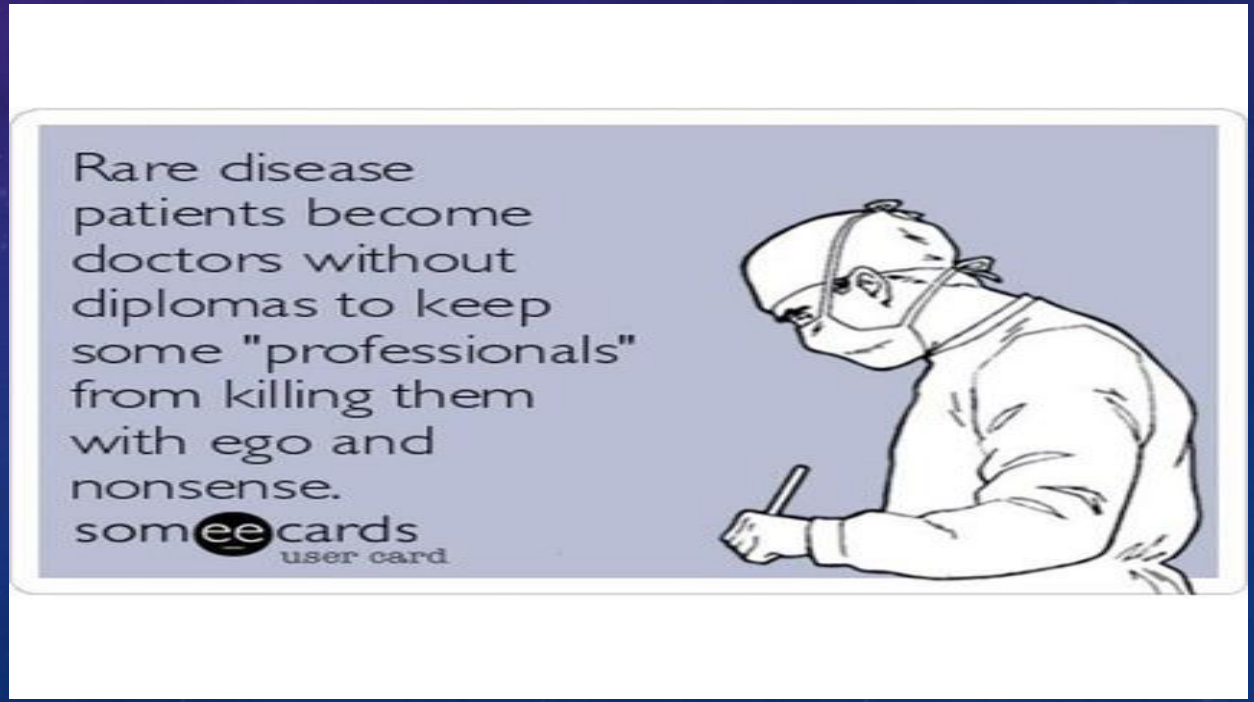
BASICS ON INFLAMMATORY MUSCLE DISEASE FOR THE MEDICAL STUDENT

DR EUGENE KALMAN GENGA



Medical Student

What my friends think I do.

What my mom thinks I do.

What society thinks I do.

What my lecturers think I do.

What I think I do.

What I actually do.

INFLAMMATORY MYOPATHIES

- Rare heterogeneous group of acquired diseases characterized by inflammatory infiltrate of skeletal muscle.
- Incidence of about 2-10 per 1 million people per year in the United States.
- Potentially treatable.

IDIOPATHIC INFLAMMATORY MYOPATHIES

- Polymyositis
- Dermatomyositis
- Juvenile dermatomyositis
- Inclusion body myositis
- Myositis associated with collagen vascular disease
- Myositis associated with malignancy

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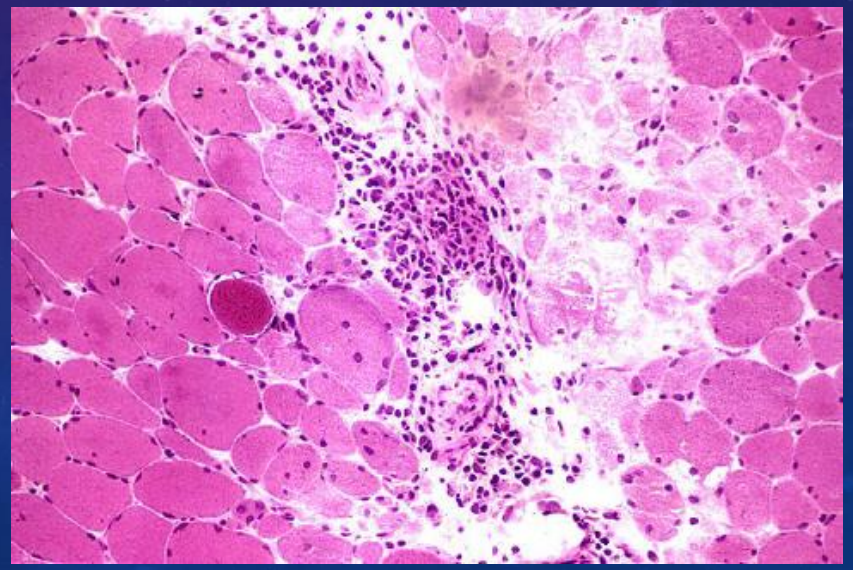
POLYMYOSITIS/DERMATOMYOSITIS

- Occur sporadically or in association with other systemic autoimmune disease
- More common in women than men.
- DM common than PM.
- DM can clinically manifest with heliotrope rash, Grotton’s papules, shawl rash, erythematous nailfolds, dermatomyositis sine myositis.

DERMATOMYOSITIS

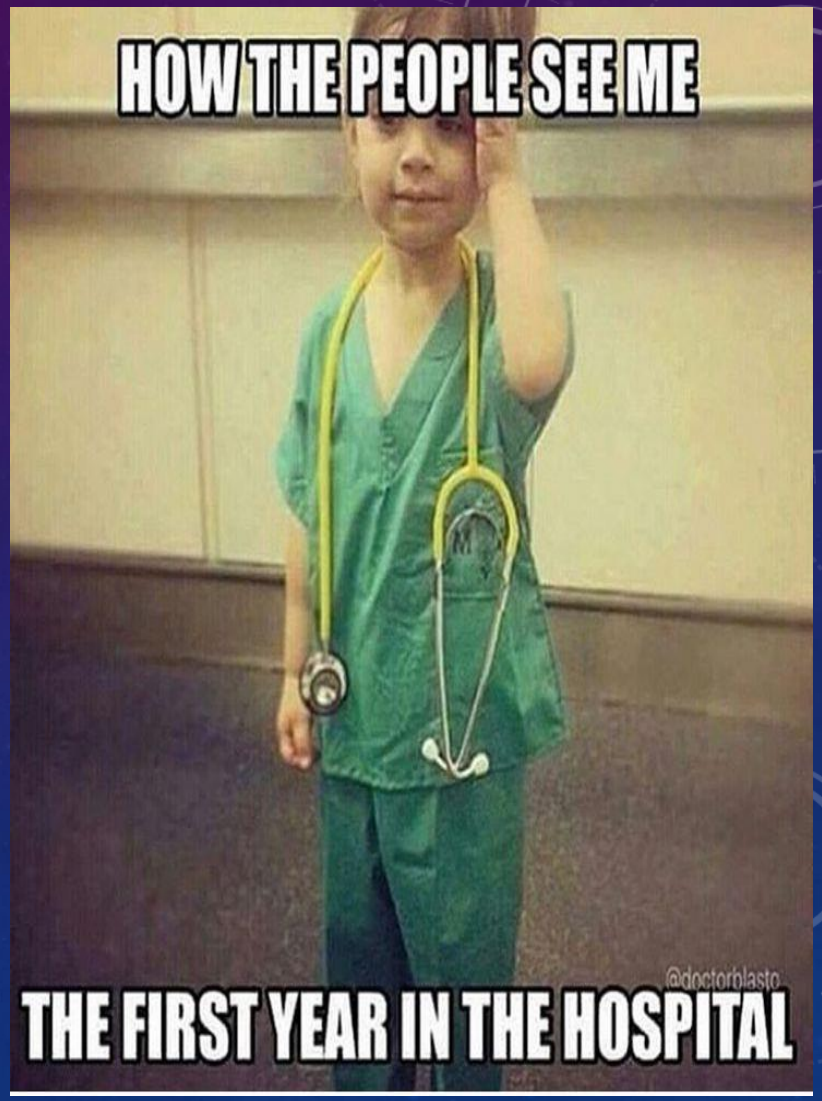
- Inflammatory myopathy
  - Prevalence: 1:100,000 in general population
  - Female to male prevalence of 2:1
  - peak incidence ages 40-50
  - Immune complex deposition in the vessels considered to be part of a complement-mediated vasculopathy

Hematoxylin and eosin stain (20x) of a muscle biopsy from a patient with dermatomyositis showing perivascular and perimysial inflammation, as well as perifascicular necrosis.



CASE 1

- 40 yr old lady has come to the hospital with c/o difficulty in using all 4 limbs-last 7 months
- Blackish discoloration face and hands-6 months
- Difficulty in swallowing 2 months
- Pain over the both great toes 1month



HISTORY

- She was apparently normal 7 months ago when developed pain over the both thighs followed by fever, she took treatment, fever subsided in 3 days but she noticed weakness of both legs, mainly in the proximal region, which is insidious in onset and slowly progressive in nature

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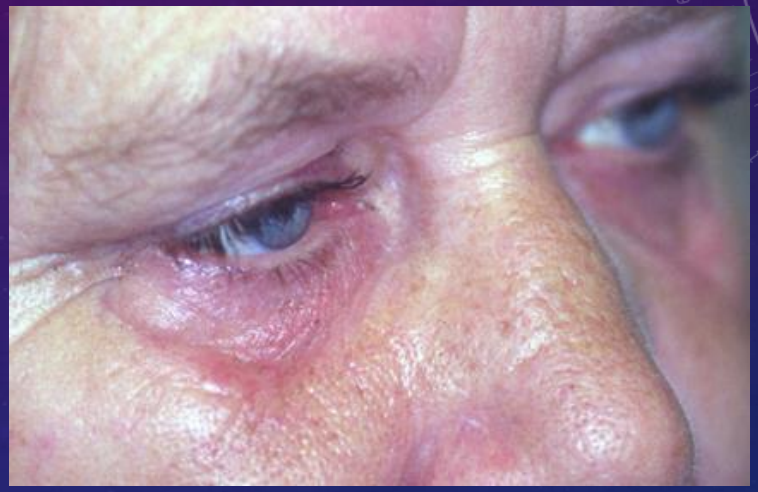
- h/o difficulty in getting up from squatting and lying posture, climbing the stairs -7months
- Difficulty in lifting the hand above the head, combing the hair and bringing the food to mouth-6 months
- h/o difficulty in lifting the head from the pillow-4 months
- Difficulty in mixing the food- 2 months
- h/o dysphagia .-last 2 months , started with solid food now even for liquid, progressive,mainly during initiation of swallowing and associated with throat pain

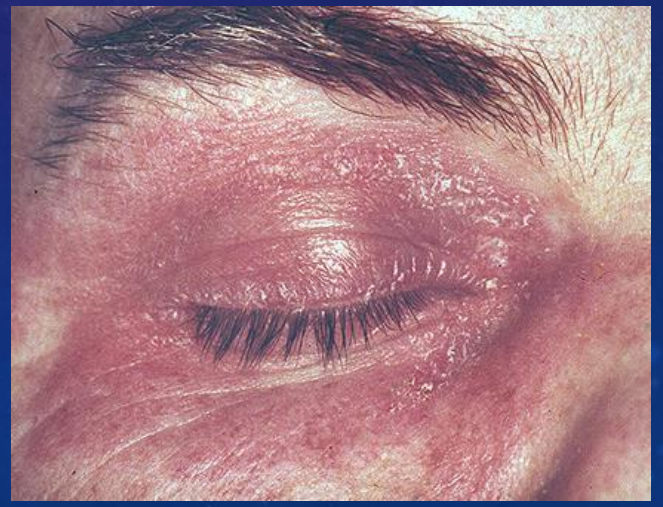
- h/o **hyper pigmentation** over the face, chest and neck-6 months, non itchy
- h/o excessive hair loss +

MALAR RASH& V SIGN

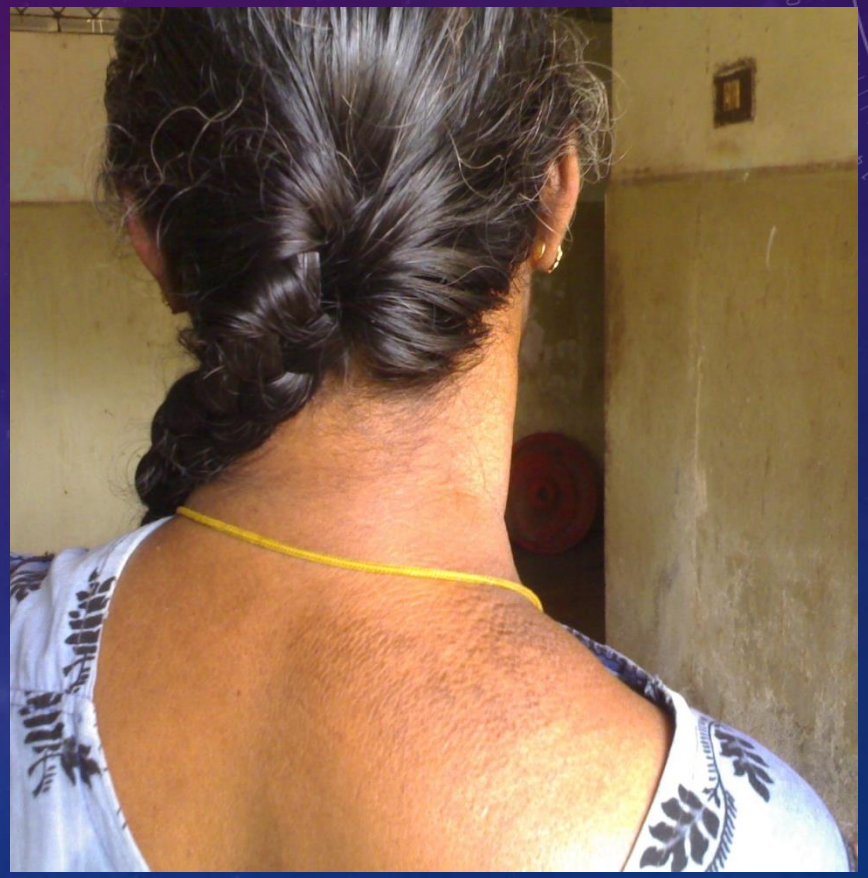
SIGNS AND SYMPTOMS

- Heliotrope rash:
  - A reddish-purple eruption on the upper eyelid
  - accompanied by swelling of the eyelid
  - Most specific rash in DM
  - Only present in a minority of patients.

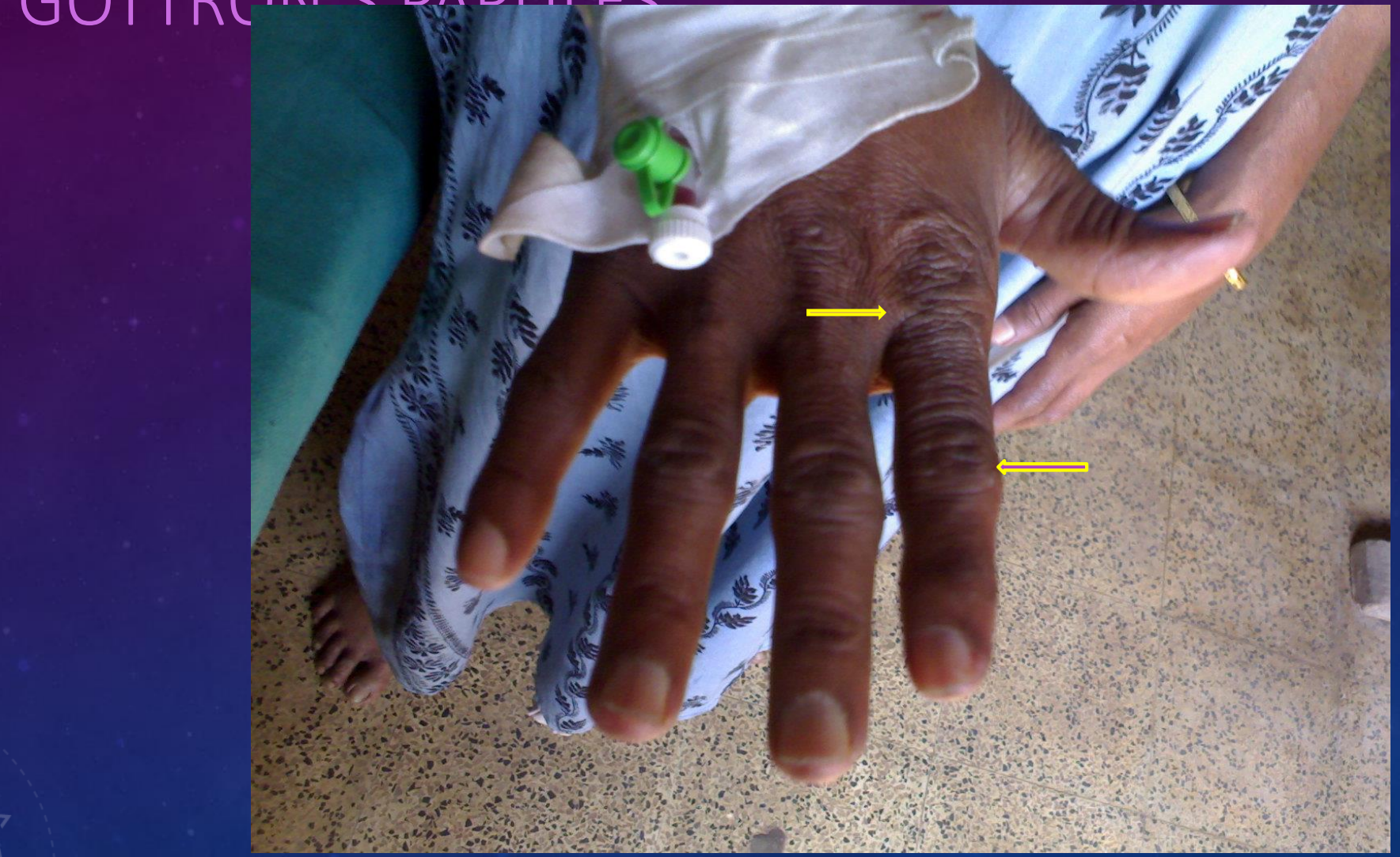




SHAWL SIGN

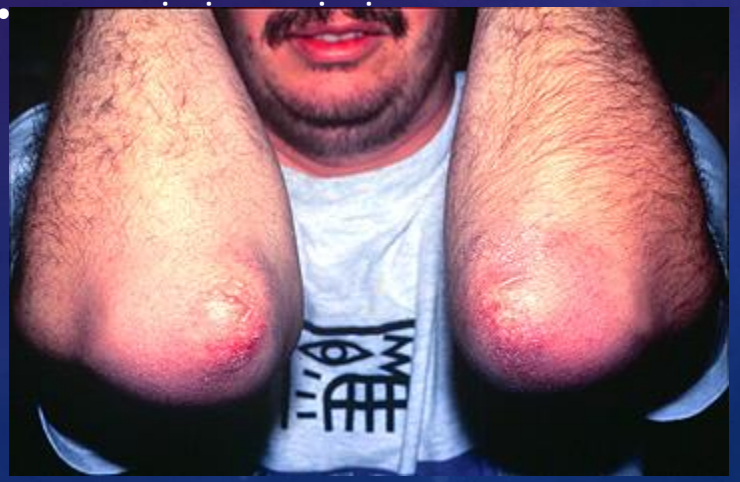


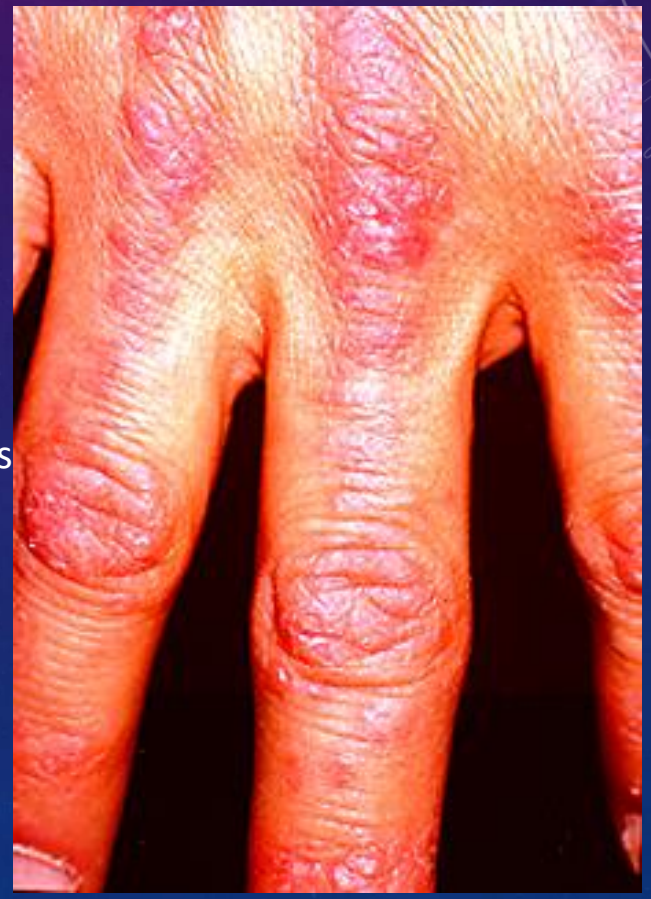
GOTTRON`S PAPULES



SIGNS AND SYMPTOMS

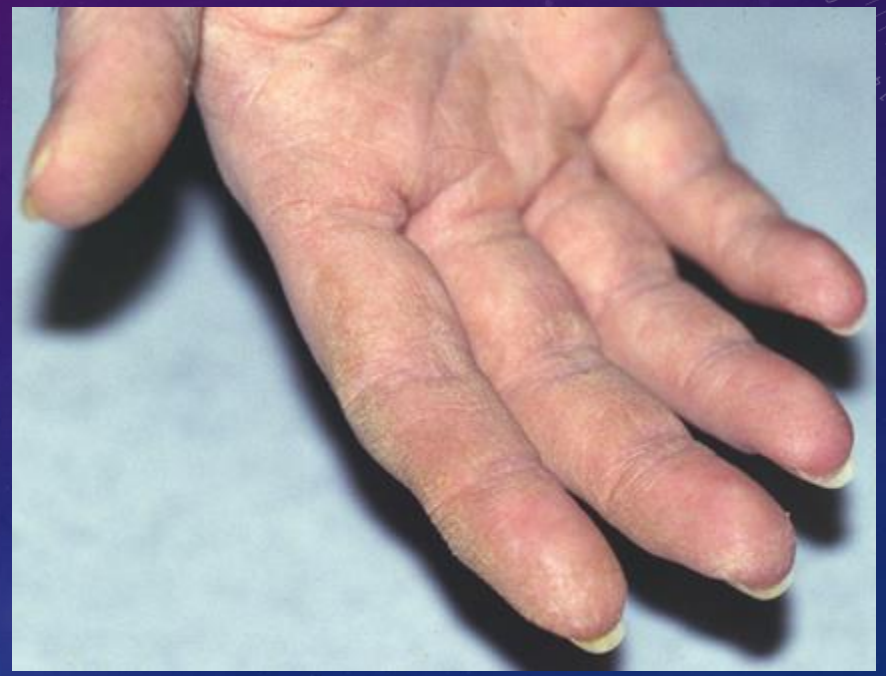
- Grotton's Sign:
  - An erythematous, scaly eruption over the extensor surfaces of the metacarpophalangeal joints and digits
  -





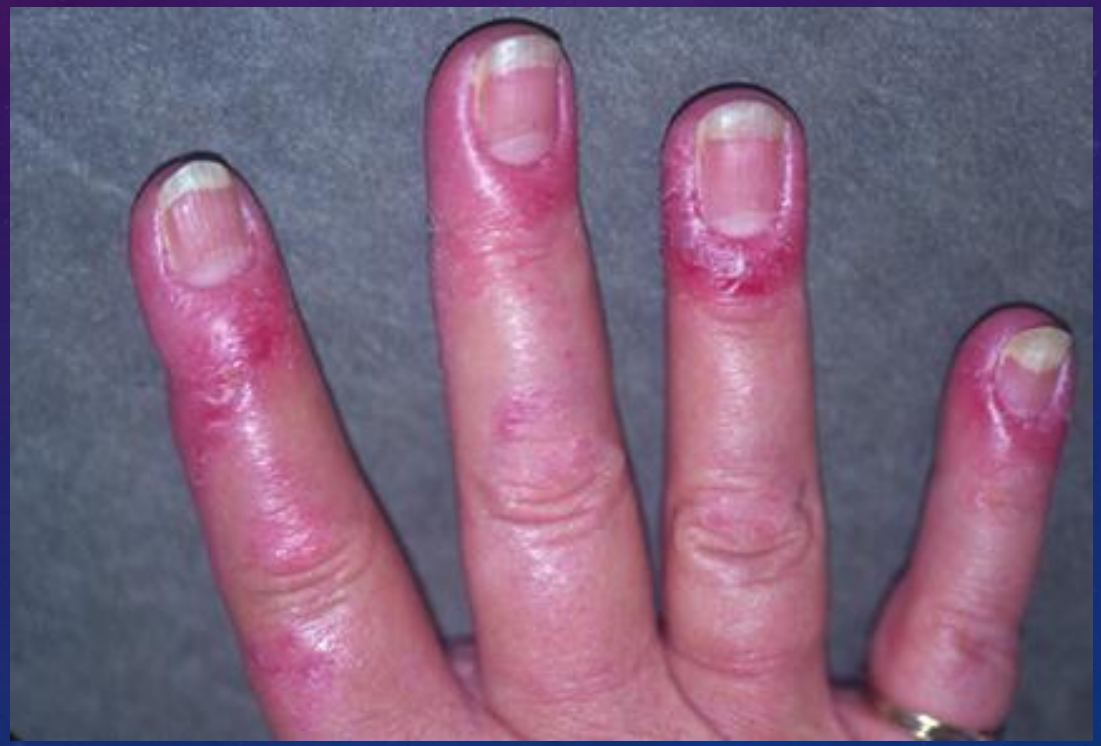
“MECHANIC’S HANDS”

- roughened, cracked skin at tips and lateral aspects of the fingers resulting in irregular, dirty-appearing lines



NAIL CHANGES

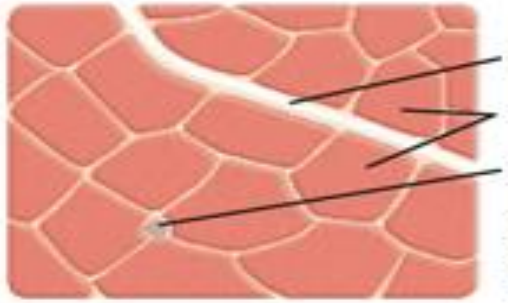
Periungual Erythema



- Tone - normal on both side
- Power - shoulder 2/5 both side
- Elbow 3/5 both side
- wrist 4/5 both side
- hand grip good
- hip 2/5 ,knee 3/5, ankle 4/5
- DTR preserved
- Plantar b/l flexor , other superficial reflexes normal
- Sensory system normal
- No cerebellor sign
- No involuntory movements
- No fasiculation
- Gait- waddling gait

DERMATOMYOSITIS - HISTOLOGY

Normal Muscle



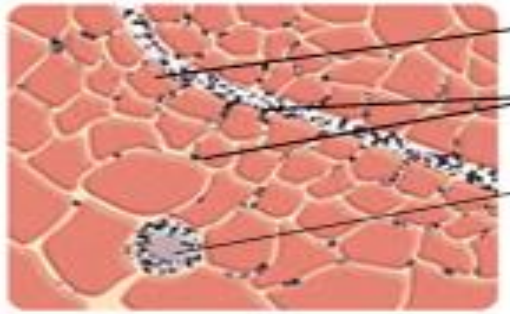
border of muscle bundle (fascicle)

normal muscle fibers

blood vessel

When normal muscle fibers are viewed under a microscope, they look like puzzle pieces that fit together neatly.

Dermatomyositis



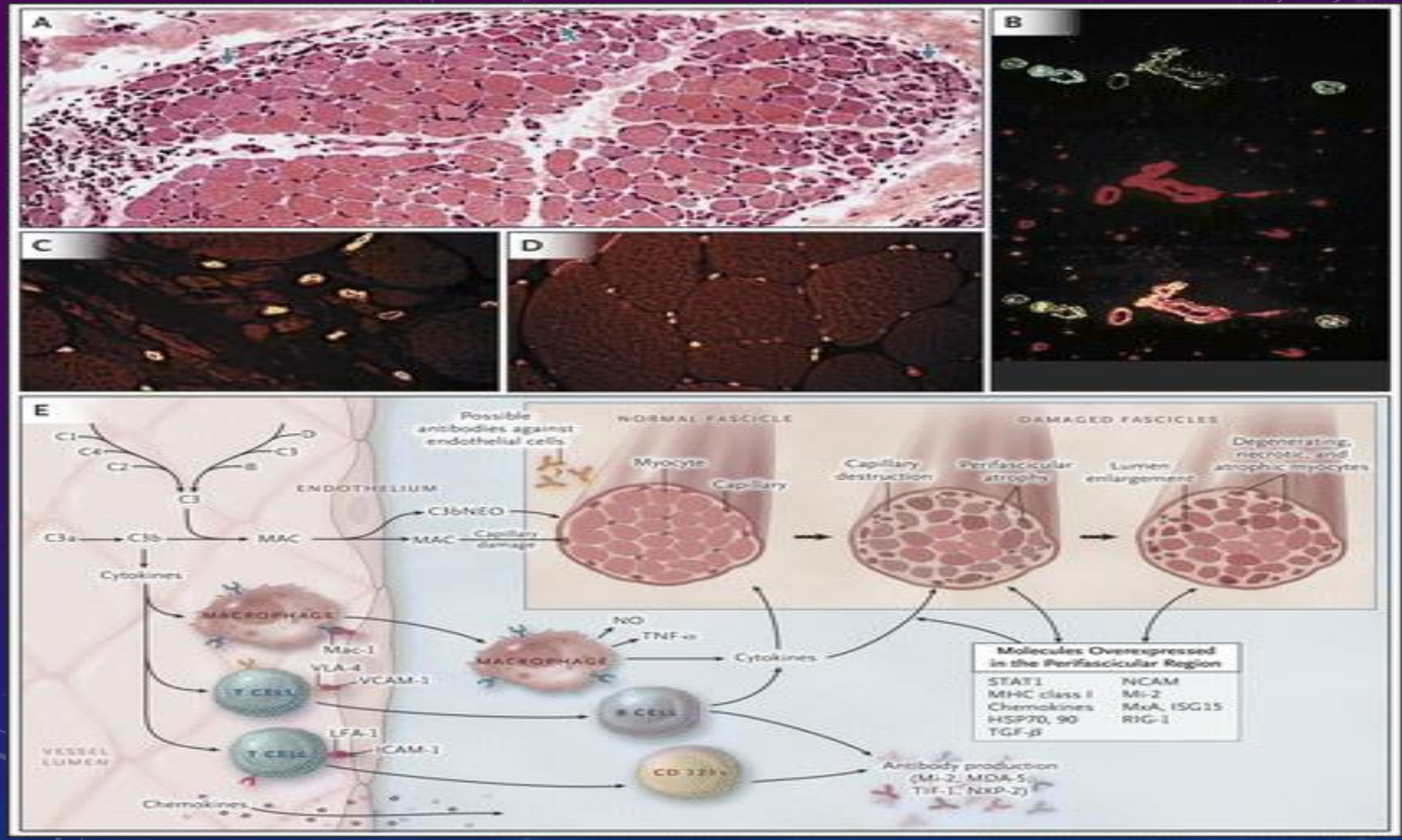
shrinkage (atrophy) of fibers near border of fascicle

inflammatory cells around fascicle and between fibers

cuff of inflammatory cells around blood vessel

DIAGNOSTIC CRITERIA

- Bohan and Peter Criteria:
  - Symmetric proximal muscle weakness
    - most common symptom
  - typical rash
  - elevated serum muscle enzymes
  - myopathic changes on EMG
  - characteristic muscle biopsy abnormalities and absence of histopathologic signs of other myopathies


A
B
C
D
E
Possible antibodies against endothelial cells
NORMAL FASCICLE
DAMAGED FASCICLES
Myocyte
Capillary
Capillary destruction
Perifascicular atrophy
Lumen enlargement
Degenerating, necrotic, and atrophic myocytes
ENDOTHELIUM
C1
C4
C2
C3
D
B
C3
C3a
C3b
MAC
C5bNEO
MAC
Capillary damage
Cytokines
MACROPHAGE
Mac-1
VLA-4
VCAM-1
T CELL
MACROPHAGE
NO
TNF-α
Cytokines
B CELL
LFA-1
ICAM-1
T CELL
CD 123+
VESSEL LUMEN
Chemokines
Antibody production
(Mi-2, MDA-5, TIF-1, NXP-2)
Molecules Overexpressed in the Perifascicular Region
STAT1
MHC class I
Chemokines
HSP70, 90
TGF-β
NCAM
Mi-2
MxA, ISG15
RIG-1

IMMUNOPATHOGENESIS

- Humorally-mediated disorder with cellular infiltrate focused around blood vessels
- Proinflammatory cytokines contribute to muscle weakness
- IL-1 and TNF-alpha are increased in muscle tissue
- Upregulation of MHC class I molecules on myocytes lead to disturbed muscle function

COMPLICATIONS

- Interstitial lung disease
  - 10% of cases
  - respiratory failure may result from diaphragmatic and chest muscle weakness
  - can result in rapid respiratory failure and death
- Esophageal disease
  - weakness of the striated muscle of the upper 1/3 of the esophagus and/or oropharyngeal muscles
  - can lead to nasal regurgitation, dysphagia, aspiration
  - More common in elderly patients
  - leads to increased incidence of bacterial pneumonia
- Myocarditis
- Malignancy

OUTCOME PREDICTORS

- Worse outcomes if:
  - delay in initial treatment of >6 months after symptom onset
  - greater weakness at presentation
  - presence of dysphagia
  - respiratory muscle weakness
  - interstitial lung disease
  - associated malignancy
  - cardiac involvement
  - advanced age

MALIGNANCY IN DM PATIENTS

- Incidence: of patients with DM, 48% over age 65 v. 9% under age 65 were found to have a malignancy
- Risk factors:
  - Evidence of capillary damage on muscle biopsy
  - DM complicated by cutaneous necrosis on the trunk
  - Cutaneous leukocytoclastic vasculitis
  - Older age at diagnosis
- Pathophysiology: paraneoplastic process
- Regenerating cells in myositis muscle, but not in normal muscle, express high levels of myositis-specific autoantigens. Same antigens are expressed at high levels in several cancers
- Types of cancer: adenocarcinoma of the cervix, lung, ovaries, pancreas, bladder and stomach make up about 70% of associated cancers

CANCER SCREENING IN DM PATIENTS

- Thorough medical history and physical exam
- Age appropriate cancer screening (mammogram and colonoscopy)
- CT of chest, abdomen and pelvis recommended only if significantly increased risk
- Pelvic US and transvaginal US for women
- Serum CA 125 and CA 19-9
- PSA
- UA for blood

CASE 2....

Patient ABC ,30 years old house wife admitted with following complaints

- Muscle pains-------- 2 months
- Gen. body weakness----- 1 month
- Difficulty in swallowing ----- 10 days

MUSCLE ACHES

- Usual state of health 2 months back
- Gradual in onset
- From lower limbs, then upper limbs then whole body
- Aggravated on trying to move limb and pressing the muscles
- Progressive
- There is also history of associated B/L knee joint pain but no inflammation associated with it

WEAKNESS

- Gradual in onset
- Unable to rise up from sitting position, climbing stairs
- Then unable to move lower limbs
- and also difficulty in combing hair then even moving her upper limbs
- Didn’t c/o any difficulty in breathing or neck movements
- There is no history of any morning stiffness.

DIFFICULTY IN SWALLOWING

- For last 10 days difficulty in swallowing
- Difficulty is more for solids than liquids
- No h/o regurgitation, vomiting.

HISTORY

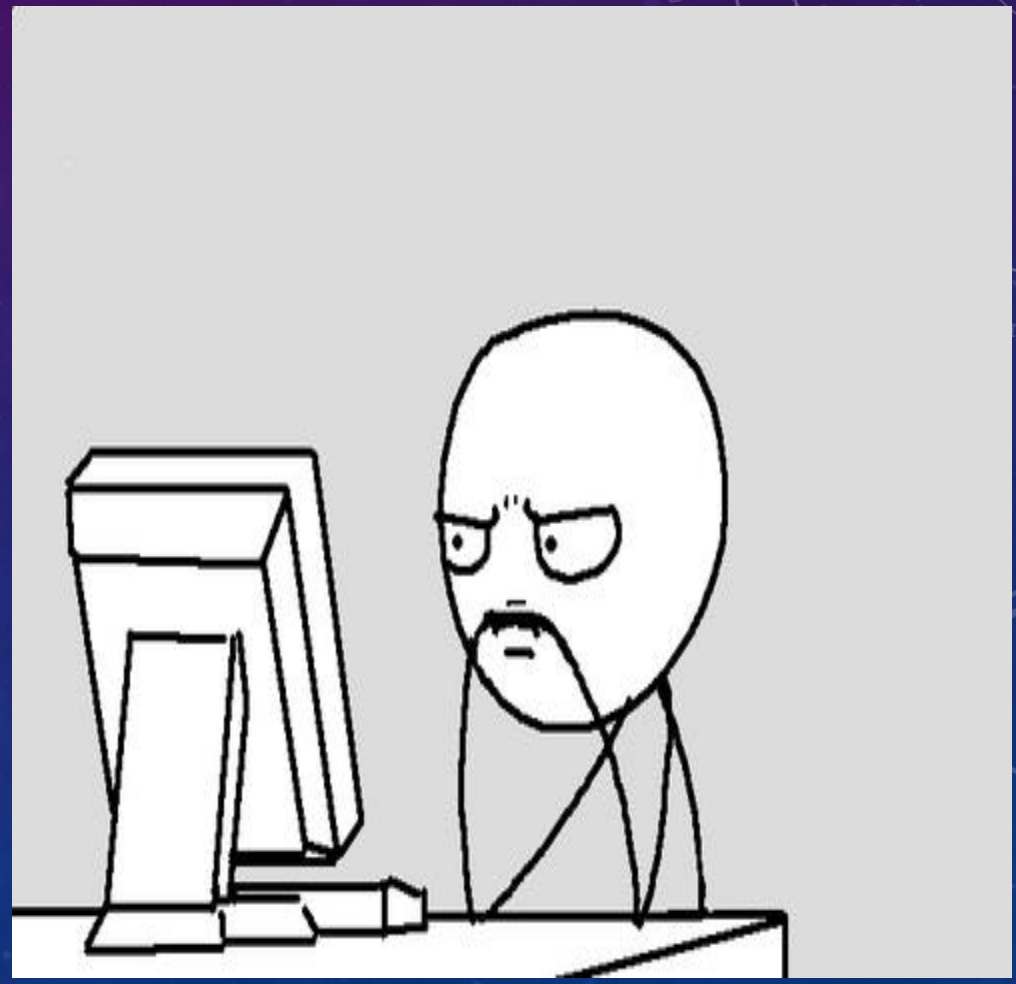
- There is no history of any associated fever, respiratory tract or GIT infection in past few weeks, palpitation, heat or cold intolerance, any change in urine color, cough, sputum.
- There is also no history of use of any drugs for a long period, also no history of any homeo or herbal medicine.
- There is no h/o mouth ulcers alopecia, sun burns, change in color of finger tips in cold.

EXAMINATION

- A middle aged ill looking female lying comfortably in the bed with I/V cannula at right arm, well cooperative during examination with following vitals
  - B.P 110/70 mmHg
  - Pulse 82/min
  - R.R 20/min
  - Temp. 98`F

GENERAL PHYSICAL EXAMINATION

- No significant finding on GPE
- No erythematous rash at face
- Shawl sign -ve
- Gottron sign -ve
- Heliotrope rash –ve
- No mechanic’s hands
- No signs of cushing’s disease
- No skin changes
- No signs of hyper/hypothyroidism



MUSCULOSKELETAL & NERVOUS SYSTEM

- Well oriented in time place and person
- GCS 15/15
- Mild tenderness in muscles of lower thigh
- Plantars B/L down going
- Power 1/5 at proximal muscles, 3/5 at distal muscles of lower limbs
- 2/5 in proximal muscles of upper limb and 4/5 in lower limbs

MUSCULOSKELETAL & NERVOUS SYSTEM

- Bulk of muscles bilateral equal and normal
- Tone was normal in all limbs
- Reflexes are normal
- All sensations intact
- All cranial nerves intact (no neurological dysphagia)

OTHER SYSTEMIC EXAMINATION

- Respiratory system:
  - Normal in shape, bilateral chest movements equal, and bilateral air entry equal. On auscultation normal vesicular breathing with few bibasal inspiratory crackles not changing character with cough.
- CVS
  - Apex beat in 5^{th} intercostal space just lateral to mid clavicular line non taping, non heaving with S1+S2+0

ABDOMEN

- Scaphoid, with umbilicus normal in shape and position, flanks not filled and no visible veins or stria
- soft, non tender, no visceromegaly
- No shifting dullness
- Bowel sounds 3/min

INVESTIGATIONS

- Serum electrolytes
  - Na 139
  - K 4.4
  - Cl 102
- RFTS
  - Urea 60
  - Creatinine 1.2
- LFTs
  - ALT 370 IU
  - AST 490 IU
  - S. bilirubin 0.7 (0.4D)
  - Alk. PO4 204
- CBC
  - Hb 10.7 g/dl
  - WBC 10800
  - PLT count 191000
  - Neut. 88%
  - Poly. 10%
  - Eosin.1%
  - ESR 100 mm/1st hr
- Urine C/E
  - Albumin nil
  - Pus cells rare
  - RBC 9-10
  - Crystals uric acid+
  - Blood ++
  - pH 7.0
  - sp. Gravity 1010
  - Casts nil

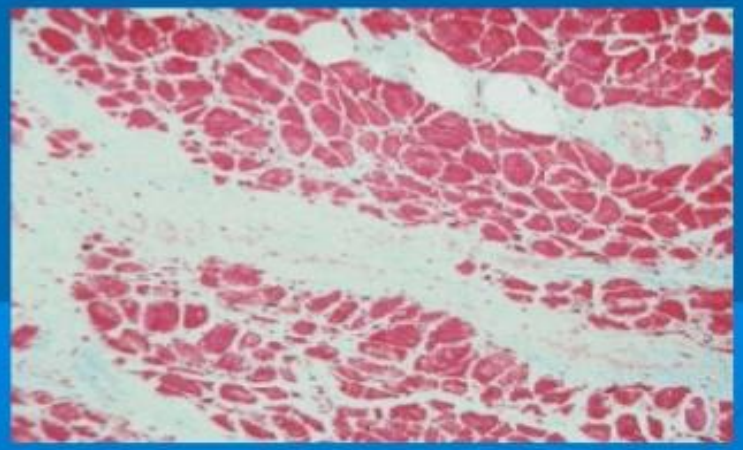
- ✓CPK 7047
- ✓LDH 2785

- NCS Normal
- EMG showed
  - Increased insertional activity with fibrillation and +ve sharp waves especially in proximal muscles. There is early recruitment of motor units and interference pattern is early and full especially in lower limbs and proximal muscles. Motor unit size and duration is decreased
  - Impression: this study is in favour of inflammatory myopathy(polymyositis)

- Biopsy of Skeletal muscle sent
- CA 125 sent

Muscle biopsy of polymyositis

- Focal and endomysial infiltration of T cell, esp. CD8, with small number of macrophage
- Muscle fiber degeneration and atrophy

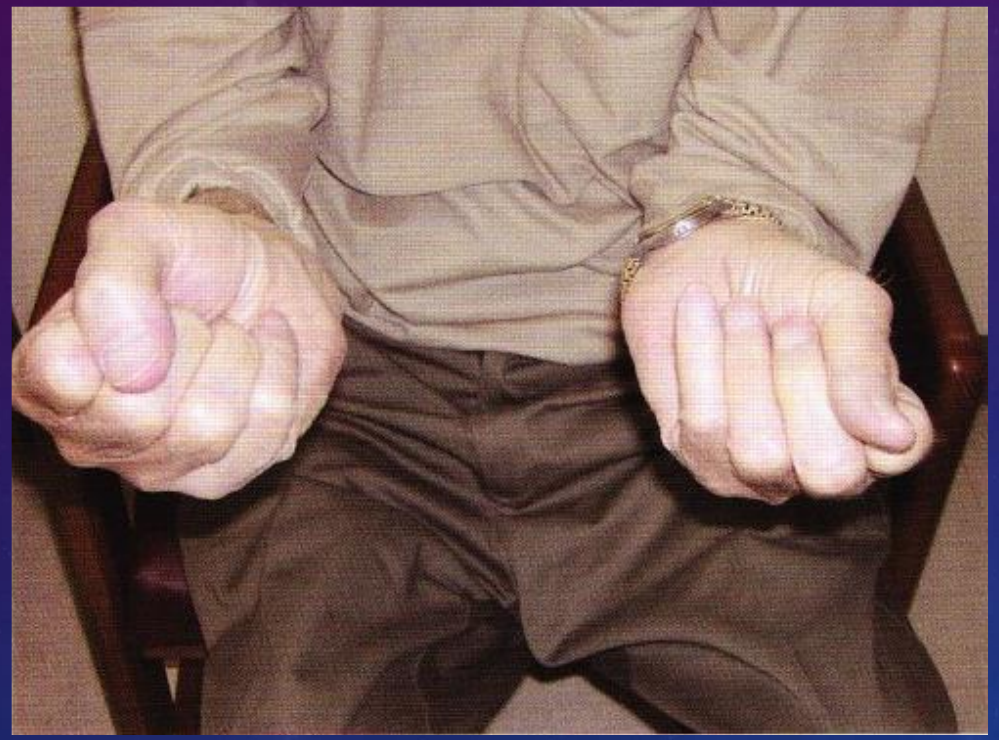


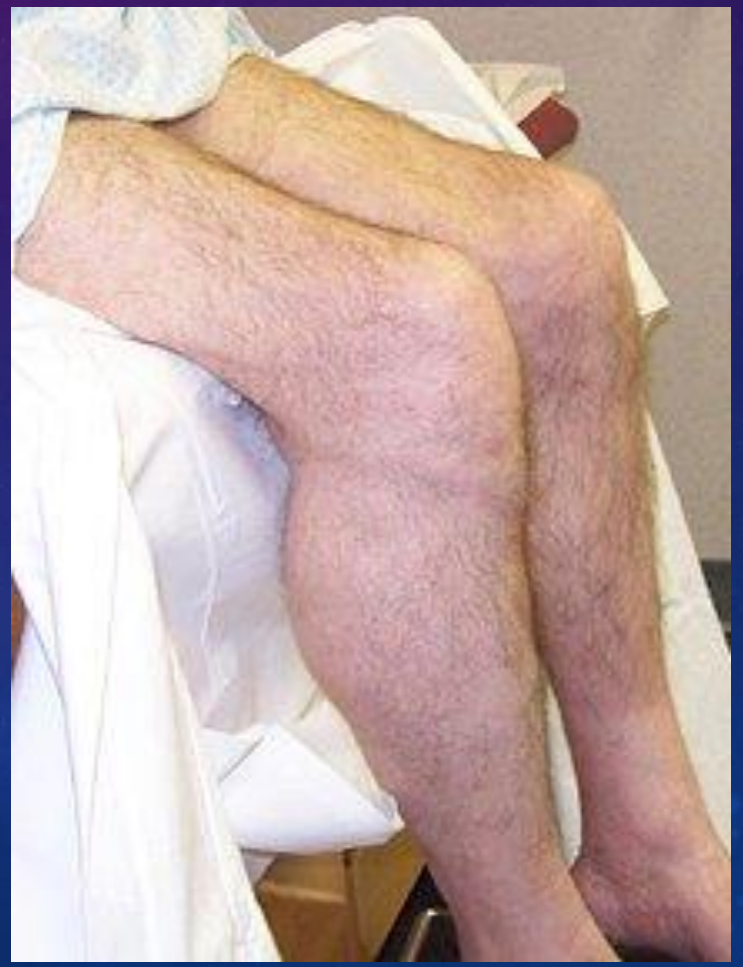
INCLUSION BODY MYOSITIS (IBM)

- Most common inflammatory myopathy after age 50 yrs
- Insidious onset, slowly progressive proximal leg and distal arm weakness
- Delayed diagnosis with average duration of symptoms prior to diagnosis is 6-7 yrs
- Male are affected more than female
- Hallmark: weakness and atrophy (2/3rd of the pts)
    - Legs: knee extensors, ankle dorsiflexors
    - Arms: wrist and finger flexors
- Upto 82% of patients have marked asymmetry
- Sparing of thenar and hypothenar muscles helps distinguish IBM from ALS
- Dysphagia occurs on 70% patients
- Mild to moderate facial weakness

IBM

marked difficulty in flexing the fingers of the left hand as compared to the right





IBM – WORK UP

- Serum CK may be normal or elevated up to 10 times normal
- ANA positive in 20% patients
- Nerve conduction studies - mild sensory axonal peripheral polyneuropathy in up to 30% of patients with IBM
- Needle examination - evidence of muscle irritation (increased insertional activity, positive sharp waves, polyphasic potentials)
- Skeletal muscle MRI scans – atrophy and signal abnormalities in affected muscle groups

	PM	DM	IBM
Age at onset	>18yrs	Adulthood, childhood	>50yrs
sex	M=F	F>M	M>F
Weakness	proximal	proximal	Proximal, early distal involvement
Familial association	No	No	Yes, in some cases /familial inflammatory myopathies /
Response to treatment	good	better	poor
CTDs	yes	yes	Yes, in up to 20%
malignacy	No	yes, in up to 15% of cases	No
Rash	Absent	Present	Absent
Biopsy	“primary” inflammation with the CD8/MHC-I complex & vacuoles	Perifascicular, perymysial, or privascular infiltrates, perifascicular atrophy	Primary inflammation with CD8/MHC-I complex; vacuolated fibers with b-amyloid deposits , cytochrome oxygenase-negative fibers ; signs of chronic myopathy

IIM - EVALUATION

- **Careful history and physical examination to define:**

1. The time\tempo of symptom onset and progression.
2. The exact nature of the problems and associated factors.
3. Medical and family history.
4. Muscle bulk/strength, rashes, cardiac, pulmonary, GI findings.
5. Environmental exposures temporally associated.

IIM – SYSTEMIC MANIFESTATIONS

- **General manifestations:** fatigue, fever, weight loss.
- **Musculoskeletal:** myalgia, muscle tenderness and weakness. Arthralgia, arthritis, contractures.
- **Dermatologic:** Photosensitive rashes and edema. Vasculitis with infarcts and ulceration. Subcutaneous inflammation (panniculitis) and calcification.

IIM – SYSTEMIC MANIFESTATIONS

- **Gastrointestinal:** oropharyngeal involvement with tongue weakness and voice changes; dysphagia and reflux.
- **Pulmonary:**Atelectasis, cough. Interstitial lung disease. Aspiration.
- **Cardiovascular:**Tachyrhythmias and other conduction abnormalities. Congestive heart failure from myocarditis or cor pulmonale. Raynaud.

IIM - EVALUATION

- **Laboratory evaluation directed by the above:**

1. Muscle enzymes, serologies, tests to R/O other diseases.
2. Radiographic studies, muscle MRI.
3. EMG, biopsies of skin, muscle, possibly other tissues.
4. Special serologic or genetic studies depending upon results from the above.

IIM – LABORATORY ABNORMALITIES

- Sarcoplasmic enzymes (CPK, LDH, ALT, AST, aldolase) – useful in assessing myositis activity.
- CPK MB fraction – correlates with diseases activity and is not usually indicative of cardiac involvement unless the ratio of CK-MB/total CK rapidly increases.
- ESR/CRP – elevated in <30% of pts.
- ANA – positive in 60-90% of pts; best single lab discriminator of IIM from other myopathies.

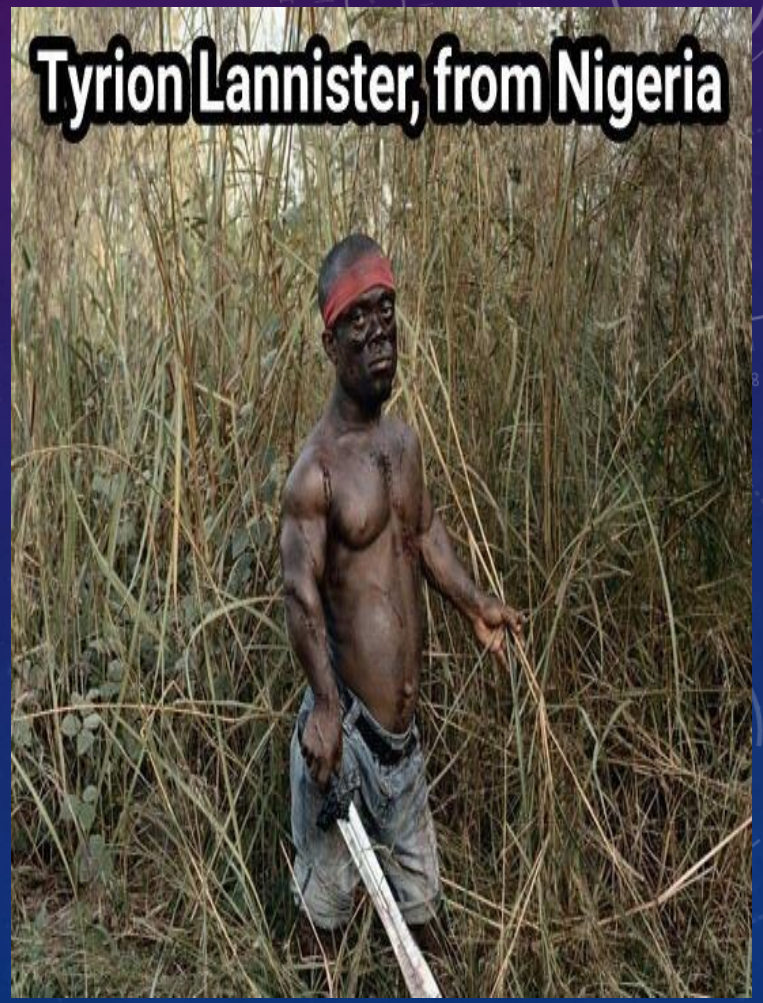
CAUSES OF ELEVATED SERUM CPK ENZYME ACTIVITY

- **Physical trauma or muscle stress.**

1. Any muscle trauma – falls, EMG studies, surgery, muscle biopsy, IM injection.
2. Strenuous, prolonged exercise-marathon running, forced marching.

- **Drug effects**

1. On muscle itself – clofibrate, ethanol, amphetamines, heroin.
2. On CK metabolism/clearance-phenobarbital, morphine, diazepam.



CAUSES OF ELEVATED SERUM CPK ENZYME ACTIVITY

- **Diseases**

1. Directly affecting muscle-non inflammatory myopathies of all kinds, MI, malignant hyperthermia, infectious myopathies, IIM.
2. Affecting blood supply to muscle-emboli to muscle, vasculitis,prolonged immobilization.
3. Affecting the CNS-cerebral ischemia, trauma,infections.

- **Possible familial cases in African-Americans.**

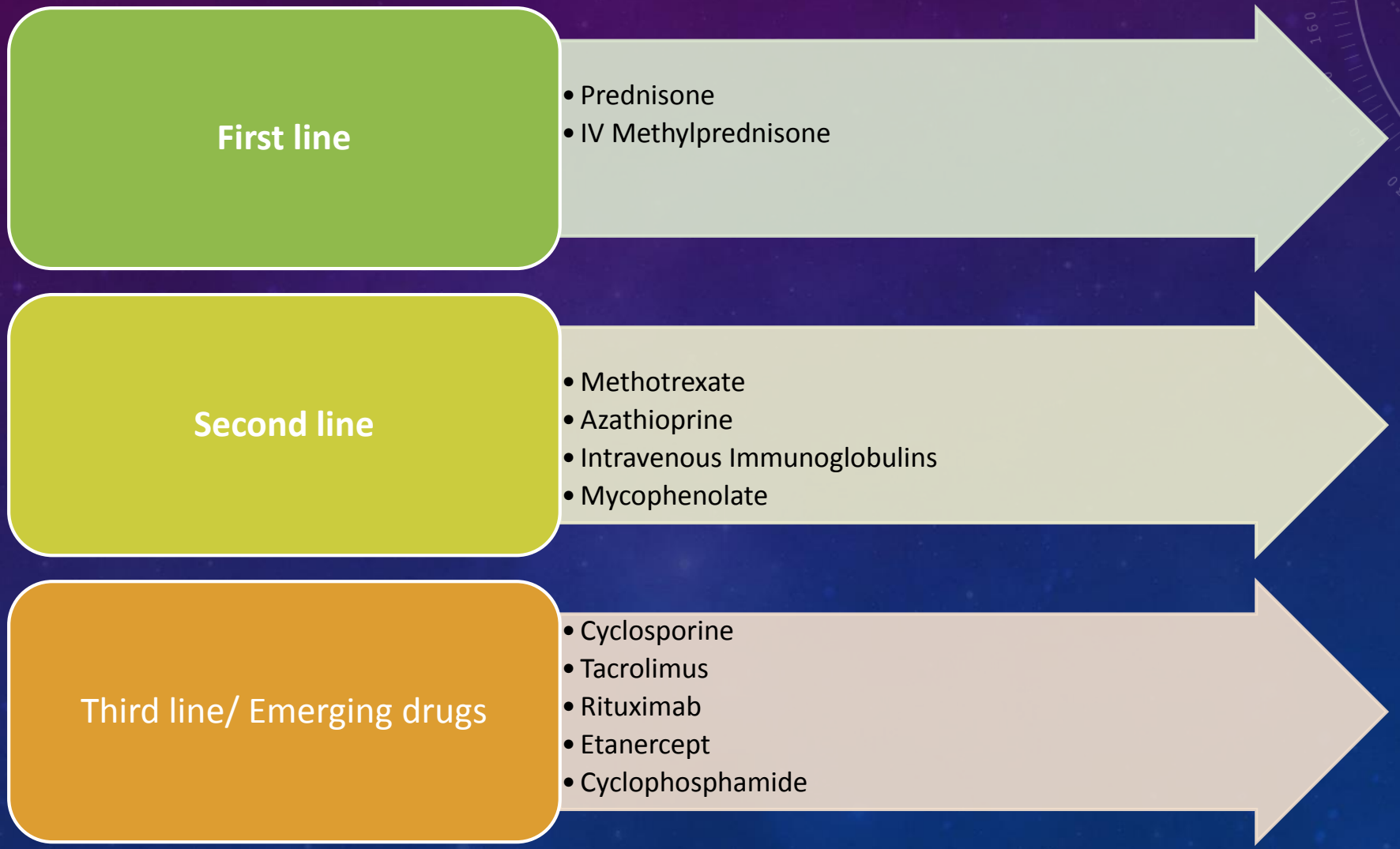
MYOSITIS SPECIFIC ANTIBODIES

Autoantibodies	Target autoantigen and function	Clinical phenotype	Autoantibody frequency, %	
			Adult IIM	JDM
Anti-ARS	ARS—intracytoplasmic protein synthesis	ASS	30–40	1–3
Anti-Jo-1	Histidyl			
Anti-PL-7	Threonyl	Myositis, mechanic's hands, Gottron's papules, arthritis, fever, RP, high frequency of interstitial pneumonia		
Anti-PL-12	Alanyl			
Anti-EJ	Glycyl			
Anti-OJ	Isoleucyl			
Anti-KS	Asparaginyl			
Anti-Ha	Tyrosyl			
Anti-Zo	Phenylalanyl			
Anti-SRP	SRP—intracytoplasmic protein translocation (six polypeptides and RNP 7SLRNA	Acute onset necrotizing myopathy (severe weakness, high CK); may be refractory to treatment	5	<1
Anti-Mi-2	Helicase protein—nuclear transcription (forms the NuRD complex)	Adult DM and JDM (hallmark cutaneous disease, milder muscle disease with good response to treatment)	<10	<10
Anti-p155/140	TIF1-y (p155)—nuclear transcription + cellular differentiation	CAM in adult DM; severe cutaneous disease in adult DM and JDM	13–21	23–29
Anti-p140	Likely to be NXP-2—nuclear transcription + RNA metabolism	JDM with calcinosis	NA	23
Anti-SAE	SAE—post-translational modification (targets include transcription factors)	Adult DM; may present with CADM first	5	NA
Anti-CADM-140	Intracytoplasmic MDA5—innate immune responses against viral infections	CADM; rapidly progressive interstitial pneumonia	Overall–unknown	NA

SRP: Signal recognition particle; NuRD: nucleosome remodeling histone deacetylase; TIF1-y: Transcriptional intermediary factor 1-gamma; NXP-2: Nuclear matrix protein NXP-2; SAE: Small-ubiquitin-like modifier activating enzyme; MDA5: Melanoma-differentiation associated gene 5; CAM: Cancer-associated myositis; NA: Not applicable/no data

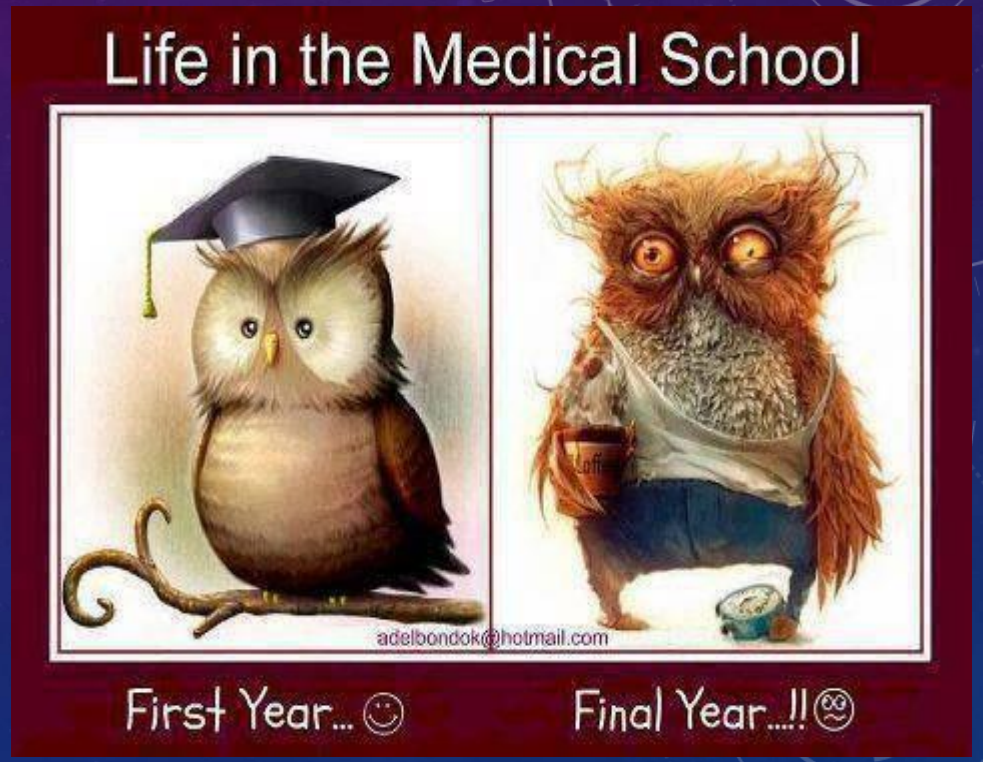
TREATMENT

IMMUNOSUPPRESSIVE THERAPY IS THE MAINSTAY OF TREATMENT

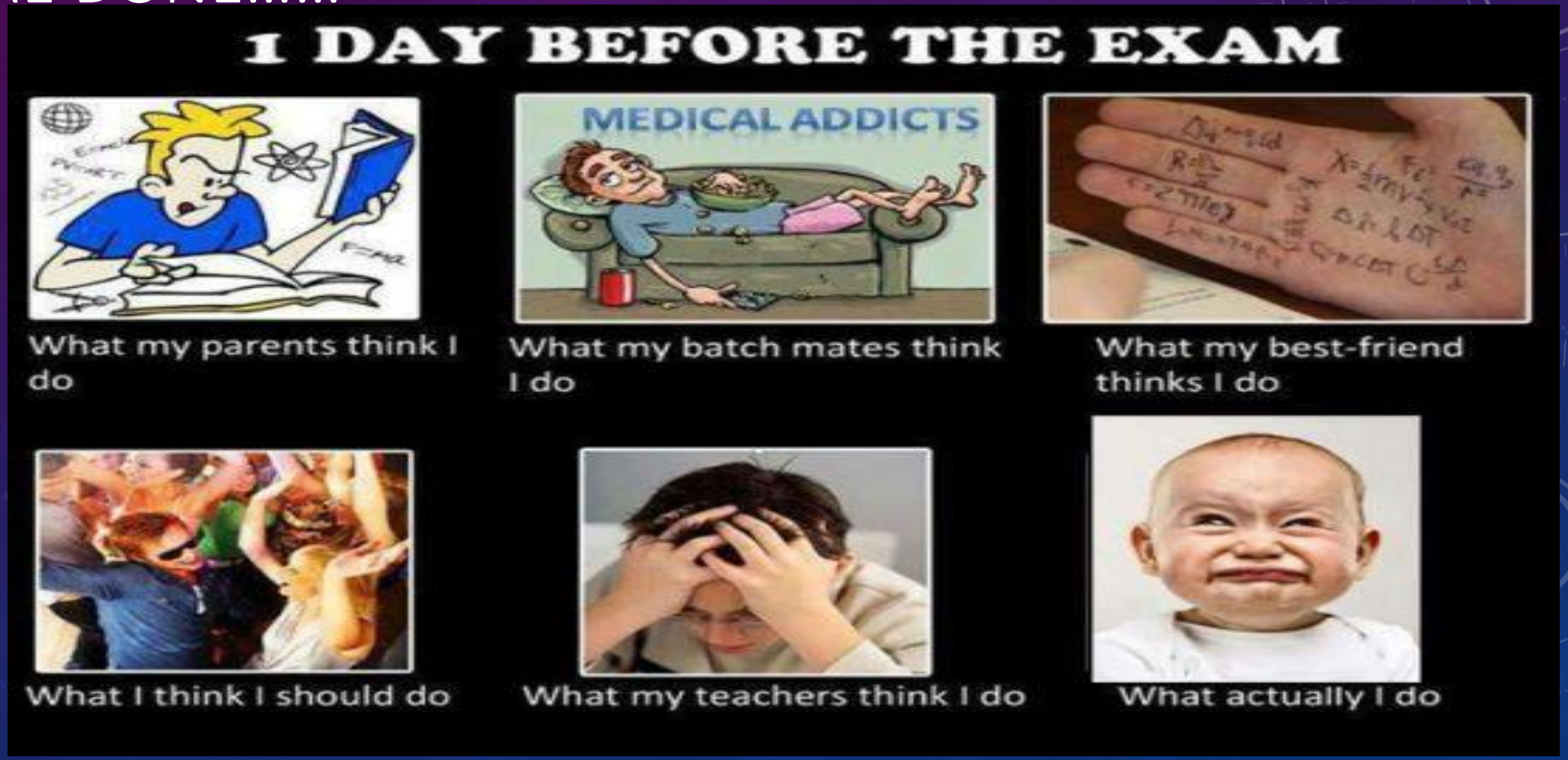


PROGNOSIS

- The prognosis of the idiopathic inflammatory myopathies is generally favorable
- Overall, drug-free remissions are rare except in JDM
- Poor prognostic factors
  - old age
  - male gender
  - non-Caucasian ethnicity
  - longer symptom duration
  - ILD, cardiac involvement
  - associated malignancy
  - dysphagia
  - serum MSA (anti Jo-1 antibodies, anti SRP antibodies)
- Mortality remains two- to three fold higher than the general population; with cancer, lung, cardiac complications, and infections being the most common causes of death



WE ARE DONE……


1 DAY BEFORE THE EXAM
What my parents think I do
MEDICAL ADDICTS
What my batch mates think I do
What my best-friend thinks I do
What I think I should do
What my teachers think I do
What actually I do