THE "ACHY-BREAKY" PATIENT INCLUDING MEDICATIONS THAT CAUSE RHEUMATOLOGICAL SYMPTOMS– HOW CAN YOU HELP?

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- Articular and Periarticular disorder
  - Tendinopathies
  - Enthesopathy

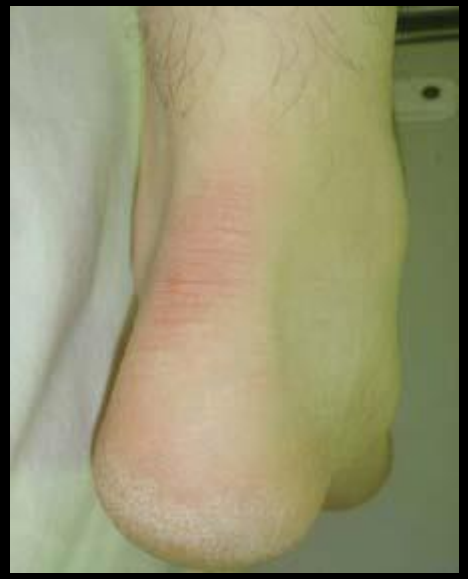
- Connective tissue disease
  - Drug induced lupus
    - Pathogenesis
      - autoantibodies
    - Causative drugs
    - Clinical manifestation
      - Systemic drug induced lupus
      - Subacute cutaneous lupus
      - ANCA positive vasculitis and renal disease
    - Diagnostic evaluation
    - treatment

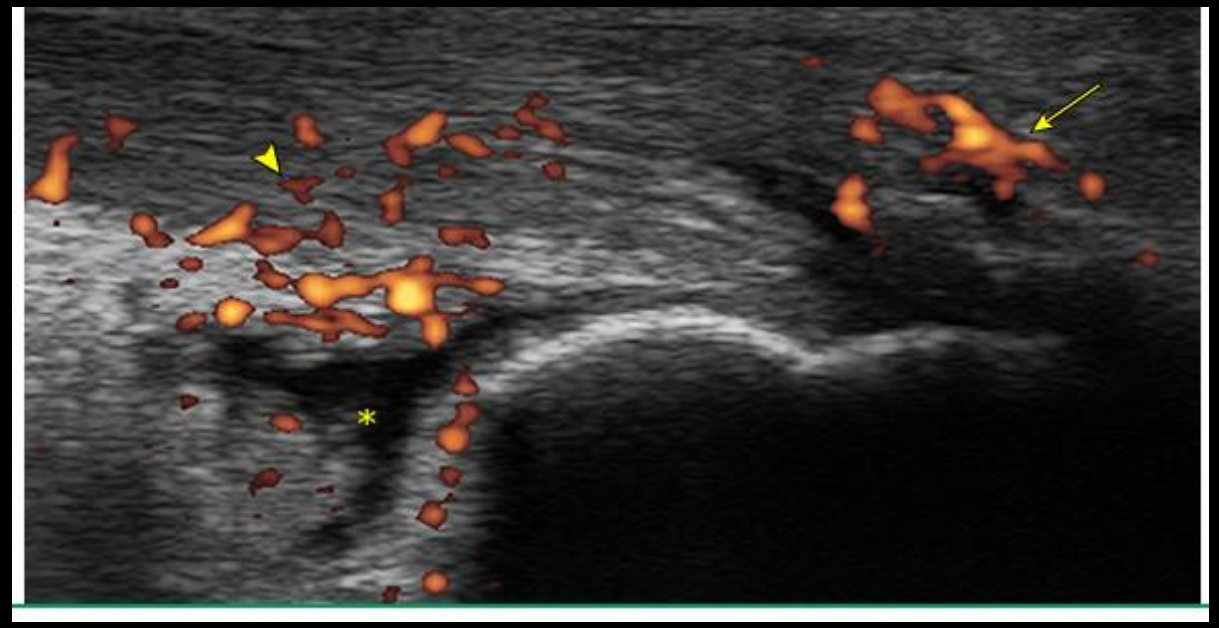
- Drug induced myopathies
  - Direct myotoxicities
    - Causative drugs
    - Statin myopathy

CASE 1

- 60 yo man with COPD, IHD, BPH
  - Dysuria
  - Flank pain
  - Incomplete bladder emptying
  - Right costovertebral tenderness
  - WCC 12.8
  - Urine culture – ciprofloxacin sensitive E. Coli
  - Ciprofloxacin 250 mg mane
  - Day 3 – acute severe left heel pain, palpable nodule and erythema right achilles tendon, pain on dorsiflexion.

CASE 1





Diagnosis: Achilles tendonitis

Management: Ciprofloxacin ceased, substituted with Amoxycillin / Clavulanate, pneumatic boot and NSAIDs.

Achilles tendonitis improved the next few days.

ARTICULAR AND PERIARTICULAR DISORDERS: FLUOROQUINOLONES

- Fluoroquinolones
  - Non erosive bilateral symmetrical arthropathies
    - Frequently lower extremities
    - Long term treatment > 3 months
    - Incidence 1.3 %

  - Tendonitis
    - 15-20 per 100 000
    - Achilles tendinopathy (odds ratio [OR] 4.3)
    - tendon rupture (OR 2.0)
    - Abrupt onset sharp pain
    - Bilateral
    - Predilection for achilles tendon
    - Proportional to treatment duration, increased tendon rupture after 3 weeks.
    - Predisposing factors:
      - > 60 yo (OR 8.3),
      - non obese (OR 7.7),
      - oral glucocorticoids (OR 9.1),
      - Female sex was significantly associated with tendon rupture (OR 4.0)

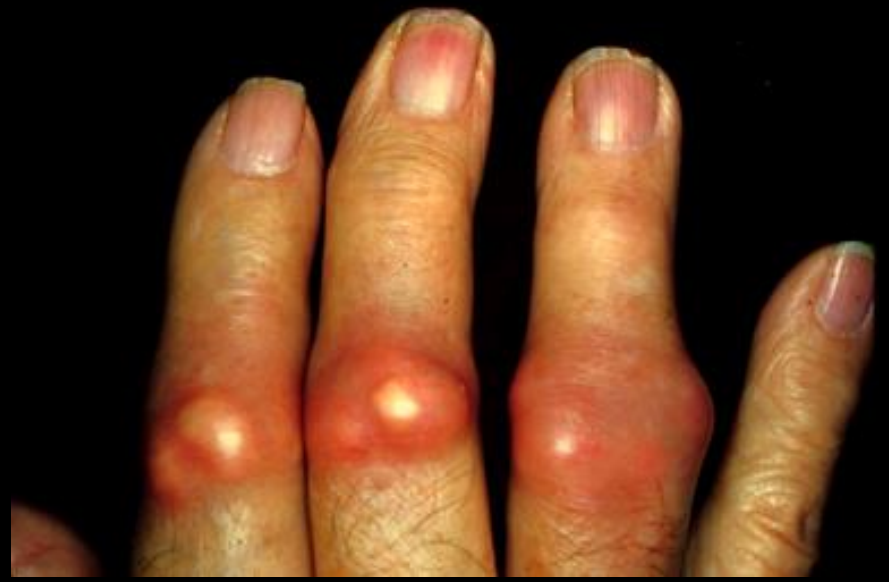
ARTICULAR AND PERIARTICULAR DISORDERS: FLUOROQUINOLONES

- Management:
  - stop taking the fluoroquinolone,
  - avoid exercise and use of the affected area
  - tendon evaluation
  - transition to a non-fluoroquinolone antibiotic
  - Achilles tendinopathy
    - rest, ice, tendon support with heel lift or elastic bandage or taping

CASE 2

- 40 yo Samoan man with CCF and hyperuricaemia.
  - Recently started on Frusemide for CCF
  - Acute onset of polyarthritis, worse in the ankles and 1st MTPs.
  - Urate 0.60
  - Creatinine 0.15
  - CRP 60 ESR 50

  - Diagnosis: Polyarticular gouty arthritis
  - Treated with Colchicine, then Allopurinol progressive dose elevation to 300 mg mane.
  - Urate improved to 0.30.
  - Gouty arthritis flare up frequency reduced.
  - Gouty tophi resolve over the next few years.



ARTICULAR AND PERIARTICULAR DISORDERS

- Drug induced hyperuricaemia and gout
  - Low dose salicylate
  - Diuretics
    - Frusemide
    - Thiazides
  - Ethambutol and pyrazinamide
  - Cyclosporin
    - Increased hyperuricaemia in 50% cases.

CASE 3

- 48 yo man with Type II diabetes
  - Previously well controlled
  - HbA1C trending upward.
  - Sitagliptin added
  - 2 weeks later
    - Morning stiffness
    - Pain & erythema of MCPs
    - Difficulty writing, typing, driving and walking up stairs
    - Rheum work up NAD
  - Sitagliptin ceased with improvement of arthralgia 6 weeks later.
  - Then began Saxagliptin → arthralgia after a few weeks.
    - Resolved after stopping Saxagliptin.

  - Diagnosis: Gliptin induced arthralgia.

ARTICULAR AND PERIARTICULAR: GLIPTIN

- Gliptin (Sitagliptin, Vidagliptin, Saxagliptin)
  - Inhibition of dipeptidyl peptidase-4 (DPP4)
  - Blocks the degradation of incretins such as glucagon-like-peptide-1
  - Stimulating insulin secretion from pancreatic β cells
  - Decreasing glucagon release from pancreatic a cells

ARTICULAR AND PERIARTICULAR: GLIPTIN

- Musculoskeletal reactions
  - Monica et al
    - Spanish pharmacovigilance
    - 332 spontaneous reports
    - Final sample with MSk reactions included 34 reports, 10.2% of all gliptin reports
      - 27 Sitagliptin
      - 6 Vidagliptin
      - 1 Saxagliptin
    - 26 out of 34 cases gliptins the only suspected drug
    - 64.7% women 35.3% man
    - Reporting odd ratio for myalgia and arthralgia strongly associated with Gliptin use (ROR 1.96, 95% CI 1.12 -3.43, $p<0.05$ and ROR 2.69, 95% CI 1.38-5.24, $p<0.05$)
    - Latency period 2 days to 5 months.
    - 18 out of 26 cases MSK complaints improved after gliptin withdrawal

ARTICULAR AND PERIARTICULAR : GLIPTIN

- Gliptin (Sitagliptin, Vidagliptin, Saxagliptin)
  - 34 reports
    - Described 45 MSK ADRs
      - 13 cases myalgia
      - 10 pain in extremity
      - 9 arthralgia
      - 4 muscle weakness
      - 2 joint stiffness
      - 2 muscle spasm
      - 1 cervical pain
      - 1 back ache
      - 1 joint swelling
      - 1 musculoskeletal discomfort
      - 1 polyarthritis

ARTICULAR AND PERIARTICULAR : GLIPTIN

- Management:
  - Mostly resolved within a month after discontinuing the drug
  - Some has recurrent severe arthralgia after restarting the same or a different DPP-4 inhibitor
  - Discontinue & assessed for resolution
  - Use different class of diabetes medication
  - If symptoms persist > 1 month, unlikely the result of DPP-4 inhibitor use, and alternative causes for the symptoms should be sought

CASE 4

- 55 yo lady with breast cancer treated with Anastrozole.
  - 3 months later developed polyarthralgia
  - Improved with cessation of Anastrozole.
  - Recurrence of polyarthralgia when rechallenged with Anastrozole.

  - Autoimmune serology negative
  - Mildly elevated inflammatory markers.

  - Diagnosis: Aromatase inhibitor associated musculoskeletal syndrome

  - Management: Polyarthralgia improved with physio and duloxetine.

ARTICULAR AND PERIARTICULAR : AROMATASE INHIBITOR ASSOCIATED MUSCULOSKELETAL SYNDROME

- Aromatase inhibitor (AI)
  - Suppress plasma estrogen by inhibiting or inactivating aromatase.
  - Used in treatment of breast cancer
  - Improved outcome in hormone receptor positive breast cancer compared to Tamoxifen.
  - Arthralgia and joint stiffness
    - 40 to 50 %
    - AI-associated musculoskeletal syndrome
      - Arthralgia, joint stiffness, bone pain.
      - Risk factor not characterised.
      - Rx discontinuation in 10-20%
      - Decreased estrogen may play a role.

Aromatase inhibitors

Generation	Steroidal (type 1)	Nonsteroidal (type 2)
First (nonselective)	-	Aminoglutethimide
Second (selective)	Formestane	Fadrozole
Third (superselective)	Exemestane	Anastrozole
		Letrozole

ARTICULAR AND PERIARTICULAR : AROMATASE INHIBITOR

- Aromatase inhibitor (AI)
  - Hormones and Physical Exercise (HOPE) trial
    - 121 with AI associated arthralgia
      - Exercise regime - twice-weekly supervised resistance and strength training plus moderate aerobic exercise for 150 minutes per week

        Vs
      - usual care

      - Exercise regime
        - A significantly greater reduction in their worst pain score (20 versus 1 % average score reduction, respectively) and pain severity (21 versus 0 % reduction) compared with usual care
        - dose-response relationship between exercise and symptom severity

ARTICULAR AND PERIARTICULAR : AROMATASE INHIBITOR

- Aromatase inhibitor (AI)
  - preliminary results of the Southwest Oncology group 1202 (SWOG S1202) trial
    - 299 patients with stage I to III disease on Ais
    - those randomized to duloxetine (30 mg daily for 1 week, then 60 mg daily for 11 weeks, then 30 mg daily for 1 week) experienced improvement in joint pain through the 12 weeks of treatment relative to placebo
    - results between the groups were similar at 24 weeks

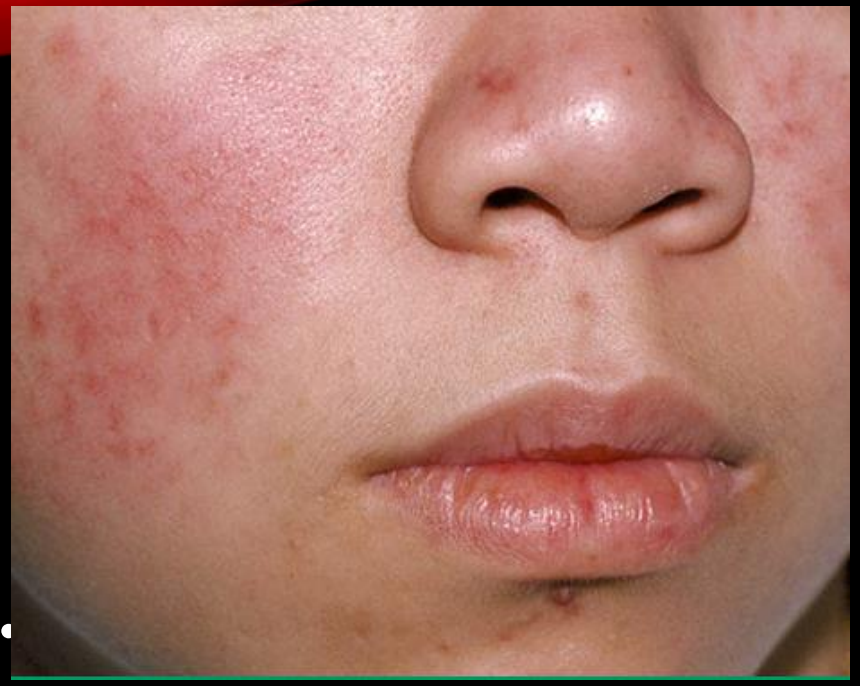
CASE 5

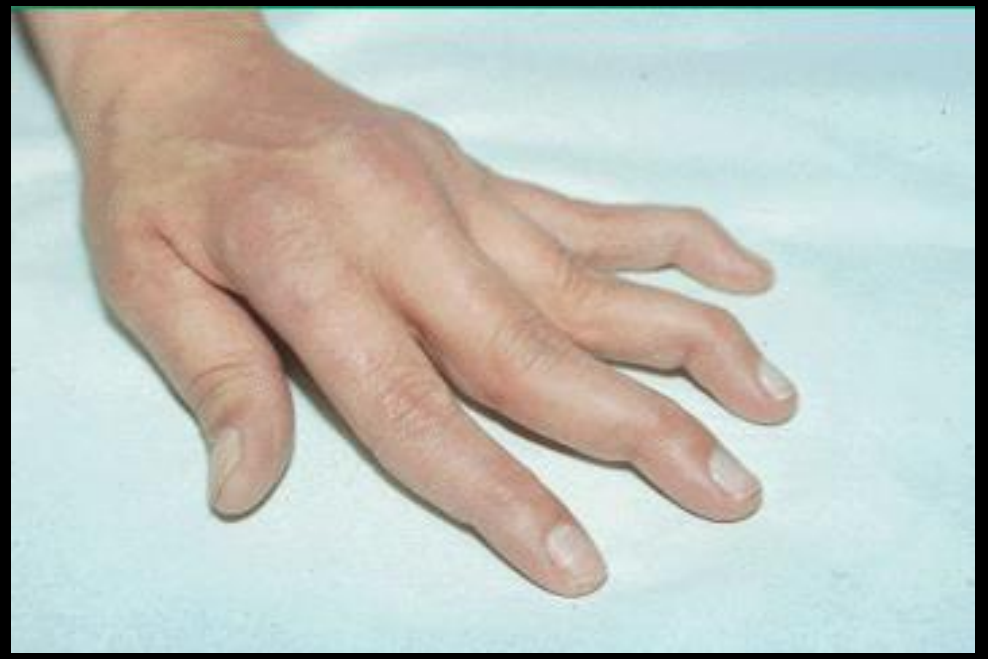
- 40 yo lady with severe seropositive anti CCP +ve rheumatoid arthritis
  - Poorly controlled despite Methotrexate 25 mg weekly, Sulfasalazine 1.5 g bd and Hydroxychloroquine 400 mg mane.
  - Polyarthritis
  - ESR 60
  - CRP 40
  - ANA, ENA and DsDNA -ve

  - Adalimumab 40 mg two weekly with resolution of polyarthritis, ESR 15 and CRP < 5
  - Sulfasalazine and Hydroxychloroquine ceased.

  - 12 months later
    - Increasing polyarthralgia and myalgia
    - Photosensitive rash - malar area, neck and upper chest
    - Mucositis and alopecia
    - Dyspnoea

CASE 5





- ANA 2560, ENA SSa and SSb +ve, DsDNA 60.
- Anti Histone +ve
- ESR 80, CRP 90
- CXR – small bilateral pleural effusion

CASE 5

- Diagnosis:
  - Adalimumab induced SLE

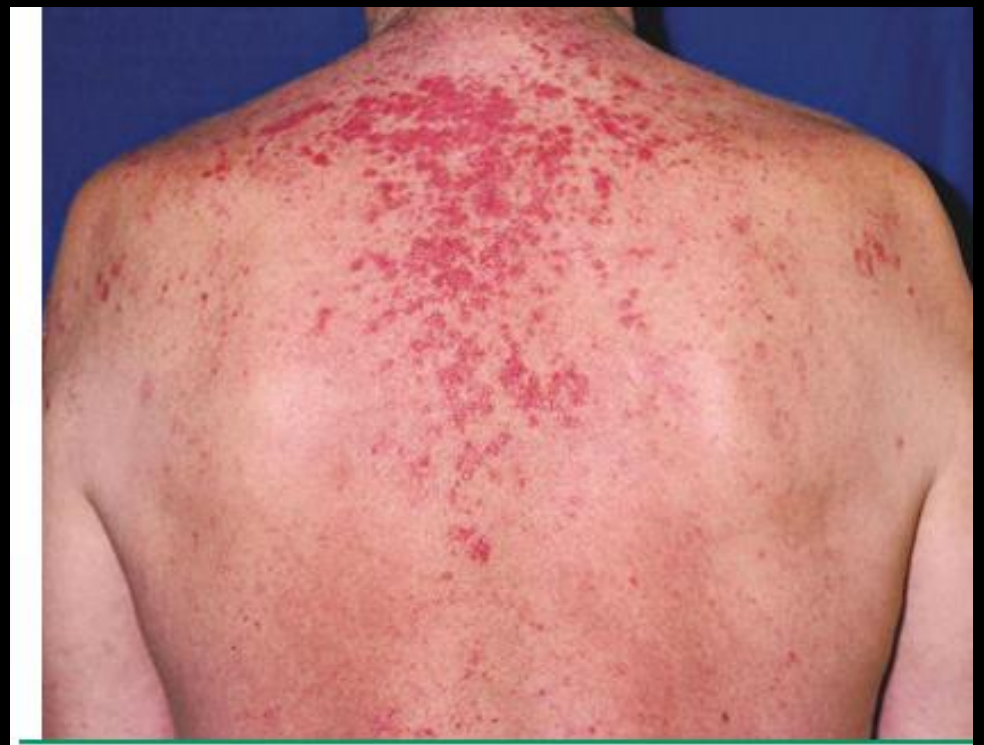
- Management:
  - Adalimumab ceased.
  - Prednisolone
  - Resolution of photosensitive rash, polyarthralgia and pleural effusion.
  - DsDNA return to normal.
  - ANA low +ve
  - Patient declined all DMARDs.

DRUG INDUCED CONNECTIVE TISSUE DISEASE: SYSTEMIC LUPUS ERYTHEMATOSUS

- Definite
  - Procainamide 1/3 drug induced lupus.
  - Hydralazine 5-10%
  - Minocycline 1 in 1000 patient exposed
  - Diltiazem
  - Penicillamine
  - Isoniazid – 15 % ANA +ve, lupus rare
  - Quinidine - rare
  - TNF alpha inhibitor (esp. Infliximab and Etanercept, Adalimumab) ANA 13-83%, anti DNA 3-32%,
  - Interferon alpha
  - Methyldopa
  - Chlorpromazine - rare
  - Practolol

DRUG INDUCED CONNECTIVE TISSUE DISEASE: DRUG INDUCED CUTANEOUS LUPUS

- Subacute cutaneous lupus
  - Hydrochlorothiazide
  - calcium channel blockers (e.g., diltiazem)
  - Angiotensin-converting enzyme inhibitors
  - Statins
  - Anti-TNF-alpha therapy
  - Proton-pump inhibitors



Multiple erythematous, scaly papules are present on the upper back.

Features of spontaneous and drug-induced lupus

Clinical feature	Idiopathic SLE	Drug-induced lupus
Gender predisposition (F:M)	9:1	1:1
Acetylation type	Slow = Fast	Slow (described for hydralazine and procainamide)
Symptom onset	Gradual	Abrupt
Usual age	20 to 40	Drug-dependent, tends to be older population than idiopathic (>50)*
Race	All	Less likely to occur in black patients
Fever/malaise	40 to 85 percent	40 to 50 percent
Arthralgias/arthritis	75 to 95 percent	80 to 95 percent
Rash (all)	50 to 70 percent	10 to 30 percent
Rash (discoid)	20 percent	Rare¶
Rash (malar/acute cutaneous)	42 percent	2 percent
Raynaud's	35 to 50 percent	<25 percent
Pleuritis/pleural effusion	16 to 60 percent	10 to 50 percent (procainamide)
Pulmonary infiltrates	0 to 10 percent	5 to 40 percent (procainamide)
Pericarditis	6 to 45 percent	2 to 18 percent
Hepatomegaly/splenomegaly	10 to 45 percent	5 to 25 percent
Renal involvement	30 to 50 percent	0 to 5 percent
CNS/neurologic involvement	25 to 70 percent	0 to 2 percent
Hematologic	Common	Unusual

FEATURES OF SPONTANEOUS AND DRUG INDUCED LUPUS

Laboratory feature	Idiopathic SLE	Drug-induced lupus
ANA	95 to 98 percent	95 to 100 percent
Anti-dsDNA	50 to 80 percent	<5 percent (rare)
Anti-Smith	20 to 30 percent	<5 percent (rare)
Anti-RNP	40 to 50 percent	20 percent
Anti-Ro/SS-A	30 to 40 percent	Uncertain[§]
Anti-histone	60 to 80 percent	90 to 95 percent[Δ]
Low complement levels	40 to 65 percent	Rare
Anemia	30 to 90 percent	0 to 46 percent
Leukopenia	35 to 66 percent	2 to 33 percent
Positive Coombs' test	18 to 65 percent	0 to 33 percent[◇]

DRUG INDUCED CONNECTIVE TISSUE DISEASE: SYSTEMIC LUPUS ERYTHEMATOSUS

- Management:
  - Stop the offending medication
  - Arthralgia, arthritis and serositis
    - NSAIDs
  - Cutaneous eruptions
    - Topical steroid
  - Severe manifestation
    - Systemic steroid
  - Persistent symptoms within 4-8 weeks
    - Hydroxychloroquine

CASE 6

- 36 yo lady with Grave's disease diagnosed Dec 2006
  - Propylthiouracil (PTU) 200 mg mane in May 2007
  - October 2009
    - Dark red haemorrhagic rash on ears, nose, inner thighs and cheeks
    - 2 mouth ulcers
    - Migratory polyarthralgia – knees, wrists, red swollen left elbow, sore feet and fingers
    - Blistering on finger PIPs, arms and legs.
  - PTU stopped end of Oct 2009
  - Investigations:
    - P-ANCA 2560 → 640 in May 2010
    - PR 3-ANCA 14 → improved to < 7 in Jan 2010.

  - Diagnosis: PTU induced ANCA vasculitis

DRUG INDUCED CONNECTIVE TISSUE DISEASE: ANCA VASCULITIS

- Strongest links:
  - Propylthiouracil
    - 27% MPO-ANCA +ve
    - Small proportion develop clinical vasculitis
    - Resolves with discontinuation of PTU
  - Hydralazine
    - Frequently associated with pauci-immune glomerulonephritis.
    - Anti DsDNA, MPO-ANCA
    - Withdrawal + immunosuppression
    - 9 out of 10 had renal involvement.
  - Minocycline
    - P-ANCA
    - Reversible polyarthralgia or arthritis, morning stiffness, livedo reticularis, occasional chronic active hepatitis.

DRUG INDUCED CONNECTIVE TISSUE DISEASE: ANCA VASCULITIS

- Management:
  - Mild case – withdrawal of offending agent
  - Severe case with lung and kidney involvement – withdrawal + steroid + cyclophosphamide

CASE 7

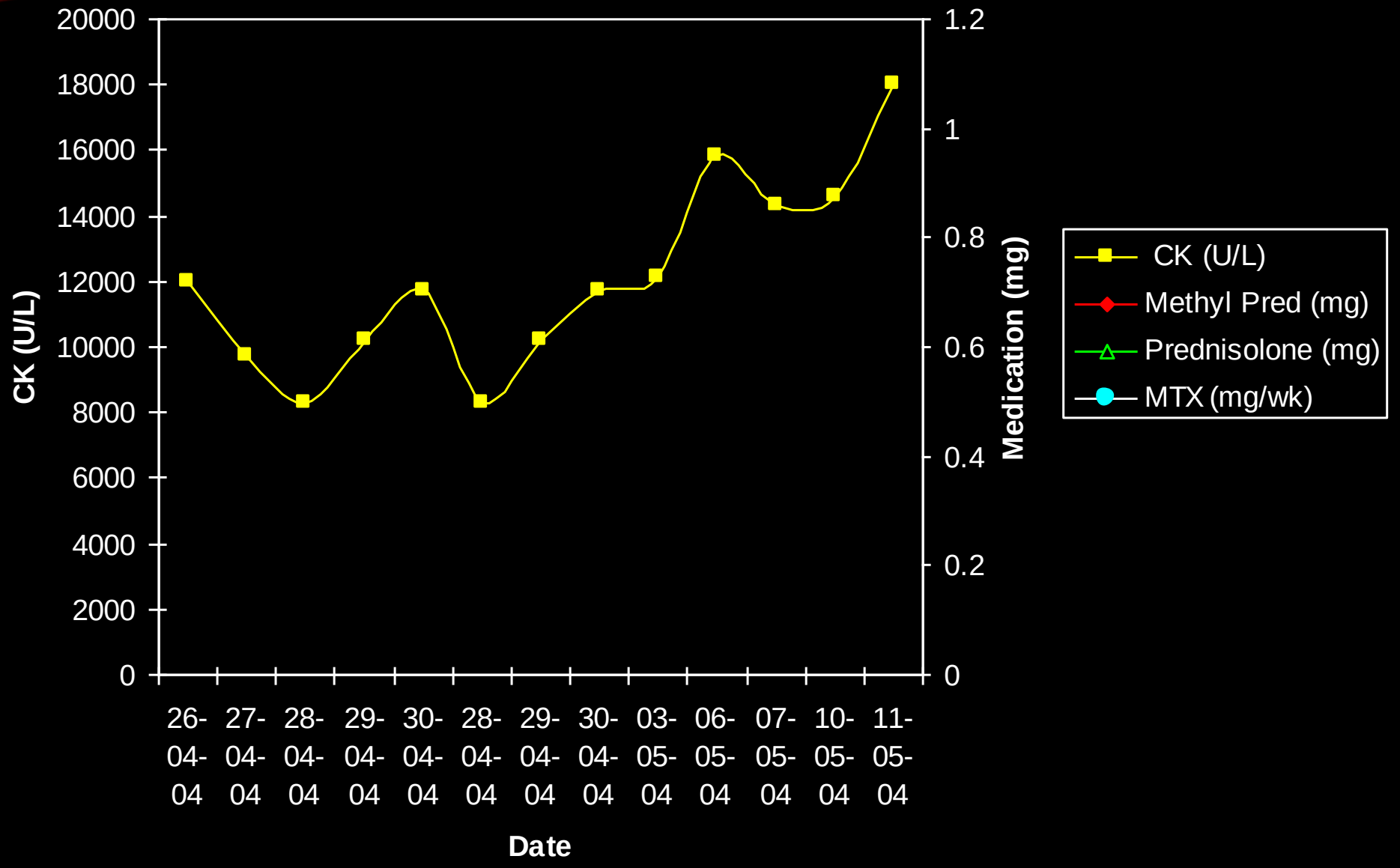
- 78 yo polish lady,
  - Medical hx:
    - HT - amlodipine
    - Hypercholesterolaemia – atorvastatin x 5 yrs
    - previous PE – warfarin
  - Gradual progression of myalgia.
  - Low back pain
    - Worse with walking
  - Bilateral leg pain
    - " all over legs"
    - Esp. calves / thighs
    - Partly eased by resting
  - Bilateral Shoulder pain

CASE 7

- Examination:
  - Proximal myopathy – UL / LL proximal power 4
  - no facial muscle involvement
  - Proximal LL tender

- Investigation:
    - TFT NAD
    - CRP 11
    - ESR 30
    - Urine Myoglobin 2920
    - Creat NAD K 3.7

CASE 7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06-05-04
07-05-04
10-05-04
11-05-04
Date
CK (U/L)
Methyl Pred (mg)
Prednisolone (mg)
MTX (mg/wk)

CASE 7

- Mx:
  - Atorvastatin stopped
  - Malignancy screen
  - Analgesia
  - DVT prophylaxis
  - Awaiting MRI & muscle bx

- D 12 post admission
  - CK ↑ 15800
  - Ongoing pain
  - Creatinine 0.20
  - Dysphagia

- D 16
  - CK ↑ 18000
  - Progression of proximal LL + UL weakness
  - Hip flexion 2+/5
  - Unable to abduct shoulder

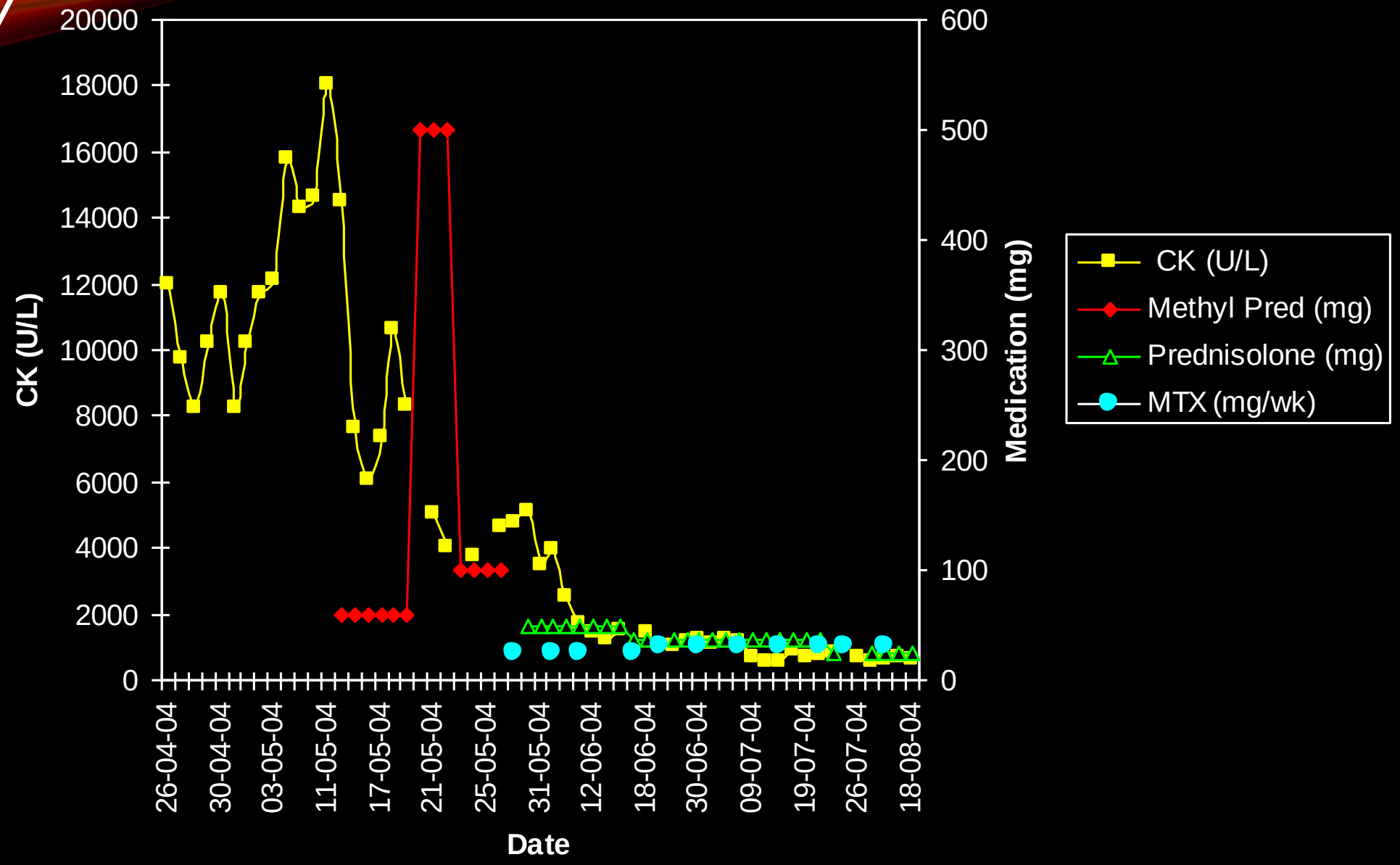
CASE 7

- D 18
  - Unable to hold arms or legs against gravity
  - Barium swallow → pooling & aspiration → NG feeding
  - Quadricep muscle bx – Necrotising myopathy
  - IV Methylprednisolone 1 g/daily x 5 days, then Prednisolone 60 mg daily
  - Methotrexate 10 then 20 mg weekly
  - CK (13/5) 14500 → CK (15/5) 7650

- D 24
  - Improvement of muscle strength.
  - Rehab

- DDx:
  - Necrotising myopathy
  - Rhabdomyolysis secondary to Atorvastatin

CASE 7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26-07-04
18-08-04
Date
CK (U/L)
Methyl Pred (mg)
Prednisolone (mg)
MTX (mg/wk)

DRUG INDUCED MYOPATHIES

- Statin myopathy
  - Myalgia
    - Muscle discomfort with normal CK
  - Myopathy
    - Muscle weakness with or without CK elevation
  - Myositis
    - Muscle inflammation
  - Myonecrosis 0.5%
    - Muscle enzyme elevation
      - Mild - 3-10 fold
      - Moderate 10-50 fold
      - Severe 50 fold
  - Clinical rhabdomyolysis 0.1%
    - Myonecrosis, acute renal failure, myoglobinuria

2-11%

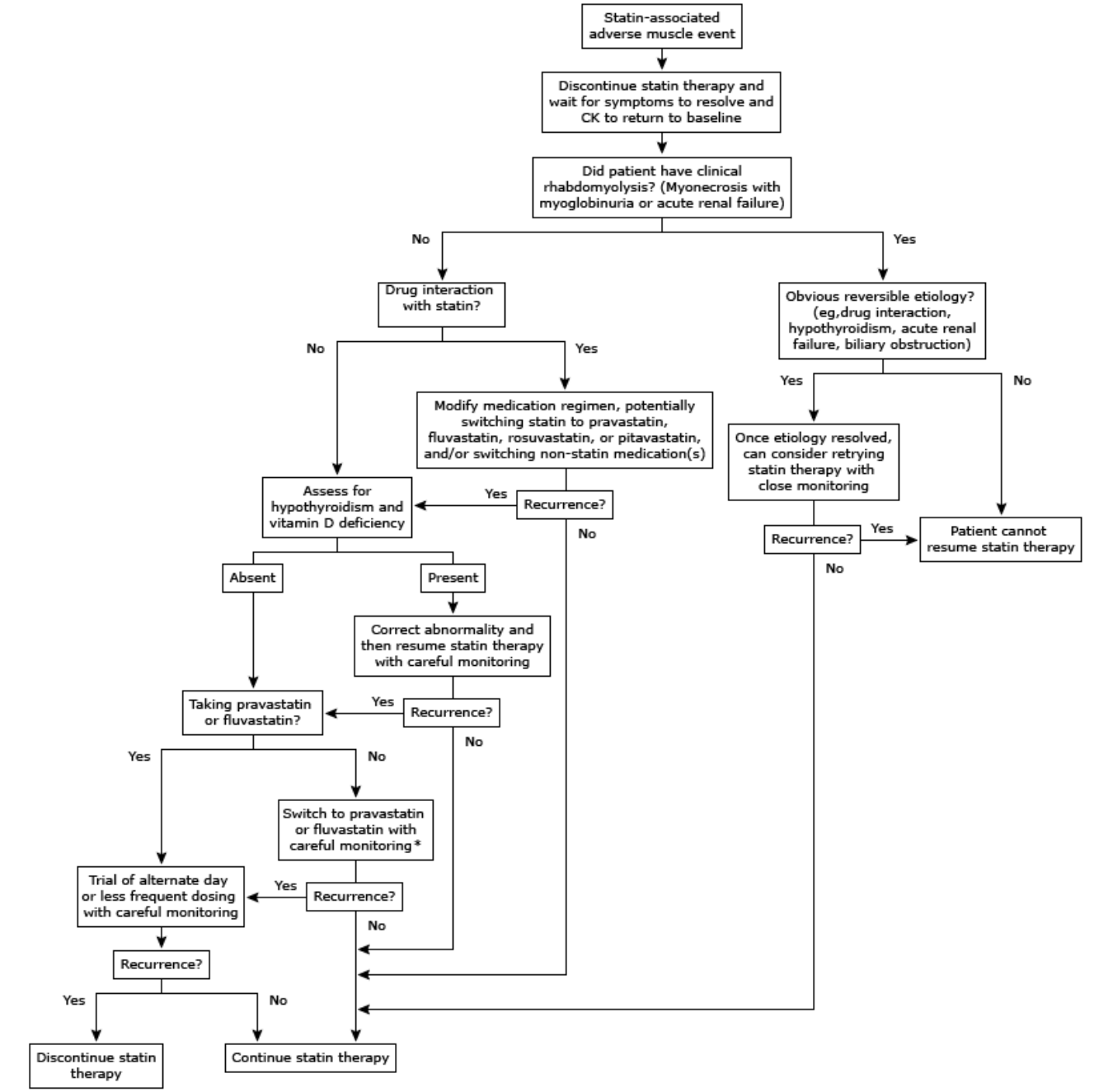
DRUG INDUCED MYOPATHIES

- Statin myopathy
  - Myalgia
    - Atorvastatin 80 mg daily 9.3% vs Placebo 4.6%
  - Clinically myonecrosis : CK >10 + muscle symptom.
    - < 0.5 %
  - Rhabdomyolysis
    - Primarily
      - Statin + cyclosporin, gemfibrozil, protease inhibitor

DRUG INDUCED MYOPATHIES

- Statin myopathy
  - Risk factor
    - Statin characteristics:
      - Lowest risk - pravastatin and fluvastatin – more hydrophilic, less drug interaction (not extensively metabolised by CYP3A4).
    - Underlying neuromuscular disorder
    - Hypothyroidism, acute or chronic renal failure and obstructive liver disease.
    - Patient characteristics.
      - Genetic factors
      - Chinese vs European -
        - Simvastatin 40 mg mane – 1.3% vs 0.4%.
        - increased statin myopathy if Simvastatin > 20 mg daily combined with niacin
      - Advanced age > 80 yo, female, small body frame, decompensated liver disease, severe renal disease.

Management of statin myopathy



DRUG INDUCED MYOPATHIES

- Statin myopathy
  - Management:
    - Discontinue if significant muscle toxicity.
    - Assess for drug interactions
    - Assess for vitamin D deficiency and hypothyroidism
    - If no drug interactions, appropriate levels of vitamin D and thyroid hormone, & the patient was on a statin other than pravastatin or fluvastatin
      - switch therapy to pravastatin or fluvastatin with careful monitoring

SUMMARY:

- Drugs should be considered as the potential cause when patients present with:
  - articular and periarticular disorders
  - myalgia
  - multisystem manifestations.
- Failure to recognise drug-induced disorders will lead to delay in diagnosis and prolonged morbidity.
- Symptoms frequently disappear when offending drug is stopped.