Approach to abnormalities of the full blood count

Dr Nick Weber

Haematologist, RBWH
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

<table>
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<tr>
<th>Test Name</th>
<th>Result</th>
<th>Units</th>
<th>Reference Interval</th>
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<td>Platelets</td>
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</table>
Leucocytosis: differential diagnosis

- **Reactive leucocytosis**
  - Very common; usually mild-moderate (10-20 x $10^9$/L), with variable elevation of neutrophils, lymphocytes and monocytes; *occasional* immature forms; platelets may be normal or elevated
    - infection
    - drugs (eg steroids)
    - inflammatory conditions
    - pregnancy
    - smoking
    - trauma/surgery/burns ("leukaemoid reaction")

- **Chronic myeloid leukaemia**
  - Peripheral blood *PCR testing for BCR-ABL fusion gene* is simple and ~99% sensitive/specific

- **Other myeloproliferative neoplasms**: polycythaemia vera, myelofibrosis
  - Generally distinguishable by associated findings of erythrocytosis, abnormal red cell morphology
  - *JAK2 and CALR mutation testing* may be helpful to confirm

- **Chronic myelomonocytic leukaemia**: usually older patients, dysplastic findings on film with prominent, chronic monocytosis
68 year old male painter presents with 3 months fatigue and abdominal discomfort, vague weight loss. Massive splenomegaly on abdominal examination.

What is the most likely diagnosis?

a) Reactive  
b) Chronic myeloid leukaemia  
c) Acute 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
69 year old non-smoking IT technician presents with lethargy for last 2 years
Mild cervical lymphadenopathy, no splenomegaly

What is the most likely diagnosis?
   a) HIV
   b) Lymphoma
   c) EBV infection
   d) Chronic lymphocytic leukaemia

What is the next appropriate investigation?
   a) Serum electrophoresis
   b) CRP/ESR
   c) BCR-ABL fusion gene testing
   d) Cell surface markers (by flow cytometry)
Peripheral Blood Surface Markers

Lymphocytes comprise 68%.
T-cells 33% CD4/CD8: 1.0
B-cells 60% kappa/lambda: >100.0
NK-cells 7%
A monoclonal B-cell population comprises 59% of lymphocytes
The phenotype is:
CD5 +ve  CD10 -ve  CD19 +ve  CD20 +ve (weak)
CD23 +ve  FMC7 -ve  CD79b -ve  SMIg kappa (weak)
ZAP-70 -ve  CD38 -ve

Comments

Results are most consistent with the diagnosis of B-cell chronic lymphocytic leukaemia (CLL).
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
Approach to polycythaemia

- **Primary** - “polycythaemia vera”
  - *Serum EPO usually below normal*
  - 95% of cases carry *JAK2 V617F mutation*, detectable on peripheral blood
  - Often associated with increased platelets and WCC

- **Secondary**
  - *Serum EPO usually normal or increased*
  - Smoking
  - Chronic lung disease, sleep apnoea
  - Testosterone replacement or abuse
  - Dehydration: “spurious” polycythaemia
  - EPO-secreting tumours (RCC, HCC, endometrial…)

Red flags

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

• Most commonly a reactive finding in response to:
  − Infection or inflammation
    o 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
  o visual disturbance
  o headache
  o epistaxis
69 year old retired farmer, presents with fatigue

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<td>g/L</td>
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**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

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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

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
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**Monoclonal IgM Kappa and Kappa Light Chains**
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:
  − Hypercalcaemia
  − New Renal dysfunction
  − Anaemia
  − Bone 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

What is the next most appropriate investigation?

a) CRP/ESR
b) Serum electrophoresis and free light chains
c) PSA
d) B12/folate
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<th>Test Name</th>
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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)

<table>
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<tr>
<th>Red flags</th>
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</table>
| - 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
Summary

• FBC abnormalities should not be interpreted in isolation

• Always consider film comments and results of the ELFT and coagulation profile

• If red flags are absent and first-line investigations are normal, it is entirely appropriate to monitor abnormalities with periodic FBC review
  – assess chronicity and trend
  – emergence of new abnormalities
  – spontaneous resolution

• If in doubt, a quick phone call to the Haematologist on call may spare the patient unnecessary appointments and investigations