Updates in Polymyalgia Rheumatica and Giant Cell Arteritis

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• I have no disclosures
• I will discuss off-label use of medication
What’s new in PMR and GCA of interest to internists?

Emerging imaging technologies may aid in diagnosis of GCA

Advances in understanding biology of disease has led to new FDA approved treatment and potentially dramatically different treatment course
• 78 y/o woman with joint pain and increased inflammatory markers
• 1 month of shoulder and hip pain, worse in the morning, associated with severe morning stiffness. “I feel like I am 100 years old.”
• New headache for the past 2 weeks, with no previous history of headaches
• No fevers, scalp tenderness, shoulder/hip girdle symptoms, or jaw claudication
• Exam: Well appearing. Right temporal artery is tender with normal pulses bilaterally
• Symmetric blood pressures in arms and legs, no carotid bruits. ESR 88, CRP 97 (normal <8.0 mg/dL)
PMR – Clinical Features

• 50 years or older
• Proximal musculoskeletal pain – neck, shoulders, hips, upper arms, and thighs
• Prolonged morning stiffness
• Constitutional symptoms (40-50%)
• ESR of 40 mm/h or higher
• Exclusion of other diagnoses
• Rapid response to low dose steroid treatment (prednisone 15 mg or less)
• Not true muscle weakness
PMR – Clinical Features

Subset can present with swelling and pitting edema of hands and feet

Peripheral arthritis present in ~30-40% of patients; synovitis of the feet is typically absent

Giant cell arteritis

• Large vessel vasculitis

• Granulomatous arteritis of the aorta and/or its major branches; predilection for the branches of the carotid and vertebral arteries

• Epidemiology:
  • Extremely rare in individuals < 50 y/o
    • Average age of diagnosis is 70-79 y/o
  • Highest incidence in individuals of European descent
  • F:M 2:1
  • Most frequent systemic vasculitis (1:500 in individuals > 50 y/o)
# Giant cell arteritis: Clinical presentation & labs

<table>
<thead>
<tr>
<th>Clinical Manifestation</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td>Constitutional symptoms (including fevers/FUO)</td>
<td>Almost all</td>
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<tr>
<td>New onset headache</td>
<td>76%</td>
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<td>Jaw claudication: most specific</td>
<td>34%</td>
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<tr>
<td>Vision loss: painless, sudden, complete or partial; unilateral or bilateral; rarely reversible</td>
<td>15-20%</td>
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<td>Diplopia: highly specific</td>
<td>5%</td>
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<tr>
<td>Polymyalgia rheumatica</td>
<td>40-50%</td>
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<tr>
<td>Temporal artery abnormality</td>
<td>&lt;50%</td>
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<tr>
<td>ESR ≥ 50 mm</td>
<td>90%</td>
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<tr>
<td>Increased alkaline phosphatase</td>
<td>~25%</td>
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ACR slide collection
The blood supply to the eye and brain

GCA: Vision Loss

• 25-50% untreated pt develop vision loss in unaffected eye within 1 week of initial loss
  • Risk of vision loss essentially removed with adequate steroid treatment

• Anterior ischemic optic neuropathy (80%): due to occlusion of posterior ciliary artery
  • 5% of AION due to GCA

• Central retinal artery occlusion (10%): consider GCA in older pt with bilateral CRAO
  • 2% of CRAO with underlying GCA

• Posterior ischemic optic neuropathy (<5%)
• Branch retinal artery occlusion (uncommon)
• Occipital lobe infarct (<5%): homonymous hemianopia

• Diplopia high specificity in other symptoms suggestive of GCA

Optic disc edema in patient with AION from GCA
GCA: Cerebrovascular events

• Uncommon, usually occur within one month of the diagnosis of GCA; can be initial presentation

• Preventable with steroids

• Result of stenosis/occlusion of the extradural vertebral or carotid arteries

• Involvement of the intracranial arteries is rare (these vessels have little or no elastic tissue and lack vasa vasorum)
Relationship between GCA and PMR

• Closely related diseases

• Similar epidemiology: elderly, female predominant (2-3:1 F:M), N. European genetic associations (HLA DRB1*04, DRB1*01)

• Highest incidence in populations of N. European ancestry: GCA 18-29 cases per 100,000; PMR 41-113 cases per 100,000 among people >50 yo

Weyand, CM – oral presentation on GCA, ACR 2017 annual meeting.
Relationship between GCA and PMR

• 40-60% of GCA patients have PMR at time of diagnosis

• 10-20% of PMR patients go on to develop GCA

Relationship between GCA and PMR

- PMR pts can have evidence of subclinical temporal artery involvement histologically
- Some PMR pts with subclinical large vessel disease by PET
- Similar cytokine expression in TA biopsy specimens (IL-1, IL-2, IL-6) but gamma interferon also present in GCA
- Significance of subclinical vascular involvement in PMR unknown
- PMR pts should be alerted to GCA signs and symptoms

Case

• 78 y/o woman with joint pain and increased inflammatory markers
• 1 month of shoulder and hip pain, worse in the morning, associated with severe morning stiffness. “I feel like I am 100 years old.”
• New headache for the past 2 weeks, with no previous history of headaches
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• Exam: Well appearing. Right temporal artery is tender with normal pulses bilaterally
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What the next step should be performed in the diagnostic evaluation?

- **Biopsy** the temporal artery
- Obtain color Doppler **ultrasound** of the temporal and/or axillary arteries
- Obtain high resolution **magnetic resonance angiogram** of the cranial arteries
- Obtain **positron emission tomography** with low-dose computed tomography imaging of the cranial arteries
GCA: Biopsy

- Obtain within 2-4 weeks of starting prednisone
- At least 1 cm (ideally > 2 cm), consider bilateral
  - 3-25% of pts with positive findings on contralateral side (if unilateral negative)
- Sensitivity ~70-90%
- ~20-30% of suspected GCA pts have positive bx

GCA: What is the role of imaging?
GCA: Temporal artery imaging
Color Doppler ultrasound (temporal +/- axillary arteries)

- Stenosis, occlusion, and/or concentric hypoechogenic mural thickening (halo sign)
  - Stenosis or occlusion: sensitivity 8%-80%, specificity 73%-100%
  - Halo sign: sensitivity 55-100%, specificity 78-100%

- Extremely operator, equipment, technique dependent

- In the United States: does not replace biopsy; cannot gauge disease activity

Buttgereit F et al. JAMA 2016
Postcontrast T1-weighted FS spin-echo MRI: Axial images of 6 segments (frontal and parietal branches of TA and occipital arteries)

Wall thickening and contrast enhancement (edema) of arterial wall – different grades from 0 (normal) to 3

From Klink et al. Radiology: Volume 273: Number 3—December 2014
GCA Diagnosis: MRI compared to TA Biopsy

Rheaume M et al. Arthritis Rheumatol 2017
## GCA Diagnosis: MRI compared to TA Biopsy

<table>
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<tr>
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<th>Value</th>
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<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td>93.7% (95% CI 79-99)</td>
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<tr>
<td><strong>Specificity</strong></td>
<td>77.9% (95% CI 70-84%)</td>
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<tr>
<td><strong>Positive predictive value (in this cohort)</strong></td>
<td>48.3% (95% CI 35-62)</td>
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<tr>
<td><strong>Negative predictive value (in this cohort)</strong></td>
<td>98.2% (95% CI 94-100)</td>
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Rheaume M et al. Arthritis Rheumatol 2017
GCA: MRA of cranial vessels

• Note:
  • Experience and volume are critical
  • Rapid changes with prednisone—need to obtain within days of starting
  • Potentially consider in individuals with low suspicion and obtain biopsy in those with higher suspicion

Caveat: Single radiologist at single institution

Rheaume M et al. Arthritis Rheumatol 2017
Ultrasound provides a timely, inexpensive, and specific diagnostic modality for giant cell arteritis.

Extremely operator dependent, relatively insensitive, and limited geographically to few segments of some superficial cranial vessels.

MRI has potential for more standardized imaging, reproducible interpretation, and ability to image cranial and extra-cranial great vessels - although this expertise isn’t widely available yet in many areas.

European recommendations probably aren’t applicable to US patients at this time, including recommendations favoring ultrasound and ability to forgo a biopsy for dx.
Case

- 67 y/o woman with osteoporosis presents with R arm claudication starting 6 months ago and L arm claudication starting 1 month ago
- Denies constitutional symptoms, leg claudication, pre-syncopal symptoms, scalp tenderness, jaw claudication, new onset headache, vision loss, shoulder/hip girdle pain/stiffness
- Exam: Normal temporal arteries. R radial pulse is not palpable. L radial pulse is faint. Carotid/DP/PT pulses are 2+. No abdominal bruits.
- ESR 40, CRP 18 (normal <8.0 mg/dL)
- CT chest/arms: circumferential vessel wall thickening of subclavian to axillary arteries. No atherosclerosis in the involved areas, and no abnormalities of the aorta are noted.
GCA – not just temporal arteritis
ACR Classification Criteria – GCA (1990)

- Age 50 years or older
- New-onset localized headache or localized head pain
- Temporal artery tenderness to palpation or decreased pulsation
- ESR of 50 mm/h or higher
- Positive arterial biopsy results (vasculitis characterized by mononuclear infiltration or granulomatous inflammation, usually with multinucleated giant cells)

- 3+ criteria sensitivity 93.5%, specificity 91.2%

- What about large vessel disease? Other extracranial manifestations? How do vascular imaging modalities fit in?

GCA: large vessel/extracranial involvement

- Large artery stenosis, aortic aneurysm/dissection
- CT angiography: 25-67% of patients with large vessel involvement
  - Aorta (65%), brachiocephalic trunk (47.5%), subclavian (42.5%), carotids (35%)
  - Thoracic aorta > abdominal aorta; aneurysm > dissection
- FDG-PET: ~80%
- Autopsy: 100%

- Incidence of any large vessel manifestation high in 1st year of diagnosis
- Incidence of aortic aneurysm/dissection increased 5 years after diagnosis
- Patients with aortic manifestations are at increased risk for mortality (HR 3.5)

GCA: large vessel involvement

- Presentation: usually silent; claudication or other symptoms less common until disease more advanced

- Exam: bruits over large vessels, asymmetric pulses, BP differential

- Screening/monitoring:
  - 4 extremity blood pressures
  - Diagnosis requires imaging: CTA, MRA, PET
  - Temporal artery biopsy negative in ~50% and ESR can be low
  - Role of longitudinal imaging is undefined

Case

- 67 y/o woman with osteoporosis presents with R arm claudication starting 6 months ago and L arm claudication starting 1 month ago
- Exam: Normal temporal arteries. R radial pulse is not palpable. L radial pulse is faint. Carotid/DP/PT pulses are 2+. No abdominal bruits.
- ESR 40, CRP 18 (normal <8.0 mg/dL)
- CT chest/arms: circumferential vessel wall thickening of subclavian to axillary arteries. No atherosclerosis in the involved areas, and no abnormalities of the aorta are noted.
- R temporal artery biopsy: lymphocytic inflammation within the muscular wall and a histiocytic infiltration disrupting the internal elastic lamina. Narrowed lumen. Rare multinucleated giant cells.
GCA: Traditional treatment paradigm

• Prompt initiation of glucocorticoids can be sight-saving! Treat first, biopsy second

• Prednisone 1 mg/kg/day x 2-4 weeks; dose then gradually tapered every 1-2 weeks by ~10%

• Timing is the most important: early (within 24h) treatment is the only factor shown to be associated with improvement in visual symptoms once they occur

• Majority of patients will experience a durable remission but 40% will relapse

• Relapse can be usually be treated with increases of 10-20% prednisone dosage and are rarely associated with ischemic complications

What about steroid-sparing options for GCA?
GCA: The need for steroid-sparing agents

• Long term corticosteroid exposure associated with significant morbidity

• Search for steroid-sparing agents generally disappointing
  • Methotrexate
  • Azathioprine
  • Infliximab and other anti-TNF therapies

Mahr AD et al., Arth Rheum 2007
A steroid-sparing option for GCA

Tocilizumab = antibody to the iL-6 receptor complex

Inhibition of IL-6 signaling -> marked reduction in acute phase inflammatory response

Inflammation in GCA is thought of as a prototypically IL-6 driven disease

The NEW ENGLAND JOURNAL of MEDICINE

Trial of Tocilizumab in Giant-Cell Arteritis

GiACTA protocol

52-week double blind (part 1)
- TCZ 162 weekly
  - Prednisone
    - $n = 100$

104-week open-label extension (part 2)
- Patients in remission at 52 weeks
  - Long-term followup off the study drug
  - Patients with disease activity or flare
  - Open-label TCZ 162 mg weekly

Primary efficacy endpoint:
sustained remission at 52 weeks
GiACTA: Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>TCZ weekly + prednisone (6 months) (n=100)</th>
<th>TCZ qowk + prednisone (6 months) (n=49)</th>
<th>Placebo + prednisone (6 months) (n=50)</th>
<th>p</th>
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<tbody>
<tr>
<td>Sustained remission at 52 weeks, n (%)</td>
<td>56 (56)</td>
<td>26 (53)</td>
<td>7 (14)</td>
<td>&lt;0.001</td>
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<tr>
<td>Cumulative prednisone dose, median (range)</td>
<td>1862 (630-6602)</td>
<td>1862 (295-9912)</td>
<td>3296 (932-9778)</td>
<td>&lt;0.001</td>
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Safety:
- Similar incidence of infection, injection site reactions
- 6 TCZ pts developed neutropenia
- 1 TCZ pt with anterior ischemic optic neuropathy
- No GI perforations

Stone JH et al. NEJM 2017
GiACTA: Results

No. at Risk

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<th>100</th>
<th>93</th>
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<td>Tocilizumab weekly</td>
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<td>Tocilizumab every</td>
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<tr>
<td>Placebo + 26-wk taper</td>
<td>50</td>
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<tr>
<td>Placebo + 52-wk taper</td>
<td>51</td>
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<td>22</td>
<td>17</td>
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Stone JH et al. NEJM 2017
TCZ plus 26-week prednisone taper was superior to either a 26-week or 52-week prednisone taper in maintaining sustained corticosteroid-free remission

TCZ associated with reduced cumulative exposure to corticosteroids and fewer flares during corticosteroid taper

Long term outcomes still need to be assessed in open label extension study and real-world clinical use

Expedited FDA approval of TCZ for GCA May 2017

Increasingly used as first-line therapy
PMR – Treatment

- Prednisone 15-20 mg daily x 2-4 weeks, usually leads to rapid improvement in symptoms
- Taper by 2.5 mg every 2-4 weeks until at 10 mg daily, then by 1 mg each month until discontinuation or flare
- Most patients are on treatment for 1-2 years
- Relapses (and steroid morbidity) are common
What about tocilizumab in PMR?

• Promising results from two small studies
  • Prospective open-label study of 20 newly diagnosed PMR patients treated with 3 monthly tocilizumab infusions followed by prednisone taper
  • Prospective open-label phase Iia trial of tocilizumab with newly diagnosed PMR treated with monthly TCZ infusions for a year with rapid prednisone taper

• Anti-IL-6 treatment may be effective, but RCT lacking at this time

Updates in PMR and GCA: Summary

• Temporal artery biopsy remains the gold standard for diagnosis of GCA

• Role of imaging modalities (MRI and ultrasound) is promising but needs further study

• A negative MRI is helpful in ruling out disease (and thus avoiding biopsy) in a patient with low suspicion for GCA

• Tocilizumab is an FDA-approved steroid sparing agent for GCA and is increasingly being used as first-line therapy with rapid prednisone taper

• Role for tocilizumab in PMR remains to be defined
Thank you!

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