Urgent Calls in Pathology- Hematology

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Presentation Summary

- This presentation is intended to highlight the clinical and morphologic features of hematologic disease processes encountered during general pathology call that necessitate recognition and urgent communication with providers.
- Learning Objectives: At the conclusion of this presentation, participants will be able to:
  - Recognize common clinical presentations and peripheral smear morphology of urgent hematologic conditions including general neoplastic, hemolytic, and infectious entities.
  - Make appropriate recommendations for additional clinical and pathologic testing based upon review of peripheral smear findings.

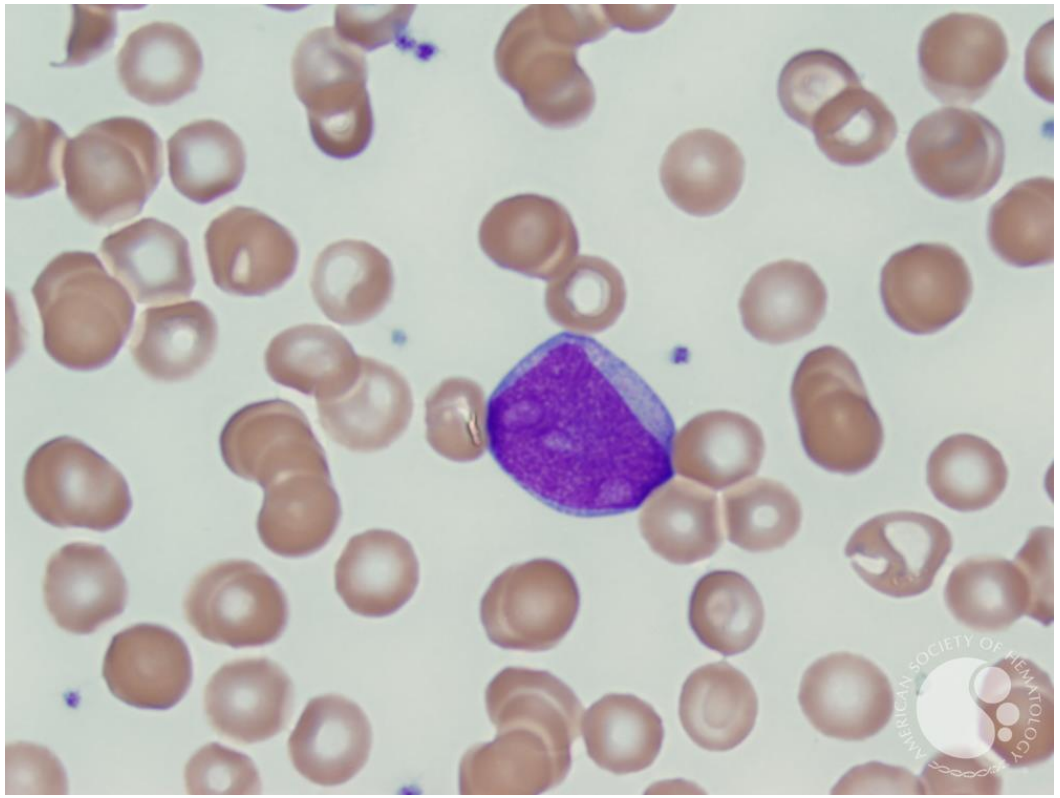
Scenario #1

The phone rings. You answer, and you hear the nervous voice of one of the hematology techs. “Doctor…there is a patient in the E.D., and I think I am seeing some blasts on the peripheral blood smear. Could you come in and confirm?”

Things to know before you go…

- Clinical history is vitally important to morphologic interpretation in hematopathology
  - Things I like to know:
    - CBC values (essential): focus on WBC, Hgb, and Plt
      - The more values are abnormal the more worried you should be
      - The more abnormal the values are the more worried you should be
    - Disease history (helpful to essential)
      - Diagnoses to recognize: AML, ALL, CLL, MPNs (CML, PV, PMF, ET), lymphoma, solid tumors
      - Is patient receiving chemotherapy?
      - Is patient receiving G-CSF therapy (Neulasta/Neupogen/Granix/filgrastim/pegfilgrastim)?
    - Duration of count abnormalities (helpful)
    - Clinical presentation (helpful)
- Diagnostic criteria for acute leukemia is 20% or more blasts in the peripheral blood or bone marrow

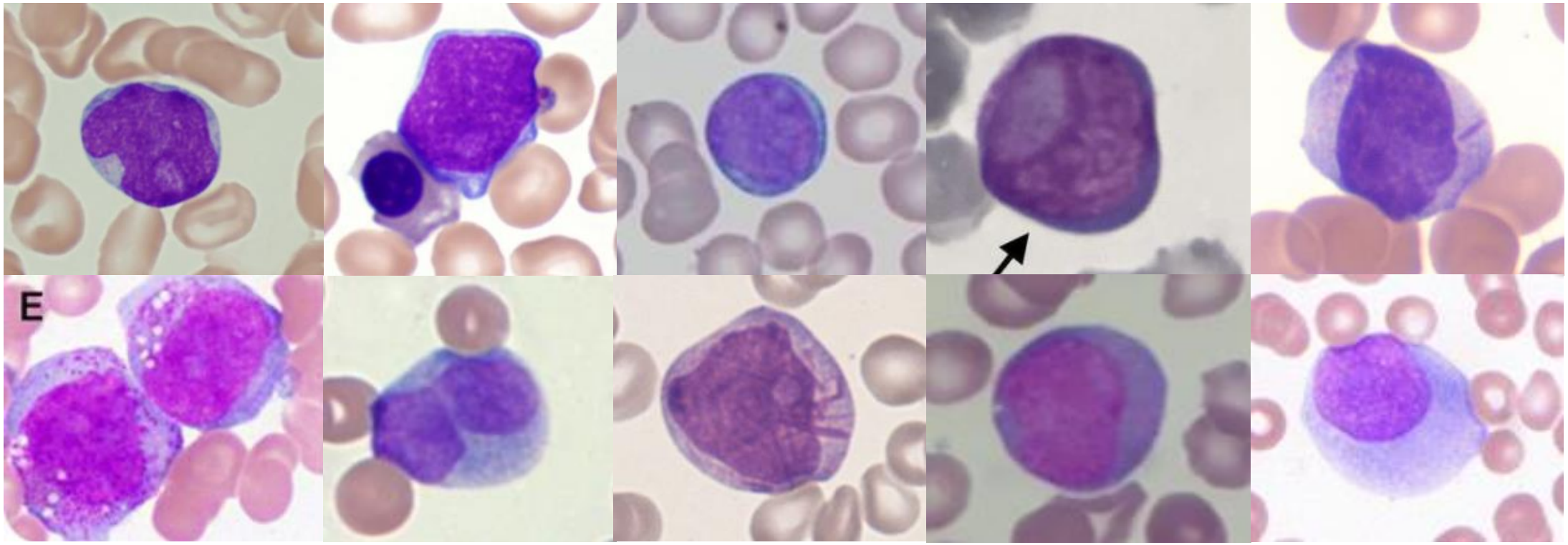
Morphologic Identification of Blasts



ASH Image Bank- Courtesy of Dr. Elizabeth L. Courville, MD

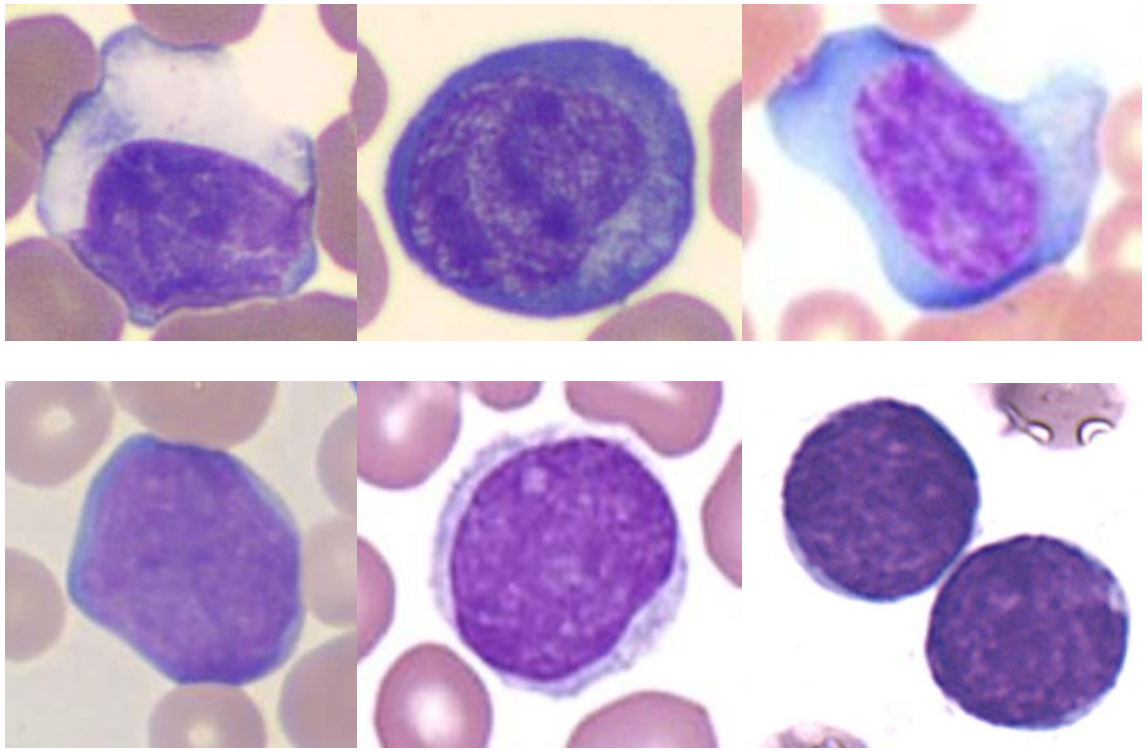
- <u>No single characteristic identifies a blast</u>
- In general:
  - Medium to large cell size (typically ≥ monocyte)
  - Large nucleus (high N:C ratio)
  - Immature chromatin (speckled/lacy)
  - Prominent nucleoli (1-2)
  - Scant cytoplasm, few to no cytoplasmic granules
    - Exception: APML
  - Auer rods

Morphologic Identification of Blasts



ASH Image Bank- Courtesy of Drs. Elizabeth L. Courville, Perla Vicari, Timothy Carll, Megan Parilla, Jie Xu, Wendy Moreland, Marco Gambassi, and Maria Proytcheva

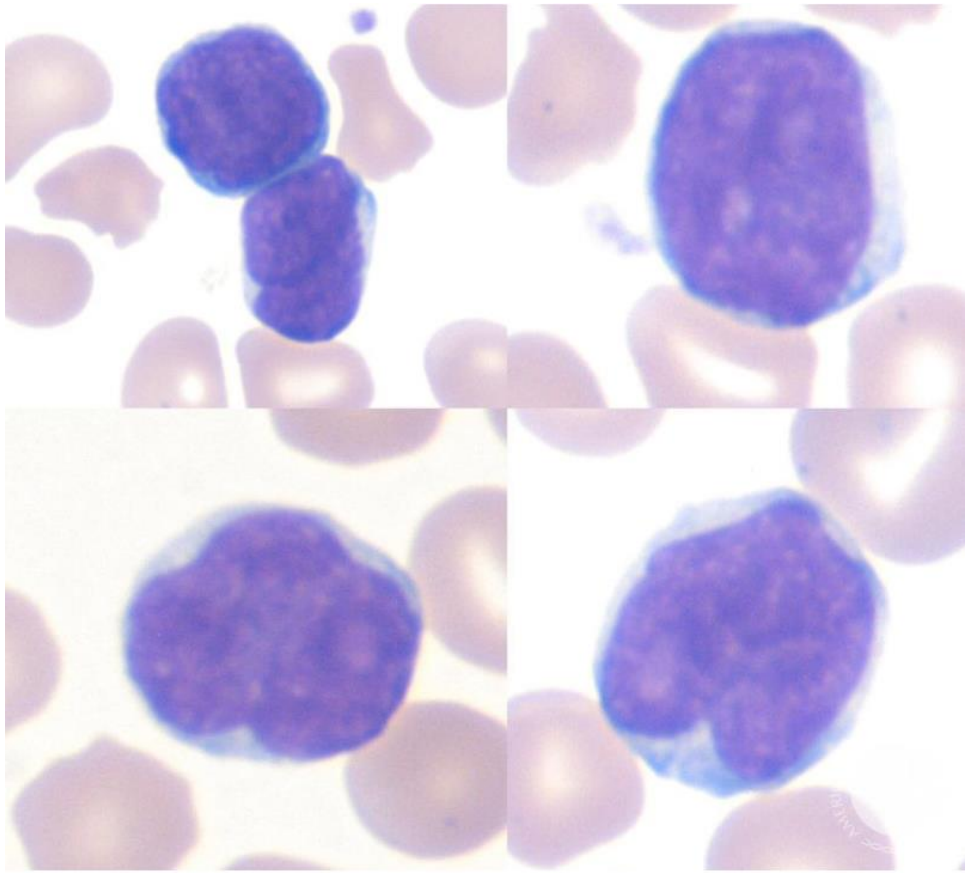
Blast Identification- Blasts vs. Reactive Lymphs



ASH Image Bank- Courtesy of Peter Maslak, Mark Frattini, Dr. Girish Venkataraman, John Lazarchick, Dr. Teresa Scordino

- Helpful clues:
  - Reactive lymphocytes should form a polymorphic spectrum of cells
  - Reactive lymphocytes tend to maintain nuclear shape and have lower N:C ratio
  - Reactive lymphocytes have a more mature chromatin pattern that can look “pulled”
  - Reactive lymphocytes have less conspicuous nucleoli
  - Reactive lymphocytes “reach out” for neighboring cells and show dark blue cytoplasm at interface
- <u>Know the CBC values!</u>

Blast Identification- Kiddie Lymphocytes

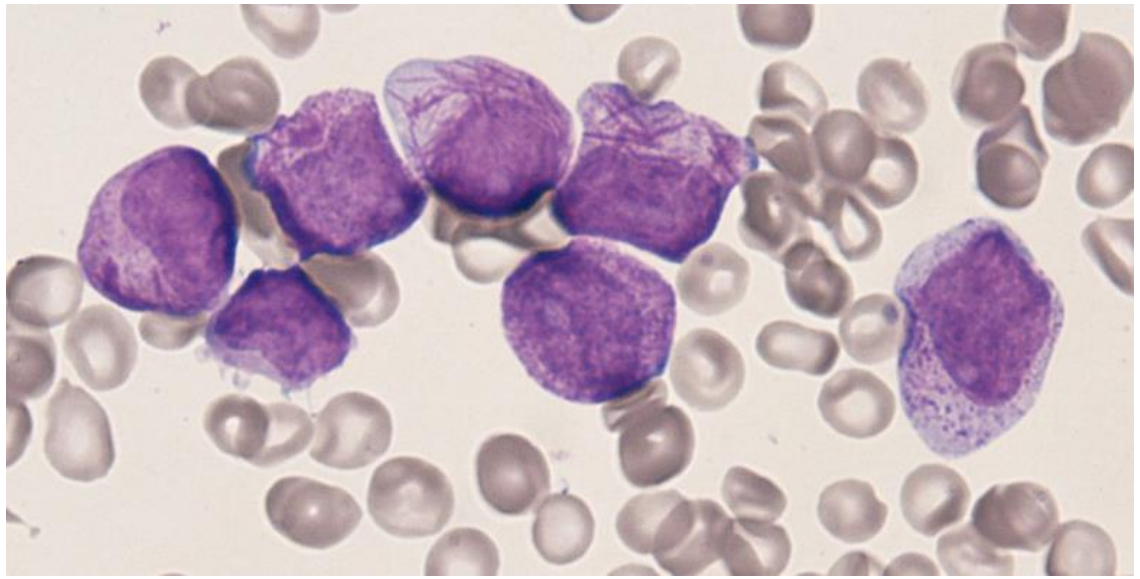


ASH Image Bank- Courtesy of Peter Maslak

ASH Image Bank- Courtesy of Dr. Girish Venkataraman

- Children have a normal spectrum of polymorphous lymphocytes that look “atypical” relative to those of adults
- Lymphocytes show a higher N:C ratio, finer chromatin pattern, and clefted and irregular nuclei
- May see an atypical lymphocytosis in association with infection- Pertussis
- Can show morphologic overlap with lymphoblastic leukemia cells
  - Remember to look at many cells for polymorphism
  - Know the CBC counts and clinical presentation
- Flow cytometry may be necessary in challenging cases

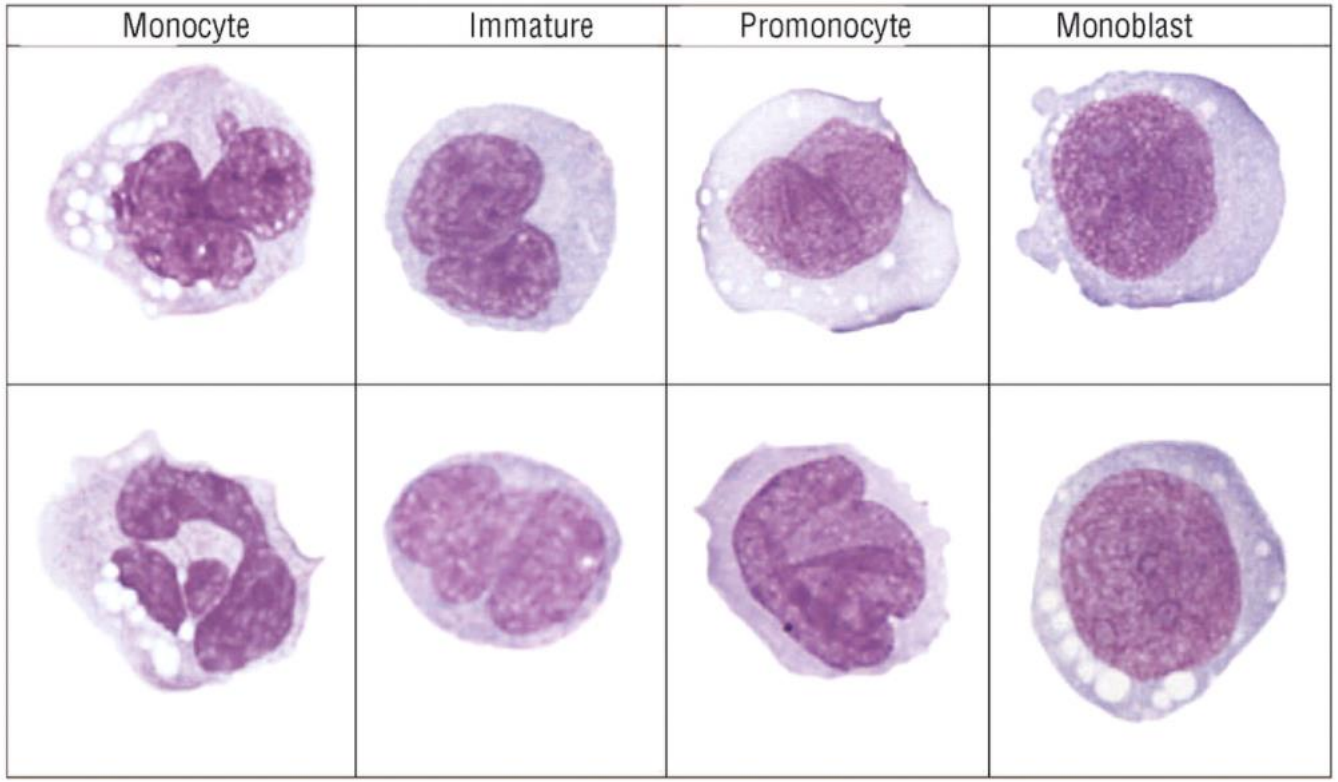
Blast Identification- Acute Promyelocytic Leukemia (APML)



ASH Image Bank- Courtesy of Marco Gambassi

- APML is important to recognize (or at least suggest) because:
  - Potentially severe bleeding (disseminated intravascular coagulation) requiring prompt clinical management
  - Specific therapy (ATRA)
- Blast morphology:
  - Large cells with abundant cytoplasm
  - Nuclei eccentric, sometimes bilobed, with folded contour
  - Granular cytoplasm* with sometimes abundant Auer rods
- If you suspect the diagnosis, share your concerns with the treatment team and arrange for PCR testing for the PML-RARA fusion

Blast Identification- Monocytic Leukemias



Jean E. Goasguen, John M. Bennett, Barbara J. Bain, Teresa Vallespi, Richard Brunning, Ghulam J. Mufti

Vol. 94 No. 7 (2009): July, 2009 https://doi.org/10.3324/haematol.2008.005421

- Spectrum of cells from immature monoblasts to mature monocytes (± atypia)
- May see only more mature forms in peripheral blood smear
- DDx: AML vs. CMML
- Clear blasts <20%? Have a low index for deferring to bone marrow biopsy
  - Atypical monocytic population, bone marrow biopsy pending

What if there aren't 20% blasts?

- Blast count ≥20%
  - Acute leukemia
- Blast count 5-19%
  - Acute leukemia—but bone marrow evaluation will be required
  - Myeloproliferative neoplasm
  - Myelodysplastic syndrome
  - MPN/MDS overlap
- Blast count 1-5%
  - Any of the above
  - Bone marrow replacing processes (leukoerythroblastosis)
  - Reactive causes (severe infection, G-CSF therapy)
- Rare blasts <1%
  - Any of the above
  - Chemotherapy/marrow regeneration
  - Severe infection

- Bottom Line: Blasts seen with any reproducible frequency in the peripheral blood and no clear reactive clinical explanation require further evaluation (generally bone marrow sampling and flow cytometry).

Where can things go wrong?

- Avoid the temptation to sub-classify acute leukemia based only on morphologic or clinical features
- Do not interpret blood smears without knowing the CBC values
- Make sure you can look around the slide to get a feel for the full spectrum of WBC morphology before calling blasts in a potentially clinically meaningful situation
  - Beware the “tech pic”- reactive lymphocytes, prolymphocytes, etc.
- Kids have weird lymphocytes
- Do not interpret poorly stained or smeared slides
- Be sure to check the edges of the smear

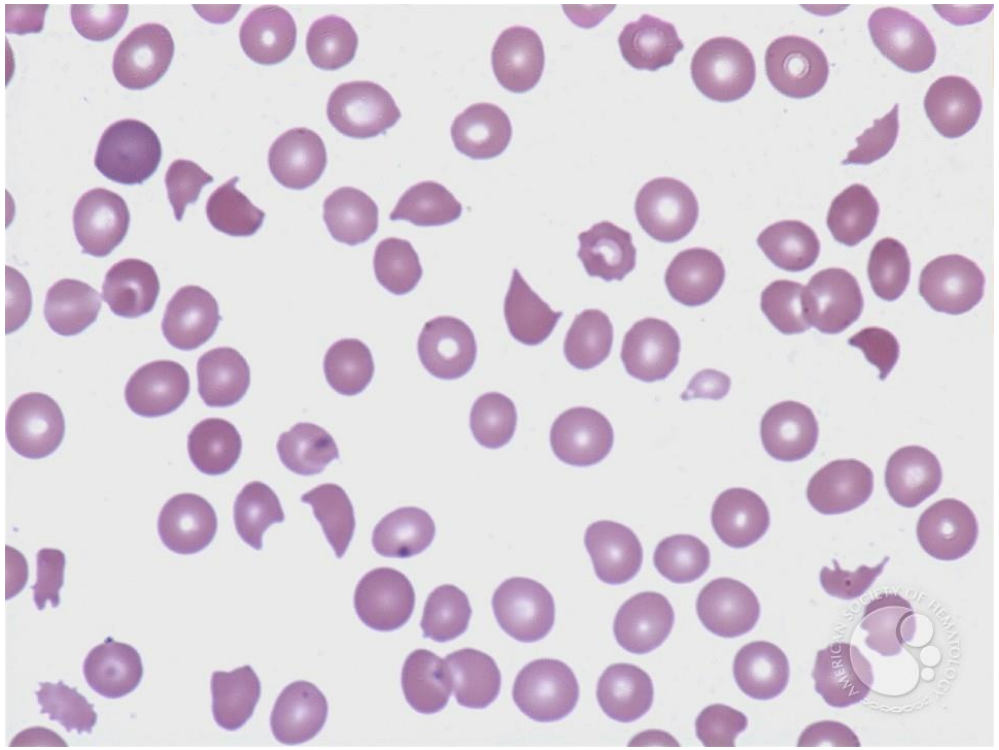
Scenario #2

- The phone rings. You answer, and one of your colleagues in oncology rapidly begins providing you clinical information. “I’m seeing a guy up on the floor whose platelets keep dropping, his creatinine is rising, he has neurologic symptoms, and I think he may be hemolyzing. Can you look as his peripheral blood—I want to rule out TTP.”

Microangiopathic Hemolytic Anemia (MAHA)

- MAHAs:
  - Thrombocytopenic thrombotic purpura (TTP)
  - Hemolytic uremic syndrome (HUS/atypical HUS)
  - Disseminated intravascular coagulation (DIC)
  - HELLP syndrome/pre-eclampsia
  - Other: mechanical shearing (artificial valves, etc.), medication-induced, malignancy, autoimmune disease
- Common pathophysiology is intravascular mechanical red cell hemolysis due to fragmentation by physical obstruction, endothelial damage, and platelet consumption
- Generally enters the clinical differential in situations of concurrent anemia and thrombocytopenia
- Laboratory studies:
  - CBC: Hgb ↓ and Plt ↓ (nadir often in the 20k to 30k range, lower in classical TTP)
  - Hemolysis pattern: ↑ LDH, ↑ indirect bilirubin, ↓ haptoglobin, ↑ reticulocyte count
  - DAT: negative
  - Basic Coagulation: PT and aPTT variable
  - ADAMTS13: activity ≤ 10% highly indicative of thrombotic thrombocytopenia purpura (TTP) in an appropriate clinical setting

Smear Morphology



ASH Image Bank- Courtesy of Peter Maslak

- Red cell fragments (schistocytes)
  - Size: variable, usually microcytic
  - Shape: varies from triangular to helmet to unclassifiable fragments
  - Small fragments lack central pallor of a normal RBC
- Note: Iron deficiency anemia can show small poikilocytes that can be mistaken for fragments
- Quantification: usually more than 2/HPF (100x)
  - Normal blood smears will show rare fragments (up to 0.2-0.3%)
  - In most microangiopathies, schistocytes should account for 1%+ of all erythrocytes
    - 2-3 fragments/HPF
    - TTP: 4-8 fragments/HPF

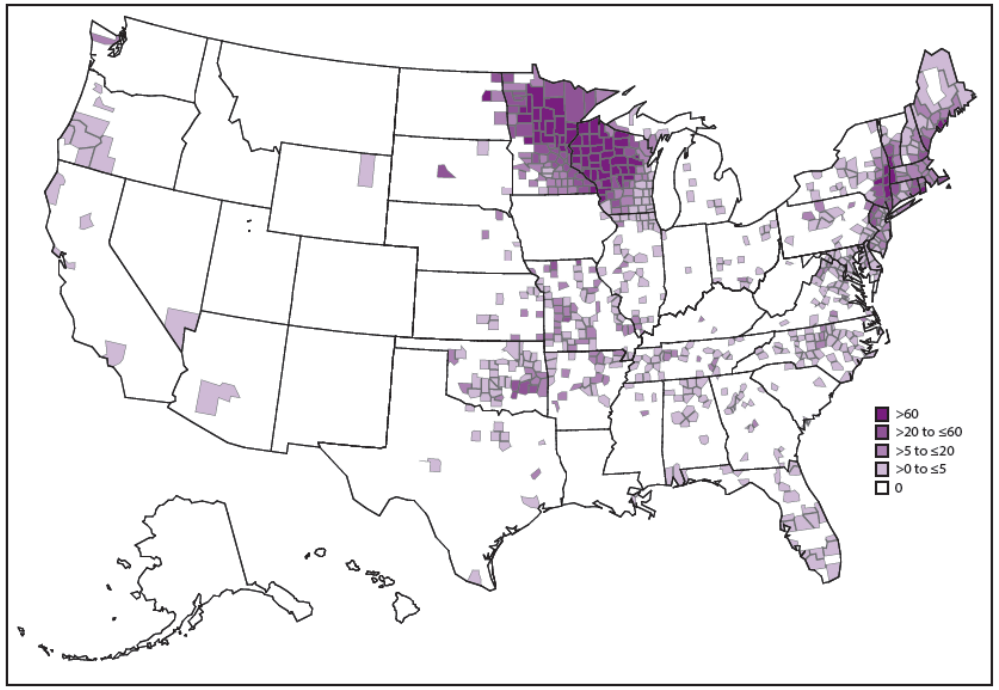
What do I need to do?

- Slide review should establish microangiopathy and thrombocytopenia
  - Confirm the presence of red cell fragments
  - Quantification of schistocytes (range of number/high power field)
  - Confirm true thrombocytopenia (exclude platelet clumping)
  - Exclude morphologies suggestive of alternative etiologies for hemolysis
    - Microspherocytes (immune-mediated destruction)
    - Infection (Malaria/Babesiosis)
    - Obvious hematologic malignancy (APML, CLL, etc.)
- Specific disease classification requires clinical correlation and is generally out of scope of smear review

Scenario #3

- The phone rings. You answer, recognizing the hematology diff bench phone extension on you caller ID. “Doctor…we are seeing some intracellular organisms on a blood smear. Infectious disease already has the IV placed and is ready to begin treatment. They think he had a tick bite last month. Would you come in and confirm the identification?”

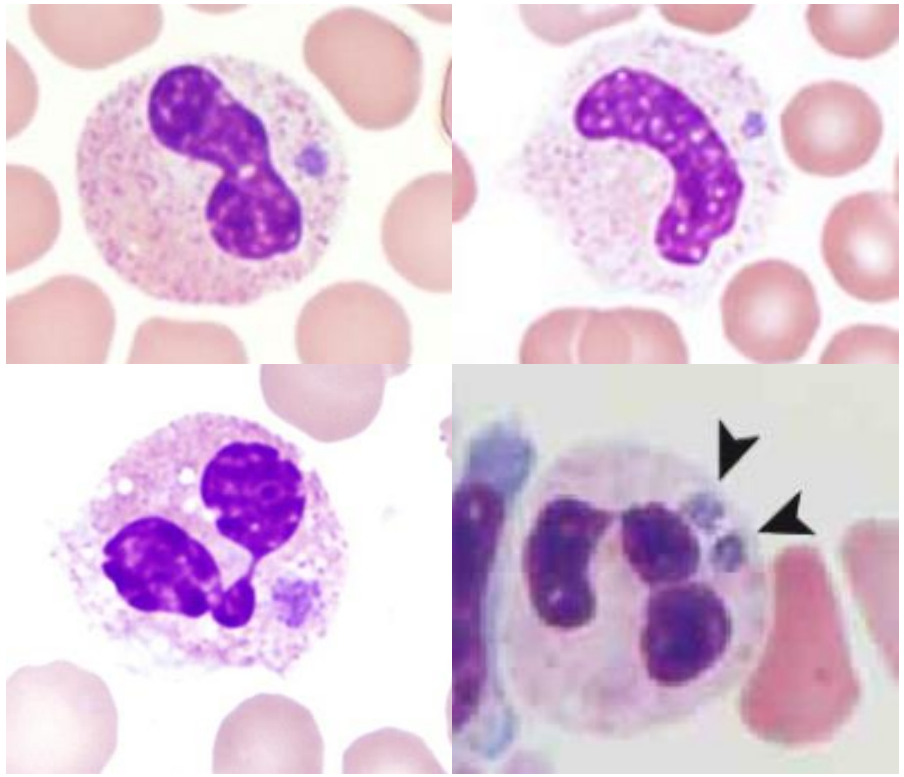
Anaplasmosis- Overview



Biggs HM, Behravesh CB, Bradley KK, et al. Diagnosis and Management of Tickborne Rickettsial Diseases: Rocky Mountain Spotted Fever and Other Spotted Fever Group Rickettsioses, Ehrlichioses, and Anaplasmosis — United States. MMWR Recomm Rep 2016;65(No. RR-2):1–44.

- Anaplasmosis (Human Granulocytic Ehrlichiosis) is caused by a rickettsia-like obligate intracellular bacteria (*Anaplasma phagocytophilum*)
- Tick-borne disease transmitted by Ixodes scapularis (Lyme Disease)
- Clinical signs and symptoms: fever, chills, malaise, myalgia, gastrointestinal, rash (<10%)
- Laboratory findings: mild anemia, thrombocytopenia, leukopenia, transaminitis
- Diagnostic testing: blood smear, PCR, antibody titers (IgG), IHC

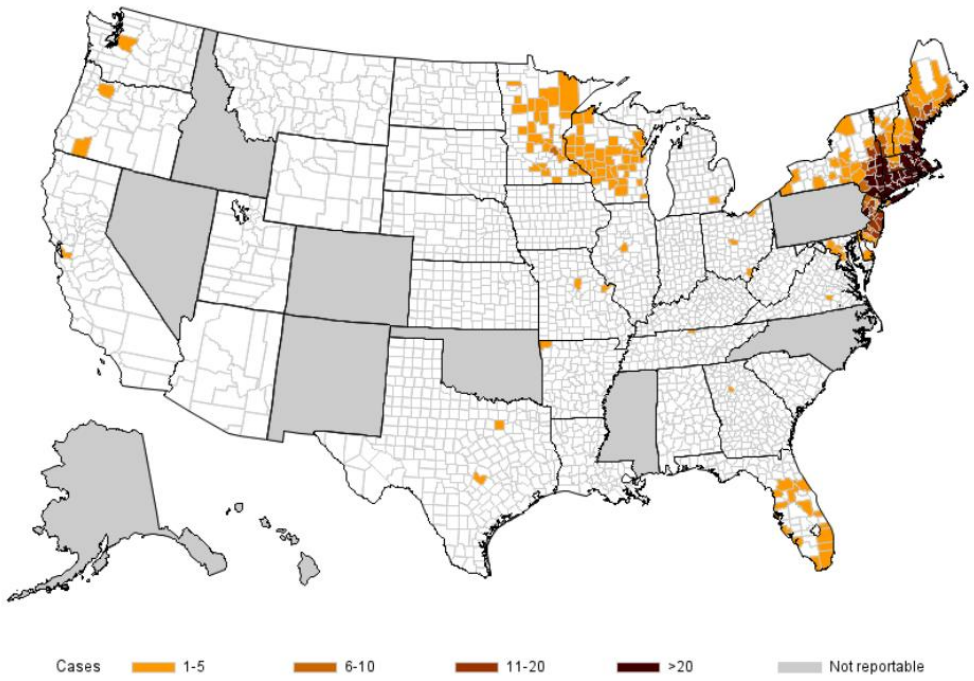
Smear Morphology



CDC- MMWR
ASH Image Bank- Courtesy of John Lazarchick and Ginell Post

- Observation of morulae is highly suggestive of infection by *Ehrlichia* or *Anaplasma spp.*
- Morphology:
  - Collections of punctate, 1-2 µm round to angular inclusions, gray-blue to deep blue in color
  - Sphere-like configuration
  - Usually one morula per infected cell
  - Rate of infectivity often low (<0.2% WBCs)
- Other smear findings: toxic changes, reactive lymphocytes
- Caveats:
  - Blood smear examination is relatively insensitive (30-70%) and should not be relied upon solely to diagnose anaplasmosis
  - The observance of morulae in a particular cell type cannot conclusively differentiate between Anaplasma and Ehrlichia species

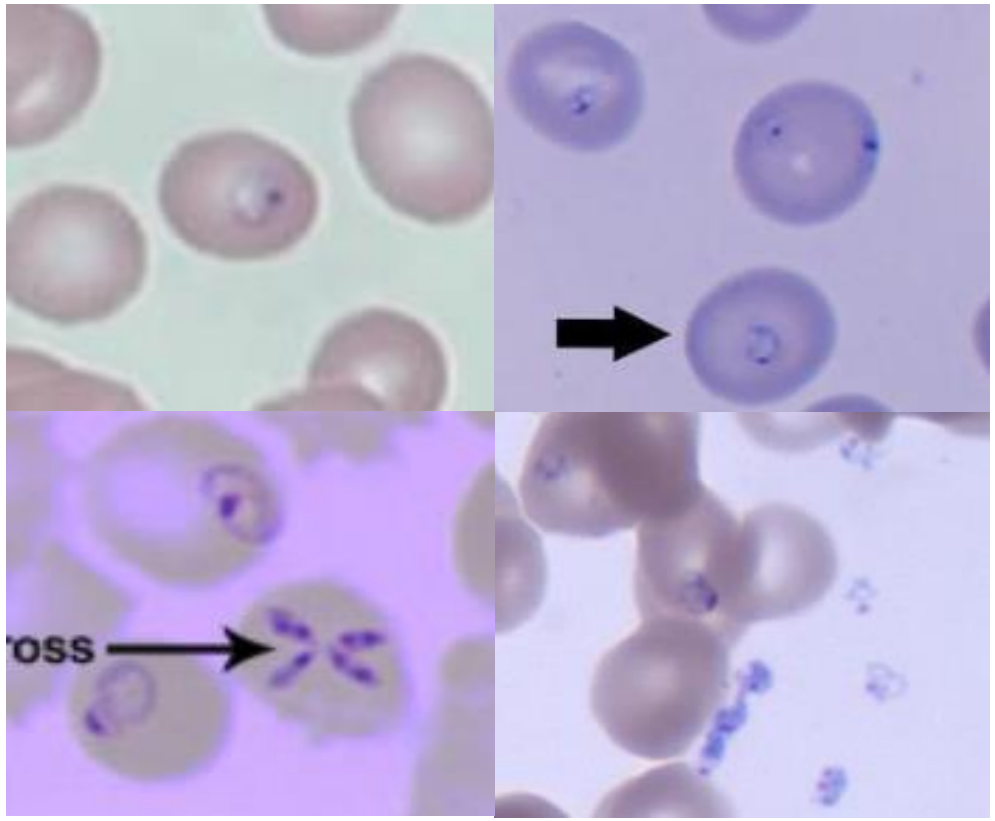
Babesiosis- Overview



CDC: Surveillance for Babesiosis - United States, 2019 Annual Summary
https://www.cdc.gov/parasites/babesiosis/resources/Surveillance_Babesiosis_US_2019.pdf

- Babesiosis is caused by protozoan parasites (*Babesia microti,* others)
- Tick-borne disease transmitted by Ixodes scapularis (Lyme Disease)
- Clinical signs and symptoms: fever, chills, malaise, myalgia, gastrointestinal, headache
  - Note- severity generally low, but high risk factors include immunosuppression and history of splenectomy
- Laboratory findings: hemolytic anemia, thrombocytopenia, transaminitis
- Diagnostic testing: blood smear, PCR, antibody titers (IgG)

Smear Morphology



ASH Image Bank- Courtesy of Eric Cross, MD,PhD; Andrew Lytle, MD, PhD; Julianne Qualtieri, MD; Dale Frank, MD

- Morphology:
  - Morphology similar to *Plasmodium spp.* ring forms
  - Intraerythrocytic protozoa, 1-5 µm in size
    - Note: generally smaller than malarial organisms
  - Shape highly variable (round, oval, elongate, ameboid, pyriform)
  - Erythrocytes may have multiple ring forms present
  - Extracellular organisms may be seen- assists in differentiation from malaria
  - Lack Schuffner's pigment granules, schizont, and gametocyte forms of malaria
  - Parasitemia highly variable (1-80% of RBCs)
    - Note: >10% parasitemia considered severe infection- may trigger RBC exchange transfusion

Where can things go wrong?

- Avoid overcalling smear artifacts as blood microorganisms
  - Potential pitfalls: overlying platelets, Döhle bodies, phagocytosed bacteria, toxic granulation, apoptotic nuclear debris, and stain precipitate
  - Look for reproducible findings!
- Provide information needed for immediate clinical management
  - Understand lab policies on identification
- Know (or find out) any pertinent travel history
- Do not interpret poorly stained or smeared slides
- Request recollection and antibody/molecular testing if findings are suspicious but not definitively diagnostic
- Communicate findings with provider to ensure that appropriate antimicrobial therapy is promptly started

Summary: Tips for Successful Heme Call

- Know your resources and their availability
  - When will the next pathologist covering heme be in?
  - When is the next flow cytometry coverage?
- Provide only the information needed for immediate management
  - Confirm blasts and suggest acute leukemia when appropriate
  - Defer classification to flow and bone marrow assessment
  - Recognize APML due to its unique therapy and DIC association
  - Accurately confirm the presence of schistocytes/red cell fragments
  - Confirm the presence of blood microorganisms on peripheral smear
- Know (or have access to) appropriate clinical history
- Be skeptical of images sent in isolation
- Talk directly to providers whenever possible

Questions?