SYSTEMIC LUPUS ERYTHEMATOSUS: CURRENT CONCEPTS AND CLINICAL PEARLS

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Listen to the Patient

- **Concepts**
  - Diagnosis
  - Immunopathogenesis

- **Clinical Pearls**
  - Disease Manifestations
  - Complications
  - Therapy
The patient

- 49/M/F Longstanding manic-depressive on Lithium
- Recent admission to Nephrology for “transient ARF” attributed to poor oral intake
- Fever, cough and SOB x 2-3 weeks
Relevant Findings

- Diffuse alopecia, pale, hemoptysis
- Tachypnoeic SpO2 85% (100% NRM)
- Pancytopenia (TW 2.35x10^9/L, Hb 6.2g/dL, plt 80K)
- ANA 1:640, anti-dsDNA>250IU (<25IU)
Diagnosis

- SLE is frequently overlooked
  - Up to 2 year delay

- Protean manifestations that evolve over time

- Inappropriately diagnosed
  - Narain et al: 0f 263 presumed SLE, 50% confirmed SLE, 30% +ANA w/o AI disease

- Classification criteria ≠ Diagnostic criteria
  - Use in clinical practice → underdiagnosis
Diagnosis
Why Me?
Immunopathogenesis

Environment
Sun exposure
Infections
Hormones

Triggers

Genetic susceptibility → Autoimmunity → Tissue Damage

Pre-clinical SLE → Clinical SLE

Sx → Dx

Amplification and determinant spreading

Crow M. Arth Res Ther 2009;11:245
Immunopathogenesis

Arbuckle et al. NEJM 2003; 349:1526
What went wrong?

Environmental triggers

Multiple genes

Neuro-endocrine system

Sex and sex hormone milieu

Immune dysregulation

Defective clearance mechanisms

Loss of suppressor activities and idioype control

DNA, apoptotic cells

Defective clearance

Autoantibodies

Immune complexes

Complement activation

Tissue injury and damage

Over-responsive troops

Susceptibility to damage

Poor Garbage disposal

Poor defence

C2
C4
C1q
TREX1

IRF5
PTPN22
STAT4
FCGR2A
IRAK1
TNFAIP3

HLA-DR
PTPN22
BLK
BANK1
FCGR2A
PXK
LYN
OX40L

KLK1
KLK3
ITGAM
Pearl #1: Clinical Manifestations

- Galloping disease: organ to organ
- Accrue “classification criteria” over time

Hopkins cohort:
1/3 had renal involvement at diagnosis →25% 1-5y →20% >5y
Lupus does not burn out!
New manifestations after menopause, ESRD

Reyes et al. Lupus 2010;191365
I. The Skin

i. The malar rash of SLE is not transient

ii. The clinical effects of UV exposure may be delayed by MONTHS

iii. Oral ulcers centred on the wetline and do not extend beyond VB
II. The Kidneys

i. Early response (↓ proteinuria) within 6m predicts long-term outcome

ii. Efficacy of other Rx
- Eurolupus Nephritis Study/
- MMF study/ ALMS Maintenance Study
- Blacks, Hispanics do better with MMF
- Whites, Asians → CYC

iii. Adjunctive Rx crucial!

Target BP<125/75mmHg, UTP<1g/d

Isenberg et al. Rheumatol 2010;49:128
The Patient

- Drowsy
- Not moving limbs well, no witnessed seizures
- CT Brain

DIAGNOSIS?
Not all lesions in SLE are inflammatory!
III. Antiphospholipid Syndrome

i. 30% of SLE patients have +aPL; 50% have APS within 10 years

ii. Any vascular bed can be affected

iii. Recognise associations NOT included in the classification criteria!
- Livedo reticularis
- Migraine
- Cardiac valve disease
- ↓platelets
- Nephropathy

Petri. Lupus 2010;19:419
Khamashta NEJM 1995
Pearl #2: Complications

I. Increased CV Disease

SLE is an independent risk factor for atherosclerosis. 50x increase risk of CV disease in women 35-44y!

Roman M. NEJM 2003; 349:2399
Pearl #2: Complications
II. Increased Bone Disease

5x increase fracture rates in SLE
Inflammation contributes!
Pearl #2: Complications

III. Increased Cancer Risk

- Controversial area
- Recent large study 9547 SLE patients
  - Increased risk of cancer esp NHL
  - No strong association between IS use and cancer

<table>
<thead>
<tr>
<th>Type of malignancy</th>
<th>SIR Tarr [17]</th>
<th>SIR Bernatsky [18]</th>
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<tr>
<td>All types</td>
<td>0.89</td>
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<td>Breast</td>
<td>0.62</td>
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<td>Ovarial</td>
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<td>Cervix</td>
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<td>Hematological</td>
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<td>NHL</td>
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<td>Skin</td>
<td>0.04</td>
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<td>Lung</td>
<td>0.48</td>
<td>1.37</td>
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<td>Colorectal</td>
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<td>Gastric</td>
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<td>Oral</td>
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<td>Undetermined</td>
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<td>Urinary bladder</td>
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<td>1.23</td>
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<td>Hepatobiliary</td>
<td>0.67</td>
<td>2.60</td>
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The Patient

How to Manage?

- Pulse IV Methyprednisolone 3g, IV CYC, Plasma exchange
  - Persistent pulmonary hemorrhage x 4 weeks
- Followed by:
- IV Rituximab x 2 doses
  Stabilised over the next 8 weeks
  20\textsuperscript{th} week in hospital
Goal is **Remission**
- Treatment-free remission rare (3.4% Hopkins cohort)

- **Non-pharmacologic measures**
  - Patient education is key: Non-compliance → flares!
  - Avoid Sun & Smoking (↓ responsiveness to HCQ)
  - Vaccinations

- **Prednisolone is the problem**
  - Judicious use, prompt taper

- **Immunosuppressive regime *tailored* according to organ involvement**
Pearl #3: Therapy
Old Friends

**Hydroxychloroquine**

“Lupus Health Insurance”- M Petri

- Reduces SLE flares
  - Canadian HCQ Group. NEJM 1991;324:150

- Reduces incidence of nephritis
  - Fessler. A+R 2005;52:1473

- Diminishes likelihood of thrombosis
  - Petri. Sc and J Rheum 1996

- Synergistic effect with other Rx eg. MMF
Pearl #3: Therapy
Old Friends

Cyclophosphamide (CYC)

- Eurolupus trial:
  - Mini-pulse CYC 0.5g vs NIH regime
  - Equally efficacious, less toxic

- 10 y followup:
  - No difference in outcomes between groups (renal outcomes, death, damage scores)

- Generalisability to non-White populations?

Houssiau. ARD 2010;69:61
Pearl #3: Therapy
More Recent Friends

**Mycophenolate Mofetil**

- **2000**
  - Retrospective study:
    - Equally efficacious cf CYC

- **2005**
  - Open-label randomised trials:
    - Efficacy advantage of MMF over CYC- induction in mod severe LN
    - Equally effective in maintenance

- **2009**
  - Large, multinational RCT
    - Did not meet 1* endpoint of superiority over CYC – induction
    - Clear advantage over Azathioprine – maintenance

Ginzler NEJM 2005
Contreras NEJM 2005
ALMS ARD 2010
Pearl #3: Therapy
New Acquaintances
B cell Targets: Failures

Main lessons:
- Clinically heterogenous
- Immunologically complex
- No straightforward targets
- Relook at trial design
- Outcome measures refined
B cell Targets: Success

Belimumab
Pearl #3: Therapy
Other Targets

<table>
<thead>
<tr>
<th>Table 1. Summary of treatments and clinical trials in the treatment of SLE.</th>
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<td>Molecular target</td>
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<td>Immune cell-targeted therapies</td>
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<td>B cell tolerogen</td>
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<td>BAFF receptor, BCMA, TACI</td>
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The Changing Face of Lupus
The Final Word

NOTICE

THANK YOU
FOR NOTICING THIS
NEW NOTICE

YOUR NOTICING IT
HAS BEEN NOTED

AND WILL BE REPORTED TO THE AUTHORITIES