In Memory of Dr. H. R. Schumacher
Is synovial analysis useful in diagnosing arthritis?

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Goals:

- What is the nature of the crystal arthritis or arthropathy?
  - Inflammatory
  - Non-inflammatory

- Is synovial analysis helpful for diagnosing arthritis and How?
  - Recognize common and uncommon crystals

- Updates about crystals arthritis/arthropathy?
  - Gout (Monosodium Urate Crystals)
  - Calcium Pyrophosphate Dihydrate Crystals (CPPD)
What Does He Have?

- 85 WM with PMH of HTN and Hyperlipidemia
- Multiple joint pain in L Wrist & hand (MCPs), both knees and R elbows for more three months.
- The pain was 7-8 on 1-10, associated with swelling, warmth and profound morning stiffness (more than one hour).
- The worst time was in the morning and the pain was relieved by physical activity or stretching.
- System review: unremarkable
- He has been given oral prednisone 20 mg qd with tapering for 1-2 weeks and colchicine 0.6 mg po qd with some relief.
What Is the DDX list?
What is Your Differential Diagnosis and Why?

- Polyarticular Inflammatory arthritis:
  - Crystal (Gout, CPPD)
  - Rheumatoid arthritis
  - Others (infections, infiltrative, Malignancy)

- Non-inflammatory
  - Osteoarthritis
Lab Results:

- Normal WBC, Low HGB at 11.6 with normal MCV, mild elevated Plat at 416
- Normal CMP (comprehensive metabolic panel)
- Uric acid at 5.8. 5.2 5.6 on the monthly measurements.
- ESR at 90 (nl <20). CRP at 1.4 (nl.<0.7)
- Negative RF and anti-CCP-ab.
- Normal SPEP and UPEP
How To Confirm The Diagnosis?
Synovial Fluid Analysis
Rice Bodies
What can cause this “cream of tomato soup” synovial fluid?
What kind of crystals can we expect to see in the joint fluid?

- Monosodium Urate Crystals
- Calcium Pyrophosphate Dihydrate Crystals
- Apatite Calcium Phosphates Crystals
- Calcium Oxalate Crystals
- Lipid Crystals
- Protein Crystals (Immunoglobulin, Amyloid Crystal)
- Synthetic Depot Corticosteroid Crystals
- Foreign Bodies (bacteria, others)
MSU crystals can vary widely in size
Single cell containing MSU and CPPD crystals
CPPD crystals may be more brightly birefringent.
CPPD Crystals Can Be Rhomboid or Rod Shaped
What do you see here?
Apatite crystal clumps by regular light microscopy
Alizarin red S stain for calcium must be passed through a millipore filter
Alizarin red S stained apatite clumps
Calcium oxalate crystal
Pyramidal aspect of oxalate crystals are accentuated by polarized light
Calcium oxalate crystal stained with Alizarin red S
Conditions Associated With Oxalosis

- Renal failure
- Inflammatory bowel diseases
- Vitamin B6, magnesium or thiamine deficiency
- Familiar Oxalosis
Cholesterol and lipid liquid crystals
LIPID LIQUID CRYSTAL-MALTESE CROSS

Negatively birefringent MSU crystal overlying positively birefringent Maltese cross lipid liquid crystal
Lipid Crystals Can Be Seen:

- Inflammatory arthritis: Rheumatoid arthritis or gouty arthritis
- Fracture
- Pancreatitis
- Complicate types II and IV Hyperlipidemias
What do you see here?
Cryoglobulin and other protein crystals stain with toluidine blue.
Synovial Fluid From a Patient with Multiple Myeloma
Amorphous clump of synovial fluid amyloid
Apple green birefringence of amyloid with plain polarized light
Congo red positive amyloid
Gram stain showing gram positive cocci
Celestone soluspan can mimic CPPD or cholesterol
Depot medrol is very bright and irregular
Corn starch from gloves
CPPD in the Synovial Fluid of this Patient
CLINICAL MANIFESTATIONS of CPPD

- Pseudogout (“acute CPPD crystal arthritis”)
- Pseudo-rheumatoid arthritis (“chronic CPPD crystal inflammatory arthritis”)
- Asymptomatic disease (“asymptomatic CPPD”)
- Pseudo-osteoarthritis, with or without superimposed acute attacks (“osteoarthritis with CPPD”)
- Spinal involvement: most commonly encountered in familial CPPD crystal deposition disease
Pseudogout
("acute CPP crystal arthritis")

Pseudogout is characterized by self-limited acute or subacute attacks of arthritis involving only one or several extremity joints (monoarthritis and pauci(oligo)arthritis, respectively).
Pseudo-rheumatoid arthritis (chronic CPPD crystal inflammatory arthritis)

- Inflammatory arthritis in which CPPD crystals are demonstrable in joint fluid. It occurs in 5 percent or less of patients with symptomatic CPPD crystal deposition disease.

- The clinical picture may closely resemble that of rheumatoid arthritis, with significant morning stiffness, fatigue, synovial thickening, localized edema, and restricted joint motion due either to active inflammation or flexion contracture.

- Radiographic changes are more typical of osteoarthritis than of rheumatoid arthritis despite the pattern of clinical joint involvement.
Scapholunate Advanced Collapse (SLAC)

Sclerosis and joint space narrowing between the lunate and capitate, and the capitate will eventually migrate proximally into the space created by the scapholunate dissociation.
Pseudo-osteoarthritis ("OA with CPPD")

- Approximately 50 percent of patients with symptomatic CPPD crystal deposition disease show progressive joint degeneration.
- The arthritic process occurs in joints typical for osteoarthritis (such as the first carpometacarpal joints, the knees, or bunion joints)
Asymptomatic CPPD crystal deposition ("asymptomatic CPPD")

Most joints in which CPPD crystal deposition is readily apparent on radiographs are asymptomatic.

Plain radiograph shows chondrocalcinosis of the knee in a patient with hemochromatosis. There is calcification within the cartilage in the tibiofemoral joint space (arrows).

Courtesy of Jonathan Kruskal, MD.
Spinal involvement (Pseudo AS)

- CPPD crystal deposition in and about the spine has been associated with a number of clinical manifestations. Spine stiffness, sometimes associated with bony ankylosis, can resemble that of ankylosing spondylitis (AS) or diffuse idiopathic skeletal hyperostosis (DISH).
- Such symptoms have been most commonly encountered in familial CPPD crystal deposition disease.
- Crystal deposition in the ligamentum flavum at the cervical spine level or in the posterior longitudinal ligament at lower levels of the spine may lead to spinal cord compression syndromes or to symptoms of either acute nerve compression or chronic spinal stenosis.
Calcium Pyrophosphate Dihydrate Crystal Deposition Diseases (Spine)
## Endocrine and metabolic disorders associated with CPPD crystal deposition disease

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Probability of association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemochromatosis</td>
<td>Definite</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>Definite</td>
</tr>
<tr>
<td>Hypophosphatasia</td>
<td>Definite</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>Definite</td>
</tr>
<tr>
<td>Gittleman's syndrome</td>
<td>Definite</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Probable</td>
</tr>
<tr>
<td>Gout</td>
<td>Possible</td>
</tr>
<tr>
<td>X-linked hypophosphatemic rickets</td>
<td>Possible</td>
</tr>
<tr>
<td>Familial hypocalciuric hypercalcemia</td>
<td>Possible</td>
</tr>
<tr>
<td>Hemosiderosis</td>
<td>Possible</td>
</tr>
</tbody>
</table>
Treatment of pseudogout involving more than two joints

Established diagnosis of pseudogout

Acute attacks

Rest

Immobilization education

NSAIDs* in anti-inflammatory doses (for duration of acute attack)

No

Are NSAIDs contraindicated?*

Yes

Oral colchicine*

No

Chronic management

Are attacks frequent? (≥3 attacks/year)

No

Observe

Educate

Treat acute attacks

Yes

Is colchicine contraindicated?

No

Oral colchicine*

Yes

Chronic NSAID* therapy

Oral or intramuscular glucocorticoids

* Adjust dosage with renal insufficiency.
  - NSAID contraindications: renal insufficiency, HF, peptic ulcer disease, hypersensitivity.

Acute Synovitis with Vascular Congestion.
Advanced Gout.
Advanced Gout

Tophaceous Deposits

- Solid urate deposits in tissues
  - Irregular, destructive nodularities produced

Risk factors include

- Long duration of hyperuricemia
- High serum urate levels
- Long periods of active, untreated gout

1. ACR Clinical Slide Collection on the Rheumatic Diseases, 1998.
Dual Energy CT (DECT) for Gout

- Dual-energy computed tomography (CT) may be used to differentiate urate crystals from calcium by using specific attenuation characteristics, which may help diagnose gout.
- In patients with known tophaceous gout, dual-energy CT may be used for serial volumetric quantification of subclinical tophi to evaluate response to treatment.
Termination of the Acute Flare

• Resolution of acute flare by controlling crystal-induced inflammation and pain
  • Not a cure for gout. Only resolves the symptoms
    • Urate crystals remain in the joint
  • Medication options:
    • NSAIDs, oral colchicine, corticosteroids, ACTH
  • Cold applications may decrease drug need

• The critical issues are
  • Contraindications due to comorbidities
  • Rapid initiation of therapy
  • Adequate dosing
  • Appropriate duration of therapy
### Medications Used to Terminate the Acute Flare

<table>
<thead>
<tr>
<th>Agents</th>
<th>Contraindications / Use With Caution</th>
<th>Drug Interactions</th>
</tr>
</thead>
</table>
| **NSAIDs**      | • Peptic ulcer disease  
                  • GI bleeds  
                  • Aspirin- or NSAID-induced asthma  
                  • Renal impairment | • Warfarin        |
| • Indomethacin, 50 mg tid  
                  • Naproxen, 500 mg bid |                                                                                                           |
| **Colchicine**  | • Dialysis patients contraindicated  
                  • Renal or hepatobiliary dysfunction | • Cyclosporine  
                  • Statins  
                  • Macrolides |
| • 0.6 mg tid  
                  – Adjust for creatinine clearance in renal impaired patients |                                                                                                           |
| **Corticosteroids** | • Diabetic patients  
                           • Possible septic arthritis |                                                                                                           |
| • Prednisone, 20-40 mg daily  
                  • Intra-articular methylprednisolone 20-40 mg |                                                                                                           |
Hyperuricemia and Preventing Disease Progression

• **Goals**
  - Improve patient understanding through education
  - Lower urate to <6.0 mg/dL to allow depletion of total body urate pool and deposited crystals

• **Address optimal time to initiate urate lowering therapy**
  - One Canadian study describes cost effectiveness after 1 attack and cost saving after 2
  - Urate kidney stone, polyarticular gout arthritis, Tophus.

• **Therapy should be lifelong**
  - Intermittent therapy or withdrawal of agents leads to recurrence of acute attacks, tophi, etc

• **Approved urate-lowering agents for gout include**
  - Uricosuric agents
  - Xanthine oxidase inhibitor
Allopurinol and oxypurinol block the conversion of hypoxanthine to xanthine to uric acid

Allopurinol and metabolite oxypurinol are purine analogs and both substrates and inhibitors of xanthine oxidase
Allopurinol given to patients with gout

49 patients given standard doses of allopurinol (300 mg/day)

Current data support

Totally different structure than allopurinol

Ability to administer in renal insufficiency and mild or moderate hepatic insufficiency with no dosage adjustments

Shown to be safe, effective, and well tolerated in the limited data of allopurinol-intolerant patients

Febuxostat Phase 3 Clinical Trial Primary End Points

Randomized, double-blind, 52-week, multicenter trial of 760 patients

- Primary end points:
  - Last 3 SUA <6.0 mg/dL
  - Week 52 SUA <6.0 mg/dL

*P<.05 for each febuxostat group vs allopurinol group.

Febuxostat (40mg or 80mg po qd)

- Diarrhea and abnormal LFTs may occur in patients, especially those concomitantly taking colchicine
- Acute flares of gout occur during early stages of treatment
- Long term safety under investigation
Colchicine prophylaxis during allopurinol initiation reduced frequency and severity of flares. Likelihood of recurrent flares. Best results with dual therapy for 6 months.

New Medications

- Lesinurad in combination with allopurinol: results of a phase 2, randomised, double-blind study in patients with gout with an inadequate response to allopurinol

  - Fernando Perez-Ruiz, John S Sundy, Jeffrey Miner, Matthew Cravets, Chris Storgard for the RDEA594-203 Study Group
Lesinurad 200mg PO QD

- **Lesinurad 200mg tablets** inhibits the urate transporter, URAT1, which is responsible for the majority of the renal reabsorption of uric acid. By inhibiting URAT1, Lesinurad increases uric acid excretion and thereby lowers serum uric acid (sUA).
- Lesinurad also inhibits organic anion transporter (OAT) 4 a uric acid transporter involved in diuretic-induced hyperuricemia.
- **Side effect:** Renal-related adverse reactions, including blood creatinine increases, renal failure, and nephrolithiasis
Recommended Lifestyle Modifications for Gout

- Weight reduction
- Decrease alcohol consumption
- Diet Modification
- Address co-existing metabolic syndrome
Conclusion:

1. Crystal arthritis and arthropathy could be Inflammatory and Non-inflammatory.
2. Synovial Analysis is very useful in identifying and confirm the cause of arthritis and arthropathy.
3. CPPD can manifested as Pseudogout, Pseudo RA, Pseudo-OA, Pseudo AS
4. Gout with its many comorbidities present with challenges and opportunity for gout management.
Thank You !