

AUTOIMMUNITY I

TOLERANCE, SYSTEMIC VASCULITIS, RHEUMATOID ARTHRITIS THE BREAKDOWN OF SELF-TOLERANCE AND THE INITIATION OF AUTOIMMUNITY

- I. Introduction-Autoimmune disease may be defined as an immune reaction against self-antigens secondary to a loss of self-tolerance. This may form the basis for the pathogenesis of a variety of distinct human diseases which involve either isolated single organ injury or multi-organ, systemic dysfunction.

- II. Mechanisms of tissue injury in autoimmunity
 - A. B cell activation-synthesis of autoantibodies (humoral immunity)
 1. antibody-mediated cellular cytotoxicity [ADCC] (type II)
 2. antibody-mediated activation of complement (type II)
 3. anti-receptor antibody (type II)
 4. immune-complex-mediated injury (type III)

 - B. Cell-mediated immune injury (type IV)
 1. tissue injury typically mediated by T cells and macrophages

 - C. Cytokines play a key role in mediating both humoral and cell-mediated autoimmune reactions

- III. Loss of tolerance
 - A. Clonal deletion-immature clones of lymphocytes that bear receptors for self-antigens are eliminated from the immune system during development.

 - B. Clonal anergy-immature B cells go through a phase during which contact with an antigen leads to functional paralysis without physical deletion.

 - C. suppression of auto-reactive lymphocytes-self-tolerance is maintained by mechanisms that actively suppress immune responses against self (i.e. autoreactive lymphocytes are competent to respond but are ordinarily prevented from doing so by some form of suppression).

- IV. Determining factors in the onset of autoimmune disease
 - A. Genetic factors
 1. association with HLA phenotypes
 2. clustering in families

 - B. Microbiologic agents-role in autoimmunity is suspected, especially in regards to viruses, but no clear demonstration established

 - C. Drugs-certain drugs are known to induce autoimmune disease in susceptible hosts (e.g. drug-induced SLE).

* Thus, the onset of autoimmunity may occur on the basis of a perturbation of the immune system (?microbiologic agent, drug) leading to loss of self-tolerance in a genetically susceptible host. The specific genotype of the host, and the environmental perturbation, determines the nature of the autoimmune disease.

V. Broad classification of autoimmune disease

- A. Connective tissue (collagen-vascular) disease-multisystem autoimmune disease involving a broad array of target self-antigens. In the case of immune complexes injury is relatively tissue-non-specific.
- B. Single organ autoimmunity-the autoimmune reaction targets one or a limited number of self-antigens specific for a single organ; often involves endocrine organs.
- C. Vasculitis-Blood vessels are primarily targeted for injury, but the target antigens may not be specific for blood vessel components.
- D. Both humoral and cell-mediated immune injury may be involved in any of the three categories of autoimmune disease.

SYSTEMIC VASCULITIS

I. Introduction

- A. A heterogeneous group of clinical disorders which are characterized by inflammation and damage to blood vessels.
- B. The injury to the vascular lumen results in distal ischemia to the tissues supplied by a given involved vessel. It is this reduction in blood flow, and the systemic features of fever, weight loss, and anorexia accompanying widespread inflammation, which causes an array of symptoms and clinical expressions.
- C. Involvement may include only one, or many, organ systems and vessels of predominantly one or of many types.
- D. Vasculitis syndromes can be stratified according to the predominant type and size of blood vessel that is affected.

II. Common vasculitis syndromes (in order of descending vessel size)

- A. Takayasu's arteritis (aorta and its branches)
- B. Temporal arteritis (aorta and its branches, large and medium-sized arteries)
- C. Polyarteritis nodosa [PAN] (large and medium-sized arteries, medium- sized muscular arteries, small muscular arteries)
- D. Churg-Strauss arteritis (large and medium-sized arteries, medium- sized muscular arteries, small muscular arteries)
- E. Isolated CNS vasculitis (medium-sized muscular arteries, small muscular arteries)
- F. Wegener's granulomatosis (medium-sized muscular arteries, small muscular arteries, venules and arterioles)
- G. Vasculitis associated with connective tissue diseases (small muscular arteries, venules and arterioles)

III. Common features of the Systemic Vasculitides

- A. Etiology thought to involve immune-complex deposition in vascular wall with complement activation and chemo-attraction of inflammatory cells. Cell-mediated immune destruction (e.g. granulomatous inflammation) also implicated.

- B. Immune complex deposition may be enhanced by release of vasoactive amines from platelets and IgE-triggered basophils, and is augmented by blood flow turbulence and hydrostatic forces (preferred locations: lower extremities and vessel bifurcations).
- C. Except for PAN, which is associated with hepatitis B surface antigenemia, the inciting antigens are unknown.
- D. Generally a multisystem disease with certain organ preferences typical for each type of vasculitis.
- E. Often, the patient presents with non-specific signs and symptoms of systemic inflammation: fever, malaise, fatigue, myalgias, muscle weakness, and increased erythrocyte sedimentation rate (ESR). Pain, in the distribution of the involved vessels also typical. Specific end-organ failure often a final outcome.
- F. No diagnostic laboratory findings. The diagnosis is typically established by:
 1. clinical setting
 2. arteriographic changes (e.g. aneurysmal dilatations and vessel narrowing)
 3. typical histologic changes in biopsied blood vessel.
- G. Likely to progress to significant and often life-threatening end-organ dysfunction without therapy. Early diagnosis critical to prevent irreversible end-organ injury. Generally treated with corticosteroids with or without cytotoxic drugs (e.g. cyclophosphamide).

IV. Polyarteritis nodosa (PAN)

A. Epidemiology

1. sex ratio-2: 1 male to female
2. average age-mid 40's to mid 60's
3. incidence-4.6-9.0/1,000,000; 77/1,000,000 in HBV endemic area
4. racial-observed in all racial groups

B. Etiology

1. Viruses-antigens form immune complexes
 - a. 10-55% HBV antigen thought to initiate immune complex-induced vasculitis; remainder of cases also typically secondary to immune complexes but inciting antigen is unknown.
 - b. HIV has been associated with a PAN pattern of disease
 - c. other viruses (cytomegalovirus, hepatitis A, human T cell leukemia-lymphoma virus 1, and parvovirus).
2. Immune complex-mediated endothelial cell injury leads to alteration in endothelial-derived mediators which results in :
 - a. vasoconstriction
 - b. thrombosis (blood clot)
 - c. endothelial cell proliferation
3. Inflammatory cell infiltration of vessel wall contributes to injury

C. Pathology

1. focal, yet pan-mural, necrotizing inflammatory lesions in small and medium-sized arteries
2. vessels in all parts of body (pulmonary and splenic arteries less-involved)
3. predominantly neutrophils in early lesions; also lymphocytes and eosinophils.
4. early-necrosis, thrombosis, and aneurysmal dilatation; late-fibrosis and endothelial proliferation with occlusion

D. Clinical

1. disease may present in variety of ways with wide spectrum of severity
2. constitutional features-fever, malaise, weight loss, diffuse aching, anemia, and elevated erythrocyte sedimentation rate (ESR)
3. multisystem involvement (major features):
 - a. cutaneous-purpura, ulcerations, livedo vasculitis, ischemic changes of the distal digits
 - b. peripheral neuropathy-50-70%; upper and lower extremities; pain, paraesthesias, and motor deficit.
 - c. asymmetric polyarthritis-50%
 - d. renal-70%; glomerular-proteinuria and hematuria
 - e. gastrointestinal-abdominal pain and bleeding

E. Treatment

1. corticosteroids; if severe can add a cytotoxic agent (e.g. cyclophosphamide)

F. Prognosis

1. untreated-5 year survival <15%; with treatment-5 year survival 50-60%

V. Wegener's Granulomatosis

A. epidemiology

1. male: female 1:1;
2. vast majority in Caucasians
3. mean age at diagnosis-41 yrs (16% occur in children)

B. etiology and pathogenesis

1. multisystem disease of unknown etiology; various inhaled substances may be trigger in susceptible host
2. ANCA's-anti-neutrophil cytoplasmic antibodies
 - a. may be implicated in pathogenesis
 - b. target antigen is proteinase-3
 - c. specificity-98%, sensitivity-30-99%
 - d. rise in serum levels of ANCA associated with clinical activity

C. pathology

1. small and occasionally medium-sized vessel vasculitis
2. granuloma formation with giant cells

D. clinical (greatest morbidity results from respiratory, renal, auditory and ocular disease)

1. vasculitis with necrosis and granuloma formation of the upper and lower respiratory tracts
 - a. nasal, sinus, tracheal, and/or ear abnormalities initial symptoms in 73%
 - b. inflammatory pulmonary infiltrates and nodules
2. glomerulonephritis develops in 75% of patients
3. constitutional-elevated ESR, anemia, fever, weight loss
4. Ocular-50%
 - a. inflammation in the retro-orbital space-proptosis (15%); ; optic nerve ischemia with loss of vision; entrapment of extra-ocular muscles

E. treatment and prognosis

1. corticosteroids and cyclophosphamide
2. prognosis-without treatment (18% 1 year survival); with treatment (87% 5 year survival)

VI. Temporal Arteritis (Giant cell arteritis)

A. epidemiology

1. almost exclusively in Caucasians
2. incidence-18/100,000
3. 3:1 female to male
4. familial aggregation and HLA association (HLA-DR4)
5. mean age of onset-70 years (range 50-90)

B. etiology and pathogenesis

1. unknown
2. evidence for a role of cellular immunity (presence of activated CD4⁺ T cells and macrophages in vascular lesion).

C. pathology

1. dense granulomatous inflammatory infiltrates, including multi-nucleated giant cells, involving full thickness of vessel wall
2. large and medium-sized arteries, with patchy involvement and "skip" areas
3. intimal proliferation with luminal narrowing and thrombosis at sites of inflammation
4. most frequently involved vessels-superficial temporal arteries, vertebral arteries, and ophthalmic and posterior ciliary arteries

D. clinical

1. constitutional (majority)-fever, fatigue, anorexia, weight loss, and depression; ESR is greatly elevated
2. polymyalgia rheumatica
 - a. bilateral, symmetrical pain and stiffness in the muscles of the shoulder and pelvic girdle; muscle strength is not impaired
 - b. muscle atrophy in late stages
 - c. no evidence of inflammation; serum CK is normal; electromyography is normal
 - d. little evidence that symptoms are related to vasculitis
3. headache
 - a. most common symptom (present in 2/3 patients)
 - b. pain severe and localized to the temple
 - c. temporal vessels are thickened, tender, and nodular with absent or reduced pulsation
4. Ophthalmic features
 - a. visual disturbances in 25-50%
 - b. visual loss in 6-10%; usually sudden, painless, and permanent
 - c. commonest lesion-ischemia of the optic nerve
5. claudication of the jaw muscles (pain on chewing); up to 2/3 of patients

E. treatment and prognosis

1. early treatment with corticosteroids are mandatory, especially to reduce incidence of blindness; response usually dramatic and occurs within days
2. 1/3-1/2 can discontinue treatment after 2 years; most stop taking after 4-5 years
3. monitor for relapse from 6 mos. to 1 year after stopping steroids

RHEUMATOID ARTHRITIS

- I. Introduction-An autoimmune disease involving chronic inflammation of synovial linings of joints, bursae, and tendon sheaths leading to erosion of articular cartilage and subchondral

bone with subsequent joint destruction. Extra-articular features are common, numerous, and are due to serositis, vasculitis, and nodule (granuloma) formation.

II. Epidemiology

- A. sex distribution-2-3:1 female to male
- B. annual incidence-30/100,000
- C. genetic associations-HLA-DR4, HLA-DR1
- D. age of onset-peak incidence in young adults and pre-menopausal women; however may occur at all ages

III. Clinical features

- A. typically begins as pain, tenderness, and swelling of one or more of the small joints of the hands and feet, in a symmetrical fashion.
- B. although the course of the disease varies, severe joint destruction with deformity and loss of function is a frequent outcome.
- C. Extraarticular manifestations (subcutaneous nodules, pulmonary fibrosis, digital vasculitis, and skin ulceration) correlate with persistence of articular disease, and with poor prognosis for crippling and early mortality.
- D. A generalized vasculitis having many of the manifestations of PAN may be seen.

IV. Etiology, Pathogenesis, and Pathology

- A. Acute synovitis is triggered by exposure of an immunogenetically susceptible host to an arthritogenic microbial antigen
 - 1. microbial antigen unknown but EBV is a prime suspect
 - 2. other viruses (retroviruses, parvoviruses) and bacteria (Borrelia, Mycoplasma, mycobacteria) also under consideration
 - 3. autoimmunity to type II collagen (cartilage) in most patients may reflect cross-reaction with microbial antigen
- B. Continuation of autoimmune reaction within synovium by CD4⁺ T cells and the cytokines which they secrete responsible for chronic destruction of joint:
 - 1. activation of endothelial cells lining synovial capillaries with upregulation of adhesion molecules (ICAM-1, ELAM-1, and VCAM-1) and recruitment of additional inflammatory cells (enhanced by IL-1, TNF- α , and IFN- γ).
 - 2. macrophage activation with release of IL-1 and TNF- α
 - 3. activation of B cells with synthesis of autoantibodies
- C. Rheumatoid factor
 - 1. autoantibodies to Fc portion of autologous IgG (usually IgM antibody)
 - 2. forms immune complexes that are found in 80% of patients in sera, synovial fluid and synovial membranes
 - 3. underlie many of the extraarticular manifestations of RA
 - 4. activate complement within synovium leading to augmentation of inflammation, but their presence is likely not critical for causation
 - 5. sometimes observed in other disease states and even some healthy people
- D. Joint destruction mediated by:
 - 1. neutrophils and synoviocytes which release proteases and elastases
 - 2. actions of TNF- α and IL-1 produced locally by macrophages:

- a. resorption of cartilage and bone by stimulating release of collagenases from synovial cells
- b. up-regulate endothelial cell adhesion molecules with enhanced recruitment of inflammatory cells
- c. inhibit synthesis of proteoglycans in cartilage
- d. stimulate proliferation of fibroblasts via platelet-derived growth factor
- e. osteoclast-activating factor
- f. chemoattractant for neutrophils and lymphocytes

E. Pannus (inflammatory synovium)

1. synovium becomes edematous, thickened, and hyperplastic
2. synovial stroma filled with inflammatory cells (CD4⁺ T cells, plasma cells, and macrophages)
3. increased vascularity and deposition of fibrin and hemosiderin
4. spread of pannus throughout synovium with erosion and spread into cartilage and subchondral bone
5. pannus eventually bridges apposing bones forming a fibrous ankylosis; eventually ossifies resulting in bony ankylosis
6. deformation of joint and loss of joint function