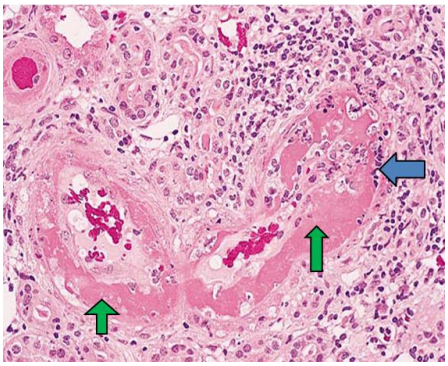
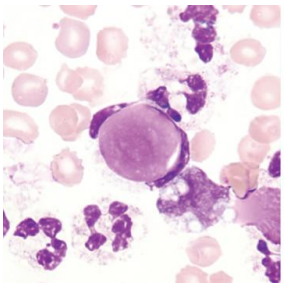
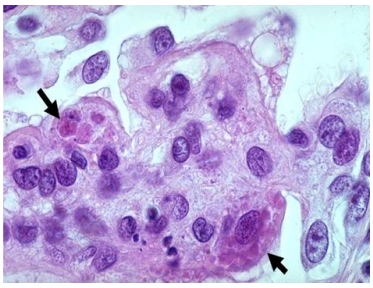
Unit IX – Problem 4 – Pathology: Pathogenesis of SLE

- **Pathogenesis of SLE:**
  1. **There is genetic susceptibility**: by the presence of genes which make the patient more prone to develop the disease. These genes include:
     - Immunoregulatory genes.
     - HLA-DR2 and HLA-DR3
     - Complement deficiency (C1q, C2 and C4). Notice that these fragments are part of the classic complement pathway.
     - FCγRIIb polymorphism.
  2. When a patient develops an autoimmune disease, there will be ups and downs of the condition which are mediated by **external triggers:**
     - UV-radiation.
     - Infections.
     - Gender.
     - Smoking.
  3. Notice that both genetic and external factors will lead to **increased apoptosis (programmed cell death) and deficiency in clearance of apoptotic bodies.**
  4. All of the above will result in **failure of self-tolerance, self reactive B and T-cells and generation of autoantibodies leading to the formation of immune complexes.**
  5. These immune complexes will stimulate dendritic cells to produce type-I interferons leading to stimulation of B and T cells → **high levels of autoantibodies (IgG).**
  6. Vasculitis and nephritis are commonly seen in type-III hypersensitivity which is responsible of SLE (there are circulating **immune complexes which will be deposited in many different areas in the body**).
- **Mechanisms of tissue injury by autoantibodies:**
  - **Type-III hypersensitivity (deposition of immune complexes):** commonly resulting in lupus nephritis and vasculitis:
    - ✓ Anti-DNA is detected in glomeruli by immunofluorescence.
    - ✓ There will be reduced serum C3 and C4 with granular immunofluorescence deposits of complement and immunoglobulin in glomeruli.
    - ✓ Mechanism of vasculitis:
      1. *Phase-I*: formation of immune complex (when antigens bind to antibodies which are secreted by plasma cells).
      2. *Phase-II*: deposition of the immune complex in the endothelial wall of the vessel.
      3. *Phase-III*: immune complex-mediated inflammation with platelet aggregation.
    - ✓ Histologic characteristics of vasculitis:
      - ❖ There are inflammatory cells in the wall of blood vessels.
      - ❖ Pinkish material representing fibrinoid necrosis.
      - ❖ Some blood vessels are congested with thrombosis.



  - **Type-II hypersensitivity (autoantibody-mediated):** commonly resulting in cytopenias such as autoimmune hemolytic anemia and thrombocytopenia (ITP). How cells get destroyed?
    - ✓ Phagocytosis by splenic macrophages via binding to Fc receptors.
    - ✓ Antibody dependent cell-mediated cytotoxicity.

- **Demonstration of ANA binding to cell nuclei:**
  - **In vivo**: hematoxyphil bodies in biopsies (image: right)
  - **In vitro**: LE cell (nucleus of a neutrophil around a homogenous pink-staining nucleus – image: left).

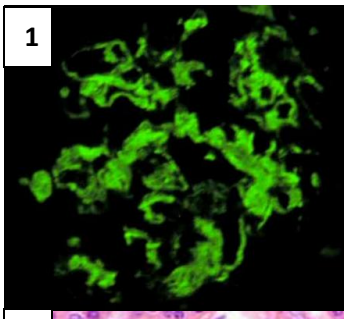
- **Lab investigations show low serum C3, C4 (Why?)**
  - Due to the activation of classical pathway of complement system and increased utilization.
- **Lab investigation show:**
  - Decreased white blood cells (leucopenia).
  - Decreased lymphocytes (lymphopenia).
  - Decreased platelets (thrombocytopenia): resulting in ITP.
  - Increased ESR (which is associated with inflammation).
  - Positive direct Coomb's test.
  - Autoimmune hemolytic anemia.
- **Antibodies in SLE:**
  - Antinuclear antibody (ANA): detected by ELISA or indirect immunofluorescence.
  - Anti-dsDNA antibody.
  - Anti-Sm antibody: highly specific for SLE.
  - Anti-phospholipid antibodies: they lead to prolongation of APTT.
- **There is multisystem involvement in SLE:**

Blood vessels	Vasculitis, atherosclerosis
Kidney	Nephritis
Skin	Erythematous rash
Heart	Pericarditis, myocarditis and endocarditis
Joints	Synovitis
CNS	Small vessels angiopathy
Lungs	Pleuritis and interstitial fibrosis
Liver	Portal tract inflammation
Polyserositis	Effusions

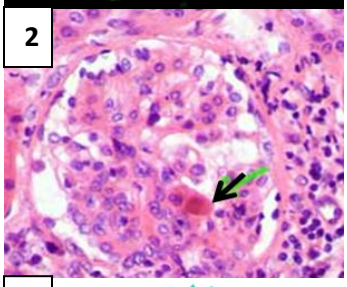
- **Criteria for diagnosing SLE (according to: American Rheumatoid Association): at least 4 are required:**
  1. Malar/ butterfly rash.
  2. Discoid rash.
  3. Photosensitivity (sensitivity to sunlight).
  4. Oral ulcers.
  5. Arthritis.
  6. Serositis (pleuritis and pericarditis).
  7. Renal disorder (nephritis).
  8. Neurologic disorder.
  9. Hematologic disorder (autoimmune hemolytic anemia, leucopenia, lymphopenia and thrombocytopenia).
  10. Immunologic
  11. Presence of high titer of antinuclear antibody (ANA) in the serum of the patient.
- **Nephritis:**
  - It is the most serious asymptomatic manifestation of SLE (leading to death within 10 years of diagnosing a patient with SLE).

- Classification is histologic (focusing on glomerular disease) and renal biopsy is useful in planning management.
- **Remember that nephrotic syndrome is characterized by:**
  - ✓ Hypoalbuminemia.
  - ✓ Proteinuria (> 3.5 grams/day).
  - ✓ Hyperlipidemia.
  - ✓ Edema.
- **ISN/RPS classification of lupus nephritis:**
  - ✓ Class-I (minimal mesangial lupus nephritis – image: 1): glomeruli appears to be normal when viewed by light microscope but mesangial immune deposits –composed of immunoglobulins or complement- are found when using immunofluorescence.
  - ✓ Class-II (mesangial proliferative lupus nephritis – image: 2 and notice that the arrow is pointing to hematoxyphil body): purely mesagnial hypercellularity of any degree or mesangial matrix expansion is seen when using light microscope. In addition, there are mesangial immune deposits.
  - ✓ Class-III (focal proliferative lupus nephritis – image: 3): involving < 50% of all glomeruli
    - ❖ Segmental (involving only part of the glomerulus) and/or global (involving the whole glomerulus).
    - ❖ Focal subendothelial immune-complex deposits.
    - ❖ Mild microscopic proteinuria and hematuria.
  - ✓ Class-IV (diffuse proliferative lupus nephritis – image: 4): involving > 50% of all glomeruli (global)
    - ❖ Wire-loop lesions: subendothelial immune complex deposits.
    - ❖ Moderate-severe: hematuria, proteinuria, hypertension and renal insufficiency.
  - ✓ Class-V (membranous glomerulonephritis – image: 5): global or segmental subepithelial immune deposits (with spikes) resulting in nephrotic syndrome.
  - ✓ Class-VI (advanced sclerosing lupus nephritis): ≥90% of glomeruli are globally sclerosed without residual activity:
    - ❖ There are signs of nephrotic syndrome.
    - ❖ Microscopic hematuria and hypertension may also be seen.
    - ❖ Plasma creatinine is usually normal or slightly elevated.

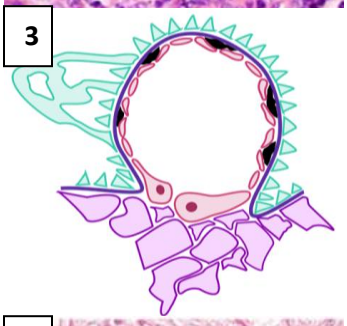
1



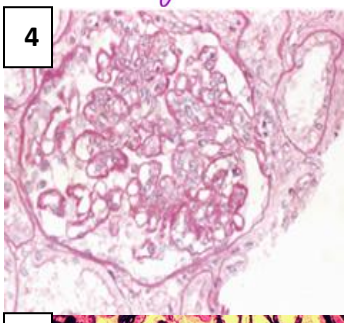
2



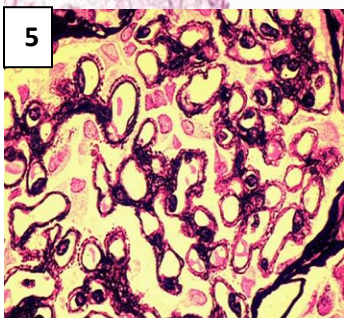
3



4

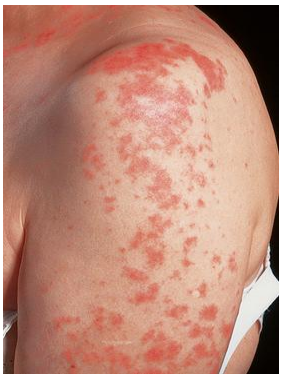
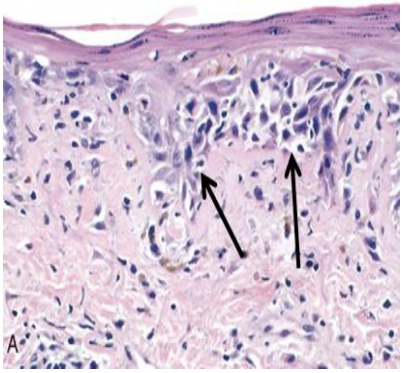


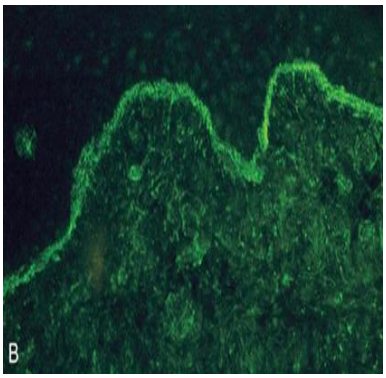
5



Notice that class III, IV and IV should be treated with aggressive immunosuppression because there is a high risk of end-stage renal disease if patient is left untreated.

- **Skin lesions:**
  - **Image (left):** a photosensitive skin eruption (طفح جلدي حساس لضوء الشمس) in a female with SLE (notice the sparing of the skin beneath her shoulder straps because this area was not exposed to sunlight).
  - **Image (middle):** H&E-stained section of the skin showing liquifactive degeneration of the basal layer of the epidermis and edema at the dermo-epidermal junction (arrows).
  - **Image (right):** immunofluorescence micrograph stained for IgG reveals deposits of immunoglobulins along the dermo-epidermal junction.



Cardiopulmonary manifestations:

- **Pulmonary**: pleuritis (with or without pleural effusion) and interstitial fibrosis.
- **Cardiac**: pericarditis, myocarditis or endocarditis:
  - ✓ Endocarditis (see the image below): characterized by single or multiple 1-3 mm warty deposits (ترسبات تشبه الثآليل) on any heart valve, distinctively on either surface of the leaflets; can lead to valvular insufficiencies, most commonly of the mitral or aortic valves, or to embolic events.