Giant cell arteritis and polymyalgia rheumatica: pearls and pitfalls

Noémie Gionet Landry
MD FRCPC
April 23rd 2021

Objectives

1. Recognize the classic presentation of polymyalgia rheumatica and being able to recognize when the diagnosis of polymyalgia rheumatica is unlikely
2. Recognize the classic presentation and the various atypical presentations of giant cell arteritis and establish a timely diagnosis
3. Review the treatment of polymyalgia rheumatica and giant cell arteritis

Disclosures

- Consulting fees:
  Amgen, Pfizer, Sanofi Genzyme, Gilead, Novartis
- Grants/research support: Jenssen
- Speaker's bureau/honoraria: BMS, Jenssen, Merck, UCB, Pfizer, Amgen

Key points PMR

- PMR never occurs before 50 y.o.
- If the clinical presentation is not classic of PMR, an alternative diagnosis should be sought
- The sedimentation rate is a useless test, always order a C reactive protein
- Treatment of PMR should last at least 12 months
- Rheumatoid arthritis often starts with a PMR like presentation in the elderly

Key points GCA

- GCA also never occurs before 50 y.o.
- The sedimentation rate is still a useless test!
- There is no “classic GCA headaches”; any new headache in someone > 60 should raise the question of possible GCA
- Do not delay initiation of corticosteroids for temporal artery biopsy
- The presence of visual symptoms in GCA is a medical emergency and an indication for pulse steroids

Bonus key points

- ALL patients should receive a prophylaxis against glucocorticoid induced osteoporosis

POLYMYALGIA RHEUMATICA

Who is more at risk of PMR?

PMR

Epidemiology

- Disease of the elderly – (almost) never before 50
- Peak incidence 70 – 80
- Female 2 – 3 X more affected
- Much less common in Asian, African-American and Latino

Key point #1

PMR never occurs before 50 y.o.

Mr Stiff

- 82 y.o male
- 4 weeks history of pain in shoulders, neck, hips, back of the thighs
  - Started quite abruptly
  - Stiff until 1PM
  - Functional impairment +++
- What else do you want to know?

Mr Stiff

- Tired +++, but no other constitutional symptoms
- No symptoms of GCA
- No peripheral joint pain except mild chronic knee pain

Mr Stiff

- On physical examination:
  - Shoulders and hips very stiff, ROM painful in all directions, active > passive
  - No synovitis in peripheral joints
  - Muscle strength normal
  - Temporal arteries normal X2, no vascular murmur, pulses symmetrical

PMR

Clinical features

- Classic inflammatory pain of the hip and shoulder girdle
  - Prolonged morning stiffness
  - Gelling phenomenon
- Can be unilateral at first, but rapidly becomes bilateral
- Significant functional impairment
- Onset fairly abrupt (sometime overnight)
- No true weakness (antalgic)
- Constitutional symptoms ++ (but fever rare – think GCA)

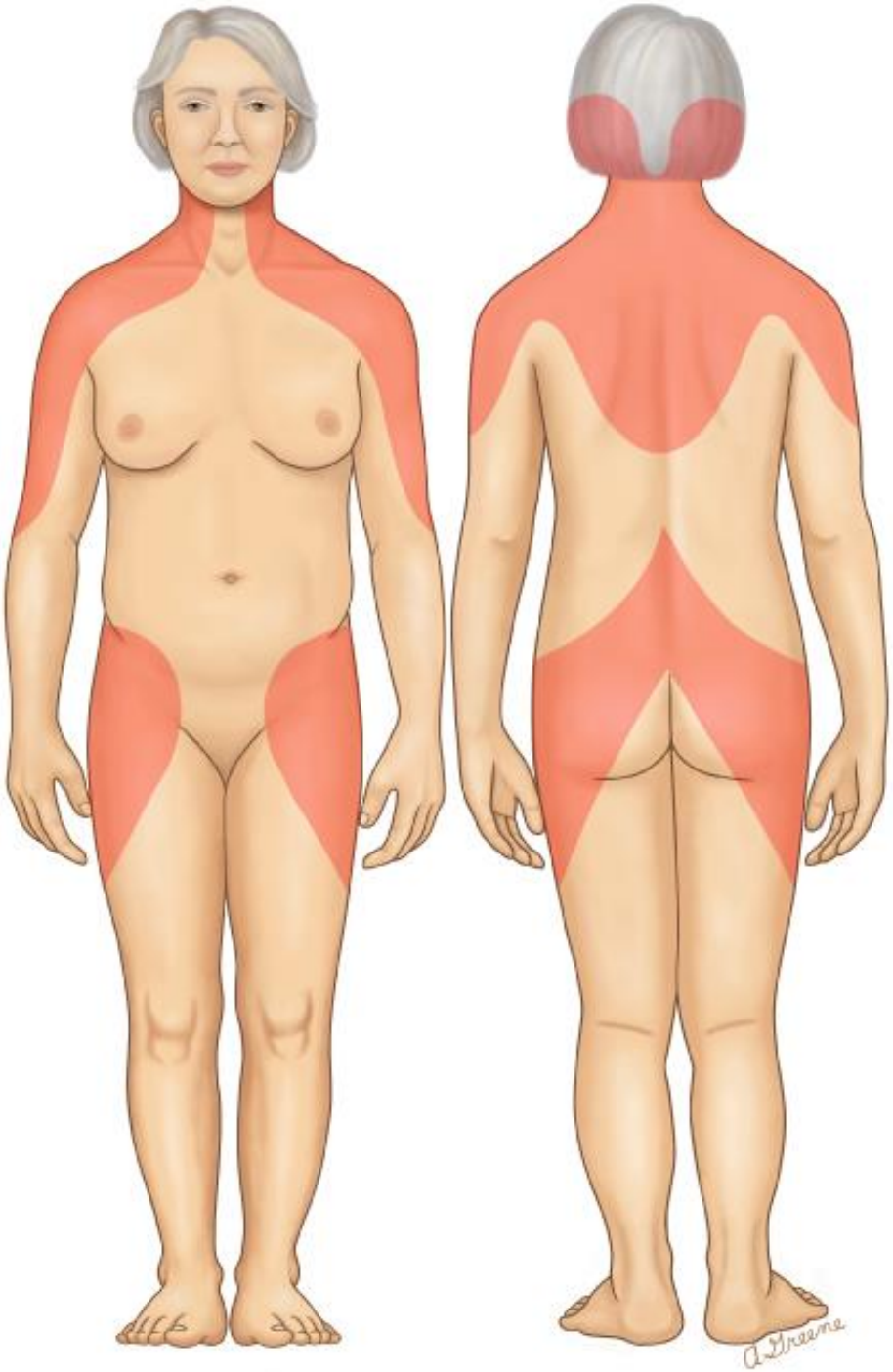
What hurts in PMR ?

a) Joints (synovitis)
b) Bursa (bursitis)
c) Muscles (myositis)
d) Tendon (tendonitis)

What hurts in polymyalgia rheumatica?

Not the muscles!

- Upper extremities
  - Subdeltoid/subacromial bursitis
  - Biceps tenosynovitis
  - Glenohumeral synovitis
- Lower extremities
  - Trochanteric bursitis
  - Hip synovitis
  - Iliopsoas bursitis



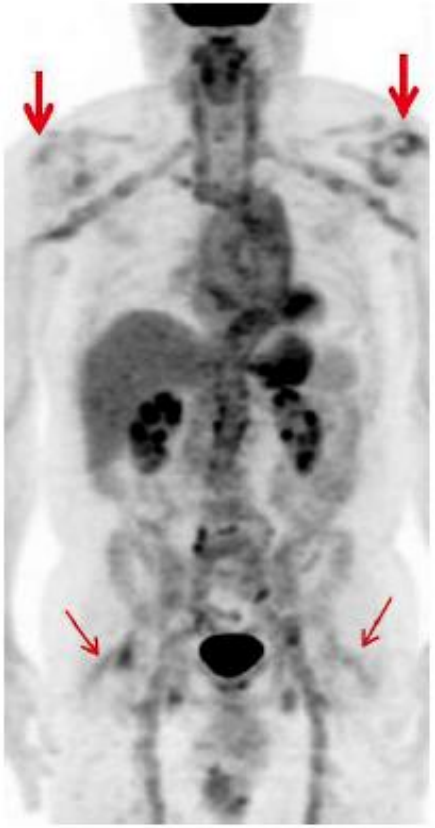


Figure 4. Positron emission tomography with 18-F fluorodeoxyglucose uptake showing bilateral glenohumeral synovitis (thick arrows), periarticular hip soft-tissue inflammation (thin arrows), and diffuse large-vessel arteritis involving the thoracoabdominal aorta and bilateral carotid, subclavian, and femoral arteries.

Mr Stiff

- Classic presentation of polymyalgia rheumatica without symptoms of associated GCA

- What test to order?
- How to treat?

PMR

Diagnosis

- No diagnostic test
- Comprehensive history and physical examination to R/O differential diagnosis
- Suggested work-up
  - CRP ~~or ERS~~ (elevated in > 95% of patients)
  - CBC (anemia, thrombocytosis)
  - Blood glucose
  - As needed: TSH, CK, RF, anti-CCP, SPE, etc.

ESR vs CRP

- Sed rate increase with…
  - Advanced age
  - Female gender
  - Obesity
  - Anemia
  - …
- CRP
  - More sensitive
  - Increase faster if flare-ups ; decreases faster in response to treatment

Correction = $\frac{\text{Age (+ 10 if female)}}{2}$

So 70 y.o. female (healthy weight) = 40…

Key point #2

The sedimentation rate is a useless test, always order a C reactive protein

PMR

Treatment

- Prednisone
  - 12.5 – 25 mg daily
    - 15 mg daily is usually enough
  - Aim for **12 months** of treatment
  - For example:
    - 15 mg daily X 1 month, 12.5 X 1 month, 10 X 1 month, then reduce by 1 mg every month
  - Ca, vit D and bisphophonate in all patients
  - Monitor for glucocorticoid side effects

Key point #3

Treatment of PMR should last at least 12 months

Bonus Key point

ALL patients should receive a prophylaxis against glucocorticoid induced osteoporosis

Mr Stiff

- Started on prednisone 20 mg daily
- 2 days later – Cured!
- Prednisone tapered slowly until 7 mg daily then pain reappears…

PMR

Treatment - Relapse

1) Confirm that the pain is really 2airy to PMR
2) Re-increase prednisone to the dose where symptoms were controlled and try slower tapering (q 6 weeks)
3) Add Methotrexate
4) Other steroid sparing agents: Tocilizumab? Leflunomide? HCQ?

Ms Achy

- 69 y.o.
- 4 weeks history of pain everywhere
  - Worse shoulders and hips but also in various other joints
  - 1 - 2 hours morning stiffness
  - Weight loss 20 pounds, fatigued +++

Ms Achy

- On physical examination:
  - Very limited ROM shoulders and hips
  - Various other tender joints ; no clear synovitis
- CRP 40
- CBC normal except Hb 105
- Creatinine, LFT's, electrolytes normal

Ms Achy

- Started on prednisone 20 mg daily
- 2 weeks later – Only 25 % better…

- Is it PMR?

When should an alternative diagnosis be considered?

When should an alternative diagnosis be considered?

- Anytime the presentation is not classic:
  - Pain that is not inflammatory
  - Significant peripheral joint involvement
  - Asymmetrical involvement
  - Normal inflammatory markers
  - Poor response to treatment

Key point #4

If the clinical presentation is not classic of PMR, an alternative diagnosis should be sought

“Refractory PMR”: Three main things to consider

- Associated subclinical GCA
- Rheumatoid arthritis with PMR like onset (rhizomelic)
- Malignancy

Differential diagnosis of Polymyalgia Rheumatica

- Elderly-onset rheumatoid arthritis
- Inflammatory myopathies
- Malignancy
- Infection (viral myalgias and other infections)
- Hypothyroidism
- Fibromyalgia
- Multifocal local musculoskeletal disease
- Crowned dens syndrome
- Osteoarthritis
- …

Differential diagnosis of Polymyalgia Rheumatica

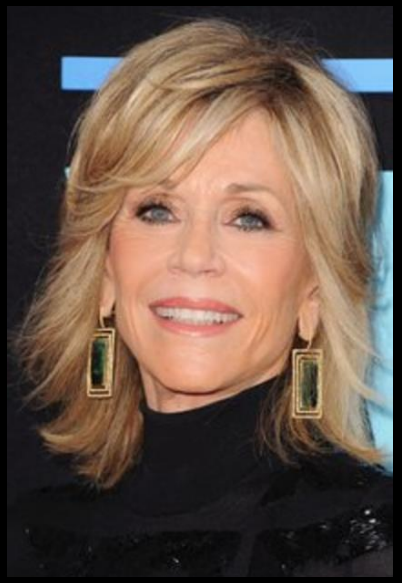
- **Elderly-onset rheumatoid arthritis**
  - RA in the elderly frequently start as a PMR like syndrome
  - 30% of RA are seronegative
  - Be very suspicious of a "PMR patient" with significant peripheral joint pain (wrists, MCP's, feet, ankles…)
  - Peripheral joint symptoms and synovitis often appears with steroid tapering

Key point #5

Rheumatoid arthritis often starts with a PMR like presentation in the elderly

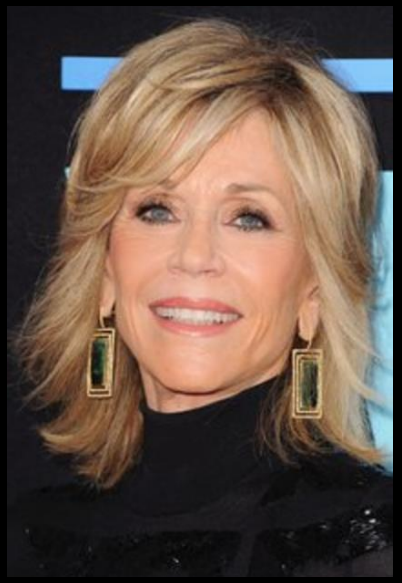
GIANT CELL ARTERITIS

Ms Blind



- 70 y.o. female
- 1 month history of headaches
  - Back of the head, radiate to the front ; L > R
  - Scalp tender, brushing her hair is painful
  - Weight loss 15 pounds
  - Fatigue +++

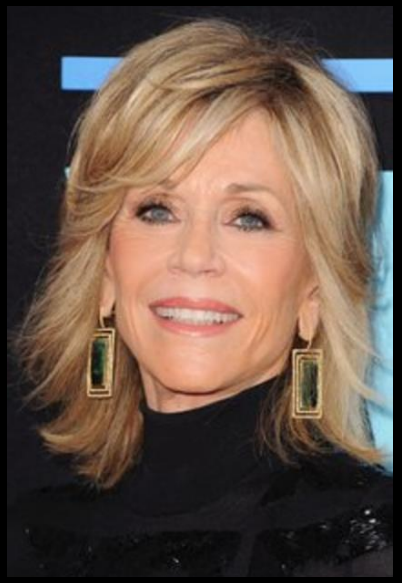
Ms Blind



- Pain in her jaw when she chews
- No visual symptoms
- Physical examination:
  - BP 140/80 L ; 170/95 R
  - Temporal arteries normal
  - Scalp tender
  - No vascular bruit
  - Peripheral pulses symmetrical
  - Auscultation heart/lungs normal

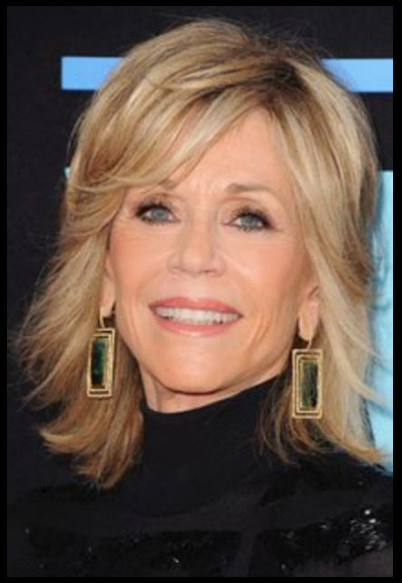
Ms Blind

- CRP 100
- Hb 102, Plt 480



Ms Blind

- What to do ?



Which patient does NOT have GCA

a) 68 y.o. female with vertigo, ataxia, dysarthria and homonymous hemianopsia

Which patient does NOT have GCA

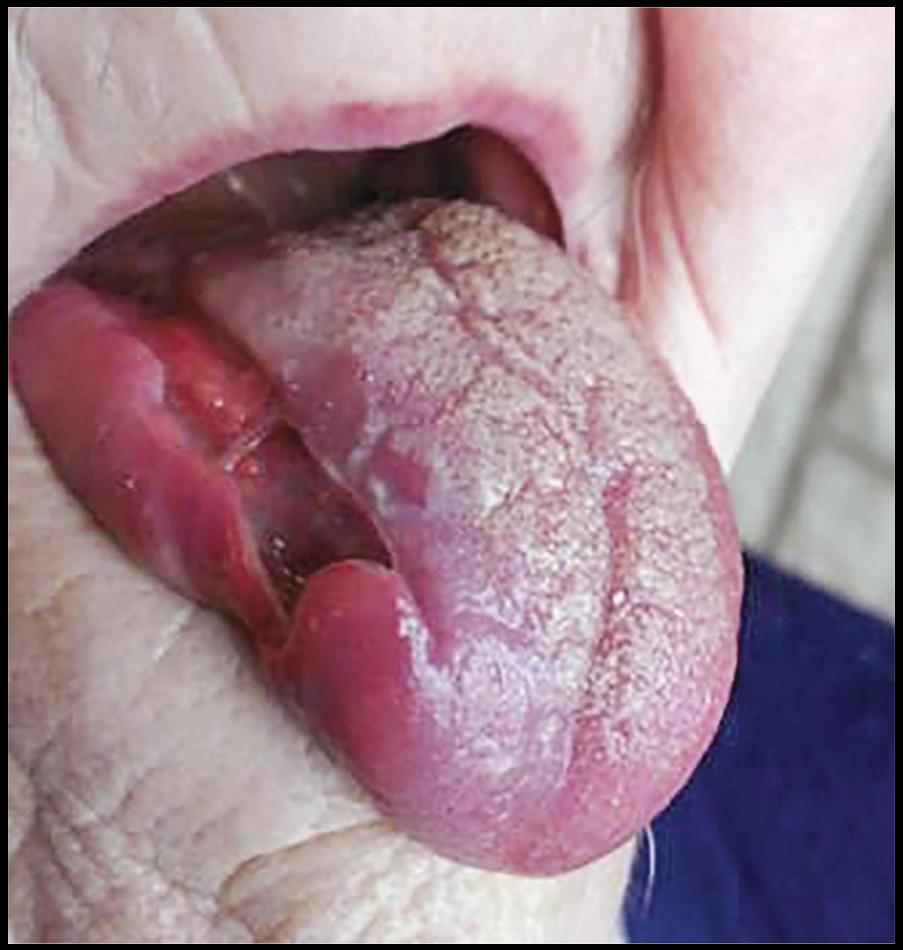
b) 75 y.o. male with FUO, CRP 80, non productive cough

Which patient does NOT have GCA

c) 73 y.o women with dysphagia and 50 pounds weight loss

Which patient does NOT have GCA

d) This lady



Which patient does NOT have GCA

Of course, they all have GCA!

GCA

Epidemiology

- Same as PMR
  - Disease of the elderly – (almost) never before 50
    - Meta-analysis 26 studies, 1435 patients with Bx proven GCA, two were < 50
  - Peak incidence 70 – 80
  - Female 3 – 2 X more affected
  - Much less common in Asian, African-American and Latino

Key point #1

GCA also never occurs before 50 y.o.

PMR and GCA

- 10 - 20% of PMR have/will have GCA; 40 - 50% of GCA have/will have PMR
- Same epidemiology
- Several similarities in pathophysiology
- Spectrum of the same disease?

GCA

Common clinical features

- *Common features related to vascular injury*
  - Headache
  - Scalp tenderness
  - Jaw claudication
  - Ocular symptoms, vision loss
- *Common features related to systemic inflammation*
  - Constitutional symptoms
  - Polymyalgia rheumatica

GCA

Less common clinical features

- Claudication of various body parts (dysphagia, tongue, limbs)
- Respiratory symptoms (pathophysiology unclear – 10 %)
- Ischemia of the central nervous system (typically vertebrobasilar)
- Aortitis
- Myocardial infarction
- Peripheral neuropathy
- Deafness
- Tissue gangrene

What is the classic GCA headache?

a) Unilateral temporal pulsating
b) Bitemporal chronic dull
c) Occipital and constant
d) Frontal and severe

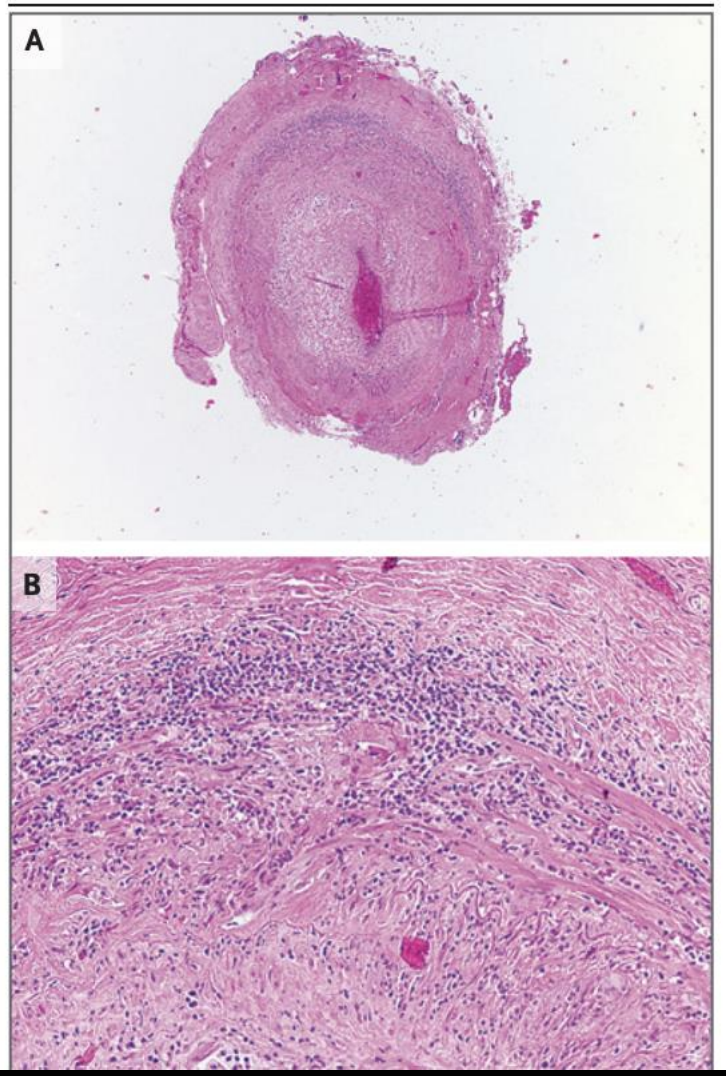
Key point #2

There is no “classic GCA headaches”; any new headache in someone > 60 should raise the question of possible GCA

Chewing Gum Test for Jaw Claudication in Giant-Cell Arteritis

TO THE EDITOR: Claudication of the jaw is a specific symptom with high predictive value for giant-cell arteritis.[1] However, a standardized clinical test to differentiate claudication from other causes of jaw pain is lacking. We report two cases in which a "chewing gum test" for jaw claudication showed abnormal results.

In the first case, a woman, 61 years of age, who had received a clinical diagnosis of giant-cell arteritis 2 years earlier, presented with recurrence of pain in her right jaw, temporal headache, and lethargy after having been weaned from oral prednisolone therapy. The findings from a clinical examination were normal. She was asked to chew gum at the rate of one chew per second. After 2 minutes of chewing, she reported an ache in her right jaw that was similar to what she had felt 2 years earlier. The pain disappeared with rest but could be reproduced consistently after 2 to 3 minutes of chewing. The dose of her oral prednisolone therapy was increased, and her subjective symptoms resolved. The chewing gum test was repeated a few days later and showed normal results; no jaw ache was reported after 4 minutes of chewing.



Fever of unknown origin

- Up to one in six fevers of unknown origin in older adults is due to GCA

Vision loss

- Painless and sudden
- Can be partial or complete, and unilateral or bilateral.
- Sometimes preceded by amaurosis fugax
- Once established → **Irreversible**
- **Loss of vision in the *unaffected* eye ensues in 25 to 50% of untreated patients within 1 week**
- **Risk decreases abruptly to almost zero with treatment**
- Amaurosis fugace is the strongest (only?) predictor of subsequent permanent visual loss

Vision loss

Even in the era of effective therapy, permanent partial or complete loss of vision in one or both eyes is reported in 15 to 20 percent of patients with GCA

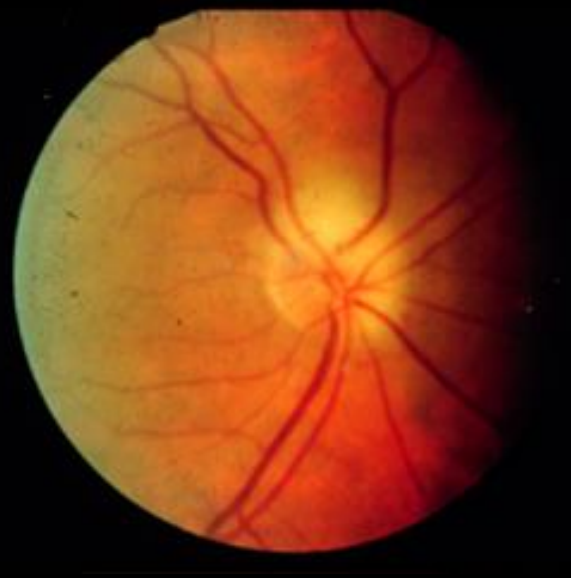
Key point #3

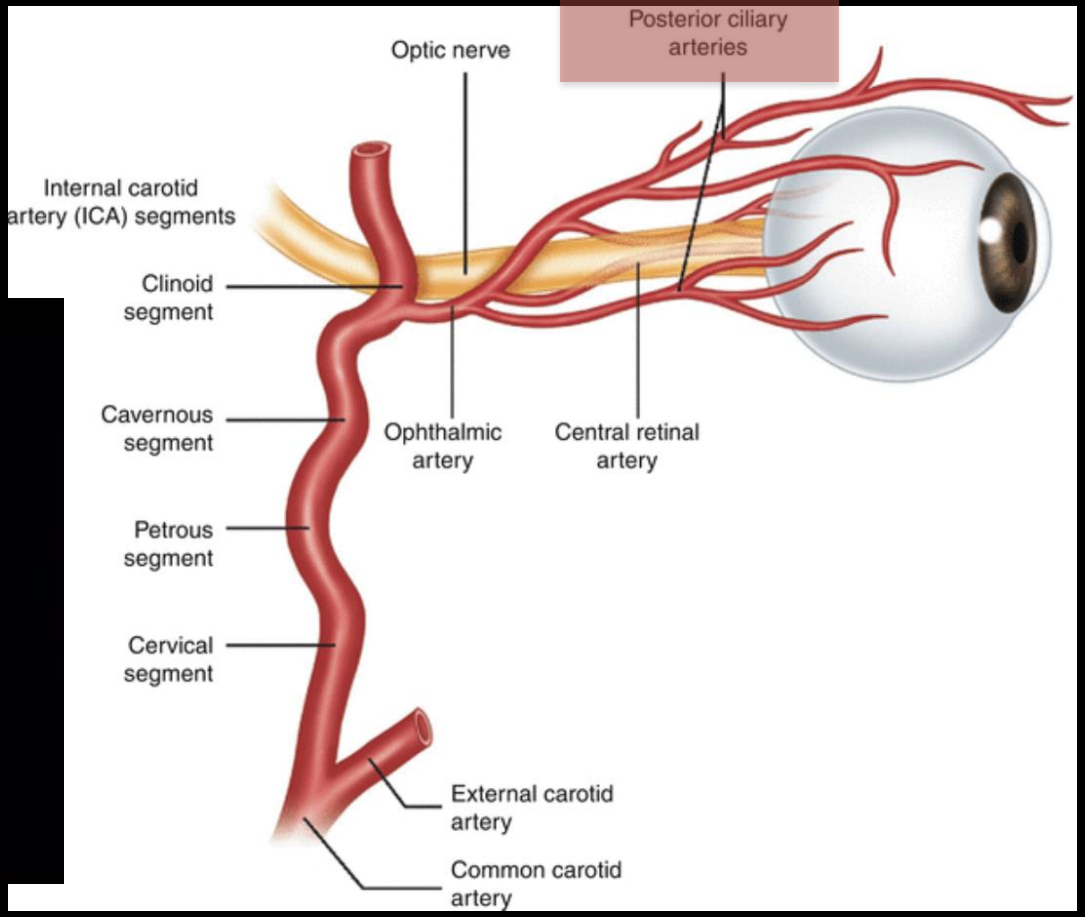
The presence of visual symptoms in GCA is a medical emergency

Five causes of vision loss in GCA

1) **Anterior ischemic optic neuropathy** (> 80 %)
2) Central retinal artery occlusion (10 percent)
3) Posterior ischemic optic neuropathy (< 5%)
4) Branch retinal artery occlusion
5) Cerebral ischemia

AION




Posterior ciliary arteries
Optic nerve
Internal carotid artery (ICA) segments
Clinoid segment
Cavernous segment
Petrous segment
Cervical segment
Ophthalmic artery
Central retinal artery
External carotid artery
Common carotid artery

Other ophthalmic syndromes

- **Diplopia** (5 %)
- **The Charles Bonnet syndrome**
  - Visual hallucinations in psychologically normal individuals who have visual loss due to lesions in either peripheral or central visual pathways.

What should the physical examination include?

- Careful head and neck examination
  - Erythema, tenderness, nodularity, thickening of temporal artery, decreased pulse (vs. unaffected temporal artery)
- Eye examination
  - Visual acuity and visual fields
  - Optic disc and retinal vessels
- Assess pulse and blood pressure in all 4 extremities
- Listen for vascular bruits
- Listen for aortic regurgitation

Table 1. Likelihood ratios for symptoms and signs among patients with suspected GCA*

Symptom/sign	Number of patients with data	Positive LR (95% CI)	Negative LR (95% CI)
Symptoms			
Anorexia	674	1.2 (0.96–1.4)	0.87 (0.75–1.0)
Weight loss	1,417	1.3 (1.1–1.5)	0.89 (0.79–1.0)
Arthralgia	582	1.1 (0.86–1.4)	1.0 (0.92–1.1)
Diplopia	703	3.4 (1.3–8.6)	0.95 (0.91–0.99)
Fatigue	1,095	1.2 (0.98–1.4)	0.94 (0.86–1.0)
Fever	1,708	1.2 (0.98–1.4)	0.92 (0.85–0.99)
Temporal headache	386	1.5 (0.78–3.0)	0.82 (0.64–1.0)
Any headache	2,475	1.2 (1.1–1.4)	0.7 (0.57–0.85)
Jaw claudication	2,314	4.2 (2.8–6.2)	0.72 (0.65–0.81)
Myalgia	681	0.93 (0.81–1.1)	1.1 (0.87–1.3)
Polymyalgia rheumatica	1,383	0.97 (0.76–1.2)	0.99 (0.83–1.2)
Unilateral vision loss	341	0.85 (0.58–1.2)	1.2 (1.0–1.3)
Any vision symptoms	2,083	1.1 (0.93–1.3)	0.97 (0.9–1.0)
Vertigo	212	0.71 (0.38–1.3)	1.1 (0.93–1.2)
Signs			
Optic atrophy or ischemic optic neuropathy	142	1.6 (1.0–2.5)	0.8 (0.58–1.1)
Scalp tenderness	923	1.6 (1.2–2.1)	0.93 (0.86–1.0)
Synovitis	734	0.41 (0.23–0.72)	1.1 (1.0–1.2)
Beaded temporal artery	323	4.6 (1.1–18.4)	0.93 (0.88–0.99)
Prominent/enlarged temporal artery	508	4.3 (2.1–8.9)	0.67 (0.5–0.89)
Tender temporal artery	755	2.6 (1.9–3.7)	0.82 (0.74–0.92)
Absent temporal artery pulse	68	2.7 (0.55–13.4)	0.71 (0.38–0.75)

* GCA = giant cell arteritis; LR = liklihood ratio; 95% CI = 95% confidence interval. Adapted, with permission from ref. 1.

How is GCA diagnosed?

- Laboratory tests show features of systemic inflammation
  - Marked elevations in ESR and CRP
  - Hypochromic or normochromic or normocytic anemia and thrombocytosis
- No autoantibody tests help identify GCA

Key point #4

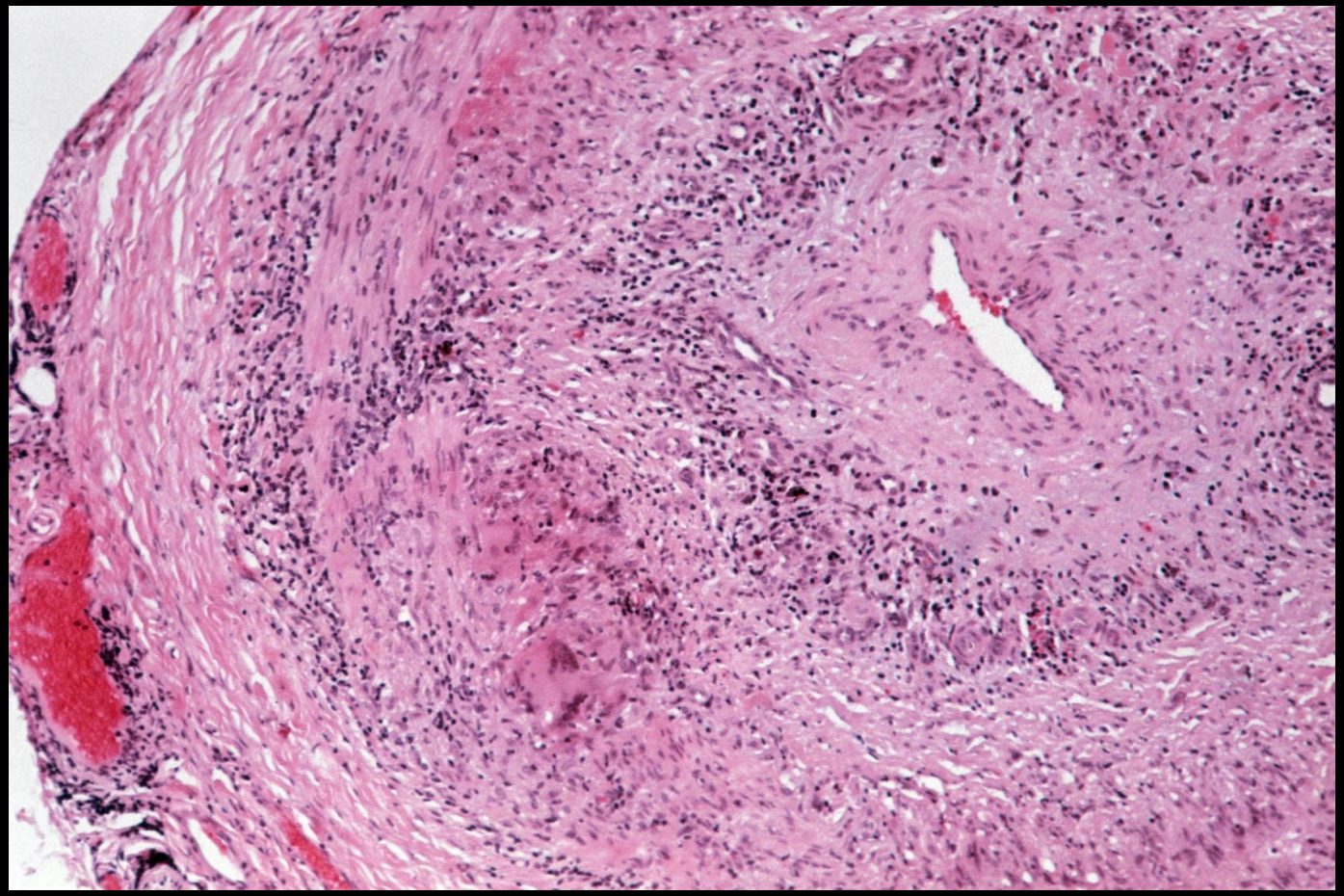
The sedimentation rate is still a useless test!

How is GCA diagnosed?

Temporal artery biopsy

- Gold standard (but not perfect)
- Characteristic histologic lesions confirms diagnosis
- 10 – 15% false –ive rate (maybe more)
- To increase diagnostic yield:
  - Specimen should be ≥1 cm long and multiple sections examined
  - Uni vs bilateral? (controvertial)
- Preferred site: Anterior temporal artery

TA biopsy findings in GCA include inflammatory infiltrates consisting of lymphocytes, dendritic cells, macrophages, and multinucleated giant cells mainly in the media and adventicia



How is GCA diagnosed?

Imaging studies

- Color duplex ultrasound of temporal artery
  - Approximately 40-75% sensitivity and 79-83% specificity for diagnosis
  - Varies between center - Operator dependent

How is GCA diagnosed?

Imaging studies

- Other imaging studies
  - For imaging of the temporal arteries – Very limited role
  - For imaging of large vessels
    - CTA
    - MRA
    - FDG-PET
- Pros and cons to each ; choice depends on availability/local expertise, consideration of exposure to ionizing radiation, the need for intravenous contrast, cost, etc.

Treatment of GCA

Overview

- High dose oral prednisone
  - *Visual loss*: IV pulse corticosteroids
- Low-dose aspirin?
- Relapse/comorbidities/corticosteroid toxicities: Steroid sparing agent
  - ?MTX, ?LEF
  - Anti-IL6 (tocilizumab)
- If little improvement within 5 days: reconsider diagnosis

Treatment of GCA

Corticosteroids

- High dose oral corticosteroids
  - Prednisone 1 mg/kg/day, up to 60 mg/d
    - Vision loss: Methylprednisolone 500 - 1000 mg/d for 3 d
  - Treat 2 to 4 weeks at high dose
  - Start **slow taper** after symptoms and signs of active disease resolve
    - e.g. decrease by 10 mg q month until 20 mg, then 2.5 mg q month until 10 mg, then 1 mg q month
    - Aim at 12 – 18 months of treatment

Treatment of GCA

Corticosteroids

- **Do not delay initiation of corticosteroids for temporal artery biopsy**
  - Resolution of the inflammatory infiltrate of GCA occurs slowly
  - Histopathologic evidence will be evident for at least 2 weeks (probably one month) after glucocorticoid onset

Key point #5

Do not delay initiation of corticosteroids for temporal artery biopsy

Treatment of GCA

ASA

- Controversial
- Studies suggest that low-dose aspirin diminishes risks of cerebral or ocular and cardiovascular events
- Prescribe low dose aspirin to patients who have another indication for it's use

Treatment of GCA

Steroid sparing agents

- MTX
  - 3 randomized controlled trial – various results (low dose MTX 10 – 15 mg)
  - Moderate efficacy at best
- Leflunomide
  - Low quality evidence
- Tocilizumab (humanized monoclonal antibody to IL-6 receptor): GiACTA trial

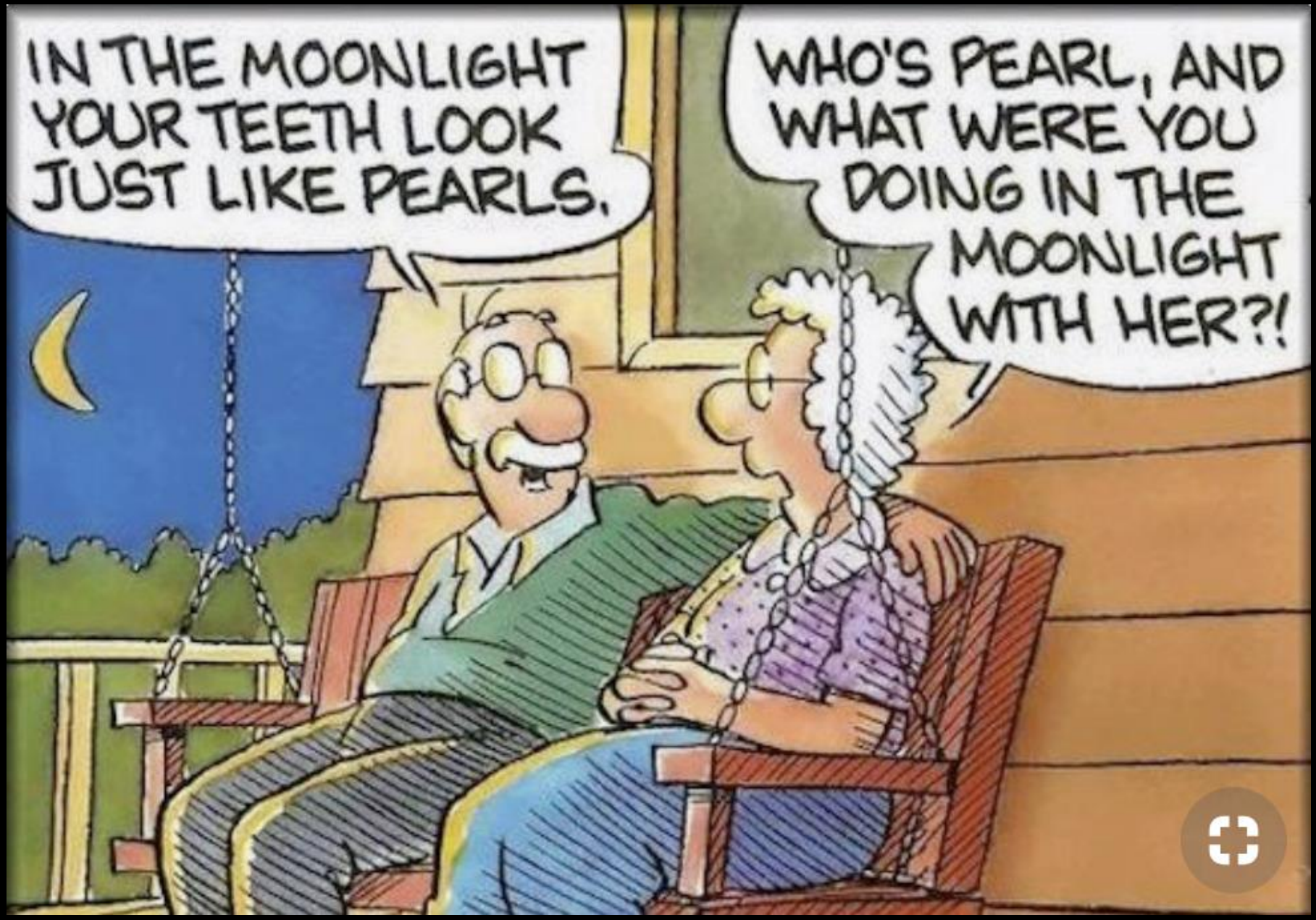
Treatment of GCA

Adjunct

- Monitor and treat glucocorticoid complications
  - ALL patients should receive a prophylaxis for GIO
- Vaccination
  - Avoid live/attenuated vaccines during periods of significant immunosuppression

Bonus key points

- ALL patients should receive a prophylaxis against glucocorticoid induced osteoporosis


IN THE MOONLIGHT YOUR TEETH LOOK JUST LIKE PEARLS.
WHO'S PEARL, AND WHAT WERE YOU DOING IN THE MOONLIGHT WITH HER?!