Lupus Involvement in Kidney Disease

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Meet “Jean”

Jean is a 23 year old female who was diagnosed with lupus at age 16. Her disease flares are usually marked by fever, swelling in her elbows and knees and a facial butterfly rash. Over the last few weeks, Jean has noticed that her urine appears “frothy”. She is also noticing swelling around her eyes in the morning and her legs and feet (worsens throughout the day).
What is SLE?

• Stands for systemic lupus erythematosis

• Systemic autoimmune disease where the body makes antibodies to cell nucleus products

• Hyperactivity and Hypersensitivity of the immune system

• Patients commonly present with general symptoms:
  – Fatigue, fevers, weight loss, joint aches/swelling

• Has the capacity to encompass every organ
What Causes Lupus?

• Predisposing genes
  • HLA II DR- (DR2, DR3) and DQ
  • HLA III C’2 and C’4
  • HLA-B8

Genetic + Environmental Factors

Abnormal gene expression

SLE
Epidemiology: Who gets lupus?

- Primarily a disease of young women
- Women to men ratio is 9:1
- African Americans and Hispanics affected more frequently than Caucasians (3:1)
- Concordance rates:
  - Identical twins 25 - 60%
  - Fraternal twins 2 - 9%
- Overall prevalence ~24 per 100,000 in U.S.
  - That’s ~1.4 million people!
What is Lupus Nephritis?

- Inflammation of the kidney due to lupus disease
- Wide spectrum of disease severity
How can I find out if I have lupus nephritis?
Lupus Nephritis

• Persistent **proteinuria** or cellular **casts**
• Clinical detection based on:
  – Hypertension
  – Proteinuria (protein in the urine)
  – RBC/WBC in urine (without infection, stones)
  – Elevated double-stranded DNA antibody titers
  – Low complements (C3, C4)
Lupus nephritis

• Abnormal urinalysis common finding – with or without renal impairment

• Proteinuria most frequently observed abnormality (80%)

• evidence of decreased renal function is uncommon in first few years of diagnosis but still present in up to 30%
Urinary casts

WBC/granular cast

Best detected in a first AM urine

RBC cast
Diagnosis

• Clinical manifestations

• Immunological tests

• Renal biopsy
Back to Jean

Jean decided to make an appointment with her rheumatologist. After checking blood and urine studies, he informs Jean that he is concerned she may have lupus nephritis. He has noted protein, blood cells, and casts in her urine. Her serum creatinine is also elevated signifying a decrease in her kidney function. He schedules her to be seen by a local nephrologist the following day.
Jean continued...

- Jean visits the nephrologist the following day who decides to admit her for further studies and treatments. He gives her a dose of intravenous (IV) corticosteroids. Jean is feeling better about her visit until Dr. nephrologist informs her that he would like to do a renal biopsy later in the afternoon to determine the next course of action. Jean is upset......
Renal Biopsy

- Usually a “percutaneous” needle biopsy with ultrasound guidance
- Rarely requires an “open” or laparoscopic procedure in the operating room
- Risk of bleeding or infection very low
- Minimum interruption of daily activities
- Important for guiding therapy and prognosis
2002 ISN/RPS Consensus Conference on the Classification of Lupus Nephritis

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Minimal mesangial lupus glomerulonephritis (LN)</td>
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<tr>
<td>Class II</td>
<td>Mesangial proliferative LN</td>
</tr>
<tr>
<td>Class III</td>
<td>Focal LN (Involving &lt; 50% of glomeruli)</td>
</tr>
<tr>
<td>Class IV</td>
<td>Diffuse LN (Involving &gt;= 50% glomeruli)</td>
</tr>
<tr>
<td>Class V</td>
<td>Membranous LN</td>
</tr>
<tr>
<td>Class VI</td>
<td>Advanced sclerotic LN (&gt; 90% sclerotic glomeruli)</td>
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</tbody>
</table>
Jean

Jean’s nephrologist informs her that she has Class IV lupus nephritis. In his opinion and the pathologist who interpreted the biopsy, there was only a mild degree of scarring but there was a lot of inflammation. For this reason, he recommends an aggressive course of action with 6 monthly IV cyclophosphamide infusions and continued oral corticosteroids.
Treatment

• Induction
  – Initial short course of therapy meant to control active disease

• Maintenance
  – Extended therapy administered after a disease has been brought under control
Corticosteroids

• Used during both induction and maintenance phases

• Given IV during induction and flares due to perceived “rapid action”

• Short-term use: increased appetite, high blood pressure, weight gain, acne, sleep disturbances

• Long-term use: bone loss (osteoporosis), increased diabetes risk, growth retardation (in children)
Cyclophosphamide (Cytoxan)

• Highly immunosuppressive and reserved for moderate to severe disease

• Most common protocol established by NIH in the 1980s. IV therapy once a month for 6 months for induction then every 3 months for 2 years for maintenance

• Side effects include anemia, low WBC count, and concerns for decreased fertility and future malignancies
Mycophenolate Mofetil (Cellcept®)

- Inhibits B and T cell function
- Taken orally
- Side effects include nausea, diarrhea, infections
- Recent trials suggest MMF may be as effective as IV cyclophosphamide in some patients with moderate to severe lupus nephritis
- Birth defects have been described
Azathioprine (Imuran)

• Relatively safe
• Used mostly for mild forms of lupus nephritis or maintenance therapy
• Safe in pregnancy
• Side effects: low WBC count, liver toxicity, slightly increased risk of malignancy (skin)
Rituximab (Rituxan®)

• Therapy targeted against B-Cells

• IV infusion given as 2 doses 2 weeks apart or 4 doses weekly for 4 weeks

• Side Effects include: low WBC count, anemia, serious infections, allergic response to infusion

• Results from LUNAR trial which compares the safety of Rituximab + MMF for maintenance versus MMF Failed to meet primary endpoint
Treatment Paradigm for Lupus Nephritis

Increase in serum creatinine > 30% and or proteinuria > 2g/day with active urine sediment

Three MP pulses +
Oral cyclophosphamide +
Oral prednisone (0.5 – 1 mg / Kg/day)

IV Cyclophosphamide pulses
Oral prednisone (0.5 – 1 mg/ Kg/day)
MP pulses in severe forms

Response

MMF +
Low dose prednisone

Azathioprine +
Low dose prednisone

Cyclosporine +
Low dose prednisone

Flare

No response

Rituximab or IVIG
Adjunct therapy

- Blood pressure control
  - Ace Inhibitors (ACEIs)
    - decrease proteinuria
    - prevent kidney scarring
  - Angiotensin Receptor blockers: (similar to ACEIs)
  - Diuretics

- Hydroxychloroquine (plaquenil)

- Vitamin D and calcium
  - Important for bone health
Checking on Jean

• After 6 months of cyclophosphamide, Jean’s nephrologist and rheumatologist determined that she was in remission. Her proteinuria resolved and kidney function returned to normal. Together they made a decision to begin maintenance therapy with MMF.
Jean

2 years later, Jean decided to discontinue all of her lupus medications without notifying her physicians. 9 months after this, she noticed her urine looked frothy and she was experiencing leg swelling again. She was only urinating a small amount each day and was experiencing horrible headaches. She decided to give her nephrologist a call.
Jean continued

To Jean’s disappointment, her nephrologist informed her that she was having a lupus “flare” and the nephritis was again active. Blood work determined that her kidney function was extremely low. She underwent a repeat renal biopsy. The results this time was Class VI lupus nephritis with widespread scarring. Due to the irreversibility of this scarring, Jean’s doctor recommended discussing options for kidney replacement therapy; dialysis or transplantation.
Jean

Jean was started on hemodialysis 3 days a week but was able to undergo transplantation of a kidney donated by her sister a few months later. Now at age 31, Jean has had a kidney transplant with good function in place for 5 years. She gave birth to a healthy infant 1 year ago and has not any active lupus symptoms for several years. She takes medicines each day to maintain her transplant but is thankful to be able to live a “normal” life
Treatment Goals

• Recognize early kidney involvement

• Induce & maintain remission & decrease risk of progression to End stage kidney disease (ESKD)

• Minimize treatment related toxicity (esp. during maintenance phase)
Prognosis

• Predictors of poor prognosis:
  – Black race
  – Male
  – Anemia
  – High serum creatinine (decreased kidney function)
  – Massive proteinuria
  – Glomerular scarring seen on biopsy
Prognosis

• > 30 yrs ago
  – few patients with severe class IV nephritis survived > 1-2 yrs
  – 50% with less severe disease died within 5 yrs

• Marked improvement in treatment
  – 10 – 15% progress to ESRD

• Transplant
  – recurrence rare
Questions left to Answer

• What are the most reliable ways to monitor remission?

• What really defines remission? Should everyone get follow kidney biopsies?

• How long should patients stay on maintenance therapy once remission is achieved?
How are researchers expanding knowledge?

- Following patients with long-term registries
- Enrolling patients in new clinical trials for novel therapies
- Studies to understand the genetic predisposition to this disease
- Studies evaluating the interaction between environmental and genetic factors
How Can I get Involved?

• Encourage people (esp. women) to talk about their health

• Be a mentor

• Help spread the word and encourage participation in clinical trials.

• Visit the lupus foundation of america for more information: www.lupus.org

• Visit www.clinicaltrials.gov and search lupus nephritis for information on current clinical trials