

# Palindromic Rheumatism as an 'Adolescent' Form of RA



# 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
- **What is this?**

# Beginning of a Disease?

## PALINDROMIC RHEUMATISM

A "NEW," OFT RECURRING DISEASE OF JOINTS (ARTHRITIS, PERIARTHRITIS,  
PARA-ARTHRITIS) APPARENTLY PRODUCING NO ARTICULAR RESIDUES—  
REPORT OF THIRTY-FOUR CASES; ITS RELATION TO "ANGIO-  
NEURAL ARTHROSIS," "ALLERGIC RHEUMATISM" AND  
RHEUMATOID ARTHRITIS

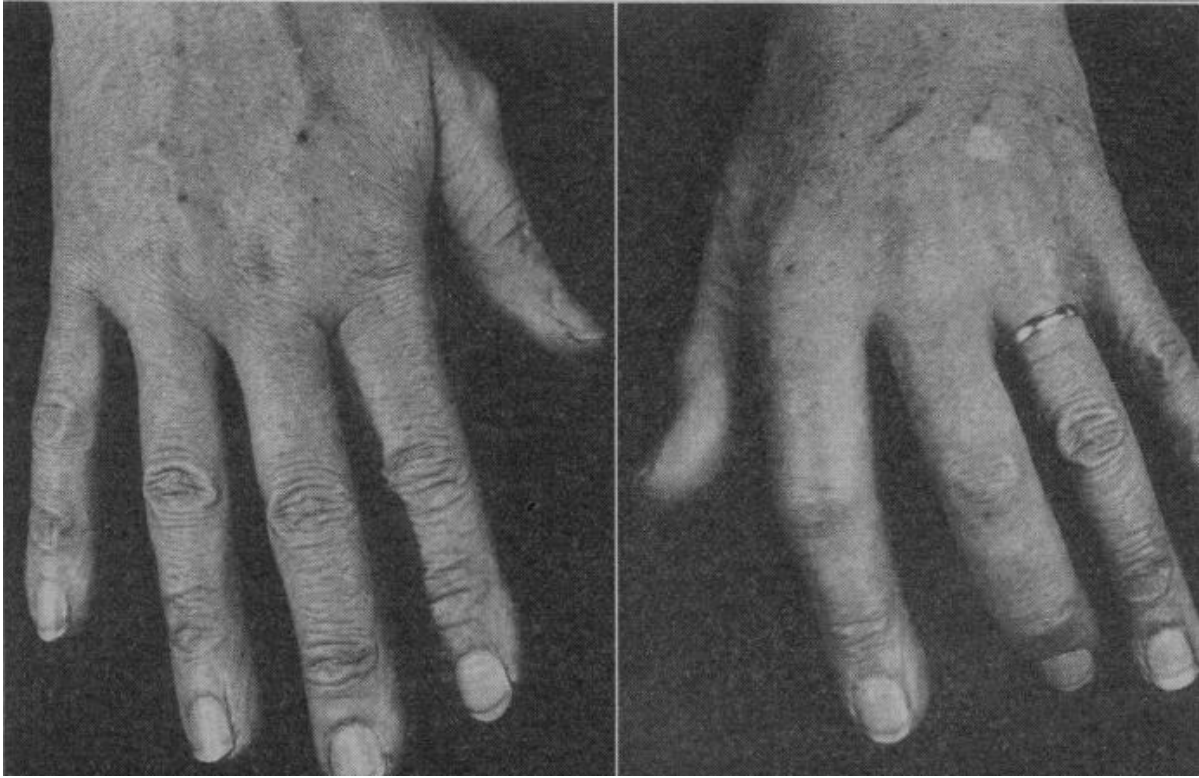
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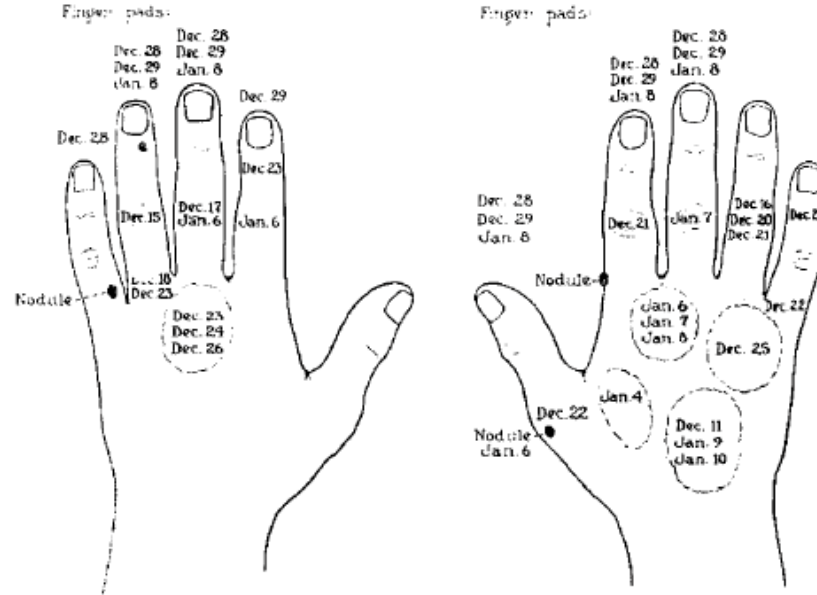


Fig. 7 (case 16) – Sites involved by attacks which occurred in the hands while the patient was under observation at the clinic (Dec. 11, 1936 to Jan. 10, 1937).

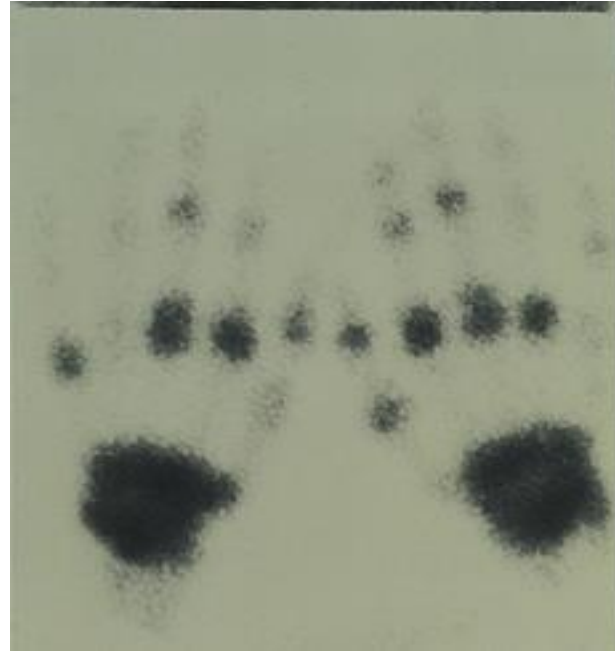
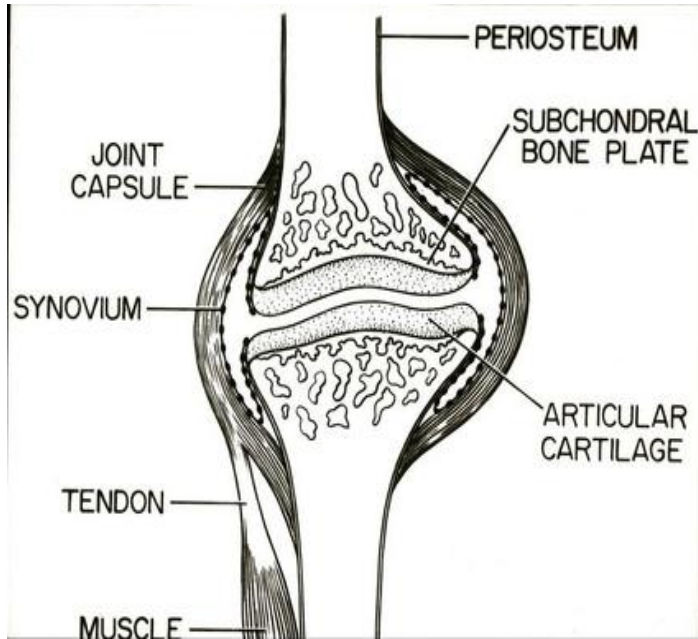
CASE 20 (table 1).—*The case of a noted orthopedist with multiple articular and para-articular attacks.*

A noted orthopedic surgeon, aged 73, was admitted to the clinic Jan. 31, 1938, because of "rheumatism" of thirteen years' duration. In 1924, after he played golf, his right shoulder suddenly became painful for two weeks and then cleared up. Ever since then he has had recurrent attacks of acute arthritis (in various joints) "time and again," according to his estimate five hundred or six hundred attacks in thirteen years. Despite their frequency, all attacks disappeared completely, leaving no residual disability. He stated the

# Learning Objectives

- Understand the relationship of Palindromic Rheumatism (PR) and progression to RA
  - Should we try to prevent? How?
- Understand the biology of intercritical PR
- Comprehend the yield of imaging in PR and how it informs RA pathophysiology
  - Do we treat?

# RA Centers in Synovium, Destroying All Around It?





# 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

TNF, IL-6, GM-CSF

No treatment shown to  
eliminate systemic process

Where does MTX work?

Joint Inflammation  
MΦ, FLS, Cartilage, Bone



# 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.

# 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

# 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%

# Does PR Evolve to RA?

- UK 1959-1977
  - 44-64% progression within 10 years
- Finland 1987
  - 67% over 20 years nearly all within 10yrs

Retrospective, pre-ACPA

More recently.....slightly different?

# In RP Clinic: Progression 16/64 (25%)

*Table 1.* Demographic and serological characteristics of patients with palindromic rheumatism at the time Of fist 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
Follow up**, 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 follow up, 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 pts 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.

# 4 Year Progression to RA: ACPA 30%

## 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 ± 12.2	0.2
Female, no. (%)	13 (81.3)	35 (74.5)	0.4
Disease duration*, mo, mean ± SD	17.1 ± 17.2	65.4 ± 79.3	0.01
Follow up**, 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 <sup>†</sup>	282.5 ± 405.5	169.7 ± 132.9	0.3
ACPA+, n(%)	11 (68.8)	26 (55.3)	0.3
ACPA values, mean ± SD <sup>†</sup>	628.4 ± 547.4	737.2 ± 617.8	0.6
Hydroxychloroquine treatment	12 (75)	37 (78.7)	0.5

\*From initial symptoms first ACPA serum determination. \*\* From first serum ACPA measurement to last visit. † Mean values in sera of patients with positive results. RA: rheumatoid arthritis; PR: palindromic rheumatism; RF: rheumatoid factor; ACPA: antibodies against citrullinated peptide/proteins.

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

# Contrasting Data?

- 61 patients with PR <1 yr
- Retrospective sera<sup>1</sup>
  - 27 pts (47%) progressed to RA at 5 yr
  - 24/27 were ACPA+ (83%)
- Different duration to ACPA following onset (< 1 yr (83%) vs 4.5 yrs (30%))
  - Selection for slow progressors?

# Frequency of Progression of ACPA+ Palindromic Rheumatism to Seropositive RA

Progression to seropositive RA over 5 years:

- a) 10%
- b) 30% if sx for over 4 years
- c) 50%
- d) 70%
- e) >80% if sx for 1 year

Older longer studies 44 — 67%



# 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 PR patient is 30% over 5 years...lower if no progression over years
- What do you do?

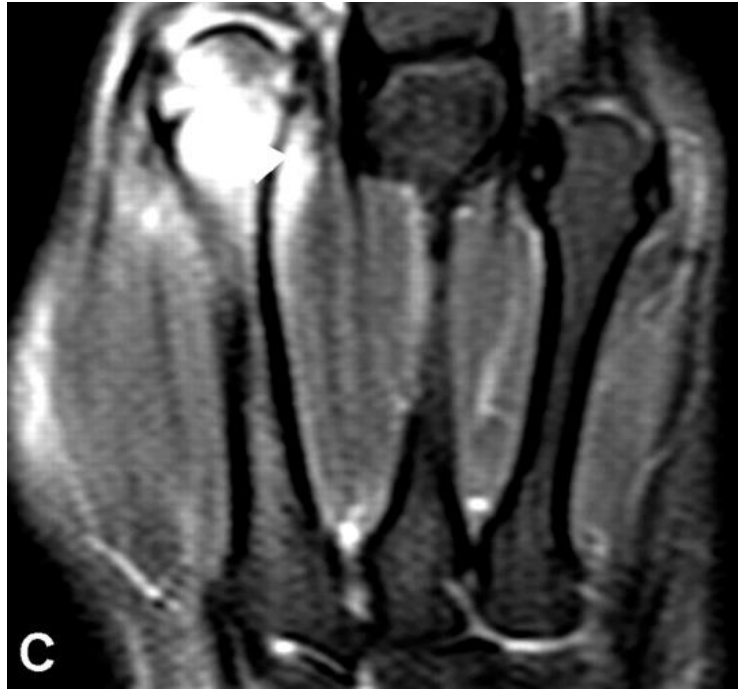
Is PR Intermittent RA  
or  
RA Waiting to Happen?

# Curious Finding #1

## Is Synovitis Present in PR at Flare?

- 15 ACPA+ patients US & 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

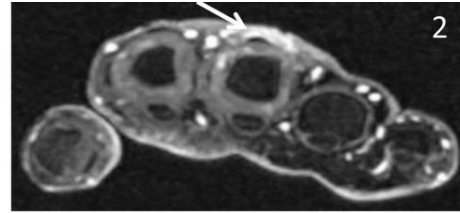
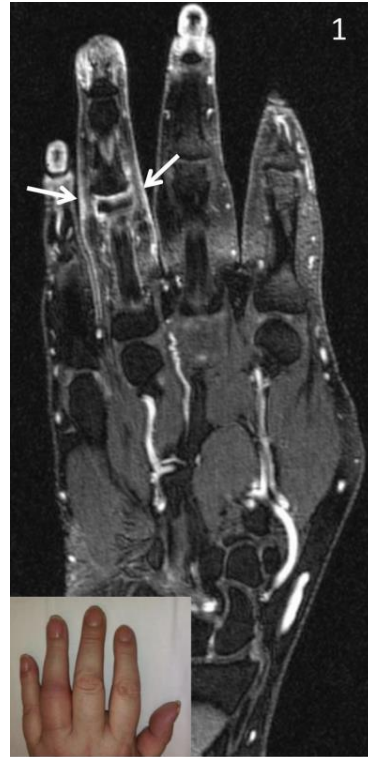
# Bone Marrow Edema W/O Synovitis in 2<sup>nd</sup> MCP Head in RP



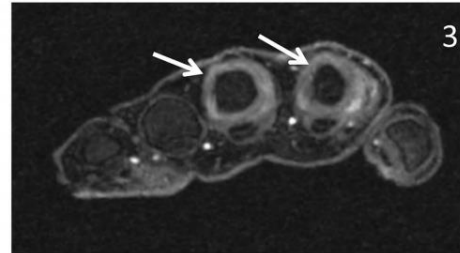
# Palindromic Rheumatism Not Palindromic Arthritis!

- 19/31 (61%) had 'extra-capsular inflammation' ECI
- 12/19 (63%) had no synovitis
- ECI w/o synovitis was specific for PR (42% PR vs 4% NORA ( $p=0.003$ ) and 6% CCP+ at risk ( $p=0.0012$ ))
- Eleven PR flares were captured by MRI

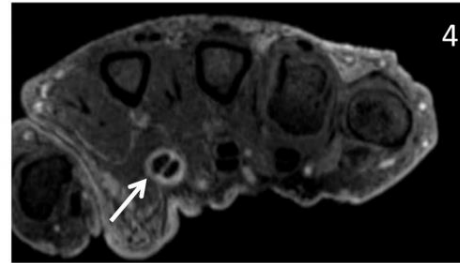
Extra-synovial  
enhancement  
4th PIP



Peri-tendinous edema



MCP synovitis



Tenosynovitis

# Palindromic Rheumatism Is Not Synovial

Systemic inflammation



Single Joint 'Peri-Arthritis'

# Revised Model: Palindromic Rheumatism

Systemic inflammation



Peri-articular Disease that can remit  
w/o damage?

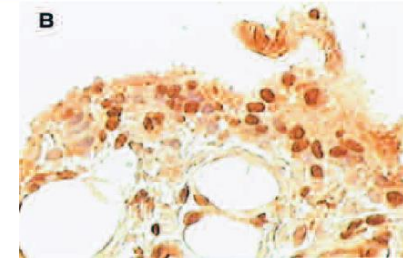
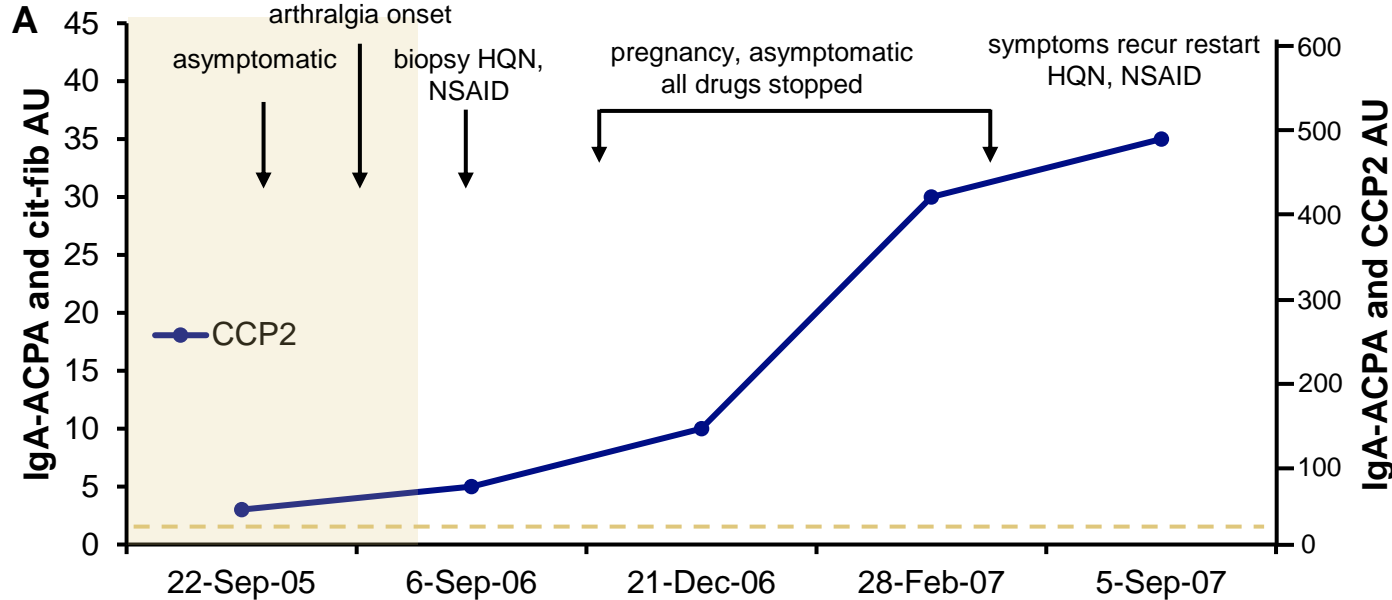


Synovitis gets involved & chronicity results

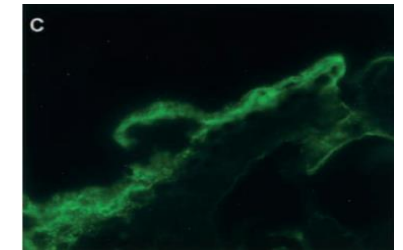
**Is this how RA starts?**



# Standard Model: 18-Year Old Asymptomatic Female in Multi-RA Family



Synovial staining for citrullinated antigens



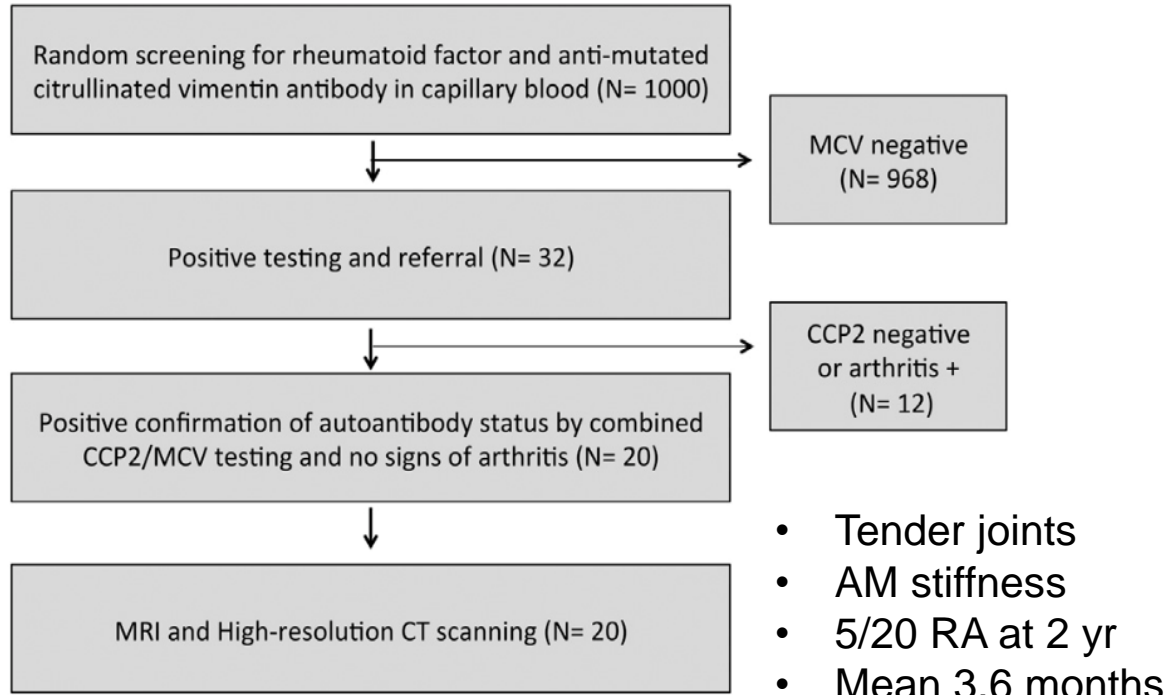
Synovial staining for C3  
Similar results were seen with IgG, IgA, and fibrin staining

\*ACPA

RA=rheumatoid arthritis; CCP=anti-cyclic citrullinated peptide; ACPA=anti-citrullinated protein/peptide antibodies; RF=rheumatoid factor; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; cit-fibrinogen=citrullinated fibrinogen; HQN=hydroxychloroquine  
Adapted from Willemze A et al. *J Rheumatol.* 2008;35(11):2282-2284.

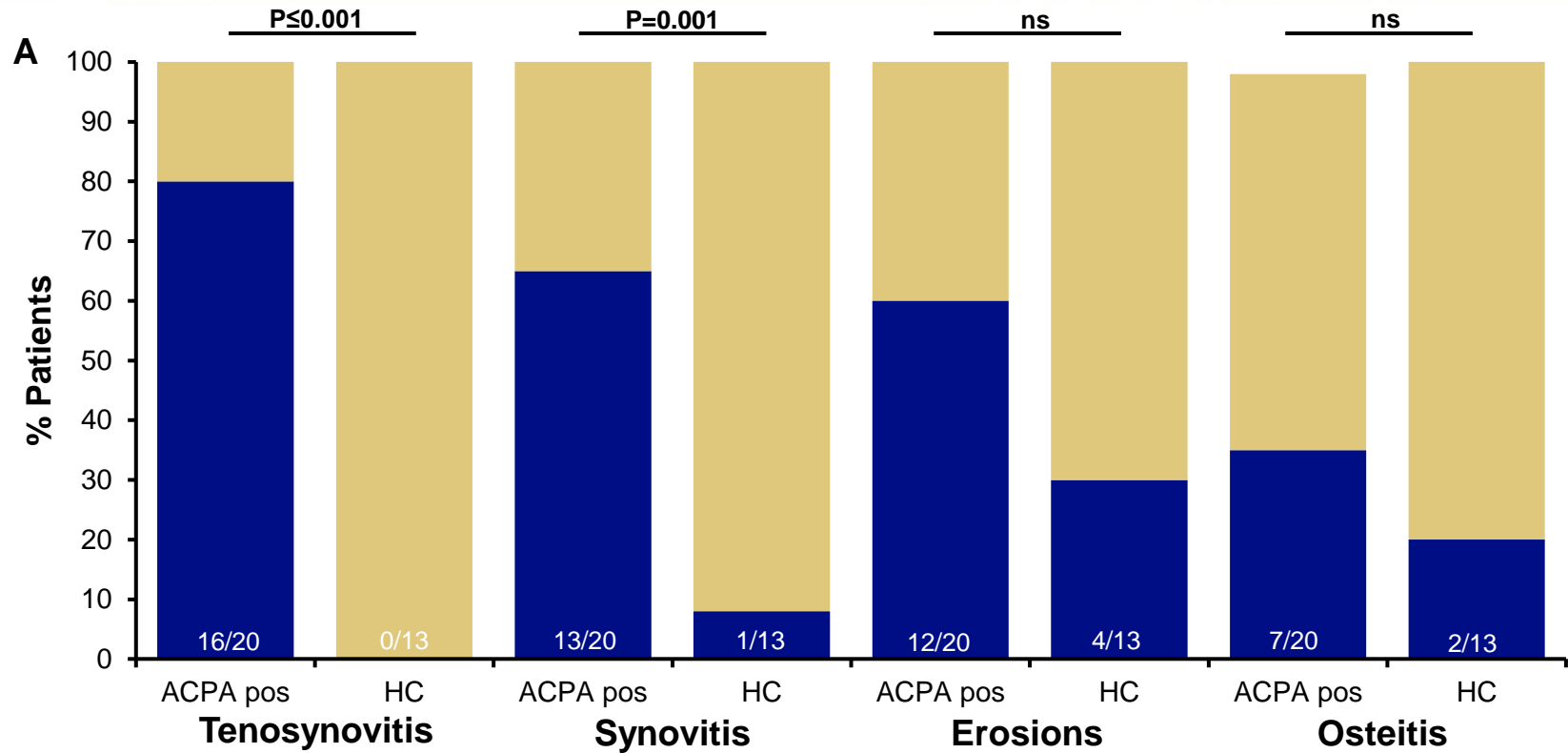
# How Does Systemic Inflammation Target the Synovium? Overlap Permitted

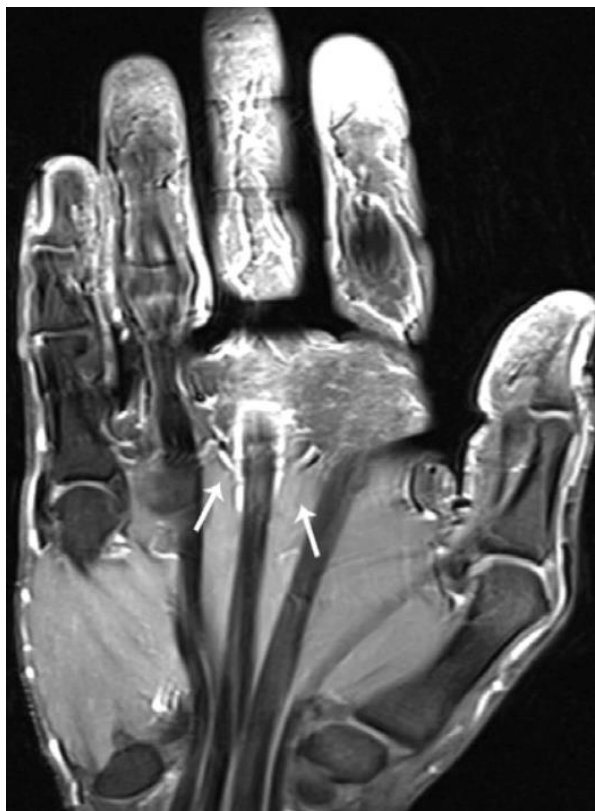
- The immune complex deposition model
  - ‘Outside In’
- The osteitis model
  - ‘Inside Out and In’ Marrow → Synovium
- The tendon/enthesis as way station?
  - How do you prove?

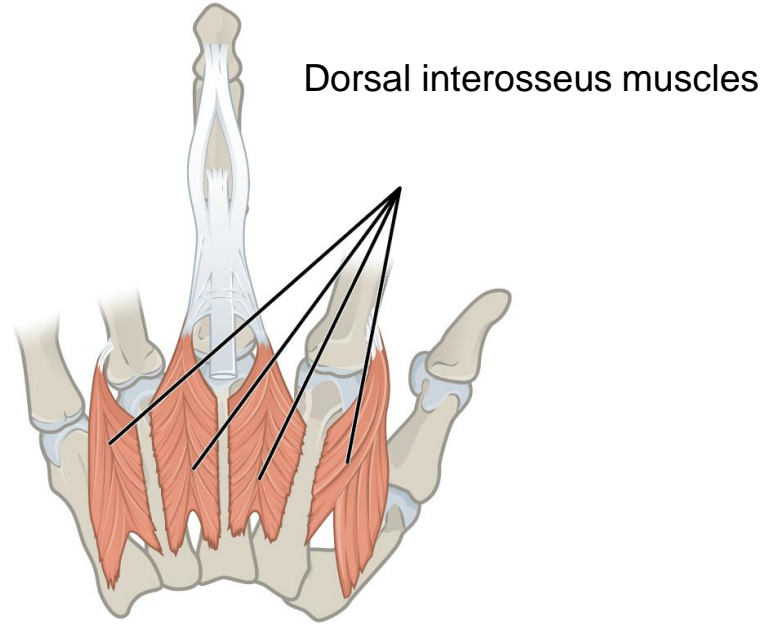


# Tenosynovitis: 80% ACPA+/No Healthy Controls

## Proximal = Distal Compartments







Explains loss of MCP  
extension without MCP swelling?

# Palindromic Rheumatism as an 'Adolescent' Extra-Syform of RA

- Confirmation that transition to RA requires the synovium preceded by 'residence' tendinous or enthesal gateways<sup>1,2</sup>

# Learning Objectives

- Appreciate the relationship of Palindromic Rheumatism (PR) and progression to RA
- Should we try to prevent? How?
- Understand the biology of intercritical PR
- Comprehend the yield of imaging in PR and how it informs RA pathophysiology
- Do we treat?



# 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

# Three Months Later...

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

# 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)

# 2017 Take Home Points on PR

- More frequent than thought
- Not obviously a synovial disease
- ACPA predictive of progression, ~16% per year at onset?
- Optimal therapy for PR is unclear. HCQ worth a try it would seem for sx, not prevention of RA