QUESTION 38 SLE

A 40-year-old woman with a 20-year history of systemic lupus erythamatosus (SLE) presents with severe anterior chest pain, dyspnoea and nausea.

Her SLE has manifested previously as arthritis, rash, mucosal ulceration and focal proliferative glomerulonephritis. She has had two miscarriages and delivered two normal children. Treatment has included hydroxychloroquine, prednis(ol)one in doses of 7.5 mg to 100 mg daily, intermittent cyclophosphamide and azathioprine. At presentation she is taking prednis(ol)one 7.5 mg daily and hydroxychloroquine.

Physical examination reveals obesity, pulse rate of 105/minute, blood pressure of 105/75 mmHg, normal heart sounds, and clear lung fields. The jugular venous pulse and pressure are obscured by fat.

Laboratory results show:

- **haemoglobin**: 124 g/L [115-165]
- **white cell count**: 3.4 x10^9/L [3.5-11.0]
- **lymphocytes**: 0.9 x10^9/L [1.5 – 4.0]
- **erythrocyte sedimentation rate (ESR)**: 35 mm/hr [0-20]

ECG shows ST-segment elevation in the anterior chest leads and sinus tachycardia. During the assessment, the patient develops ventricular fibrillation and dies. Which of the following is the most likely cause of her death?

A. Vasculitis involving the coronary arteries.
B. Libman-Sacks endocarditis with coronary artery embolisation.
C. Viral myocarditis.
D. Coronary atherosclerosis.
E. Pericardial effusion with tamponade.

**SLE**

**Pathologenesis & Etiology**

**Immune responses**

- Hyperactivity and hypersensitivity of T and B lymphocytes
- Ineffective regulation of antigen availability and of ongoing Ab responses
- Autoantibodies are directed against DNA/protein or RNA/protein complexes such as nucleosomes, nucleolar RNA and spliceosomal RNA

**Autoantibodies of SLE**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Prevalence</th>
<th>Clinical Utility</th>
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<tbody>
<tr>
<td>Antinuclear Ab</td>
<td>98%</td>
<td>Best screening test: repeated –ve test make SLE unlikely</td>
</tr>
<tr>
<td>Anti-dsDNA</td>
<td>70%</td>
<td>High titers are SLE-specific and in some patients correlate with disease activity</td>
</tr>
<tr>
<td>Anti-SM</td>
<td>25%</td>
<td>Specific for SLE, no definitely clinical correlation</td>
</tr>
<tr>
<td>Anti histone</td>
<td>70%</td>
<td>More frequent in drug induced lupus</td>
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**Pathology**

**Biopsy of affected skin**

Deposition of Ig at dermal-epidermal junction (DEJ). Injury to basal keratinocytes and inflammation dominated by T lymphocytes in the DEJ and around blood vessels and dermal appendages

**Renal Bx:**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>no histologic changes</td>
</tr>
<tr>
<td>2</td>
<td>proliferative changes confined to the mesangium</td>
</tr>
<tr>
<td>3</td>
<td>proliferative changes in -- if 10 – 50% of mesangium</td>
</tr>
<tr>
<td>4</td>
<td>diffuse proliferative glomerulonephritis affecting &gt; 50% of glomeruli</td>
</tr>
<tr>
<td>5</td>
<td>predominantly membranous changes with various degree of proliferation</td>
</tr>
<tr>
<td>6</td>
<td>End stage, scarred glomeruli</td>
</tr>
</tbody>
</table>

Treatment not recommended in pt with class I or II disease or with extensive irreversible changes.
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Aggressive treatment for rest of classes to prevent deterioration to ESRD

**Diagnosis**

- Based on characteristic clinical features and autoantibodies
- Combination of 4 or more of 11 criteria makes it likely that the pt has SLE
- ANA are +ve in >95% pts
- High titer IgG to double stranded DNA and Ab to Sm antigen are both specific for SLE

<table>
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<tr>
<th>System</th>
<th>Clinical manifestations</th>
</tr>
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</table>
| Musculoskeletal | 1) Intermittent polyarthritis  
2) Visible synovitis – suggest active disease  
3) If pain persists in a single jt (knee, shoulder, hip), consider ischemic necrosis of bone  
4) Myositis |
| Skin         | 1) Discoid lupus erthematosus  
- circular with slightly raised, scaly hyperpigmented erythematous rims and depigmented atrophic centers  
2) Systemic rash  
3) Subcutaneous lupus erythematosus  
  - scaly red patches similar to psoriasis or attacks of circular red rimmed lesions  
  - exquisitely photosensitive  
  - most have Ab to Ro (SS-A)  
4) Small painful ulcerations on oral or nasal mucosa are common |
| Renal        | 1) Nephritis  
- Asymptomatic  
2) Dangerous proliferative forms of glomerular damage – microscopic hematuria and proteinuria  
3) 50% develop nephrotic syndrome  
4) Membranous glomerular changes have better outcome |
| CNS          | 1) Diffuse CNS lupus  
  - cognitive dysfunction – difficulties with memory and reasoning  
2) Headaches are common (excruciating – indicate SLE flare)  
3) Seizures  
4) Psychosis – can be dominant manifestation of SLE  
  - must be distinguished from glucocorticoid-induced psychosis  
  - occurs in 1st week of glucocorticoid therapy at doses > 40mg  
5) Myelopathy  
  - high dose glucocorticoid therapy recommended  
  - should be started within hrs or few days of onset |
| Vascular     | 1) Prevalence of TIA, Strokes and MI is increased  
- Ab to aPL (antiphospholipids) – increased risk of vascular events  
- Ischemia in brain can be caused by focal occlusion or by embolization from carotid artery plaque or from fibrinous vegetations of Libman-Sachs endocarditis |
| Pulmonary    | Most common pulmonary manifestations  
1) Pleuritis with or without pleural effusion  
- Respond to NSAIDS |
I- f more severe, need steroids
2) Pulmonary infiltrates
   - difficult to distinguish from infection
3) Life threatening
   - interstitial inflammation → fibrosis, intraalveolar hemorrhage

**Cardiac**

Most frequent: pericarditis

More serious:
1) Myocarditis
2) Fibrinous endocarditis of Libman Sachs
3) Endocardial involvement can lead to valvular insufficiencies – mitral or aortic valves

Increased risk for myocardial infarction – accelerated atherosclerosis

**Hematologic**

Most frequent: Anemia (normochromic, normocytic – chronic illness)

Hemolysis
- rapid in onset and severe
Leukopenia (common)
Thrombocytopenia

**GIT**

Nausea, vomiting and diarrhea – manifestations of SLE flare

Diffuse abdominal pain
- autoimmune peritonitis

Increase in AST/ALT common when SLE active

Vasculitis involving intestine
- perforations,
- ischemia
- bleeding
- sepsis

**Ocular**

Most common: Sicca syndrome and conjunctivitis – rarely threaten vision

Serious manifestations
Retinal vasculitis and optic neuritis
Blindness can develop over days to weeks
Aggressive immunosuppression is recommended

Complications of glucocorticoid therapy include cataracts and glaucoma

**Laboratory tests**

Most important autoantibodies
1) ANA
   - positive in > 95%
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- few will develop ANA within 1 yr of Sx
- ANA negative SLE exists but very rare and is usually associated with other autoantibodies (anti-Ro or anti-DNA)

2) IgG to dsDNA
   - specific for SLE

3) Anti Sm
   - specific for SLE
   - assist in diagnosis
   - do not correlate with disease activity
   - identify pts at increased risk for venous or arterial clotting, thrombocytopenia and fetal loss

4) Anti-Ro
   - not suited for diagnosis but indicates increased risk for neonatal lupus, sicca syndrome and SCLE
   - women with child-bearing potential and SLE should be screened for anti phospholipid and anti-Ro.

Test for monitoring disease course

Hb level, platelets, urinalysis, serum levels of Cr or albumin

No reliable indicators or response or flare such as anti-DNA Ab, C3, soluble IL2, urinary monocyte chemotactic protein 1.

Treatment

Conservative therapies for non life threatening disease

Suppression of Sx

1) NSAIDS
   - For arthritis/arthralgias
   - At risk for NSAID-induced aseptic meningitis, HT and renal dysfunction

2) Anti malarials
   - Hydroxychloroquine, chloroquine and quinacrine
   - Reduce dermatitis, arthritis and fatigue
   - Potential retinal toxicity – should have ophthalmologist examinations

Life threatening SLE

Proliferative forms of lupus nephritis

1) Systemic glucocorticoids (0.5-2mg /kg per day orally)
   - Standard practice to initiate therapy for active, potentially life threatening SLE with high dose IV glucocorticoid pulses
   - Response within 24hrs

2) Cytotoxic drugs
   a) Cyclophosphamide (alkylating agent)
      - Standard drug for controlling life threatening active lupus nephritis
      - Responses begin 3 – 16 wks after tx initiated
      - High rate of irreversible testicular or ovarian failure, nausea, malaise, alpecia and frequent infections
   b) Azothioprine (purine antagonist)
      - Fewer side effects than cyclophosphamide
      - Cyclophosphamide more effective
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c) Mycophenolate mofetil
- lymphocyte-specific inhibitor of inosine monophosphate dehydrogenase

**Preventive measures**
Vaccinations
Prevent osteoporosis
Control of HT
Prevent atherosclerosis
Management of hyperglycemia and obesity

**Pregnancy and lupus**

- Increased risk (3X) of fetal loss
- 1st line: Prednisolone
  - placenta has enzyme that deactivates prednisolone
  - Maternal SLE should be controlled with prednisolone at the lowest effective doses for the shortest time required

- SLE pts with aPL and previous fetal loss
  - Treatment with heparin plus low dose aspirin has been shown in prospective controlled trials to increase significantly the proportion of live births

- Anti- RO +ve
  - Associated with neonatal lupus (rash and congenital heart block)
  - Vigilant monitoring of fetal heart rates

**Prognosis**

Poor:
High serum creatinine level (>124)
Anemia (<124)
Hypertension
Nephrotic syndrome
Hypoalbuminemia
Hypocomplementemia
aPL
African americans

Leading cause of death in 1st decade: systemic disease activity, renal failure and infections
Subsequently thromboembolic events