Polymyalgia Rheumatica and Giant Cell Arteritis: From Etymology to a Clinical Understanding

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Sir William Osler, the “Father of Modern Medicine,” once said, “When an arthritis patient walks in the front door, I feel like leaving by the back door.”

**Goals**

- Review the clinical manifestations of polymyalgia rheumatica and giant cell arteritis and an evidence based approach to diagnosis, pathophysiology, and management
- Consider if PMR and GCA are separate entities or are they related
- Review factors associated with the development and expression of musculoskeletal disorders with age including: genetics, environment, regional body anatomy

**Polymyalgia Rheumatica**

- Poly- many (Greek)
- Myo- one or more muscles (Greek)
- Algia- painful condition (Greek)
- Rheumatica- “rheuma” (Greek)

Hippocrates, 4th century BC, phleghm- one of the four primary humors

- **Polymyalgia rheumatica** was coined by Barber in 1957.
- Prominently affects the synovium of certain joints and bursae, not the muscles per se.
**PMR Epidemiology**

- In the United States, the average annual incidence of PMR is 52.5 cases per 100,000 persons aged 50 years and older. The prevalence is approximately 0.5-0.7%.

- Worldwide, the frequency varies by country. In Europe, the frequency decreases from north to south, with a high incidence in Scandinavia and a low incidence in Mediterranean countries. In Italy, for example, the incidence is 12.7 cases per 100,000 persons.

- Whites are affected more than other ethnic groups. PMR is only occasionally reported in African-American persons. PMR is twice as common in females.

- The incidence increases with advanced age. PMR rarely affects persons younger than 50 years. The median age at diagnosis is 72 years.

**Figure 4. Ultrasonography (A), MRI (B) of the hip and Fluorodeoxyglucose PET (C) of patients with isolated untreated PMR. (A) Ultrasonography: the presence of fluid within the trochanteric bursa (surrounding white line and arrows). (B) An axial T2 weighted section: trochanteric bursitis (arrows) and joint effusion (arrowhead). (C) Fluorodeoxyglucose PET: inflammatory fluorodeoxyglucose uptake in the hips (arrows) and absence of vascular uptake.**

**Polymyalgia Rheumatica**

- Clinical Presentation:
  - Age 50 or older at onset—often abrupt
  - Bilateral aching and morning stiffness which lasts 30 min or more for 1 month or more involving at least 2 of 3 areas
  - Neck or torso
  - Shoulders or proximal arms
  - Hips or proximal thighs
  - ESR = 40 mm/hr or greater

**Figure 4. Shoulders of patient with isolated PMR—no signs or symptoms of GCA. (A) Ultrasonography fluid within the subacromial bursa (arrows) and surrounding the long biceps tendon groove (arrowheads). (B) Axial T2 weighted MRI: subacromial and subdeltoid bursitis (pentagon), joint effusion (arrow), and tenosynovitis of the long head of the biceps (arrowhead). (C) Fluorodeoxyglucose PET: inflammatory fluorodeoxyglucose uptake in the shoulders (arrows).**

**Figure 4. Ultrasoundography (A), MRI (B), and Fluorodeoxyglucose PET (C) of patients with isolated untreated PMR. (A) Ultrasoundography: fluid within the trochanteric bursa (surrounding white line and arrows). (B) An axial T2 weighted MRI: trochanteric bursitis (arrows) and joint effusion (arrowhead). (C) Fluorodeoxyglucose PET: inflammatory fluorodeoxyglucose uptake in the hips (arrows) and absence of vascular uptake.**

**Table 1. Polymyalgia rheumatica vs late-onset rheumatoid arthritis**

<table>
<thead>
<tr>
<th></th>
<th>PMR</th>
<th>Late onset RA</th>
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<tbody>
<tr>
<td>Synovitis</td>
<td>23%</td>
<td>&gt; 80%</td>
</tr>
<tr>
<td>Age</td>
<td>Younger</td>
<td>Older</td>
</tr>
<tr>
<td>Arthritis ofPIP, MCP and wrist joints</td>
<td>Less frequent</td>
<td>More myalgia</td>
</tr>
<tr>
<td>ESR &amp; CRP</td>
<td>Higher ESR, CRP &amp; IL-6</td>
<td>Main sign</td>
</tr>
<tr>
<td>HLA allele</td>
<td>HLA-DRB1 allele</td>
<td>HLA-DRB1 allele</td>
</tr>
<tr>
<td>Response to 15 mg steroid</td>
<td>Dramatic response</td>
<td>Slower response</td>
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</table>
Rheumatoid arthritis
Overview of joints affected

- Joints most frequently affected in RA include:
  - The proximal interphalangeal (PIP) and metacarpophalangeal (MCP) joints of the hands
  - The wrists
  - The elbows
  - The knees
  - The ankles, and
  - The metacarpophalangeal (MTP) joints of the feet
- Distal interphalangeal (DIP) joints are typically spared in RA.

PMR: Etiology/Pathogenesis

- The cause of PMR is unknown.
- PMR is closely linked to giant cell arteritis although it is controversial whether GCA and PMR are two separate diseases or part of the same spectrum of disease.
- One hypothesis is that in a genetically predisposed patient, an environmental factor, possibly a virus, causes monocyte activation, which helps determine the production of cytokines that induce manifestations of PMR and GCA.
- PMR is associated with the HLA-DR4 haplotype. High level of IL-6 is associated with increased disease activity.
- Although several infectious agents have been investigated as possible triggers, results are inconclusive.

PMR treatment

- Dramatically responsive to steroids
- Most response to Prednisone <20mg/day (ACR guidelines 12.5-25 mg)
- Dose gradually tapered
- Tapering an art not science!
- Monitor for relapse, features of GCA, side-effects of corticosteroids
- Clinical course
- Methotrexate in resistant cases
Giant Cell Arteritis

**Presenting symptoms**

- Headache
- Scalp tenderness
- Thickened temporal arteries
- Jaw claudication
- Acute visual loss
- Weight loss, anorexia, fever, night sweats,
- Malaise, depression

**1990 ACR criteria for the classification of giant cell arteritis**

<table>
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<th>Clinical Feature</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Temporal artery biopsy</td>
<td>ESR &gt; 50 mm/h by the Westernern method</td>
</tr>
<tr>
<td>Presence of temporal claudication</td>
<td>70-80%</td>
</tr>
<tr>
<td>Presence of visual loss</td>
<td>30-60%</td>
</tr>
<tr>
<td>Presence of fever, night sweats, and malaise</td>
<td>15-45%</td>
</tr>
<tr>
<td>Presence of headache, facial pain, jaw claudication, and diplopia</td>
<td>5-20%</td>
</tr>
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</table>

*For purposes of classification, a patient with vasculitis is said to have giant-cell (temporal) arteritis if at least three of these five criteria are present. The presence of any three or more criteria yields a sensitivity of 95-5% and a specificity of 63-2%. Adapted from ref. 2.*

**Table 1**

<table>
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<th>Signs and symptoms of giant cell arteritis (GCA)</th>
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**GCA - clinical features**

- Many of the clinical features commonly found with the disease are unhelpful in predicting the likelihood of positive temporal artery biopsy results.
- Jaw claudication and diplopia substantially increase the probability of positive biopsy results (positive LR = 4.2 and 3.4, respectively).
- No historical findings help rule out the diagnosis by their absence.
Among physical examination findings, synovitis makes the diagnosis of TA less likely, while beaded, prominent, enlarged, and tender temporal arteries each increase the likelihood of positive biopsy.

Beaded, prominent, or enlarged arteries confer the highest positive LRs of any clinical or laboratory feature and substantially increase the probability that a patient with suspected TA will have positive biopsy results.

While these findings increase the chance of having TA, they are variably sensitive, from 16% (beaded temporal artery) to 65% (any temporal artery abnormality).

A normal ESR (LR = 0.2) or ESR less than 50 mm/h (LR = 0.35) each make positive biopsy results unlikely, but setting the ESR threshold at 100 mm/h is less efficient, as patients with an ESR less than 100 mm/h have an LR (0.8).

Clinically suspected of disease, those with an ESR greater than 100 mm/h have a modestly increased likelihood of biopsy-proven TA (LR = 1.9).

Review of clinical series of patients with suspected TA does not allow a determination of the predictive value of selected combinations of clinical and laboratory features.

In addition, it is not possible to determine whether certain combinations of features would sufficiently increase the likelihood of disease that a clinician should treat presumptively for TA and not perform a biopsy at all.

The morbidity of a prolonged course of corticosteroids, however, is such that most clinicians would favor confirmation of disease by biopsy even if the clinical probability is high.

A protective response involving host cells, blood vessels and proteins
- Goals are:
  - eliminate the initial cause of cell injury
  - Remove necrotic cells and tissue
  - Initiate the process of repair

Also a potentially harmful process
- Components of inflammation that are capable of destroying microbes can also injure bystander normal tissue

Components of the inflammatory process include white blood cells and plasma proteins
- Normally present in the blood
- The inflammatory reaction’s goal is to bring these to the site of infection and/or tissue damage

Inflammation is induced by chemical mediators produced by damaged host cells
- Cytokines and other mediators

Inflammation is normally controlled and self-limited
Acute Inflammation

Histopathological features of giant-cell arteritis. Transverse sections of temporal artery—untreated GCA (A) Granulomatous inflammation and multinucleated giant cells (arrows) at junction of media and intima.. (B) A mononuclear transmural infiltrate without giant cells (C) Vasculitis involving small vessels (arrows) close to a non-inflamed temporal artery.

Stimuli for Acute Inflammation

- **Infections** (bacterial, viral, fungal, parasitic) & microbial toxins
- **Tissue necrosis**: ischemia, trauma, physical or chemical injury (e.g., thermal injury; irradiation; some environmental chemicals)
- **Foreign bodies** (splinters, dirt, sutures)
- **Immune reactions** (aka hypersensitivity reactions)

Causes of chronic inflammation

- **Persistent** injury or infection
  - Ulcer, tuberculosis
- **Prolonged** exposure to a toxic agent
  - Pulmonary silicosis (silica in the lung)
- **Autoimmune disease**—self-perpetuating immune reaction that results in tissue damage and inflammation
  - Rheumatoid arthritis
  - Systemic lupus erythematosus
  - Multiple sclerosis

Features of chronic inflammation

- **Chronic inflammation** = long duration
- **Components**:
  - Lymphocyte, plasma cell, macrophage (mononuclear cell) infiltration
  - Tissue destruction by inflammatory cells
  - Repair with fibrosis and angiogenesis (new vessel formation)
Consequences of blood vessel wall inflammation

Figure 1 Pathogenetic mechanisms operating in GCA


The pathogenic pathways implicated in granulomatous lesions in giant cell arteritis


Gross architecture of a granuloma with macrophages, dendritic cells, and multinucleate giant cells forming the core of the sphere, surrounded by a shell of lymphocytes

The systemic inflammatory response in giant cell arteritis and polymyalgia rheumatica. ILVessel wall inflammation is preceded and accompanied by an intense acute phase response. Circulating macrophages are activated and release interleukin (IL)-1 and interleukin-6, critical inducers of a multiorgan reaction involving the liver, the central nervous system, the vascular system, the bone marrow, and the immune system. Hepatic acute phase reactants are useful in the laboratory diagnosis of giant cell arteritis and polymyalgia rheumatica. The systemic inflammatory response can exist in the absence of fully developed vasculitis, as in the case of polymyalgia rheumatica. CRP = C-reactive protein.

Figure Legend:


The final common pathway: Mechanisms of arterial wall destruction in GCA

Figure 3 Pathologic analysis of sections adjacent to those containing VZV antigen from GCA-positive temporal arteries Temporal arteries (TAs) in which varicella-zoster virus (VZV) antigen was detected immunohistochemically were further analyzed pathologically.
Pathogenesis of RA

Giant cell arteritis and polymyalgia rheumatica

Incidence of severe giant cell arteritis in the arteries of head and neck. ST indicates superficial temporal artery; V, vertebral; O, ophthalmic; PC, posterior ciliary; IC, internal carotid; EC, external carotid artery and branches in the neck; CR, central retinal

More pearls about temporal artery biopsy
Hayreh & Zimmerman

363 cases of suspected GCA referred for TA Bx (106+, 257-)

- 21.2% with visual loss and +TA Bx - no other symptoms
- 55.7% with +TA Bx had new onset localized HA- so did 45.5% with a negative TA Bx.
- 19.8% with +TA Bx had tenderness or decreased pulsation- so did 12.8% with negative TA Bx.
- Normal ESR did not rule out GCA.

Hayreh & Zimmerman Study

Temporal Artery Biopsy

“Skip lesions” - fact or fiction?

In the HZ study, taking a 3.5cm biopsy with serial sectioning yielded a 100% positive TAB rate in GCA patients

TABs for every patient?
1. GCA is a well-known masquerader
2. The risks of steroid-related systemic complications

Low yields (3-4%) from bilateral TABs suggests unjustified
Steroids therapy does NOT significantly alter pick up rate
***DO NOT WITHOLD STEROIDS TO WAIT FOR TAB***

Ultrasonographical findings for GCA

Clinical features of polymyalgia rheumatica and giant cell arteritis


Therapeutic Approaches to Giant-Cell Arteritis and Polymyalgia Rheumatica.

A: Giant Cell Arteritis

Induction Therapy
- Prednisone 1 mg/kg/day
- Oral corticosteroids, oral prednisolone
- Methotrexate 5-20 mg/week
- Intra-articular injection of hydrocortisone or triamcinolone

Maintenance Therapy
- Oral prednisone to 10-20 mg/day
- Methotrexate 15-25 mg/week
- Intra-articular injection of hydrocortisone or triamcinolone

Management of Flares
- Prednisone tapering of 10-15 mg/day
- Monitoring for disease activity
- Increased frequency of monitoring

B: Polymyalgia Rheumatica

Induction Therapy
- Oral steroids 15-20 mg/day, tapering to maintenance dose
- Methotrexate 7.5-15 mg/week
- Hydroxychloroquine 200 mg/day

Maintenance Therapy
- Methotrexate 7.5-15 mg/week
- Hydroxychloroquine 200 mg/day
- Normal ESR and CRP

Management of Flares
- Prednisone tapering of 10-15 mg/day
- Monitoring for disease activity
- Increased frequency of monitoring


Initial Prednisone Dose
- 40-60 mg OD

Commence Prednisone Tapering
- Once ESR* has normalized

Tapering Schedule
- Decrease dose by 5 mg/week until 20 mg; then by 2.5 mg every 2 weeks, as tolerated

Goal Prednisone Dose at Six Months
- 7.5-15 mg OD

Expected Duration of Therapy
- 1-2 years

*ESR: erythrocyte sedimentation rate

Case 1

- A 74-year-old woman has the recent onset of daily bitemporal headache but is otherwise well. Her general physical examination results are normal and the erythrocyte sedimentation rate (ESR) is moderately elevated at 64 mm/h. You wonder whether additional history or physical examination findings will modify your suspicion of possible temporal arteritis (TA) or whether the historical features alone warrant proceeding to temporal artery biopsy.

Case 2

- 53-year-old man has a 1-month history of fever and fatigue and reports a single episode of transient partial loss of vision in 1 eye. You believe that TA is among the diagnostic considerations but suspect that he is too young for this diagnosis. You wonder if additional history, physical examination, or laboratory testing will change the probability of TA sufficiently to alter your decision about the role of temporal artery biopsy rather than pursuing diagnostic evaluation for carotid artery stenosis or other considerations first.

In our first clinical scenario, the history of bitemporal headache and a modestly elevated ESR would be among those factors that may lead a clinician to suspect TA. In this setting, one would seek the potential additional history of jaw claudication or diplopia, and determine the presence of a prominent, tender, or beaded temporal artery. If present, these factors would substantially increase the likelihood of positive temporal artery biopsy results.

In the second scenario, TA is among the diagnostic considerations for transient partial monocular visual loss in the setting of a constitutional illness. The history in this case is sufficiently compelling to justify a temporal artery biopsy. Given the high prior probability and the poor performance of historical and examination features in excluding disease, an otherwise normal history and physical examination would not sufficiently reduce the likelihood of TA to avoid the need for a temporal artery biopsy. A normal ESR would, however, reduce the likelihood of disease by a factor of 0.2 and should prompt consideration of alternative diagnoses.