DISEASES OF THE IMMUNE SYSTEM
SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

- An autoimmune disease involving multiple organs, characterized by a vast array of autoantibodies, particularly antinuclear antibodies, in which injury is caused mainly by deposition of immune complexes (type III hypersensitivity) and binding of antibodies to various cells and tissues (type II hypersensitivity).
  - LE Cells – A phenomenon of type II hypersensitivity where antibody coated nuclei of damaged cells are engulfed by neutrophils or macrophages.

- Implicated autoantibodies:
  - Anti-DS DNA – Specific for SLE; associated with nephritis; diffuse and/or peripheral staining pattern on indirect IF.
  - Anti-Smith (SM) antigen – Specific for SLE; speckled staining pattern on indirect IF.
  - Anti-phospholipid-protein complexes – Associated with anti-phospholipid antibody syndrome.

- The fundamental defect is a failure of mechanisms that maintain self-tolerance.
  - Environmental insults (UV irradiation) lead to cellular apoptosis creating a large burden of nuclear antigen; defects in self-tolerance result in self-reactive B and T-cells against nuclear antigens with the production of antibody; antibody and cytokine activity cause more cell injury releasing more nuclear antigen (a cycle).
SYSTEMIC LUPUS ERYTHEMAOSUS (SLE)

• MORPHOLOGY AND CLINICAL FEATURES:
  • BLOOD VESSELS – ACUTE NECROTIZING VASCULITIS LEADING TO FIBRINOID NECROSIS DUE TO ANTIGEN-ANTIBODY COMPLEXES
  • KIDNEY – SIX PATTERNS OF GLOMERULAR DISEASE ARE RECOGNIZED DUE TO ANTIGEN-ANTIBODY COMPLEX DEPOSITION
    • MINIMAL MESANGIAL LUPUS NEPHRITIS (CLASS I) – LEAST COMMON; IMMUNE COMPLEX DEPOSITION IN THE MESANGIUM SEEN BY IF AND EM BUT NO STRUCTURAL CHANGES SEEN BY LIGHT MICROSCOPY
    • MESANGIAL PROLIFERATIVE LUPUS NEPHRITIS (CLASS II) – MESANGIAL CELL PROLIFERATION AND DEPOSITS WITH ACCUMULATION OF MESANGIAL MATRIX
    • FOCAL LUPUS NEPHRITIS (CLASS III) – SEGMENTAL OR GLOBAL GLOMERULAR LESIONS INVOLVING <50% OF GLOMERULI; GLOMERULI EXHIBIT SWELLING AND PROLIFERATION OF ENDOTHELIAL AND MESANGIAL CELLS ASSOCIATED WITH LEUKOCYTE ACCUMULATION, CAPILLARY NECROSIS AND HYALINE THROMBI
    • DIFFUSE LUPUS NEPHRITIS (CLASS IV) – MOST COMMON; LESIONS ARE IDENTICAL TO THOSE SEEN IN CLASS III BUT INVOLVE >50% OF GLOMERULI; SUBENDOTHELIAL IMMUNE COMPLEX DEPOSITS CREATE CIRCUMFERENTIAL THICKENING OF THE CAPILLARY WALL FORMING ‘WIRE LOOP’ STRUCTURES
    • MEMBRANOUS LUPUS NEPHRITIS (CLASS V) – DIFFUSE THICKENING OF THE CAPILLARY WALLS DUE TO SUBEPITHELIAL IMMUNE COMPLEX DEPOSITS WITH A “SPIKY” APPEARANCE ON SILVER STAIN
    • ADVANCED SCLEROSING LUPUS NEPHRITIS (CLASS VI) – SCLEROSIS OF >90% OF GLOMERULI AND REPRESENTS END STAGE RENAL DISEASE
SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

• MORPHOLOGY AND CLINICAL FEATURES:
  • SKIN – CHARACTERISTIC ERYTHEMA AFFECTS THE FACE ALONG THE BRIDGE OF THE NOSE AND CHEEKS (BUTTERFLY/MALAR RASH) AND IS INCITED/ACCENTUATED BY SUNLIGHT (PHOTOSENSITIVITY)
    • INVOLVED AREAS SHOW VACUOLAR DEGENERATION OF THE BASAL LAYER OF THE EPIDERMIS AND IF MICROSCOPY SHOWS DEPOSITS OF IMMUNOGLOBULIN AND COMPLEMENT AT THE DERMOEPIDERMAL JUNCTION
    • CHRONIC DISCOID LUPUS – SKIN MANIFESTATIONS MIMIC SLE BUT WITHOUT SYSTEMIC MANIFESTATIONS
  • JOINTS – A NONEROSIVE PAINFUL SYNOVITIS WITH LITTLE DEFORMITY
  • CENTRAL NERVOUS SYSTEM – OCCLUSION OF SMALL VESSELS BY INTIMAL PROLIFERATION STIMULATED BY AUTOANTIBODIES AND IMMUNE COMPLEXES CAUSING PSYCHOSIS OR CONVULSIONS
  • PERICARDITIS – INFLAMMATION CAN RESULT IN A FIBRINOUS PERICARDITIS OFTEN WITH EFFUSION CAUSING PLEURITIC CHEST PAIN
  • CARDIOVASCULAR SYSTEM – MAY INVOLVE ALL THREE LAYERS OF THE HEART
    • LIBMAN-SACKS ENDOCARDITIS – STERILE ENDOCARDITIS SHOWING 1-3 MM VERRUCOUS DEPOSITS THAT MAY FORM ON EITHER SURFACE OF ANY HEART VALVE
    • Atherosclerosis and coronary artery disease
  • DISEASE FLARES ARE TREATED WITH CORTICOSTEROIDS OR OTHER IMMUNOSUPPRESSIVE DRUGS WITH EXCELLENT 5 AND 10 YEAR SURVIVALS
  • DRUG-INDUCED LUPUS ERYTHEMATOSUS – SLE-LIKE SYNDROME CAUSED BY A VARIETY OF DRUGS (HYDRALAZINE, PROCAINAMIDE, ISONIAZID, ANTI-TNF THERAPY); PATIENTS DEVELOP ANA PARTICULARLY ANTI-HISTONE ANTIBODIES
SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)
SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)
SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)
SJOGREN SYNDROME

• CHRONIC DISEASE CHARACTERIZED BY DRY EYES AND DRY MOUTH RESULTING FROM IMMUNOLOGICALLY MEDIATED DESTRUCTION OF THE LACRIMAL AND SALIVARY GLANDS

• OCCURRS AS AN ISOLATED DISORDER (SICCA SYNDROME) OR IN ASSOCIATION WITH OTHER AUTOIMMUNE DISEASES

• AUTOANTIBODIES:
  • SS-A (RO) – MORE SENSITIVE; ASSOCIATED WITH EARLY DISEASE ONSET, LONGER DISEASE DURATION AND EXTRAGLANDULAR MANIFESTATIONS
  • SS-B (LA) – MORE SPECIFIC

• DUE TO ACTIVATION OF AUTOREACTIVE T AND B-CELLS FOLLOWING VIRAL INFECTION OF THE SALIVARY GLANDS

• MORPHOLOGY – NOT SPECIFIC AND CAN MIMIC LYMPHOMA AND CHRONIC SIALADENITIS
  • EXTENSIVE PERIDUCTAL AND PERIVASCULAR LYMPHOCYTIC INFILTRATION WITH GERMINAL CENTERS
  • DUCTAL EPITHELIUM BECOMES HYPERPLASTIC WITH OBSTRUCTION CAUSING ACINAR ATROPHY AND FIBROSIS
SJOGREN SYNDROME
SYSTEMIC SCLEROSIS (SCLERODERMA)

• CHARACTERIZED BY EXCESSIVE FIBROSIS IN MULTIPLE TISSUES, OBLITERATIVE VASCULAR DISEASE, AND EVIDENCE OF AUTOIMMUNITY (AUTOANTIBODIES)

• CLASSIFIED INTO TWO GROUPS:
  • DIFFUSE SYSTEMIC SCLEROSIS – INITIAL WIDE SPREAD SKIN INVOLVEMENT WITH RAPID PROGRESSION AND EARLY VISCERAL INVOLVEMENT
  • LIMITED SYSTEMIC SCLEROSIS – MILD SKIN INVOLVEMENT (FINGERS AND FACE) WITH LATE VISCERAL INVOLVEMENT
    • CREST SYNDROME – CALCINOSIS, RAYNAUD PHENOMENON, ESOPHAGEAL DYSMOTILITY, SCLERODACTYLY, TELANGIECTASIA

• AUTOANTIBODIES:
  • ANTI-DNA TOPOISOMERASE I (ANTI-SCL70) – HIGHLY SPECIFIC; ASSOCIATED WITH PULMONARY FIBROSIS AND PERIPHERAL VASCULAR DISEASE
  • ANTI-CENTROMERE – ASSOCIATED WITH CREST SYNDROME

• PATHOGENESIS – CD4+ T-CELLS RESPONDING TO AN UNIDENTIFIED ANTIGEN ACCUMULATE IN THE SKIN AND RELEASE CYTOKINES THAT ACTIVATE INFLAMMATORY CELLS AND FIBROBLASTS TRIGGERING ENDOTHELIAL DAMAGE/PROLIFERATION AND EXCESSIVE COLLAGE PRODUCTION
SYSTEMIC SCLEROSIS (SCLERODERMA)

• MORPHOLOGY:
  • SKIN – DIFFUSE FIBROSIS BEGINS DISTALLY IN THE FINGERS AND EXTENDS PROXIMALLY
    • WITH PROGRESSION THERE IS INCREASING FIBROSIS OF THE DERMIS AND HYALINE THICKENING OF THE WALLS OF DERMAL CAPILLARIES
    • IN ADVANCED STAGES THE FINGERS APPEAR CLAW-LIKE AND THE FACE BECOMES A DRAWN MASK
  • ALIMENTARY TRACT – FIBROUS REPLACEMENT OF THE MUSCULARIS IN THE LOWER ESOPHAGUS GIVES RISE TO GASTROESOPHAGEAL REFLUX
  • KIDNEY – ARTERIES SHOW INTIMAL THICKENING/CONCENTRIC PROLIFERATION CAUSING HYPERTENSION
  • LUNGS – PULMONARY HYPERTENSION AND INTERSTITIAL FIBROSIS
  • HEART – PERICARDITIS WITH EFFUSION AND MYOCARDIAL FIBROSIS
SYSTEMIC SCLEROSIS (SCLERODERMA)
PRIMARY (INHERITED) IMMUNODEFICIENCIES

• SEVERE COMBINED IMMUNODEFICIENCY (SCID)
  • SPANS A CONSTELLATION OF GENETICALLY DISTINCT SYNDROMES, ALL HAVING IN
    COMMON IMPAIRED DEVELOPMENT OF MATURE T- AND/OR B-CELLS AND DEFECTS IN
    BOTH HUMORAL AND CELL-MEDIATED IMMUNITY
  • CHILDREN ARE EXTREMELY SUSCEPTIBLE RECURRENT SEVERE INFECTIONS BY A WIDE RANGE
    OF PATHOGENS (C. ALBICANS, P. JIROVECI, PSEUDOMONAS, CMV, OTHER BACTERIA)
  • TWO MAJOR FORMS:
    • X-LINKED SCID – CAUSED BY MUTATIONS IN THE GENE ENCODING THE COMMON GAMMA
      CHAIN SHARED BY THE RECEPTORS FOR THE CYTOKINES IL-2, IL-4, IL-7, IL-9 AND IL-15
    • AUTOSOMAL RECESSIVE SCID – APPROXIMATELY HALF CAUSED BY MUTATIONS IN
      ADENOSINE DEAMINASE (ADA), AN ENZYME INVOLVED IN PURINE METABOLISM

• X-LINKED AGAMMAGLOBULINEMIA (BRUTON DISEASE)
  • CHARACTERIZED BY THE FAILURE OF PRE-B CELLS TO DIFFERENTIATE INTO MATURE B-CELLS
    RESULTING IN ABSENCE OF ANTIBODIES IN THE BLOOD
  • B-CELL MATURATION STOPS AFTER THE INITIAL HEAVY CHAIN GENE REARRANGEMENT DUE
    TO MUTATIONS IN THE BRUTON TYROSINE KINASE (NO LIGHT CHAINS ARE PRODUCED)
  • AT 6 MONTHS OF AGE PATIENTS DEMONSTRATE RECURRENT BACTERIAL INFECTIONS OF
    THE RESPIRATORY TRACT DUE H. INFLUENZAE, S. PNEUMONIAE AND S. AUREUS (NORMALLY
    OPSONIZED ORGANISMS)
PRIMARY (INHERITED) IMMUNODEFICIENCIES

• DIGEORGE SYNDROME (THYMIC HYPOPLASIA)
  • CAUSED BY A CONGENITAL DEFECT IN THYMIC DEVELOPMENT RESULTING IN DEFICIENT T-CELL MATURATION
  • EXTREMELY VULNERABLE TO VIRAL, FUNGAL AND PROTOZOAL INFECTIONS
  • CAUSED BY A DELETION IN CHROMOSOMAL REGION 22Q11 WHICH CAUSES DEVELOPMENTAL MALFORMATION AFFECTING THE THIRD AND FOURTH PHARYNGEAL POUCHES WHICH GIVES RISE TO THE THYMUS, PARATHYROID GLANDS (CAUSING HYPOCALCEMIA) AND PORTIONS OF THE FACE AND AORTIC ARCH

• HYPER-IGM SYNDROME
  • CHARACTERIZED BY THE PRODUCTION OF NORMAL (OR EVEN SUPRANORMAL) LEVELS OF IGM ANTIBODIES AND DECREASED LEVELS OF THE ISOTYPE-SWITCHED HIGH AFFINITY ANTIBODIES (IGG, IGA AND IGE ISOTYPES)
  • THE UNDERLYING DEFECT IS AN INABILITY OF T-CELLS TO ACTIVATE B-CELLS
    • 70% DUE TO MUTATIONS (X-LINKED) IN CD40 LIGAND PRESENT ON ACTIVATED T-CELLS
    • THE REST CAUSE BY LOSS-OF-FUNCTION MUTATIONS (AUTOSOMAL RECESSIVE) IN EITHER CD40 OR ACTIVATION-INDUCED CYTIDINE DEAMINASE (AID) WHICH IS REQUIRED FOR IMMUNOGLOBULIN CLASS SWITCHING
  • PATIENTS PRESENT WITH RECURRENT PYOGENIC INFECTIONS BECAUSE OF LOW LEVELS OF OPSONIZING IGG ANTIBODIES
  • THE IGM ANTIBODIES REACT WITH BLOOD CELLS GIVING RISE TO AUTOIMMUNE HEMOLYTIC ANEMIA, THROMBOCYTOPENIA AND NEUTROPENIA
PRIMARY (INHERITED) IMMUNODEFICIENCIES

• COMMON VARIABLE IMMUNODEFICIENCY (CVID)
  - A HETEROGENEOUS GROUP OF DISORDERS IN WHICH THE COMMON FEATURE IS HYPOGAMMAGLOBULINEMIA, GENERALLY AFFECTING ALL THE ANTIBODY CLASSES BUT SOMETIMES ONLY IGG
  - PATIENTS HAVE NORMAL NUMBERS OF MATURE B-CELLS BUT PLASMA CELLS ARE ABSENT SUGGESTING A BLOCK IN B-CELL DIFFERENTIATION
  - PATIENTS ARE PRONE TO DEVELOP TO AUTOIMMUNE DISORDERS AND LYMPHOID TUMORS
  - PATIENTS PRESENT WITH RECURRENT SINOPULMONARY BACTERIAL INFECTIONS
  - IN CONTRAST TO X-LINKED AGAMMAGLOBULINEMIA, CVID AFFECTS BOTH SEXES EQUALLY AND THE ONSET OF SYMPTOMS IS IN CHILDHOOD OR ADOLESCENCE

• ISOLATED IGA DEFICIENCY
  - MOST COMMON PRIMARY IMMUNE DEFICIENCY DISEASE
  - PREDISPOSE PATIENTS TO RECURRENT SINOPULMONARY INFECTIONS AND DIARRHEA
  - INVOLVES A BLOCK IN THE TERMINAL DIFFERENTIATION OF IGA-SECRETING B-CELLS TO PLASMA CELLS
PRIMARY (INHERITED) IMMUNODEFICIENCIES

- **WISKOTT-ALDRICH SYNDROME**
  - X-LINKED DISEASE CHARACTERIZED BY THROMBOCYTOPENIA, ECZEMA AND A MARKED VULNERABILITY TO RECURRENT INFECTION THAT RESULTS IN EARLY DEATH
  - THE THYMUS IS NORMAL BUT THERE IS PROGRESSIVE LOSS OF T-CELLS FROM THE BLOOD AND T-CELL ZONES OF LYMPH NODES
  - IGM LEVELS IN THE SERUM ARE LOW, BUT LEVELS OF IGG ARE USUALLY NORMAL AND IGA AND IGE ARE OFTEN ELEVATED
  - CAUSED BY MUTATIONS IN THE GENE ENCODING WISKOTT-ALDRITCH SYNDROME PROTEIN (WASP)

- **ATAXIA TELANGIECTASIA**
  - AUTOSOMAL RECESSIVE DISEASE CHARACTERIZED BY ABNORMAL GAIT (ATAXIA), VASCULAR MALFORMATIONS (TELANGIECTASIA), NEUROLOGIC DEFICITS, INCREASED INCIDENCE OF TUMORS AND IMMUNODEFICIENCY
  - HAVE DEFECTIVE PRODUCTION OF IGA AND IGG2
  - EXPERIENCE UPPER AND LOWER RESPIRATORY TRACT BACTERIAL INFECTIONS, AUTOIMMUNE DISEASE AND LYMPHOID TUMORS
  - CAUSED BY MUTATIONS IN THE GENE ENCODING ATAXIA TELANGIECTASIA MUTATED (ATM) PROTEIN WHICH IS A SENSOR OF DNA DAMAGE
DEFECTS IN INNATE IMMUNITY

• LEUKOCYTE ADHESION DEFICIENCIES (LAD)
  • INHERITED DEFECTS IN ADHESION MOLECULES THAT IMPAIR LEUKOCYTE RECRUITMENT TO SITES OF INFECTION RESULTING IN RECURRENT BACTERIAL INFECTIONS
  • LAD1 – CAUSED BY DEFECTS IN THE BETA 2 CHAIN SHARED BY INTEGRINS LFA-1 AND MAC-1
  • LAD2 – CAUSED BY DEFECT IN A FUCOSYL TRANSFERASE REQUIRED FOR SYNTHESIS OF SIALYLATED OLIGOSACCHARIDE (RECEPTOR FOR SELECTINS)

• CHRONIC GRANULOMATOUS DISEASE
  • INHERITED DEFECTS IN THE GENES ENCODING COMPONENTS OF PHAGOCYTE OXIDASE CAUSING DECREASED OXIDATIVE BURST RESULTING IN DECREASED BACTERIAL KILLING/RECURRENT BACTERIAL INFECTIONS
  • GRANULOMATOUS INFLAMMATION IS SEEN AT THE SITE OF INFECTION

• CHEDIAK-HIGASHI SYNDROME
  • CAUSED BY DEFECTIVE FUSION OF PHAGOSOMES AND LYSOSOMES
  • AFFECTED LEUKOCYTES CONTAIN GIANT GRANULES SEEN ARE PERIPHERAL BLOOD SMEARS
  • ALSO ABNORMALITIES IN MELANOCYTES (CAUSING ALBINISM), CELLS OF THE NERVOUS SYSTEM (NERVE DEFECTS) AND PLATELETS (BLEEDING DISORDERS) ARE SEEN
  • THE IMPLICATED GENE ENCODES A LARGE CYTOSOLIC PROTEIN CALLED LYST RESPONSIBLE FOR LYSOSOMAL TRAFFICING
ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

- A DISEASE CAUSED BY THE RETROVIRUS HUMAN IMMUNODEFICIENCY VIRUS (HIV) AND IS CHARACTERIZED BY PROFOUND IMMUNOSUPPRESSION (PRIMARILY AFFECTING CELL-MEDIATED IMMUNITY) THAT LEADS TO OPPORTUNISTIC INFECTIONS, SECONDARY NEOPLASMS AND NEUROLOGIC MANIFESTATIONS
  - TRANSMISSION OCCURS UNDER CONDITIONS THAT FACILITATE EXCHANGE OF BLOOD OR BODY FLUIDS — SEXUAL TRANSMISSION, PARENTERAL TRANSMISSION, MOTHER-TO-INFANT TRANSMISSION

- NATURAL HISTORY:
  - ACUTE PHASE:
    - VIRUS ENTERS THROUGH MUCOSAL SURFACES AND EARLY INFECTION IS CHARACTERIZED BY INFECTION OF MEMORY CD4+ T-CELLS IN MUCOSAL LYMPHOID TISSUES (WITH DEATH OF MANY INFECTED CELLS)
      - BINDING MEDIATED BY GP120 TO CD4 AND OTHER CHEMOKINE CORECEPTORS LEADING TO FUSION VIA GP41
    - DENDRITIC CELLS CARRY THE VIRUS TO LYMPH NODES WHERE VIRAL REPLICATION OCCURS LEADING TO VIREMIA AND DISSEMINATION THROUGHOUT THE BODY
      - CAN CAUSE ACUTE HIV SYNDROME WHICH PRESENTS AS A FLU-LIKE ILLNESS (WITHIN 3-6 WEEKS)
    - ANTIVIRAL HUMORAL AND CELL-MEDIATED RESPONSES, SPECIFICALLY HIV-SPECIFIC CD8+ CYTOTOXIC T-CHELLS, RESULT IN A DROP IN VIREMIA

  - CHRONIC PHASE:
    - LYMPH NODES AND SPLEEN SERVE AS SITES OF CONTINUOUS HIV REPLICATION AND CELL DESTRUCTION
      - THERE ARE LITTLE SYMPTOMS DURING THIS TIME WHICH IS KNOWN AS THE CLINICAL LATENCY PERIOD

  - AIDS:
    - A BREAKDOWN IN HOST DEFENSE RESULTING IN SEVERE LIFE-THREATENING DISEASE AND DEVELOPING OF AIDS-DEFINING ILLNESSES
ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

• IN THE ABSENCE OF TREATMENT, MOST PATIENTS PROGRESS TO AIDS AFTER A CHRONIC PHASE LASTING 7-10 YEARS
  • RAPID PROGRESSORS – THE CHRONIC PHASE LASTS 2-3 YEARS
  • LONG-TERM NON-PROGRESSORS – REMAIN ASYMPTOMATIC FOR >10 YEARS WITH STABLE CD4+ COUNTS AND LOW LEVELS OF PLASMA VIREMIA (5-15%)
  • ELITE CONTROLLERS – HAVE UNDETECTABLE PLASMA VIRUS (1%)

• CLINICAL FEATURES:
  • OPPORTUNISTIC INFECTIONS – ACCOUNT FOR THE MAJORITY OF DEATHS IN UNTREATED PATIENTS
    • PNEUMONIA CAUSED BY THE FUNGUS PNEUMOCYSTIS JIROVECI (15-30%)
    • CANDIDIASIS – SEEN IN THE ORAL CAVITY, VAGINA AND ESOPHAGUS; ORAL CANDIDIASIS OFTEN HERALDS THE TRANSITION TO AIDS
    • CYTOMEGALOVIRUS – AFFECTS THE EYE AND GI TRACT CAUSING RETINITIS AND ESOPHAGITIS/COLITIS WITH ASSOCIATED ULCERATION, RESPECTIVELY
    • MYCOBACTERIAL INFECTION AND TUBERCULOSIS
    • CNS INFECTIONS INCLUDING CRYPTOCCOCCOSIS (MENINGITIS), TOXOPLASMA GONDII (ENCEPHALITIS) AND JC VIRUS (PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY)
ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

- TUMORS – SEEN IN 25-40% OF UNTREATED PATIENTS AND ARE OFTEN CAUSED BY ONCOGENIC DNA VIRUSES
  - KAPOSI SARCOMA
    - A VASCULAR TUMOR CHARACTERIZED BY A PROLIFERATION OF SPINDLE CELLS FORMING SLIT-LIKE VASCULAR SPACES
    - CAUSED BY THE KS HERPESVIRUS (KSHV) ALSO KNOWN AS HUMAN HERPESVIRUS 8 (HHV8)
    - IN HIV/AIDS, THE TUMOR IS WIDESPREAD AFFECTING THE SKIN, MUCOUS MEMBRANES, GI TRACT, LYMPH NODES AND LUNGS
  - LYMPHOMAS
    - B-CELLS LATENTLY INFECTED WITH ONCOGENIC VIRUSES SUCH AS EBV AND KSHV UNDERGO UNCHECKED PROLIFERATION IN THE SETTING OF SEVERE T-CELL DEPLETION PREDISPOSING PATIENTS TO MUTATIONS AND B-CELL LYMPHOMAS
      - THESE LYMPHOMAS TYPICALLY OCCUR IN EXTRANODAL SITES
      - THESE PATIENTS ARE ALSO PRONE TO RARE LYMPHOMAS THAT PRESENT AS MALIGNANT EFFUSIONS (PRIMARY EFFUSION LYMPHOMA)
      - HODGKIN LYMPHOMA IS ALSO SEEN AND IS EBV-ASSOCIATED
    - BURKITT LYMPHOMA AND DIFFUSE LARGE B-CELL LYMPHOMA – RELATED TO PROFOUND GERMINAL CENTER B-CELL HYPERPLASIA THAT OCCURS IN HIV INFECTION (OFTEN ASSOCIATED WITH MYC AND BCL6 MUTATIONS)
  - CARCINOMA OF THE CERVIX AND ANUS
    - ASSOCIATED WITH HUMAN PAPILLOMAVIRUS (HPV) INFECTION
  - CENTRAL NERVOUS SYSTEM DISEASE
- HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) HAS GREATLY IMPROVED THE PROGNOSIS FOR THESE PATIENTS THOUGH THERE ARE SOME SIDE EFFECTS
AMYLOIDOSIS

• CONDITION ASSOCIATED WITH A NUMBER OF DISORDERS IN WHICH EXTRACELLULAR DEPOSITS OF FIBRILLAR PROTEINS ARE RESPONSIBLE FOR TISSUE DAMAGE AND FUNCTIONAL COMPROMISE

  • THESE ABNORMAL FIBRILS ARE PRODUCED BY THE AGGREGATION OF IMPROPERLY FOLDED PROTEINS
    • COMPOSED OF NON-BRANCHING FIBRILS EACH FORMED OF INTERTWINED POLYPEPTIDES IN A BETA PLEATED SHEET CONFORMATION
  • ALTHOUGH AMYLOID HAS THE SAME MORPHOLOGIC APPEARANCE, IT IS BIOCHEMICALLY HETEROGENEOUS (AT LEAST 30 DIFFERENT PROTEINS CAN AGGREGATE WITH THE APPEARANCE OF AMYLOID)

• THE THREE MOST COMMON FORMS OF AMYLOID ARE:
  • AL (AMYLOID LIGHT CHAIN) AMYLOID – MADE UP OF IMMUNOGLOBULIN LIGHT CHAINS
  • AA (AMYLOID-ASSOCIATED) AMYLOID – DERIVED BY PROTEOLYSIS FROM A LARGER PRECURSOR IN THE BLOOD CALLED SAA (SERUM AMYLOID ASSOCIATED) PROTEIN
  • BETA-AMYLOID PROTEIN – DERIVED BY PROTEOLYSIS FROM A LARGER TRANSMEMBRANE GLYCOPROTEIN CALLED AMYLOID PRECURSOR PROTEIN
AMYLOIDOSIS

• PRIMARY AMYLOIDOSIS: PLASMA CELL PROLIFERATIONS ASSOCIATED WITH AMYLOIDOSIS
  • THE MOST COMMON TYPE
  • AMYLOID IS OF THE AL TYPE AND IS USUALLY SYSTEMIC IN ITS DISTRIBUTION
  • CAUSED BY A CLONAL PROLIFERATION OF PLASMA CELLS THAT SYNTHESIZE ABNORMAL IMMUNOGLOBULIN MOLECULES – OCCURS IN 5-15% OF INDIVIDUALS WITH MULTIPLE MYELOMA
    • FREE UNPAIRED KAPPA OR LAMBDA LIGHT CHAINS ARE PRONE TO AGGREGATING AND DEPOSITING IN TISSUES AS AMYLOID (LAMBDA 6X MORE LIKELY THAN KAPPA)
    • OF NOTE, NOT ALL PATIENTS WITH AL AMYLOID HAVE MULTIPLE MYELOMA OR ANY OTHER B-CELL NEOPLASM

• REACTIVE SYSTEMIC AMYLOIDOSIS
  • AMYLOID IS OF THE AA TYPE AND IS SYSTEMIC IN ITS DISTRIBUTION
  • SECONDARY TO AN ASSOCIATED INFLAMMATORY CONDITION
    • SAA PROTEIN SYNTHESIS BY LIVER CELLS IS STIMULATED BY INFLAMMATORY CYTOKINES SUCH AS IL-6 AND IL-1

• ENDOCRINE AMYLOID
  • FOUND IN CERTAIN ENDOCRINE TUMORS (MEDULLARY THYROID CARCINOMA, PANCREATIC ISLET CELL TUMORS) AND ARE OFTEN DERIVED FROM HORMONES
AMYLOIDOSIS

- HEREDOFAMILIAL AMYLOIDOSIS – A VARIETY OF FAMILIAL FORMS HAVE BEEN DESCRIBED; TWO OF THE MOST COMMON ARE:
  - FAMILIAL MEDITERRANEAN FEVER
    - AUTOSOMAL RECESSIVE
    - AMYLOID IS OF THE AA TYPE, SUGGESTING IT IS RELATED TO RECURRENT BOUTS OF INFLAMMATION
    - PATIENTS PRODUCE EXCESSIVE AMOUNTS OF IL-1 RESPONSE TO INFLAMMATORY STIMULI AND IS CHARACTERIZED BY FEVER AND SEROSAL INFLAMMATION
  - A GROUP OF AUTOSOMAL DOMINANT FAMILIAL DISORDERS IS CHARACTERIZED BY DEPOSITION OF AMYLOID DERIVED FROM MUTANT TRANSTHYRETIN (TTR)
    - DEPENDING ON THE MUTATION, AMYLOID CAN DEPOSIT IN DIFFERENT ORGANS

- HEMODIALYSIS-ASSOCIATED AMYLOIDOSIS
  - PATIENTS ON LONG-TERM HEMODIALYSIS CAN DEVELOP AMYLOIDOSIS DERIVED FROM BETA2-MACROGLOBULIN
  - WITH NEW DIALYSIS FILTERS, THE INCIDENCE OF THIS COMPLICATION HAS DECREASED SUBSTANTIALLY

- AMYLOID OF AGING
  - THE SYSTEMIC DEPOSITION OF AMYLOID IN ELDERLY PATIENTS
  - THERE IS DOMINANT INVOLVEMENT AND DYSFUNCTION OF THE HEART
  - DERIVED FROM NORMAL TRANSTHYRETIN (TTR)
AMYLOIDOSIS

• MORPHOLOGY:
  • INVOLVED ORGANS MAY BE ENLARGED AND THE TISSUE APPEARS GRAY AND HAS A WAXY, FIRM CONSISTENCY
  • HISTOLOGICALLY, THE DEPOSITION IS ALWAYS EXTRACELLULAR AND SLOWLY ENCROACHES UPON AND DESTROYS THE CELLS (PRESSURE ATROPHY)
  • WITH H&E STAIN, AMYLOID APPEARS AS AN AMORPHOUS, EOSINOPHILIC, HYALINE, EXTRACELLULAR SUBSTANCE
  • WITH CONGO RED STAINING, AMYLOID SHOWS AN APPLE GREEN BIREFRINGENCE WHEN OBSERVED BY POLARIZING MICROSCOPY
  • SUBTYPING OF AMYLOID IS MOST RELIABLY DONE BY MASS SPECTROSCOPY

• CLINICAL FEATURES:
  • AMYLOIDOSIS CAN BE CLINICALLY SILENT PRODUCING NO CLINICAL MANIFESTATIONS OR IT MAY CAUSE SERIOUS CLINICAL PROBLEMS AND EVEN DEATH
  • RENAL INVOLVEMENT GIVES RISE TO PROTEINURIA/NEPHROTIC SYNDROME, CARDIAC INVOLVEMENT GIVES RISE TO CONGESTIVE HEART FAILURE AND CONDUCTION ABNORMALITIES, GI INVOLVEMENT INCLUDES TONGUE ENLARGEMENT AND MALABSORPTION/DIARRHEA AND VASCULAR INVOLVEMENT CAUSES VASCULAR FRAGILITY AND BLEEDING
  • THE PROGNOSIS FOR GENERALIZED AMYLOIDOSIS IS POOR, HOWEVER, PATIENTS WITH REACTIVE SYSTEMIC AMYLOIDOSIS DO SLIGHTLY BETTER IF THE UNDERLYING CONDITION IS CONTROLLED
AMYLOIDOSIS