Common Haematology Problems

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Topics covered

- 1. Anaemia
- 2. Neutropenia
- 3. Thrombocytosis
- 4. Monoclonal proteins
- 5. Lymphocytosis
- 6. Haemochromatosis

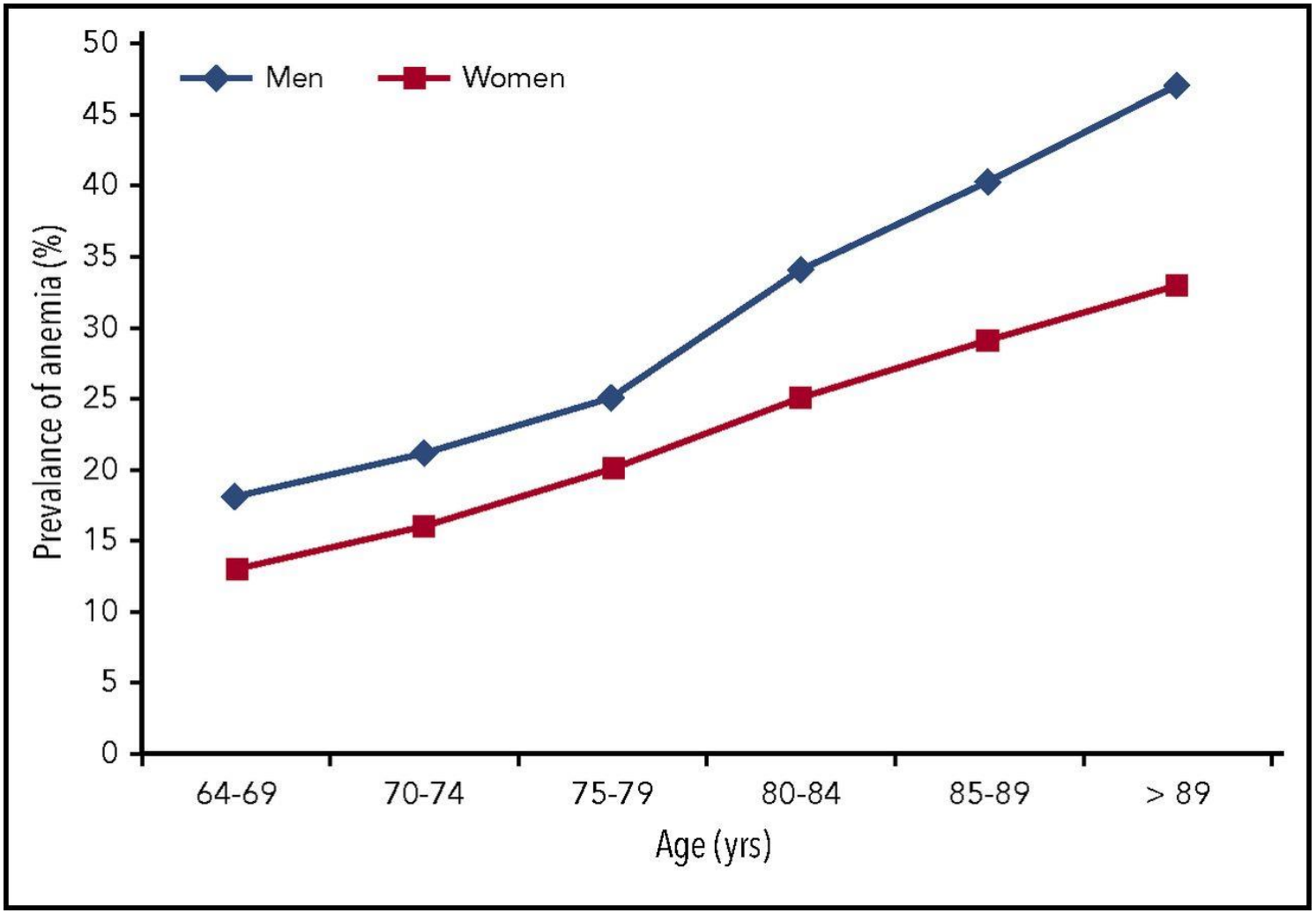
- Not covered but can discuss; clotting bits and bobs, cancer, low platelets, polycythaemia etc.

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

Common problem, common referral

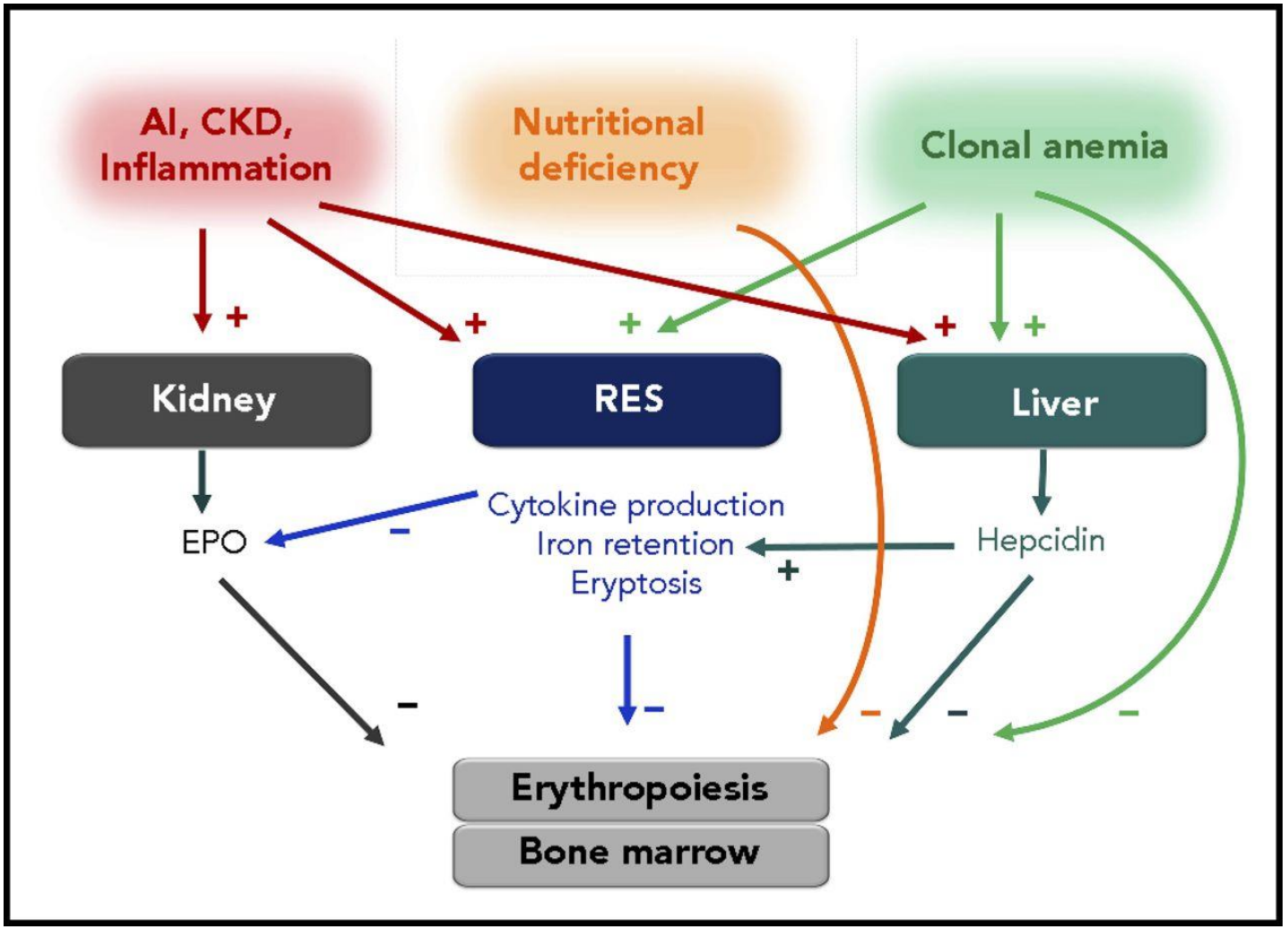
- Prevalence 17% age >65 years
- Defined by WHO Hb <130g/l men, <120g/l women
- Only minority have primary haematological disorder
- Emerging concept of ‘inflammaging’

Increase in prevalence of late-life anemia.



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

Possible mechanisms of anemia in older adults.



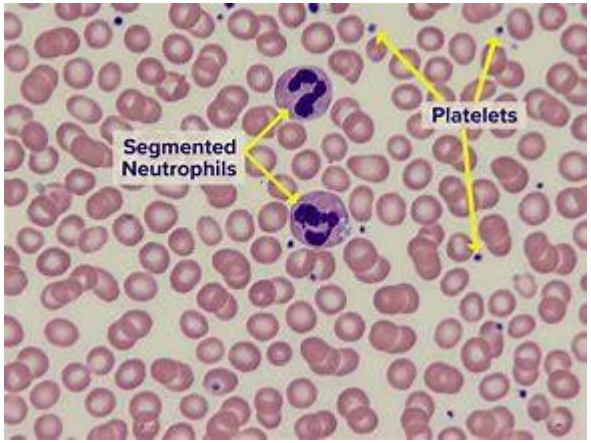
Reinhard Stauder et al. Blood 2018;131:505-514

Case 1

86 year old male

Attends surgery main complaint ‘tired’

Nil on physical examination



<u>PMH</u>

Diabetes

COPD

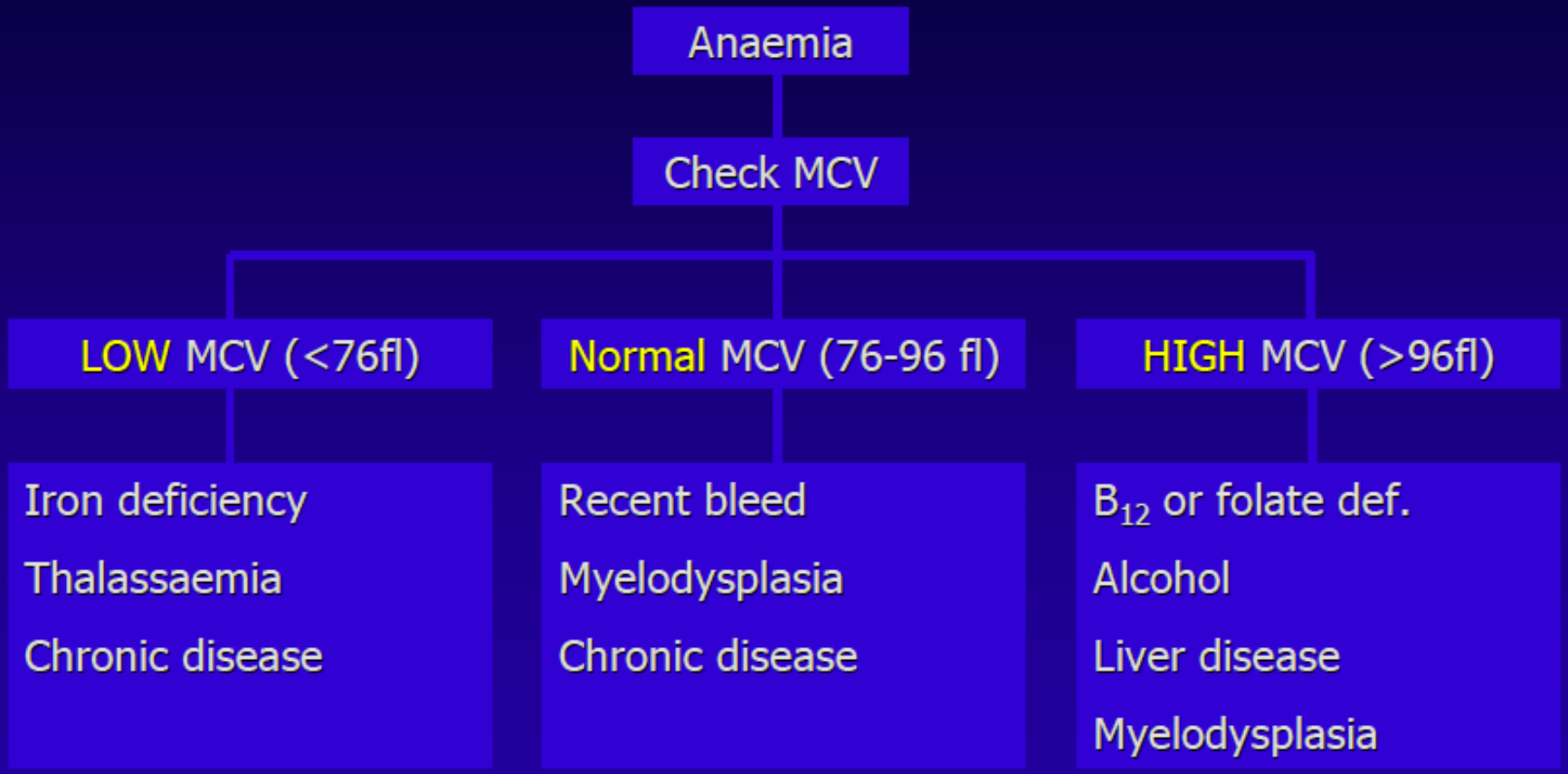
CKD3

<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

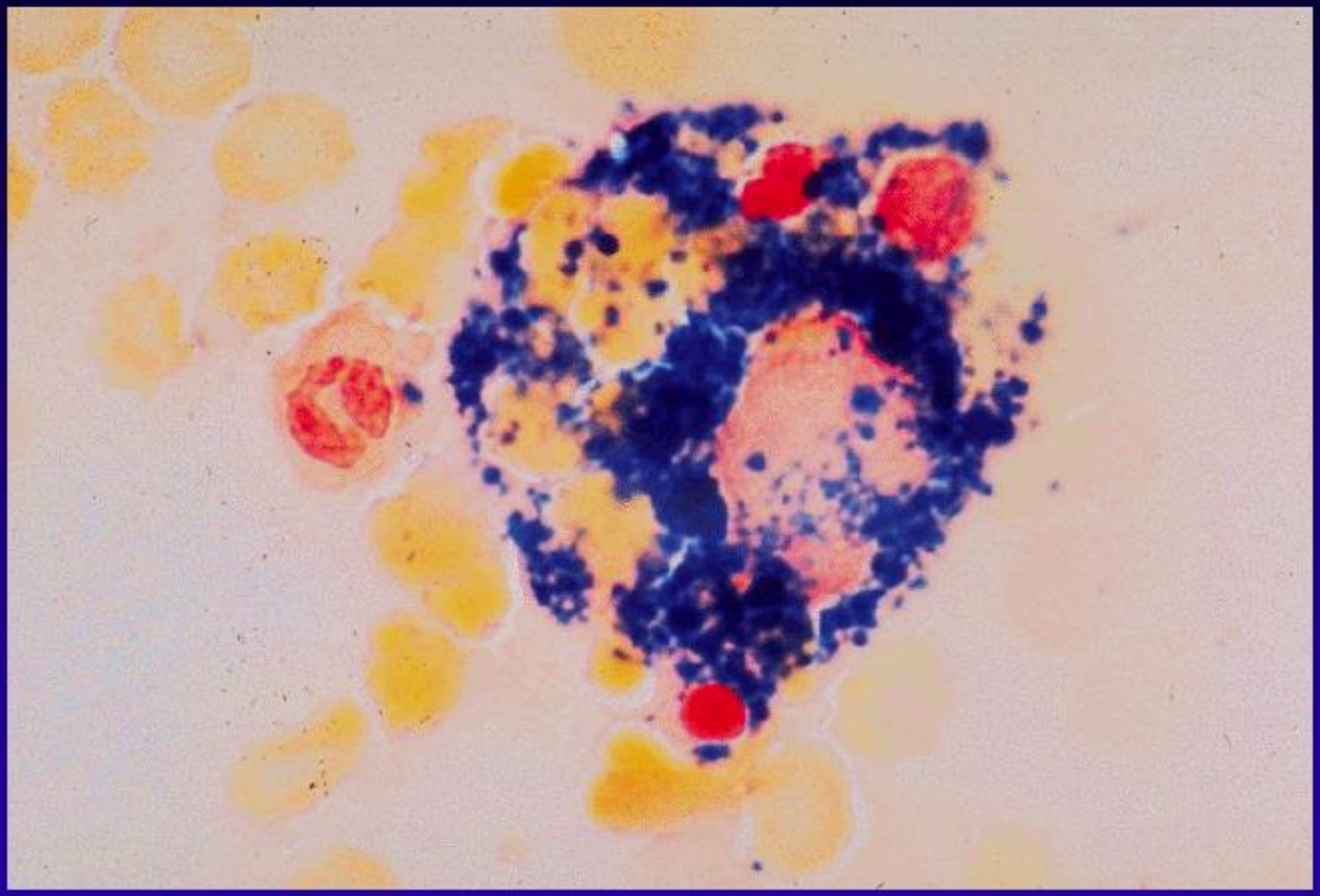
Anaemia of Chronic Disease

- 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



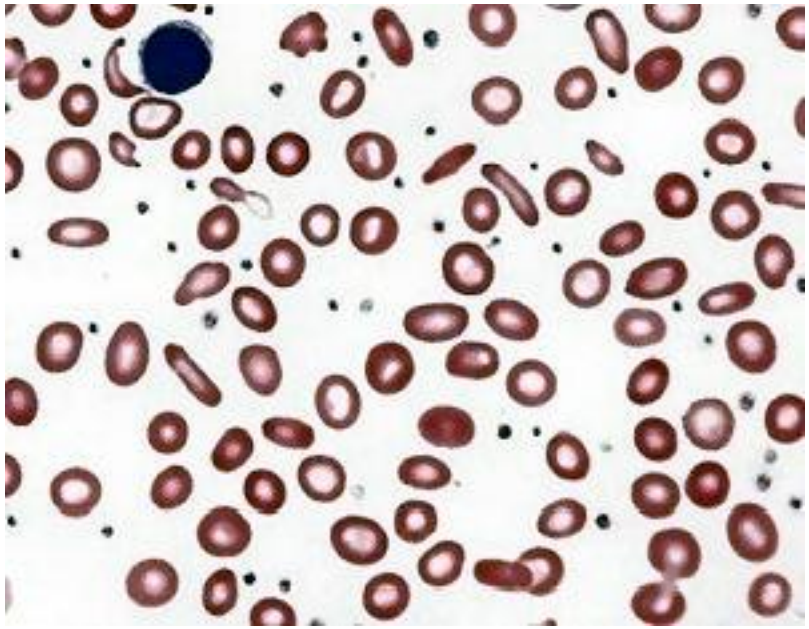
Bone marrow macrophages fail to release iron (blue) to developing RBCs

Case 2

36 year old female, heavy periods

FBC

Hb 8.3 g/dl	(11.5--16.5)
RCC 3.7	(3.8--5.8)
MCV 71 fl	(76--95)
MCH 21.9	(27--32)
MCHC 29.9	(32--36)



Diagnosis of iron deficiency is (usually) easy

- Full blood count (FBC)
- Serum ferritin
- Blood film
- Trial of iron therapy

Diet	Seldom sole/major cause (western societies)
↑↑Demand	Toddlers (cow''s milk), infection, premature adolescence, females, pregnancy
Blood loss	commonest cause in adults: Menstrual blood loss: premenopausal females GI tract bleeding: males, post-menopausal males
Malabsorption	Coeliac, Crohn's, partial gastrectomy etc

No cause found 20% -- generally benign outcome

Iron Deficiency

- Almost never due to a primary haematological disorder

- If patient referred to haematology, we give oral iron and refer to gastroenterology or gynaecology

- Any medical/surgical speciality can give an iron infusion (haematology not the guardian of the iron infusion)

- Iron infusion not risk free

  -Small risk of allergy or anaphylaxis

  -Small risk of abnormal skin pigmentation

  -If underlying cause of iron loss not dealt with, iron deficiency will recur

  -Giving iron without investigating cause can miss serious pathology

Iron deficiency with normal ferritin

- Clues, MCV/MCH within normal range but falling over time
- MCV trend downwards e.g. 97fl→85fl over a period of months

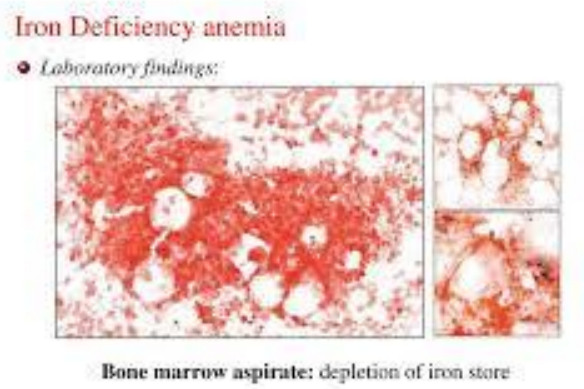
- Inflammation/cancer/infection with Ferritin <100 ?iron deficiency
  Often have reduced transferrin saturation/iron level

How I think of Ferritin

- Ferritin <20 or below normal range *deficient*
- Ferritin <50 *reduced* iron stores
- Ferritin >50 *normal*
- Low iron → IDA, ACD, inflammation, cancer

Recent clinic patient

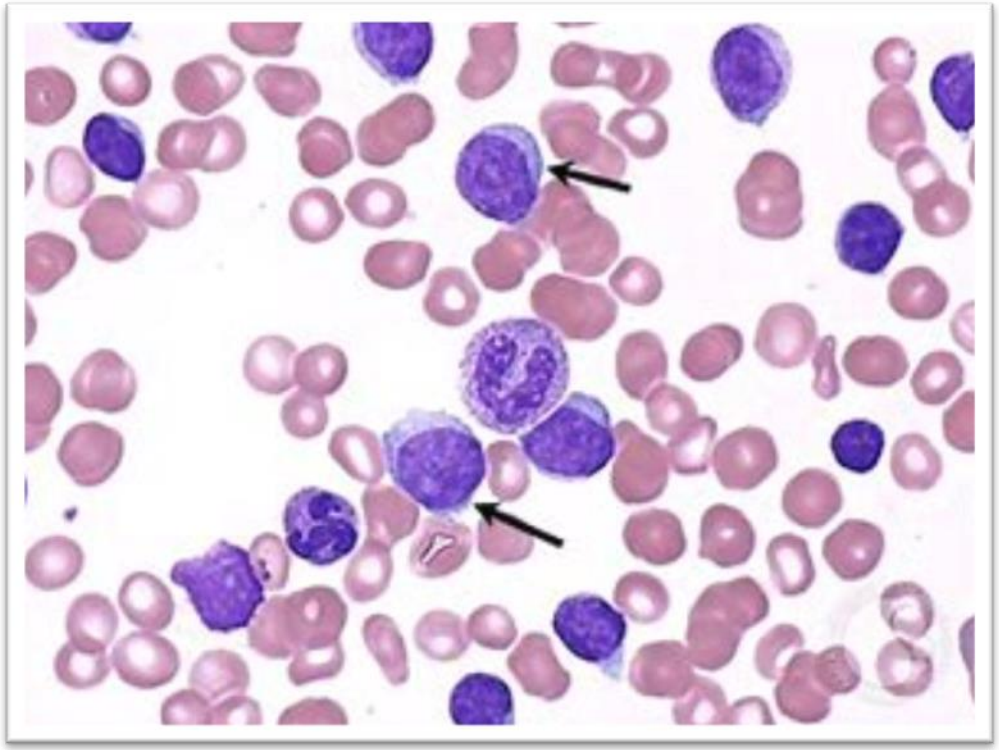
New diagnosis haem cancer
-Anaemia (normocytic)
-Ferritin 77
-Marrow biopsy performed as cancer staging→ no iron



Closer questioning, persistent
PR blood loss

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**

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 etc.

New(ish) concept of 'Monoclonal B-Cell Lymphocytosis Undetermined Significance'

-Clonal B cells found

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

-Prefer to diagnosis 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 1 year
3. Lymphocytes 3.5-10 in presence of LN, organomegaly, B symptoms → refer to haem

4. If clinical concern, refer to haematolgy.

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

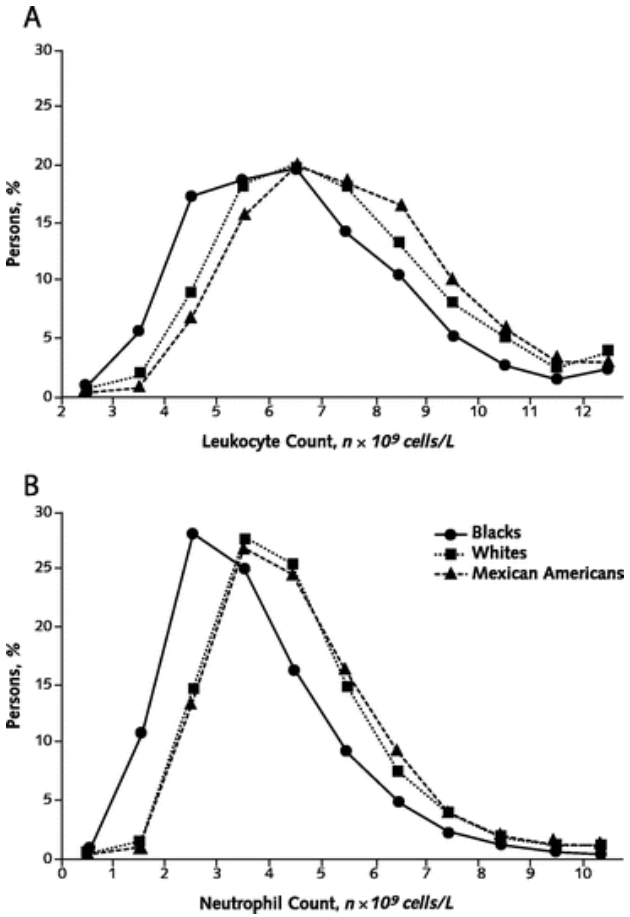
3. Drugs

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, likely ethnic variation

Ethnic Variation

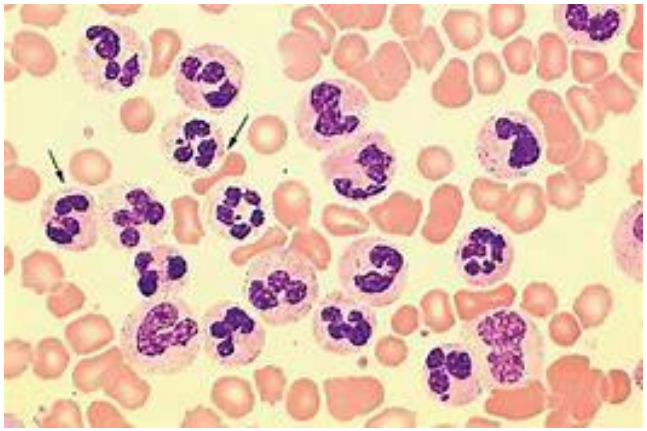
Neutrophils usually >1.0

Common in patients with middle eastern or African ancestry

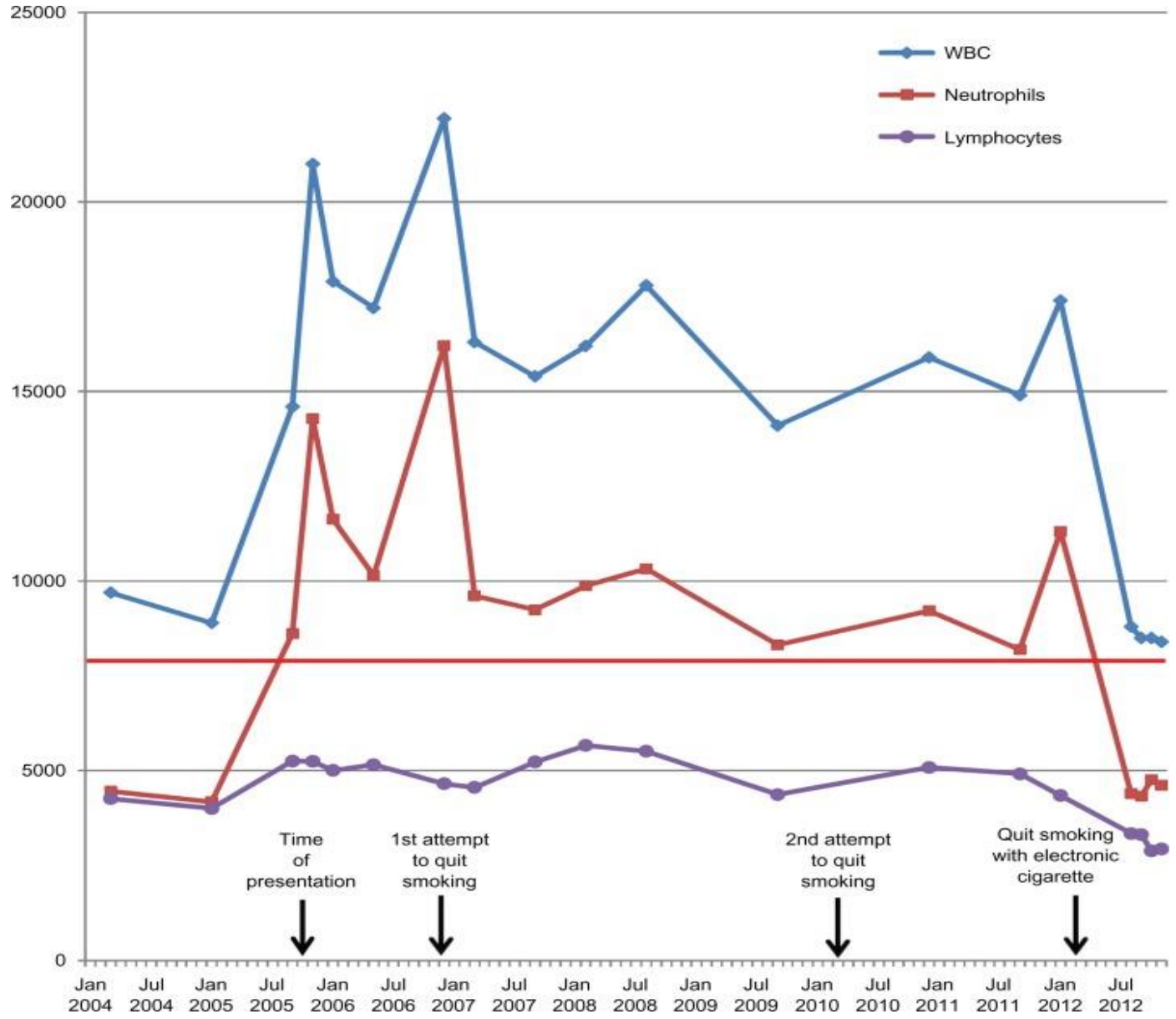
Benign

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!)



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).

Persistent risk of progression to LPM, 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

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

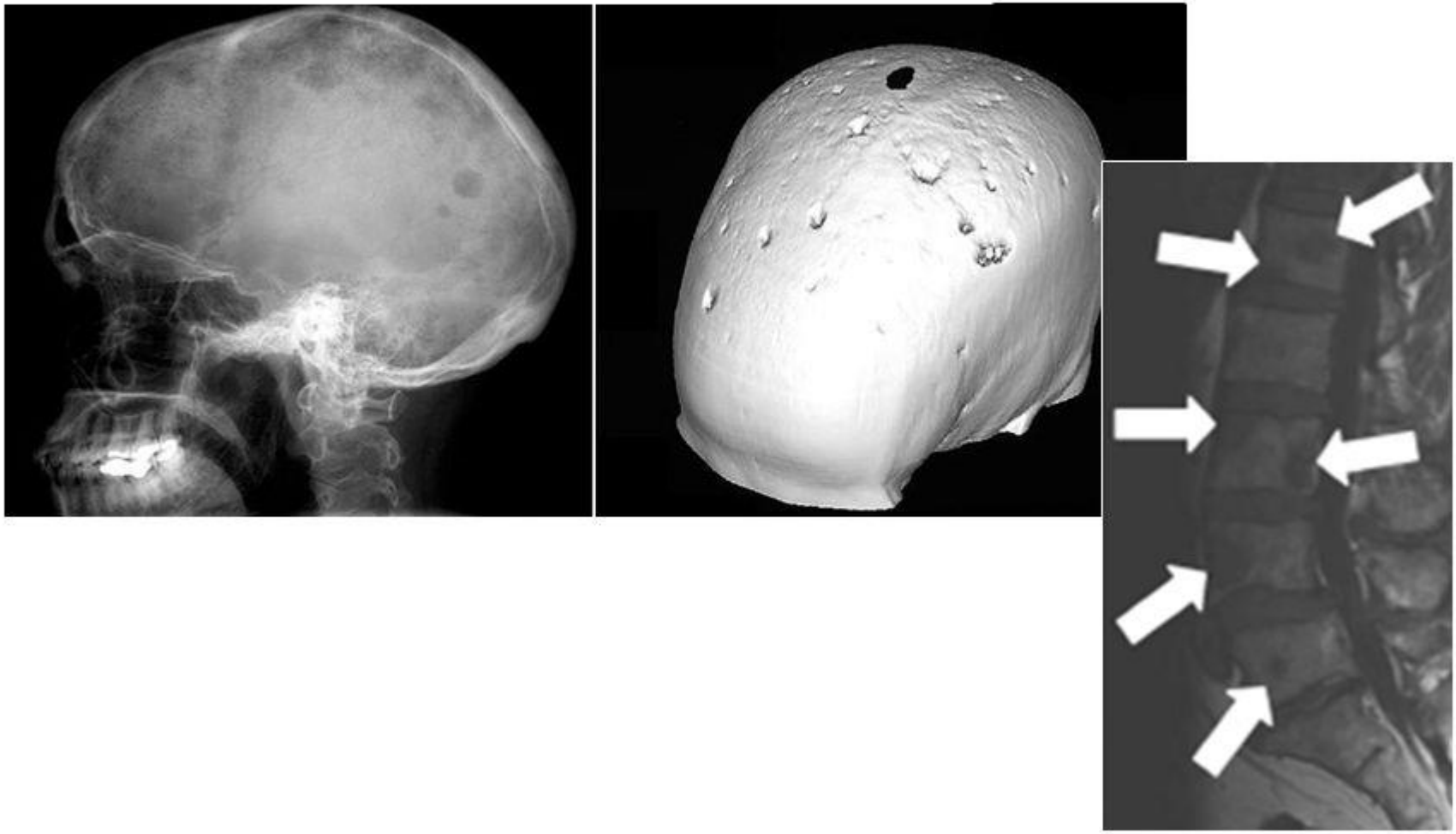
- How to monitor?

No consensus…

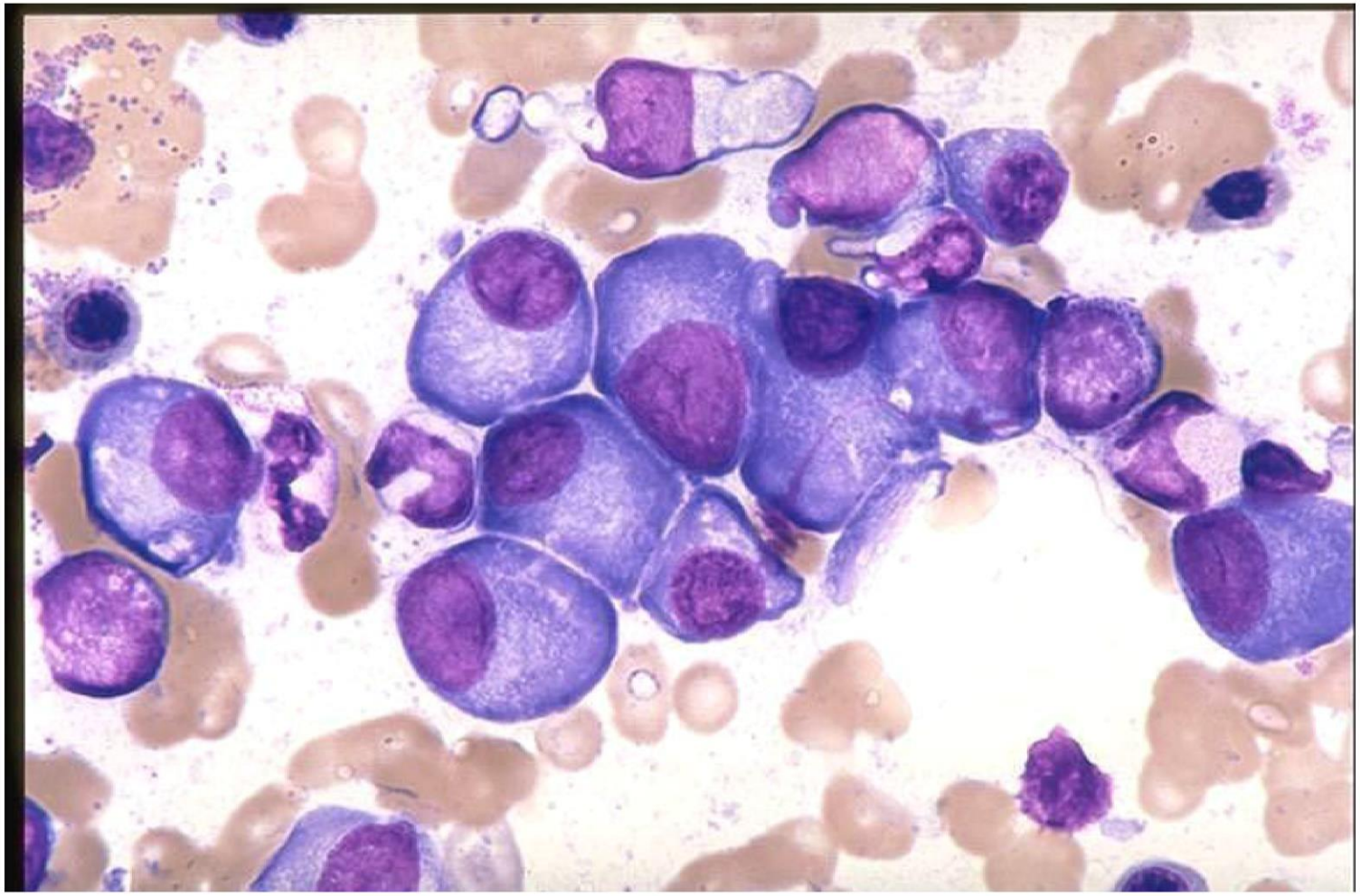
- I tend to keep ‘higher risk MGUS’ in clinic

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

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)

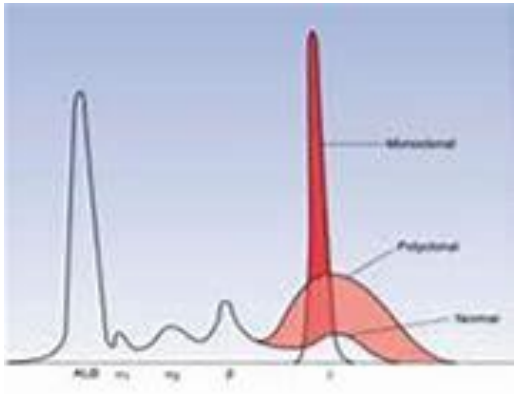


Image University Wisconsin

- 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

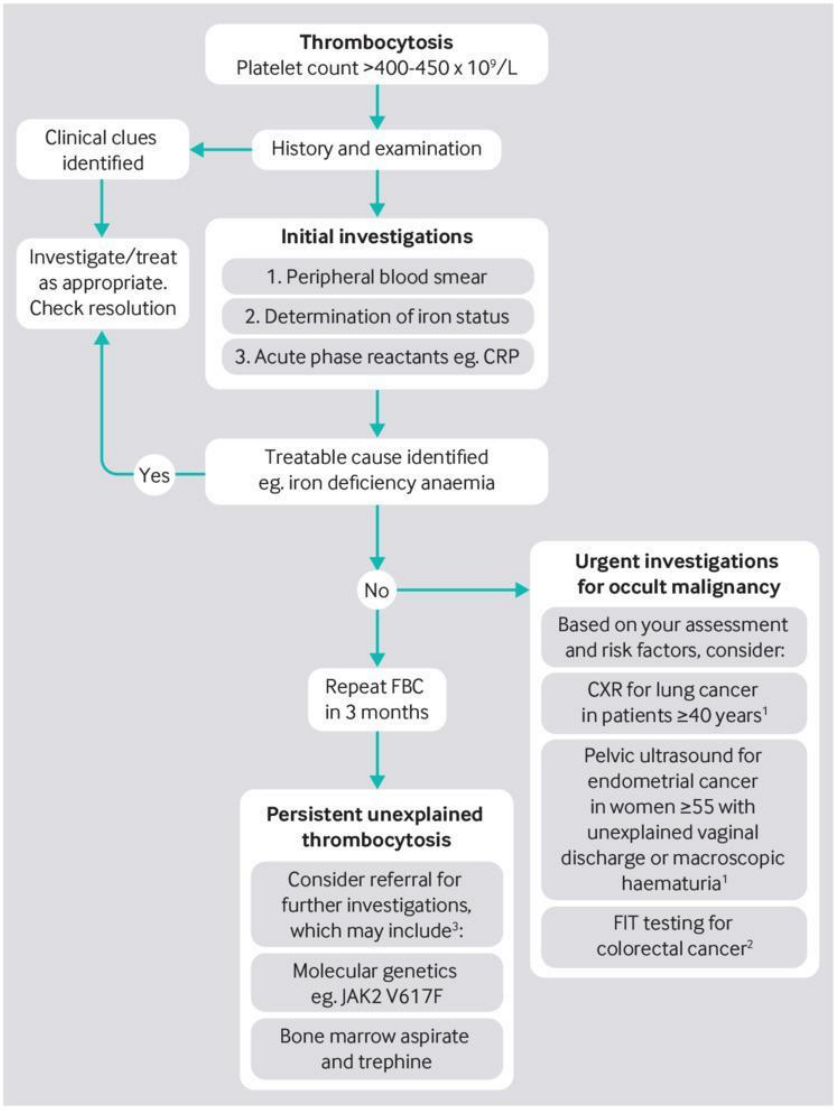
Less common cause include Angioimmunoblastic T-Cell Lymphoma…

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

Case 4

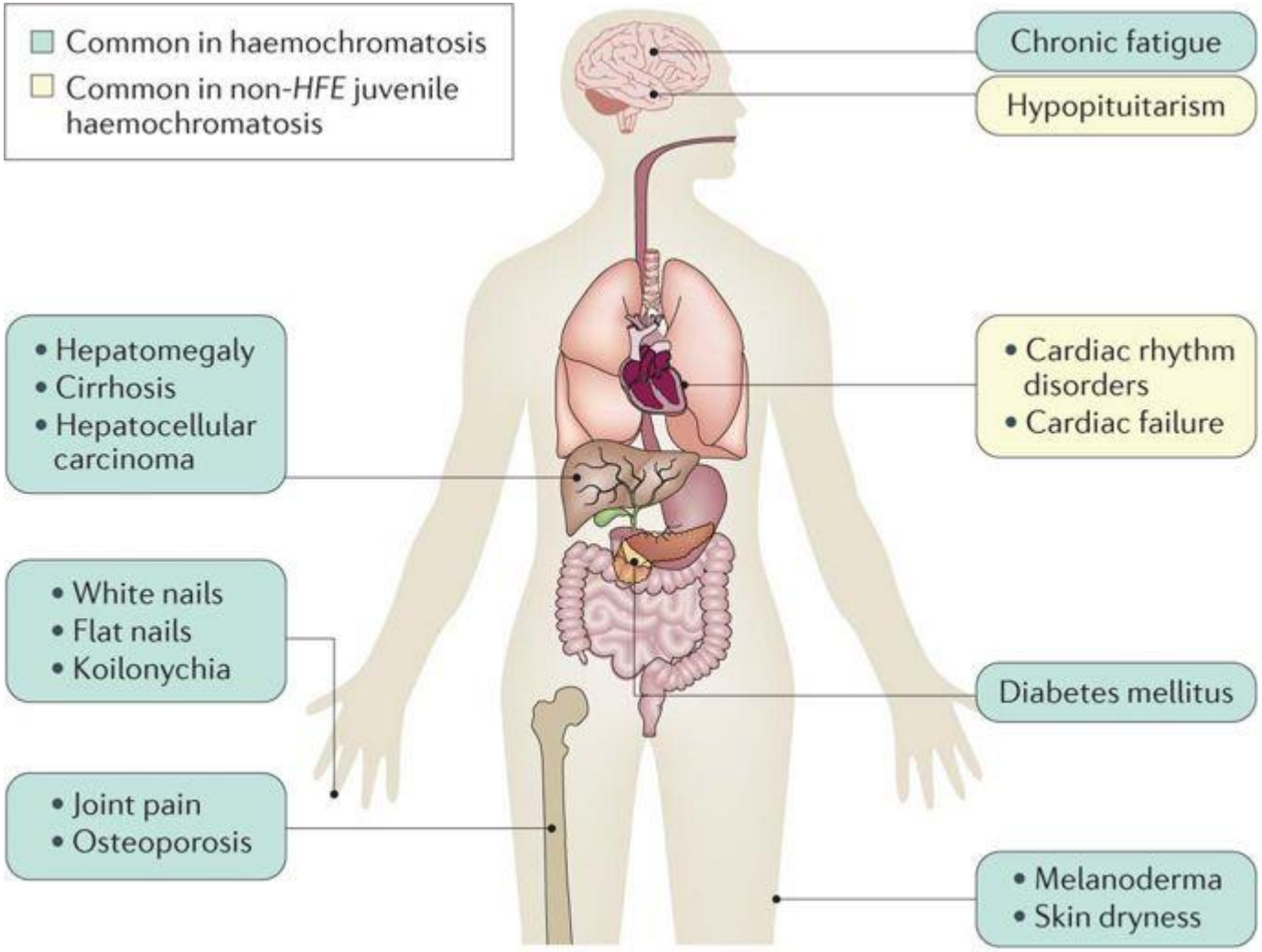
- 62 year old man presents with tiredness
- Background; Type II diabetes, raised BMI at 30
- Ferritin of **631**, minor elevation GGT, ALT and AST

- 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…

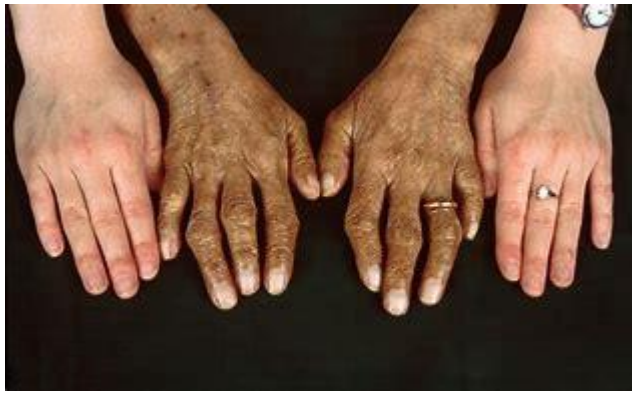


Image Merck Manual

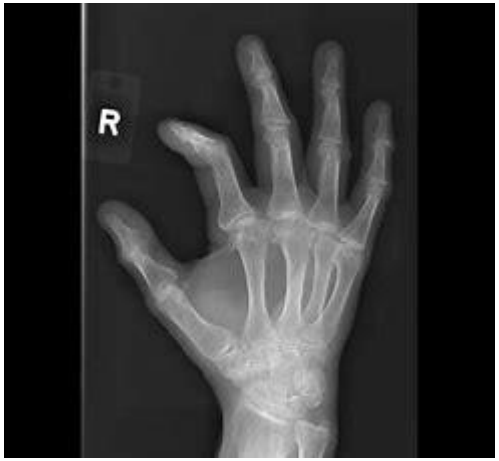


Image radiopaedia.org

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

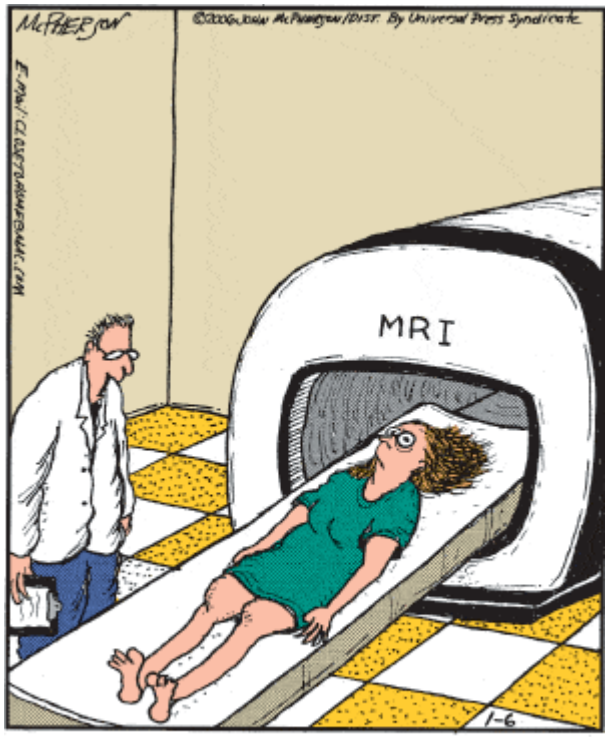
Pro-thrombotic if persists

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."