Case # 3

• 17-years-old female with systemic juvenile arthritis, was treated with low dose of chloroquine for 13 months, later increased to 500 mg/day for 5 months. Presented with persistent proteinuria:
  – UA: trace proteins, occult blood, granular casts
  – 24-hour urine protein 1.6 mg.
  – Serum creatinine level - 1.0 mg/dL.

• 24-hour urine sample, collected 2 and 4 months later:
  – Range – 1.5-1.8 mg of protein
  – Creatinine clearance – 70-73 mL/min
  – Serum creatinine level - 1.0-1.2 mg/dL
  – Urinary sediment - inactive.

• Kidneys - normal size on US.
• The biopsy was performed:
Summary of histologic findings

• Mild enlargement of glomeruli
• Cytoplasmic granules in visceral epithelial cells and endothelial cells
• Capillary endothelial cells with vacuolated cytoplasm
• Similar granules in proximal and distal tubular epithelial cells
Electron microscopy

- Whorled cytoplasmic inclusions
- No immune complex deposits
- No thickening of GBM
<table>
<thead>
<tr>
<th>Podocyte involvement</th>
<th>Enzyme Deficiency</th>
<th>Light Microscopy</th>
<th>Electron Microscopy</th>
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<td>Fabry’s disease</td>
<td>α-galactosidase A</td>
<td>Vacuolated podocytes, variable lipid accumulation in glomerular and vascular endothelium, mesangium, tubular epithelium, interstitial histiocytes, vascular monocytes</td>
<td>Multiple electron dense, multilamellated myelin figures (Zebra bodies)</td>
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<td>Infantile nephrosialidosis</td>
<td>α-neuraminidase</td>
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<td>Membrane-bound, almost empty vacuoles containing occasional granular and electron-dense material</td>
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<td>β-galactosidase</td>
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<td>Membrane-bound, empty inclusions</td>
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<td>I-Cell disease (Mucolipidosis, type 2)</td>
<td>N-acetylgalactosamine phosphotransferase</td>
<td>Vacuolated podocytes; vacuoles can be stained with Sudan black, alcian blue and colloidal iron</td>
<td>Membrane-bound empty vesicles containing occasional residual membranous structures</td>
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<td>Hurler’s syndrome</td>
<td>A-L-iduronidase</td>
<td>Finely vacuolated podocytes</td>
<td>Vacuoles containing granular material</td>
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<td>Niemann-Pick disease</td>
<td>Sphingomyelinase</td>
<td>Vacuolated foamy podocytes and intracapillary foam cells</td>
<td>Empty vacuoles and concentrically laminated, tightly packed myelin-like figures</td>
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<td>Farber’s disease</td>
<td>Ceramidase</td>
<td>Histiocytes with clear vacuoles, granulomas with lymphocytes and giant cells</td>
<td>Osmiophilic granules and bundles of rectilinear structures</td>
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*Bracamonte et al. AJKD 2006, 48(5), 844-50*
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Fabry’s Disease:

X-linked metabolic storage disorder
Long arm of the X chromosome (Xq22-24)

Deficiency of lysosomal α-galactosidase A

Progressive accumulation of globotriaosylceramide
Predilection for vascular endothelium and smooth muscle
Renal glomerular and tubular epithelium
Myocardium, valvular fibrocytes
Fabry’s Disease:

- **Diagnosis:**
  - Endothelial and epithelial cells with vacuolations and granular inclusions
  - Deposits of lipid material by EM “Zebra bodies”
  - Enzyme activity
  - Mutational analysis
Follow-up

• Features most suggestive of Fabry’s disease.
• No family history of Fabry disease
• Serum $\alpha$-galactosidase A activity within normal range, (33.2 U/ml: 8.8-42.6).
• No mutations in $\alpha$-galactosidase A gene.
• Chloroquine therapy discontinued and kidney function gradually returned to baseline level
Drug-induced phospholipidosis

- Amiodarone
- Chloroquine: ? mechanism
  - Can be sequestered in tissues: liver, spleen, kidneys, lungs
  - Inhibit phospholipase A and C
  - Ultrastructural lysosomal storage similar to Fabry disease
  - Reduction of α-galactosidase A activity
  - Animal studies relates kidney damage to chloroquine
Chloroquine-induced kidney damage

- Leads to reduction in GFR and creatinine clearance
- Worsening of pre-existing renal disease
- Damage can be seen as early as 4 weeks; May be reversible
- Inclusions in visceral epithelial cells, endothelial cells, mesanagial cells and infiltrating macrophages
Chloroquine-Induced Myopathy

- Proximal muscle weakness
- Normal creatinine kinase levels
- Curvilinear bodies, myelin bodies
- Similar to ceroid neuronal lipofuscinosis

Chloroquine induced cardiomyopathy

- Rare -- can be life threatening
- Can be associated with myocardial thickening, cardiac insufficiency and conduction disorders
- Diagnosis based on the clinical, hemodynamic and pathologic findings.

Other complications of Chloroquine

- Retinopathy, corneal deposits
- Hyperpigmentation
- Blood dyscrasia
- Encephalopathy, neuropathy, myopathy and impaired auditory function
It's quite serious.
Take this medicine
when it's available...
whenever you can
afford it.