# Therapy-related acute myeloid leukemia with germline *TP53* mutation (Li-Fraumeni syndrome)

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# Clinical History

HPI: 44 year old Caucasian female referred for evaluation of pancytopenia discovered on routine CBC.

PAST MEDICAL HISTORY:

- Bilateral breast carcinoma diagnosed at age 34 treated with chemotherapy and radiation
- Squamous cell carcinoma of the scalp diagnosed at age 35
- Post-radiation spindle cell sarcoma of the left breast diagnosed at age 41
- Moderately differentiated adenocarcinoma of the rectum diagnosed at age 44

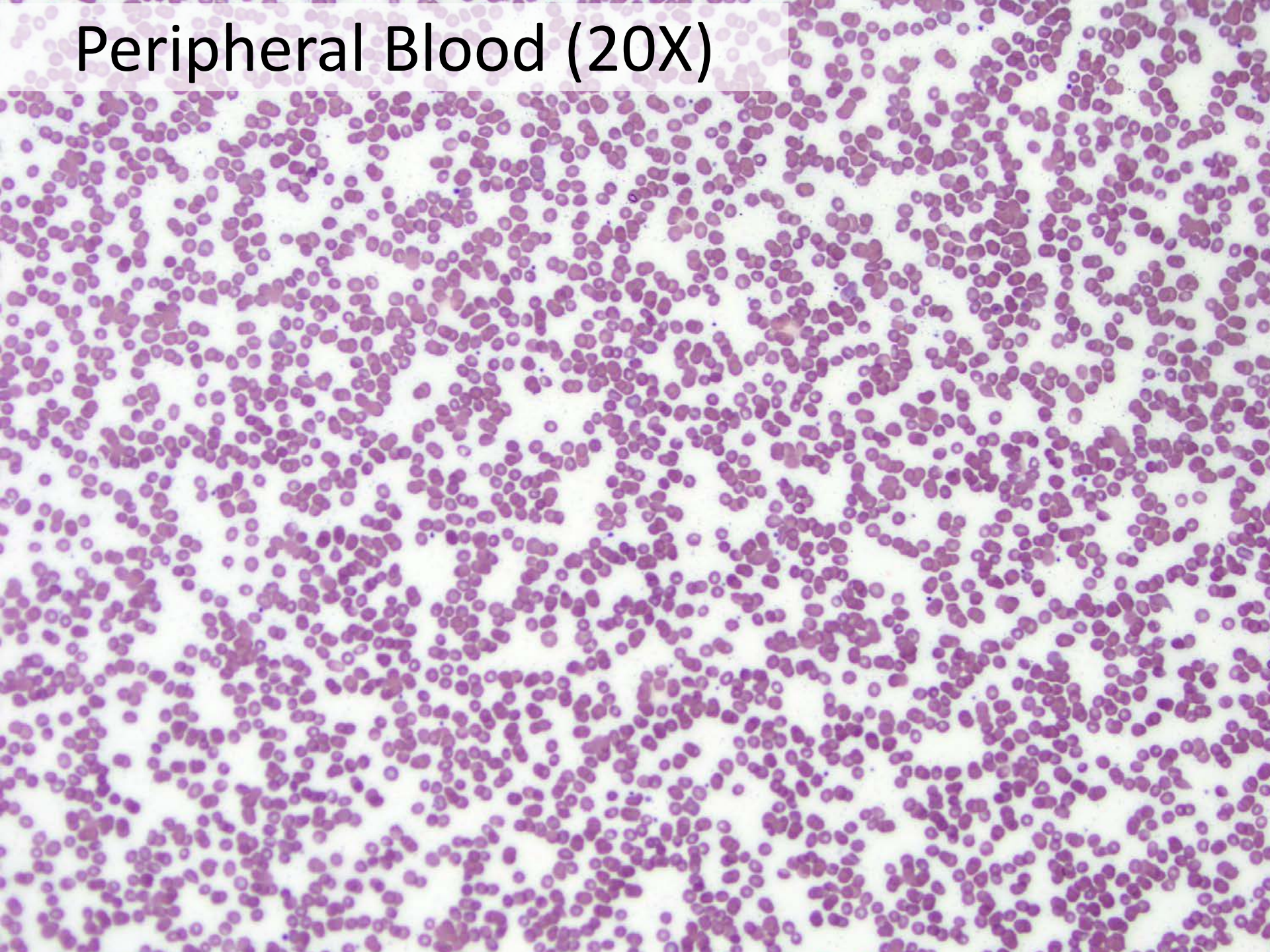
# Clinical History

FAMILY HISTORY:

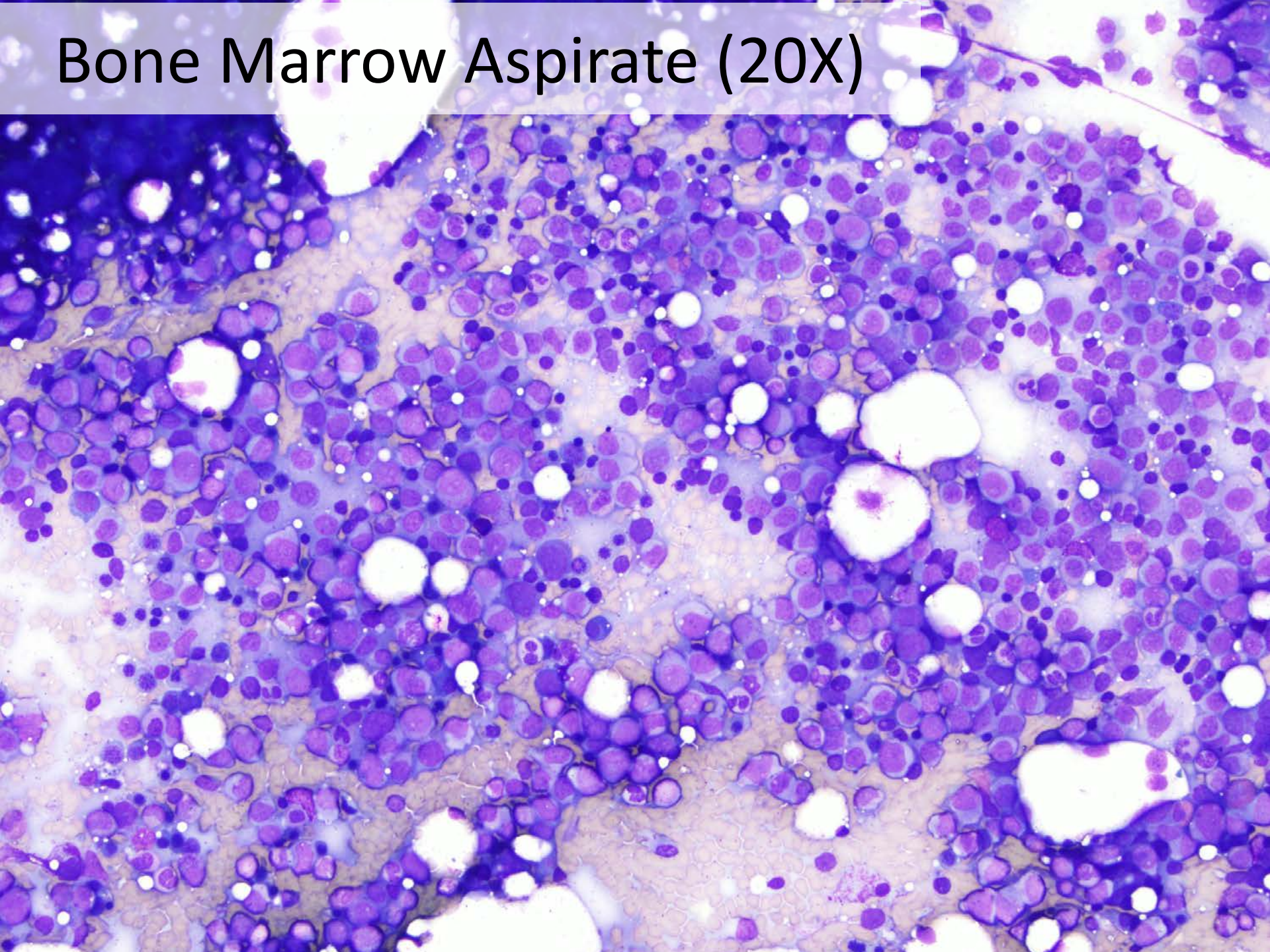
- 1 son deceased at age 3y for malignant brain tumor
- Mother deceased at age 34 from metastatic adenocarcinoma of unknown primary
- 1 maternal uncle deceased from bladder cancer at age 50's

PHYSICAL EXAM: No evidence of organomegaly or lymphadenopathy, mild right lower extremity erythema

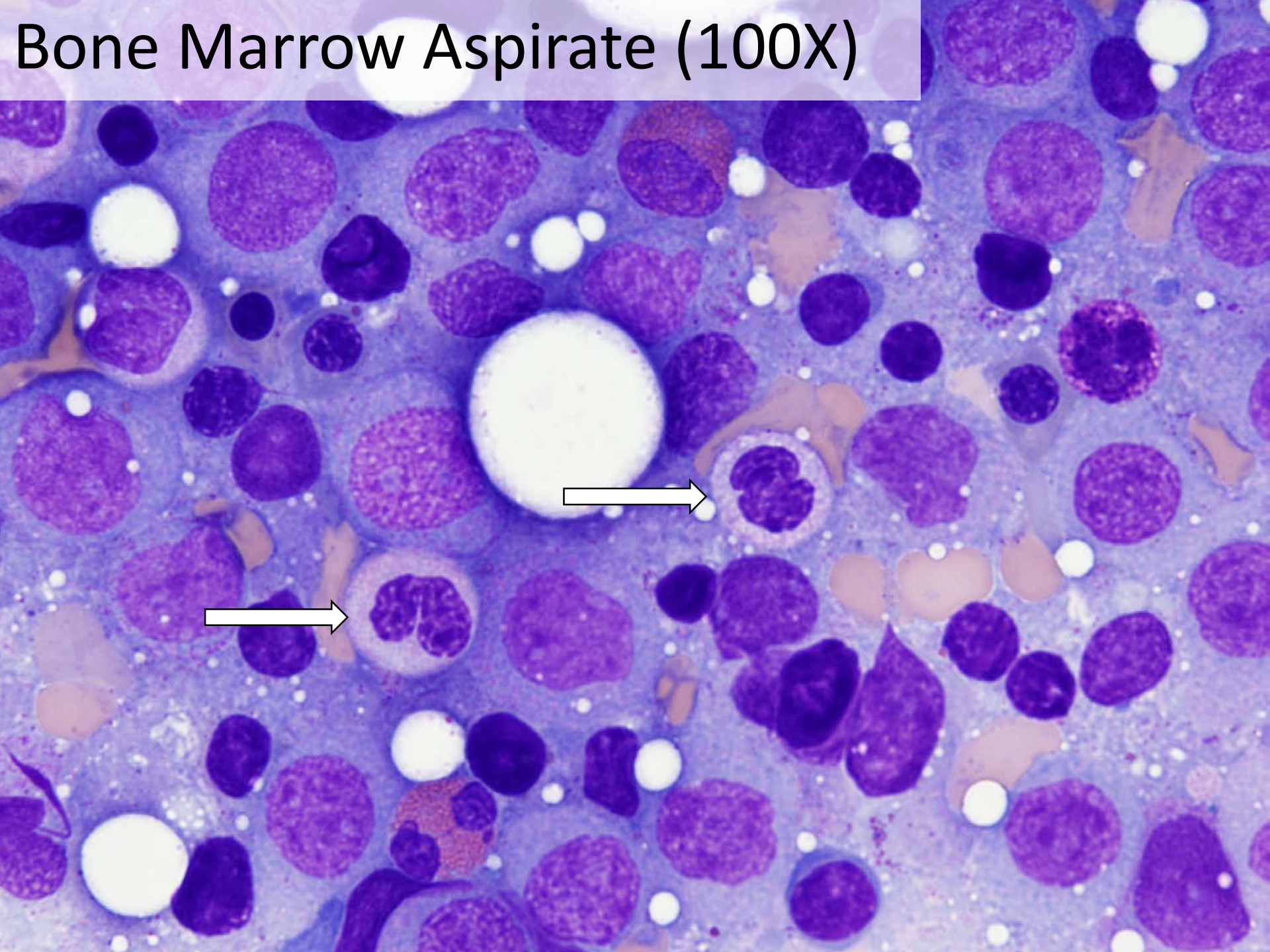
# Peripheral Blood (20X)



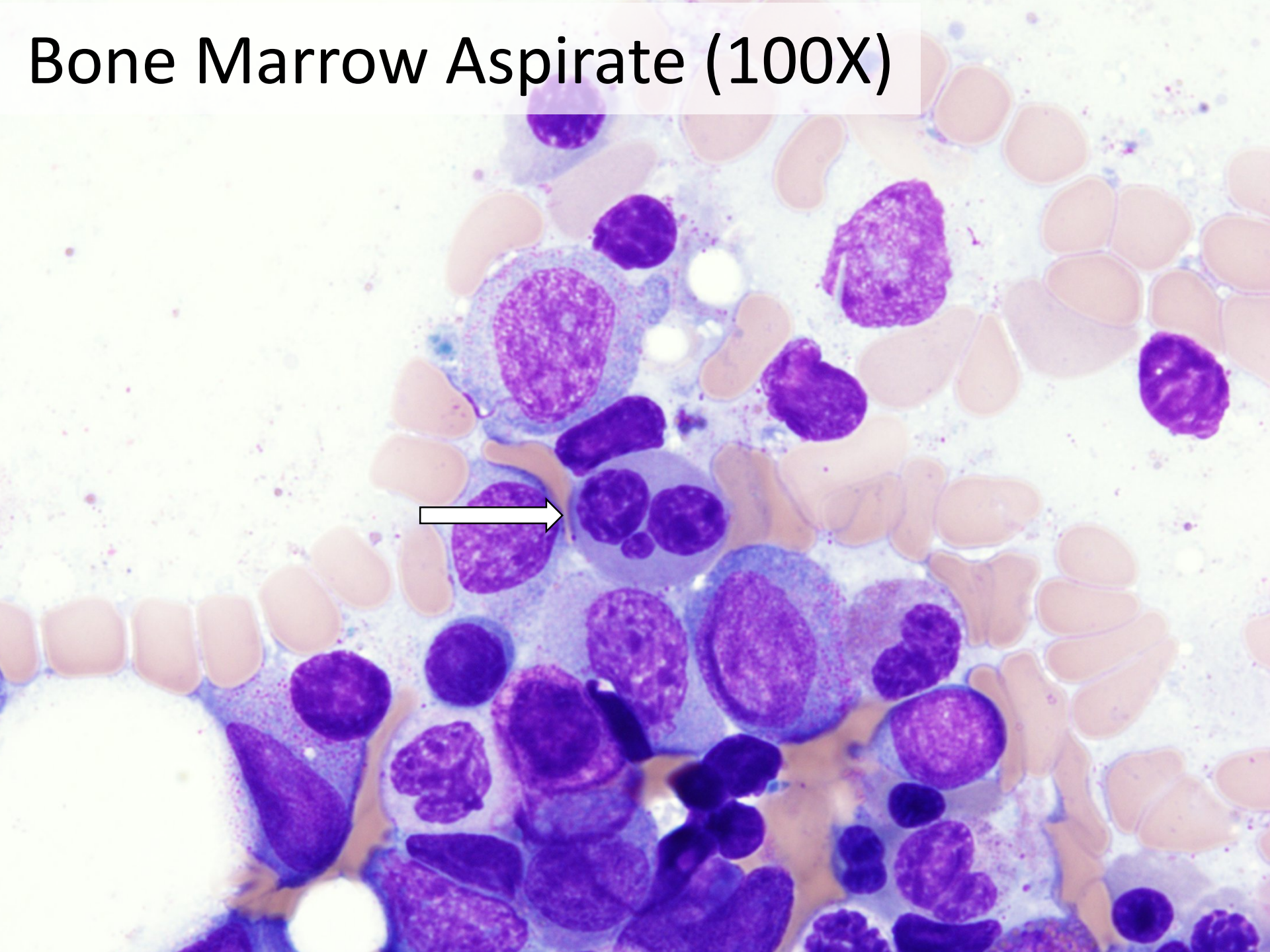
# Bone Marrow Aspirate (20X)



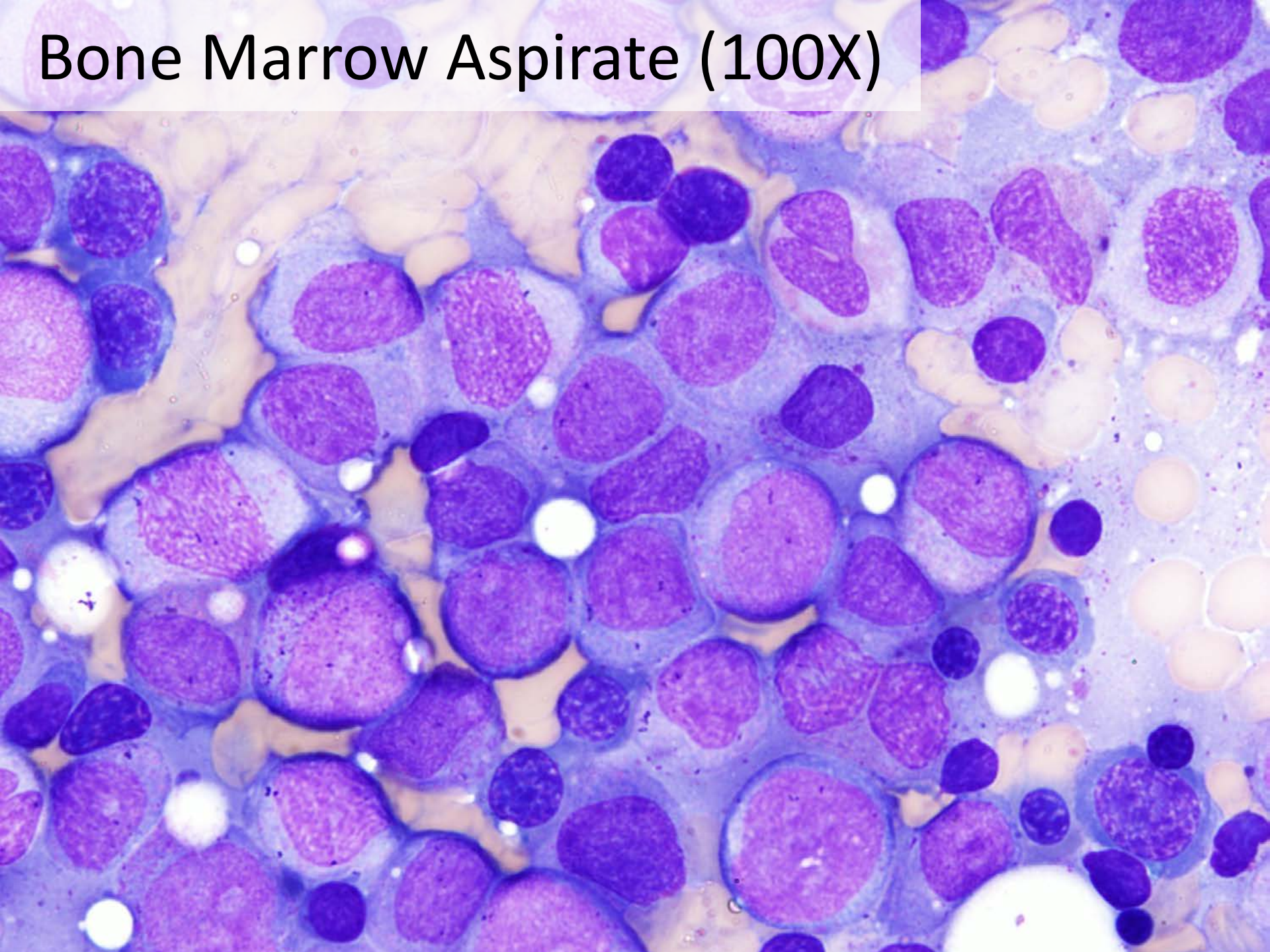
# Bone Marrow Aspirate (100X)



# Bone Marrow Aspirate (100X)



# Bone Marrow Aspirate (100X)



# Flow Cytometry

- Myeloblasts comprised 8% of events
  - Expressed CD13, CD33, CD34, CD38, partial CD117, HLA-DR, and moderate CD45
  - Partial aberrant coexpression of CD7 and CD56
- Monoblasts comprised 20% of events
  - Expressed CD4, CD13, CD14, partial CD15, CD33, CD38, CD64, HLA-DR, and CD45
  - Partial aberrant coexpression of CD56

# Cytogenetic Analysis

- Ten metaphases with 47 chromosomes
  - Monosomy 4, 7, and 13
  - Additional chromosomal materials of unknown chromosome origins attached to chromosomes 4p16, 5q11.2, and 17p13
  - Two marker chromosomes and two ring chromosomes of unknown origin
- The remaining 10 metaphases appeared normal
- 47, XX, -4, add(4) (p16), add(5) (q11.2), -7, -13, add(17) (p13), +mar1, +mar2, +r1, +r2[10]/46, XX [10]

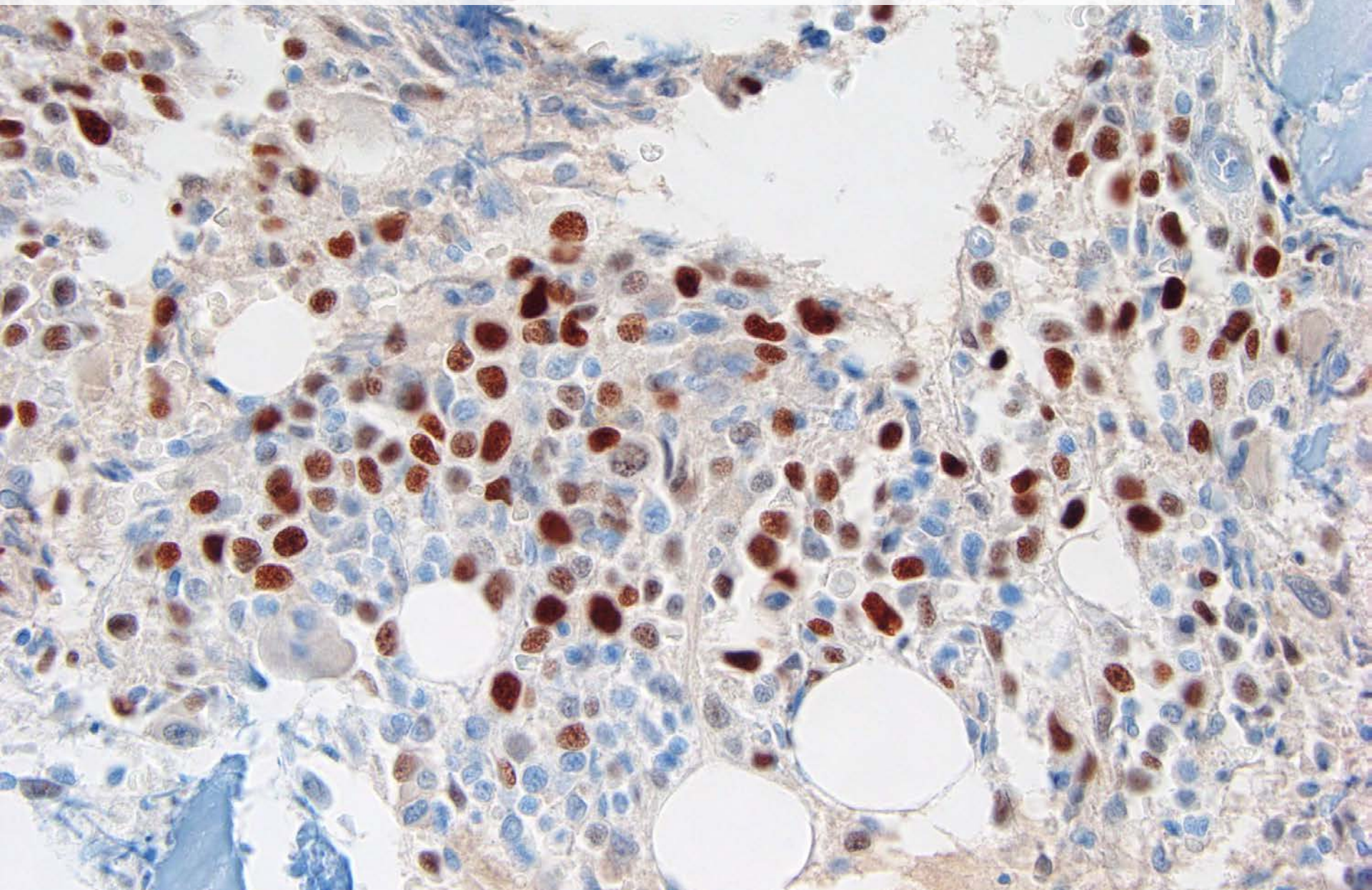
# Molecular Studies

- Negative for NPM1, DNMT3A mutations
- Silent sequence variation in exon 17 of the *KIT* gene at codon 798
- Hemavision multiplex PCR panel: No translocations detected

# Additional Molecular Studies

- Buccal swab DNA sequencing
  - A pathogenic variant c.610delG (p.E204SfsX43) was detected in the *TP53* gene

# Bone Marrow Biopsy- p53 IHC (40X)



# Summary of Findings

- 44-year-old female referred for evaluation of pancytopenia discovered on routine CBC
- Significant past medical history and family history of malignancy
- Blasts comprising 23.6% of nucleated cells in the bone marrow aspirate, expressing a myelomonocytic immunophenotype
- Significant background trilineage dysplasia
- Complex cytogenetic abnormalities
- Pathogenic *TP53* gene mutation detected on buccal swab analysis

# Diagnosis

- Therapy-related acute myeloid leukemia
- Genetic studies and family history consistent with Li-Fraumeni syndrome

# Li-Fraumeni Syndrome

- Prototypical familial cancer predisposition syndrome caused by germline mutations in the tumor suppressor gene *TP53*, encoding the TP53 transcription factor
  - TP53 plays a central role in preventing proliferation of cells with damaged DNA
- Autosomal dominant inheritance pattern
- Classic spectrum of tumors: soft-tissue sarcomas, osteosarcomas, breast cancer, brain tumors, leukemia, and adrenocortical carcinoma (six common “core” cancers)
  - Breast cancer most common in adult females
  - Soft tissue sarcoma and osteosarcoma most common in children and adolescents
  - Risk for additional malignancies, many of which develop at a younger age

# Li-Fraumeni Syndrome

- Classic LFS diagnostic criteria
  - Proband diagnosed with sarcoma before age 45 years
  - AND first degree relative with a cancer diagnosed before age 45 years
  - AND a first degree or second degree relative with any cancer with onset before age 45 years OR a sarcoma at any age

- 2009 Chompret diagnostic criteria
  - Proband with core LFS tumor before 46 years of age
  - AND at least one first degree or second degree relative with LFS-core tumor (except breast cancer if the proband has breast cancer) before 56 years of age OR with multiple tumors
  - Proband with multiple tumors (except multiple breast tumors), to of which are core LFS tumor types, first of which had to occur prior to age 46 years
  - Any patient with adrenocortical carcinoma or choroid plexus carcinoma irrespective of family history

# References


- Valdez JM, Nichols KE, Kesswerwan C. Li-Fraumeni syndrome: a paradigm for the understanding of hereditary cancer predisposition. *British Journal of Hematology.* 2017; 176: 539-552.
- Nandikolla AG, Venugopal S, Anampa J. Breast cancer in patients with Li-Fraumeni syndrome- a case-series study and review of literature. *Breast Cancer- Targets and Therapy.* 2017; 9: 207-215.
- Kratz CP, Achatz MI, et al. Cancer Screening Recommendations for Individuals with Li-Fraumeni Syndrome. *Clin Cancer Res.* 2017; 23(11): e38-e45.