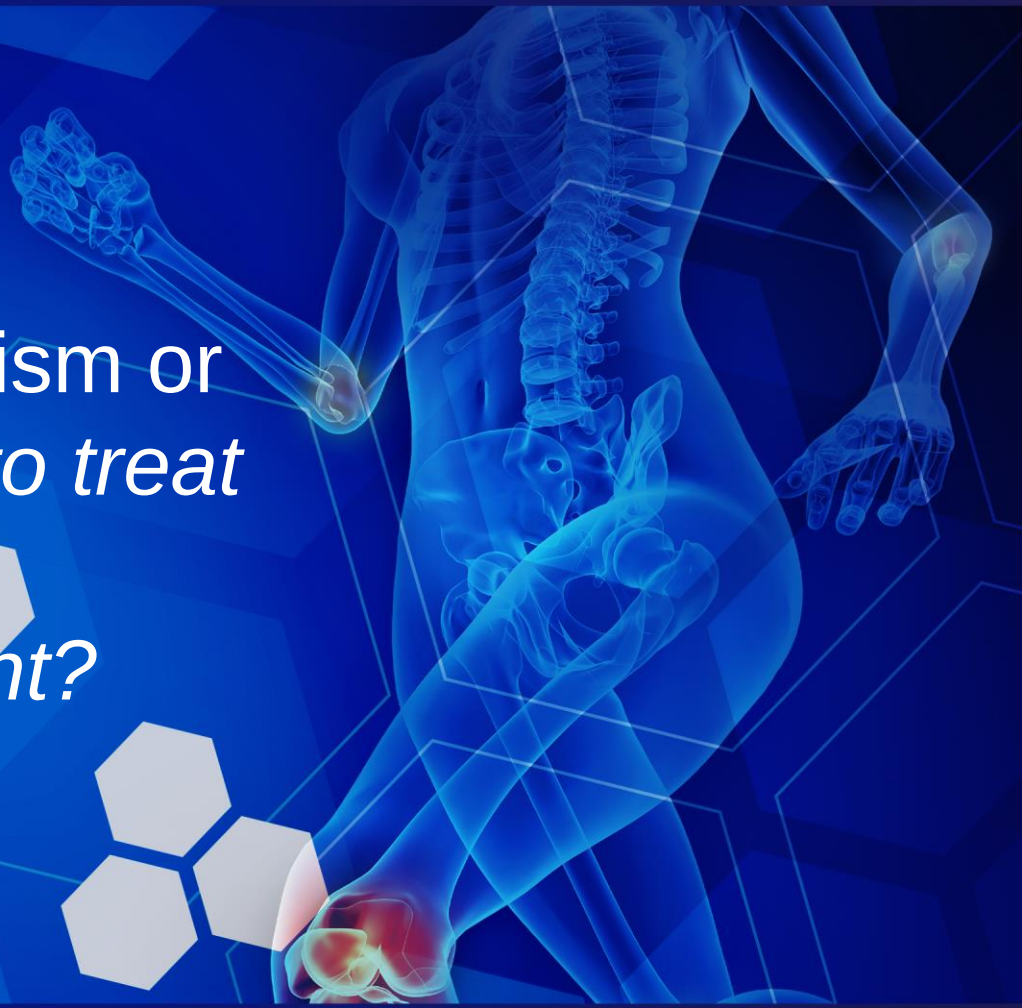
Palindromic Rheumatism or *When do you decide to treat an asymptomatic seropositive RA patient?*



What Is This?

- 11.15.15
- 56 yo man comes for 2nd opinion for bouts of severe large joint monoarthritis lasting 24 hours or longer.
- Vague about duration “10-15 years.” Had wrist synovectomy 2005 after “trauma.”
- Saw rheumatologist 2012: ACPA>500, RF 60.
- Loss of shoulder motion in all planes.

- At the conclusion of this presentation, the participant should be able to:
  - Appreciate the relationship of Palindromic Rheumatism (PR) and progression to RA
  - Understand the biology of intercritical PR
  - Define the utility of prevention strategies
  - Comprehend the yield of imaging in PR and how it informs PR pathophysiology
- Should we try to prevent? How?

Annual transition to RA is greater than 15% in which of the following ACPA+ pts?

A. Arthralgia
B. Arthralgia + Imaging + CRP
C. Palindromic Rheumatism
D. Asymptomatic Twin
E. Interstitial Lung Disease

Rheumatoid Arthritis Pathogenesis

Tolerance broken-AutoAb appear

Adaptive Immune Response
Locus and Trigger?
Systemic Nature?

↓

“Amplification”

↓

Synovial Targeting with
variable kinetics?
Innate vs Adaptive Immunity?

Joint Targeting

↓

ACPA-IC deposit or
are formed de novo in joint?
Or something else?

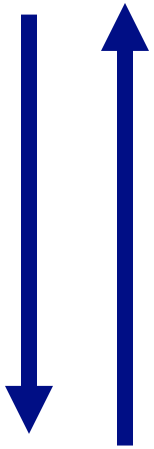
Tissue Injury

Rheumatoid Arthritis
Persistence of the Systemic Trigger?

Systemic autoimmunity & inflammation

T cells/B Cells
Immune Complexes

No treatment shown to eliminate systemic process



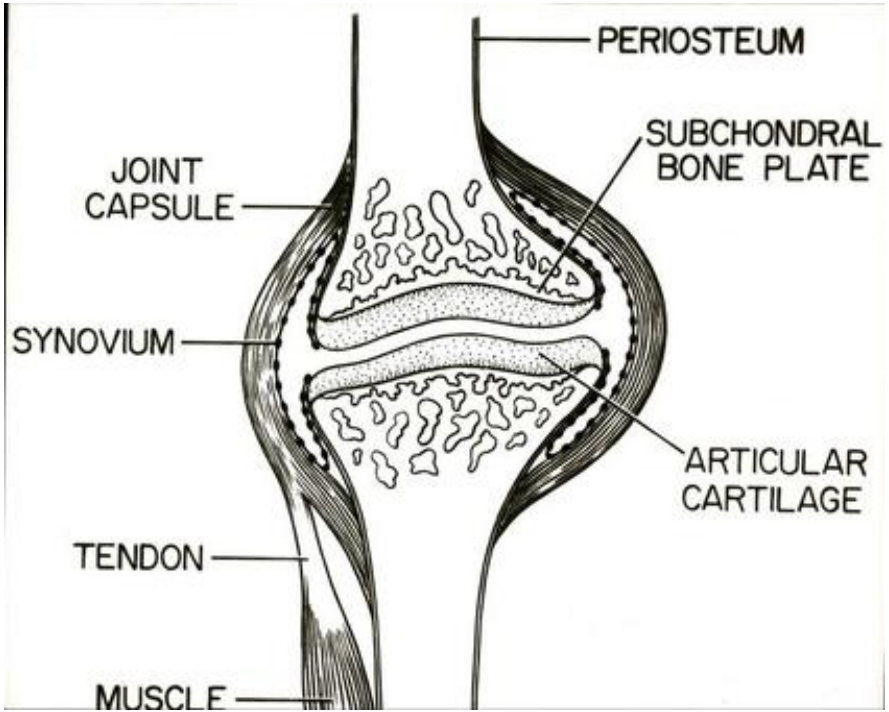
TNF, IL-6, GM-CSF

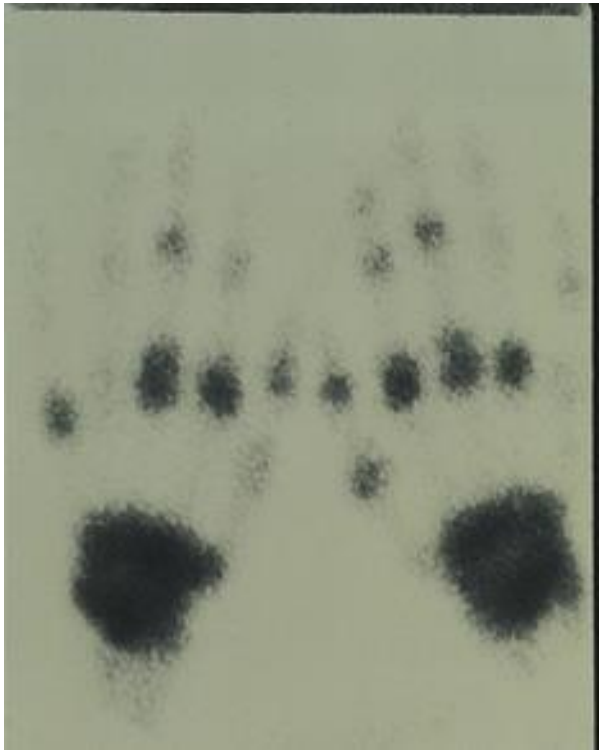
Where does MTX work?

Joint Inflammation

MF, FLS, Cartilage, Bone

RA Centers in Synovium, Destroying All Around It?





Why Is Palindromic Rheumatism Palindromic?

Systemic inflammation

Followed by resolution?
e.g. like gout?
Why does it resolve?
Why does it stop resolving?

Single Joint Inflammation

Palindromic Rheumatism (PR)

- How frequent is PR as an initial presentation of RA?
- What is the mechanism of PR?
- Is synovitis present during its intercritical phase?
- What is the frequency of progression to RA in 5 years? Treatment?

Is Palindromic Rheumatism a Common Presentation?

Frequency relative to new onset RA is:

A. 10%

B. 20%

C. 30%

D. 40%

E. 50%

Is Palindromic Rheumatism a Common RA Presentation?

- **METHODS:**
- 145 patients newly diagnosed with RA or PR between May 2004 and May 2006.
- **RESULTS:**
- 51 were diagnosed with PR and 94 with RA The average age at diagnosis of PR was 49 years as compared to 56 years for RA.

A Powell et al. *J Rheumatol*. 2008 Jun;35(6):992-4.

Is Palindromic Rheumatism a Common Presentation?

Frequency relative to new onset RA was:

A. 10%

B. 20%

C. 30%

D. 40%

E. 50%

51/145 = 35%

Is Hand/Wrist Synovitis Present in PR During Intercritical Period?

Frequency is:

A. <10%

B. <20%

C. <30%

D. <40%

E. <50%

Is Synovitis Present in PR During Intercritical Period?

- 54 patients with PR, 36 ACPA+
  - Synovial hypertrophy > 2: 33%
  - Power Doppler US: 26%
  - 4 (7.4%) had both

During attack: 7/10 PDUS: not 100%!

S. Villalba et al. *J. Rheum*. 2014, 41:8.

Is Synovitis Present in PR During Intercritical Period?

Frequency was:

A. <10%

B. 20%

C. 30%

D. 40%

E. <50%

4/54 (7.4%) +SHS & Power Doppler

What Is the Frequency of Progression of ACPA+ Palindromic Rheumatism to Seropositive RA?

Progression to seropositive RA over 5 years:

A. 10%

B. 30%

C. 50%

D. 70%

E. >80%

RP Progression After ACPA Measured (7.6 ± 4.7 yrs) Sx for Mean of 4.5 Years

Table 1. Demographic and serological characteristics of patients with palindromic rheumatism at the time of first measurement of antibodies against citrullinated peptide/proteins (ACPA).

Characteristic	Whole Group, n = 71	ACPA +, N = 37	ACPA –, N = 34	P
Age, yrs	52.4 ± 12.5	51.2 ± 10.2	53.8 ± 14.7	0.38
Female, no. (%)	54 (76.1)	31 (83.8)	23 (67.6)	0.09
Disease duration*, mo, mean ± SD	53.9 ± 69.2	27.1 ± 29.2	82.9 ± 86.9	0.001
Followup**, mo, mean ± SD	90.9 ± 56.6	99.7 ± 60.7	81.2 ± 50.9	0.17
RF+, n (%)	40 (56.3)	26 (70.3)	14 (41.2)	0.01
ACPA+, n (%)	37 (52.1)	–	–	
ACPA values, mean ± SD	704.8 ± 592.3	–	–	
RA during followup, n (%)	16 (22.5)	11 (29.7)	5 (14.7)	0.11
Hydroxychloroquine treatment, n (%)	52 (73.2)	28 (75.7)	24 (70.6)	0.41

ACPA positive patients shorter disease duration-recruitment bias

*From initial symptoms to first ACPA serum determination; **From first serum ACPA measurement to last visit.
RF: rheumatoid factor; RA: rheumatoid arthritis.
R SanMarti et al. *J Rheumatol*. 2012 Oct;39(10):1929-33.

What is the frequency of progression of ACPA+ palindromic rheumatism to seropositive RA?

Progression to seropositive RA over 5 years:

a) **10%**
b) **30%**
c) **50%**
d) **70%**
e) **>80% (other studies have suggested this value)**

Between 30%-80%

10.2-14.7% if ACPA negative

R SanMarti et al. *J Rheumatol*. 2012 Oct;39(10):1929-33

A.S. Russell et al *J. Rheum* 2006

Progression to RA Predicted by RF

HCQ No Obvious Benefit

Table 2. Characteristics of patients with palindromic rheumatism who progressed to RA in comparison with those without progression to RA or other rheumatic diseases (persistent PR).

Characteristic	PR to RA, N = 16	Persistent PR, N = 47	P
Age, yrs	56.7 ± 12.5	52 ± 12.5	0.2
Female, no. (%)	13 (81.3)	35 (74.5)	0.4
Disease duration*, mo, mean ± SD	17.1 ± 17.02	65.4 ± 79.3	0.01
Followup**, mo, mean ± SD	100.8 ± 58.9	89.2 ± 58.2	0.5
RF+, n (%)	14 (87.5)	23 (48.9)	0.006
RF+, mean ± SD†	282.5 ± 405.5	169.7 ± 132.9	0.3
ACPA+, n (%)	11 (68.8)	26 (55.3)	0.3
ACPA, mean ± SD†	628.4 ± 547.4	737.2 ± 617.8	0.6
Hydroxychloroquine treatment, n (%)	52 (73.2)	28 (75.7)	0.41

*From initial symptoms to first ACPA serum determination; **From first serum ACPA measurement to last visit; †Mean values in sera of patients with positive results.
RF: rheumatoid factor; RA: rheumatoid arthritis; ACPA: antibodies against citrullinated peptide/proteins.
R SanMarti et al. *J Rheumatol*. 2012 Oct;39(10):1929-33.

Returning to Our Patient – 11.15.15

- 56 yo man with 24 hr bouts of PR for 10-15 years
- ACPA/RF +
- Risk of getting RA in longstanding PR patient is 30% over 5 years

What do you do?

2012 Seropositive – Treat as RA?

Is PR Intermittent RA

or

RA Waiting to Happen?

Is Synovitis Present in PR During ~~Inter~~critical Period?

- 54 patients with PR, 36 ACPA+
  - Synovial hypertrophy> 2: 33%
  - Power Doppler US: 26%
  - 4 (7.4%) had both

During attack: 7/10 PDUS: not 100%!

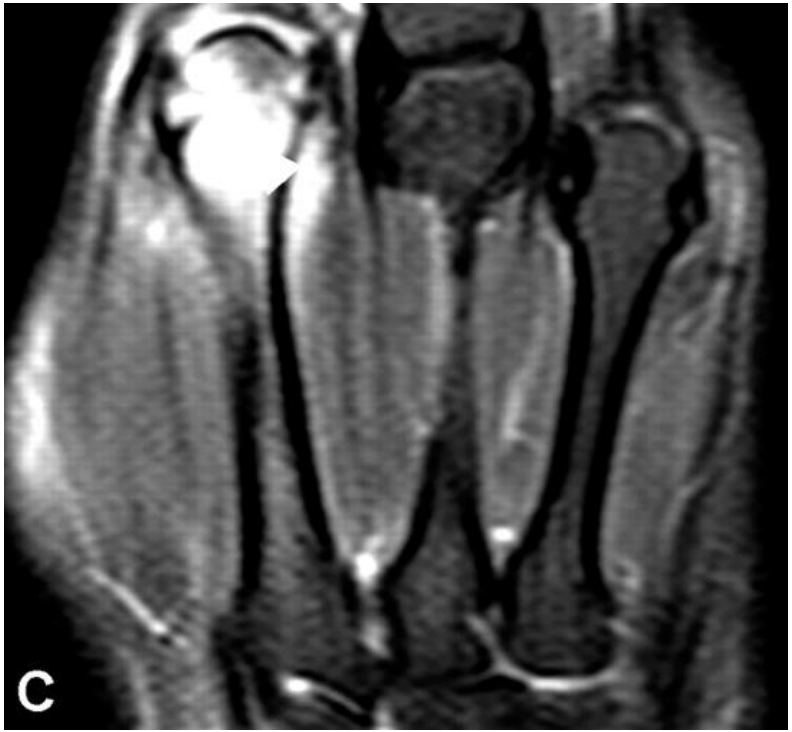
S. Villalba et al. *J. Rheum.* 2014, 41:8.

Is Palindromic Rheumatism Caused by Synovitis?

- 15 ACPA+ patients US and MRI (4) within 24 hours of “onset of arthritis”
- All patients low titer CRP/ESR
- Power Doppler +: 6/15 joints
- Synovitis: +: 9/15 joints
- MRI “florid bone edema” in all 4, 3 “mild synovitis” no PDUS

S. Bugatti et al. *Ann Rheum Dis.* 2012;71:625–626.

Bone Marrow Edema w/o Synovitis in 2nd MCP Head in RP



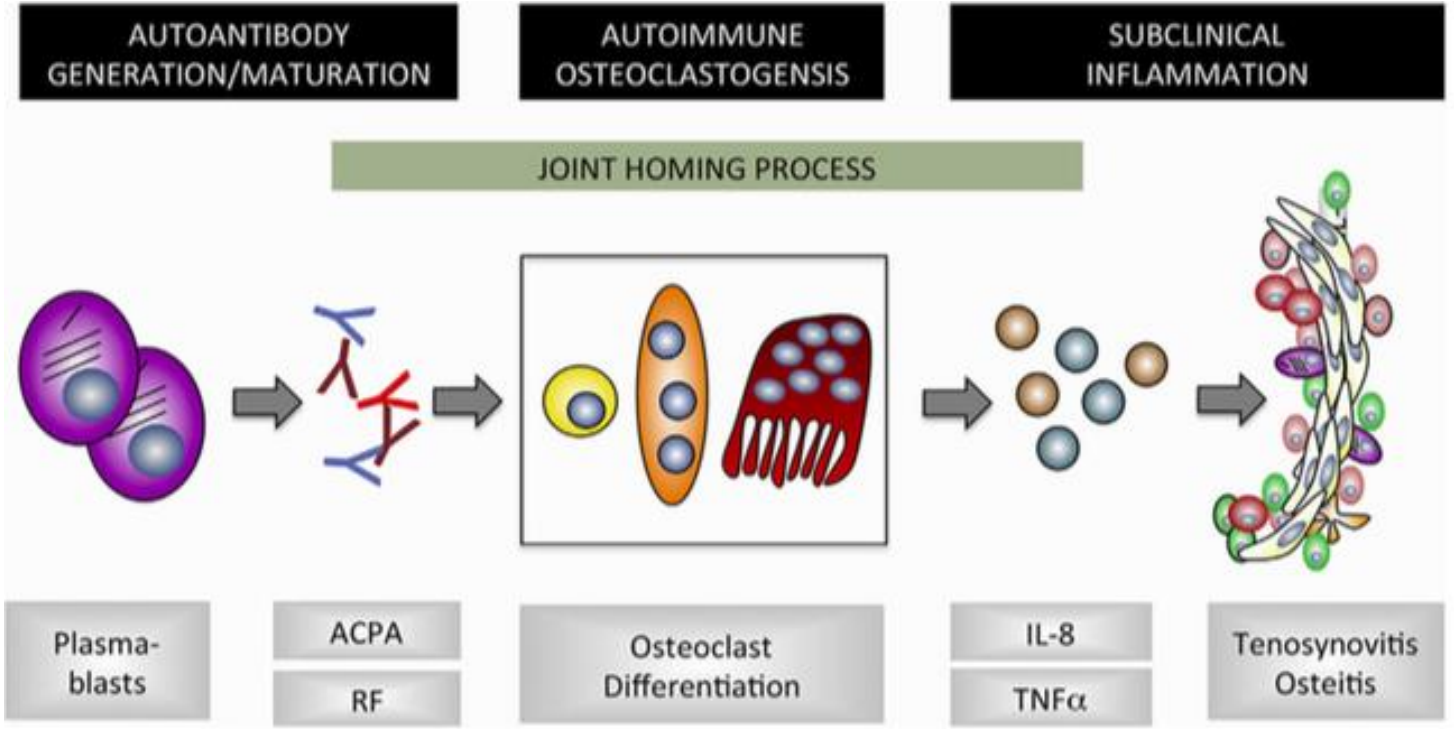
S. Bugatti et al. *Ann Rheum Dis.* 2012;71:625–626.

We Know Bone Marrow Edema on MRI Predicts Erosions.

But What Causes the Bone Marrow Edema?

McQueen FM et al. *Ann Rheum Dis*. 1999 Mar;58(3):156-63.

The Wild World of Anti-Citrullinated Vimentin ACPA and Osteoclastogenesis



G. Schett et al. *Best Practice & Research Clinical Rheumatology.* 31 (2017) 53e58.

What Is Palindromic Rheumatism?

Systemic inflammation

Single Joint Inflammation

Revised Model: Palindromic Rheumatism

Systemic inflammation

Osteoclast activation by ACPA to citrullinated-vimentin

Bone Marrow Edema

Mesenchymal cell entry into joint through vascular channels?

Synovitis

Is this RA “Lite?”

Learning Objectives

- After attending this presentation, the learner should:
  - Appreciate the relationship between Palindromic Rheumatism (PR) and progression to RA
  - Understand the biology of intercritical PR
  - Be able to define the utility of prevention strategies
  - Comprehend the yield of imaging in PR and how it informs PR pathophysiology
  - Should we try to treat PR to prevent RA? How?

The Big Question:

What to do with a seropositive individual without sx, mild sx or intermittent sx (e.g., PR)…….. and no findings?

You have a positive ACPA without sx: what's your likelihood of RA in 3 yrs?

(30-80% for Palindromic Rheumatism in 5 yrs)

A. <5%

B. <10%

C. <20%

D. <30%

E. <50%

F. 60% or greater?

If you had a positive ACPA, what would be your likelihood of getting RA?

- Serum from Swedish twin cohort (n=12,590)
- 350 of 12,590 individuals +anti-CCP2 test
- 103 had RA diagnosis at blood donation (29.4%)
- 21/247 (8.5%) +ACPA developed RA over 3 years
- Pulmonary ILD Clinic
  - 33 high titer ACPA positive patients w/ILD
  - 3 (9%) → RA w/ median follow up 449 days

Hensvold AH et al. *Ann Rheum Dis.* 2017 Jan;76(1):119-125; Fischer A. et al. *Respir Med*. 2012 106 1040–1047.

You have a positive ACPA without sx: what's your likelihood of RA in 1 yr?

(30-80% for PR in 5 yrs…6-16%/year)

A. <5% (8.5/3 years = 3%)
B. <10% (8% if ILD present)
C. <20%
D. <30%
E. <50%
F. 60% or greater?

Patient Is ACPA and/or RF+ with Arthralgia

What's his/her likelihood of RA in 1 year?

A. 10%

B. 20%

C. 30%

D. 40%

E. 50%

Seropositivity with Arthralgia

147 seropositive patients with arthralgia

- 50 ACPA, 52 RF, 45 double positive
- 29/147 (20%) → polyarthritis over 28 months
- 26/95 (ACPA+ACPA/RF) = ~27% (<14%/year)
- 26/29 who progressed were ACPA+ = 90%
- 3/52 (6%) with isolated RF ~<3%/year

Bos WH et al. *Ann Rheum Disease.* 69: 490-4. 2010.

Patient Is ACPA and/or RF + with Arthralgia

What's his/her likelihood of RA in 1 year?

A. 10% <14% if ACPA, 3% if RF
B. 20%
C. 30%
D. 40%
E. 50%

Patient is ACPA + with arthralgia **and** **+ MSUS or MRI or increased ESR/CRP**

What's his/her likelihood of RA in 1 year?

1. 10%
2. 20%
3. 30%
4. 40%
5. 50%

Seropositivity with Arthralgia and Elevated ESR + CRP

- Seropositive with arthralgia, + CRP, ESR or positive MRI/US 40 pts observation
- 16/40 (40%) at 1 year had developed RA
- 34% in RTX arm at 16.5 months

Gerlag D et al. *EULAR*. June 23, 2016.

Patient Is ACPA +, Increased ESR/CRP with Arthralgia

What's his/her likelihood of RA in 1 year?

A. 10%

B. 20%

C. 30%

D. 40%

E. 50%

Annual Transition to RA of ACPA+

- Asymptomatic Twin: 3%
- ILD: 8%
- Palin. Rheum: 6-16%*
- Arthralgia sero+ ACPA>>>RF: 10%
- Arthralgia, sero+ +ESR/CRP 40% and +MRI/MSUS

*(~31-80% in 5-7 years)

Back to Our Patient:

- 2012 seropositive 3 years-Treat as RA?
  Not obviously a synovial disease.
- 11.2015: MTX/HCQ/LEF no effect on attacks.
- Prednisone effective at breaking attack.
- Given prednisone to take for 2 days with attack.

Three Months Later…

- 2.2016: Attack frequency increased
  - Prednisone 20 mg/day x 2 days every week
  - Right shoulder impingement on exam
  - CRP 65 mg/L
  - Prednisone 10 mg/day + MTX 20 mg/week
- 5.2016: Remission!
- Prednisone 1 mg/day/month taper
- 5 mg essential for maintenance

Eighteen Months Later…

- Remission for 2016-7
  - Prednisone 5 mg/day + MTX
- 12.2017 stops Prednisone 5 mg/day
- **Palindromes resume in 3.2018**
- **Quiesce on resumption of Prednisone + MTX**

Is It Worth Trying HCQ?: The Upside

- 2013: 29 yo ACPA/RF+ woman with monthly bouts of PR, given HCQ
- 10.2.17: 4 years in remission, with return of sx approximately 3-4 weeks if she tries to stop (has tried twice)

2019 Take Home Points

- PR more frequent than thought.
- Not obviously a synovial disease. Unclear if this is distinctive from RA.
- ACPA probably predictive of progression, but 16% per year?
- Optimal therapy for PR is unclear. HCQ worth a try it would seem for sx, not prevention of RA.