When widespread pain is more than fibromyalgia: Aerial journey along rheumatology lane

11/10/2023

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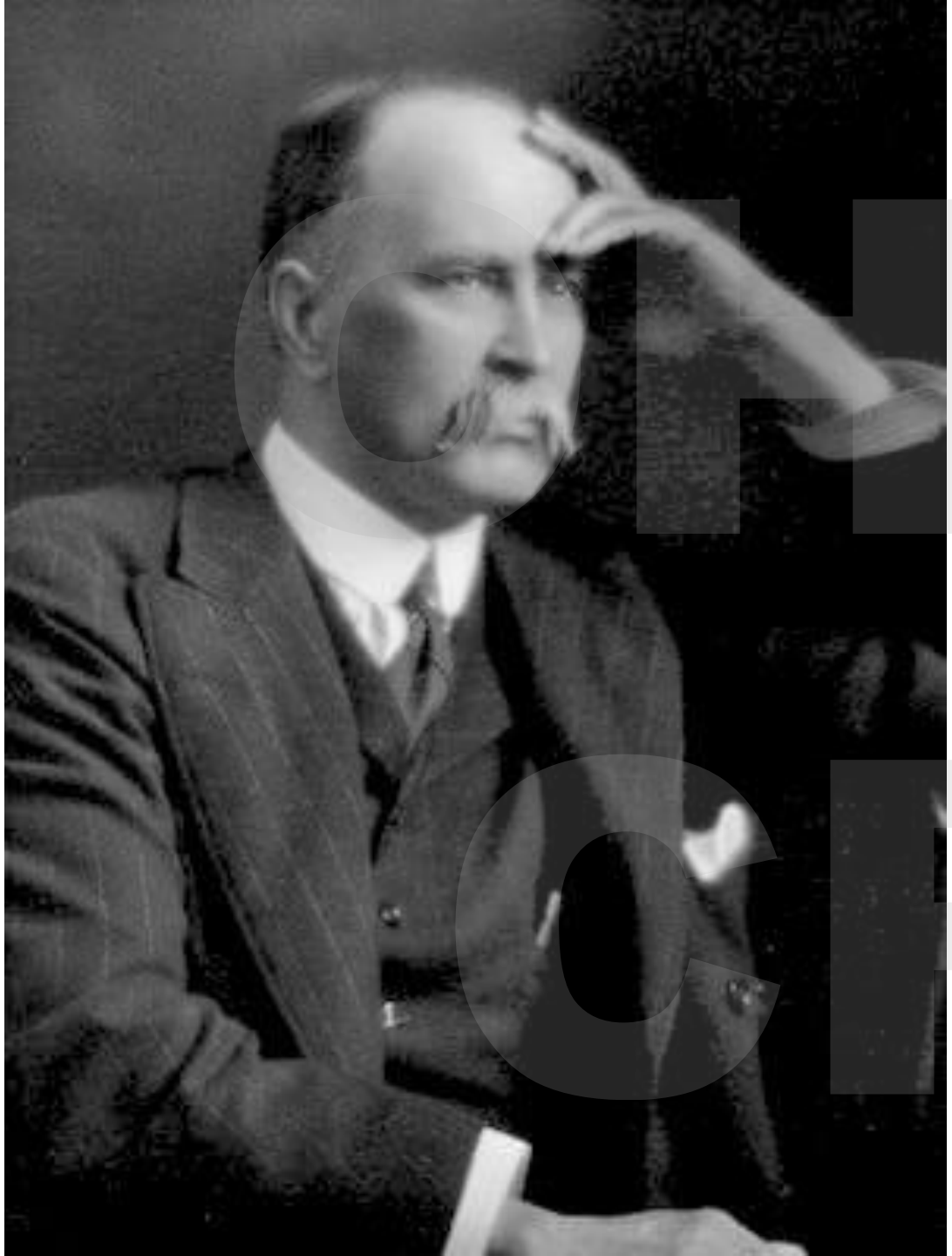
"When an arthritis patient walks in the front door, I feel like leaving by the back door."



Sir William Osler

"Father of Modern Medicine”

What you will take away

- Approach to widespread pain
  - Differential diagnosis
  - History and exam items
  - Tailored laboratory testing
  - When to consider inflammatory diseases
    - Polymyalgia rheumatica
      - Diagnosis
      - Treatment


OHSU
CPD

Case

- A 62 year-old woman is evaluated for widespread pain
- She reports gradual onset over 3 months
- Pain is diffuse over her neck and upper back, upper arms, hips and upper thighs
- Pain is associated with fatigue, poor sleep, and difficulty concentrating at work
- After searching Google, she wonders if she has developed fibromyalgia

What is Fibromyalgia?

- Widespread pain associated with fatigue, unrefreshed sleep, and cognitive dysfunction (brain fog), and multisystem symptoms
- Prevalence 2-4%, up to 20-30% in selected clinical groups
- Twice as common in women
- Genetic factors
- Associated with other chronic painful conditions as well as mood disturbances
- Unknown pathophysiology
  - Abnormal central pain processing

Sarzi-Puttini et al. Fibromyalgia: an update on clinical characteristics, aetiopathogenesis and treatment. Nature Reviews Rheumatology. 2020,16:645.

AMERICAN COLLEGE OF RHEUMATOLOGY (ACR)
PRELIMINARY DIAGNOSTIC CRITERIA FOR FIBROMYALGIA[1]

PART 1: WIDESPREAD PAIN INDEX

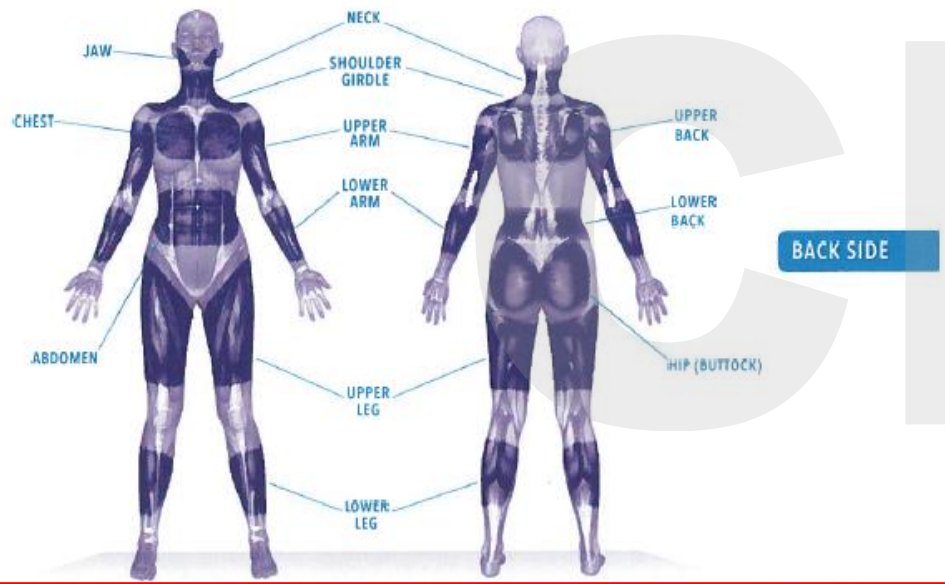
HOW TO CALCULATE THE PATIENT'S WIDESPREAD PAIN INDEX (WPI)

1. Using the list of 19 body areas, identify the areas where the patient felt pain over the **past week**. As a visual aid, front/back body diagrams are included.
   – Each area identified on the list counts as 1
2. Total the number of body areas (the WPI score can range from 0 to 19).

Write the patient's WPI score here: _____.

Identify the areas where the patient felt pain over the **past week**

❑ Shoulder girdle, left	❑ Lower arm, right	❑ Lower leg, left	❑ Abdomen
❑ Shoulder girdle, right	❑ Hip (buttock), left	❑ Lower leg, right	❑ Neck
❑ Upper arm, left	❑ Hip (buttock), right	❑ Jaw, left	❑ Upper back
❑ Upper arm, right	❑ Upper leg, left	❑ Jaw, right	❑ Lower back
❑ Lower arm, left	❑ Upper leg, right	❑ Chest	



PART 2A: SYMPTOM SEVERITY SCALE (LEVELS OF SEVERITY)

HOW TO MEASURE THE PATIENT'S LEVEL OF SYMPTOM SEVERITY

1. Using a scale of 0 to 3, indicate the patient's level of symptom severity over the **past week** in each of the 3 symptom categories. Choose only 1 level of severity for each category.
   – The score is the sum of the numbers that correspond to the severity levels identified in all 3 categories
2. Total the scale numbers for all the 3 categories and **write the number here:** _____.

Fatigue	Waking unrefreshed	Cognitive symptoms
❑ 0 = No problem	❑ 0 = No problem	❑ 0 = No problem
❑ 1 = Slight or mild problems; generally mild or intermittent	❑ 1 = Slight or mild problems; generally mild or intermittent	❑ 1 = Slight or mild problems; generally mild or intermittent
❑ 2 = Moderate; considerable problems; often present and/or at a moderate level	❑ 2 = Moderate; considerable problems; often present and/or at a moderate level	❑ 2 = Moderate; considerable problems; often present and/or at a moderate level
❑ 3 = Severe; pervasive, continuous, life-disturbing problems	❑ 3 = Severe; pervasive, continuous, life-disturbing problems	❑ 3 = Severe; pervasive, continuous, life-disturbing problems

PART 2B: SYMPTOM SEVERITY SCALE (OTHER SOMATIC SYMPTOMS)

HOW TO DETERMINE THE EXTENT OF THE PATIENT'S OTHER SOMATIC SYMPTOMS

Using the symptoms list on the following page, determine the extent of other somatic symptoms the patient may have experienced over the **past week**.

1. Determine the quantity of somatic symptoms using the list on the following page.
2. Using your best judgment, calculate the score that matches the quantity of those somatic symptoms and **write the number here:** _____.

Add the scores from Parts 2a and 2b (the Symptom Severity score, or SS score, can range from 0 to 12.)
Write the patient's SS score here: _____.

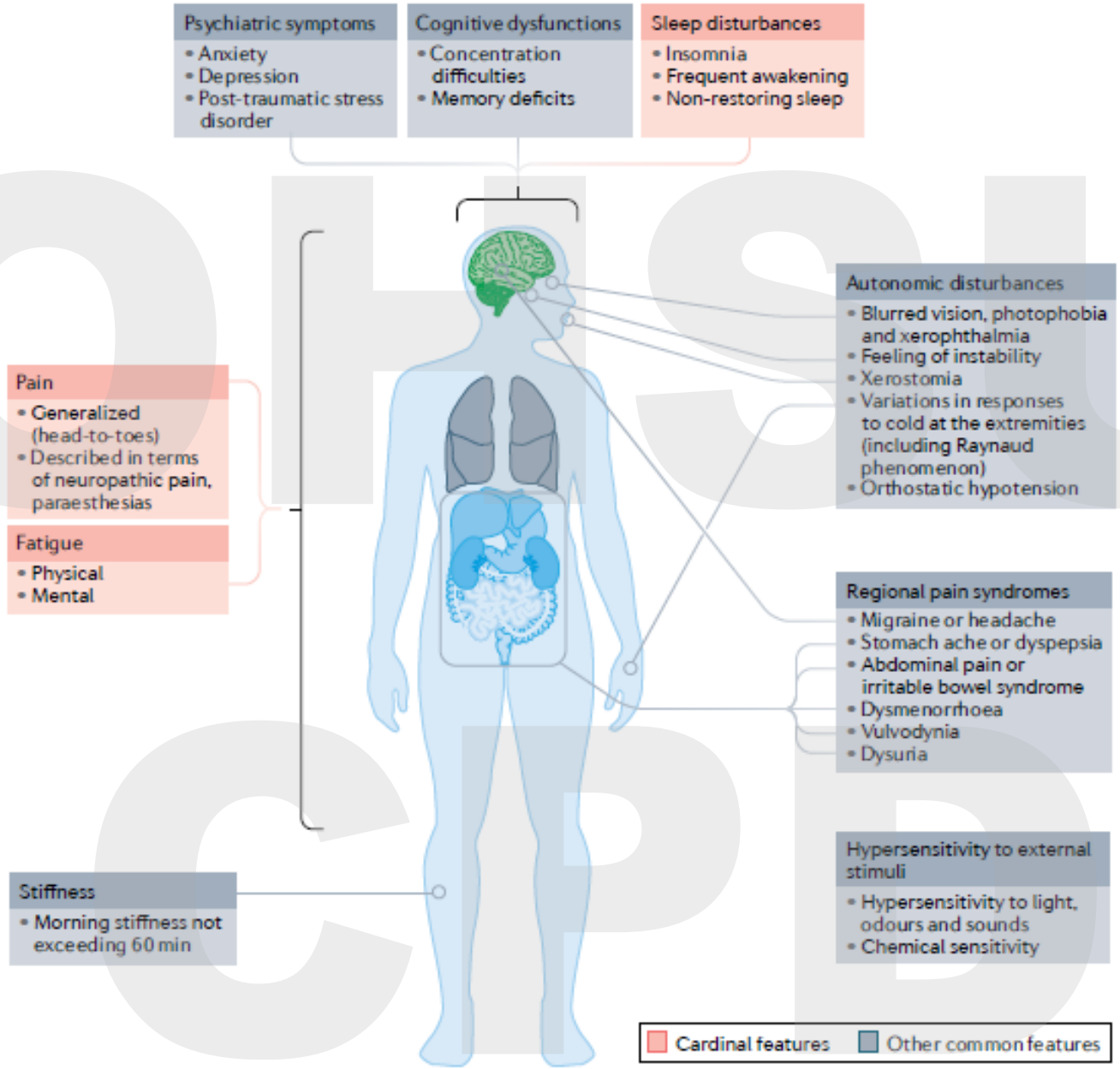
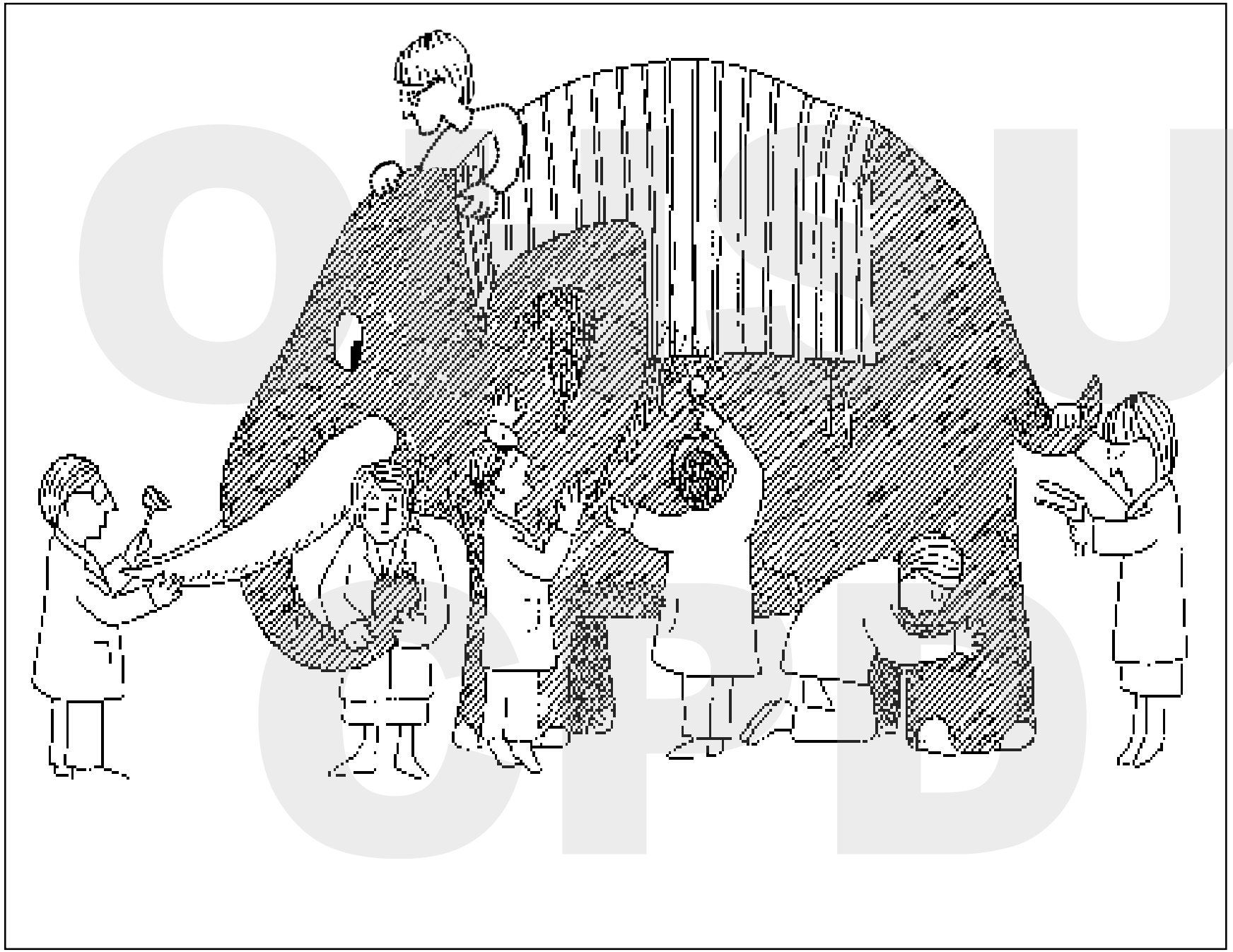


Fig. 2 | **Principal fibromyalgia symptoms.** Fibromyalgia has a complex symptomatology. Symptoms can be are divided in two groups: cardinal features (shown in pink), which include the most characteristic fibromyalgia symptoms that are pivotal for a diagnosis according to the latest criteria, and other common features (shown in in grey).

Sarzi-Puttini et al. Fibromyalgia: an update on clinical characteristics, aetiopathogenesis and treatment. Nature Reviews Rheumatology. 2020,16:645.



Courtesy Dr. Bennett

“The diagnosis of fibromyalgia is exquisitely clinical”

- Fibromyalgia has no pathognomonic feature
- Diagnostic clues needed by means of thorough history taking
- Physical examination is not diagnostically useful
  - Poor validity and poor reproducibility of tender points
  - But the exam is essential for excluding other diseases that might explain the presence of pain and fatigue
- “Diagnosis of exclusion”
  - May co-exist with inflammatory disorders
    - Up to 30% of patients with rheumatoid arthritis have fibromyalgia

Sarzi-Puttini et al. Fibromyalgia: an update on clinical characteristics, aetiopathogenesis and treatment. Nature Reviews Rheumatology. 2020,16:645.

The differential diagnosis of widespread pain is very broad.

Mechanical

- Multifocal OA
- Multifocal soft tissue rheumatism
- Hypermobility

Endocrine

- Hypothyroidism
- Hypercalcemia
- Hypoaldosteronism

Metabolic

- Vitamin deficiency (D, C, B12)
- Dietary (gluten)
- Toxins

Immune-Mediated

- PMR
- Inflammatory arthritis
  - Rheumatoid A
  - SpondyloA
  - Psoriatic A
- Connective tissue ds
  - SLE, Sjogren
  - Scleroderma
  - MCTD
  - Dermatomyositis

Infections

- Chronic viral infections (HIV, HCV, HBV, chikungunia)
- Long COVID

Drug-induced

- Statins
- Aromatase Inhibitors
- Bisphosphonates
- DPP-4 inhibitors

Cancer

- Metastatic
- Paraneoplastic

Neurologic

- Spinal stenosis
  - Cervical, lumbar
- Neuropathy
- Parkinsonism

Tailoring your history and exam with a differential diagnosis in mind

Mechanical

- Non-inflammatory symptoms
- Worse with use
- Better with rest

Endocrine

- Weight gain
- Cold intolerance
- Skin changes
- Constipation

Metabolic

- Diet
- Exposure
- Habits

Immune-Mediated

- Inflammatory arthritis
- Headaches, scalp tenderness, jaw claudication
- Rash, sicca, oral or nasal ulcers, Raynaud, serositis, nephritis
- Axial symptoms, psoriasis, IBD, uveitis, plantar fasciitis, tendonitis

Infections

- Blood transfusion
- Sexual history
- Travel history
- Recent illnesses

Drug-induced

- Medication reconciliation

Cancer

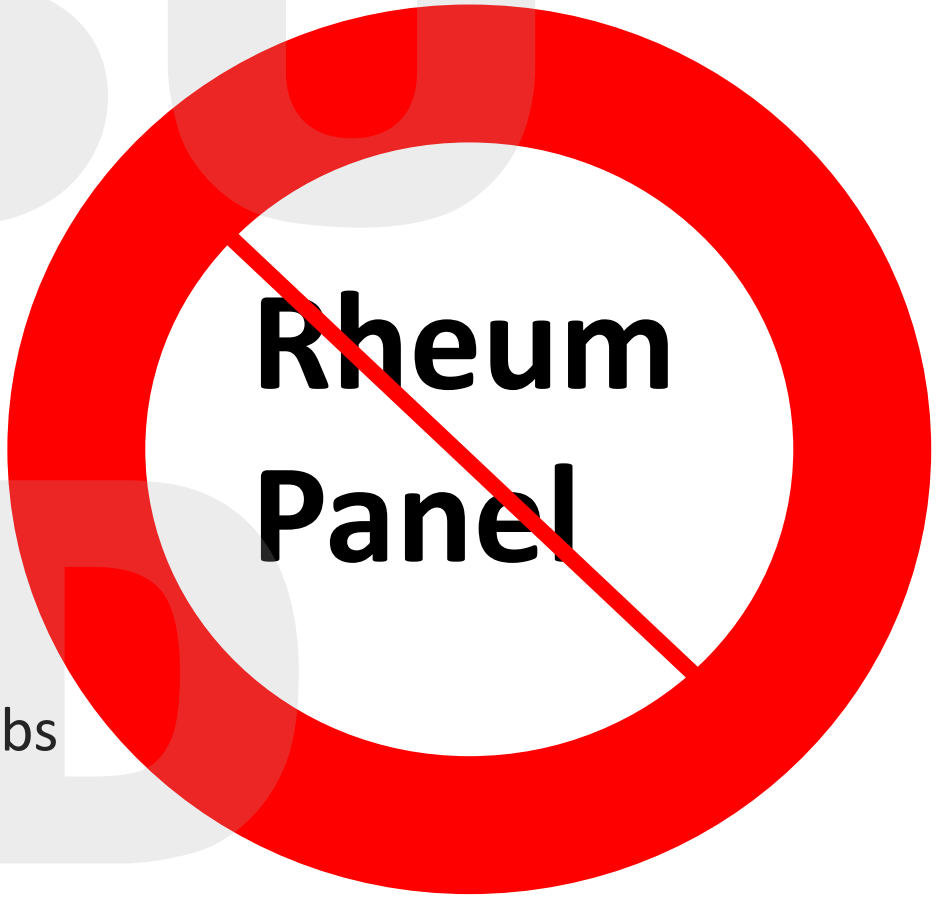
- Weight loss
- Night time pain
- Cancer screening
- Family history

Neurologic

- Paresthesia
- Weakness
- Radicular pain
- Neuropathic pain

Which tests are recommended?

- Basic labs:
  - Cbc with differential
  - Chem 7, calcium, phosphorus, magnesium
  - Liver function panel
  - ESR, CRP
  - Vitamin D, TSH, CPK
  - Urinalysis
- Additional labs
  - Based on clues from history, exam, and initial labs




CISL
CPD

Back to the case: Additional history

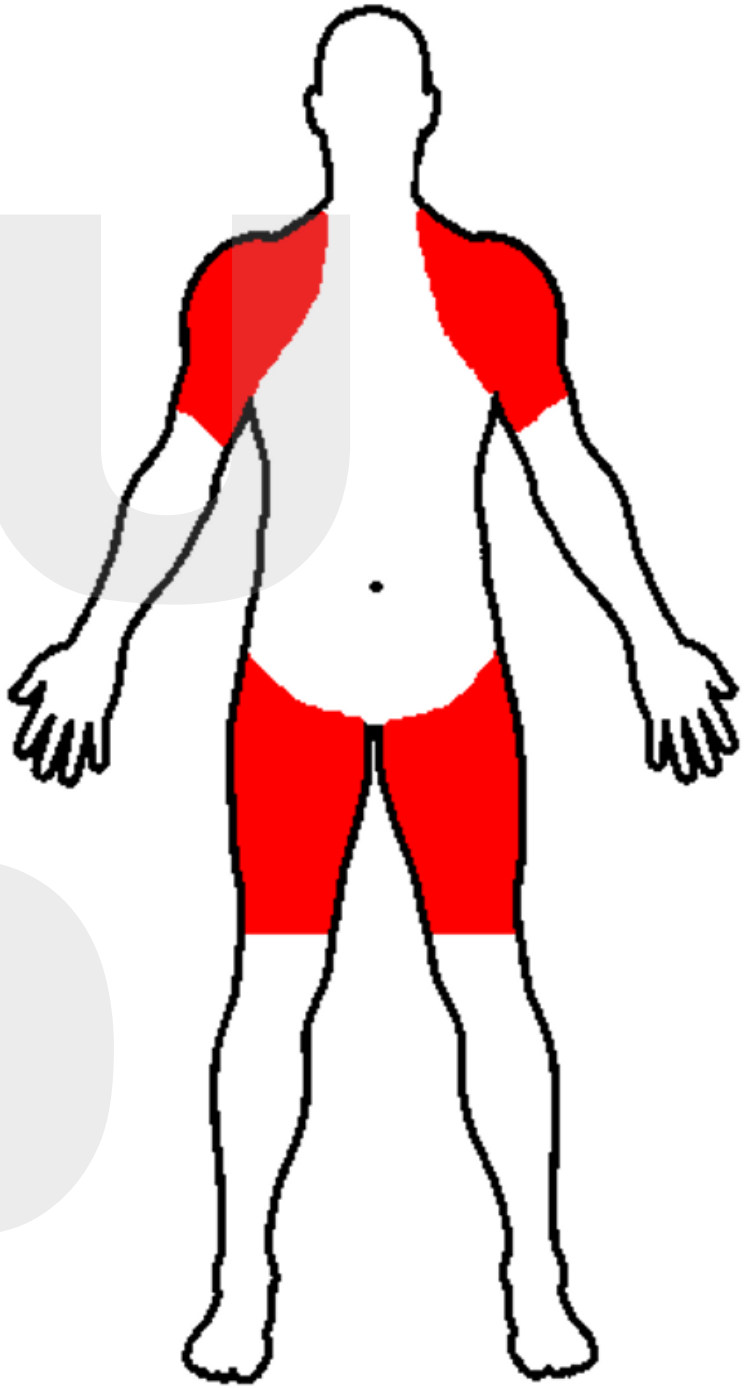
- Gradual and progressive onset over 3 months
  - Myalgias in her shoulder and hip regions
  - Neck and low back pain
  - Mornings are worse time of day, better in the afternoon
  - Wakes up at 4 am due to shoulders and hips aching
  - AM stiffness 2 hours
  - Difficulty raising her arms up to brush her teeth, wash her hair
  - Difficulty getting out of bed or out of the car after a short drive
- Not sleeping well, fatigue, brain fog
- Weight loss, low grade fever
- ROS negative for headaches, jaw claudication, dry eyes/mouth, oral/nasal ulcers, rashes, psoriasis, Raynaud, joint swelling

Back to the case: Additional history

- PMH/Medications
  - Hypertension, on lisinopril for 5 years
  - Hyperlipidemia, on atorvastatin for 5 years
  - Hypothyroidism, on levothyroxine, recent TSH nl
  - Hypovitaminosis D, on daily cholecalciferol
  - Hand osteoarthritis, occasional acetaminophen
- No alcohol, no tobacco, no drugs
- Neg mammogram, pap smear, colonoscopy
- Used to exercise regularly up until 3 months ago
- Stable family life, no stressors

Back to the case: Exam

- Slow to move in the exam room
- Weight down by 5lbs, BP & P nl
- Active ROM of the shoulders and hips is painful and limited
- Better ROM when passively ranged
- No reproducible tenderness
- Peripheral joints with non-tender hand osteoarthritis changes
- Muscles are not weak, reflexes are normal



Case Considerations

- Fibromyalgia
  - For: Widespread pain, poor sleep, fatigue, brain fog
  - Against: Age of onset atypical, no triggers, no mood disorder, no hyperalgesia on exam, no associated chronic painful conditions, presence of fever/weight loss, functional limitations

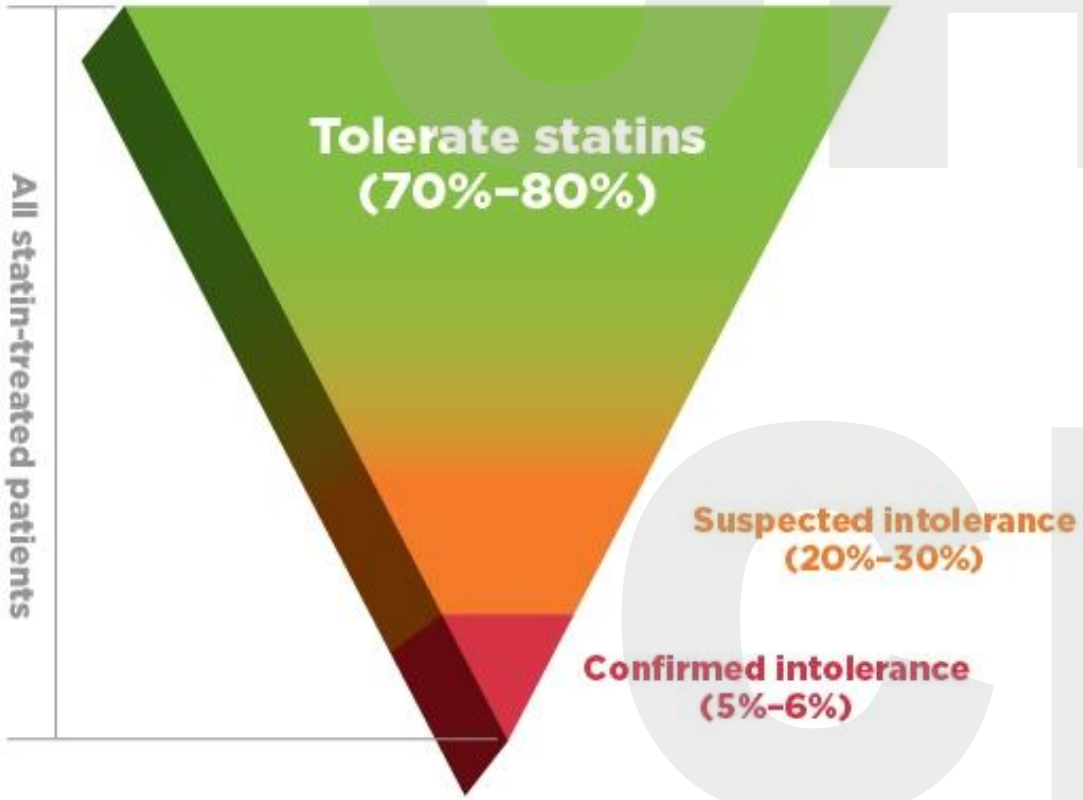
Case Considerations

- Fibromyalgia
- Widespread OA
  - For: Hand osteoarthritis, appropriate age group
  - Against: Subacute and widespread onset not typical, multiple large joints affected at once, sudden change in function, passive > active ROM

Case Considerations

- Fibromyalgia
- Widespread OA
- Statin-associated muscle symptoms

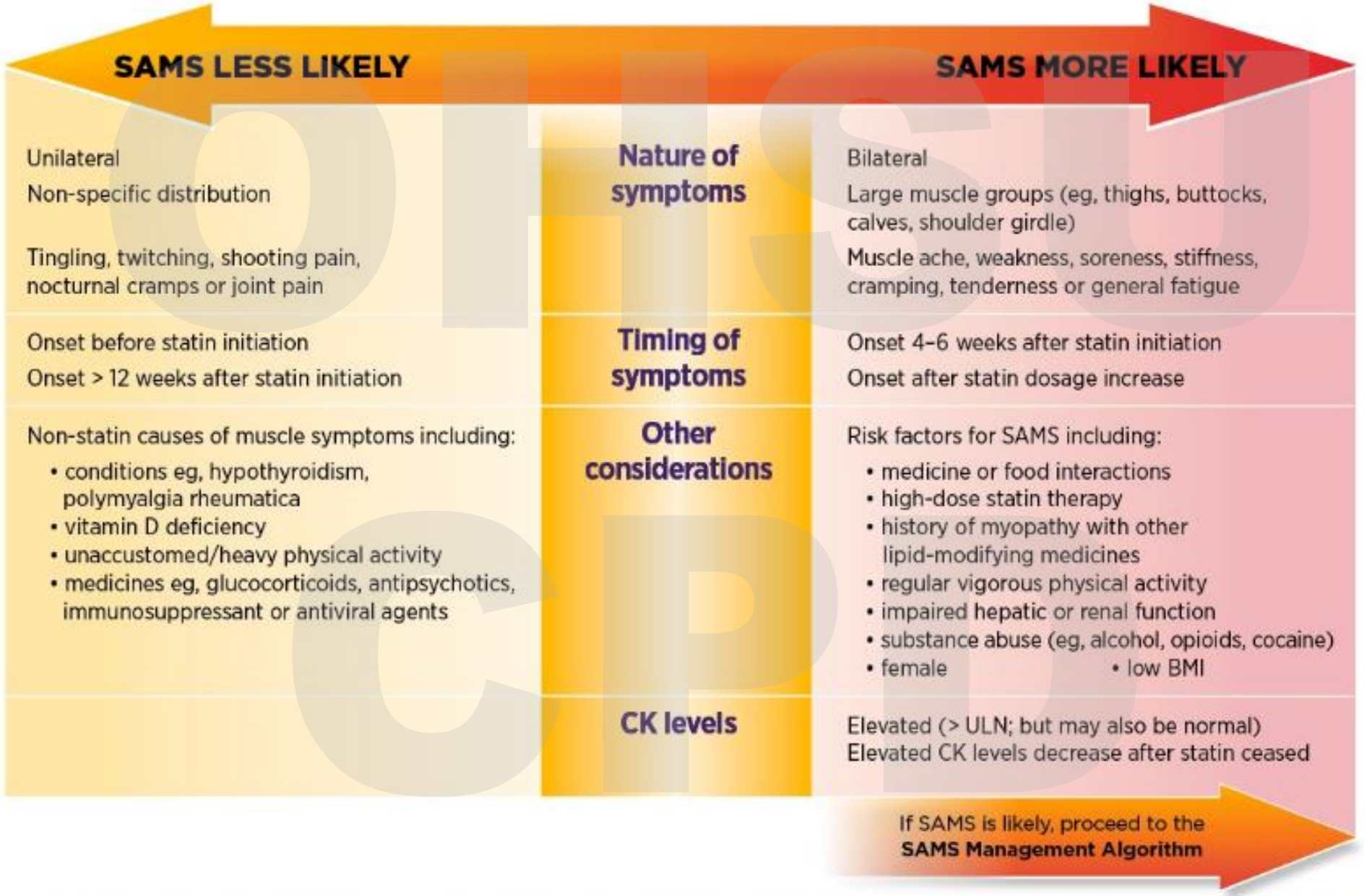
Statin-Associated Muscle Symptoms



- Statins have been associated with a nocebo effect
- Myalgia:
  - 1-5% in blinded RCT vs. 7-29% in observational studies
- Myopathy: ~1:10,000/yr
- Rhabdomyolysis: ~1:100,000/yr
- Rare autoimmune necrotizing myopathy, anti-HMGcoAR, continues even once off statins

https://www.nps.org.au/professionals/managing-lipids/statin-associated-muscle-symptoms-sams#r4

Statin-Associated Muscle Symptoms



https://www.nps.org.au/professionals/managing-lipids/statin-associated-muscle-symptoms-sams#r4

Case Considerations

- Fibromyalgia
- Widespread OA
- Statin-associated muscle symptoms
  - For: On statin
  - Against: Duration of statin use and tolerance to date

Case Considerations

- Fibromyalgia
- Widespread OA
- Statin-associated muscle symptoms
- Polymyalgia rheumatica

Back to the case

- Wbc 5
- Hgb 11.5 MCV 87
- Plt 410
- ESR 35
- CRP 13 mg/L
- Alk phos 145
- Albumin 3.8
- ALT, AST nl
- TSH 2
- Vitamin D 43
- Calcium 9.8
- Glucose 92
- CPK 67

Polymyalgia Rheumatica: Epidemiology

- Age of onset > 50, peaks at age 70-75
- Annual incidence 12-60/100,000
- Prevalence 6/1000 persons older than 50
- Highest in patients of Northern European descent
- 2/3 are women
  - Lifetime risk 2.4% for women, 1.7% for men
- Unknown etiology
  - Cyclical incidence, winter time
  - Infectious association (Mycoplasma, chlamydia pneumonia, parvovirus)
  - Genetics: HLA-DRB1, cytokine polymorphisms

Matteson & Dejaco Ann Int Med 2017
Mathmood et al. CCJM 2020

Polymyalgia Rheumatica: Clinical manifestations

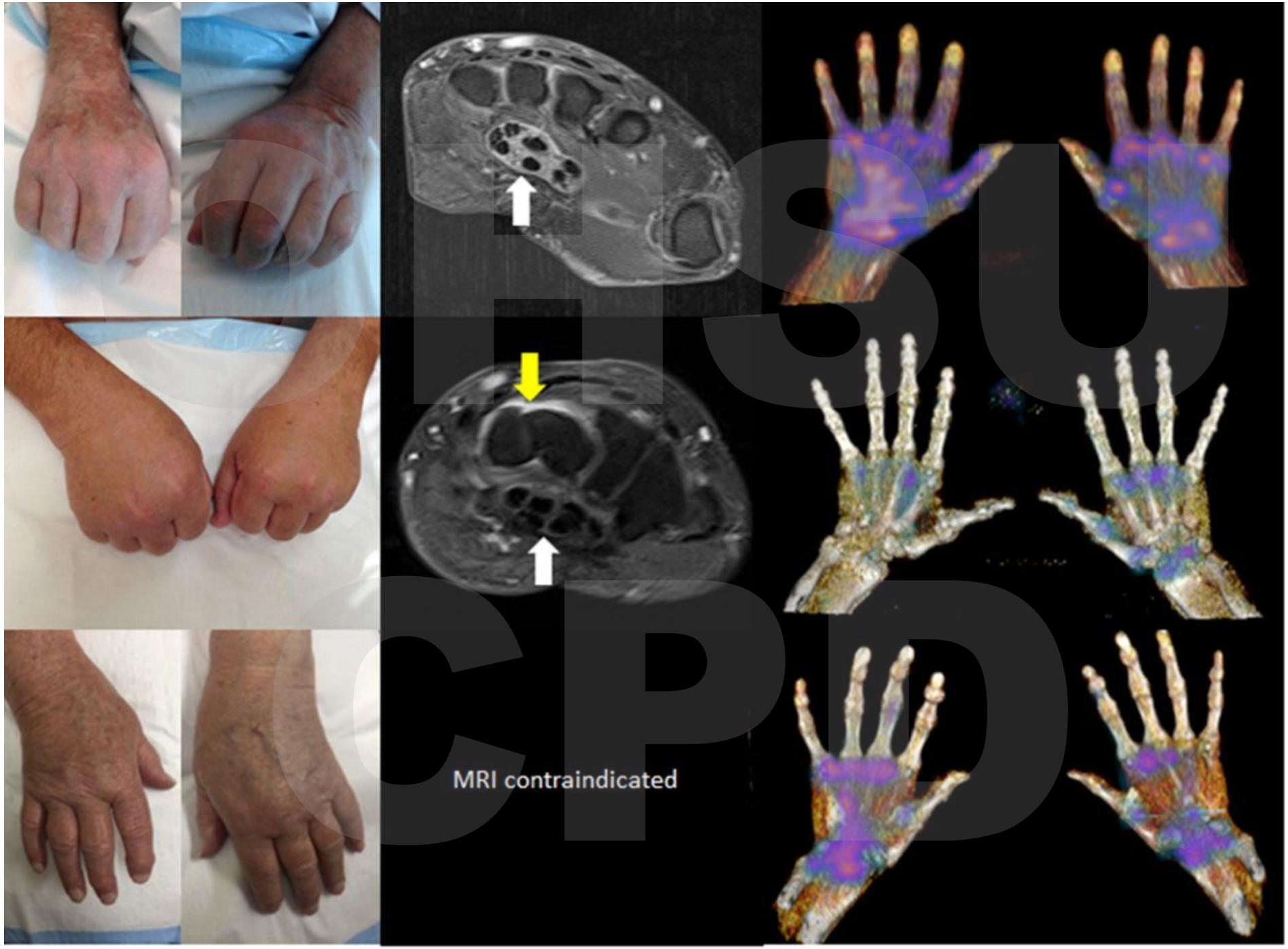
- Symptoms for 2-3 months before diagnosis
- No diagnostic criteria
- Cardinal features:
  - Abrupt onset proximal pain & stiffness neck / shoulder girdle and often hip girdle
  - Trouble rising from a chair, getting out of bed, lifting arms to comb hair
  - Bi-laterality is key
  - AM Stiffness > 30 minutes, stiffness worse after periods of rest
- Systemic symptoms > 50%
  - Low grade fever
  - Anorexia, Weight loss
  - Fatigue, malaise

Matteson & Dejaco Ann Int Med 2017
Mathmood et al. CCJM 2020

Polymyalgia rheumatica: Exam

- Reduced active & passive ROM of shoulders and hips
  - Shoulder elevation
  - Hip flexion
  - Stiffness and pain with movement, less tenderness to palpation
  - Sensation of weakness, but muscle power normal
- Distal MSK manifestations 25-50%
  - Non erosive peripheral arthritis (wrists, knees, not feet)
  - Peripheral tenosynovitis and impressive soft tissue edema (RS3PE: remitting seronegative symmetrical synovitis with pitting edema)
  - Carpal tunnel syndrome

Matteson & Dejaco Ann Int Med 2017
Mathmood et al. CCJM 2020

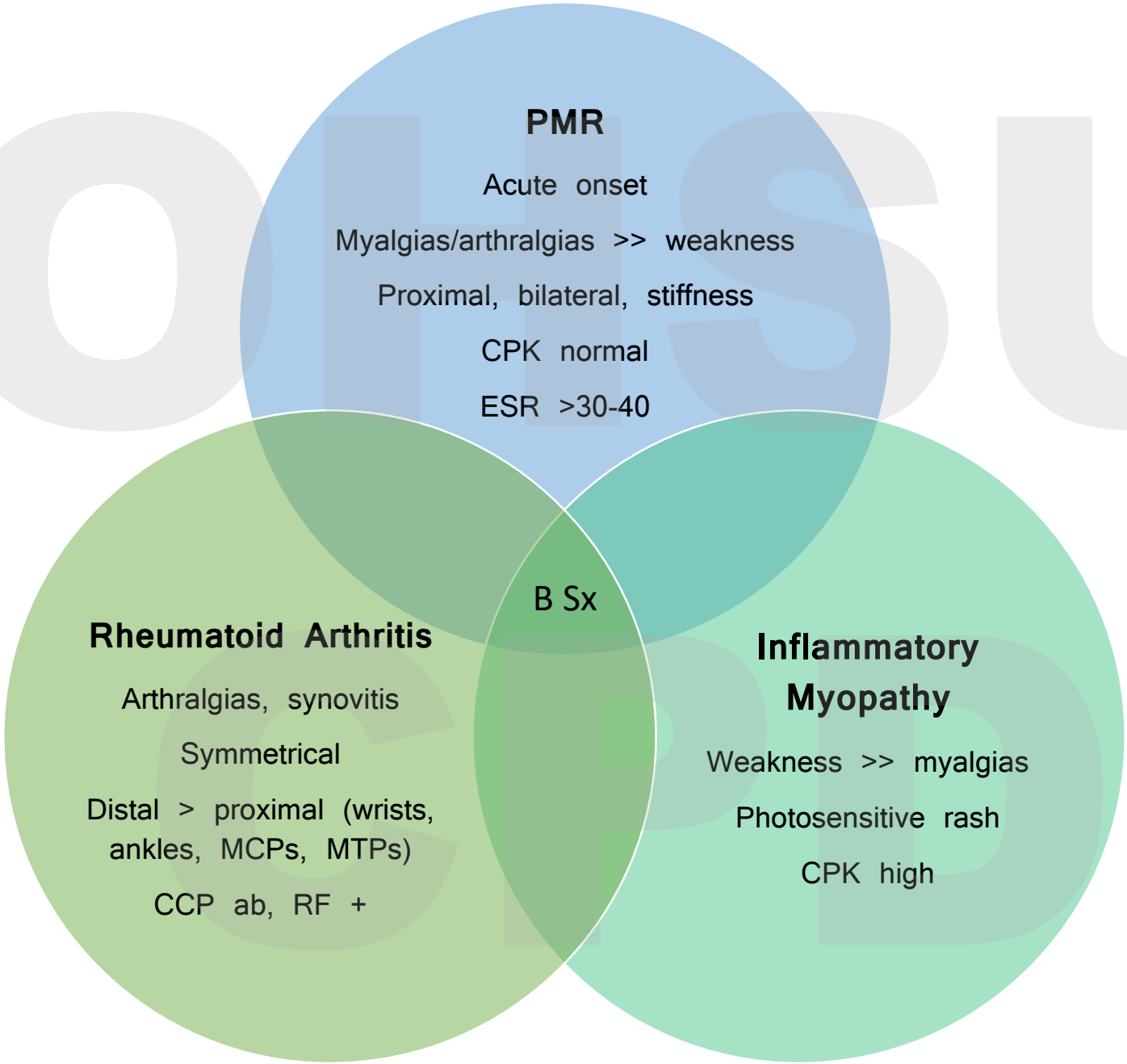


C.E. Owen et al. Ann Rheum Dis 2018;77:1479-1480

Laboratory tests when considering PMR

Differential	Tests
General	CBC with differential, LFTs (alk phos), urinalysis, ESR & CRP
Thyroid	TSH
Rheumatoid arthritis	RF, CCP antibody
Myopathy	CPK
Cancer	SPEP, age-appropriate screening
Other: SLE, CTD, vasculitis	ANA, ANCA (only if atypical features)

Dejaco et al. Ann Rheum Dis 2015;74:1799-1807


PMR
Acute onset
Myalgias/arthralgias >> weakness
Proximal, bilateral, stiffness
CPK normal
ESR >30-40
B Sx
Rheumatoid Arthritis
Arthralgias, synovitis
Symmetrical
Distal > proximal (wrists, ankles, MCPs, MTPs)
CCP ab, RF +
Inflammatory Myopathy
Weakness >> myalgias
Photosensitive rash
CPK high

Elderly onset RA may present with a PMR presentation and later evolve into RA.

Characteristics	Elderly Onset RA (>65 yo)	RA
Prevalence	2%	0.5–1%
Female: Male	2:1	3:1
HLA-DRB1	less significant	more significant
Clinical form	classical RA PMR-like form RS3PE	classical RA
Laboratory findings		
RF/ACPA positivity	less frequent	more frequent
Elevated ESR/CRP	more frequent	frequent

Imaging

- X-rays are normal but may be appropriate if there is concern for malignancy.
  - Warning: You will see degenerative arthritis!
- MSK ultrasonography– frequently used in Europe
  - Subdeltoid bursitis
  - Subacromial bursitis
  - Bicipital tenosynovitis
  - Trochanteric bursitis
  - Mild synovitis
- PET, MRI: not routine

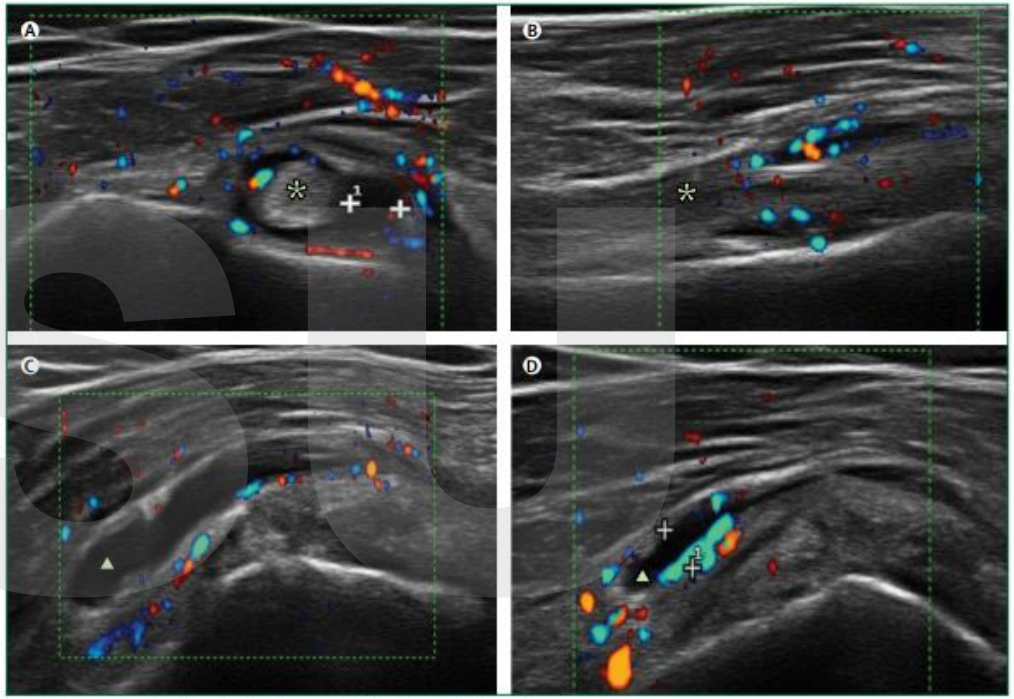


Figure 3: Ultrasonography of the shoulders in a patient with polymyalgia rheumatica

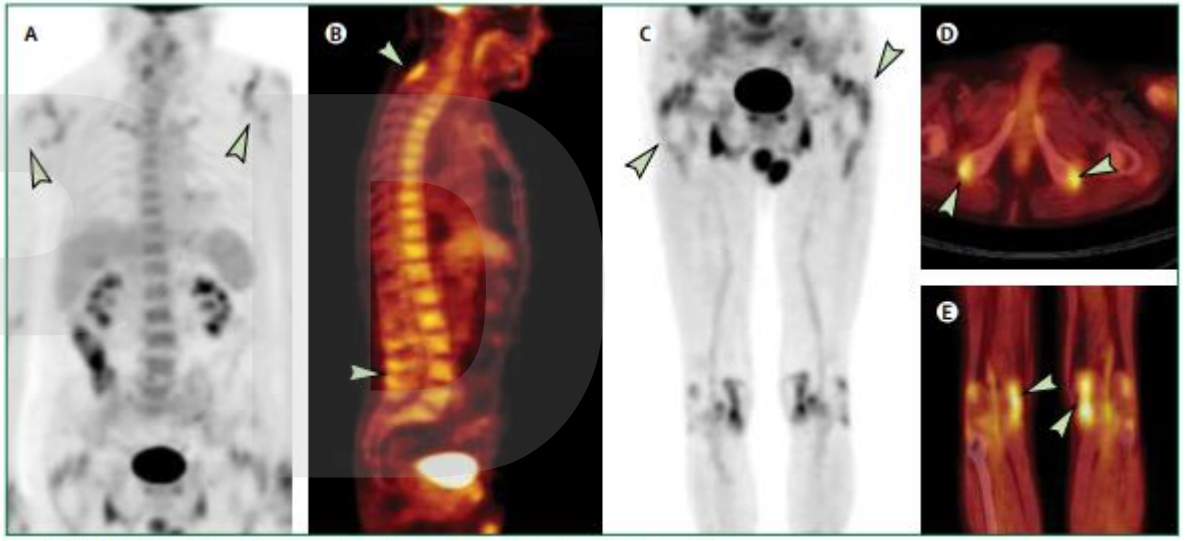


Figure 1: FDG-PET integrated with CT images in a 75-year-old man with polymyalgia rheumatica

Gonzalez-Gay et al. Lancet 2017. 390:1700-12.
Cantini et al. Shoulder ultrasonography in the diagnosis of PMR. J Rheumatol. 2001.

Required entry criteria: Age 50 or older, bilateral shoulder aching, elevated ESR or CRP > then,

Table 1. 2012 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Polymyalgia Rheumatica*

Criteria	*Points Without Ultrasonography (0–6)* 4 or more	*Points With Ultrasonography† (0–8)* 5 or more
Morning stiffness duration >45 min	2	2
Hip pain or limited range of movement	1	1
Absence of RF or ACPA	2	2
Absence of other joint involvement	1	1
≥1 shoulder with subdeltoid bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis (either posterior or axillary) and ≥1 hip with synovitis and/or trochanteric bursitis	Not applicable	1
Both shoulders with subdeltoid bursitis, biceps tenosynovitis, or glenohumeral synovitis	Not applicable	1

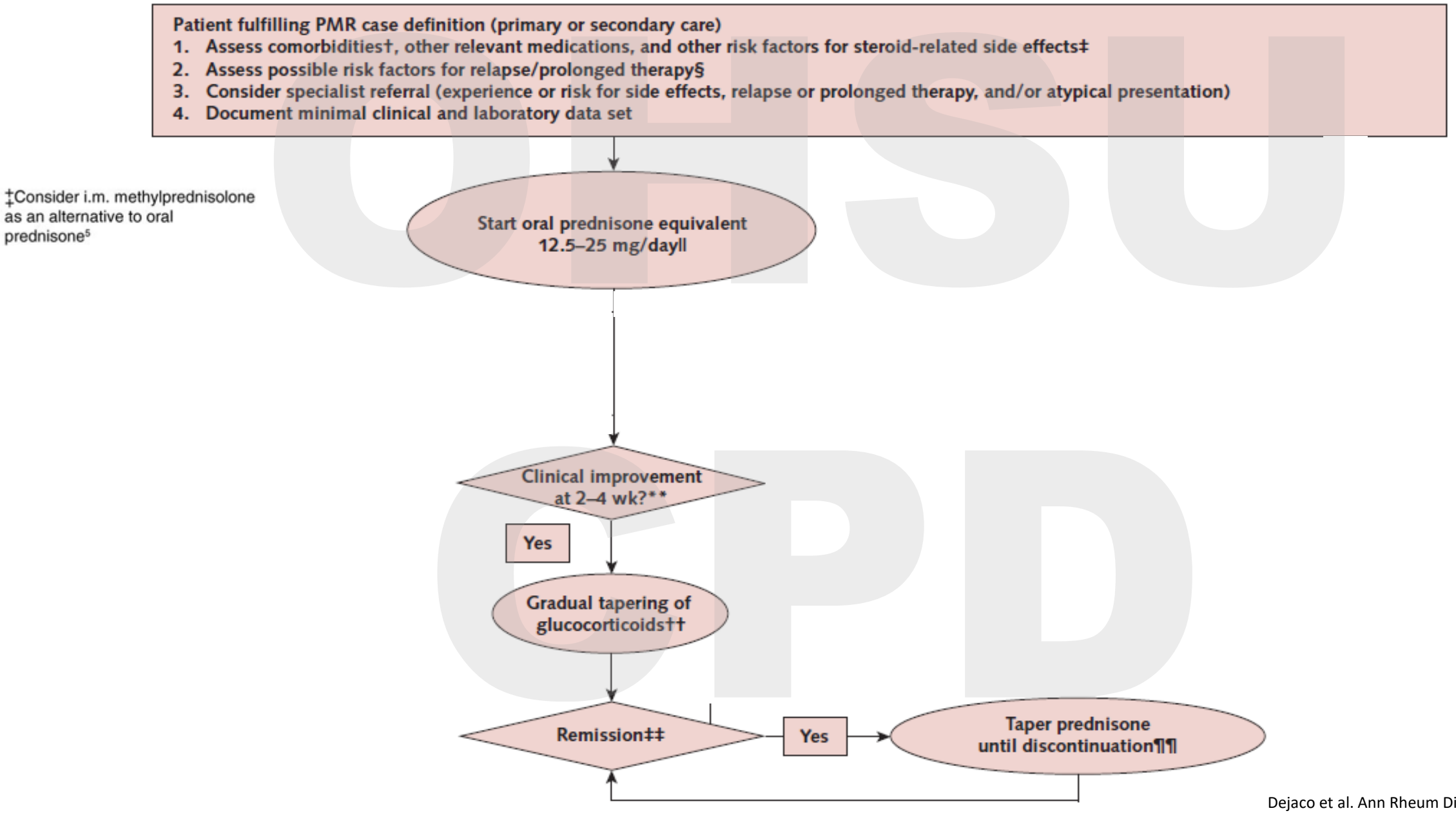
Dasgupta et al. Provisional classification criteria for polymyalgia rheumatica: EULAR/ACR collaborative initiative. ARD 2012;71:484-492.

Polymyalgia Rheumatica Treatment: What dose of prednisone to pick?

- A single-center, 2-month, open-label study compared a daily equivalent of 20 mg vs. 10 mg of prednisone in 39 patients with PMR.
  - A lower relapse rate at 2 months was found in patients initially treated with 20 mg of oral prednisone a day compared with 10 mg/day (11% vs. 65%) ($P < 0.001$)
- Retrospective analyses have reported higher cumulative GC doses and a higher prevalence of drug-related adverse events in patients treated with an initial prednisone dose > 15mg/day compared with those treated with ≤15 mg/day
- I start with 15 mg daily

Kyle et al. Ann Rheum Dis 1989; 48:658; Dejaco et al. Ann Rheum Dis 2015l 74:1808.

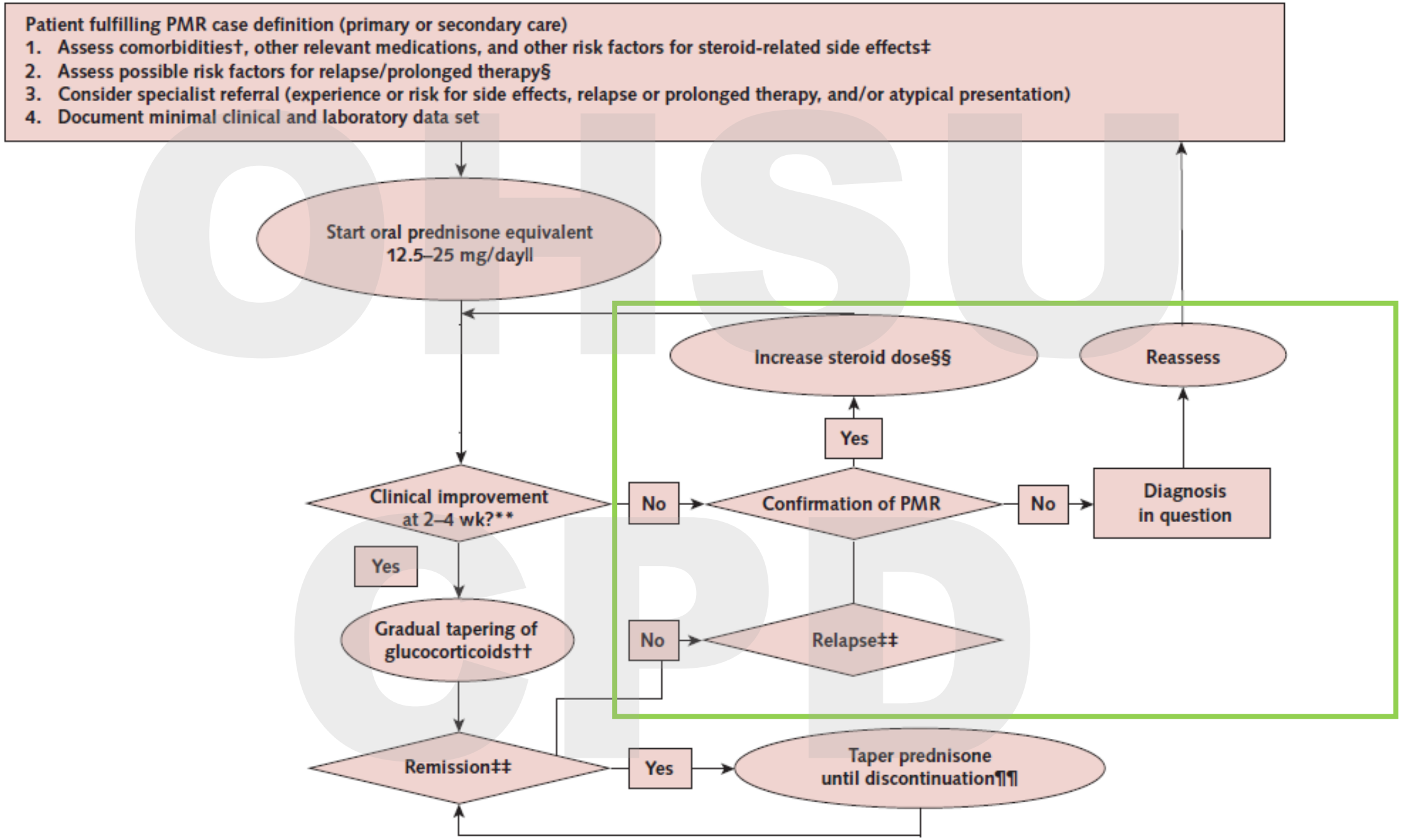
2015 EULAR/ACR recommendations for the management of polymyalgia rheumatica



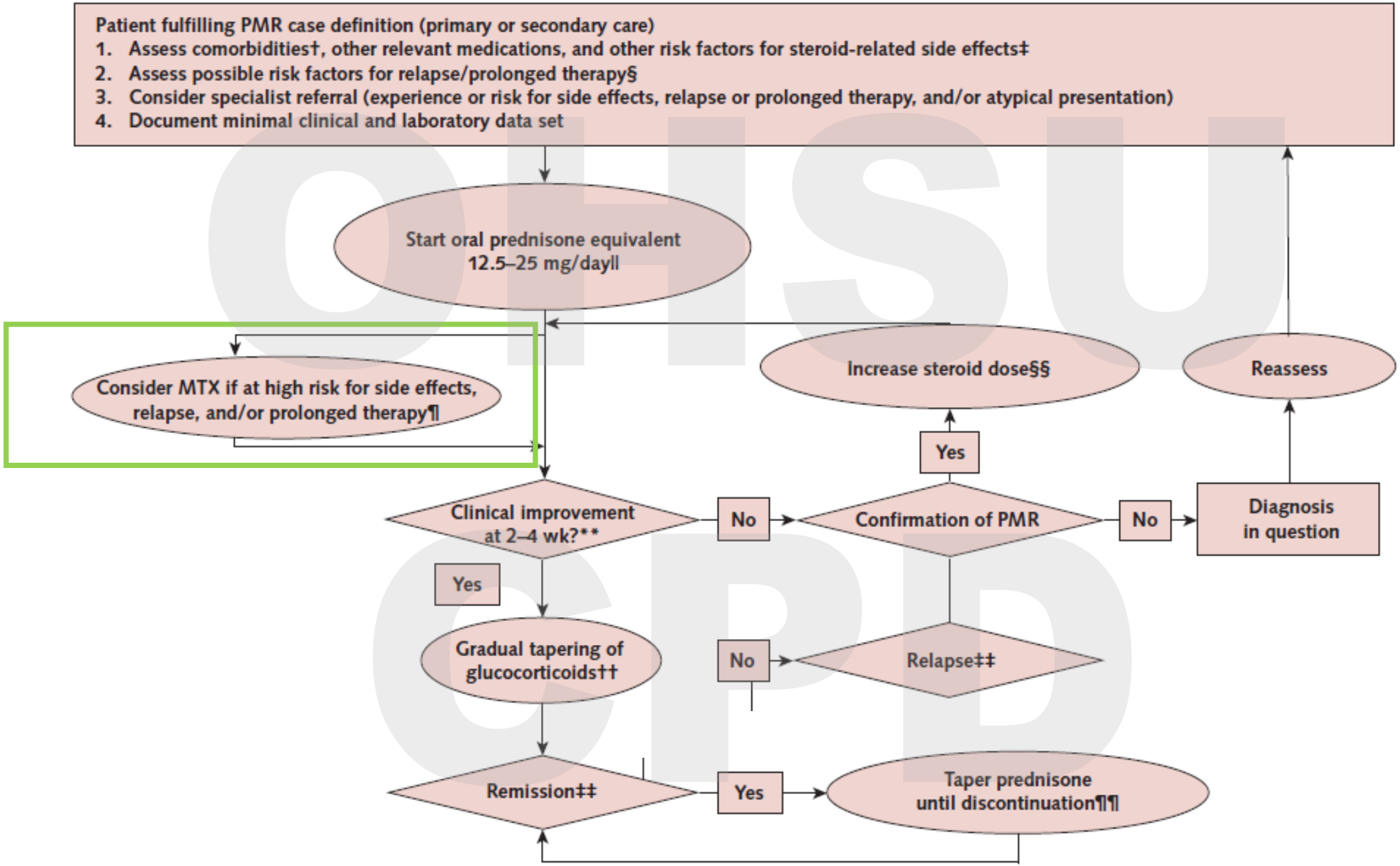
Dejaco et al. Ann Rheum Dis 2015;74:1799-1807

A dramatic relief of symptoms to low dose prednisone is sensitive but not specific…

- A lack of response to prednisone “rules out” the disease
- However, many conditions may respond to prednisone including RA, inflammatory OA, CPPD
- Poor or un-sustained response to therapy indicates an alternate diagnosis including GCA, cancer related syndrome, fibromyalgia, chronic infection, or endocrinopathy.



Dejaco et al. Ann Rheum Dis 2015;74:1799-1807



Dejaco et al. Ann Rheum Dis 2015;74:1799-1807

Polymyalgia Rheumatica Treatment Keys to Success:

- Low dose prednisone 12.5-25mg at the start
- Very slow taper by 1 mg per month
- Set expectations that relapses are common: 50%
- Increase dose back to last dose that controlled symptoms

GC side-effects will occur in 65% of PMR patients

- Weight gain
- Hyperglycemia
- Fluid retention
- Cardiovascular disease
- Bone loss
- Skin fragility
- Ocular
- Psychiatric effects
- Immunizations

Gabriel et al. Arthritis Rheum. 1997; 40:1873-8.

Glucocorticoid-sparing drugs in PMR

- Methotrexate
  - 76-week DBRCT 72 patients with new onset PMR
    - MTX 10 mg/wk + prednisone 25 mg vs. PBO + prednisone 25 mg
    - Relapse rate: 47% vs. 73% p = 0.04
    - Cumulative GC: 2.1 g vs. 3 gm p = 0/003
    - Discontinuation of GC 88% vs. 53% p = 0.003
    - No difference in GC side-effects
- Azathioprine
- Leflunomide
- IL-6 Receptor Blocker: Sarilumab (FDA approved 2/2023), Tocilizumab

Caporali et al. Ann Intern Med. 2004; 141:493
De Silva et al. Ann Rheum Dis. 1986;45:136
Diamantopoulos et al. Biomed Res Int. 2013; 2013:120638.

RESEARCH SUMMARY

Sarilumab for Relapse of Polymyalgia Rheumatica during Glucocorticoid Taper

Spiera RF et al. DOI: 10.1056/NEJMoa2303452

CLINICAL PROBLEM

Polymyalgia rheumatica is typically treated with glucocorticoids, but more than half of patients cannot successfully taper treatment, resulting in long-term glucocorticoid use and substantial glucocorticoid-related morbidity. Sarilumab, a human monoclonal antibody that blocks the interleukin-6 receptor, offers another approach for the treatment of polymyalgia rheumatica.

CLINICAL TRIAL

Design: A phase 3, multicenter, double-blind, randomized, placebo-controlled trial evaluated the efficacy and safety of sarilumab in patients with polymyalgia rheumatica that flared with glucocorticoid taper.

Intervention: 118 symptomatic patients who had had ≥1 disease flare during prednisone taper in the previous 12 weeks were assigned in a 1:1 ratio to receive 52 weeks of a twice-monthly subcutaneous injection of either sarilumab (at a dose of 200 mg) plus a 14-week prednisone taper or placebo plus a 52-week prednisone taper. The primary outcome was sustained remission at 52 weeks; sustained remission was defined as clinical remission by week 12 and absence of disease flare, sustained C-reactive protein normalization, and adherence to prednisone taper from weeks 12 to 52.

RESULTS

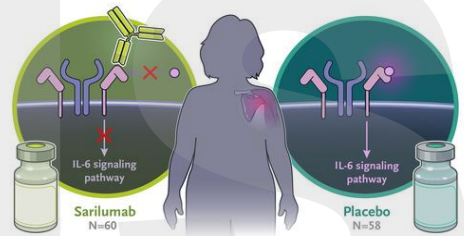
Efficacy: The proportion of patients with sustained remission at 52 weeks in the sarilumab group was nearly three times that in the placebo group.

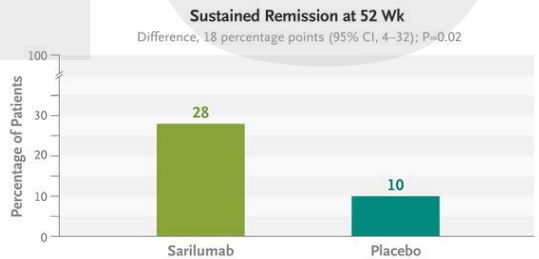
Safety: Neutropenia, arthralgia, and diarrhea were among the most common adverse events and occurred more often in the sarilumab group than in the placebo group. Treatment discontinuation because of adverse events was also more common with sarilumab.

LIMITATIONS AND REMAINING QUESTIONS

- Enrollment was stopped early because of the Covid-19 pandemic. (Planned enrollment was 280.)
- The safety analysis was limited by the small sample size.

Links: Full Article | NEJM Quick Take | Editorial





CONCLUSIONS

In patients with a relapse of polymyalgia rheumatica during prednisone taper, treatment with the human monoclonal antibody sarilumab showed significant efficacy in achieving sustained remission and reducing the cumulative glucocorticoid dose.

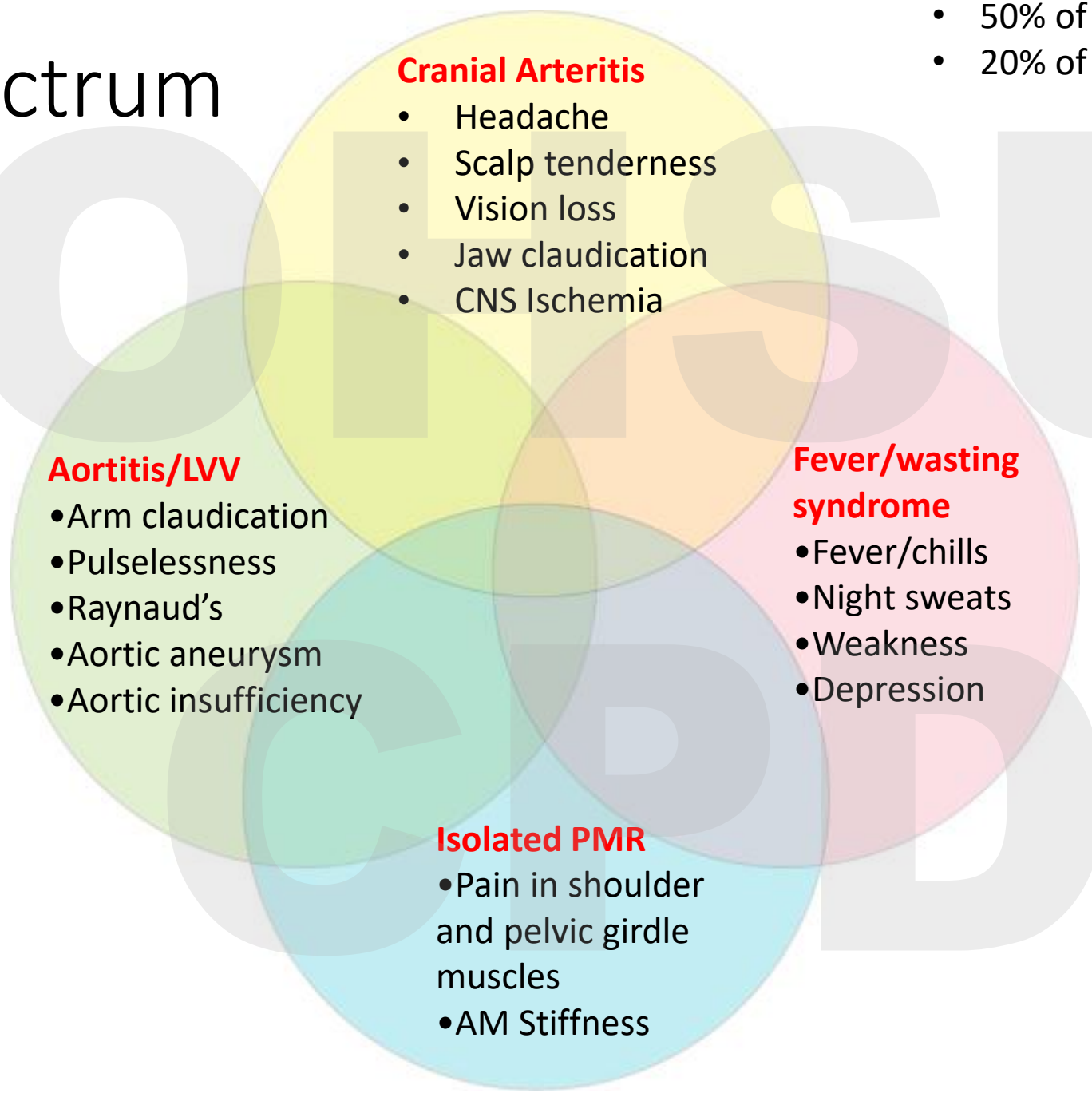
Spiera et al. N Engl J Med 2023;389:1263-1272

When should you refer to rheumatology?

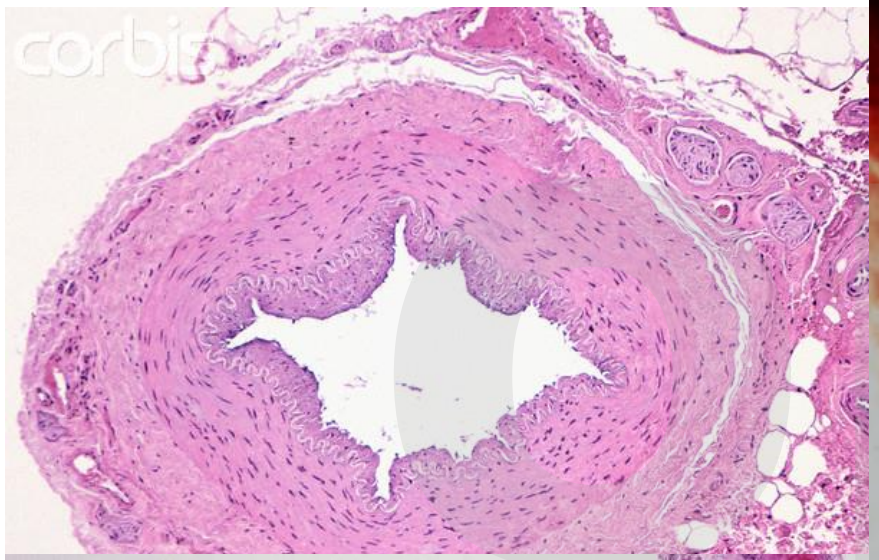
- Atypical initial presentation
  - ESR too low or too high
  - Age < 60
  - Peripheral arthritis
  - Lack of shoulder involvement
- Refractoriness to initial treatment with low dose glucocorticoids
- Inability to taper prednisone, experiencing side-effects
- Concern for giant cell arteritis

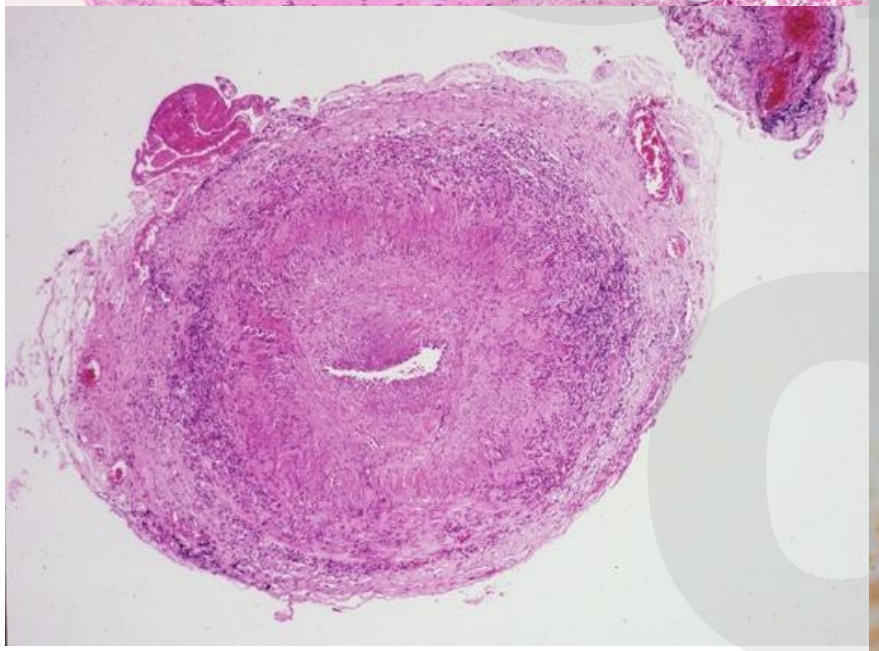
GCA Spectrum

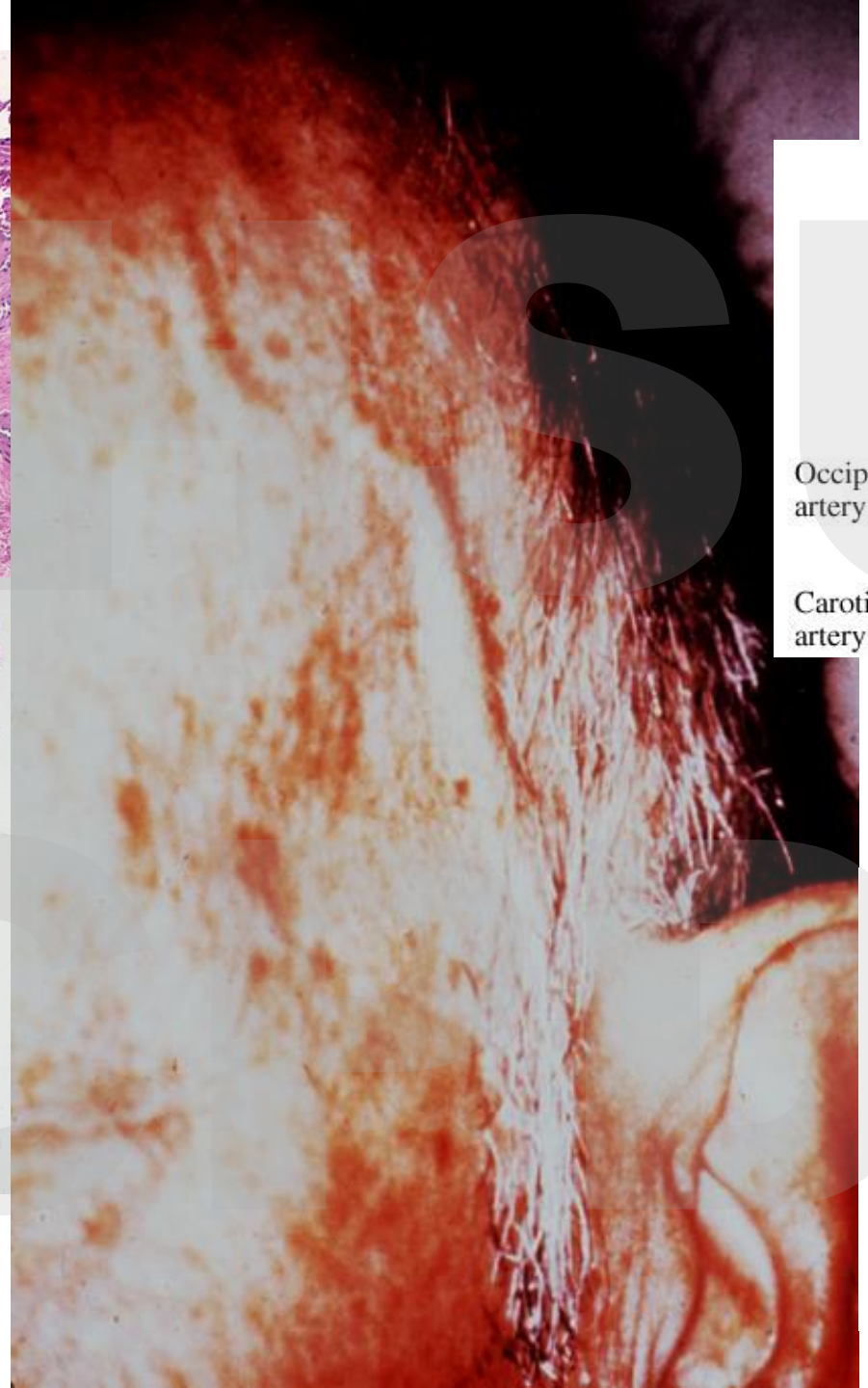
- 50% of GCA have PMR
- 20% of PMR have GCA

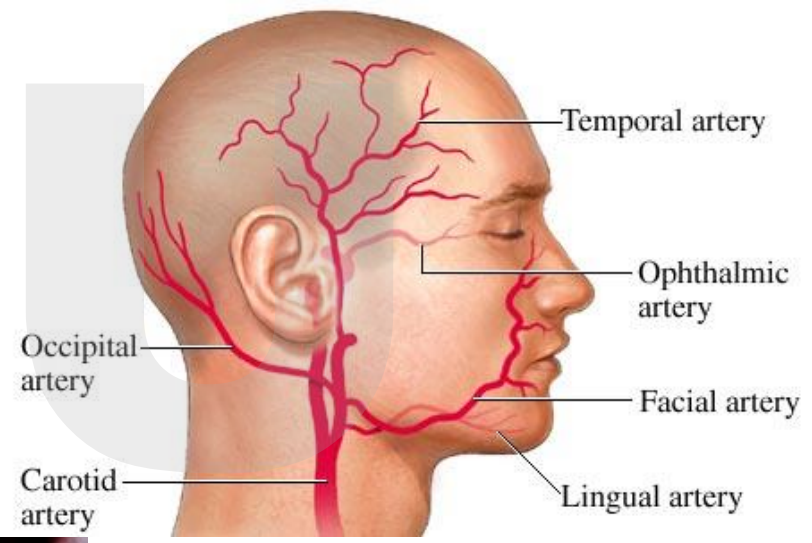


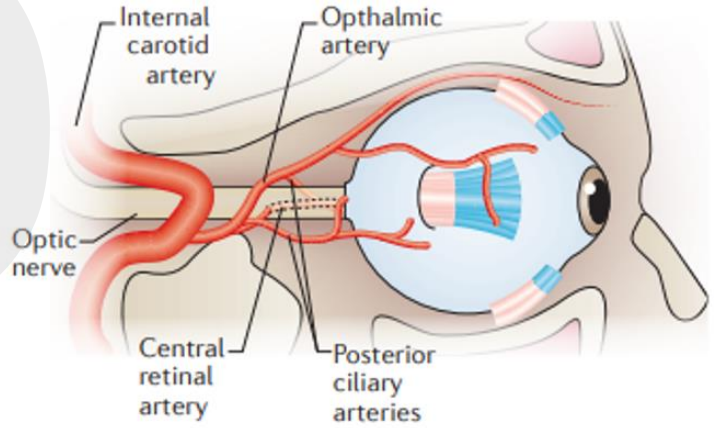
Dejaco et al. Rheumatology 2017



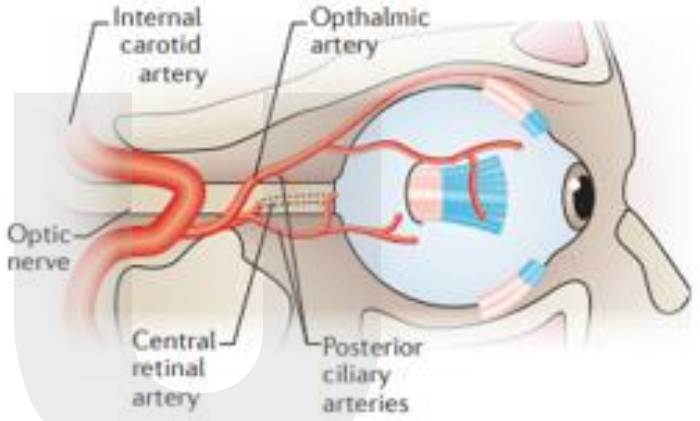




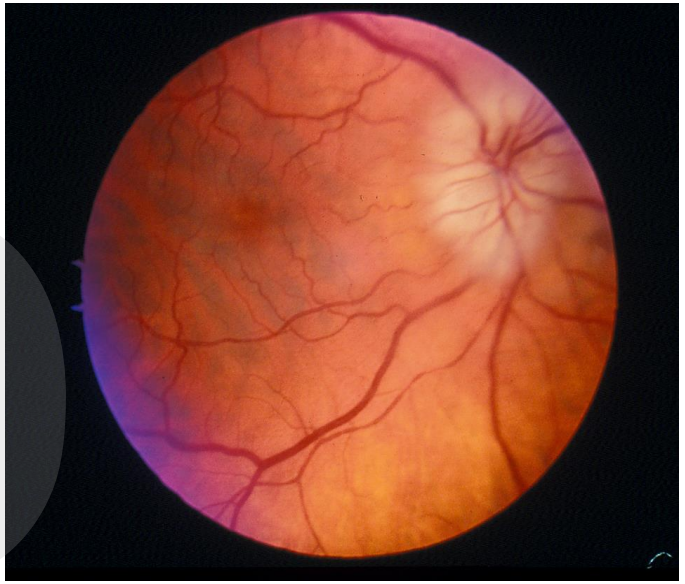

Temporal artery
Ophthalmic artery
Occipital artery
Facial artery
Carotid artery
Lingual artery


Internal carotid artery
Opthalmic artery
Optic nerve
Central retinal artery
Posterior ciliary arteries

Giant Cell Arteritis



- Risk of permanent blindness in untreated GCA: 15%
- 20% of PMR patients have or will have GCA
- GCA treated much more aggressively than PMR
  - Prednisone 60-80mg/day
  - Early initiation of tocilizumab



Narva´ez et al. Semin Arthritis Rheum. 2015;45:328

Table 2. **Clinical Features of Polymyalgia Rheumatica and Giant Cell Arteritis***

Sign/Symptom	*Polymyalgia Rheumatica*	*Cranial Giant Cell Arteritis*	*Large Vessel Giant Cell Arteritis*
Polymyalgia symptoms of shoulder and hip; neck stiffness	++	+	++
Elevated CRP/ESR	++	++	++
Peripheral arthritis/RS3PE syndrome	++	+	+
Wasting syndrome (fever, anorexia, weight loss, night sweats, depression)	++	++	++
Headache	-	++	-
Scalp tenderness	-	++	-
Arterial swelling/tenderness, bruits	-	+	+
Jaw claudication/tongue pain and claudication	-	++	-
Vision symptoms/complications	-	++	-
Painful dysphagia	-	++	-
Limb claudication, absent or asymmetrical pulses, asymmetrical blood pressure readings, Raynaud phenomenon	-	+	++
Aortic regurgitation	-	+	++

Matteson & Dejaco. Ann Int Med 2017

Final Remarks

- Develop a framework and systematic approach to widespread pain
- Look for inflammatory symptoms and signs
- Follow clues from the ROS and basic labs, including inflammatory markers
- Refer when the story does not fit or the patient is not responding to your treatment plan
- If treating for PMR, don’t forget to inquire about GCA symptoms

Questions?

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