Limping Along

Dr Timothy J Day
Royal Melbourne Hospital

Case report- 43 F

- May 2011: 43 yr, female scientist
  - PH: R sciatica, obesity surgery,
  - no systemic illness, no CT symptoms
  - FH: Nil neuromuscular, No medications
- 3-4 yrs painless weakness L ankle- limp
  - Can't stand on L toes, occas tripping
  - EX: Mod weakness L ankle PF, depressed AJs
    - Normal R leg, upper limbs, Normal sensation

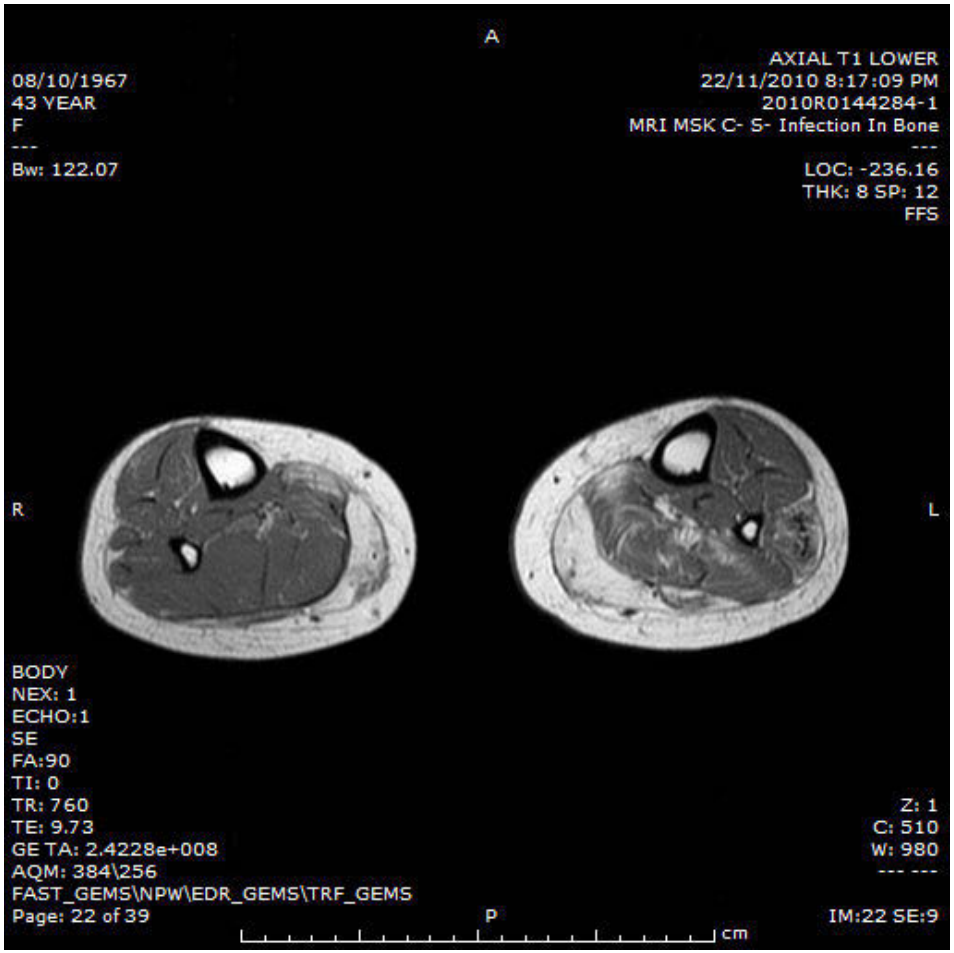
Case report- 43 F

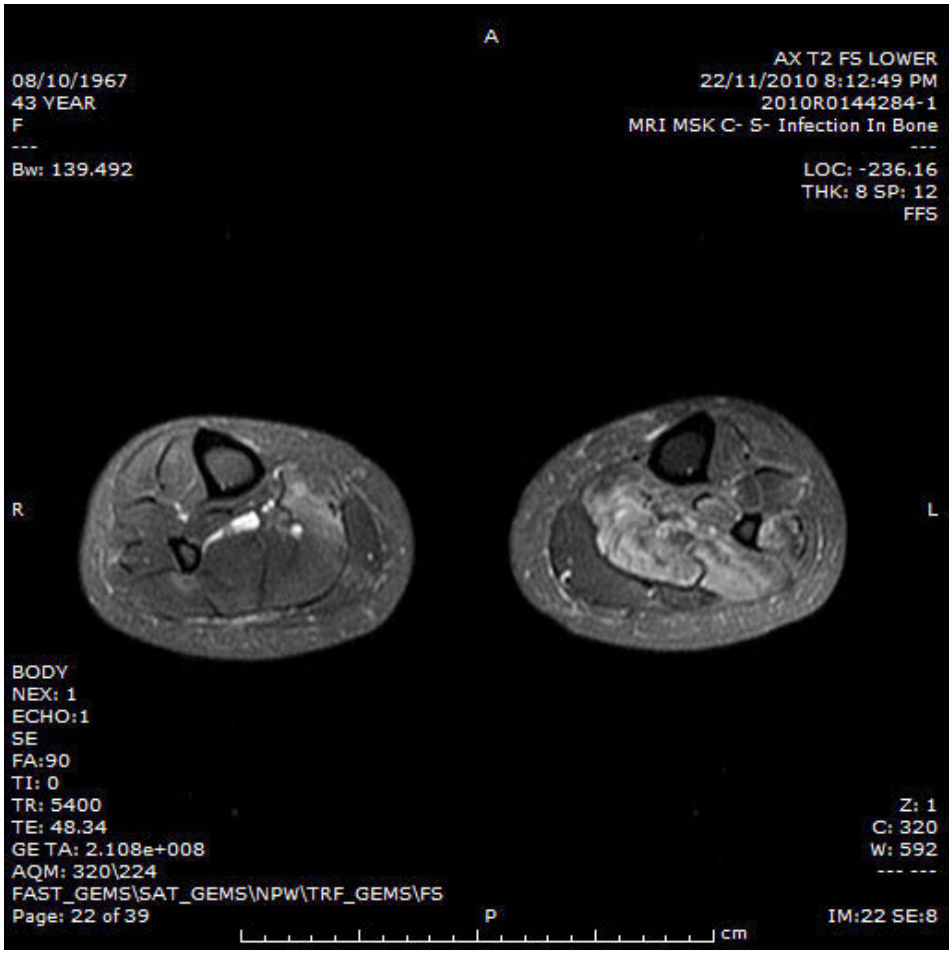
- Investigation:
  - CK 154, RhF: 2700, Abs negative
  - EMG- Patchy irritative myopathy in both calves, also in quads, gluteals, paraspinals
    - Fibrotic gastrocs
  - MRI-atrophy and abnormal signal in
    - posterior calves> ant & post thighs
      - Patchy changes in ant/lateral calf
  - Biopsy: “subtle inflammatory myositis”

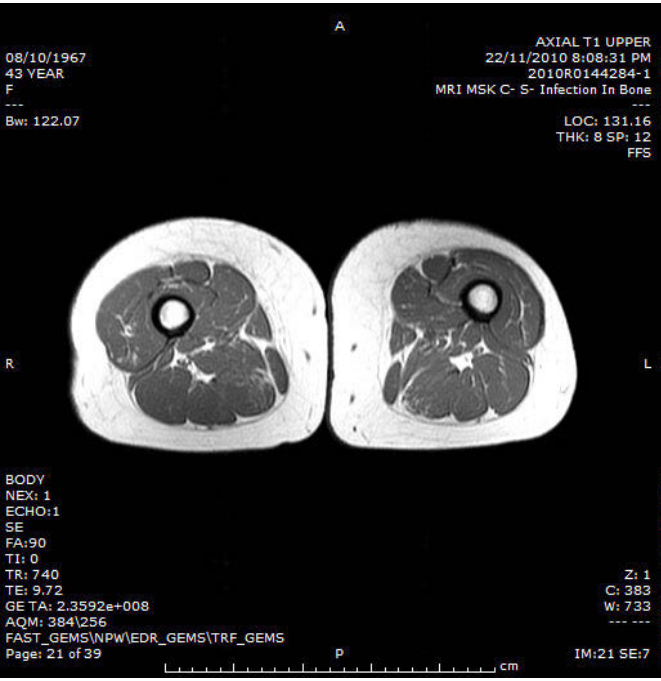
EMG Findings

Muscle (Innervation)	Interpretation	Ins.act.	Spontaneous act.			Voluntary act.			
			Fib	PSW	Fasc	Amp	Dur	Poly	IP
Left T10	Normal		Nil	Nil	0				
Left L2	Myopathy		1+	2+	0	Normal	1-	1+	
Left L5	Mod activ Neur		1+	2+	0			1+	
Left Tibialis posterior (Tibial, L5 s1)	Sl activ Neur		1+	2+		Normal	Normal	Normal	Normal
Left Medial Gastroc (Tibial, S1 s2)	Myopathy	Decr.	2+	2+	0	1-	1-	1+	1+ Early
Right Medial Gastroc (Tibial, S1 s2)	Myopathy		2+	3+		1-	1-	2+	1+ Early
Left Peroneus longus (Superficial Peroneal, S1 l5)	Sl activ Neur		1+	2+	0	Normal	1+	1+	+/- Low
Left Gluteus medius (Inferior Gluteal, l4 L5 s1)	Myopathy		Nil	Nil		1-	1-	1+	+/- Low
Left Vastus lateralis (Femoral, l2 l3 L4)	Normal		Nil	Nil	0	Normal	Normal	Normal	Normal
Left Vastus medialis (Femoral, l2 l3 L4)	Myopathy		Nil	1+		1-	1-	1+	+/- Low
Right Vastus medialis (Femoral, l2 l3 L4)			1+	1+	0	Normal	1-	2+	1-
Left Tensor fascia latae (Inferior Gluteal, l4 L5)	Myopathy		1+	2+	0	1-	1-	Normal	+/- Low
Left Tibialis Anterior (Peroneal, l4 L5)	Sl activ Neur		1+	1+	0	Normal	1+	2+	1-
Right Tibialis Anterior (Peroneal, l4 L5)	Myopathy		1+	2+	0	1-	1-	2+	1-

Muscle MRI 2010



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08/10/1967
43 YEAR
F

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BODY
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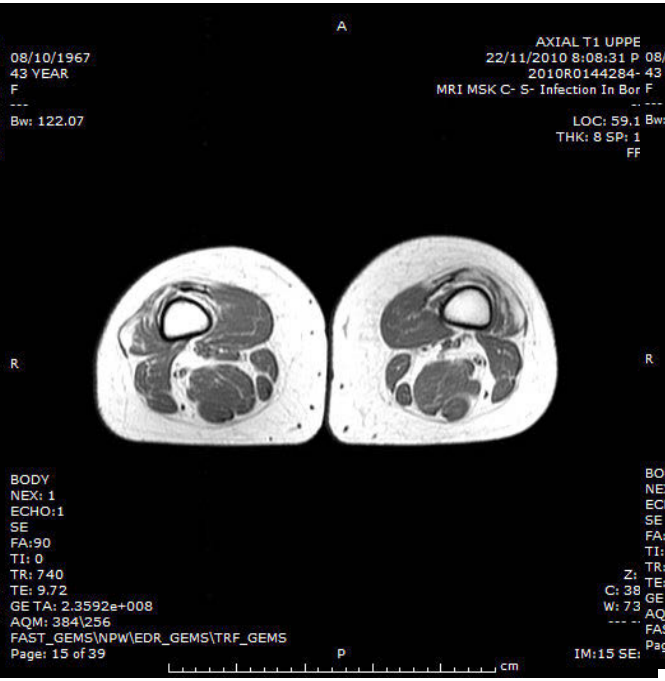
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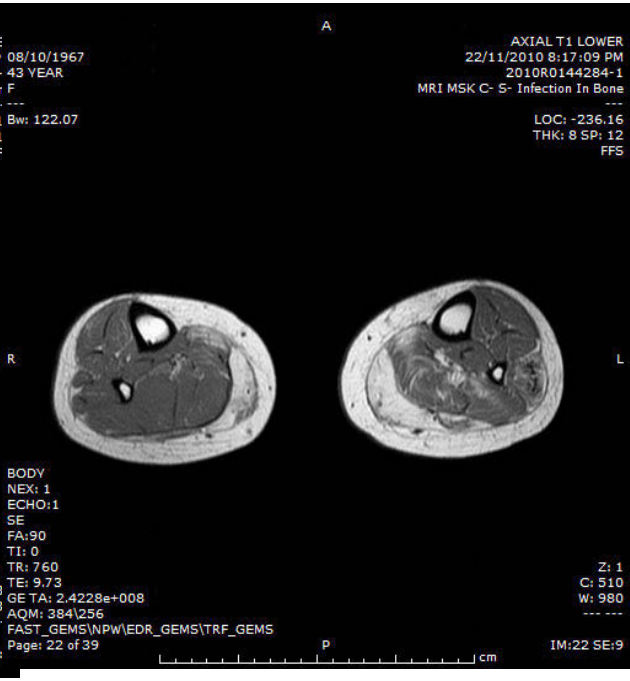
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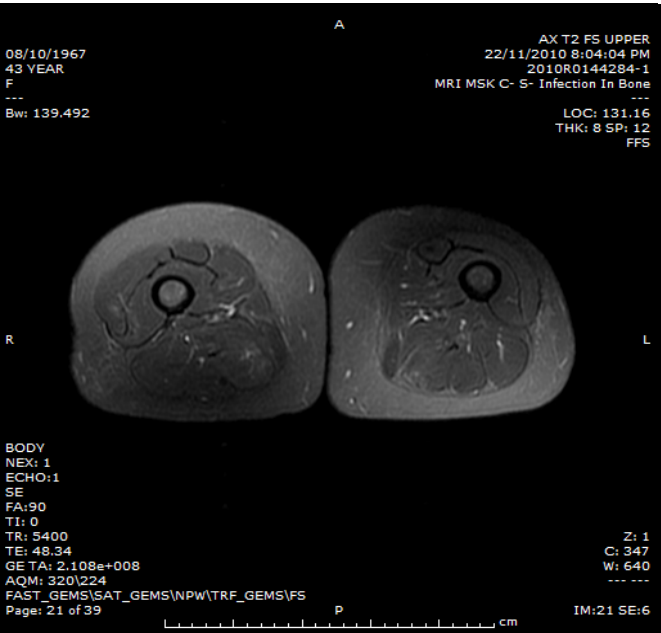
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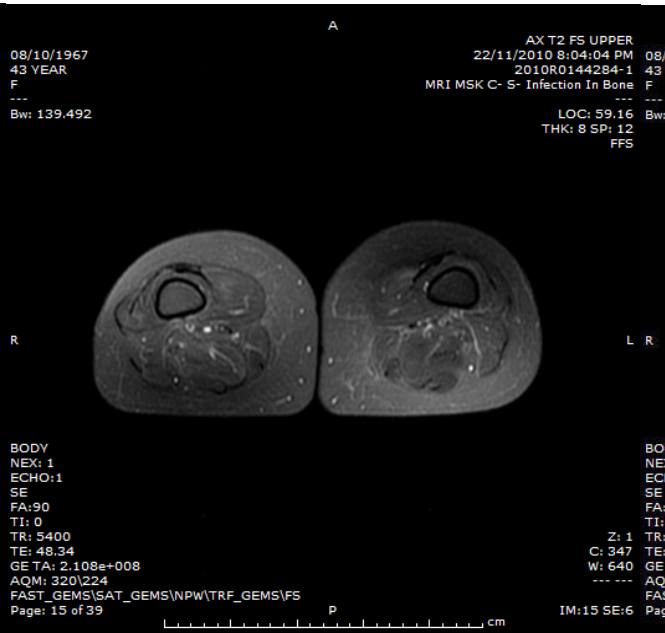
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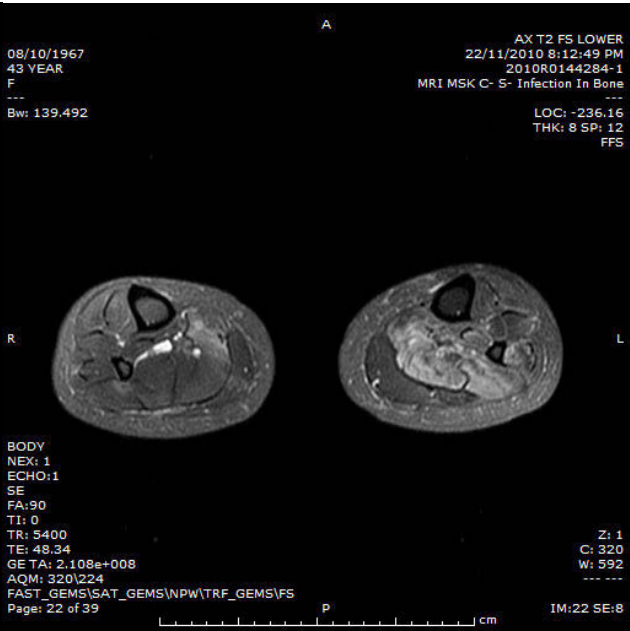
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43 YEAR
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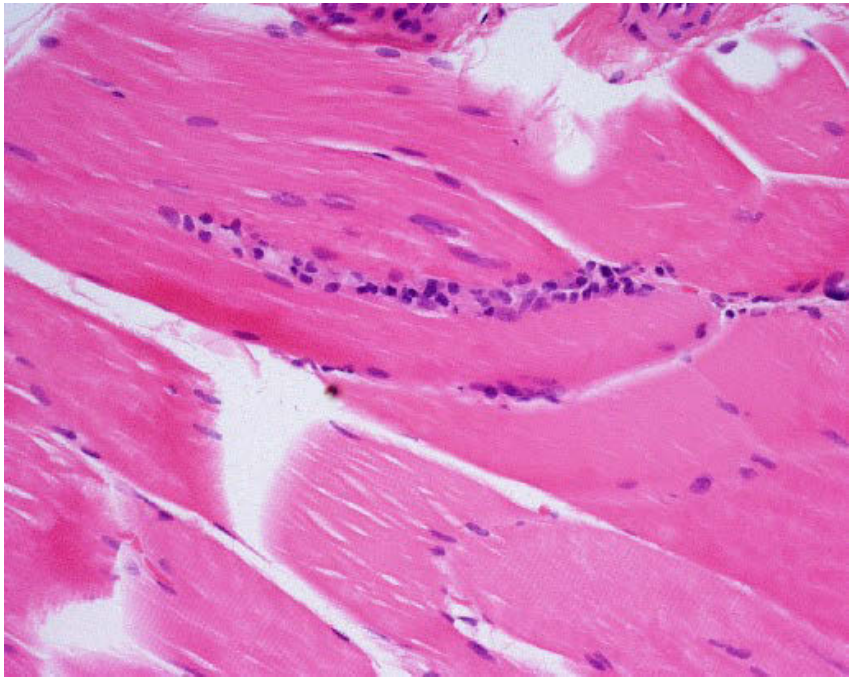
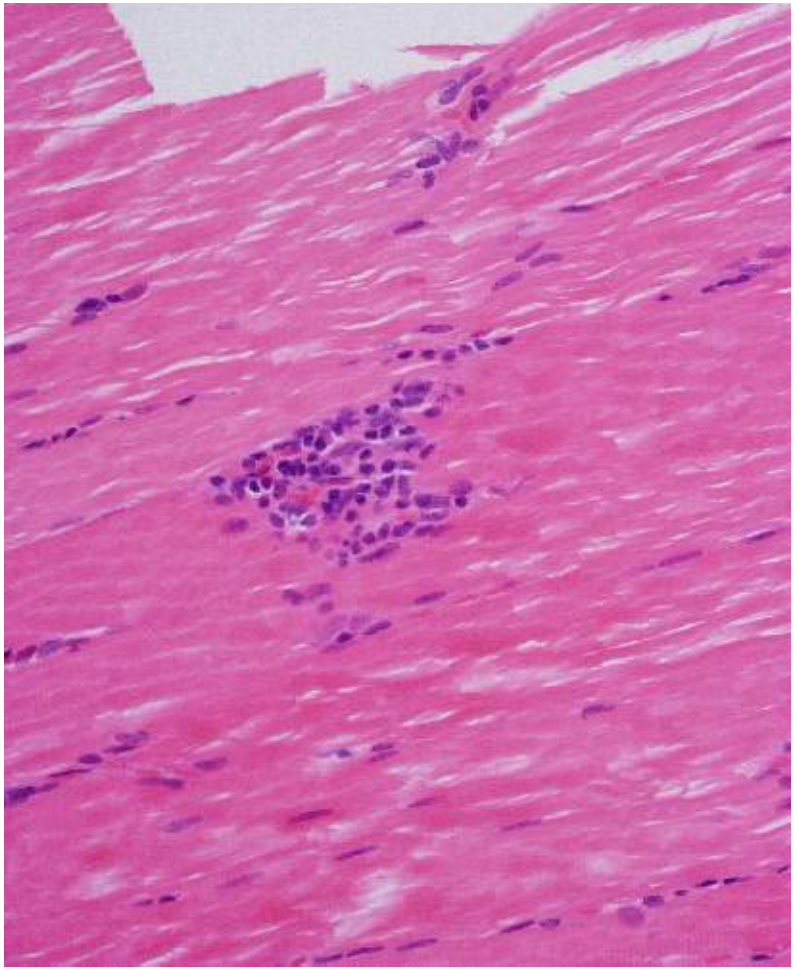
cm

Muscle Bx 2010- medial quad





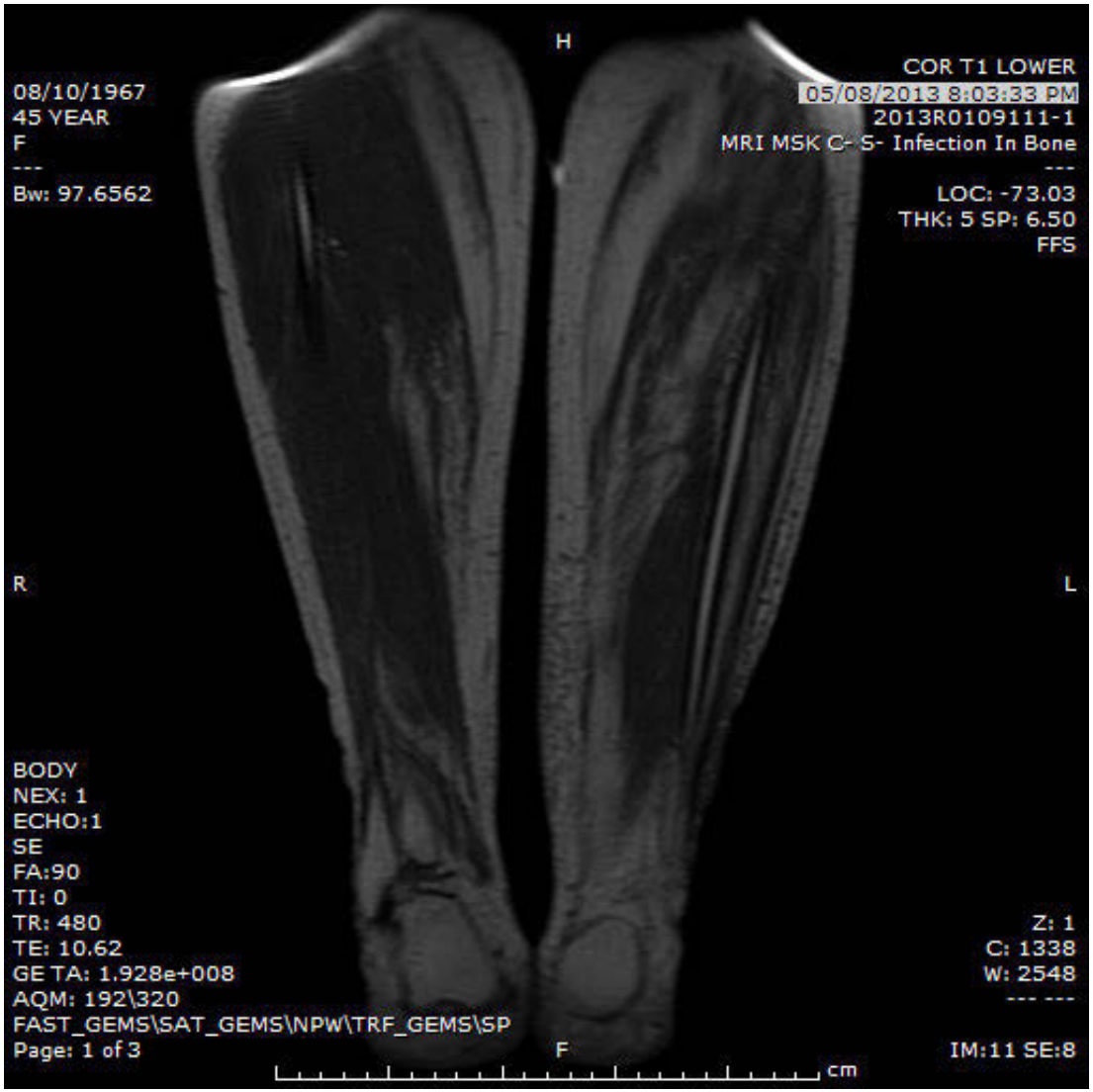
Progress- 2011-2012

- May 2011- mild limp, weak L post calf
  - CK 154 RF 2700 Bx ?polymyositis
  - Rheumatology- No CT disorder, no Rx
- Nov 2011- unchanged on no Rx
  - -CK 167 RF 1870
- Aug 2012- unchanged on no Rx
  - Mild oedema
  - CK 256 RF 2850

Progress- 2013

- Feb 2013- still limping, heaviness in legs, oedema of L calf
  - Ex: mild weakness R plantarflexion ,
    - mod-severe L plantarflexion, otherwise normal.
  - CK 287 RF 4110
  - Rheumatology review- still no features of CT disease, other Ab negative
  - MRI –increased patchy myopathic changes
  - EMG-LL patchy myositic changes

2013 MRI


H
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45 YEAR
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L
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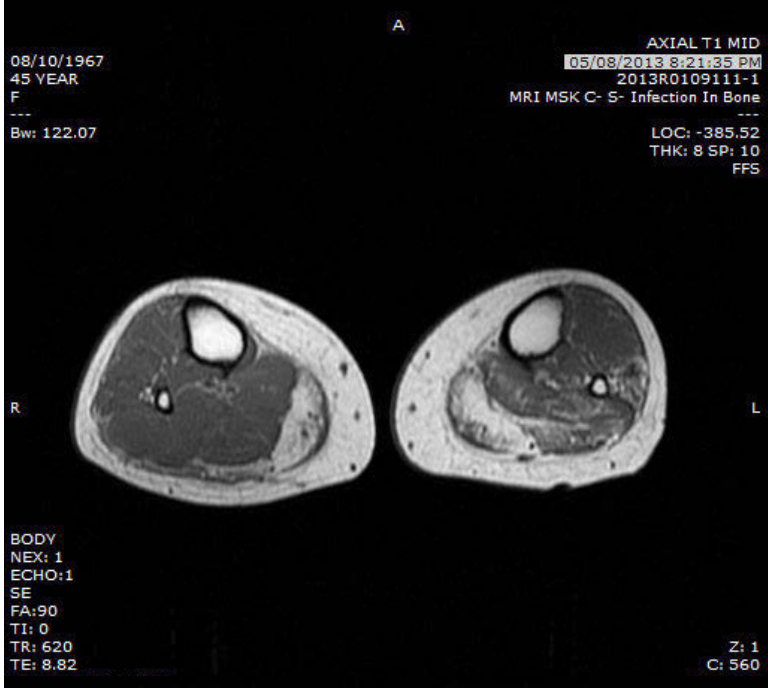
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45 YEAR
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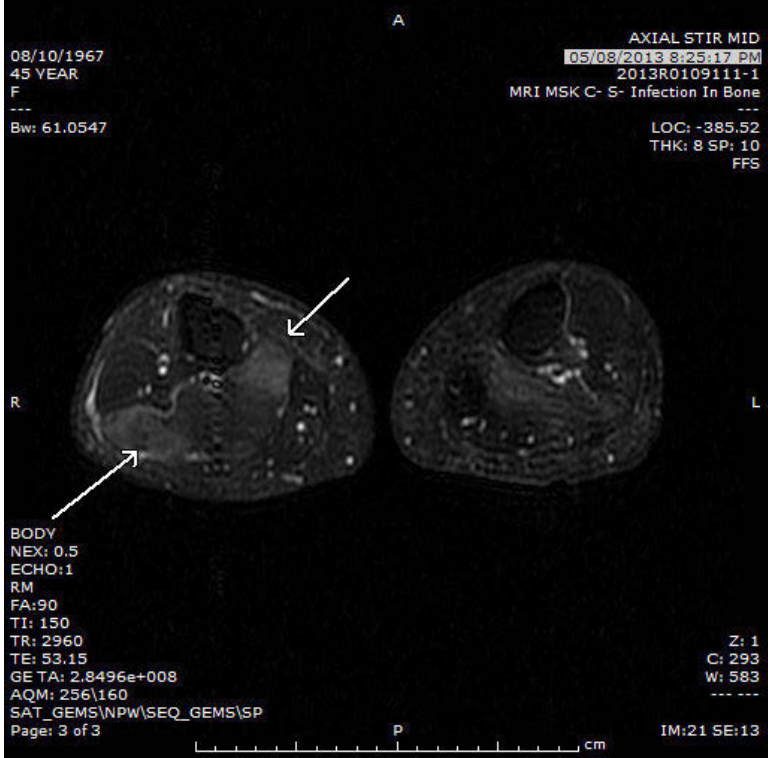
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45 YEAR
F

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MRI MSK C- S- Infection In Bone

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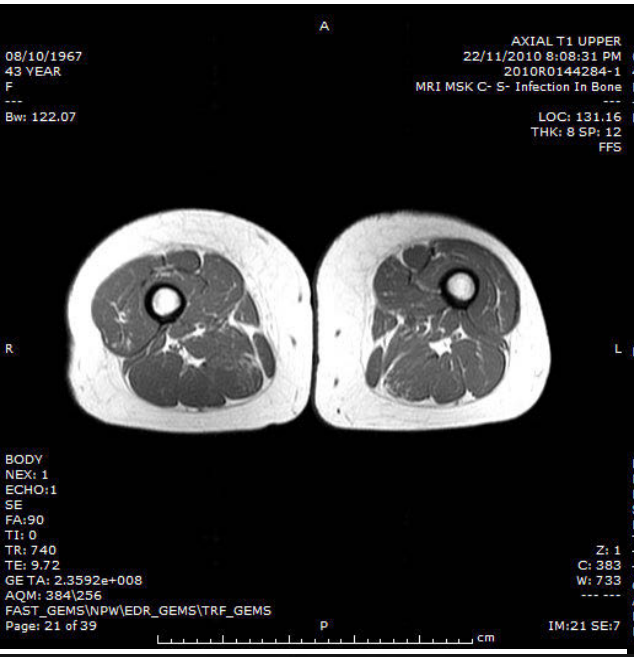
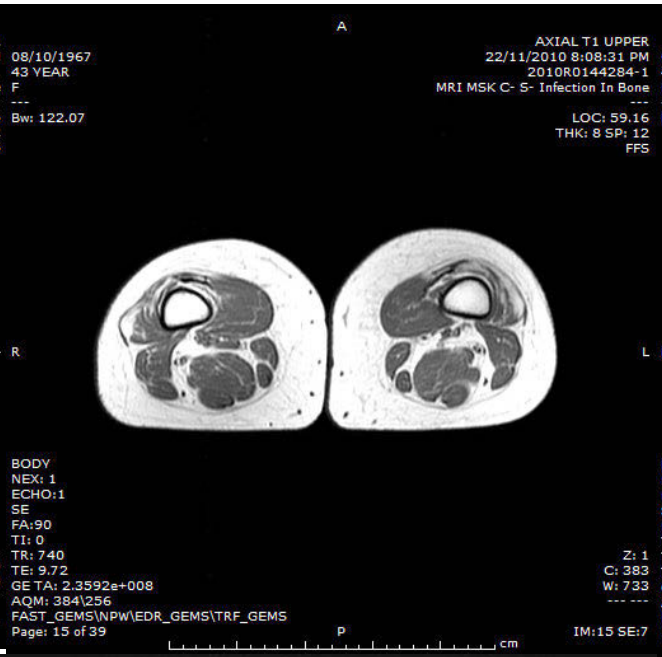
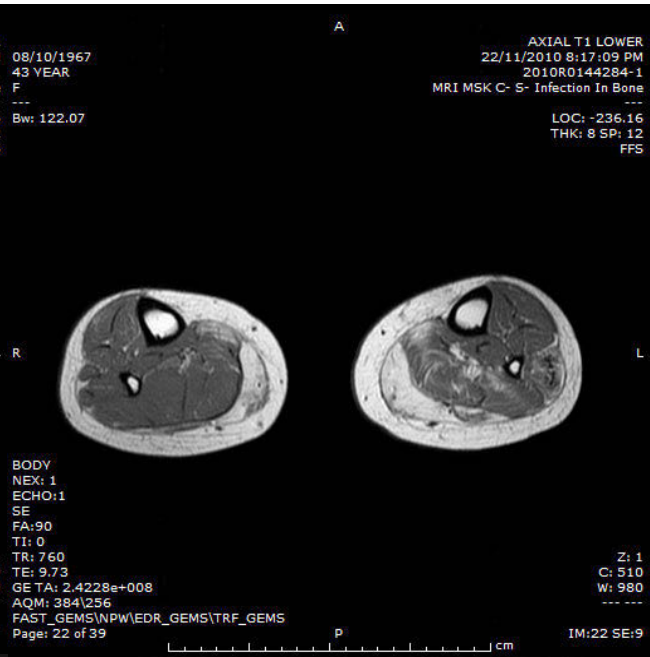
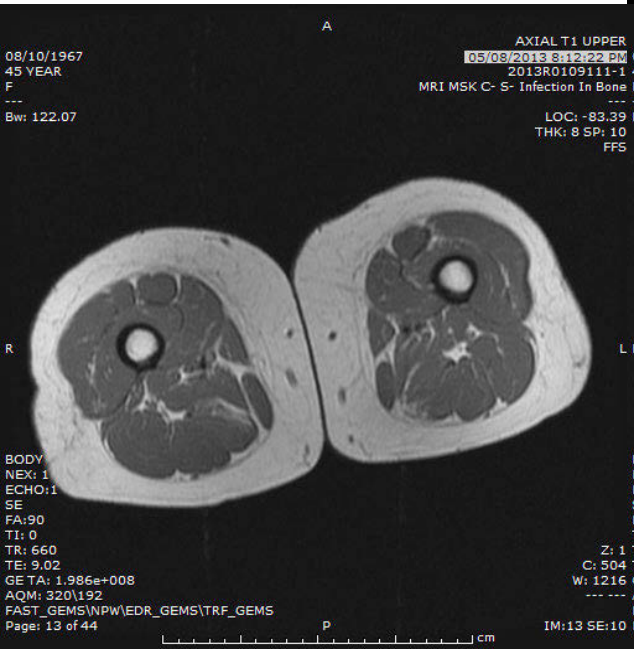
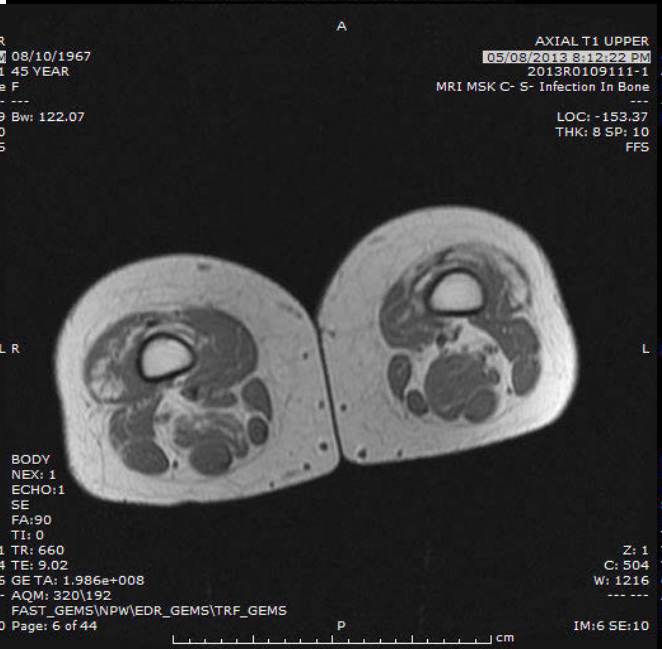
2010 c.f. 2013 MRI

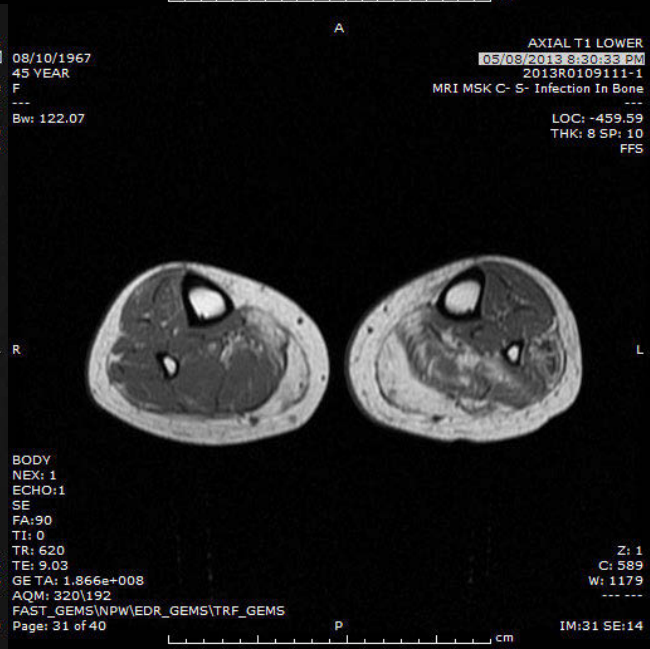










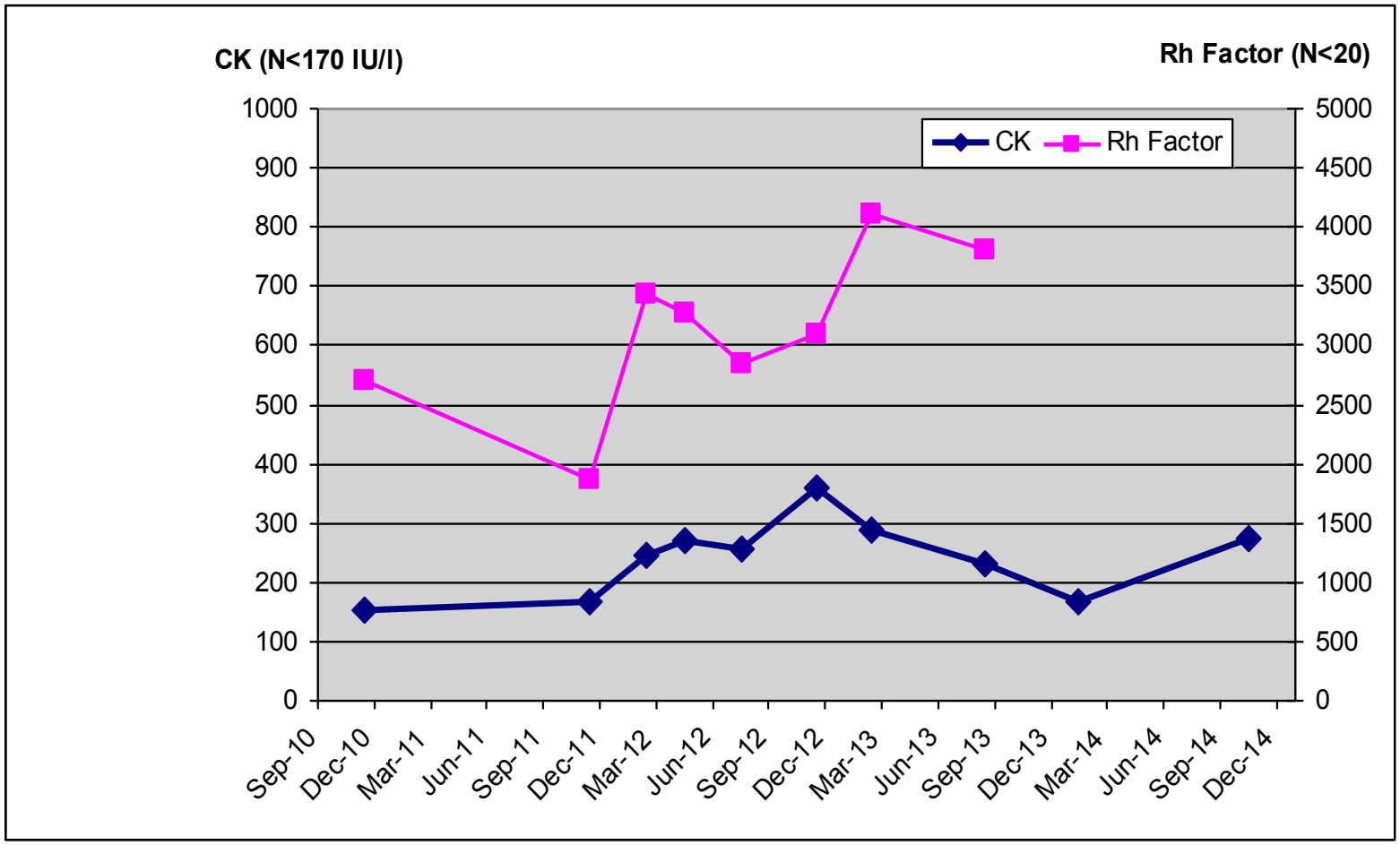


Progress- 2013

- Aug 2013- Incr leg weakness, pain and swelling
  - Ex: mild weakness R plantarflexion , mod-severe L plantarflexion, mild weakness L quads
  - Mild weakness right elbow flexion, finger extension, moderate weakness finger flexors bilaterally
  - CK 231 RF 3810 TRIM21 Ab +, others neg
  - Repeat biopsy- R calf

Progress- 2014

- March 2014- increased leg weakness
  - Problems with stairs, brisk walking
  - EX: Plantarflexion -2/-3
  - Finger flexors -2/-2, Elbow ext -1/-1.
  - CK 169
- Oct 2014- sl worse leg weakness
  - aPF -2/-3 EEx -1/-1 FF -2/-2
  - CK 274 RhF 711


CK (N<170 IU/l)
Rh Factor (N<20)
CK
Rh Factor
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900
800
700
600
500
400
300
200
100
0
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
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Mar-11
Jun-11
Sep-11
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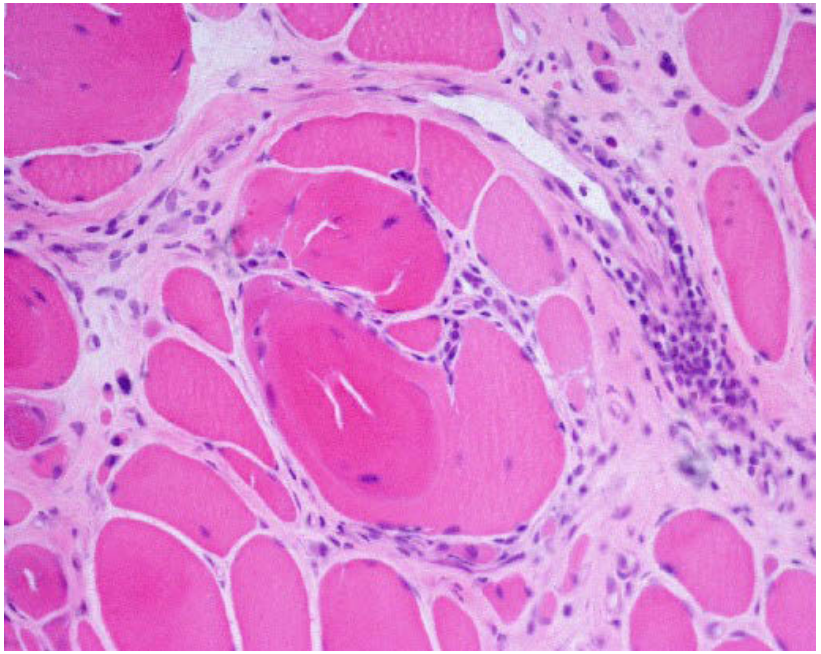
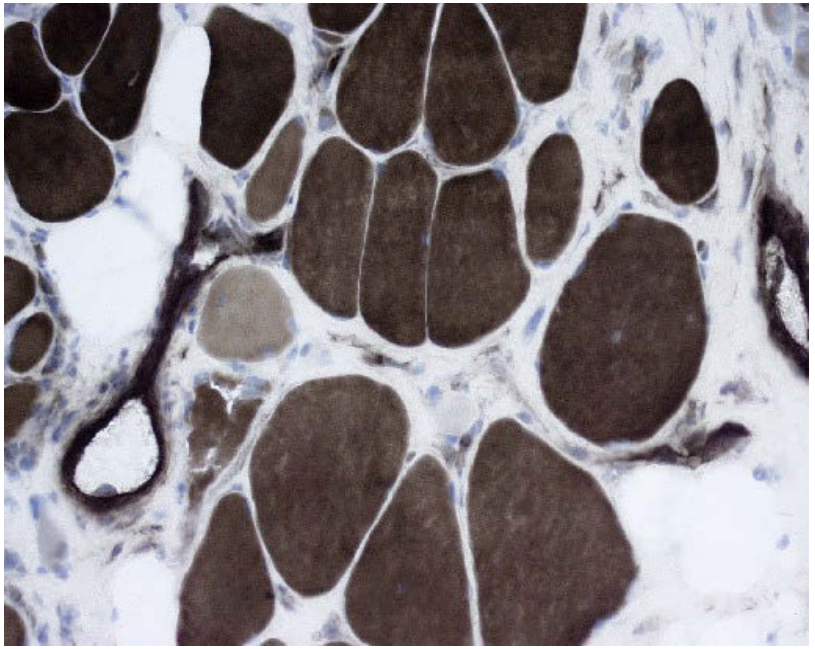
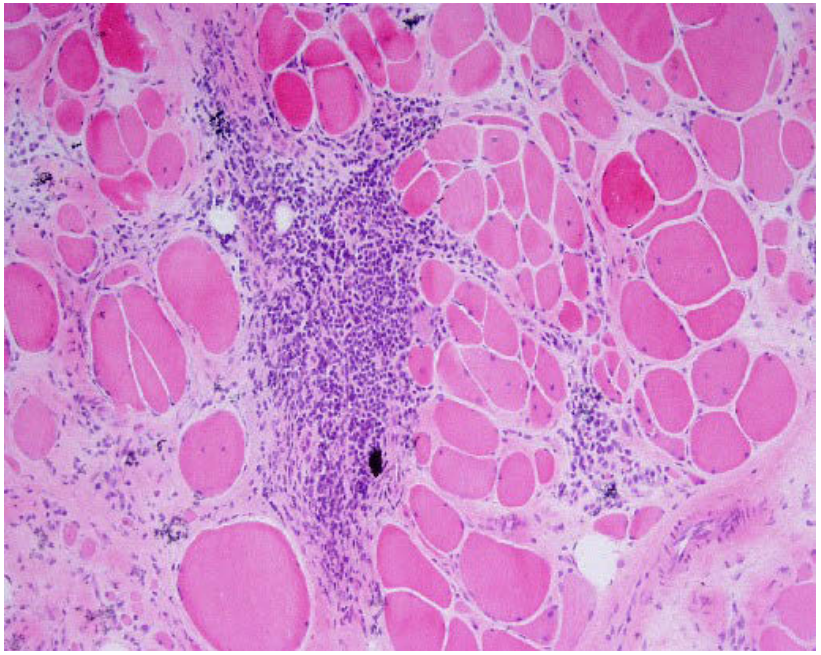
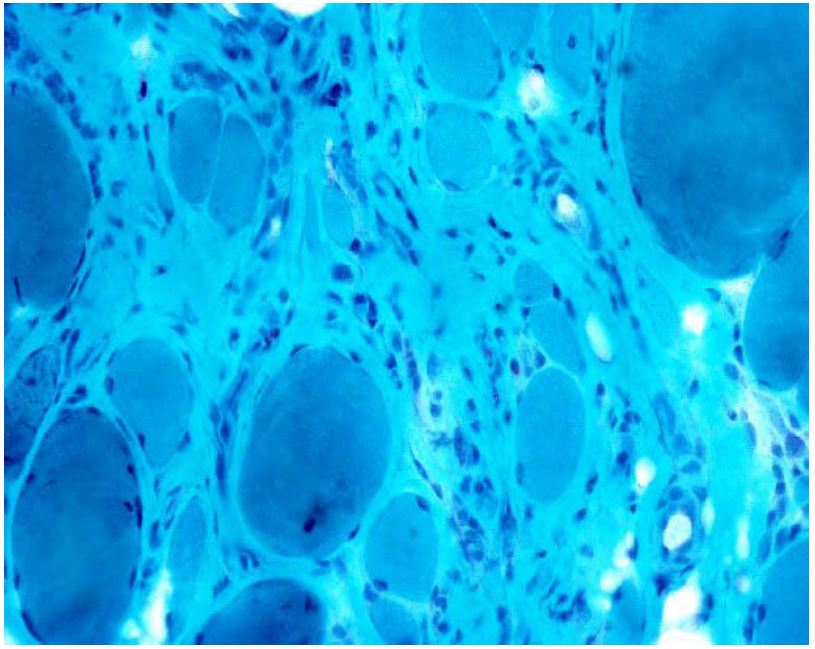
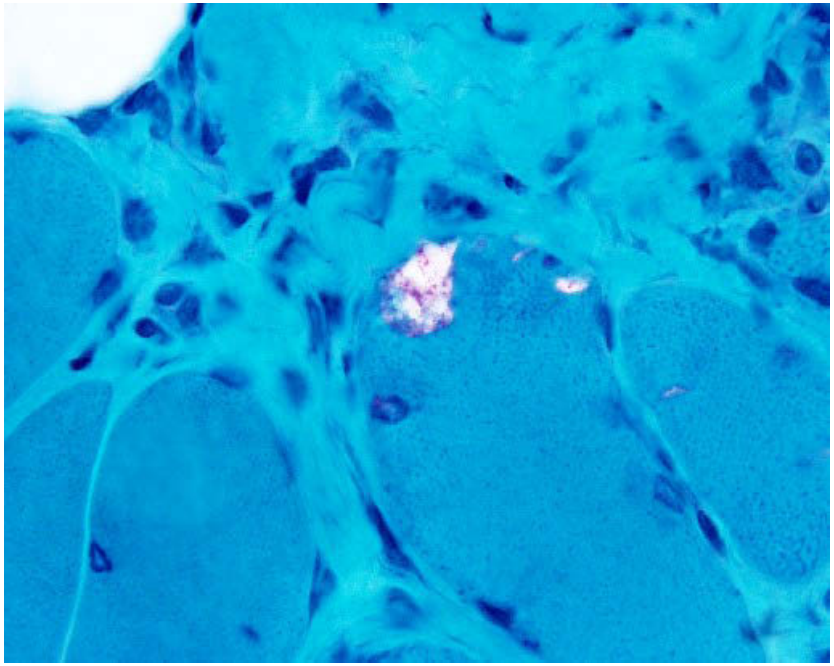
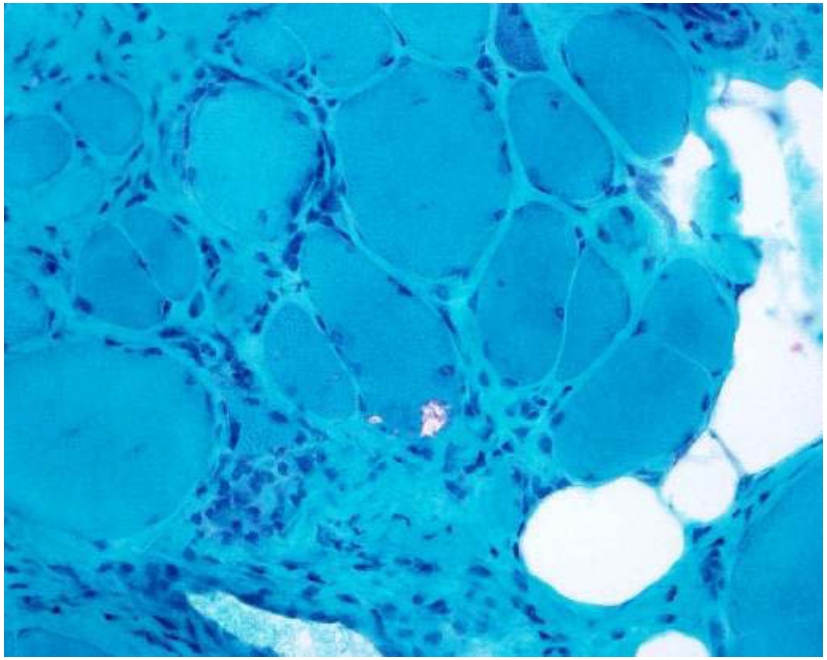
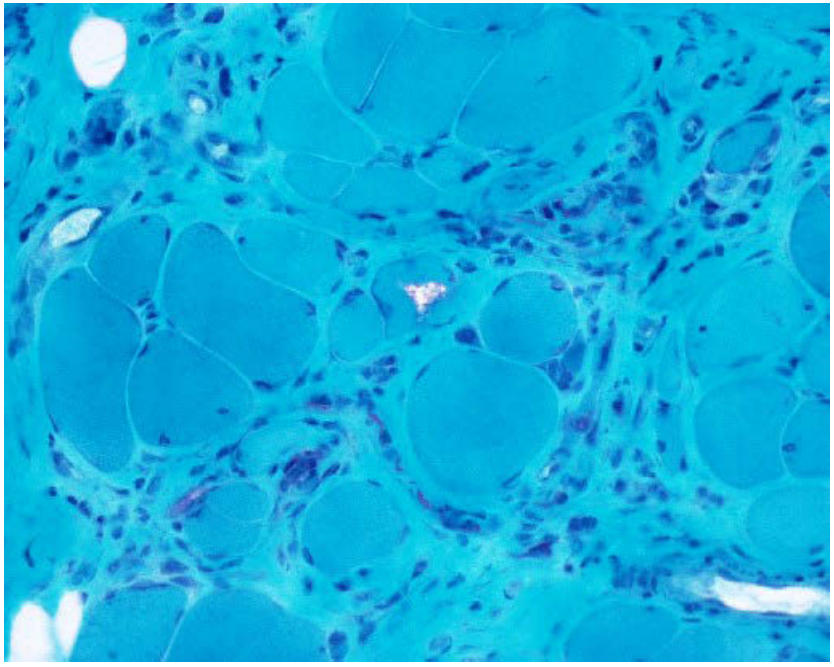
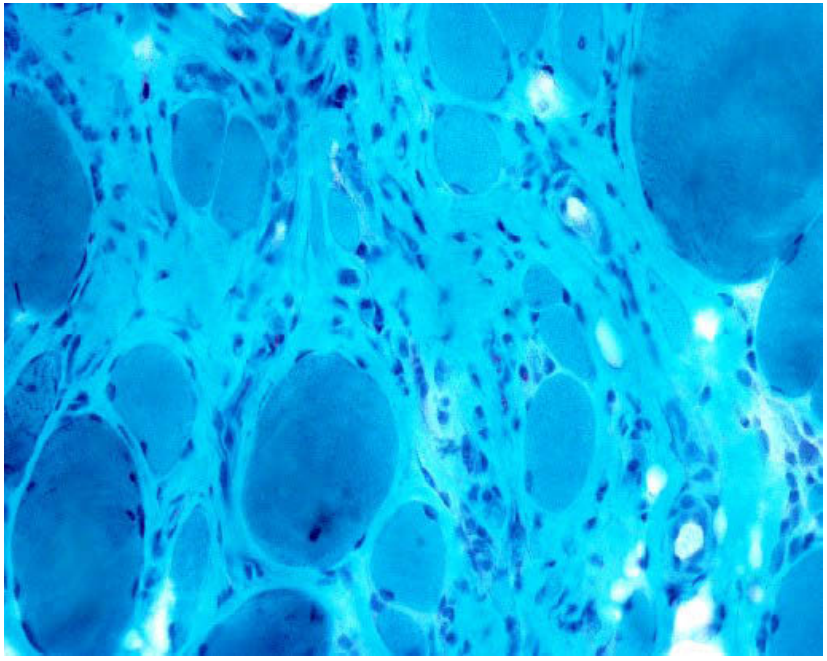




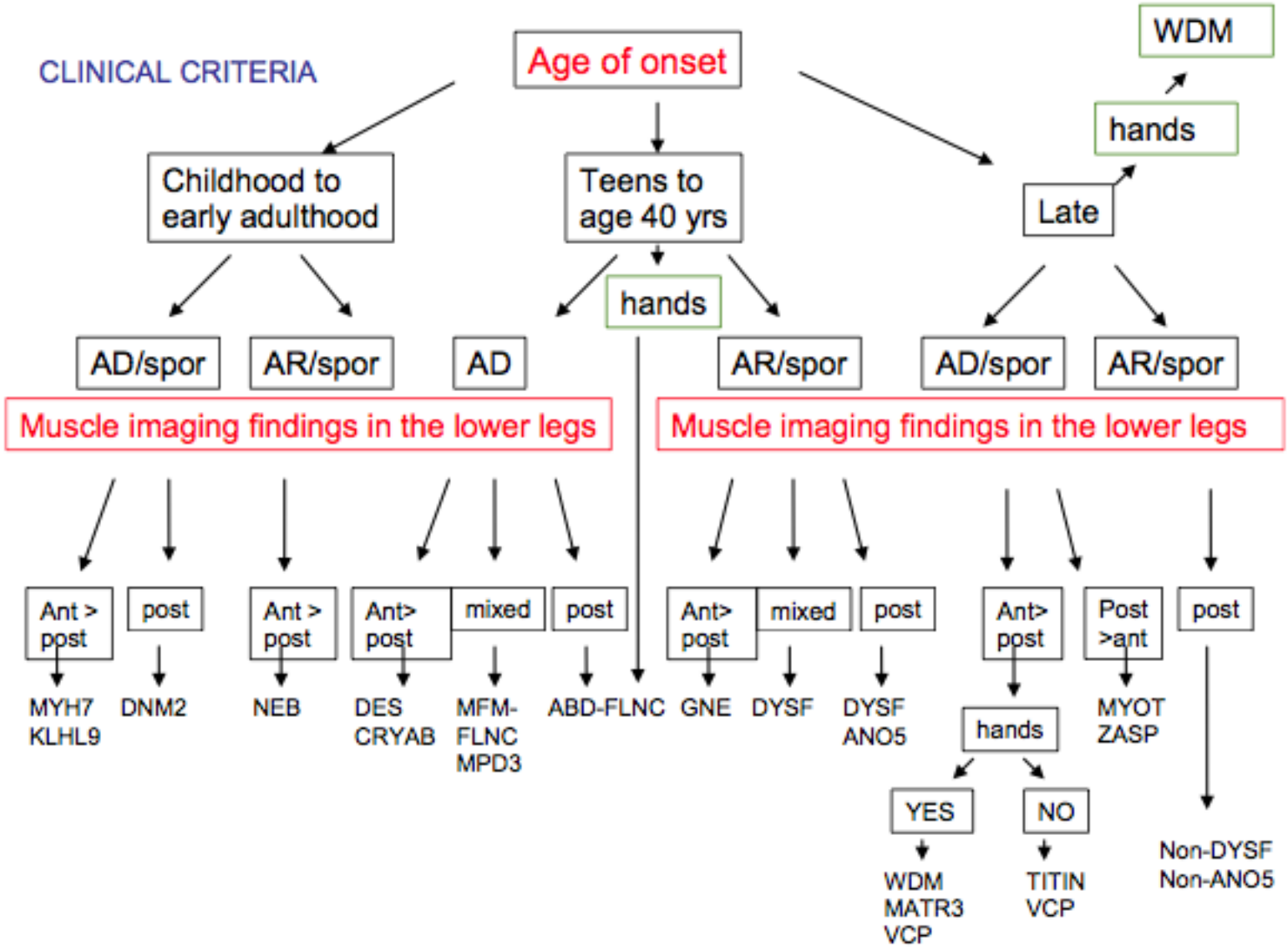




- Selective and indolent presentation
- Dystrophic muscle
- Inflammatory infiltrate and ++RhFactor
- Rimmed vacuoles

- ?Distal dystrophy
- ?atypical IBM


CLINICAL CRITERIA
Age of onset
Childhood to early adulthood
Teens to age 40 yrs
Late
WDM
hands
hands
AD/spor
AR/spor
AD
AR/spor
AD/spor
AR/spor
Muscle imaging findings in the lower legs
Muscle imaging findings in the lower legs
Ant > post
post
Ant > post
Ant> post
mixed
post
Ant> post
mixed
post
Ant> post
Post >ant
post
MYH7 KLHL9
DNM2
NEB
DES CRYAB
MFM-FLNC MPD3
ABD-FLNC
GNE
DYSF
DYSF ANO5
hands
MYOT ZASP
YES
NO
Non-DYSF Non-ANO5
WDM MATR3 VCP
TITIN VCP

Distal myopathy with posterior lower limb weakness

- Myotilinopathy – distal
- ZASP Markesberry-Griggs
- Distal ABD filaminopathy-Williams MPD4
- Miyoshi (dysferlin/anoctamin5)
- Dynamin 2

Distal myopathy with post LL weakness

- Myotilin LGMD 1A
- ZASP MFM4
- Filamin C MPD4 (Williams)
- Miyoshi

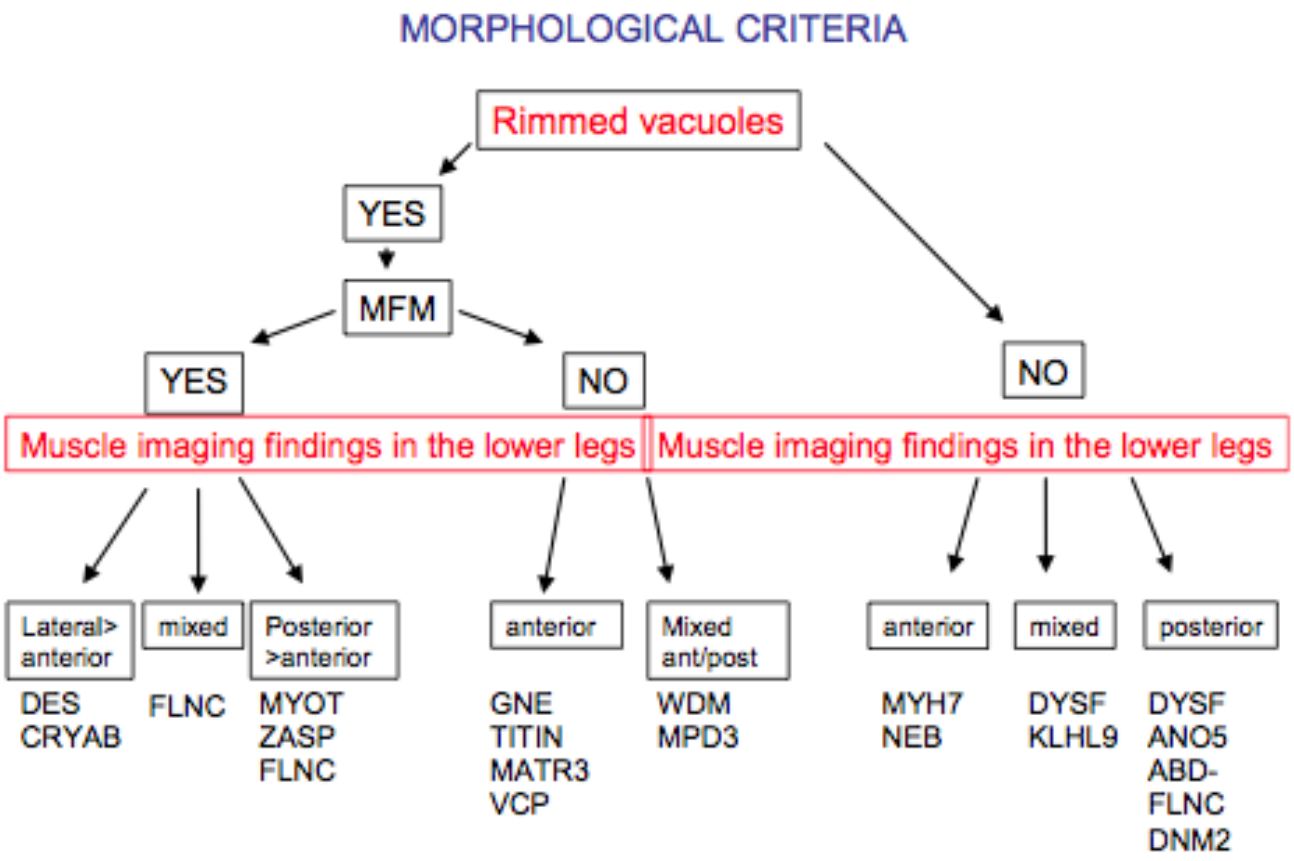
  dysferlin/anoctamin5
- Dynamin 2

. BUT

- Myofibrillar, RV+
- Myofibrillar, rare vacuoles, rarely distal
- Abs AJ but no vacuoles
- CK+++, no vacuoles
- Centronuclear, early onset

Flow chart algorithm for diagnostic purposes aiming at reducing the number of genes qualified for possible molecular genetic testing, using morphological data as the starting point.

From Udd B. Distal myopathies- New genetic entities expand diagnostic challenge Neuromuscular Disorders 22 (2012) 5-12.



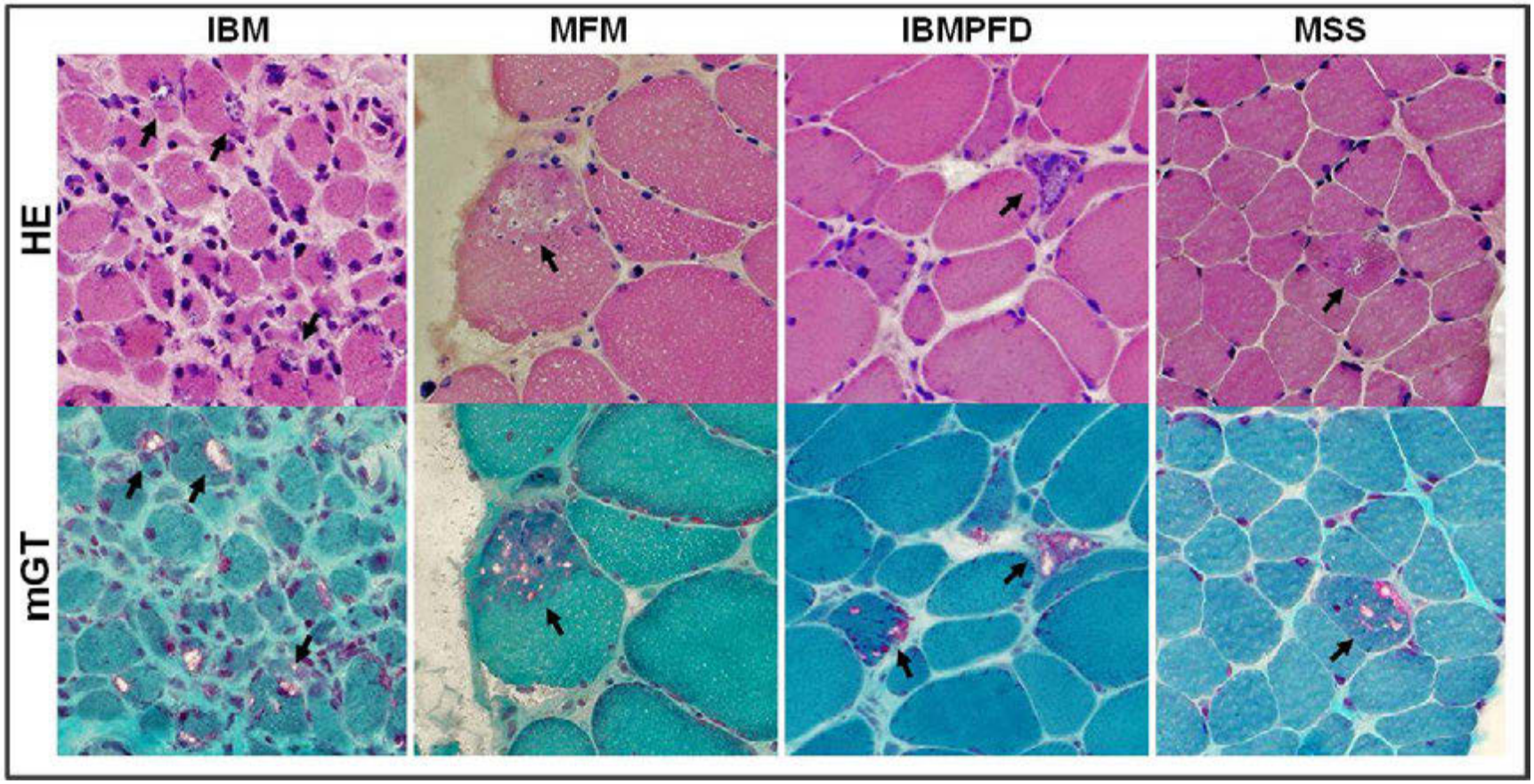
Distal myopathy with Rimmed Vacuoles

- GNE-Nonaka
- Titin- Udd, hIBM+resp failure
- VCP- hIBM+Pagets
- Welander
- MYH7-Laing myopathy
- Matrin3-MPD2
  - + vocal cord, pharyngeal
- MPD3
- LGMD 2G
- OPMD

- Anterior calf
- Anterior calf

- Anterior calf
- Anterior calf, hands
- Anterior calf
- Bulbar involvement

- Anterior & posterior calf
- Limb girdle
- Oculobulbar



- **FIGURE 4.Pathologic findings in myopathies with rimmed vacuoles.**

  Clinically and etiologically different disorders are showing same pathologic features (RVs; arrows) in skeletal muscles. HE-hematoxylin and eosin; mGT-modified Gomori trichrome; IBM-inclusion body myositis; MFM-myofibrillar myopathy; IBMPFD-inclusion body myopathy with Paget's disease of bone and frontotemporal dementia; MSS-Marinesco-Sjögren syndrome.

Best fit???

- MPD3 in non-Finnish family
- Atypical MPD4 with vacuoles
- Atypical Welander- LL onset
- MPD2 before vocal cord onset

- Next-Generation Sequencing
  - No recognised pathological mutations

MPD3 vs MPD4

- Autosomal Dominant
- Epidemiology: Single Finnish family
- Onset ~ 32 to 45 years with clumsiness of hands or legs
- Weakness ?asymmetric
  - Distal LL :Anterior & Posterior
    - TA, EDL, Gastroc, Glut medius; TFL
  - Hands -APB, OP, FDI, ADM
  - Progressive over years to more proximal limbs:
    - Forearm, Triceps, Infraspinatus, Proximal legs
- Lab- EMG: Myopathic
- CK: Normal or Slightly elevated
- Muscle biopsy
  - Myopathy: Severe; Endomysial fibrosis; Fiber size variation
  - Rimmed vacuoles
  - Cytoplasmic inclusion bodies

- Autosomal Dominant
- Epidemiology: Australian & Italian families
- Onset up to 30 years
- Weakness symmetrical
  - Distal arm & leg weakness
    - Forearm pronators, Finger flexors, Intrinsic hand muscles
    - Ankle evertors, Plantar-flexors (Calf atrophy)
    - Sparing: Anterior leg; Posterior arm
  - Slowly progressive
- Also-
  - Cramps and myalgia, worse after exercise
  - Tendon reflexes: Absent ankle jerks
  - Also: Cardiomyopathy: 2 patients
    - No respiratory involvement
- Lab- EMG: Myopathic
- CK-normal or mildly elevated
- MRI ?asymmetric involvement of posterior & lateral leg muscles
- Muscle
  - Varied fiber size: Small angular fibers
  - Internal architecture: Irregular in some biopsies
  - No myofibrillar aggregates, vacuoles or inflammation

h IBM- ?Nonaka myopathy

- CF: Distal weakness- sparing quads.
- 4 GNE assoc'd myopathies
  - Quadriceps sparing myopathy- Argov
  - Distal myopathy with rimmed vacuoles- Nonaka
  - Proximal weakness with quadriceps sparing
  - Quadriceps-sparing myopathy +inflammation
  - Variants of same disease!

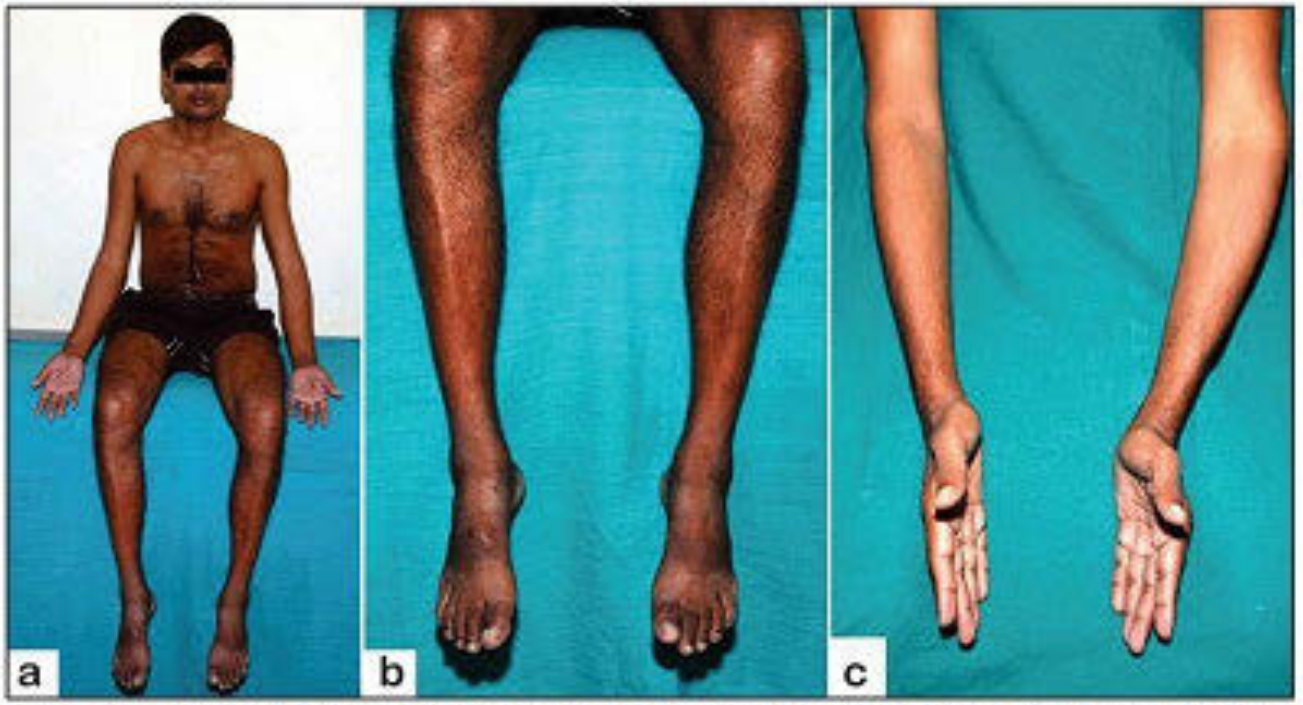
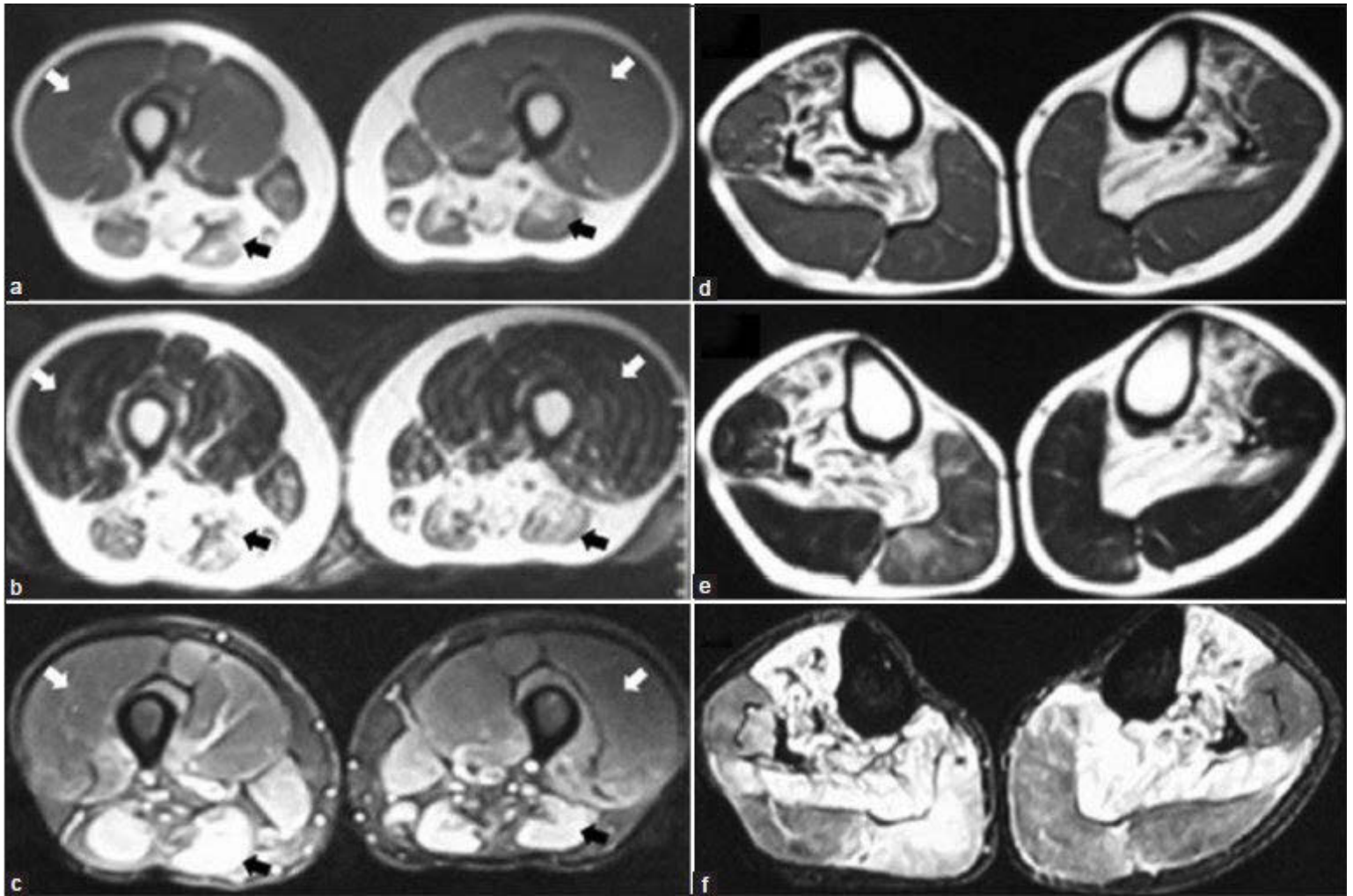
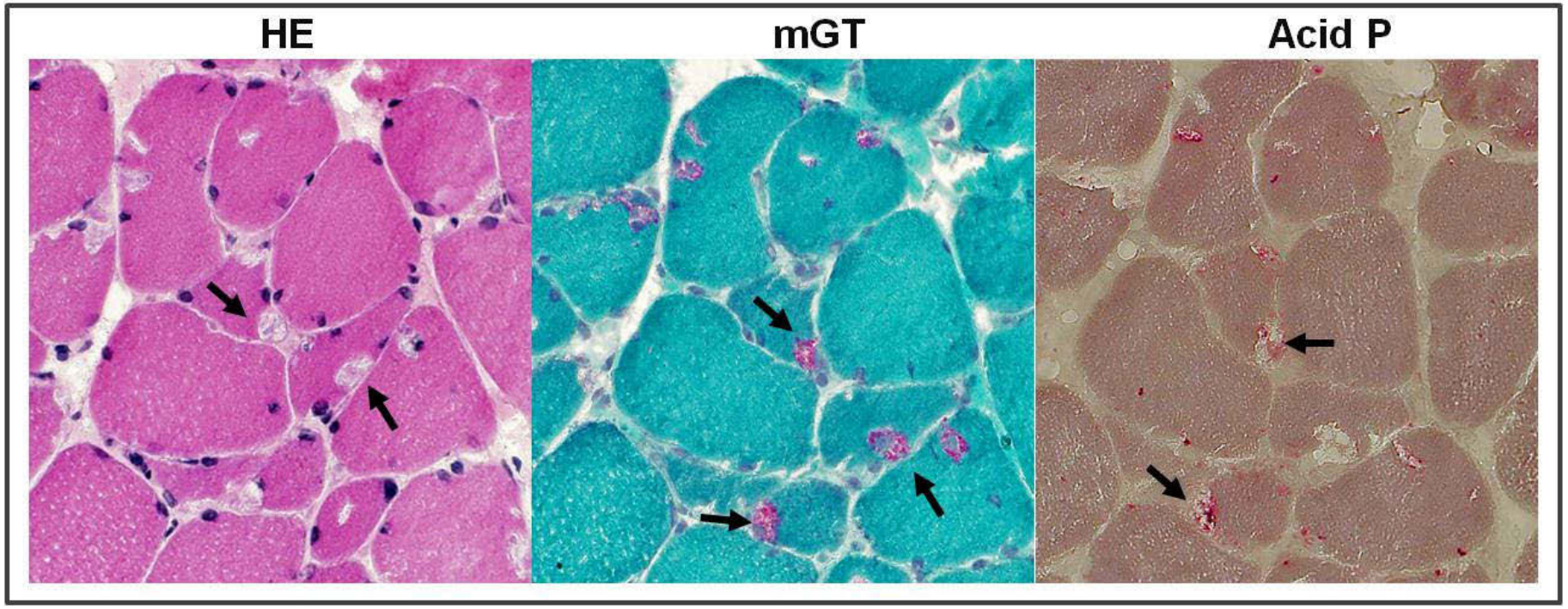


Figure 1: Patient with (a) severe wasting of the anterior leg muscles and mild wasting of the adductors but relatively spared gastrocnemius and quadriceps, (b) severe wasting of tibialis anterior with foot drop and (c) minimal wasting of forearm muscles with preserved small muscles of hands. Had mild disability

Figure 2: T1, T2, STIR (a, b, c respectively) weighted axial images of both thighs showing hyperintensities in hamstring muscles with atrophy (black arrows) sparing quadriceps (white arrowheads). T1, T2, STIR (d, e, f respectively) weighted axial images of both legs showing hyperintensities in tibialis anterior and posterior and gastro-soleous muscles on T2 and STIR

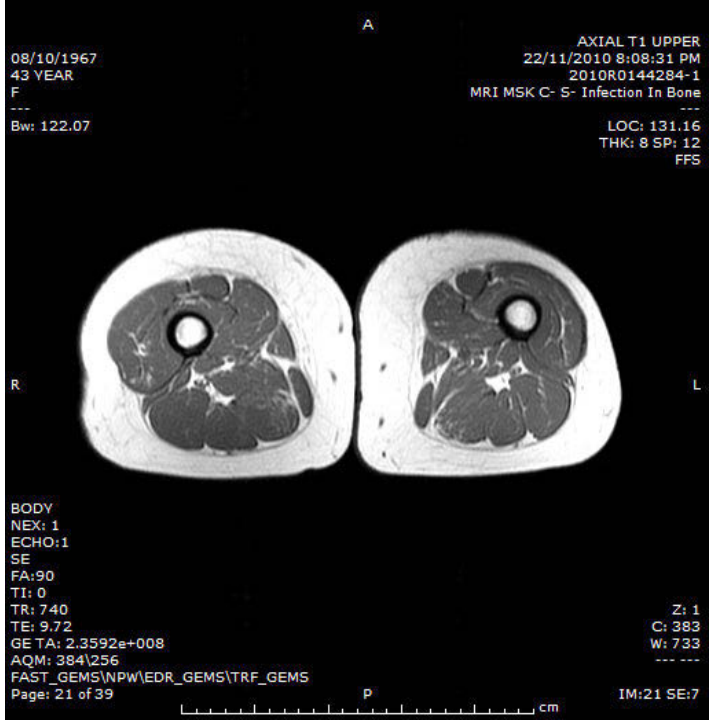




- Muscle pathology (Figure 5) is characterized by the presence of RVs predominantly in atrophic fibers, which are occasionally aggregated and form small groups. These RVs are actually clusters of autophagic vacuoles and multi-lamellar bodies. They often contain congophilic amyloid material and deposits that are immunoreactive to β–amyloid and its precursor protein, ubiquitin, and tau protein. Ultrastructurally, the filamentous inclusions measuring 15-20 nm in diameter are seen in both cytoplasm and nucleus with the presence of autophagic vacuoles. Necrotic and regenerating fibers can be rarely seen in GNE myopathy

- Bx: Filamentous inclusions and autophagic (rimmed) vacuoles
  - No inflammation
- DNA- GNE gene affects sialic acid pathways… sialyation deficiency
  - Mainly mis-sense mutations (>50 recognised)
  - Worldwide distribution, esp Persian Jews, Japanese

- Why sparing of quads?
- Why autophagic vacuoles/inclusions develop
- Can Mannose NAc supplementation help?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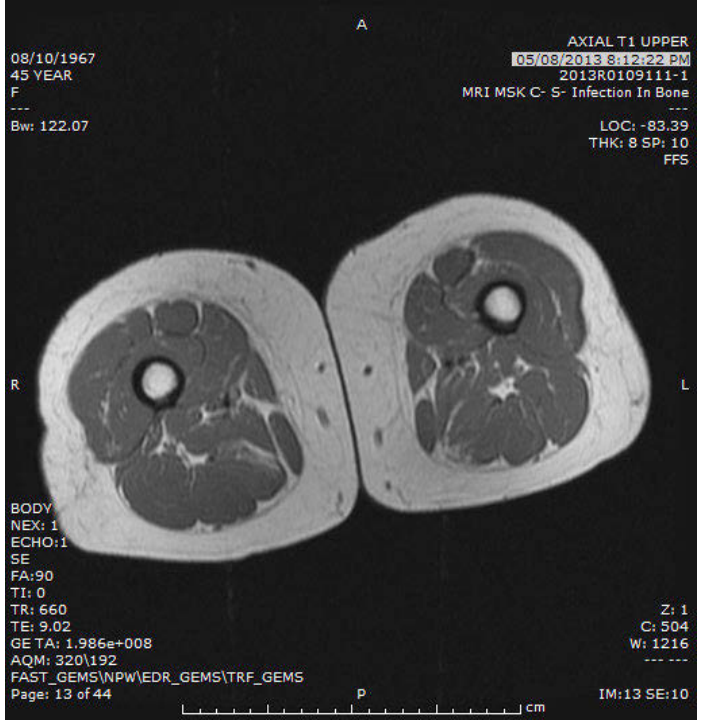
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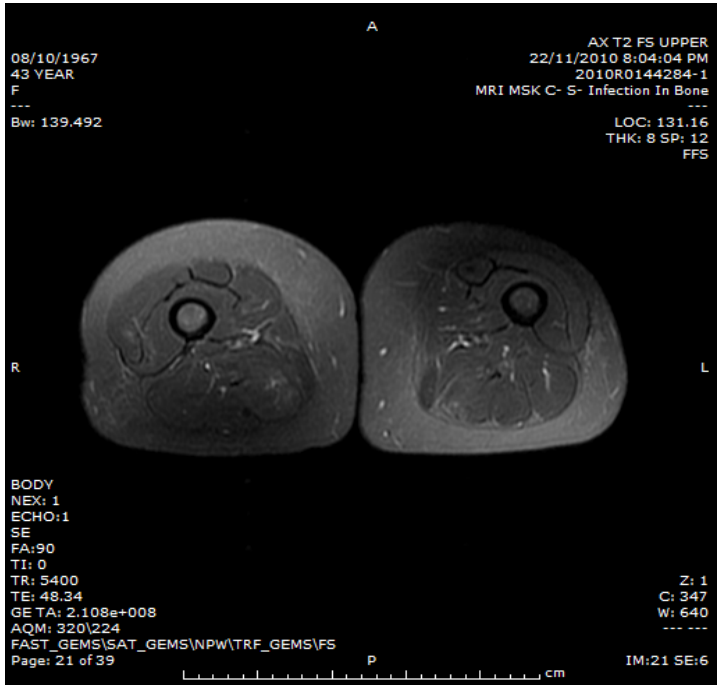
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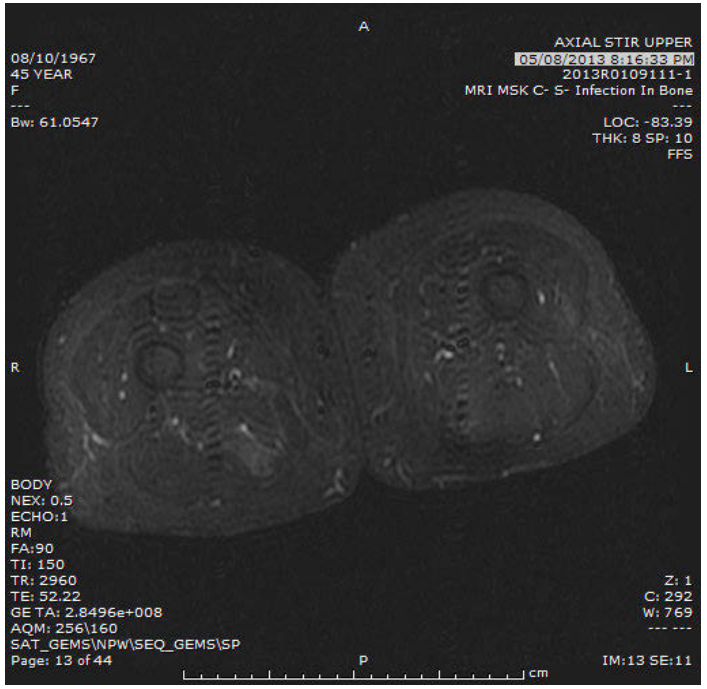
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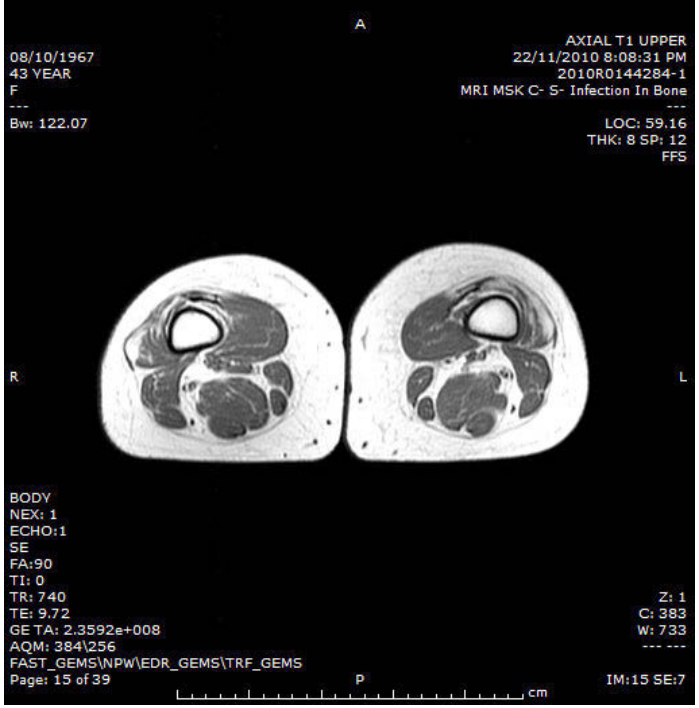
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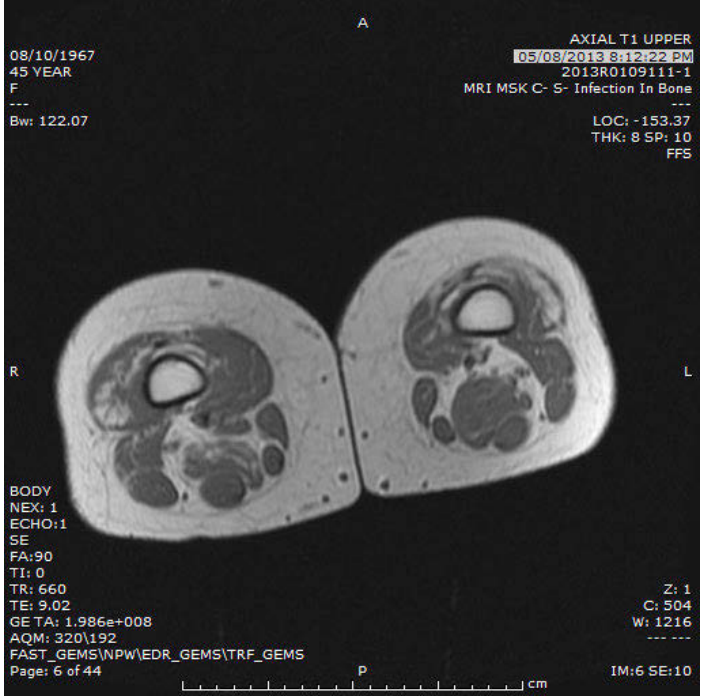
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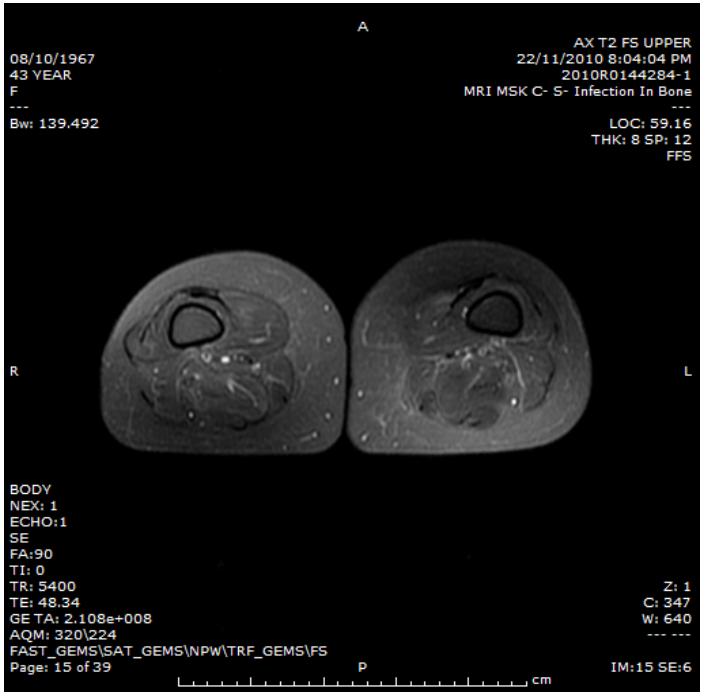
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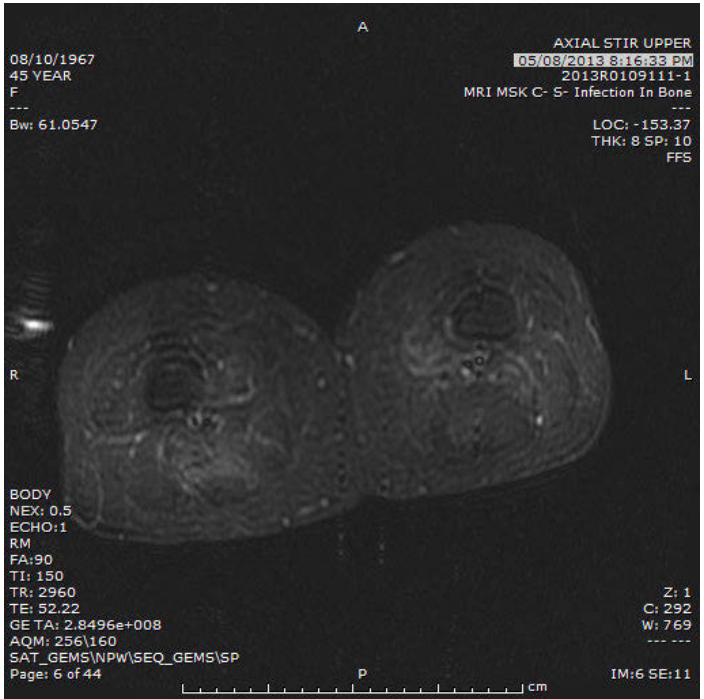
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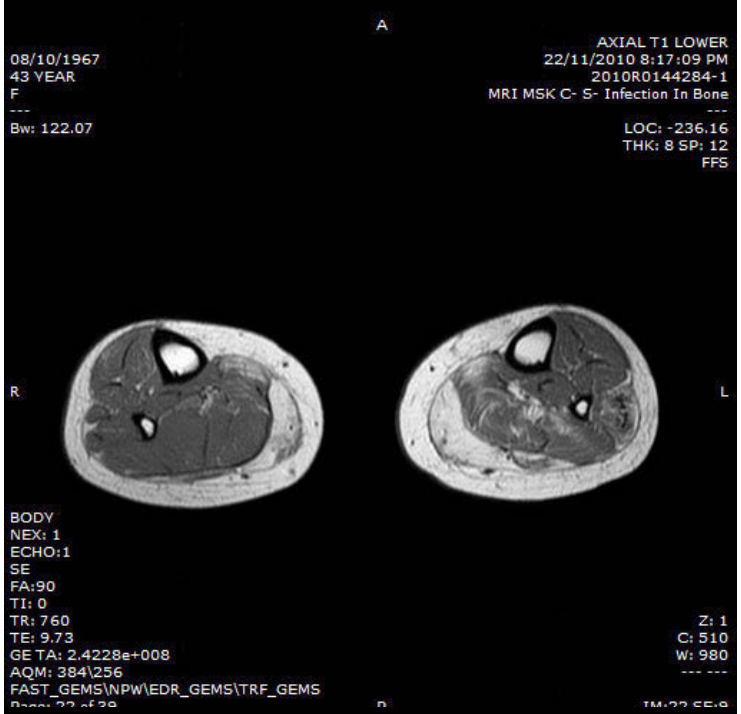
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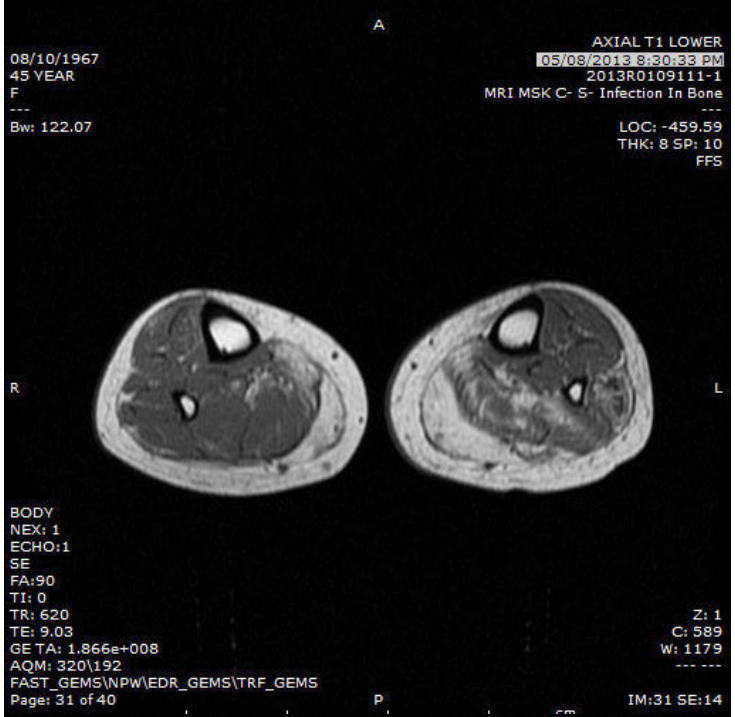
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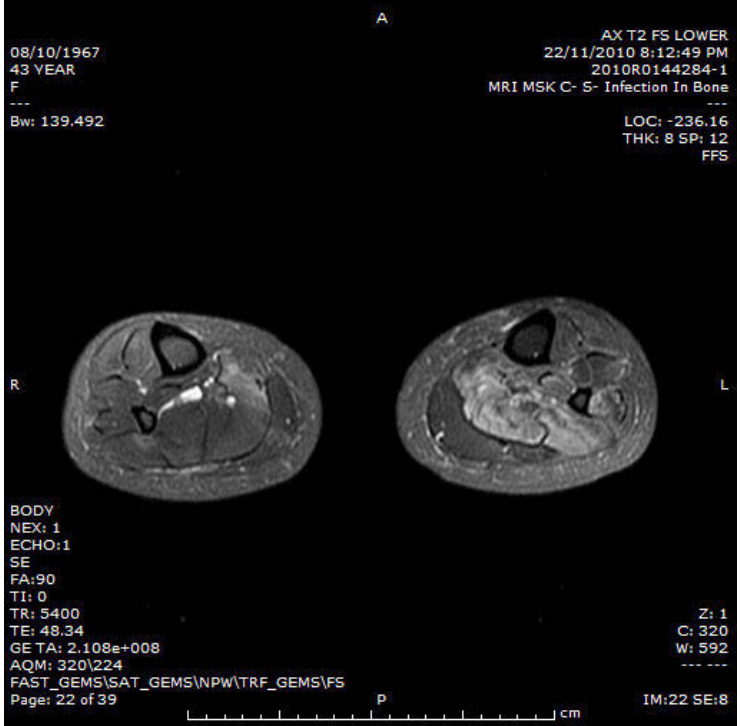
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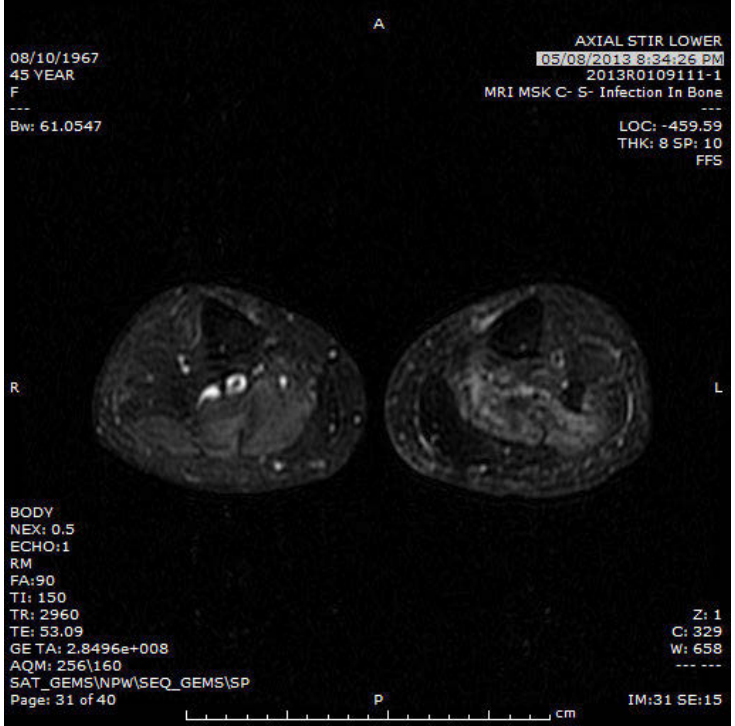
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