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Disclosure

Takeda Pharmaceuticals
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Dr. Seetha Monrad
What’s new with GOUT?

1—changing epidemiology
2—treating to Sua < 6.0
3—Newer treatments
Top 10?

- Prevalence 2X incr
- Elderly
- OA/gout coexist
- Shorter prophy
- Persistent crystals
- UA < 6.0
- Newer XO inhib

- Chronicity
- Polycyclic
- Polyarticular
- Incr. tophi
- What initiates attacks?
OBJECTIVES

The student will achieve:

1. An understanding of the clinical presentation of crystalline synovitis.
2. Understanding of the importance of polarizing microscopy in making the diagnosis.
3. Understanding of the diagnostic value of other clinical data (history, tophi, radiographs, therapeutic response).
4. Understanding of the therapeutic approaches to crystalline synovitis, including pharmacologic information.
Types of Crystalline Synovitis

- Gout (Monosodium urate)
- Pseudogout (Calcium Pyrophosphate)
- Hydroxyapatite
- Calcium Oxylate
- Miscellaneous
Differential Diagnosis

- Infectious
- Inflammatory
- Degenerative
- Traumatic
- Neoplastic

Henry William Bunbury, Origin of the Gout
Gout - Outline

- Definition
- History
- Epidemiology
- Diagnosis
- Clinical Presentation
- Associated Conditions
- Pathophysiology
- Pathology

- Therapy
  - Acute
  - Preventive
  - Chronic
  - Pharmacology

- Prognosis

Source Undetermined
“Gout” defined:

Gout: a metabolic condition characterized by excessive accumulation of uric acid in the blood stream which may lead to deposition of uric acid crystals in and around the joints, painful attacks of arthritis, impairment of renal function, and kidney stones.
Gout terminology

- Gout
- Gouty arthritis
- Acute gouty arthritis
- Podagra
- Monoarticular
- Monocyclic
- Chronic gouty arthritis
- Chronic tophaceous gout
- Polyarticular
- Polycyclic
- Tophus (plural, tophi)
- Inter-critical gout
- (others)
- Lesch-Nyhan Syndrome
- Kelley-Seegmiller Syndrome
- HGPRT deficiency
- PRPP synthetase superactivity
- Xanthine oxidase
- Allopurinol
- Uricosuric
Gout historic aspects

Famous Gout Sufferers
A. Martin Luther (1483-1546).
B. Francis Bacon (1561-1626).
C. Michelangelo (1475-1564).
D. Benjamin Franklin (1706-1790).
E. King James I (1566-1625).
F. Samuel Johnson (1709-1784).
G. William Pitt (1759-1806).
I. Isaac Newton (1643-1727).
Clinical Aspects/Epidemiology

- Hyperuricemia w/o sx (≥ 80%)
- Acute gouty arthritis
- Chronic gouty arthritis (aka, tophaceous gout)
- Associated conditions (obesity, DM, hyperlipidemia, HTN, atherosclerosis, alcohol, acute illness, pregnancy, post-operative)
- Negative association (SLE, RA, amyloid, ?dialysis)
- Renal disease
  - urate nephropathy
  - acute uric acid nephropathy
  - calculi
Hyperuricemia (>7.0 mg/dl)

- Prevalence rate of 5-10% in adult men
- >80% of hyperuricemic individuals have no associated gout
- Hyperuricemia is associated with hypertension, cardiovascular, cerebrovascular, renal diseases and metabolic syndrome
Gout epidemiology

- Asymptomatic Hyperuricemia is common
- All patients with gout have hyperuricemia chronically
- Gout is caused by hyperuricemia
- Acute gouty arthritis patients may have hyperuricemia (80%)
- Prevalence of gout ~ 1% of men
- Estrogen is uricosuric
Hyperuricemia Causes

Under-excretion (90% of cases)
- dehydration, starvation, ketosis (post-op)
- renal abnormality (RTA)
- drugs: diuretics low-dose aspirin
- toxins, ethanol, lead
- hypothyroidism

Over-production (10% of cases)
- ethanol
- HGPRT or G6PD deficiency
- PRPP synthetase superactivity
- myeloproliferative disorders
- psoriasis
Acute Gouty Arthritis

- Abrupt onset, often at night
- Subsides completely
  - 3-5 days (with Rx);
  - 10-14 days (with no Rx)
- 75% in the first MTP joint
- Urate crystals in WBCs in synovial fluid
- May have hyperuricemia (80%)
- Usually monoarticular and monocyclic
How does this fit together?

- Xanthine oxidase = XO
- Conversion of hypoxanthine to xanthine and xanthine to uric acid
- Allopurinol inhibits XO (competitive inhibitor)

- XO has Multiple sites of action
- Competes with 6MP and azathioprine
Metabolic basis of hyperuricemia

- Only 1:200 cases of gout has identifiable enzymatic defect

- HGPRT deficiency
  - Complete=
  - Partial=

- PRPP synthetase superactivity

- Others?

- Numerous mutations characterized

- Lesch-Nyhan Syndrome
- Kelley-Seegmiller Syndrome
Lesch-Nyhan Syndrome

- HGPRT deficiency
- <1% protein expression
- UA Overproduction
- Mental retardation
- Microcephaly
- Compulsive Self-Mutilation
- Mutations/Gene Rx
Kelley-Seegmiller Syndrome

- Partial HGPRT Deficiency
- Early onset, severe gout
  - Arthritis
  - Renal calculi
- Intermediate PET scan appearance in basal ganglia 2,3-FDG utilization
Purine Catabolic Pathway

GMP → IMP → AMP

- XMP
- Adenylosuccinic acid
- Guanosine → Xanthosine
- Inosine ← Adenosine
- Guanine → Xanthine ← Hypoxanthine
- Adenine
- Uric acid
- 2,8-Dihydroxyadenine

Acute Gout--Pathophysiology

- role of crystals
- role of WBC's
- unexplained features:
  - initiation of attack
  - self-limited nature of attacks
  - joint distribution
  - role of trauma
  - Supersaturation is NOT sufficient explanation
Diagnosis

“Clinical” Dx vs. “Pathological” Dx
- polarizing microscopy
- (response to therapy)
- Radiographs
- tophi
Diagnosis of Gout

- Synovial fluid aspiration and examination using polarizing microscopy
- DIY!
- Identification of intracellular monosodium urate crystals
- Needle-shaped, negative birefringence, yellow (parallel first order compensator)
- “parallel-yellow-uric acid” mnemonic
Radiologic findings in Gouty Arthritis

- Large punched-out lesions
- Overhanging edges
- Heterotopic bone growth
- Lucencies
- Quite different from OA, RA, psoriatic, etc.
Tophi & Tophaceous gout

- Pure uric acid deposits
- Extensor surfaces
- Other locations
- Heberden’s nodes
- Chronic drainage
- 2-5 yrs to reverse
- Allopurinol role
Hyperuricemia and gout

- >20% of patients with acute gout may be normo-uricemic
- ~1-2% of patients with tophaceous gout may be normo-uricemic
- Mean serum urate in tophaceous gout ~9 mg/dl
- Mean CrCl = 90 +/- 30 ml/min
- Mean UrCl = 4.5 +/- 1.75 ml/min
Acute Gouty Arthritis

- Historical Prevalence = 0.2%
- Current Prevalence = 0.4%
- Annual incidence > 0.02%
- Annual incidence rate correlates with mean serum urate levels
  - <7.0 = 0.1%
  - 7.0-9.0 = 0.5%
  - >9.0 = 5%
Diagnostic Arthrocentesis
Polarizing Microscopy

unpolarized light  light ‘resolved’ into rays on a vertical axis  light rays ‘twisted’ to a horizontal plane by crystal  only rays vibrating in a horizontal axis allowed through

crystal seen against a black background
Polarizing Microscopy

Axis of first order red compensator

Polarizer

Monosodium urate monohydrate (gout)

Calcium Pyrophosphate Dihydrate (pseudogout)
Diff Dx?
Diff Dx

(you fill in the blanks here…)


Complications

(you fill in the blanks here also)
Treatment

- Historic vs. modern
- *Colchicum autumnale*
- Hippocratic writings
- Sydenham’s treatise
- Exquisitely effective
- Matthei Botanical Gardens
3 Phases of Gout Treatment

- Acute
- Preventive
- Hyperuricemia control
Treatment--acute

- Indomethacin 25-50 mg qid, taper over 5 days
- Colchicine 0.6 mg
  - one po per hour to max. of 12 in first 24 hours;
  - then no more than 0.6 mg po TID in the next 7 days
- IV colchicine - dangerous
- Butazolidin
- IA steroids - other NSAID's
- IL-1 inhibition such as anakinra
Preventive

- indomethacin 25 mg po daily or BID
- colchicine 0.6 mg po daily or BID
Colchicine toxicity

- IV -- repeated doses are dangerous
- -- skin reactions
- Myelosuppression
- Muscle disease
- Neuropathy
- Aplastic anemia
- Thrombocytopenia
- Diarrhea
Long term anti-hyperuricemic Rx

- Allopurinol 300 mg po qd (decreases production)
- uricosuric
  - sulfinpyrazone 100 mg (titrate)
  - probenecid 500 mg qd-bid

- NOTE: Uricosuric therapies require identification of 24 hour urinary uric acid excretion
Which patients need long term anti-hyperuricemic therapy?

- Frequency of attacks
- Severity
- Other circumstances
Uricosurics

**PRO**
- ?safer than allopurinol?
- Putative role in decreasing atherogenesis
- Most people are eligible

**CON**
- Patient education
- Renal stones
- Rashes
- Tolerability
- 24 hr urine collection to establish candidacy
Uricosuric Treatment

- Establish baseline CrCl and UrCl
- Probenecid: 250 mg bid, increase to 500-1000 mg bid
- Follow up CrCl and UrCl
- Change meds to secondary uricosurics
Primary Uricosurics

- Probenecid
- Sulfinpyrazone
- Benzbromarone
- EMD 336340
Secondary Uricosurics

- Fenofibrate
- Atorvastatin
- Losartan
- Ampicillin/β-lactams
- Valproic acid
Indications for allopurinol

- Tophi
- Renal insuff (CrCI <80)
- Renal stones (any type)
- Uric acid over-excretion
- Contraindications to uricosurics
- UA >13
- Induction chemotherapy
Allopurinol Side Effects

- **Hypersensitivity syndrome**
  - Begins 2-12 weeks after treatment
  - Fever, often with maculopapular rash
  - Hepatitis, interstitial nephritis (ATN/ARF), myocarditis, rhabdomyolysis, eosinophilia

- **Incidence rate of ~0.4%, mortality 25%**

- **Complex pathophysiology**
  - Idiosyncratic, not related to dose or duration
Allopurinol Side Effects

- Toxic epidermal necrolysis (TEN/ Stevens-Johnson syndrome)
- Incidence of ~ 0.5%
- High serum levels of oxypurinol may increase risk
- Azotemia may increase risk
Allopurinol Safety

- Potentiates azathioprine serum levels
- Potentiates warfarin effects
- ACE inhibitors increase risk of TEN
- Arellano & Sacristan, Ann Pharmacother 27:337-43;1993

- 76/101 patients with hypersensitivity syndrome were receiving allopurinol for asymptomatic hyperuricemia
Allopurinol Safety


Case control study in 4 European countries to determine relative risk associated with meds and TEN-Stevens-Johnson syndrome

- RR of allopurinol = 52 (16-167)
- RR of phenytoin = 53 (11-infinity)
- RR of pen = 7, ceph = 14
New Therapeutics

- Febuxostat; a specific and potent xanthine oxidase inhibitor with hepatic metabolism
  - US FDA approval 2/13/2009

- Rasburicase; (Recombinant Aspergillus)
  - Approved for tumor lysis syndrome
    - Potential for anaphylaxis

- Uricase-PEG20 (Recombinant Candida)
  - Approved Oct. 2009 “pegloticase” for IV use
Important drug interactions

- Azathioprine
- Mercaptopurine
- Cyclosporin

(Another important "interaction" is shown: "Boston Tea Party")
Aspirin (ASA)

- Low dose (100-300 mg) ASA exhibits first-order pharmacokinetics and inhibits tubular secretion of UA
- High dose (>1.0 gm) ASA exhibits zero-order pharmacokinetics, is an effective uricosuric, and may be responsible for the historical observation that RA and gout do not co-exist
Cyclosporin

- Major cause of hyperuricemia in organ transplant patients
- Tacrolimus similar effects
- Complex pathophysiology
  - Reduced GFR
  - Reduced urate secretion from proximal tubule
  - Other effects on tubular function
Ethanol

- High dietary purines (beer)
- Ethanol -- acetate -- acetyl-CoA metabolism produces large amounts of AMP in liver
- If AMP production exceeds rates of ATP regeneration then excess AMP is metabolized to uric acid
- Ethanol inhibits UrCl (organic acids and dehydration)
Miscellaneous gout issues...

- What is the role of oxypurinol?
- Role of diet
- Co-existent gout and...
  - OA
  - CPPD
  - Septic arthritis
Co-existing conditions

- Gout can occur with infectious arthritis, CPPD, psoriatic arthritis or rheumatoid arthritis
- Joint aspiration with cultures and crystal examination is optimal approach to diagnosis and management
Hyperuricemia and Gout

- Hyperuricemia is not a disease (?)
  – Feig et al. NEJM October 23, 2008

- Gout is diagnosed by examination of synovial fluid

- Allopurinol is not the only treatment
Clinical Syndromes associated with CPPD

- Radiographic Dx (“Chondrocalcinosis”)
- Familial Clusters
- Endocrinopathies
- Intra-operative diagnosis (cause or effect?)
- Pseudogout attacks
- Polarizing Microscopy
Chondrocalcinosis Locations

- Knee
- Shoulder
- Wrist
- Symphysis Pubis
Diagnosis of Pseudogout

- Synovial fluid aspiration and examination using polarizing microscopy
- DIY!
- Identification of intracellular CPPD crystals
- Rhomboid shaped, positive birefringence, blue (parallel first order compensator)
CPPD some more clinical facts

- “DISH” diffuse idiopathic skeletal hyperostosis is common
- CPPD is a common radiographic finding in the elderly
- Radiographs and symptoms do not always correlate
- Treatment is simpler than gouty arthritis therapies
Pseudogout Treatment

- Response to Indomethacin
- Response to Colchicine
- Monophasic treatment only
- Intra-articular steroids
- Epiphenomenon/ cause or effect?/ is treatment worthwhile?
CPPD Treatment

- Symptomatic
- NSAIDS
- Colchicine
- Intra-articular steroids
- Metabolic risk factors
  - Thyroid disease
  - Hyperparathyroidism
  - Hemachromatosis
  - DM
Miscellaneous Crystals
Thank you!
Questions?
Slide 3: Henry William Bunbury, Origin of the Gout
Slide 10: Source Undetermined
Slide 11: Henry William Bunbury, Origin of the Gout
Slide 12: Source Undetermined
Slide 16: Source Undetermined
Slide 20: Sources Undetermined
Slide 24: Sources Undetermined
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Slide 58: The Boston Tea Party by Sarony and Major
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