Common Consultations in Outpatient Hematology in 30 mins

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Disclosures:

None
Objectives:

1- Decrease referrals to heme/onc for mild heme abnormalities (leukocytosis, thrombocytopenia)
2- Appropriate evaluation and management of thrombocytosis;
3- Identify areas of concern re: low platelet counts, when to worry about bleeding and when to worry about thrombosis
4- Identify normal variation in leukocytosis and common reversible etiologies
Case I

• A 22 y old woman is seen by her PCP because of her plt count of 5K. She felt healthy until 1 week ago, when she noticed that she was bruising easily and had gingival bleeding with flossing. She has no significant medical history and is not taking any medications. Her plt count 1 year ago was normal.

• On PE: scattered ecchymosis over arms and petechia over the shins. There is no lymphadenopathy or splenomegaly.

• CBC: Hgb, 12 (normal) WBC 7.9 with normal Diff; plt 3K
ITP

• Diagnosis of exclusion
• Hx and PE – normal (apart from symptoms and HX of bleeding)
• Specifically no splenomegaly, no drugs, no viral infections (incl HIV), no SLE or other autoimmune disease
• CBC -isolated thrombocytopenia
Causes of Thrombocytopenia

- Immune
  - Primary
    - Idiopathic Thrombocytopenia Purpura
      1. Drug Induced,
      2. HIV,
      3. Hepatitis C
      4. SLE,
      5. Haematological Malignancy
  - Secondary
    1. Hypersplenism
    2. Myelodysplasia
    3. Acute Leukaemia,
    4. Drug Induced Bone Marrow Suppression

- Non-immune
ITP

**Acute**
- 2-6 years old
- No sex predilection
- Prior infection
- Abrupt onset
- Plst <20 K
- 6-8 weeks duration
- Usually spontaneous remissions

**Chronic**
- 20-40 yrs
- Women 3:1
- No infection
- Insidious
- Plts 20-80K
- Chronic
- Unusual remission
Recommendations for surgery

**Surgery**
- Dental prophylaxis (cleaning/scaling)
- Simple dental extraction
- Complex Dental Extraction
- Minor Surgery
- Major Surgery
- Major Neurosurgery

**Recommended plt counts**
- >20-30,000
- >30,000
- >50,000
- >50,000
- >100,000

Cuker A and Cines DB Hematology 2010; p 377-384
ITP practice guideline- adult

• Rx with steroids is indicated
  – When plts<20-30,000
  – When plts <50,000 and there is significant mucous membrane bleeding

• Hospitalization is indicated:
  – In patients with plts<20,000 & significant mucous membrane bleeding (wet purpura) or in non-compliant pt

George JN et al, Blood 1996; 88:3-4
Wet purpura
ITP steroid Rx

• Prednisone orally 1 mg/kg
  – Improvement usually within 3 days
  – Max improvement in 14 days

• Dexamethasone orally 40 mg x4
  – Max response at 7 days, 50% sustained response
  – Plts counts < 90,000 – high relapse risk, most within 3 months

Cheng Y et al, NEJM 2003;349:831-6
Diagnosis

- Initial treatment
- Manage conservatively

Splenectomy

- TPO-ra if splenectomy contraindicated
- No response to splenectomy

TPO-ra

- Response
  - Continue for 1–5 yrs, try to taper
- No response or relapse
  - Rituximab

Anticipate splenectomy if required by tx toxicity or unresponsiveness (TPO-ra as a bridge to splenectomy may be considered)
Clinical Pearl 1- ITP

- Most pts with stable mild thrombocytopenia (plts counts 100-150K) do not develop worsening thrombocytopenia or other autoimmune disease
KEEP CALM AND Beat ITP
Case 2

- A 22 y old woman found to have gradually decreasing plt counts from 180K to 38 K over the past 4 months
- Her only medication is valproic acid started 12 months ago and which has led to good seizure control
- She reports no episodes of bleeding and there is no obvious bruising or petechia on PE
Drug-induced thrombocytopenia

- Frequency is uncertain
- Frequency of medication use increases with age
- Frequency of alternative medicine use is increasing at all ages
- Usually first diagnosed as ITP
- Correct diagnosis is essential to:
  - Avoid inappropriate treatment
  - Prevent recurrences
Clinical Pearl 2- Drug Induced Thrombocytopenia

• Thrombocytopenia caused by medication may be immune mediated or dose dependent
Case 3

• A 55 y old man was found to have a leukocytosis on routine CBC. The patient has no fatigue, fever, chills, night sweats, or unintentional weight loss. His other medical problems include well controlled HTN and allergic rhinitis.
• He has smoked 1 pack of cigarettes per day for the last 30 years.
• Meds: HCTZ
• PE: afebrile and VSS, exam is negative for lymphadenopathy or splenomegaly
• CBC: diff – elevation of absolute number of leukocytes with increase in immature neutrophilic cells
• His Hgb and plts are normal and WBC is stable in comparison with 4 weeks ago
Elevation of WBC count

• Acute rapid: changes in distribution (demargination)

• Chronic elevation: chances in production and release from storage
If myeloid cells are present, the leukocytosis should be stratified into neutrophilia, monocytois, basophilia, or eosinophilia; more than one type of leukocytosis may be present.
High WBC Count (Leukocytosis)  

Low WBC Count

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Clinical Pearl 3A-Leukocytosis

• Smoking one of the most common causes in asymptomatic patient
• The leukocyte count in smoker can be 25% higher than value within normal range
• After smoking cessation WBC can normalize
Differential Diagnosis of Neutrophilia Secondary to other illnesses

- Infection
- Acute: demargination/release storage pool
- Chronic: granulomatous dx (leukoerythroblastic)
- Stress
- Drug induced (steroids, B-agonist, lithium)
- Chronic inflammation (including smoking-one of the most common causes)
- Post-splenectomy
- Non-hematologic malignancy
- Marrow stimulation (ITP, hemolysis, CMT)
- Sterile inflammation (MI, burn)
Clinical Pearl 3B-Neutrophilia

- Neutrophilia should prompt examination for left shift, signs of activated neutrophils, basophilia, dysplasia, and degree of leukocytosis.
- Most neutrophilias are reactive in nature.
- WBC count < $50 \times 10^9$/L, but usually < $30 \times 10^9$/L, is typical.
- Signs of activated neutrophils, mild left shift, and an absence of basophilia all suggest a reactive process.
Differential Diagnosis of Neutrophilia
Primary Hematologic Disease

• CML (BCR-ABLE)
• Other myeloproliferative neoplasm- usually will have elevated Hg or plt counts or splenomegaly (JAK2)
Clinical Pearl 3C- Leukocytosis

• Marked leukocytosis of $>50 \times 10^9$/L, marked left shift, dysplasia, or basophilia should prompt a BM examination to evaluate for a myeloid malignancy.

• Basophilia, although rare, is most suggestive of a MPN, especially CML.

• PCR for $BCR-ABL1$ and $JAK2$ mutational studies can be performed in blood, but a BM examination with cytogenetic studies should also be performed.
Case 4

• 23 y old college student who plays football presents to his PCP with 2 week Hx of extreme fatigue and sore throat and new–onset fever of 101F. He has no significant PMHx.

• On PE: T 101.2F and he has posterior cervical lymphadenopathy, splenomegaly, an erythematous posterior pharynx with whitish-gray exudate and generalized macularpapular rash on his trunk and neck. He takes proton pump inhibitor fro GERD.

• His Lab work :
  – Hgb, plt- normal; WBC 12.9; differential Neutr- 22%(low); Lymp-75%( high); Mono -3% ( normal); Baso- 1%( normal)
Clinical Pearl 4A

• 50% have splenomegaly and at risk of rare complication as spontaneous or trauma-induced splenic rupture – should avoid sports
Differential diagnosis of lymphocytosis Secondary to Illness

• Viral illnesses
  – Mononucleosis s-m
  – CMV
  – EBV
  – HIV

• Pertussis
• Cat scratch disease
• Toxoplasmosis
• Babesiosis
• Drug reaction
• Reactive granular lymphocytosis
• Post splenectomy lymphocytosis
Differential diagnosis of lymphocytosis

Primary hematologic disease

- CLL
- Monoclonal B cell lymphocytosis
Clinical Pearl 4B

- Age of the patient (CLL is more common in middle-aged to elderly adults)
- Correlation with clinical findings is necessary; a monospot test for EBV or viral serologies can also be performed, Hx of prior diagnosis of lymphoma
- A pleomorphic lymphocytosis favors a reactive lymphocytosis.
- If monomorphc lymphocytosis is present, a lymphoproliferative disorder should be searched for using flow cytometric immunophenotyping.
- Depending on these results, select molecular genetic tests will be helpful. (Refer to Hematology)
- A BM biopsy or extramedullary tissue biopsy may be necessary for a final diagnosis of lymphoma.
Differential diagnosis of Eosinophilia Secondary to Illness

• Allergic rhinitis
• Asthma
• Tissue invasive parasite
• Bronchopulmonary aspergillosis
• HIV
• Vasculitis
• Adrenal insufficiency
• GI symptoms (infection, IBD)
• Occult malignancy
Differential diagnosis of Eosinophilia
Primary hematologic disease

• Hypereosinophilic syndrome
Clinical Pearl 4C

• Most eosinophilias are reactive in nature and should be evaluated
• Once reactive eosinophilias are excluded, myeloid and lymphoid neoplasms with eosinophilia and \textit{PDGFRA, PDGFRB,} and \textit{FGFR1} should be searched for by performing a BM examination, cytogenetic studies, and FISH or PCR for the \textit{PDGFRA} mutation (Refer to Hematology)
Differential diagnosis of Monocytosis Secondary to Other illnesses

- Pregnancy
- TB
- Syphilis
- Sarcoidosis
- SLE
- Aslenia
- Corticosteroids
Clinical Pearl 4D

- Most monocytoses are reactive in nature.
- If reactive causes have been excluded, a persistent monocytosis of more than 3 months or the findings of dysplasia, blast cells, or significant left shift should trigger a BM examination to evaluate for malignancy. (Refer to Hematology)
Differential diagnosis of monocytosis
Primary hematologic disease

- Juvenile myelomocytic leukemia
- Chronic myelomonocytic leukemia
- Acute monoblastic/monocytic leukemia
- CML
- Atypical (BCR-ABL negative) CML
- Myelodysplastic/myeloproliferative neoplasms, unclassifiable
Case 5

- A 45 year old previously healthy female landscaper complains of increasing fatigue and numbness on her face and legs for 3 weeks.
- CBC – plts 1,062K
- Her iron studies and inflammatory markers (Sed rate and C reactive protein)-normal
- FISH BCR-ABL: negative
- Jak-2: mutated
Blood smear of thrombocytosis

- Normal Platelets
- Thrombocytosis
Thrombocytosis

• Primary
  – Essential Thrombocythemia
  – Other forms of myeloproliferative disorders- chronic myelogenous leukemia, polycythemia vera, myelofibrosis
# 2008 World Health Organization (WHO) Diagnostic Criteria for Essential Thrombocythemia

Diagnosis requires meeting all 4 criteria

1. Sustained platelet count $\geq 450 \times 10^9$/L

2. Bone marrow biopsy specimen showing proliferation mainly of the megakaryocytic lineage with increased numbers of enlarged, mature megakaryocytes; no significant increase or left shift of neutrophil granulopoiesis or erythropoiesis

3. Not meeting WHO criteria for PV$^a$, PMF$^b$, BCR-ABL1+ CML$^c$, MDS$^d$, or other myeloid neoplasms

4. Demonstration of \textit{JAK2V617F} or other clonal marker; or in the absence of \textit{JAK2V617F}, no evidence for reactive thrombocytoysis$^e$

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CML, chronic myelogenous leukemia; ET, essential thrombocythemia; JAK, Janus-associated kinase; MDS, myelodysplastic syndrome; PMF, primary myelofibrosis; PV, polycythemia vera.

$^a$Requires the failure of iron replacement therapy to increase hemoglobin level to the PV range in the presence of decreased serum ferritin. Exclusion of PV is based on hemoglobin and hematocrit levels, and red cell mass measurement is not required.

$^b$Requires the absence of relevant reticulin fibrosis, collagen fibrosis, peripheral blood leukoerythroblastosis or markedly hypercellular marrow accompanied by megakaryocyte morphology that is typical for PMF (small to large megakaryocytes with an aberrant nuclear/cytoplasmic ratio and hyperchromatic, bulbous, or irregularly folded nuclei and dense clustering).

$^c$Requires the absence of BCR-ABL1.

$^d$Requires the absence of dyserythropoiesis and dysgranulopoiesis.

$^e$Causes of reactive thrombocytoysis include iron deficiency, splenectomy, surgery, infection, inflammation, connective tissue disease, metastatic cancer, and lymphoproliferative disorders. However, the presence of a condition associated with reactive thrombocytoysis does not exclude the possibility of ET if the first 3 criteria are met.
Primary Driver Mutations for Essential Thrombocythemia

• Jak2V617F mutation in 2005 -50% of the pts
• Clarified that mutation is a primary cause of thrombosis
  – MPLW515L &K - 5%
  – CALR – 30% in 2013
  – “Triple negative “ ET - 10%
Prediction of Thrombosis in ET, by IPSET

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<th>Score</th>
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<td>Age &gt; 60 years</td>
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<tr>
<td>Cardiovascular risk factors</td>
<td>1 point</td>
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<tr>
<td>Previous thrombosis</td>
<td>2 points</td>
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<tr>
<td>JAK2V617F</td>
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Risk Categories/score

<table>
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<tr>
<th>Category</th>
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<tr>
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<tr>
<td>Intermediate</td>
<td>2</td>
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<tr>
<td>High</td>
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Essential thrombocythemia clinical features

• Chronic thrombocytosis (often extreme, >1 million)
  – Many pts are asymptomatic
  – Vasomotor symptoms: headache, syncope, visual disturbances, atypical chest pain, erythromelalgia (typically ASA-responsive)

• Thrombocytosis major cause of morbidity and mortality
  – Both arterial and venous; unusual sites
  – No clear association with platelet counts

• Paradoxical increase in bleeding complications
  – Risk factors /associations:
    - Extreme thrombocytosis >1 million (controversial)
    - Use of ASA >325 mg/day or other NSAIDS
    - Acquired WVD

• Splenomegaly
Thrombocytosis

• Secondary
• Inflammation
• Surgery (which leads to increase inflammatory state )
• Hyposplenism or asplenia
• Hemorrhage or/ and iron deficiency
• Malignancy
• Trauma
• Infection
Clinical Pearl 5

• Increased level of inflammatory mediators IL-1β, IL-6, IL-11 have been associated with reactive thrombocytosis

• C-reactive protein is a surrogate marker for increased IL-6; can suggest an occult inflammation

• Absolute value of plt counts can not help distinguish reactive thrombocytosis from ET
CHECK YOUR STRESS LEVEL
Appendix
Life span of Myeloid cells

• Maturation in bone marrow: 7-10 days
• Circulation in peripheral blood: 3-6 hours
• Residence in tissues: 2-3 days
• Peripheral neutrophil counts <5 % of total WBC pool, 2% of the total WBC lifespan
White blood cell count

- Myeloid precursors: 20%
- Storage pool: 75%
- Marginating pool: 3%
- Circulating pool: 2%