Veiled Pain: A Rheumatologist's Journey to Reveal the Truth

Hyder Husain D.O.
Rheumatology Fellow, PGY-5

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Introduction

- HH, a 55-year-old male referred to rheumatology
- Diffuse muscle pain and elevated creatine kinase (CK)
- Muscle pain started over the last 12 months
  - Tingling and burning in muscles of his arms and legs
  - He also noted weakness
  - Bilateral proximal arms and legs
  - Muscle pain present throughout the day
- Occasional swelling of wrists and hands with morning stiffness lasting about 1 hour
- Also present:
  - Trouble sleeping, headaches, chronic back pain
- He did not have fevers, weight loss, shortness of breath, Raynaud's
- Medical History: Gout, Osteoarthritis, Hypertension
- Medications: Amlodipine, allopurinol, pregabalin

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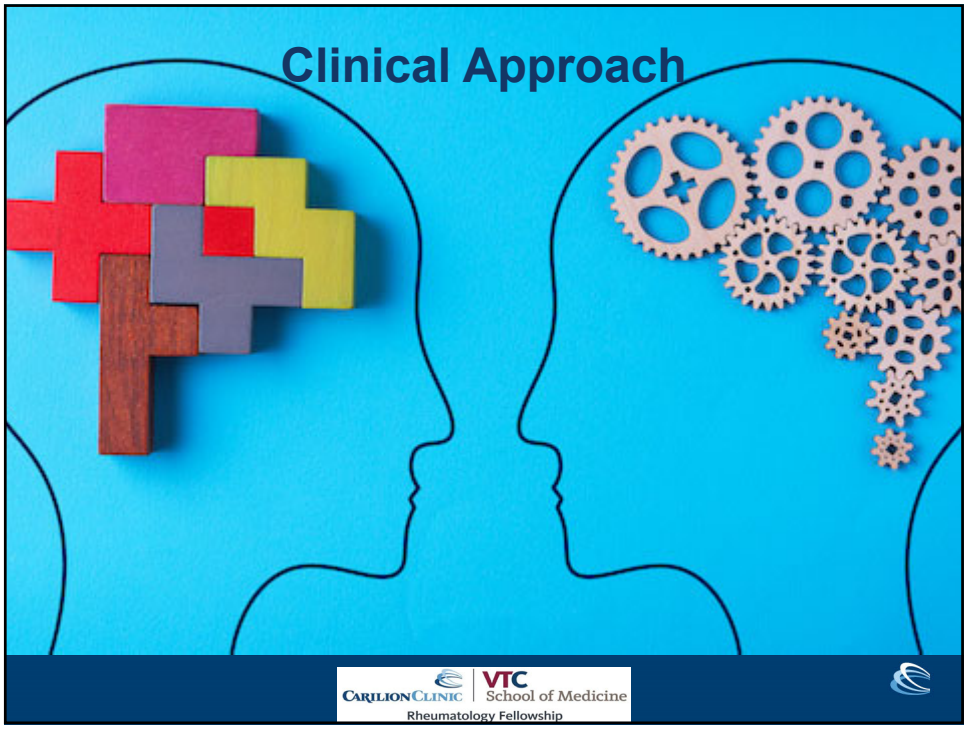

Clinical Approach

- Infection
  - Bacterial, fungal, atypical, and viral
- Malignancy
  - Primary or metastatic
- Myositis
  - Other Inflammatory process (RA, sarcoidosis, etc.)
- Drug reaction

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Initial visit

- Physical Exam
  - General: no acute distress, appropriate mood and affect
  - Skin: warm, dry, no rash
  - Musculoskeletal: no deformities, ROM intact, no erythema, tenderness to palpation over bilateral deltoids, bilateral posterior forearms.
  - Neuro: alert, oriented, normal speech, no focal findings or movement disorder noted, 5/5 muscle strength.
- Thoughts on initial workup?

Initial Visit

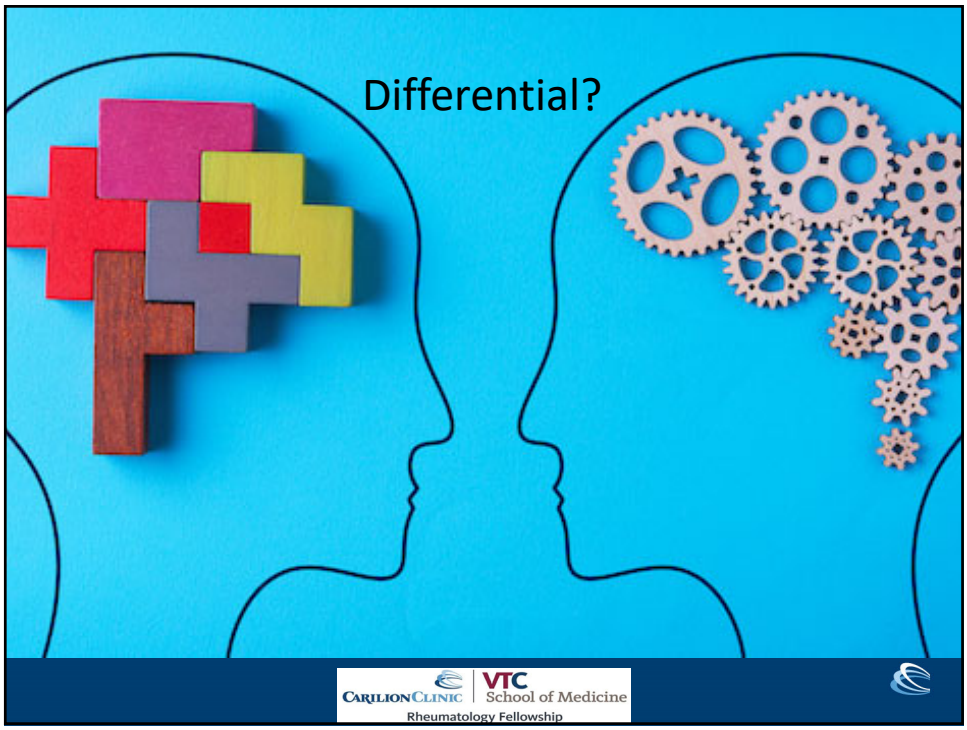
Test	Result	Reference Range
PL-7 Autoantibodies	Not detected	Not detected
PL-12 Autoantibodies	Not detected	Not detected
Mi-2 Autoantibodies	Not detected	Not detected
Ku Autoantibodies	Not detected	Not detected
EJ Autoantibodies	Not detected	Not detected
OJ Autoantibodies	Not detected	Not detected
SRP Autoantibodies	Not detected	Not detected
Jo-1 Autoantibodies	Not detected	Not detected

MRI Lower Extremities
Musculature of the right and left thighs are normal and symmetrical.
Quadriceps muscles specifically are normal without atrophy.
Hamstring muscles are normal without atrophy.
There is no inflammatory change within the musculature and there is no inflammation and myofascial planes.
Subcutaneous fat appears normal without inflammation or edema

WBC 4.0 - 10.5 K/uL	10.6 (H)		
Hemoglobin 13.0 - 16.0 g/dL	16.1 (H)		
Hematocrit 37 - 49 %	44.4		
Platelets 130 - 400 K/uL	262		
Urea Nitrogen 6 - 20 MG/DL	7		
Creatinine 0.5 - 1.4 MG/DL	0.69		
Alkaline Phosphatase, Serum 42 - 121 IU/L	95		
AST 10 - 42 IU/L	30		
ALT 10 - 60 IU/L	39		
CK, Total 26 - 308 IU/L	425 (H)	798 (H)	973 (H)
Ld 135 - 214 IU/L	176		
C-Reactive Protein <1.0 mg/dL	<0.40		
Sed Rate 0 - 20 mm/HR	1		
Uric Acid 2.6 - 7.2 MG/DL	7.1		

Follow Up Visit

- Chronic lower back pain
- Muscle cramps
- No proximal muscle weakness
- No rashes
- Occasional hand weakness



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Differential Diagnosis

- Inflammatory muscle disease
- Glycogen storage disease
  - Acid maltase deficiency
- Drug-induced myositis
- Overlap myositis
- Inclusion body myopathy
- Neuropathic myopathy
  - Demyelinating polyradiculoneuropathy
  - Emergent management of myasthenia gravis
  - Late-onset distal myopathies
  - Motor neuron disease
- Myofibrillar myopathies
- Post-polio syndrome
- Autophagic Vacuolar Myopathies

Electromyography (EMG)

- EMG unremarkable for myopathic or neuropathic process

Muscle Biopsy

- Endomysial chronic inflammation involving the non-necrotic myofibers
- Scattered atrophic and angulated fibers with internalized nuclei
- There is no increase in fibrosis or rimmed vacuoles seen
- There is no evidence of:
  - Perifascicular atrophy
  - Perivascular inflammation
  - Vasculitis
- Conclusion: in the absence of other findings, this biopsy is consistent with polymyositis

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Treatment Thoughts?

- Azathioprine and Hydroxychloroquine
  - Switched to hydroxychloroquine & mycophenolate as allopurinol was needed for hyperuricemia
- Poor clinical response
  - What to add next?
    - Added Tacrolimus
- Insurance change, tacrolimus stopped
  - What to add next?
  - Refused repeat biopsy
- Started on Rituximab and methotrexate
- Restart physical therapy
- Unchanged muscle weakness and pain, progressive muscle atrophy

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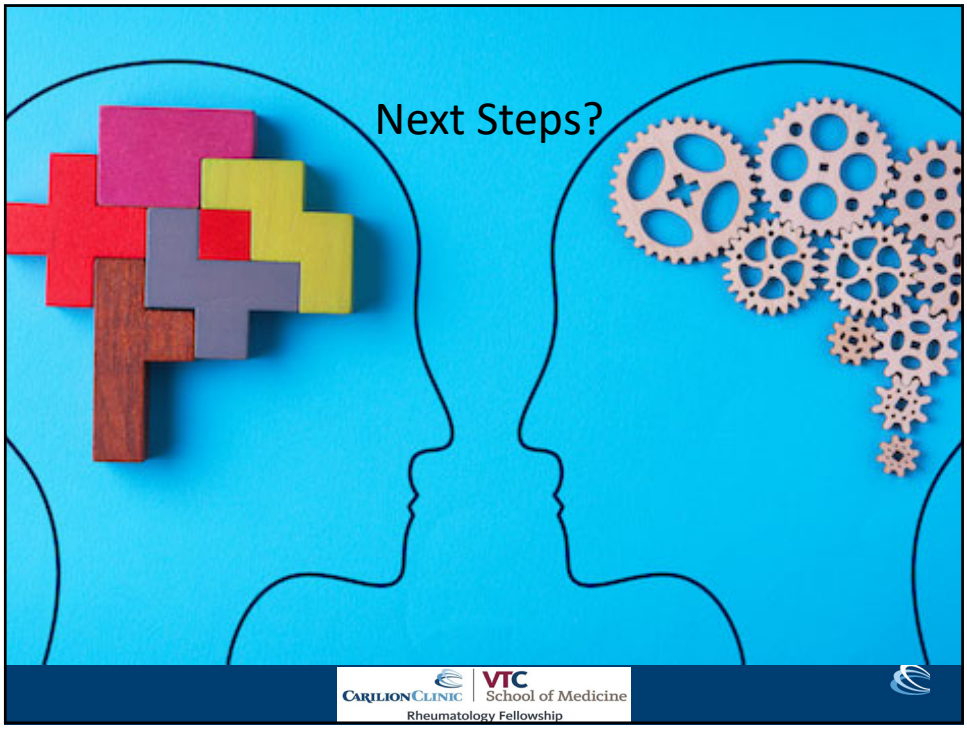

Next Steps

- Repeat MRI:
  - Musculature/tendons: No abnormal T2 signa
    musculature of the pelvic girdle or proximal f
    suggest ACUTE myositis
- Repeat Myositis Panel

Jo-1 Ab <11 SI	<11
PL-7 Ab <11 SI	<11
PL-12 Ab <11 SI	<11
Ej Ab <11 SI	<11
OJ Ab <11 SI	<11
SRP Ab <11 SI	<11
Mi-2 Alpha Ab <11 SI	<11
Mi-2 Beta Ab <11 SI	<11
MDA-5 Ab <11 SI	<11
TIF-1y Ab <11 SI	<11
NXP-2 Ab <11 SI	<11
WBC 4.0 - 10.5 K/uL	12.2 (H)
Hemoglobin 13.0 - 16.0 g/dL	17.4 (H)
Hematocrit 37 - 49 %	47.9
Platelets 130 - 400 K/uL	273
Sed Rate 0 - 20 mm/HR	3
C-Reactive Protein <1.0 mg/dL	0.48
Ld 135 - 214 IU/L	355 (H)
Aldolase <=8.1 U/L	19.9 (H)
CK, Total 26 - 308 IU/L	1026 (H)
HMGCR Ab (IgG) CU <20	<2
cN 1A Ab (IgG) <15: NEGATIVE > OR = 20: POSITIVE	5
GAD-65 Ab <5 IU/mL	<5

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Next Steps

- Repeat MRI:
  - Musculature/tendons: No abnormal T2 signal with respect to the musculature of the pelvic girdle or proximal femoral soft tissues to suggest ACUTE myositis
- Repeat Myositis Panel
- Repeat EMG
  - Needle EMG revealed increased insertional activity, fibrillation potentials and positive sharp waves along with low amplitude, short duration motor unit action potentials and increased recruitment in both vastus lateralis muscles
- Repeat Muscle Biopsy
  - Muscle biopsy shows skeletal muscle with a significant lymphocytic inflammatory infiltrate with foci of myonecrosis, rimmed vacuoles, endomysial fibrosis, and type 2 fiber atrophy, supportive of the diagnosis of inflammatory myopathy
  - TPD-43 immunostain highlights focus of sarcoplasmic inclusions- suspicious for inclusion body myositis

Inclusion Body Myositis (IBM)

- Clinical hallmarks of IBM
  - Weakness and atrophy of the quadriceps and forearm flexors
  - Weakness in the distal finger flexor
- Distinguishing features of IBM from other inflammatory myopathies
  - Asymmetric and distal muscle involvement
    - The predilection for wrist or finger flexors and foot extensors
  - Slow and progressive
  - Muscle atrophy
    - Wasting of finger flexors, wrist flexors, and quadriceps

Evaluation Of IBM

- Laboratory testing
  - Elevated creatinine kinase, Aldolase, LDH, Alanine transaminase, and Aspartate transaminase
  - Inflammatory markers like ESR and CRP may be normal
  - Mup44 antibody against the cytosolic 5'nucleotidase 1A antigen
- EMG findings
  - Resting irritability of the muscle fibers (fibrillation, complex repetitive discharges, and positive sharp waves) and at needle insertion.
  - Myopathic motor unit potentials
    - Short duration, low amplitude and polyphasic during contraction
- MRI
  - May show edema, fatty infiltration, and atrophy
- Biopsy
  - Looking perivascular/endomysial infiltrates of CD8+T Cells invading the non-necrotic muscle fibers that express MHC Class I antigen
  - Gomori Trichrome stain shows "rimmed vacuoles", although the extent of myofibers having classic rimmed vacuoles varies
  - Ubiquitin, B-amyloid, B-amyloid precursor protein (APP), α-synuclein, tau, **TDP43**, and LC3B

Treatment

- At present no known beneficial pharmacological therapy
- Goal of therapy
  - Symptom management
  - Preserving muscle function
- Physical therapy and assistive devices
- Ongoing trials
  - Follistatin gene therapy
  - Arimoclomol
  - Natalizumab
- Surgical steps for complications
  - Cricopharyngeal dilation
  - Myotomy
  - Gastrostomy tube

Barriers to Care

- Low Health Literacy
  - Patient's sister advocate
- Insurance changes
- Missed followups/Location of patient
- Slow and progressive disease necessitates a high index of suspicion
- Lack of Beneficial Pharmacological Therapy

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References

- Naddaf E, Barohn RJ, Dimachkie MM. Inclusion Body Myositis: Update on Pathogenesis and Treatment. Neurotherapeutics. 2018 Oct;15(4):995-1005.
- Amato AA, Sivakumar K, Goyal N, et al. Treatment of sporadic inclusion body myositis with bimagrumab. Neurology. 2014 Dec 09;83(24):2239-46.
- Panginikkod S, Musa R. Inclusion Body Myositis. [Updated 2022 Jul 18]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538200/

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