no association with malignancy or other connective tissue diseases.
- D. Creatine kinase is normal or only minimally elevated.
- E. Resistance to corticosteroids or immunosuppressive drugs.
- F. Muscle biopsy
 - 1. vacuoles with basophilic granules in myocytes
 - 2. intranuclear and intracytoplasmic inclusions in myocytes.
- G. Probably immune-mediated mechanism of muscle injury (cellular immunity as in PM).

SJOGREN'S SYNDROME

I. INTRODUCTION-A slowly progressive, inflammatory, autoimmune disease of the connective tissue type leading to atrophy of exocrine glands, especially the lacrimal (dry eyes-keratoconjunctivitis sicca) and salivary glands (dry mouth-xerostomia), and an increased risk of lymphoid malignancy.

II. EPIDEMIOLOGY

- A. Sex preponderance and age of onset-9:1 female to male with peak incidence in the 30's and 40's.
- B. Association with other connective tissue diseases-Rheumatoid arthritis [30%], systemic sclerosis [30%], and SLE.
- C. Prevalence-prevalence in general population is unknown but considered to occur relatively frequently.
- D. Genetic factors
 - 1. family members of affected patients have higher incidence of Sjogren's and higher incidence of serologic autoimmune abnormalities.

2. Several HLA associations.

E. Differential diagnosis with dry eyes and dry mouth in the elderly.

III. ETIOLOGY, PATHOGENESIS, AND IMMUNOLOGY

A. Evidence for viral etiology

1. 30% have serum antibodies to retroviral capsid glycoprotein
2. transgenic mice expressing *tax* gene of HTLV-1 develop Sjogren's-like pathology
3. retroviral particles isolated from some patients

B. Immune cell activation

1. Hypergammaglobulinemia and autoantibody production
2. infiltration of exocrine glands by B cells, in addition to T cells
3. lymphoid infiltration leads to glandular epithelial destruction

C. Increased incidence of B cell lymphomas-44x increased risk relative to general population

D. Autoantibodies

1. Anti-SS-A (anti-Ro) and anti-SS-B (anti-La) both specific for ribonucleoprotein antigens.
2. anti-SS-A (anti-Ro)-40-45% in Sjogren's and 25-30% in SLE
3. anti-SS-B (anti-La)-50% in Sjogren's syndrome and 10% in SLE
4. presence of anti-SS-A or anti-SS-B antibodies in primary Sjogren's patients is associated with:
 - a. earlier disease onset
 - b. longer disease duration
 - c. recurrent parotid gland enlargement
 - d. splenomegaly and lymphadenopathy
 - e. vasculitis

IV. CLINICOPATHOLOGIC FEATURES

A. Xerostomia (dry mouth)

1. lymphocytic infiltration and destruction of minor and major salivary glands
2. chronic or episodic enlargement of parotid glands may be unilateral or bilateral.
3. clinical consequences due to decreased saliva production:
 - a. difficulty swallowing dry food
 - b. inability to speak continuously
 - c. changes in sense of taste
 - d. burning sensation in the mouth
 - e. increase in dental caries
4. sialometry measures salivary flow rate
5. sialography assesses anatomic changes in salivary duct system

B. Keratoconjunctivitis sicca (dry eyes)

1. lymphocytic infiltration and destruction of lacrimal glands leading to reduced tear production
2. lacrimal gland enlargement
3. destruction of conjunctival epithelium
 - a. dilation of conjunctival vessels
 - b. peri-corneal erythema
 - c. itchiness, burning, and photosensitivity
4. Rose Bengal staining demonstrates punctate or filamentary keratitis
5. Schirmer's test shows wetting of less than 5 mm/5 min of the filter paper strip.

C. Exocrinopathy-Other organ involvement

1. dryness of upper respiratory tract and oropharynx (hoarseness)
2. recurrent bronchitis and pneumonitis
3. loss of pancreatic function
4. hypochlorhydria
5. dry skin
6. loss of vaginal secretions

D. Extraglandular manifestations

1. arthritis-50% patients, non-erosive
2. Raynaud's-35% of patients, do not develop digital ulcers
3. Pulmonary-manifestations from trachea to pleura frequent, but rarely clinically important.
4. Gastrointestinal
 - a. dysphagia
 - b. nausea, epigastric pain, and atrophic gastritis
5. Hepatic
 - a. hepatomegaly (25-28%)
 - b. elevated alkaline phosphatase (25-33%)
 - c. anti-mitochondrial antibodies
 - d. chronic inflammatory infiltrates
6. Renal-distal renal tubular acidosis due to interstitial lymphocytic infiltrates (10% of patients)
7. Neuromuscular
 - a. peripheral sensorimotor neuropathy due to small vessel vasculitis
 - b. cranial neuropathy
 - c. CNS involvement-multifocal, recurrent, and progressive

V. Management

- A. Various supportive therapies for consequences of exocrine gland atrophy
- B. Systemic corticosteroids and immunosuppressive drugs (e.g. cyclophosphamide) for severe extraglandular disease-impact on natural disease course not well-established.