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Crystalline Arthritis

Seetha Monrad M.D.
What is gout?

• Disease state arising from the deposition of monosodium urate crystals in assorted tissues, with accompanying inflammatory and/or degenerative consequences
  – In joints -> inflammatory arthritis
  – In soft tissue -> tophi
  – In kidneys -> nephrolithiasis, nephropathy

• Most common inflammatory arthritis in men >40
Purine metabolism
Normal uric acid metabolism

Endogenous purine synthesis, tissue nucleic acid breakdown

Dietary purines

Total Body Urate Pool
Men: 1200 mg
Women: 600 mg

Renal excretion (>2/3)

Intestinal uricolyis (<1/3)

Normal serum urate levels (+2)
Men: 5.0 mg/dL, Women: 4.0 mg/dL
Renal handling of uric acid

Normal: 500-800 mg/24 hours
Hyperuricemia

- Serum uric acid >6.8 mg/dL
- Caused by uric acid overproduction and/or underexcretion
- Total body urate pool >2000 mg -> becomes insoluble
  - Non-tophaceous gout: 2-4 g
  - Tophaceous gout: 10-1000 g
Uric acid overproduction

- 10% of cases
- 24 hour urinalysis >1000 mg/d
- Causes
  - Genetic
    - Glucose-6-phosphatase deficiency (glycogen storage disease type I)
    - Hypoxanthine guanine phosphoribosyltransferase deficiency (HGPRT)
    - PRPP-synthetase superactivity
Uric acid overproduction

• Causes (con’t)
  – Excessive purine intake
  – Ethanol
  – Drugs: nicotinic acid, warfarin, chemotherapy (tumor lysis)
  – Obesity
  – Malignancies (myeloproliferative, lymphoproliferative)
  – Psoriasis
  – Hemolytic anemia
  – Tissue destruction (hypoxia, ischemia, trauma)
Uric acid underexcretion

- 90% of cases
- <500 mg/d excretion

Causes
- Genetic (polycystic kidney disease, etc.)
- Decreased GFR
- Organic acidosis
- Lead nephropathy
- Drugs
Drugs

- **Cyclosporin**
  - Reduced GFR
  - Reduces urate secretion

- **Aspirin**
  - Low dose (eg. 81 mg): inhibits urate secretion
  - High dose (>3g): decreases tubular reabsorption

- **Diuretics**
  - Volume depletion -> increased reabsorption
  - Thiazides interfere with secretion

Teng, 2006
Ethanol

- **Overproduction**
  - High purines (especially beer)
  - Produces excess AMP
    -> metabolized into uric acid

- **Underexcretion**
  - Dehydration
  - Organic acids -> overwhelm urate transporter
Hyperuricemia is NOT Gout

- Hyperuricemia present in 5-10% of adult men
- 80% of hyperuricemic patients do not develop gout
Is hyperuricemia bad?

- Hyperuricemia is associated with hypertension, renal disease, metabolic syndrome, cardiovascular disease
- Studies are beginning to suggest that uric acid is an independent risk factor for these conditions and may be involved in their pathogenesis
  - An elevated uric acid level consistently predicts the development of hypertension.
  - An elevated uric acid level is observed in 25–60% of patients with untreated essential hypertension and in nearly 90% of adolescents with essential hypertension of recent onset.
  - Raising the uric acid level in rodents results in hypertension with the clinical, hemodynamic, and histologic characteristics of hypertension.
  - Reducing the uric acid level with xanthine oxidase inhibitors lowers blood pressure in adolescents with hypertension of recent onset
- However, currently not sufficient evidence to support treatment of asymptomatic hyperuricemia

Epidemiology of gout

- Most common inflammatory arthritis in men >40
- Total prevalence ~3%; 6-9% if >80
- U.S. incidence may be rising (>2 fold)

Arromdee, Drugs, 2002
3 phases of gout

- Asymptomatic hyperuricemia
- Acute gout flares
- Chronic (tophaceous) gout
Acute gout

“The victim goes to bed and sleeps in good health. About 2 o'clock in the morning, he is awakened by a severe pain in the great toe; more rarely in the heel, ankle or instep. This pain is like that of a dislocation, and yet the parts feel as if cold water were poured over them. Then follows chills and shiver and a little fever. The pain which at first moderate becomes more intense. With its intensity the chills and shivers increase. After a time this comes to a full height, accommodating itself to the bones and ligaments of the tarsus and metatarsus. Now it is a violent stretching and tearing of the ligaments—now it is a gnawing pain and now a pressure and tightening. So exquisite and lively meanwhile is the feeling of the part affected, that it cannot bear the weight of bedclothes nor the jar of a person walking in the room.”

Thomas Sydenham
Acute gout

- 4th-6th decade (men); later in women
- Sudden onset, rapid escalation
- 1st MTP (podagra)
  - 50% have as first attack
  - 90% will have eventually
- Other lower extremity joints
- Systemic symptoms
- Extraarticular (bursitis, tenosynovitis)
- Triggered by: trauma, surgery, sepsis, overindulgence (alcohol, purine-rich foods), drugs
Intercritical gout

- Asymptomatic periods between acute flares
- Body urate load still increasing
- Joints still with MSU crystals
Chronic gout

- Chronic destructive arthritis
- Flares become polyarticular, additive, ascending
- Can be mistaken for rheumatoid arthritis
Tophaceous gout
Renal Disease

• Acute uric acid nephropathy (tumor lysis syndrome)

• Chronic urate nephropathy (tubulointerstitial disease)
  – MSU deposition in renal medulla
  – Not seen in the absence of gouty arthritis

• Uric acid nephrolithiasis
  – 10-25% of gout patients
  – Increased non-urate nephrolithiasis as well
Diagnosis: Arthrocentesis

- Can be performed even if not in acute attack
- Inflammatory joint fluid, sometimes septic appearing
Serum uric acid

• If high, suggestive but not diagnostic
• Up to 1/3 of patients having an acute gout attack may have a uric acid <7
• 24 hour urine collections for uric acid
  – Difficult to perform
  – May be useful in select cases (young patient, history of urolithiasis)
Treatment

Asymptomatic hyperuricemia → No treatment

Acute gout → Antiinflammatory Preventative

Chronic gout → Uric acid lowering therapy
Acute treatment

- NSAIDs
- Steroids
  - Intraarticular
  - Oral/IV
- ACTH
- Anakinra

- Colchicine
  - Never IV
  - Used prophylactically in intercritical periods
  - Toxicities: diarrhea (common), neuromyopathy, bone marrow suppression, hematologic abnormalities
  - Not dialyzable
Lowering uric acid

- Adjust offending medications (ex. diuretics)
- Weight loss
- Dietary adjustments
  - Less meat, seafood
  - Less alcohol (particularly beer)
  - Less fructose containing soft drinks
  - More dairy

- Purine rich foods
  - Beer, other alcoholic beverages.
  - Anchovies, sardines in oil, fish roes, herring
  - Yeast
  - Organ meat (liver, kidneys, sweetbreads)
  - Meat extracts, consomme, gravies
  - Mushrooms, spinach, asparagus, cauliflower, legumes (dried beans, peas) less associated with gout
Indications for uric acid lowering medication

- Tophaceous gout
- Erosive gout
- Unacceptably frequent attacks (>3-4/year)
- Nephrolithiasis
- Serum uric acid >12 with other risk factors for gout or nephrolithiasis

Goals: lower serum urate <6.0 (<5.0 if tophi)
- Should not be initiated during an acute flare
Treating undersecretion: uricosurics

- Suppress URAT1 -> decreases tubular reabsorption
- **Probenecid**
- (sulfinpyrazone, benzbromarone)
- Others: losartan, fenofibrate
- Limitations:
  - Require adequate GFR
  - Increases risk of uric acid stone formation/ urinary crystallization
  - Numerous drug-drug interactions (ampicillin, salicylates, indomethacin, heparin, etc.)
Treating overproduction
Allopurinol

• Purine analog of xanthine
• Competitive xanthine oxidase inhibitor
• Active metabolite = oxypurinol
• Potentiates azathioprine and warfarin
• Side effects:
  – Rash/toxic epidermolysis/Stevens Johnson syndrome
  – GI intolerance/liver enzyme elevation
  – Cytopenia
Allopurinol hypersensitivity syndrome

- Idiosyncratic; usually develops within first 3 months of initiation
- Fever, rash, hepatitis, interstitial nephritis, myocarditis, rhabdomyolysis, eosinophilia
- Incidence ~0.4%, mortality 25%
- Arellano, et al. 1993: ~75% of patients developing syndrome were receiving allopurinol for asymptomatic hyperuricemia
Renal dosing?

- Guidelines for dose adjustment in patients with renal insufficiency to minimize toxicity
- However,
  - Unclear if this is successful
  - Results in significant undertreatment of gout
- Recommend carefully advancing allopurinol as high as needed to lower serum urate
Other urate lowering therapies

• Febuxostat
  – Non-purine selective xanthine oxidase inhibitor
  – Hepatically metabolized -> ?safer in renal insufficiency
  – Side effects: transaminitis

• Uricase
  – Converts uric acid to allantoin
  – Prevents/manages tumor lysis syndrome
  – Infusion reactions; anti-uricase antibodies
Special instances of gout

• Organ transplant patients on cyclosporine
  – More likely to develop rapidly, be tophaceous, involve atypical joints
  – Steroid use may mask acute attacks despite accumulation of total body urate load

• Gout in young men (<25) or premenopausal women: likely genetic
CPPD disease

- Calcium pyrophosphate deposition disease
  - Pseudogout
  - Also pseudo-septic, pseudo-RA, pseudo-OA
- Associated with aging
- Also associated with
  - Hemochromatosis
  - Hyperparathyroidism
  - Hypomagnesemia/hypophosphatemia
  - Gout
  - Trauma
  - Hypothyroidism
Pseudogout

- Acute inflammatory attacks
- Asymptomatic in between
- Flares involve large joints: knees, shoulders, wrists, ankles
- Also can involve MCPs
- May take longer to reach peak intensity, longer to subside than gout
- Not due to uric acid
Diagnosis

- Joint aspiration
  - Crystals more rhomboid
  - Weakly positive birefringence

Source Undetermined
Chondrocalcinosis
CPPD arthritis
CPPD arthritis
Management of pseudogout

- NSAIDs
- Steroids
- Colchicine
- Treat associated disorders (hemachromatosis, hyperparathyroidism)
Other crystals: Hydroxyapatite
Additional Source Information
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Slide 6: Seetha Monrad
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