Immunopathology

Q). SLE. CF — 30y female
butterfly rash on face,
Knee joint pain, chest pain,
photosensitivity.

Q) diagnosis? SLE.
Q) Etiopathogenesis?
Q) specific diagnostic criteria
Q) morphology of kidney. / Spleen.
Q) Anti nuclear ab.
Q) Antiphl ab. Q) LE Bodies & LE cell. Hematoxylin bodies. Q) Tart cell?
Q) Morphology of other organs in SLE.

Etiopathogenesis

- SLE is a chronic autoimmune d/s involving multiple organs, characterized by presence of vast array of Auto Ab particularly - Antinuclear ab (ANA), in which injury is mainly caused by deposition of Immune complexes & binding of Ab to various cells & tissues.

- Chronic + remitting + relapsing.
- predominantly affects woman (9:1)
- age - 20s - 30s.
- can affect any organ.
  mainly - skin, kidney, joints, heart, Serous membrane.

Etiopathogenesis

The fundamental defect in SLE is failure of mechanisms that maintains self tolerance.

1. Genetic factors
2. Immunologic factors.
3. Environmental factors.

Genetic factors:

1. * familial association - family members have ↑ risk of SLE
   - high rate of concordance in monozygotic that dizygotic twins.
2. * HLA association → risk of SLE when HLA-DR2 / HLA-DR3 alleles are there. (HLA)
3. * Genetic deficiency → of early complements.
   $C1q$, $C2$, $C4$
   lead to.
   - defective phagocytic clearance of apoptotic cells.
   - Impaired removal of immune complexes by mononuclear phagocytic system.
4. * polymorphism in Fc FcγIIb inhibitory receptor.
   ↓
   Increased activity of B cell activation

② Immunological factors.

① failure of self tolerance in B cells due to defective elimination of self reactive B cells.

- due to defects in central & peripheral tolerance.

↓

↑ autoreactive B cells.

② activation of $CD4^+$ T cells. specific for nucleosomal Ag, that has escaped tolerance.

③ Type 1 interferon – IFN-α is ↑ in SLE, produced in dendritic cell.

④ Nuclear DNA/RNA in IC

↓

via engagement of TLR

↓

further activation of B cells.

↓

↑ production of antinuclear autoantibodies.

Normally. Microbes → engage → TOLL like receptor.

SLE.

Nucleic acid mimicking microbe → TLR → Type 1 IFN

⊕ B cells → pathologic Auto Ab

Environmental.

- UV exposure.
- sex hormones – 10x in women of reproductive age than men
- drugs – isoniazid, D penicillamine.
- cigarette smoking.

Pathogenesis. – Explanation.

genetic susceptibility. → autoreactive B & T cells.

apoptosis – defective clearing → persistence of nuclear Ag

→ anti nuclear auto Ab

→ IC Ag–Ab.

→ binds to Fcγ receptors on B & DCs & get endocytosed

→ inside, DNA/RNA from IC binds & ⊕ TLR 7, TLR 9

→ ⊕ B cells & DCs

→ plasma cytoid DCs produce IFN-α.

→ ⊕ B cells.

→ plasma cells → auto ab.

persistent production of IgG auto ab.

Robbins

Genetic factors

HLA associated susceptibility gene {HLA-DR2, 3}

failure of self tolerance

B cells

T cells

B & T cells specific for self nuclear Antigens

Environmental factors

Sex hormone, UV radiation, Smoking, drug

normal tissue

apoptosis

defective clearance of apoptotic bodies

increased burden of nuclear Antigens

anti-nuclear antibodies

Immune complex

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Endocytosis of Ag-Ab-complex

✓TLR engagement by nuclear Antigens

✓TLR ⊕ of B cells & DCs

✓⊕ of B cells & T cells by IFN-α

B cell

Dendritic cell

(plasmacytoid DC)

IFN-α

T cell

plasma cell

persistent production of IgG autoab

B cell

correct figure DC

TLR

Ag

Auto Antibodies.

- Hallmark of SLE is the production of auto Ab.

Importance.

1. useful for diagnosis & management of patients
2. responsible for pathogenesis of tissue damage.

Types

Auto ab are against →

1. plasma proteins → complement components, clotting factors.
2. proteins, phospholipid complex.
3. cell surface Ag → Lympho, neutro, RBC, platelet
4. Intracellular cytoplasmic components → mitochondria, microtubules, lysosome etc..
5. nuclear DNA, RNA, histones.

Antinuclear Antibody (ANAs)

These are directed Against nuclear self Antigens

4 categories, based on their specificity to:

1. DNA
2. Histones
3. Non histone proteins bound to RNA
4. Nucleolar Ag.
5. Ribonucleoprotein.

Most widely used method for detection of ANA's is

⇓

Indirect Immunofluorescence

↓ ↓

Pattern of nuclear fluorescence suggest type of Ab present in serum.

- Homogenous / diffuse nuclear staining → Common in SLE.
  - reflects Ab to: ds DNA, chromatin, Histones, nucleosomes
- speckled pattern → m/c pattern, least specific.
  - ab to (non-DNA) nuclear components like Sm Ag; RNP, SSA & SSB Ag.
  - seen in SLE
- Others: centromeric, peripheral/Rim, Nucleolar patterns.

☆ Ab to ds DNA & Sm-Ag [directed] most specific & diagnostic of SLE.

Other Ab in SLE:

Ag against

- Blood cells → RBC's, Lymphocytes, platelets.
- proteins-in complex with PL → anti-phospholipid Ab's

type of ANA	Ag recognized	
Anti-ds DNA	ds DNA	most sensitive & specific
Anti-Sm.	non histone protein, bound to RNA	most specific
anti-histone Ab	Histone assn DNA	
Anti-RO (SSA)	U1 RNP	specific Ab in neonatal Lupus with congenital Heart Block.

ANA's → Most Sensitive Antibodies

Mechanism of Tissue Injury

(1) Immune Complex deposition {Type III HSR}

- most systemic lesions are caused by Immune complexes deposition.
  - ↓ granular deposits of IC, complement

(2) Auto-Ab mediated destruction of Blood cells. {Type II HSR}

- blood cells are tagged by autoab.
  - ↓ phagocytosis & destruction {cytopenia}

m/c → (ITP)

(3) Antiphospholipid Antibody Sx.

✓ recurrent thrombosis
✓ recurrent spontaneous miscarriage
✓ cerebral / other ischemia.

MORPHOLOGY

The most characteristic lesions of SLE are due deposition of IC in

- blood vessel — read further.
- kidney ✓
- connective tissue
- skin

KIDNEY — Lupus Nephritis.

- Kidney involvement is seen in 50% of SLE patients.

Pathogenesis of glomerulonephritis in SLE

dsDNA + anti-dsDNA ab
↓
IC
↓
deposition in glomeruli
↓
inflammation
↓
proliferation of cells: mesangial, endothelial, epithelial cells

Morphological Classification of Lupus Nephritis.

- 6 patterns are recognized.

Class-I - Minimal mesangial L.N
Class II - mesangial proliferative L.N
Class III - focal L.N
Class IV - diffuse L.N
Class V - membranous N.L
Class VI - advanced sclerosing L.N

My mother fights dragons, murder Aliens.

Class-I Minimal mesangial

- best prognosis but least common.
- Characterized by Immune complex deposition in Mesangium.
↓
demonstrated by IF & EM (Imx)

★ No structural changes in (QQ) Light microscopy

Class II mesangial proliferative

- Characterised by
→ mesangial cell proliferation } mild-moderate
→ mesangial matrix deposition ↑

Glomerular capillaries are not ★ involved (QQ)

on (IF) → granular deposits on mesangium
↓
IC, Ig, Complements

Class III Focal L.N.

- Less than 50% of Glomeruli are involved {in number}.

ie, FOCAL

Glomeruli involved can be

Segmental
↓
only portion of the glomeruli is affected

Global
↓
the entire part of Glomeruli affected.

proliferation of:

- endothelial cells
- mesangial cells.
- parietal epithelial cell → crescent formation.

→ Leukocyte accumulation.

→ fibrinoid capillary necrosis

→ intracapillary hyaline thrombi

⇒ focal, necrotizing lesions & crescent formation.

Class IV – Diffuse L.N

- m/c & most severe form – poor prognosis.
- m/c pattern associated with **wire loop pattern** (QQ)
- >50% glomeruli are affected.
- Marked proliferation of: mesangial, endothelial, parietal epithelial cells. {crescent formation}

Sub ENDOTHELIAL – IC deposits.

↓

Causes {circumferential thickening of capillary walls

↓

Indicate active ds

WIRE LOOP LESION ⇒ poor prognosis

- IC are diluted by IF & EM.
- pt's symptomatic – hematuria, proteinuria.

- wire loop lesions are also seen in - 3, 4, 5 m/c.

indicate active ds → poor prognosis.

Class - V Membranous.

- m/c associated with **Renal vein thrombosis.**
- **Diffuse** thickening of capillary walls.

↓ due to **Sub-EPITHELIAL IC**

- ↑ production of Basement membrane.

→ (nephrotic syndrome like)

severe proteinuria.

Class VI advanced Sclerosing.

- Sclerosis of >90% of Glomeruli

* **WORST prognosis**

→ End stage disease.

Q **CVS morphology** Impt!

Other Questions