1. History and examination
    a. Why was the test done? Is the patient unwell or is this an incidental finding?
    b. Abnormal PE findings: splenomegaly, lymphadenopathy, rash, bleeding etc?
2. Isolated versus combined abnormality
    a. “-penia versus -osis”
    b. One lineage vs multiple lineages
    c. Marked or persistent “left shift”
    d. Morphologic abnormalities, MCV
3. Time-course
    a. One-off? Acute and/or rapidly progressive? Chronic and stable?
4. Correlation with basic biochemical and coagulation panel
5. Need for further testing versus simple monitoring
    a. Haematinics, thyroid function, inflammatory markers etc.
    b. Flow cytometry
    c. Molecular testing
    d. Tissue or BM biopsy

54 year old female presents with fatigue, arthralgias and 2kg weight loss

What is the most likely diagnosis?

a) Acute myeloid leukaemia
b) Reactive leucocytosis
c) Chronic myeloid leukaemia
d) Polycythaemia vera

What is the next appropriate investigation?

a) Serum electrophoresis
b) CRP/ESR
c) BCR-ABL fusion gene testing
d) Flow cytometry


To help protect your privacy, PowerPoint has blocked automatic download of this picture.

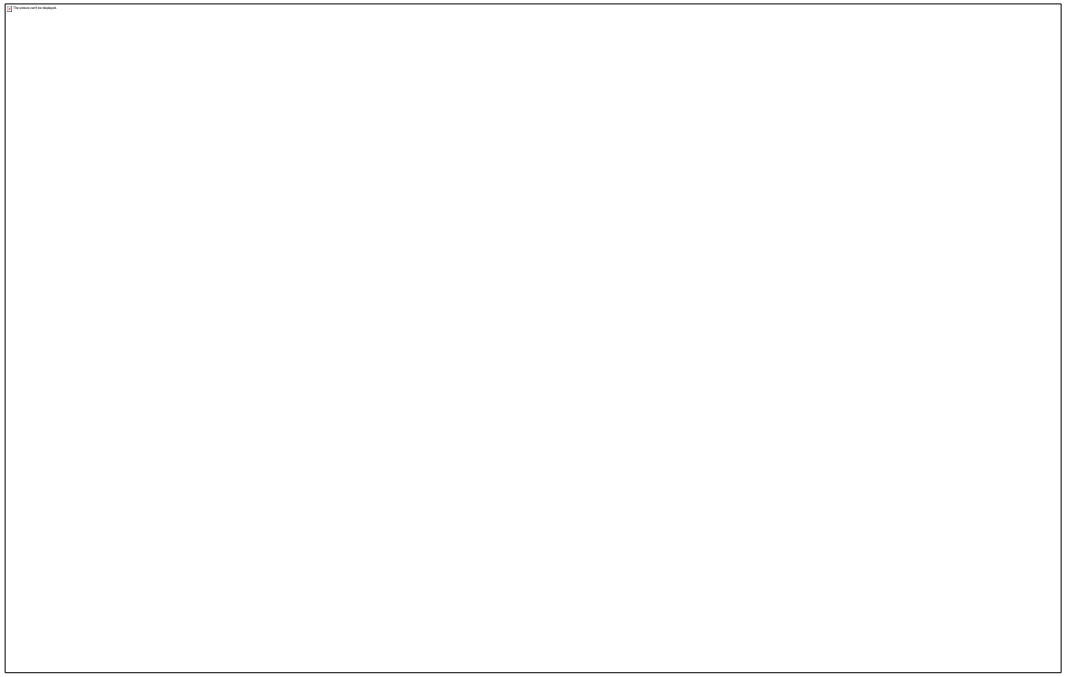
Chronic lymphocytic leukaemia

- Most commonly diagnosed after FBC performed either as “routine” or for “nonspecific” symptoms such as fatigue, sweats
- FBC shows elevated lymphocyte count
  - +/- other cytopenias (anaemia, thrombocytopenia), due to marrow infiltration, splenomegaly and/or immune destruction

- Abnormal circulating lymphocytes are **monoclonal B-cells** that have a characteristic profile of cell surface markers that can be identified by **flow cytometry** (“lymphoid marker studies”)
  - Consider this test if a patient has a persistent lymphocytosis not explained by other conditions (esp infection, inflammatory conditions, smoking)
  - And especially if associated with lymphadenopathy, splenomegaly, or other count abnormalities
- In contrast, reactive lymphocytosis is usually **polyclonal** and predominantly **T-cell**

- Monoclonal B lymphocytosis: precursor state to CLL in which monoclonal B-cells are present in peripheral blood with absolute level $<5x10^9/L$, and without associated symptoms or adenopathy/hepatosplenomegaly.

56yo male presents with headaches and lethargy; smoker 30/day



What is the most likely diagnosis?

a) Chronic myeloid leukaemia
b) Secondary polycythaemia
c) Iron deficiency
d) Polycythemia vera

What is the next appropriate investigation?

a) CRP/ESR
b) JAK2 mutation testing
c) BCR-ABL fusion gene testing
d) Chest x-ray

Red flags

- Active ischaemia (TIA, angina, PVD)
- Venous thrombosis
- Hyperviscosity symptoms
  - visual disturbance
  - headache
  - epistaxis

JAK2 Mutation Testing

Specimen:	EDTA Peripheral Blood
JAK2 p.Val617Phe:	**Mutation Detected ***

This variant is commonly referred to as V617F. Note this variant is known as c.1849G>T, p.Val617Phe according to HGVS nomenclature; RefSeqGene: NG_009904.1 (JAK2).

Patient commences aspirin and venesection on advice of haematologist.

Presents 3 months later with fatigue

Serum ferritin = 5ug/L (30-300ug/L)

What is the appropriate course of action?

a) Refer for IV iron infusion
b) Colonoscopy
c) Counsel re: smoking cessation
d) Commence oral ferrous sulfate 325mg daily

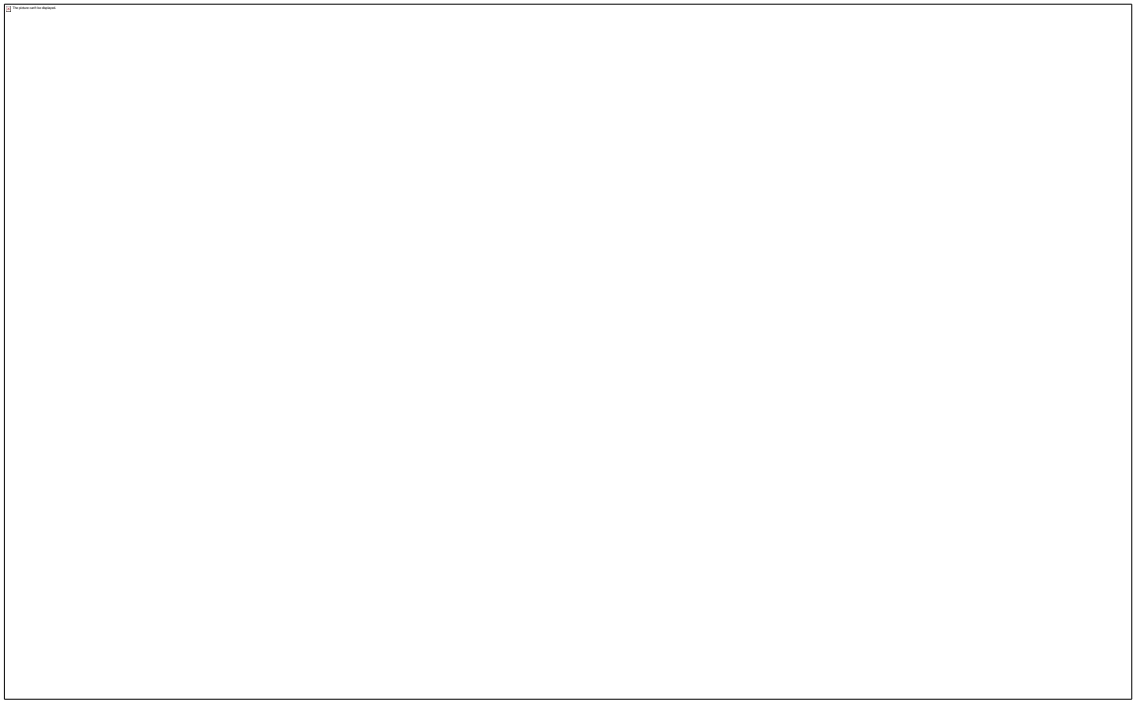
- Most commonly a reactive finding in response to:
  - Infection or inflammation
    - Particularly rheumatoid arthritis and other connective tissue disease
  - Iron deficiency
  - Post-splenectomy (chronic)

- Persistent thrombocytosis >450 x10^9/L in the absence of a clear cause and with normal inflammatory markers and serum ferritin should be investigated for myeloproliferative disease:
  - ***JAK2 V617F mutation testing***: present in 60% of cases
  - ***CALR gene mutation testing*** (if JAK2 V617F negative)
  - ***MPL gene mutation testing*** (if CAR negative)

Red flags

- Severe thrombocytosis >1000 x 10^9/L
- Ischaemia (TIA, angina, PVD)
- Hyperviscosity symptoms
  - visual disturbance
  - headache
  - epistaxis

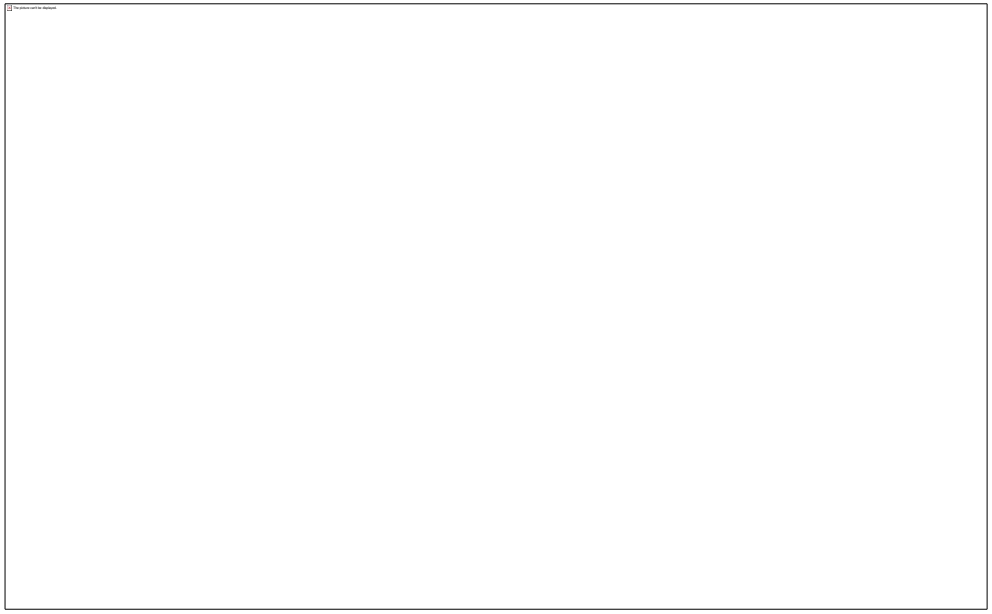
69 year old retired farmer, presents with fatigue



Anaemia

- Look for other cytopenias, and review film comments for signs of marrow failure or infiltration (circulating blasts, leucoerythroblastic changes)
- If anaemia is an isolated abnormality, consider MCV:
  - Low MCV:
    - **Iron deficiency**
    - Thalassaemia: screen appropriate ethnic groups using Hb electrophoresis
  - High MCV:
    - **B12/folate deficiency**: coeliac disease and pernicious anaemia
    - **Alcohol excess/liver disease**
    - Hypothyroidism
    - Haemolytic anaemia: look for high LDH/bilirubin, reticulocytosis and positive Coombe's test
    - Myelodysplastic syndrome
  - Normal MCV:
    - **Anaemia of chronic disease**
    - Mixed pathology
    - Multiple myeloma

69 year old retired farmer, presents with fatigue



Significant rouleaux is present.

Supplementary Report
Pancytopenia. Causes may include vitamin B12/ folate deficiency, drug effect, bone marrow infiltration, primary bone marrow disorders, hypersplenism, immune disorders.

69 year old retired farmer, presents with fatigue

Test Name	Result	Units	Reference Interval
Sodium	137	mmol/L	135 - 145
Potassium	5.2	mmol/L	3.5 - 5.5
Chloride	109	mmol/L	95 - 110
Bicarbonate	23	mmol/L	20 - 32
Anion Gap	5	mmol/L	5 - 15
● Calcium (Corrected)	**2.66 H**	mmol/L	2.10 - 2.60
Phosphate	1.44	mmol/L	0.80 - 1.50
● Urea	**11.5 H**	mmol/L	3.5 - 9.5
● Uric Acid	**0.517 H**	mmol/L	0.200 - 0.500
● Creatinine	**195 H**	umol/L	60 - 115
● eGFR	**27 L**		>59
Random Glucose	5.0	mmol/L	3.6 - 7.7
● Total Protein	**86 H**	g/L	63 - 80
Albumin	33	g/L	32 - 44
● Globulin	**53 H**	g/L	23 - 43
Bilirubin	12	umol/L	4 - 20
Alk Phos	74	U/L	35 - 110
AST	13	U/L	10 - 40
ALT	12	U/L	5 - 40
Gamma GT	14	U/L	5 - 50
LDH	151	U/L	120 - 250
● Cholesterol	**3.4 L**	mmol/L	3.9 - 5.5
Iron	12	umol/L	5 - 30
Haemolysis Index	2		0 - 40

What is the most likely diagnosis?

a) Iron deficiency anaemia
b) Multiple myeloma
c) Metastatic prostate cancer
d) DIC

What is the next appropriate investigation?

a) CRP/ESR
b) Serum electrophoresis and free light chains
c) PSA
d) Bone scan

Protein Studies

Albumin	33	g/L	32 - 44
Alpha 1	3	g/L	2 - 4
Alpha 2	7	g/L	4 - 9
Beta 1	4	g/L	2 - 6
Gamma	6	g/L	6 - 15
Abnormal Band *	**33 H**	g/L	<0.1
Total Protein	**86 H**	g/L	63 - 80
Immunofixation	**Monoclonal IgM Kappa and Kappa Light Chains ***		
Immunoglobulin G (Total IgG)	**5.09 L**	g/L	5.76 - 15.36
Immunoglobulin A (Total IgA)	**0.12 L**	g/L	1.24 - 4.16
Immunoglobulin M (Total IgM)	**31.60 H**	g/L	0.48 - 3.1
Beta 2 Microglobulin	**8.39 H**	mg/L	<3.0
Kappa Free Light Chains	**2240 H**	mg/L	7 - 22
Lambda Free Light Chains	12	mg/L	8 - 27
Kappa/Lambda Ratio	**186.67 H**		0.31 - 1.56

Monoclonal protein: when should I be worried?

- 5% of people aged over 70 will have a detectable monoclonal protein
- The majority will be 'MGUS' with risk of progression to MM approximately 1% per year
- Features that raise concern for myeloma:
  - Hyper**C**alcaemia
  - New **R**enal dysfunction
  - **A**naemia
  - **B**one pain due to lytic lesions
- It is worthwhile screening patients who present with any of these features using **serum electrophoresis *and* serum free light chains**

- When *not* to be worried about myeloma:
  - Polyclonal hypergammaglobulinaemia
  - raised ESR in the absence of a monoclonal protein
  - Mildly elevated light chains with normal ratio (common in CKD)

76 yo male, new patient to your practice, complains of lethargy

Test Name	Result	Units	Reference Interval
Haemoglobin	109 L	g/L	125 - 175
Haematocrit	0.33 L		0.38 - 0.54
Red cell count	3.0 L	10^12/L	4.2 - 6.5
MCV	109 H	fL	80 - 100
White cell count	3.5	10^9/L	3.5 - 10.0
Neutrophils	1.65	10^9/L	1.5 - 6.5
Lymphocytes	1.20	10^9/L	0.8 - 4.0
Monocytes	0.50	10^9/L	0 - 0.9
Eosinophils	0.05	10^9/L	0 - 0.6
Basophils	0.10	10^9/L	0 - 0.15
Platelets	149 L	10^9/L	150 - 400

What is the next most appropriate investigation?

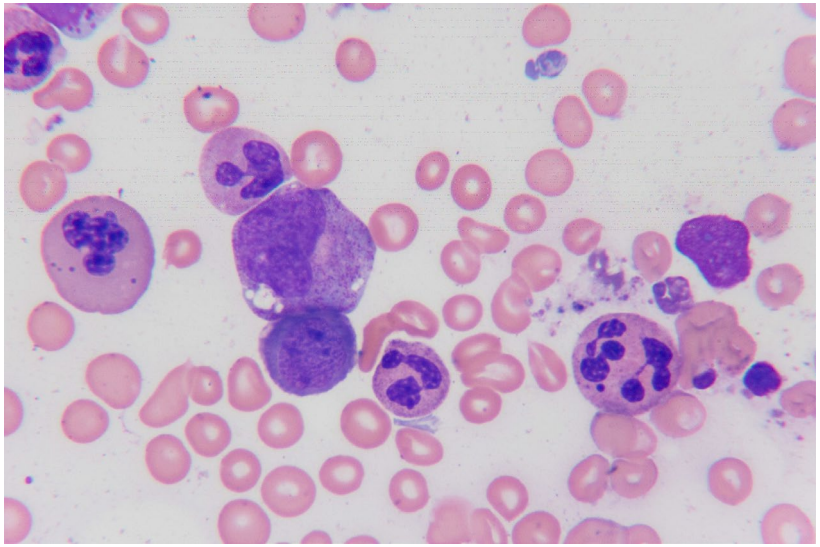
a) CRP/ESR
b) Serum electrophoresis and free light chains
c) PSA
d) B12/folate

Test Name	Result	Units	Reference Interval
Iron	22	umol/L	5 - 30
Transferrin	2.4	g/L	1.9 - 3.1
TIBC	61	umol/L	47 - 77
Saturation	36	%	20 - 45
Ferritin	120	ug/L	30 - 300
CRP	15 H	mg/L	<5
Active B12	>128	pmol/L	>35
Folate (Serum)	40	nmol/L	>7.0

								Latest Result		
Collection Date	29/08/2011	03/12/2012	12/02/2014	18/06/2015	10/05/2016	13/04/2017	04/06/2018	03/07/2018		
Collection Time	07:30	07:55	12:40	07:26	10:54	07:57	08:02	07:53		
LAB ID	584534995	590160095	595770307	616587558	623718996	634720408	642660026	642893353	Reference	Units
Haematology										
Haemoglobin	149	149	127	117 L	101 L	107 L	110 L	109 L	(125-175)	g/L
Haematocrit	0.45	0.44	0.39	0.37 L	0.32 L	0.33 L	0.34 L	0.33 L	(0.38-0.54)	
RCC	4.2	4.1 L	3.6 L	3.3 L	3.0 L	3.2 L	3.0 L	3.0 L	(4.2-6.5)	10^12/L
MCV	106 H	106 H	107 H	110 H	107 H	104 H	112 H	109 H	(80-100)	fL
WCC	4.9	5.5	5.0	3.1 L	3.5	3.2 L	3.4 L	3.5	(3.5-10.0)	10^9/L
Neutrophils	2.99	3.10	2.54	1.74	1.97	1.91	1.64	1.65	(1.5-6.5)	10^9/L
Lymphocytes	1.35	1.80	1.98	1.03	1.18	0.84	1.25	1.20	(0.8-4.0)	10^9/L
Monocytes	0.44	0.50	0.43	0.27	0.24	0.42	0.42	0.50	(0-0.9)	10^9/L
Eosinophils	0.06	0.10	0.05	0.06		0.03	0.06	0.05	(0-0.6)	10^9/L
Basophils	0.02	0.00	0.03	0.04		0.03	0.04	0.10	(0-0.15)	10^9/L
Platelets	153	155	165	190	149 L	148 L	141 L	149 L	(150-400)	10^9/L

Myelodysplastic syndrome

- Heterogeneous group of acquired marrow failure syndromes
- Incidence increases with age, prior chemotherapy and radiation exposure
- Generally see cytopenia/s in association with:
  - macrocytosis
  - abnormal cell morphology
  - left shift
  - constitutional symptoms, infections and easy bruising/bleeding



Pancytopenia

- Referral is appropriate in most cases once common causes have been excluded:
  - haematinic deficiency
  - drug effect (methotrexate)
  - hypersplenism (cirrhosis/portal hypertension)

Red flags

- Severe cytopenias
  - Hb <80g/L
  - Neut $<0.5X10^9$/L
  - Plts $<30X10^9$/L
- Abnormal film
  - Circulating blasts
  - Leucoerythroblastic features
  - Red cell fragmentation
  - Dysplastic changes
- Significantly raised LDH
- Abnormal coagulation studies

Thrombocytopenia (isolated)

- Very common and often mild (100-150x10^9/l)
- Consider common causes:
  - chronic liver disease
  - alcohol
  - hypersplenism
  - viral infection (EBV, Dengue etc)
  - medication effect
- Initial workup should include:
  - HIV and Hepatitis C serology
  - ELFT
  - Ultrasound upper abdomen
  - ANA
  - Coagulation screen

Red flags

- Severe thrombocytopenia <50x10^9/L
- Significantly elevated LDH
- New renal impairment
- Associated anaemia and/or red cell changes on film

Neutropenia (isolated)

- Infection risk increases when ANC <1x10^9/L
- Most often medication-related
  - antibiotics
  - antipsychotics
  - azathioprine, methotrexate
  - carbimazole
- Autoimmune and inherited causes are rare and usually present in childhood or young adulthood
- Ethnic variation
  - “Benign neutropenia” seen in patients from West Africa; usually > 1x10^9/L

Red flags

- Severe neutropenia <0.5x10^9/L
- Fevers/infection
- Abnormal coagulation studies
- Associated anaemia and/or red cell changes on film