Common Haematology referrals/advice questions

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Topics covered

- 1. Anaemia (skipping iron deficiency)
- 2. Neutropenia
- 3. Thrombocytosis
- 4. Thrombocytopenia
- 5. Monoclonal proteins
- 6. Lymphocytosis
- 7. Leukocytosis
- 8. Coagulation

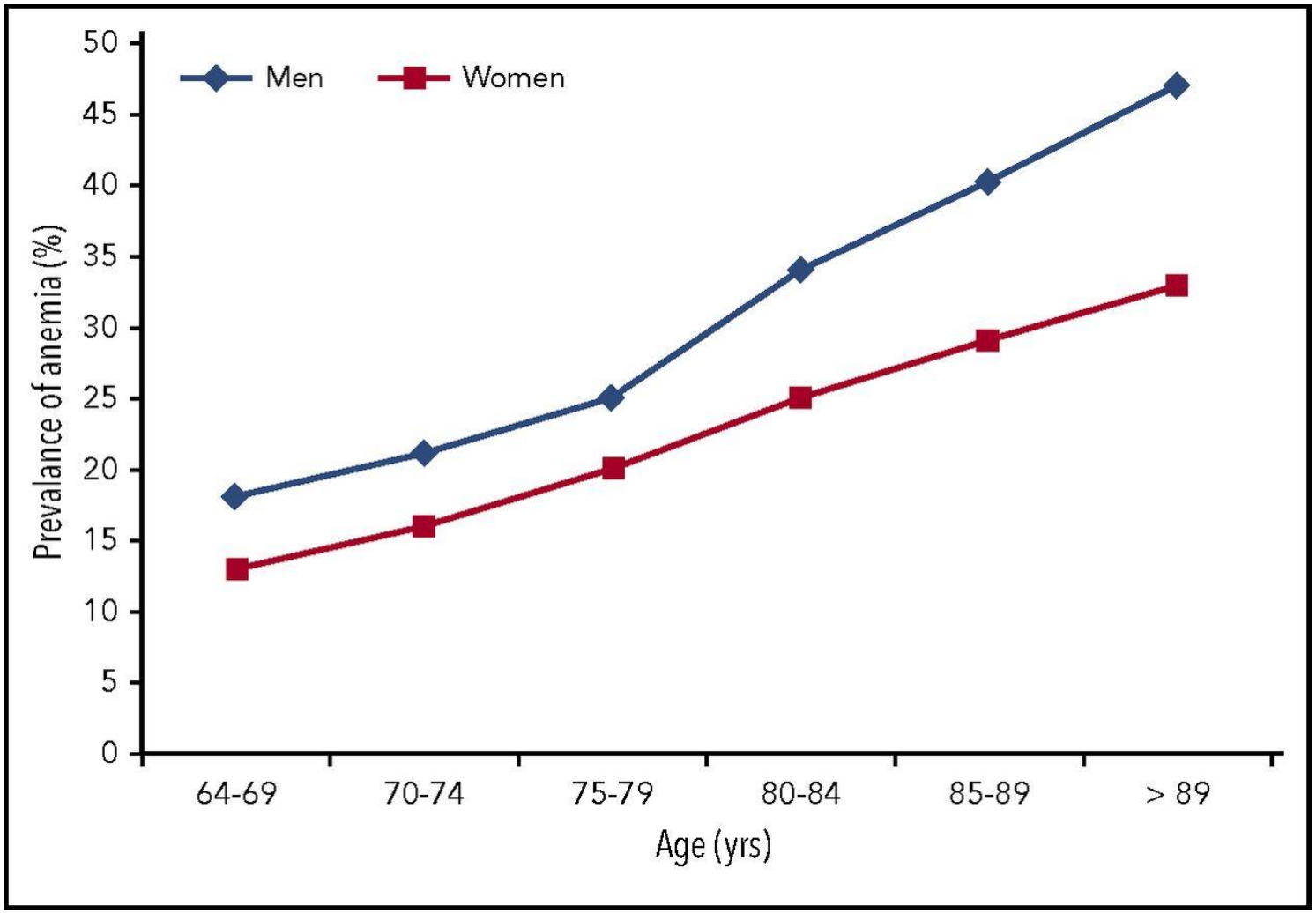
- Not covered but can discuss; clotting bits and bobs, cancer, low platelets, polycythaemia etc.

- **<u>Please ask questions as we go along!</u>**

Common problem, common referral

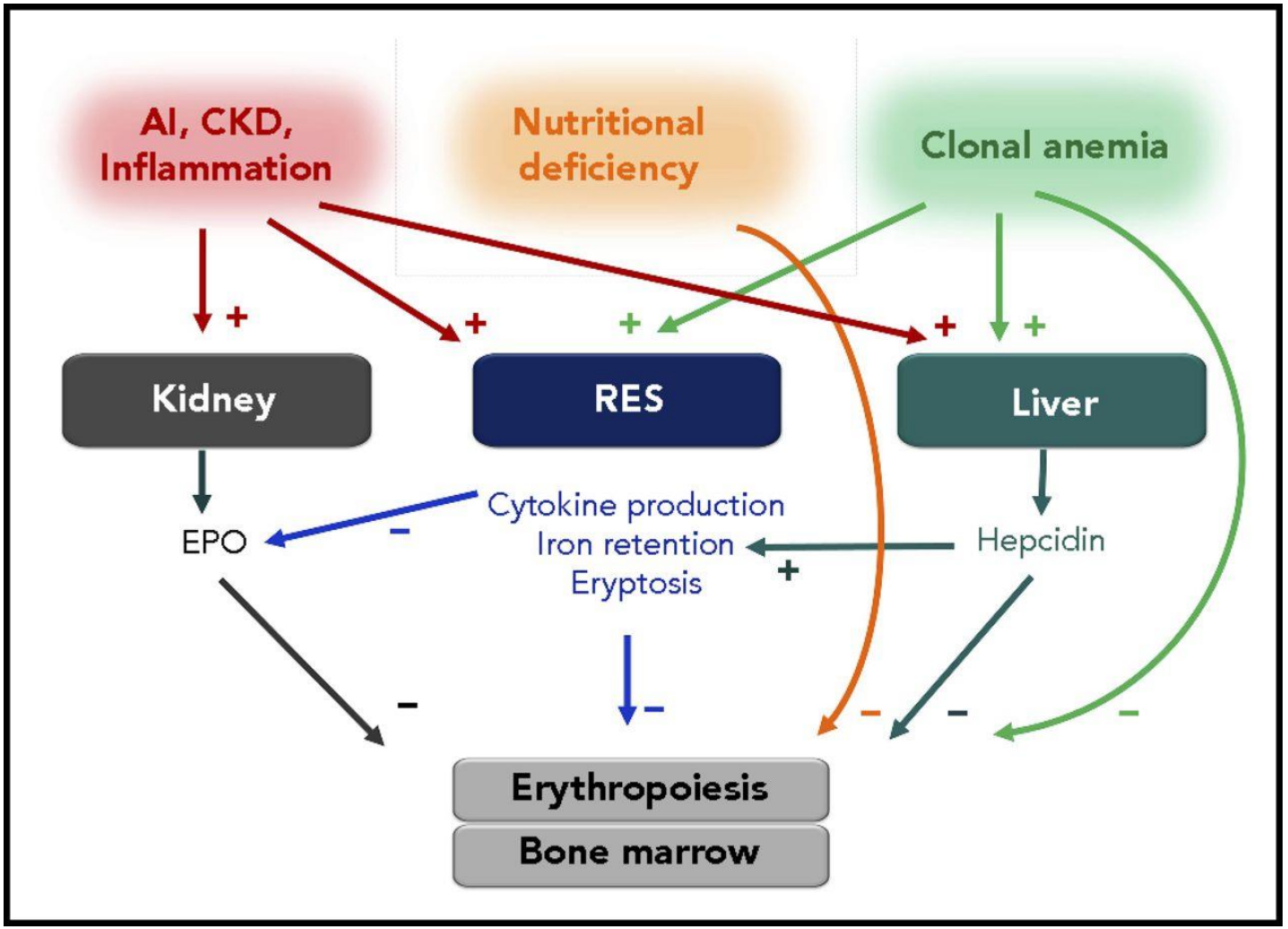
- Prevalence 17% age >65 years
- Defined by WHO Hb <130g/l men, <120g/l women
- Only minority have primary haematological disorder
- Emerging concept of ‘inflammaging’

Increase in prevalence of late-life anemia.



Reinhard Stauder et al. Blood 2018;131:505-514

Possible mechanisms of anemia in older adults.



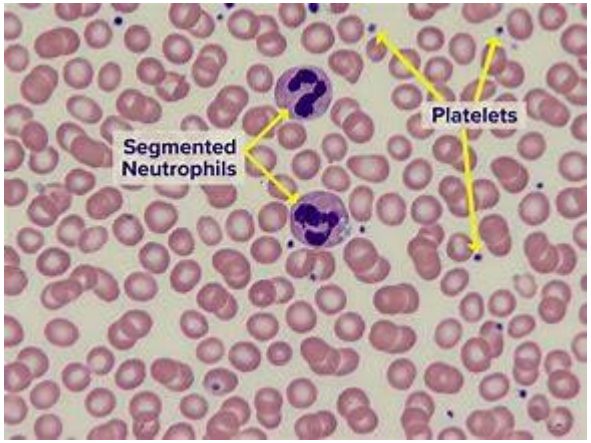
Reinhard Stauder et al. Blood 2018;131:505-514

Case 1

86 year old male

Attends surgery main complaint ‘tired’

Nil on physical examination



<u>PMH</u>

Diabetes

COPD

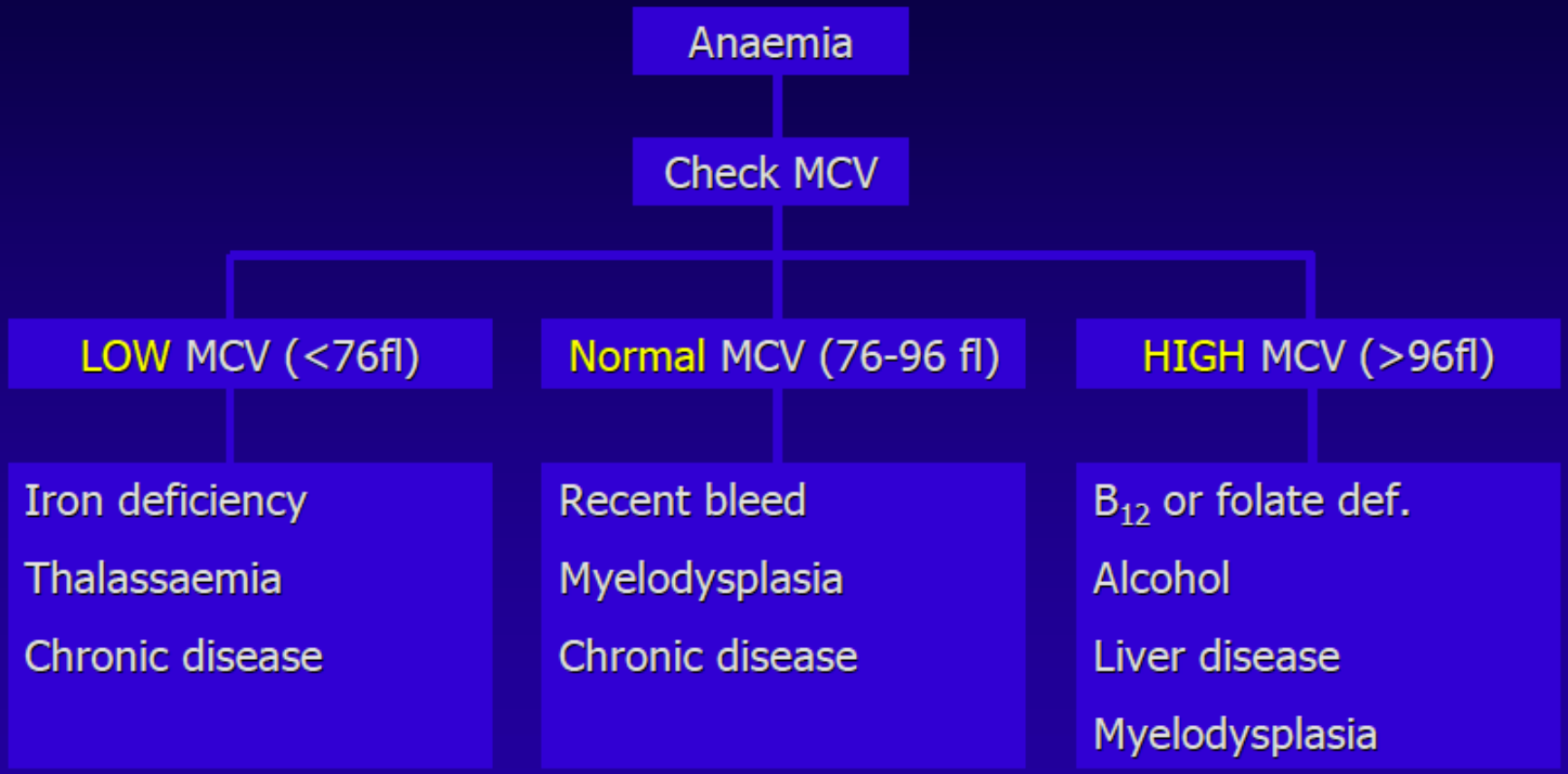
CKD3

<u>Blood film</u>

Unremarkable, normocytic anaemia. HB 103g/l, Normal morphology.

Film courtesy of LabTestsOnline.org

Pragmatic classification of anaemia (MCV)



Case 1

- Review in haem clinic
- Anaemia since 2012
- No LN or organomegaly on examination

<u>Additional tests performed in clinic</u>

- EPO, Reticulocytes, Haptoglobin, Protein and Urine Electrophoresis
- Results-Normal

- Impression; Anaemia of Chronic Disease
  Unlikely to be cause of tiredness as anaemia predates symptoms

Normal EPO often found in diabetics/CKD, blunted response to anaemia.

Features of Unexplained Anaemia

Semin Hematol. 2008 Oct; 45(4): 250–254.

Hemoglobin	10.5–12 g/dL
Reticulocyte index	Low
Mean corpuscular volume (MCV)	80–95 fL
Platelet and white blood cell counts	Normal
Peripheral smear	No dysplastic features
Serum iron	Mildly low or normal
Total iron binding capacity (TIBC)	Normal
% Iron saturation	Mildly low or normal
Serum levels of vitamin B_{12} and folic acid	Normal
Serum level of thyroid-stimulating hormone (TSH)	Normal
Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)	Normal
Serum erythropoietin level	Not elevated
Creatinine clearance	>30 to <90 mL/min

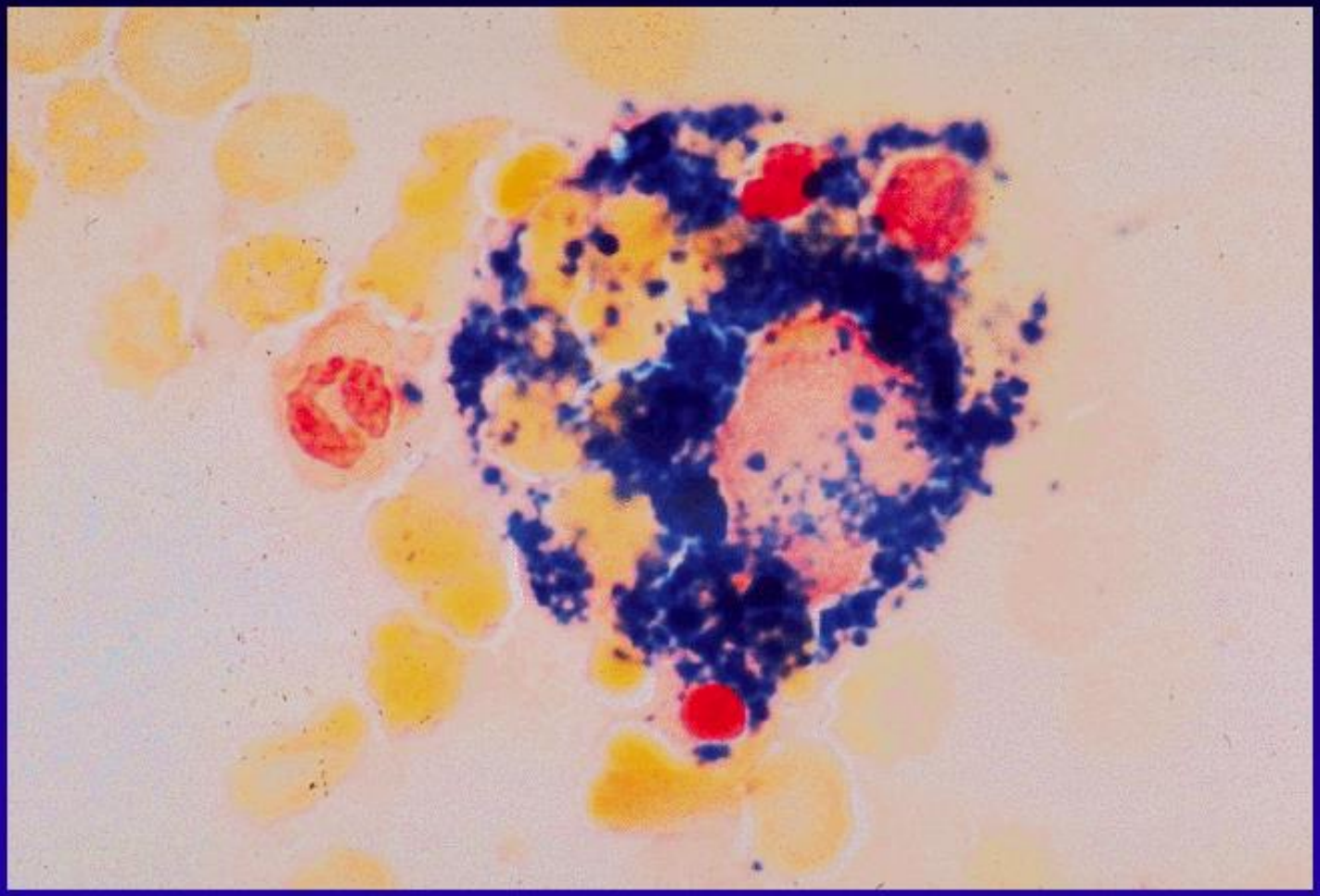
Anaemia of Chronic Disease

- Common
- Often normocytic, can be microcytic if chronic inflammation
- Haematinics normal
- Associated with Polypharmacy, CKD, Diabetes, chronic inflammation (leg ulcers etc.), heart failure (can fluctuate as plasma expands and contracts in response to diuretic therapy)

Marrow biopsy?

- WHO cytopenias as **Hb <100, Platelets <100, Neutrophils <1.8**
- ***'Cytopenia is 'sine qua non' for any MDS diagnosis. A diagnosis of MDS may be made in rare cases with milder levels of cytopenia, but at least 1 cytopenia must be present in order to make the diagnosis'***

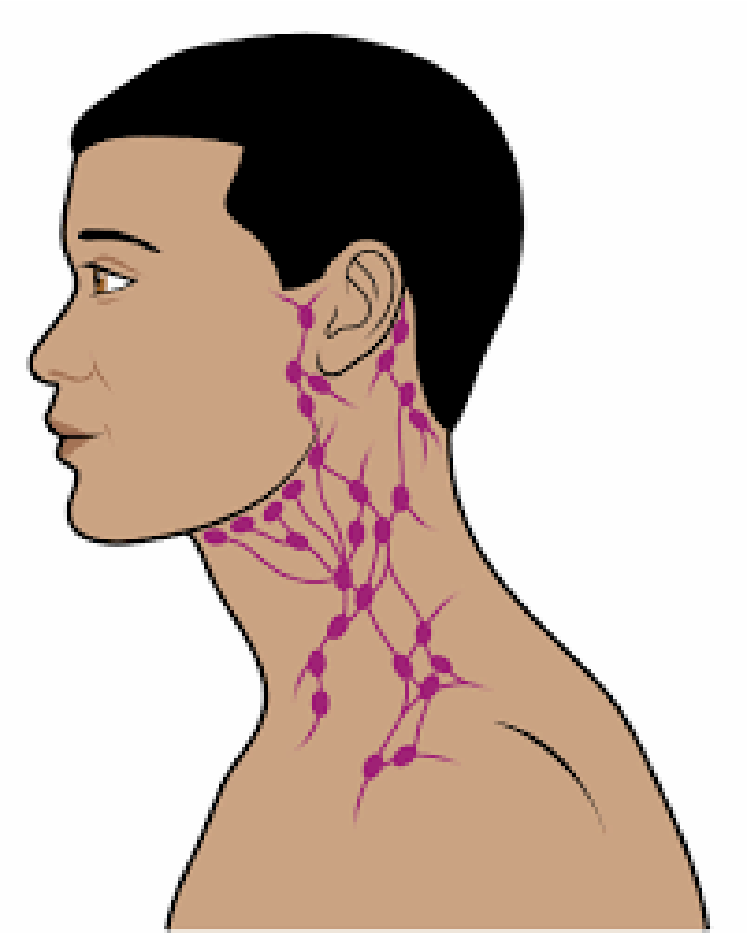
Anaemia of chronic disease: iron maldistribution



Bone marrow macrophages fail to release iron (blue) to developing RBCs

Category and Subtype	Specific Examples
Chronic inflammation	Rheumatoid, PMR, Chronic infections Chronic inflammation (leg ulcers etc)
Non-Haem Cancers	GI Tract Metastatic Disease Marrow metastasis (breast, prostate etc)
Endocrine/metabolic	Low EPO (Renal disease, Diabetes Thyroid Dysfunction
Blood Loss	Anticoagulant/NSAIDs Haemturia
Consumption of Red Cells	Immune Hypersplenism Valve lysis (artifical heart valves)
Nutrient deficiency	B12/Folate/Ferritin Copper
Drug Induced	Chemotherapy Folate (e.g. Methotrexate, anti-convulsants) Drug induced haemloysis
Haematological	**Infiltration (leukaemia, myeloma etc)** **Fibrosis** **Myelodysplasia**

Lymph nodes



Lymph nodes and sweats

Not going to talk much about lymph nodes

-progressive enlargement

-more than one place

-odd places (posterior triangle of the neck, supraclavicular fossa etc)

-no obvious reactive cause

- **Case 4**

- 34 year old woman 2-3 cm persistent groin node
- Not unwell, but anxious
- No B-symptoms (weight loss, sweats)

Lymph nodes

- Inflammatory markers Normal
- Routine bloods normal

- US→ reactive node with normal fatty hilum on US

- ? What next

- Not lymphoma so discharged back to GP

Common scenario

Lymph nodes seen in haem clinic

Causes of reactive LN (last few years)

- TB (hot node)
- Cat scratch disease (tricky)
- Dental abscess (anterior cervical/submental)
- Syphilis (Groin)
- Acute EBV infection (neck)
- Severe Eczema (everywhere, the skin was really bad)

Other pathological causes

- Lung cancer (also had a reactive thrombocytosis)
- CUP (axilla)
- Penile cancer (groin)
- Skin Cancer (groin)
- Gynaecological cancer (groin)

What I do

- Standard bloods (FBC/Renal/Liver/calcium/immunoglobulins)
- History
  - Sweats-drenching, recent onset, nocturnal
  - Fatigue
  - Weight loss
  - Examination
  - **Decision**-if I think reactive then US of affected area, reassurance
  - If I think pathological CT and US with a view to biopsy.

  - Reactive nodes. Reactive cause present, soft, mobile, occasionally tender, fluctuate in size, small (1-2cm diameter)

Sweats (no LN)

- If accompanied by weight loss and systemic upset

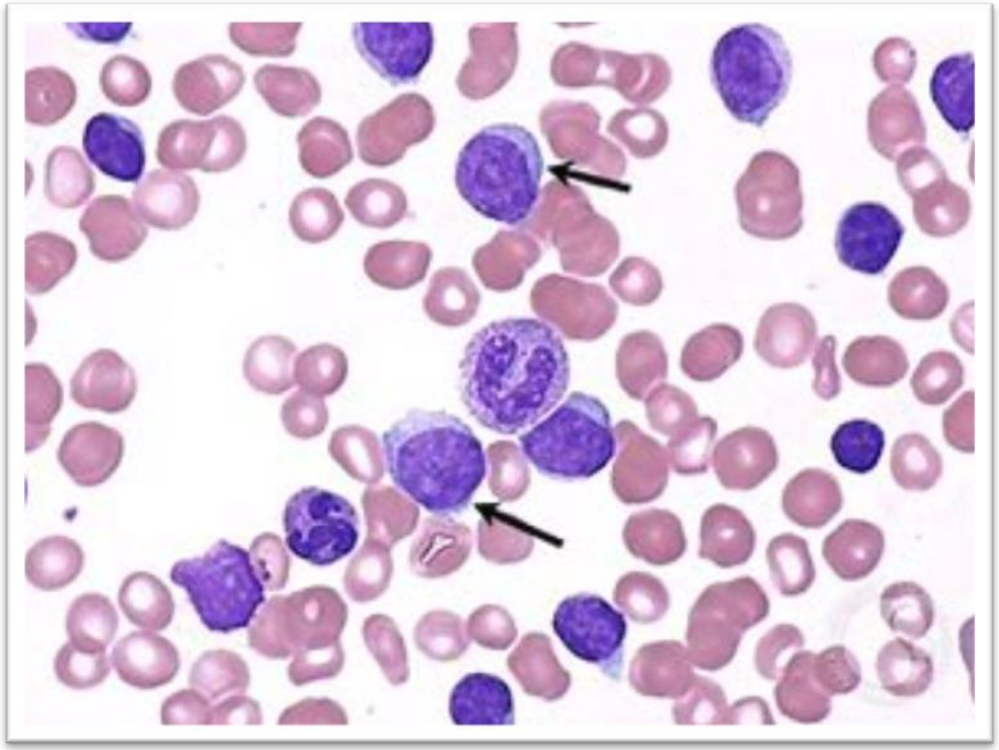
  → CT scan

If patient otherwise well with no symptoms, then often get a CT anyway

(I try to avoid in younger women CXR/US abdomen if low clinical suspicion, not good a retro-peritoneal disease)

- SSRI medication
- Diabetes
- Infection (endocarditis/TB nocturnal sweats)
- Endocrine
- Phaeochromacytoma
- Alcohol
- Acromegaly
- Thyrotoxicosis
- Anxiety

Lymphocytosis



Incidental Lymphocytosis

Common reactive cause of low level lymphocytosis (typically <10)

-Smoking (usually polyclonal T-cells)

-Viral infections, post-splenectomy, TB, whooping cough etc.

New(ish) concept of ‘

Monoclonal B-Cell Lymphocytosis Undetermined Significance’

-Clonal B cells found

-Insufficient quantity to provide a diagnosis of CLL (need >$5x10^9$ clonal lymphocytes in blood)

-Prefer to diagnose CLL if possible

Incidental Lymphocytosis

Common

Majority are incidental finding in otherwise well patients

1. Lymphocytes >10→refer to haematology (routine OPD, not 2WW)

2. Lymphocytes 3.5-10 in absence of LN, organomegaly, B symptoms→ repeat in 3-6 months. If persist at same level repeat at yearly

3. Lymphocytes 3.5-10 in presence of LN, organomegaly, B symptoms → refer to haem

4. If clinical concern, discuss/e-advice haematology.

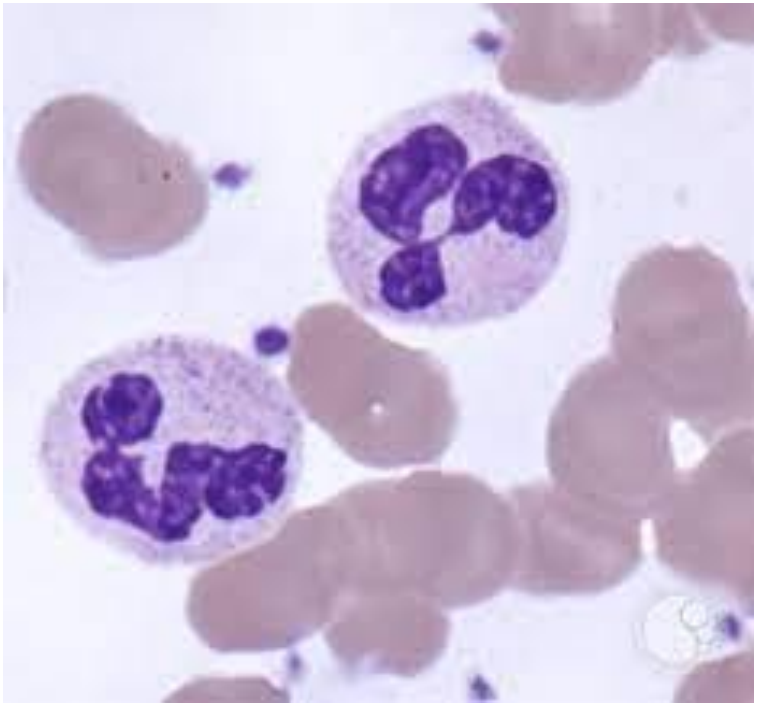
Neutropenia

Case 2

- 24 year old man, new to practice. FBC performed. Neutrophils 1.2.
- Rest of FBC normal.

Categories of neutrophils

- Mild: neutrophils 1.0 - 1.5
- Moderate: neutrophils 0.5 – 1.0
- Severe: neutrophils <0.5



Case 2

Repeated sample 2 weeks later

- Neutrophil 1.2, Hb and platelets normal

- Transient neutropenia common, often due to viral infection. Usually resolve in 2-3 weeks. But can persist for months…

- Persistent neutropenia more tricky….

Case 2

- Investigations

- Repeat FBC and Film
- Clinical details (patient ethnicity important)
- Haematinics
- Monospot if recent viral infection/atypical lymphocytes present
- Autoantibody screen
- Screen for new medications added and cross-reference with BNF or Pharmacist

- If patient ‘unwell’ or pyrexial send to hospital

Case 2

1. Viral infections

EBV, HIV, hepatitis viruses

2. Autoimmuine disorders

SLE, Rheumatoid Arthritis

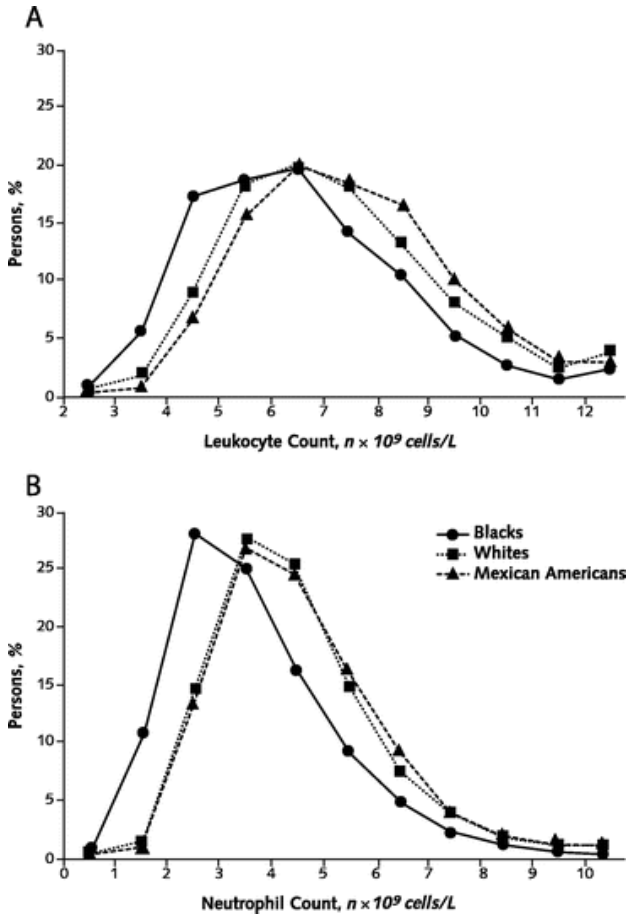
3. Drugs

Lansoprazole, Clopidogrel

4. Splenomegaly (including due to liver disease)

5. Haematological diseases

Myelodysplasia, leukaemia, lymphoma, myeloma, B12/folate deficiency etc.)



Prevalence of Neutropenia in the U.S. Population: Age, Sex, Smoking Status, and Ethnic Differences. Matthew M. Hsieh Annals of Internal Medicine April 2007.

Case 2

Case 2

Recent arrival from East Africa, first visit to GP. Morphologically normal neutrophils. Likely ethnic variation

Ethnic Variation

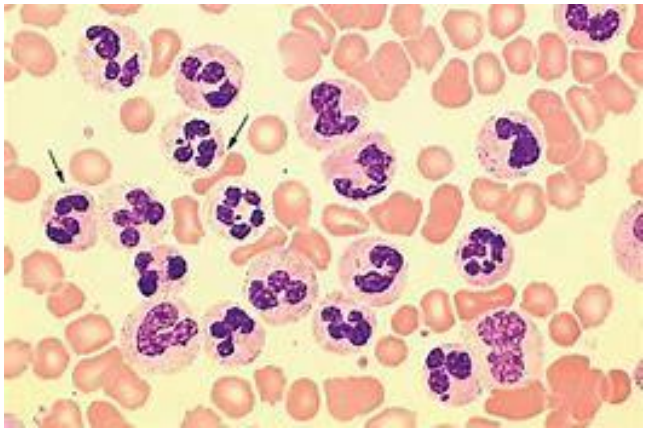
Neutrophils usually >1.0

Common in patients with middle eastern or African ancestry

Benign

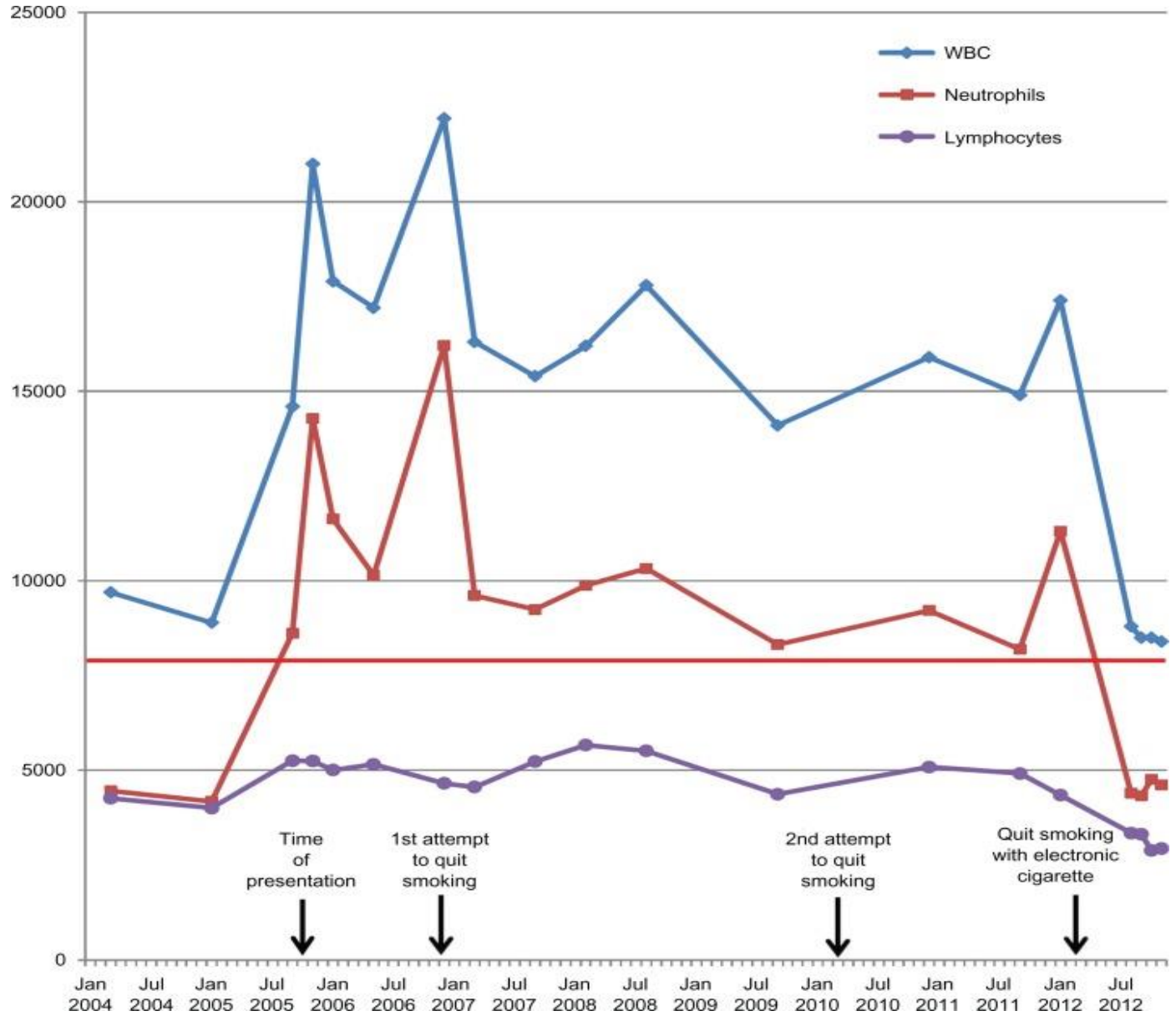
Neutrophilia

- Common as well!
  - Infection
  - Inflammation
  - Smoking
  - Steroids
  - Obesity?



  - Primary haematology?
  - **If** progressive rise in neutrophils, normal CRP, other components of FBC abnormal
  - If Blood Film report recommends referral (clinical details important!)
  - **Splenomegaly**

Clues that something else…persistent **monocytosis** and or **basophilia**



Clin Med Insights Case Rep. 2013; 6: 15–21

Case 3

- Chronic Fatigue, recently worse

- Patient acquired an allotment, lumbar pain and tiredness
- PMH; Diabetes, CKD3
- FBC → normocytic anaemia
- Creatinine →128 (baseline for patient 100)
- Bone Profile → Calcium Normal, Globulin/Total Protein raised
- No BJP, IgG paraprotein of 6g/l present….

- Referral to haematology…

Further Test Results

- IgG paraprotein 6g/l, No BJP, no immunoparesis
- No lytic lesion on Skeletal Survey X-ray
- Creatinine returned to normal following cessation of NSAIDs
- Anaemia stable for past 6 years

- Diagnosis MGUS (Monoclonal Gammopathy of Undetermined Significance)

What is MGUS?

- Monoclonal gammopathy of undetermined significance, or ‘MGUS’, is a **benign (non-cancerous) condition**. MGUS **does not cause any symptoms** and is usually diagnosed incidentally when tests are performed to investigate other problems. It does not require any treatment.

- In MGUS, abnormal plasma cells in the bone marrow release an abnormal protein, known as paraprotein. MGUS is characterised by the presence of this abnormal protein in the blood and/or urine.

- While most MGUS patients have a stable condition which has no effect on their general health, a small proportion of patients will go on to develop a cancer called myeloma. MGUS can also progress to other conditions such as Waldenström’s macroglobulinaemia, AL amyloidosis or lymphoma.

Taken from patient information Myeloma UK

MGUS

MGUS high prevalence in the general population (about 3% of people ≥50 years old have been diagnosed). Prevalence increases with age (there will be quite a few patients with this in your nursing homes)

Persistent risk of progression, its known causal association with several serious non-malignant disorders, and the high frequency with which coincidental associations are detected

Clinical features of MGUS

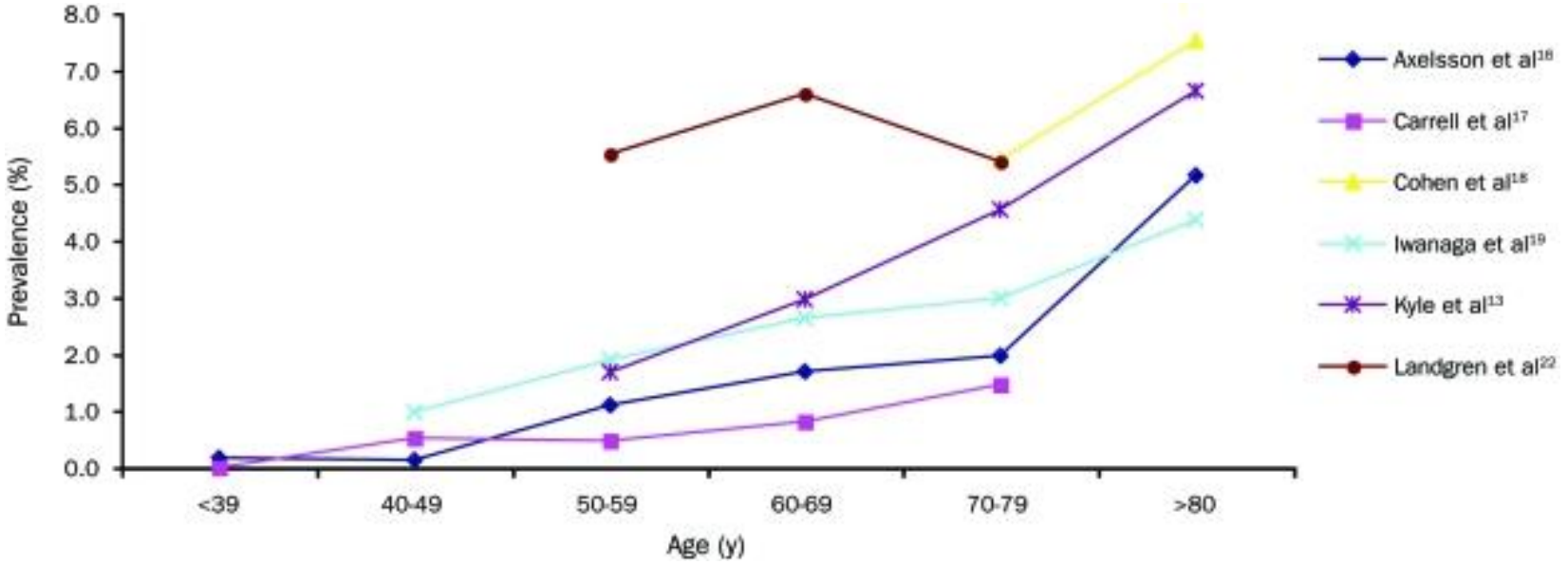
- No symptoms / signs
- Often Incidental chance finding
- Can progress; Myeloma, Lymphoma, amyloid, CLL, Plasmacytoma etc.

Overall risk of progression 1% per year. The risk remains even after 25 years

N Engl J Med. 2002 Feb 21;346(8):564-9

- How to monitor?

Prevalence MGUS with age



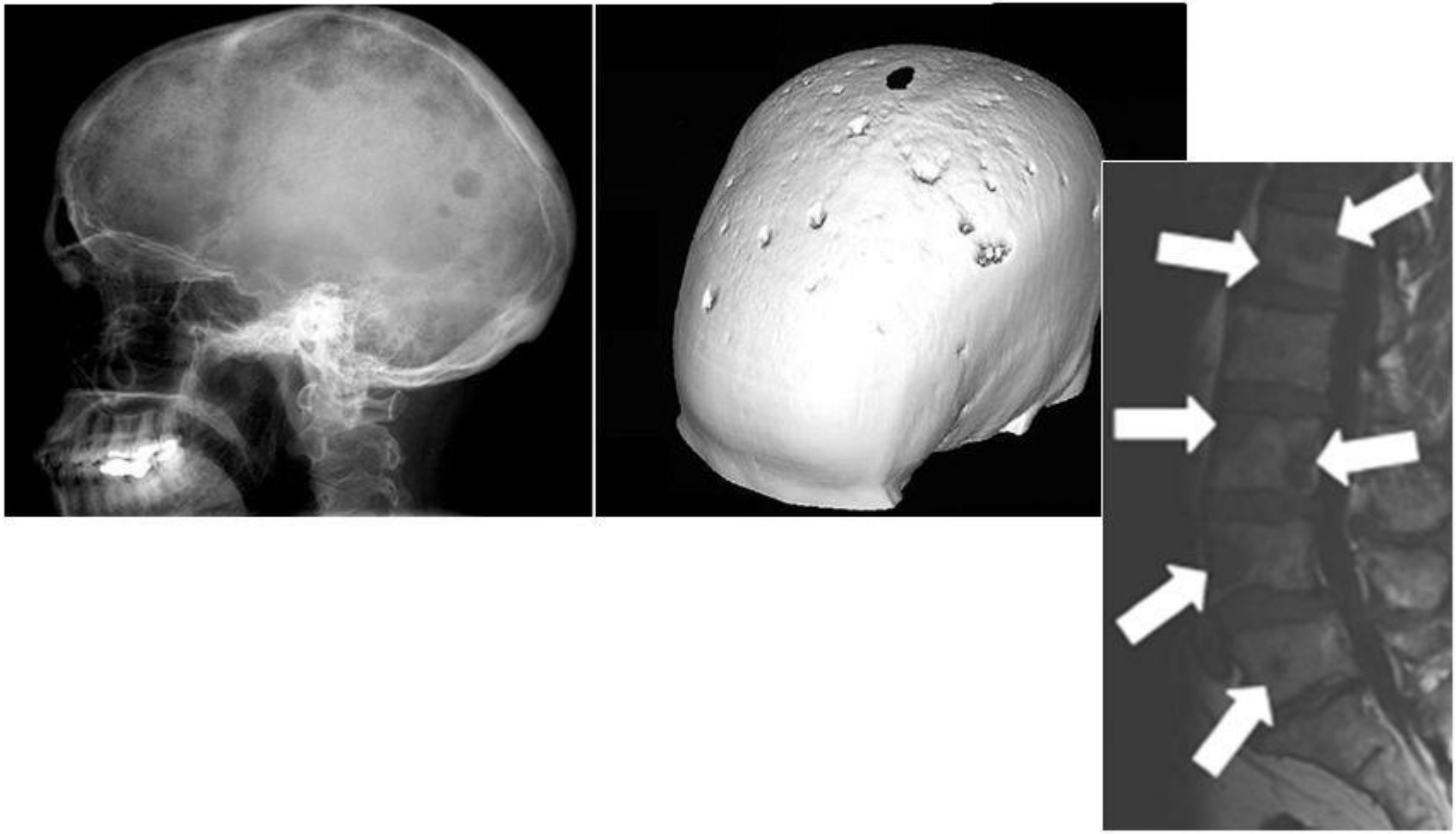
Taken from Mayo Clin Proc. 2010 Oct; 85(10): 933–942.

Monitoring ….

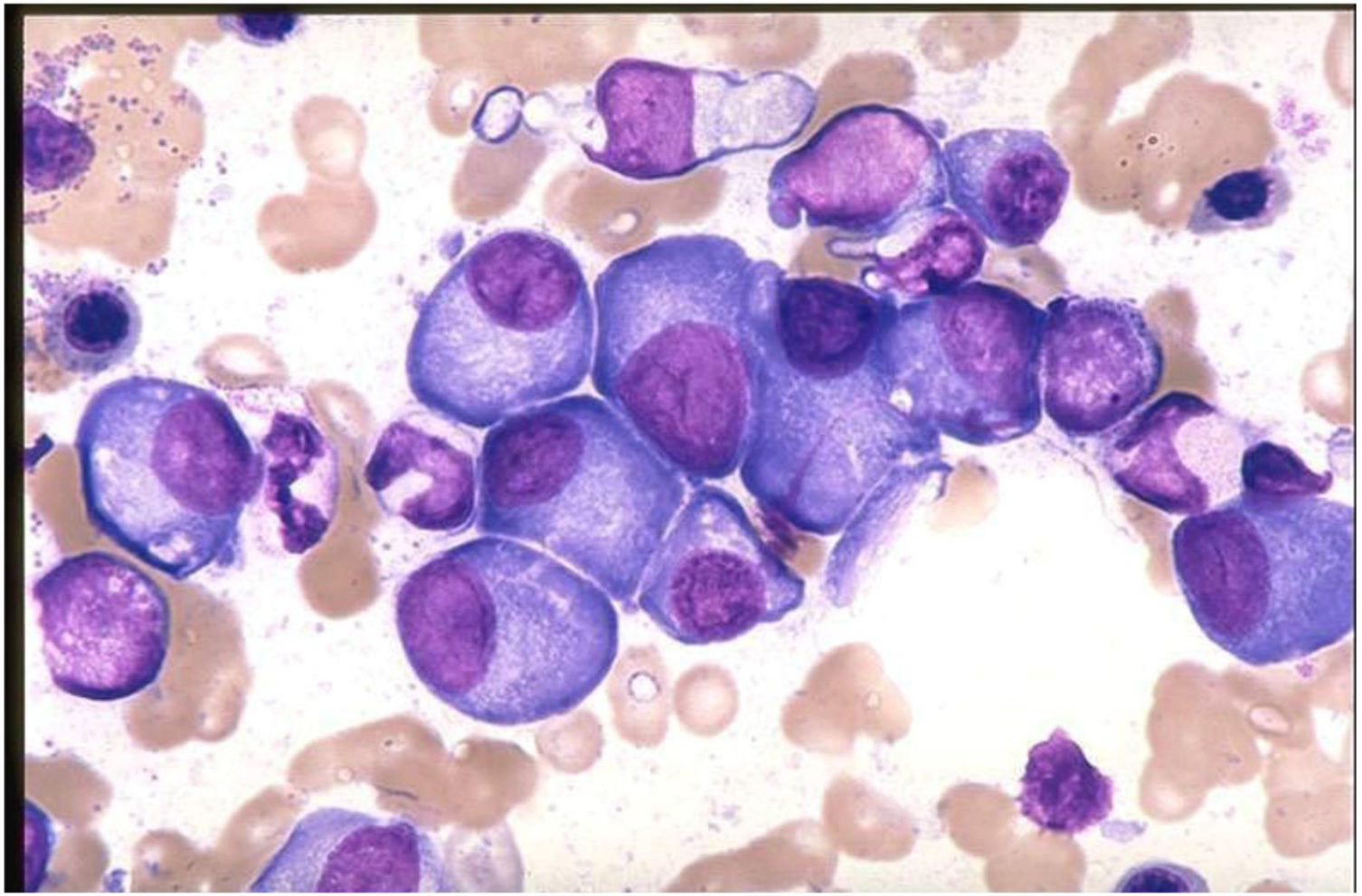
- I tend to try and keep ‘higher risk MGUS’ in clinic

MGUS risk/recommended tests	*UK Myeloma Forum/Nordic Study Group (2009)*[14]	*International Expert Consensus (2010)*[16]	*International Myeloma Working Group (2010)*[15]	*European Myeloma Network (2014)*[17]
Low-risk MGUS (IgG, <15 gm/L, and normal FLC ratio)	First year, every 3-4 mo; then every **6-12 mo** if stable	First 2 y, every 4-6 mo; then every **6-24 mo**	At 6 mo; then every 2-3 y if stable	At 6 mo; then every 1-2 y if stable or no follow-up

Multiple myeloma: lytic bone lesions



Hillengass and Landgren. *Leuk Lymphoma 2013*



Myeloma

Monoclone/Paraprotein

- Typically found as part of ‘routine screening tests’
- **Usually Benign but need to think about Myeloma and Lymphoma**

When to go looking for it?

- Liver function raised Globulin and Total Protein often a clue
- Raised calcium
- Unexplained deterioration in renal function
- Unexplained anaemia often normocytic
- New bone pain (back, ribs seem to usually symptomatic)
- **C**alcium, **R**enal, **A**naemia, **B**one destruction/pain (**CRAB**)

- Or lymphadenopathy, persistent lymphocytosis, organomegaly ?lymphoma (IgM>IgG frequency).

Main problem is differentiation from benign Monoclonal Gammopathy or Undetermined significance (MGUS)

Don’t forget….

- Majority MGUS/Myeloma produce IgG or IgA
- IgM usually evolves into lymphoma (but occasionally myeloma)

- Light chain **only** found in 20%, (no serum monoclone or low level monoclone)

- Smaller number non-secretory, usually present with bone damage etc.

- Always check ‘Bence-Jones Urine Protein’ with Immunoglobulins
- Probably in the process of change now to Serum Free Light Chain

SFLC slightly more tricky to interpret….

Confusing Bence-Jones Protein Results

- **Two** parts to the report…

First

URINE BENCE JONES SCREEN

Urine Bence Jones Screen

Urine Electrophoresis

Urine Total Protein * 0.35 g/L 0 - 0.1

Note this result is the urine protein ONLY, Bence-Jones Protein screen result (plus BJP quantitation if positive) to follow.

Second Part (a week or so later)

BJP QUANTITATION

BJP Quantitation 0.19 g/L

Polyclonal increase (hyper-gammaglobulinaemia)

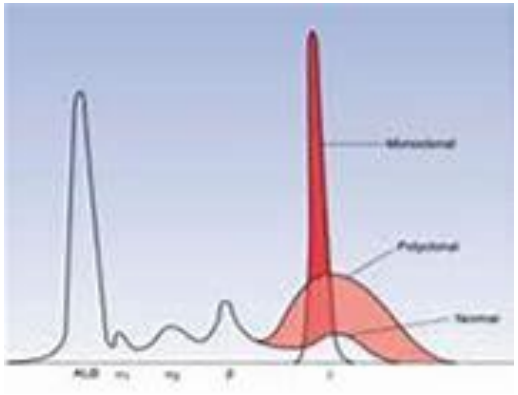


Image University Wisconsin

- Reactive phenomenon
- If no Bence-Jones proteinuria or monoclone in serum this is **not** associated with myeloma

- Common Causes

-Chronic Infection→ including HIV, hepatitis B and C

-Liver Disease→ Cirrhosis and Autoimmune Hepatitis

-Connective tissue disorder→ Rheumatoid, Lupus etc

Less common cause include Angioimmunoblastic T-Cell Lymphoma…

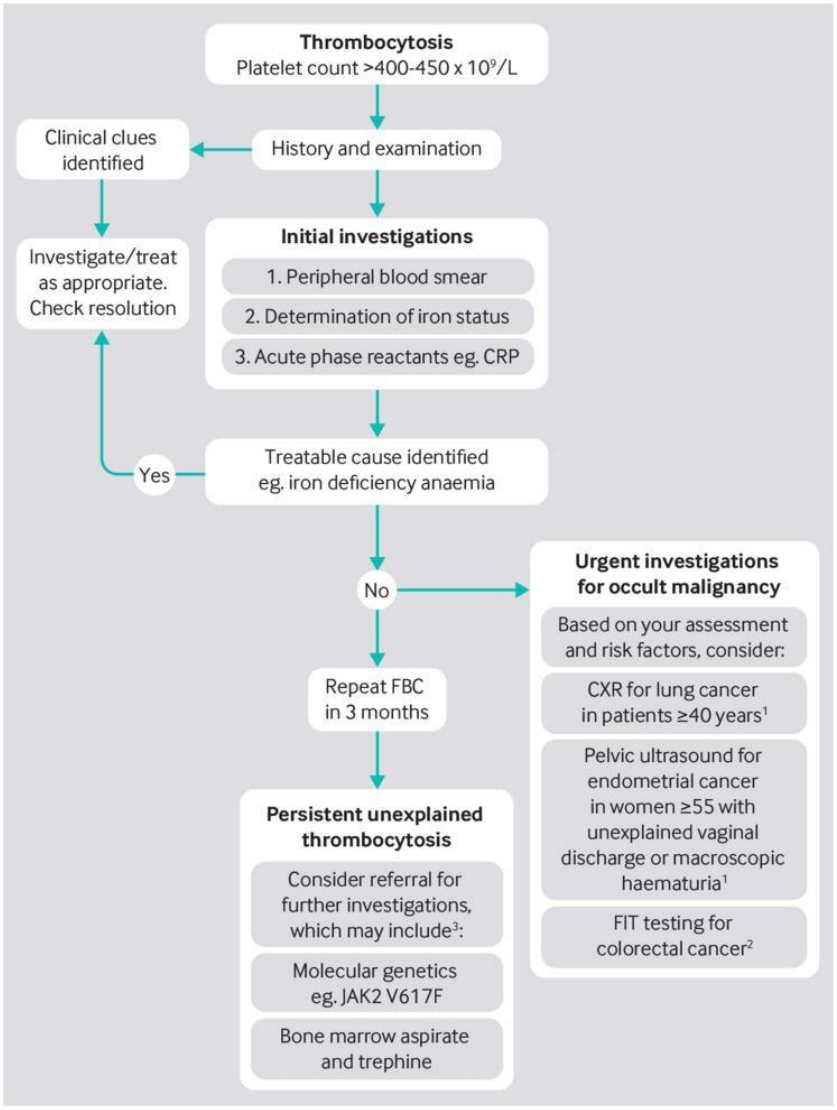
Thrombocytosis

- Common
- Most cases reactive
- New guidance from NICE/SIGN, recent BMJ publication

- **What you need to know** (BMJ 2019**)**
- Thrombocytosis is usually **reactive or** caused by **clonal** disorders
- Initial assessment includes repeat history and examination, a peripheral blood smear examination, and determination of iron and acute phase reactant status

- If no cause of inflammation is found, consider investigations for an occult malignancy or seek specialist advice for investigation of a clonal haematopoietic disorder

Algorithm for investigating thrombocytosis.



[1] NICE guideline [NG12] https://www.nice.org.uk/guidance/ng12
[2] Scottish Referral Guidelines for Suspected Cancer. http://www.cancerreferral.scot.nhs.uk/
[3] Harrison CN, Bareford D, Butt N, et al. Guideline for investigation and management of adults and children presenting with a thrombocytosis. Br Haematol 2010;149:352-75

Abhinav Mathur et al. BMJ 2019;366:bmj.l4183

DOAC

- Common questions
  - Hospital setting ‘this man/woman is bleeding into ‘brain/GI tract etc. and had taken XXX’
  - Primary care ‘This man/woman is too heavy/too light for a DOAC, can I still give it?

DOAC extremes of body weight

- Unlicensed, need to document a reason patient can't have Warfarin
- Most of the data is in VTE treatment, less clear on extended lower dose anticoagulation
- Most of the evidence is for Rivaroxaban/Apixaban
- Renal function more of a concern for safety

jth journal of thrombosis and haemostasis®

Volume19, Issue8
August 2021
Pages 1874-1882

Summary Guidance Statements for use of DOACs in Patients with Obesity
1). Consistent with the 2016 ISTH SSC recommendations, we conclude that the use of any DOAC is appropriate for patients with BMI up to 40 kg/m^2 or weight 120 kg. For patients with BMI >40 kg/m^2 or weight >120 kg, we recommend that the individual DOACs should be used as follows:
2). For treatment of VTE, we suggest that **standard doses of rivaroxaban or apixaban** are among appropriate anticoagulant options regardless of high BMI and weight. Fewer supportive data exist for apixaban than rivaroxaban. VKA, weight-based LMWH (per manufacturers' recommendations), and fondaparinux are also options.
3). For primary prevention of VTE, we suggest that standard doses of rivaroxaban or apixaban are among appropriate anticoagulant options regardless of high BMI and weight. Drug approval is restricted to elective hip and knee arthroplasty and (in some countries) extended VTE prevention following acute medical illness.
4). We suggest not to use dabigatran, edoxaban, or betrixaban for VTE treatment and prevention in patients with BMI >40 kg/m^2 or weight >120 kg, given unconvincing data for dabigatran, and lack of clinical or PK/PD data for edoxaban and betrixaban.
5). We suggest not to regularly follow peak or trough drug-specific DOAC levels because there are insufficient data to influence management decisions.
6). We suggest not to use DOAC for treatment or prevention of VTE in the acute setting after bariatric surgery (because of concerns of decreased absorption), and instead, to initiate such patients on parenteral anticoagulation in the early postsurgical phase. We suggest that switching to VKA or DOAC may be considered after at least 4 weeks of parenteral treatment, and if so, suggest obtaining a DOAC trough level to check for drug absorption and bioavailability.

What about AF?

- Disclaimer: I don't treat AF, never have done and never will.
- Always consult with stroke physician/cardiologist regarding treatment.

- Post hoc analysis of prospective AF studies with more than 2,000 patients with AF who had a BMI of greater than 40 kg/m^2 showed no evidence of inferior efficacy or safety with DOACs compared with VKAs.
- In the ARISTOTLE trial, among 982 patients with a weight of 120 kg or greater, risk of stroke, systemic embolism, and major bleeding were comparable among patients receiving apixaban and VKAs. Among the 258 patients with a weight greater than 140 kg, the risk was numerically higher but not statistically significant.

- *Wang T, Carrier C. How I treat obese patients with oral anticoagulants. Blood. 2019;135(12):904–911.*

Low body weight….?

Clinical Perspective

Apixaban is efficacious and safe across the spectrum of weight, including in low- (≤60 kg) and high-weight patients (>120 kg).

The superiority on efficacy and safety outcomes of apixaban compared with warfarin persists across weight groups, with even greater reductions in major bleeding in patients with atrial fibrillation with low to normal weight as compared with high weight.

What Are the Clinical Implications?

The superiority of apixaban over warfarin with regard to efficacy and safety for stroke prevention seems to be consistent in patients with atrial fibrillation across the spectrum of weight, including in very low– and very high–weight patients.

Apixaban is more appropriate than warfarin for patients with atrial fibrillation irrespective of body weight

Circulation, Volume 139, No 20, 2019

NEJM Journal watch

- **Even Lightweights and Heavyweights Are Protected by Apixaban**
- *Mark S. Link, MD, reviewing Hohnloser SH et al. Circulation 2019 May 14*

- **Probably best to discuss with individuals, document reasons for decision to not to give warfarin**

- **Emphasis that none of these drugs prevent thrombosis, just *reduce* risk**

- **BMI concern with renal failure? Not sure.**

Case 4

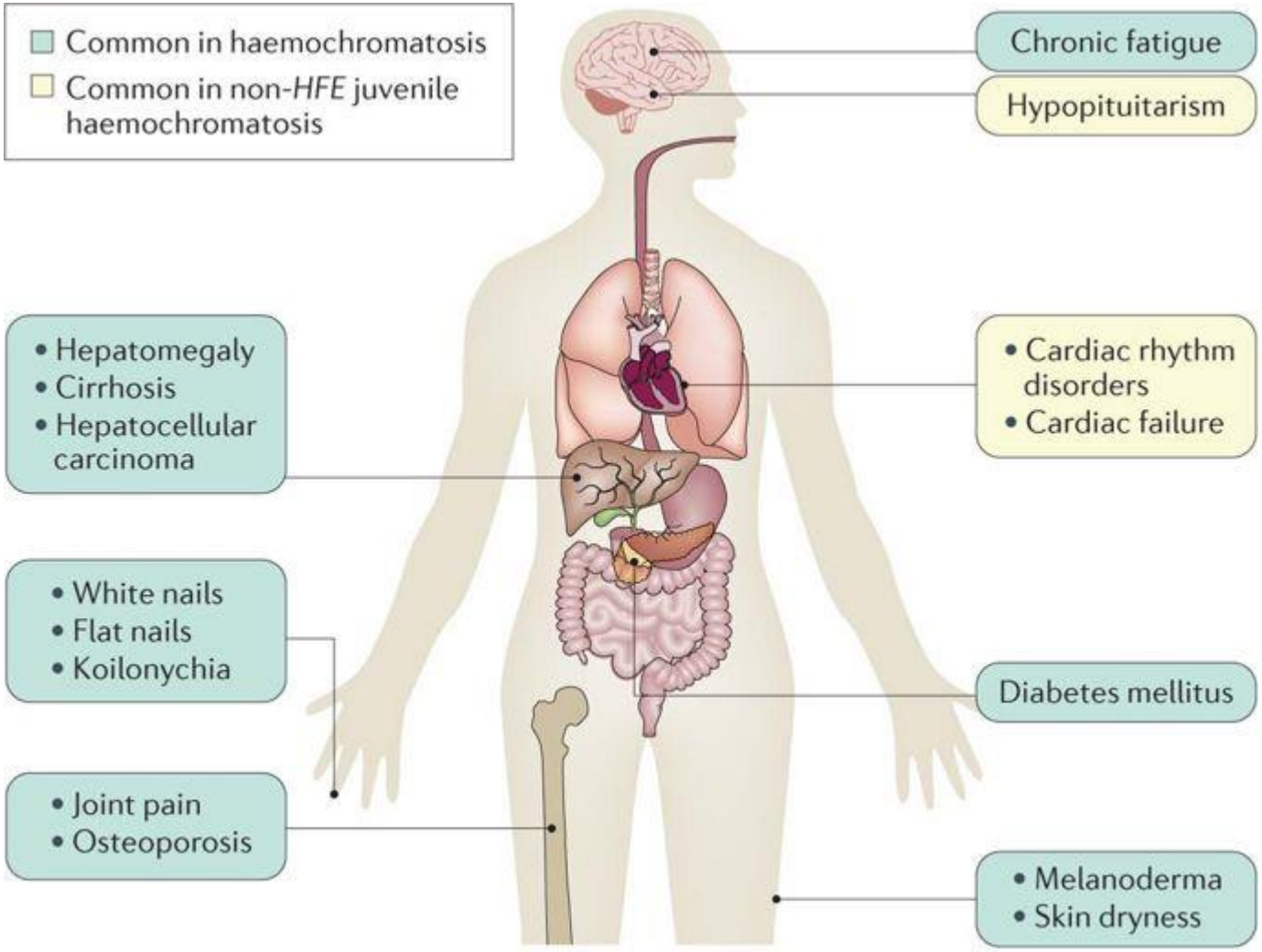
- 62 year old man presents with tiredness
- Background; Type II diabetes, raised BMI at 30
- Ferritin of **631**, minor elevation GGT, ALT and AST

- All very non-specific…Could this be Haemochromatosis?

Commonest Genetic Disorder in Northern Europeans

- 10-15% C282Y heterozygotes, **1% homozygotes**
- 20-30% H63D heterozygotes, 2% compound heterozygotes

C282Y homozygotes are most at risk of iron overload and such homozygotes are responsible for some 90% of clinical cases



Nature Reviews | Disease Primers

Usually present with biochemical changes…

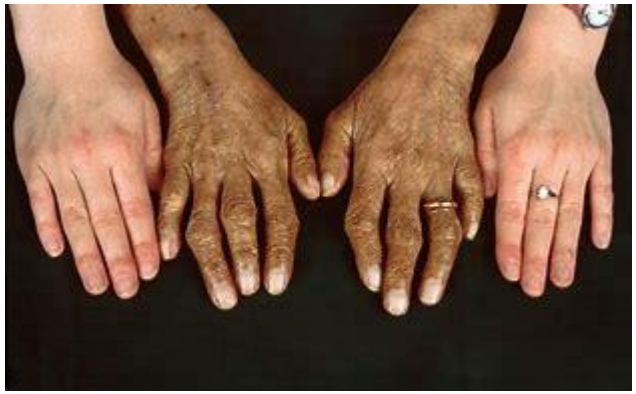


Image Merck Manual

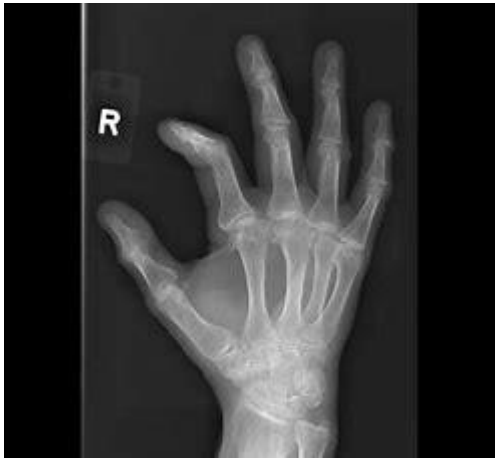


Image radiopaedia.org

Raised Ferritin

- Primary Care: 20% male patients >30 years, 17% Females >70 years
- Key tests Transferrin Saturation
- TF% <50% male, or <40% Female makes iron overloading disorder unlikely
- Causes of Raised Ferritin/**Normal** TF%
  - Alcohol
  - Fatty Liver/Hepatitis
  - Infection/inflammation
  - Malignant disease
  - Dialysis

HFE testing, who to test?

1. Patients of north European ancestry with unexplained raised Ferritin **and** random TF% (19% and 16% likelihood of being C282Y homozygotes)

2. Targeted screening of family members of an index case of C282Y homozygous GH.

Siblings, parents and children (over the age of consent) of a patient should be offered testing. Testing of partners can assist in determining the risk for children. It is not recommended that family screening be performed after identification of a heterozygote carrier or, indeed, a compound heterozygote. Initial family screening should be as above but also include HFE genotype with expected frequencies of 25% and 50% for GH when parents are either both heterozygotes.

Case 4

- Check FBC, Ferritin, Liver Function tests **and** Transferrin saturation (included with ‘iron profile’ on ICE requesting

- This mans Ferritin on repeat is 652, Transferrin saturation 30%

Case 4

- Further tests showed fatty liver on US, combined with alcohol intake of 30Units per week. No HFE testing recommended.

- Recommendation lifestyle change, optimise diabetes, cut back on alcohol.

Angry Doctors

1. Rejected thrombophilia screening tests Family/Clinical history is key

Results often do not help guide management

Expensive

Please provide as much clinical information as possible if they do need processing!

2. Rejected Haemochromatosis requests

3. Lupus Anticoagulant

Named as it interferes with the APTT clotting assay (commonly causes prolonged APTT)

Found in association with SLE, but is **not** a screening test for SLE

Found in HIV, SLE, some cancers, post-infections, most idiopathic

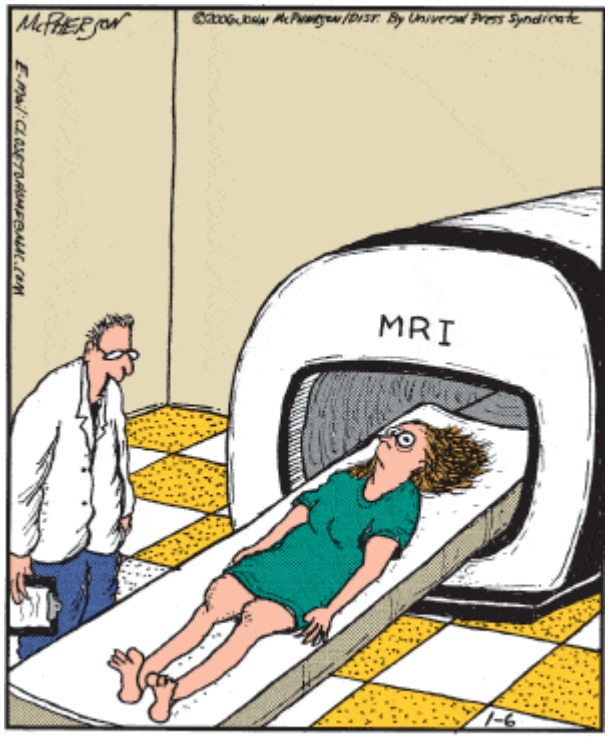
Pro-thrombotic if persists

Blood checks in the community
For the ‘not quite right patient’

Abnormalities in FBC often reflect other health/disease problems

1. Haematinics B12/Folate/ferritin deficiency
2. Reticulocytes raised, blood loss, haemolysis
3. CRP inflammation/infection
4. LFTs and Calcium (if **Total Protein** or **Globulin** raised, is there a monoclone?)
5. Renal function (eGFR <30mls/min, could this be renal anaemia, light chains?)
6. Serum and Urine electrophoresis (see point 4)
7. ESR….

Clinical History, a little goes a long way…



"OK, Mrs. Dunn. We'll slide you in there, scan your brain, and see if we can find out why you've been having these spells of claustrophobia."