When do I work up an elevated White Blood Cell count?

James Johnston MD FRCPC
Department of Medical Oncology & Haematology, CancerCare Manitoba
Dept. Internal Medicine, Section of Hematology/Medical Oncology, University of Manitoba
Disclosures

1. Grant support from Roche, Lundbeck, Gilead and Johnson & Johnson pharmaceuticals

2. Advisory boards for Roche, Lundbeck, Gilead and Johnson & Johnson pharmaceuticals

3. Participate in clinical trials sponsored by Roche, Gilead and Millenium

4. Canadian CLL Research Meeting supported by Roche, Gilead, Lundbeck, Johnson & Johnson and Glaxo-Smith Kline
Objectives

1. To know how to work up a case of leukocytosis

2. To know what flow cytometry is and how/when to order this test

3. To know when to refer a patient with leukocytosis
Work-Up of LEUKOCYTOSIS

Leukocytosis >11 (Repeated)

Blood Smear AND History & Physical Exam include nodes and spleen

Lymphocytes ↑ >4

Refer to Lymphocytosis Pathway

EMERGENT REFERRAL
Page Hematologist On-Call
StB: 204-237-2053 / HSC: 204-787-2071

Blasts on Smear

Myeloid Cells

Basophils ↑

Concerning Features
- Count >2 or increasing, or persistent
- Not explained by infection
- Dyeplasia
- Immature forms
- Anemia/thrombo-cytopenia
- Spleenomegaly

YES

NO

Consider
- Cancer
- Collagen VD
- Chronic infection
- Marrow recovery

YES

NO

REFER TO CCMB HEMATOLOGY

Treat and Observe for recovery

Monocytes ↑

Concerning Features
- Count >2 or increasing, or persistent
- Dysplasia
- Basophilia
- Spleenomegaly
- NOT associated with acute infection

YES

NO

Treat and Observe for recovery

Neutrophils ↑

Concerning Features
- Count >50
- Promyelocytes and myelocytes
- Dyeplasia
- Basophilia
- Splenomegaly

YES

NO

REFER TO CCMB HEMATOLOGY

Eosinophils ↑

Concerning Features
- Count >2 or increasing or persistent
- Dysplasia
- Anemia
- New organ damage
- NOT explained by infection, allergies or collagen vascular disease

YES

NO

Refer to Lymphocytosis Pathway

NO

REFER TO CCMB HEMATOLOGY

Treat and Observe for recovery

Pathways are subject to clinical judgment and actual practice patterns may not always follow the proposed steps in this pathway.
Work-Up of LYMPHOCYTOSIS

Lymphocytes >4 (repeated)

Any of these Concerning Features
- Lymphocytes >30
- Hgb <100
- Night sweats/ weight loss
- Splenomegaly

Flow Cytometry
AND
REFER TO CCMB HEMATOLOGY

Asymptomatic

Flow Cytometry

IF Persistent

Normal / Polyclonal

Rule out secondary causes
- Immunization
- Viral (eg. Hepatitis, CMV, EBV, adeno)
- Bacteria
- Drugs (eg. Steroids)
- Autoimmune
- Smoking
- Endocrine (eg. Myxedema, Addison’s, hypopituitarism)

Abnormal / Clonal
- B Cells
- T Cells
- NK Cells

REFER TO CCMB HEMATOLOGY

“Reactive” Lymphocytes
Patient symptoms of infection or acute illness

Work-up for secondary causes
- Immunization
- Viral (eg. Hepatitis, CMV, EBV, adeno)
- Bacteria
- Drugs (eg. Steroids)
- Autoimmune
- Smoking
- Endocrine (eg. Myxedema, Addison’s, hypopituitarism)

Pathways are subject to clinical judgment and actual practice patterns may not always follow the proposed steps in this pathway.
Secondary lymphocytosis

1. Immunization
2. Viral (eg hepatitis, CMV, EBV, adeno)
3. Bacterial
4. Drugs, eg, steroids
5. Autoimmune
6. Smoking
7. Endocrine (myxedema, Addison’s, hypopituitarism)

May be B cell, T cell or NK cell
Malignant Lymphocytosis

1. B cell
   1. Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)
   2. Lymphomas with leukemic involvement

2. T cell
   1. Large granular lymphocytic leukemia
   2. Lymphomas with leukemic involvement

3. NK cells
   1. NK cell leukemia

About 150 cluster differentiation (CD) markers to differentiate blood cell of origin
Performed at HSC or St B. Ensure you state what you are looking for!
## Flow Cytometry

<table>
<thead>
<tr>
<th></th>
<th>CD19</th>
<th>CD5</th>
<th>CD23</th>
<th>CD10</th>
<th>CD25</th>
<th>CD79b</th>
<th>FMC7</th>
<th>CD103</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
<td>-/+</td>
<td>-</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>++</td>
<td>-/+</td>
<td>-/+</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>-/+</td>
<td>-</td>
<td>++</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Marginal zone lymphoma</td>
<td>+</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Hairy cell leukemia</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Lymphoplasmacytid lymphoma</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-/+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Marginal zone lymphoma</td>
<td>+</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

Cells must be monoclonal for kappa or lambda light chains!
### Hematology
#### CBC

<table>
<thead>
<tr>
<th>Test Name</th>
<th>03/12/2014</th>
<th>Reference Range</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>9.6</td>
<td>4.5-11.0</td>
<td>x10E9/L</td>
</tr>
<tr>
<td>RBC</td>
<td>3.43</td>
<td>4.4-5.9</td>
<td>x10E12/L</td>
</tr>
<tr>
<td>Hgb</td>
<td>92</td>
<td>140-180</td>
<td>g/L</td>
</tr>
<tr>
<td>MCT</td>
<td>0.304</td>
<td>0.4-0.52</td>
<td>L/L</td>
</tr>
<tr>
<td>MCV</td>
<td>58.6</td>
<td>80-98</td>
<td>fl</td>
</tr>
<tr>
<td>MCH</td>
<td>26.8</td>
<td>26-34</td>
<td>pg</td>
</tr>
<tr>
<td>MCHC</td>
<td>303</td>
<td>320-365</td>
<td>g/L</td>
</tr>
<tr>
<td>RDW-CV</td>
<td>18.5</td>
<td>11.4-14.4</td>
<td>%</td>
</tr>
<tr>
<td>PLT</td>
<td>180</td>
<td>140-440</td>
<td>x10E9/L</td>
</tr>
<tr>
<td>MPV</td>
<td>9.2</td>
<td>9.4-12.4</td>
<td>fL</td>
</tr>
<tr>
<td>% NEUTS</td>
<td>2.0</td>
<td>1.8-5.4</td>
<td>x10E9/L</td>
</tr>
<tr>
<td>% LYMPHS</td>
<td>6.8</td>
<td>1.3-3.2</td>
<td>x10E9/L</td>
</tr>
</tbody>
</table>

**Hematopathologist Smear Review:**

Hematopathologist Interpretation: Recommend recollection of peripheral blood for flow cytometry immunophenotypic analysis to rule out a lymphoproliferative disorder. Reviewed by Dr. Ping Sun (PH: 204-258-1114, Pager: 204-915-2908).
To be malignant cells need to be monoclonal, ie, either kappa (K) or lambda (L)
- CD19+ , CD5+ and CD23+ is diagnostic for CLL cells
- ZAP-70 and CD38 are prognostic markers
- Pt has CLL

<table>
<thead>
<tr>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Phenotyping</td>
</tr>
<tr>
<td>FLOW CYTOMETRY COMMENT:</td>
</tr>
<tr>
<td>The sample contains 50% lymphocytes. 20% are T cells CD4/8=3, 7% NK cells, and the rest are K+dim, CD20+dim, CD19+, CD5+, CD23+, CD43+, CD79b+dim, CD38-, ZAP70- B cells. Phenotypic findings are consistent with chronic lymphocytic leukemia. Morphological and clinical correlation required. The ZAP-70 results ( % of CLL cells in which ZAP-70 expression is detected) provided are to be interpreted and used at the discretion of the requesting physician. Method adapted from Rassenti et al N Engl J Med 2004 August 26; 351(9):893-901.</td>
</tr>
</tbody>
</table>

Flow Cytometry Signed By: Dr. Carmen Morales
### Immunophenotype for 71 Normal Individuals >50 years with Lymphocytes >4

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>41%</td>
</tr>
<tr>
<td>CLL immunophenotype</td>
<td>38%</td>
</tr>
<tr>
<td>Other lymphomas</td>
<td>7%</td>
</tr>
<tr>
<td>NK cells</td>
<td>7%</td>
</tr>
<tr>
<td>T-cell LGL</td>
<td>7%</td>
</tr>
</tbody>
</table>

Likelihood of being abnormal increases with:
- patient age
- lymphocyte count

Take-Home Message

- If blasts on smear phone ‘hematologist-on-call’ at SBGH or HSC

- Most leukocytosis are transient and are a response to infection, inflammation or drugs

- Mild peripheral lymphocytosis is common in older patients and cause can be diagnosed by flow cytometry
Question: An asymptomatic 72 year old man is found on routine blood work to have a lymphocyte count of 56. Physical exam normal. What would be your next option:

a) Screen for EBV and HIV
b) Bone marrow
c) CT scans of chest and abdomen
d) Flow cytometry
Questions?

James Johnston
james.johnston@cancercare.mb.ca