

74y old Female with chronic elevation of Platelet count

August 18, 2005

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Hematopathology Fellow

Clinical History

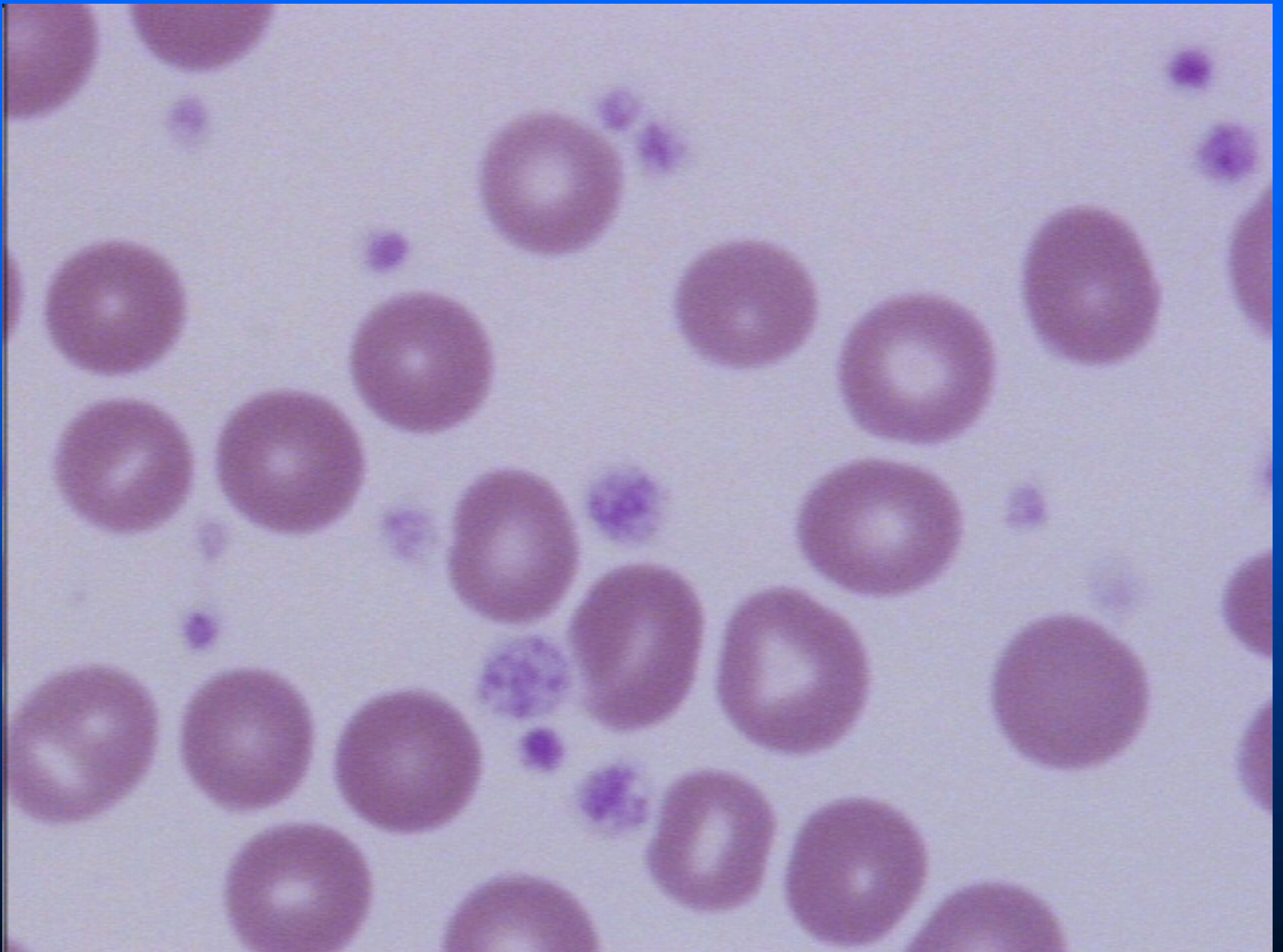
Patient is a 74y old otherwise healthy Caucasian female with no major complaint's except for mild fatigue was ordered a bone marrow biopsy for the follow-up of her elevated Platelet count and to rule out Myeloproliferative Disorder.

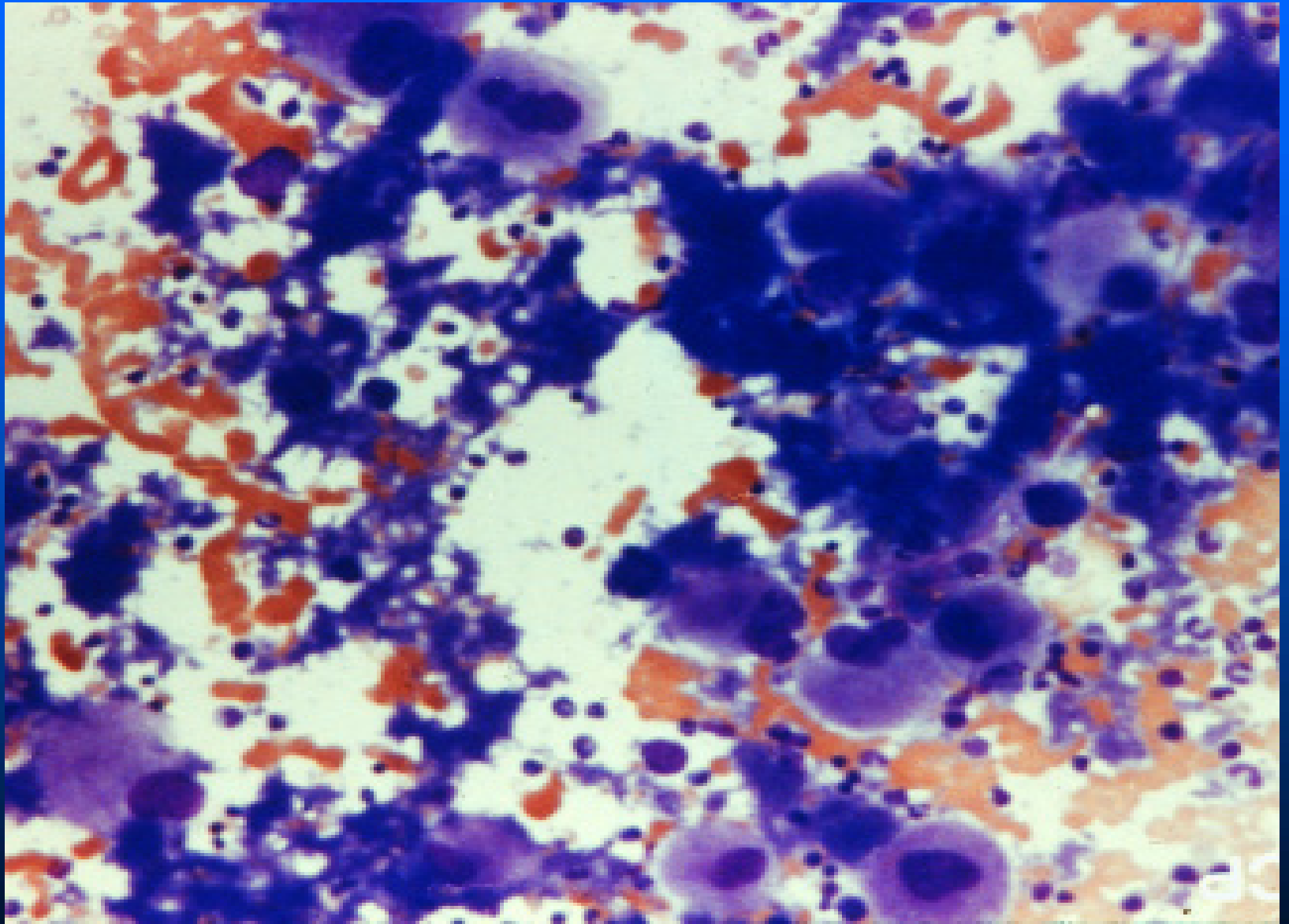
Selected CBC Trend

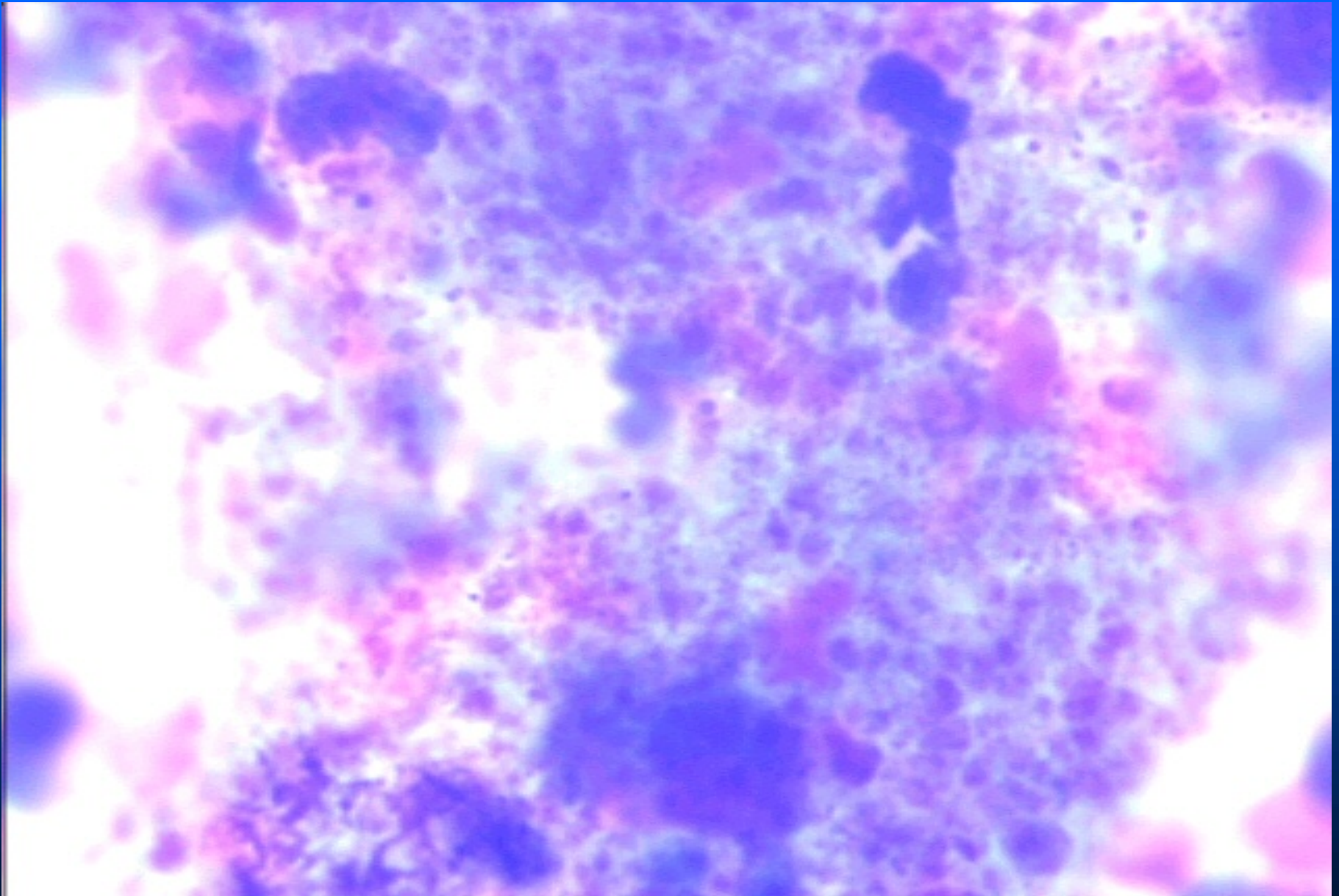
Date	WBC	RBC	HGB	HCT	PLT
Jun, 89	5.8	4.50	13.5	39.5	<u>606</u>
Mar,94	5.1	4.22	13.4	39.6	<u>348</u>
Aug,05	<u>12.4</u>	5.17	15.4	48.0	<u>592</u>

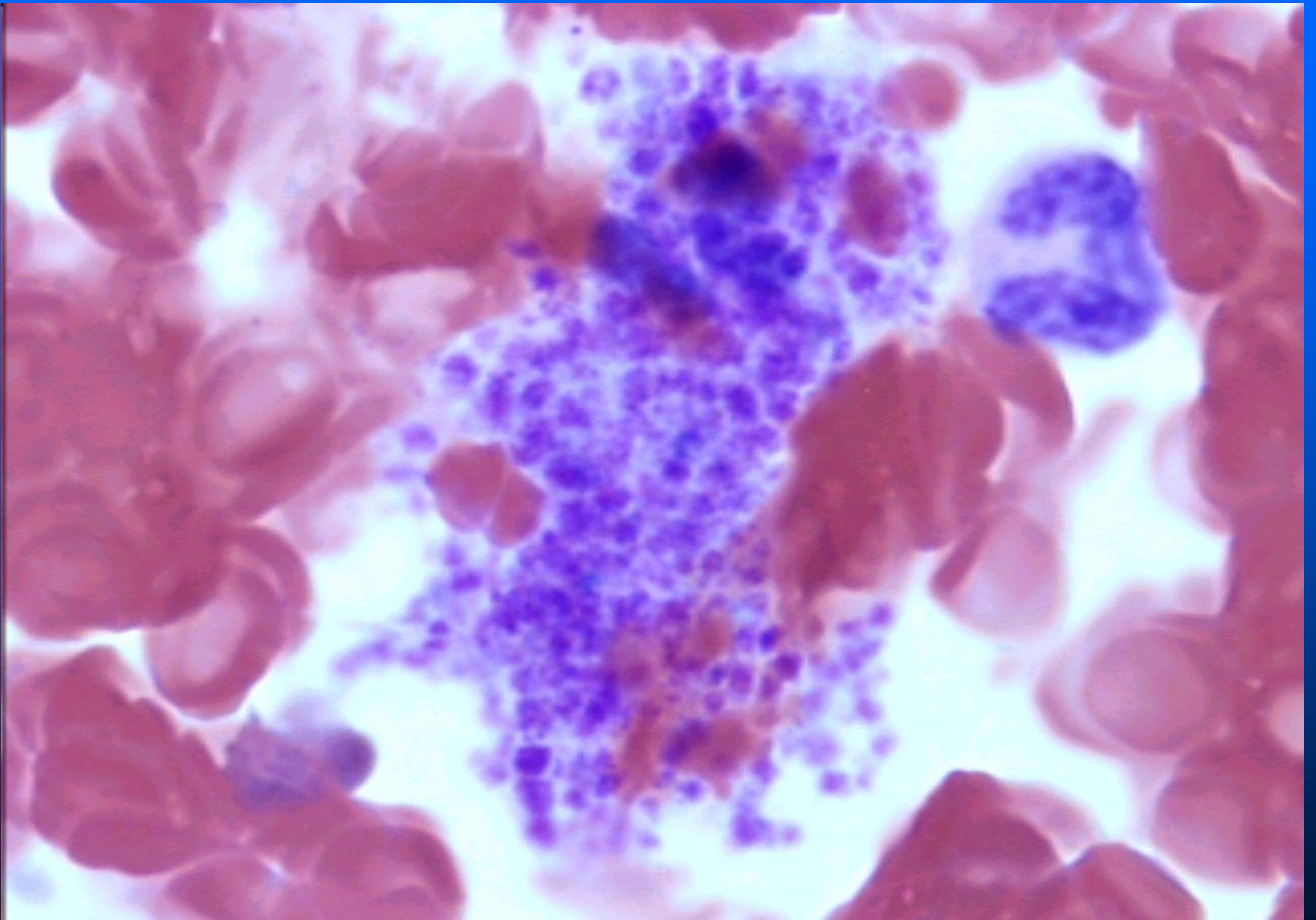
August WBC Differential

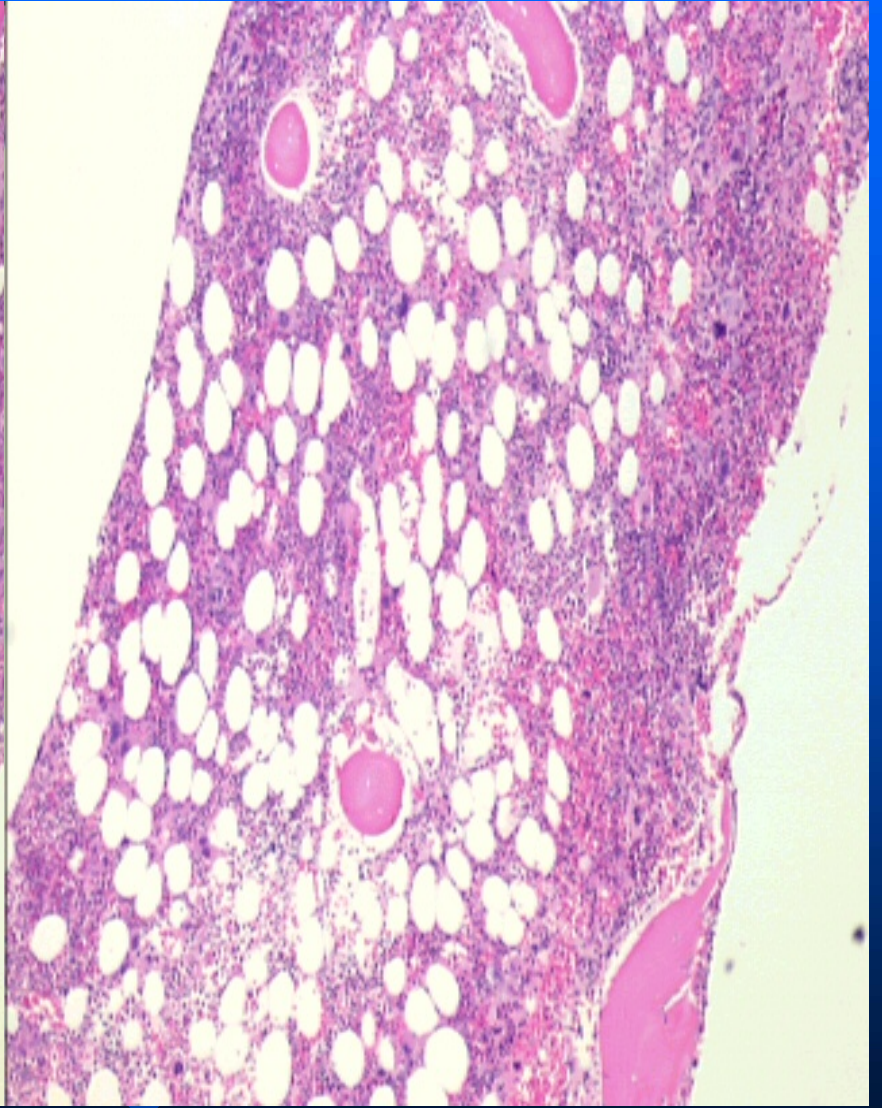
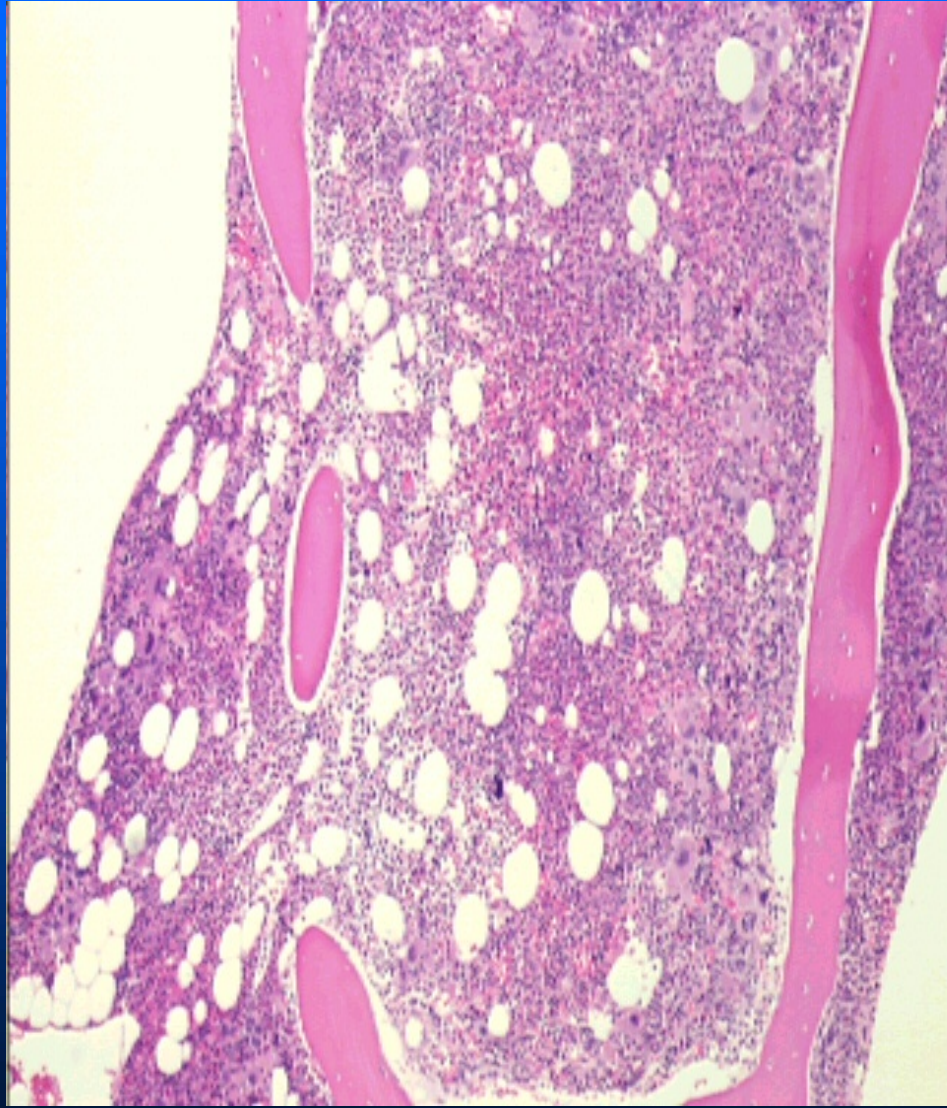
WBC	Neutro	Lymph	Mono	Eos	Baso
<u>12.4</u>	<u>9.7</u>	1.5	0.4	<u>0.6</u>	0.1

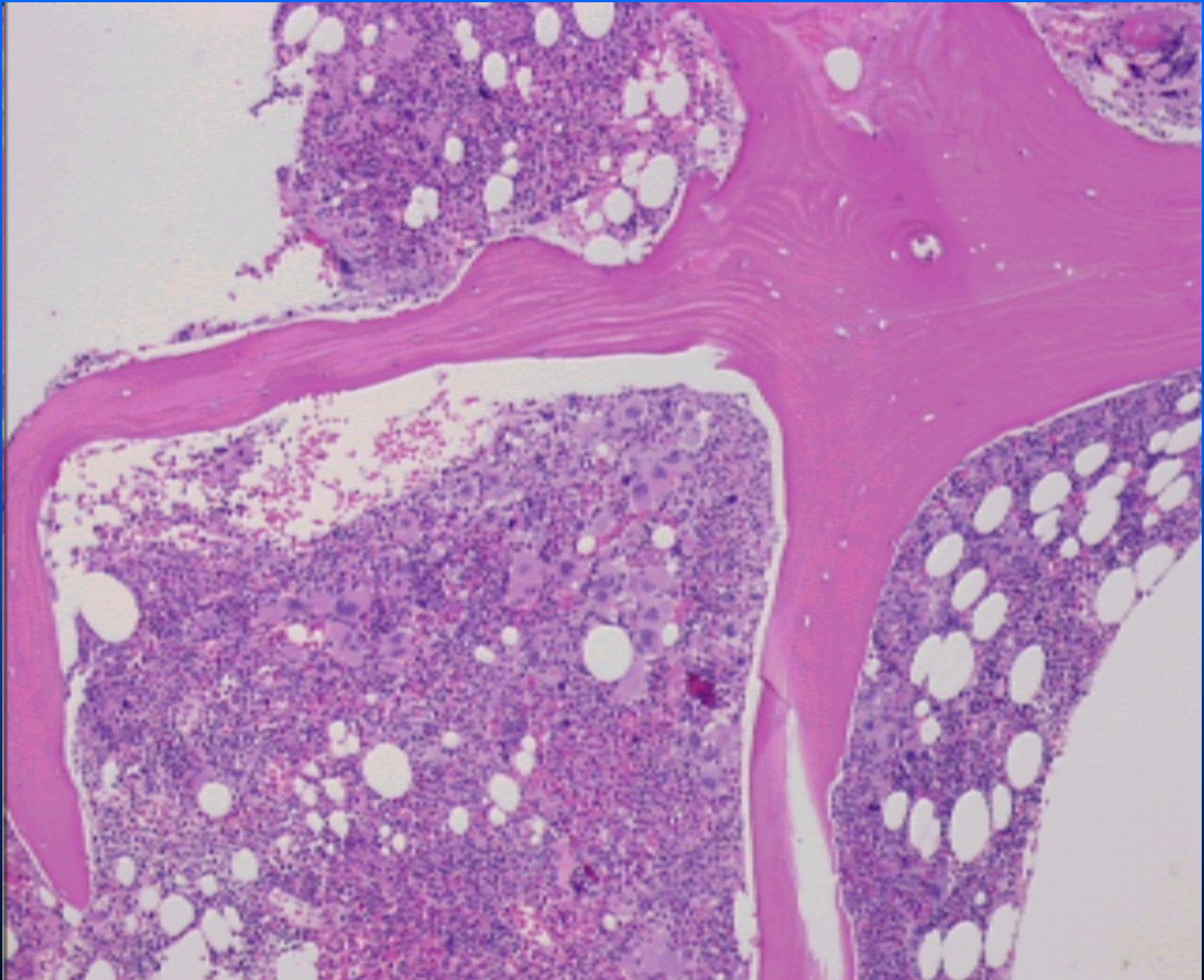


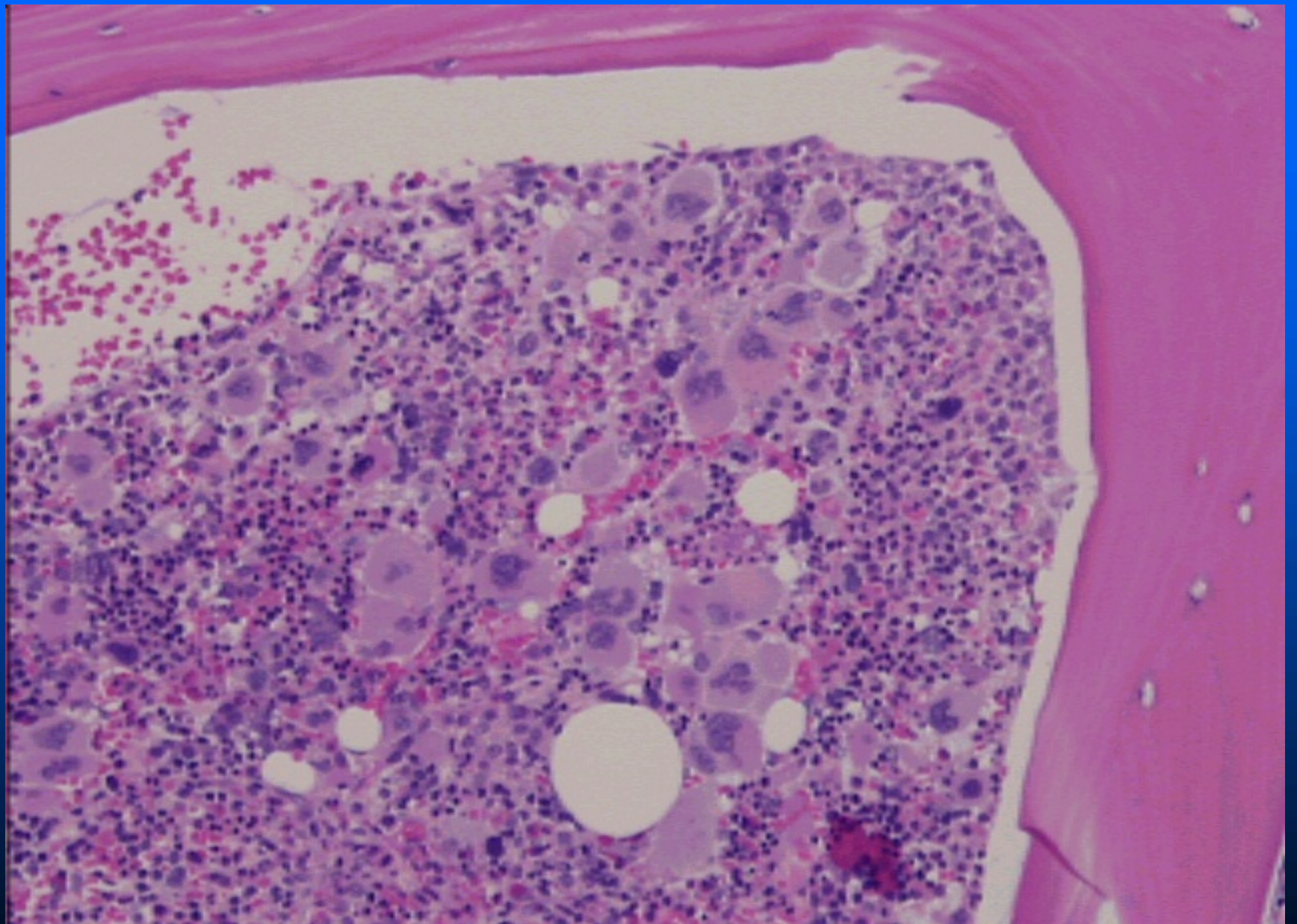


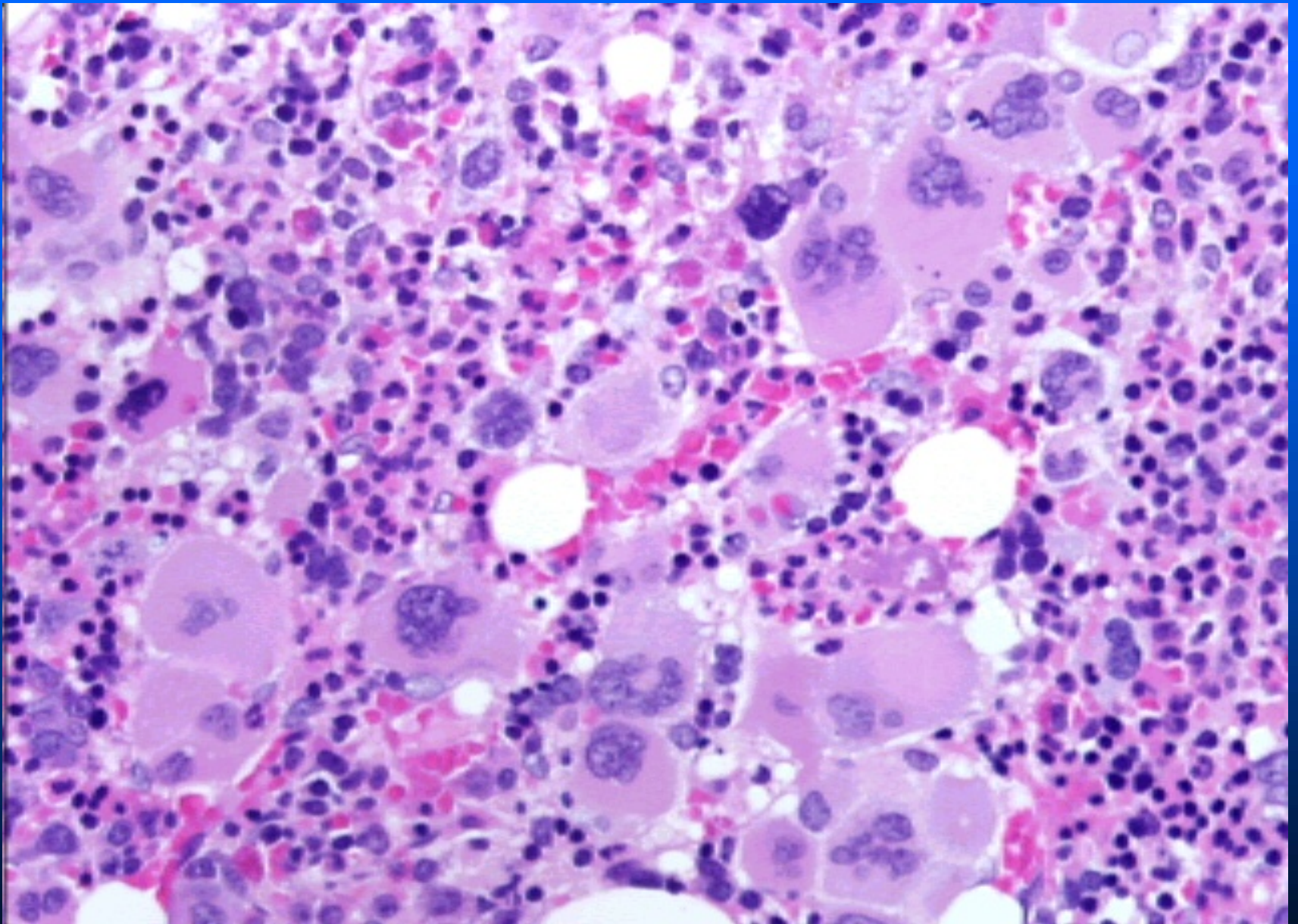


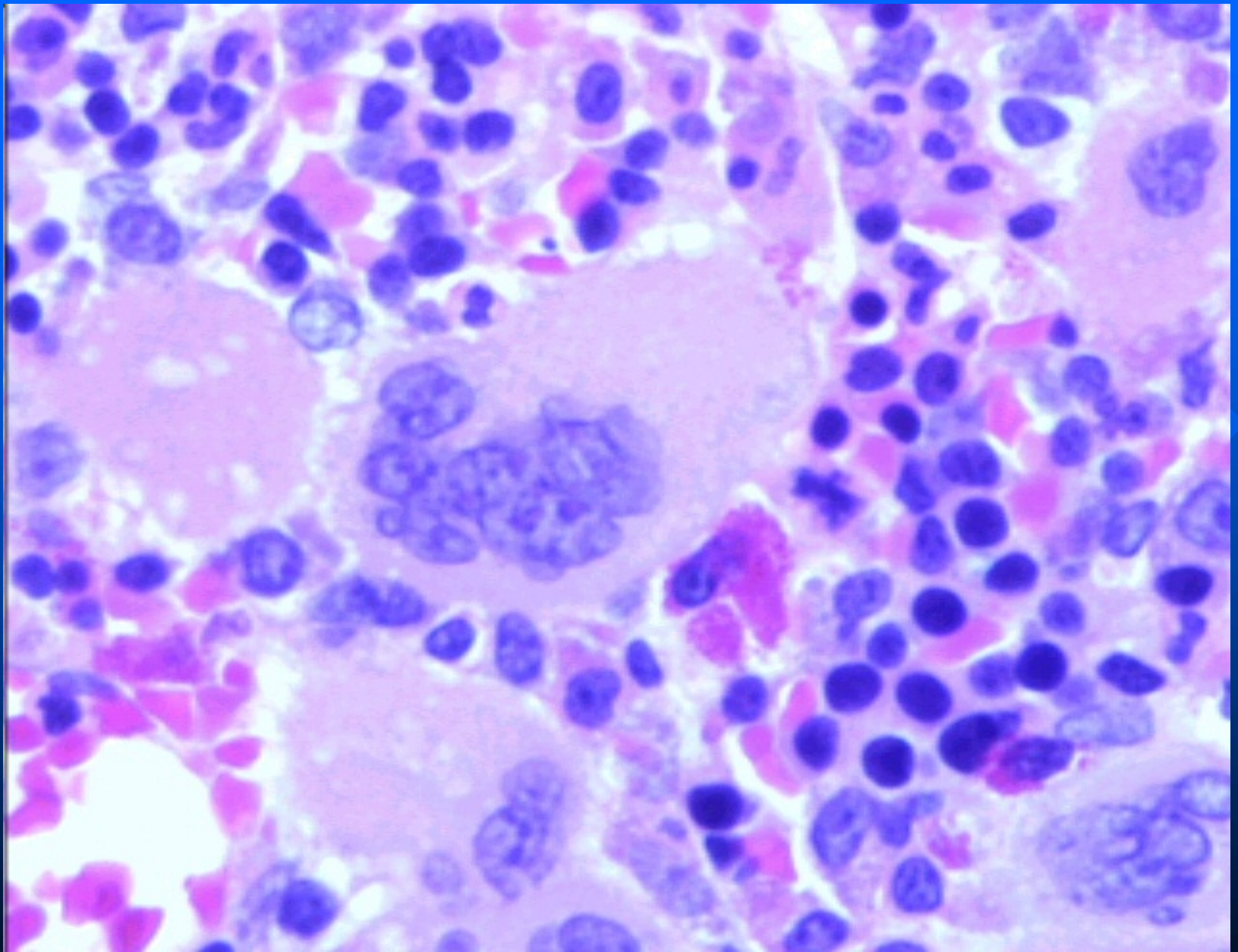


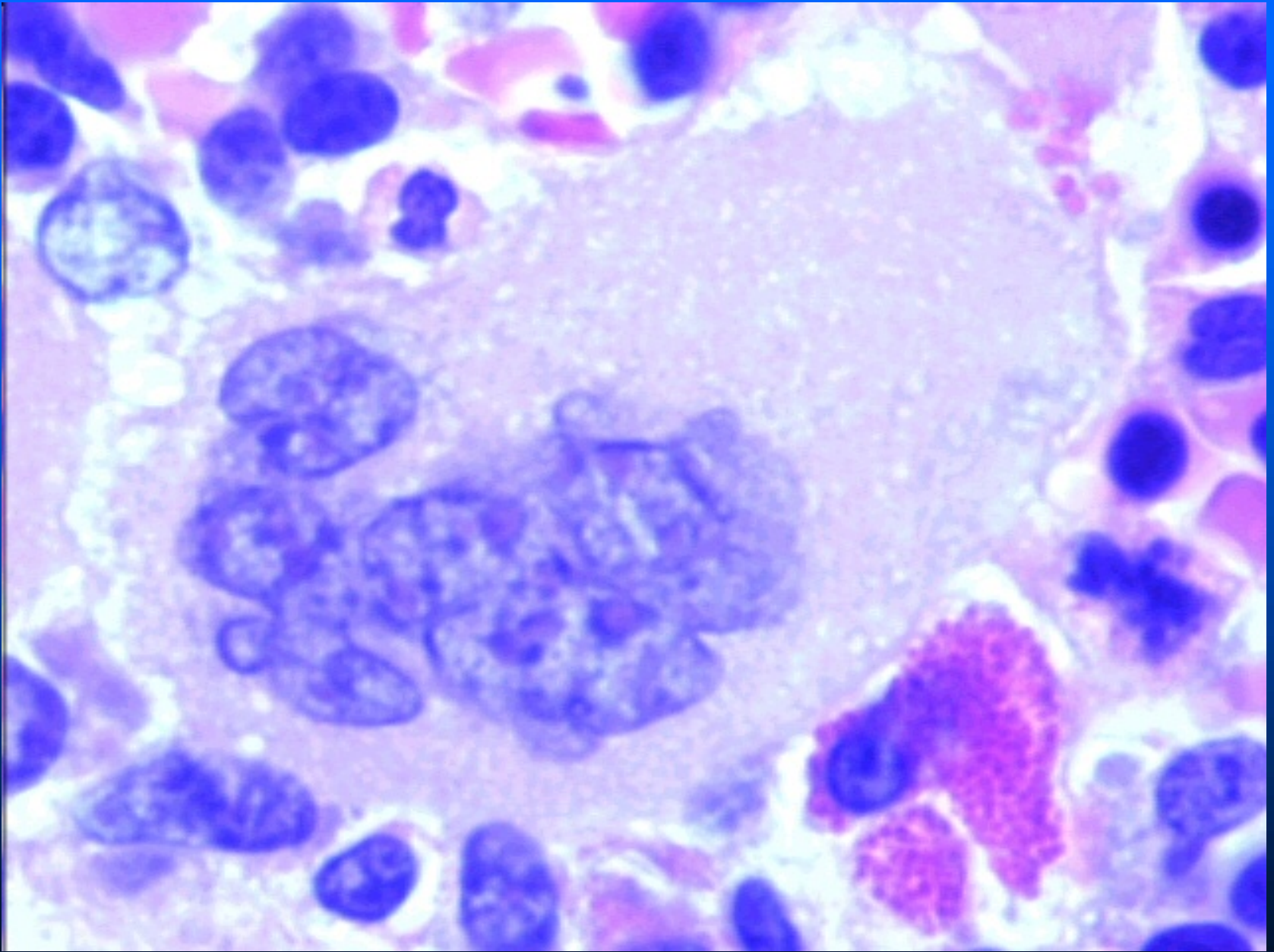


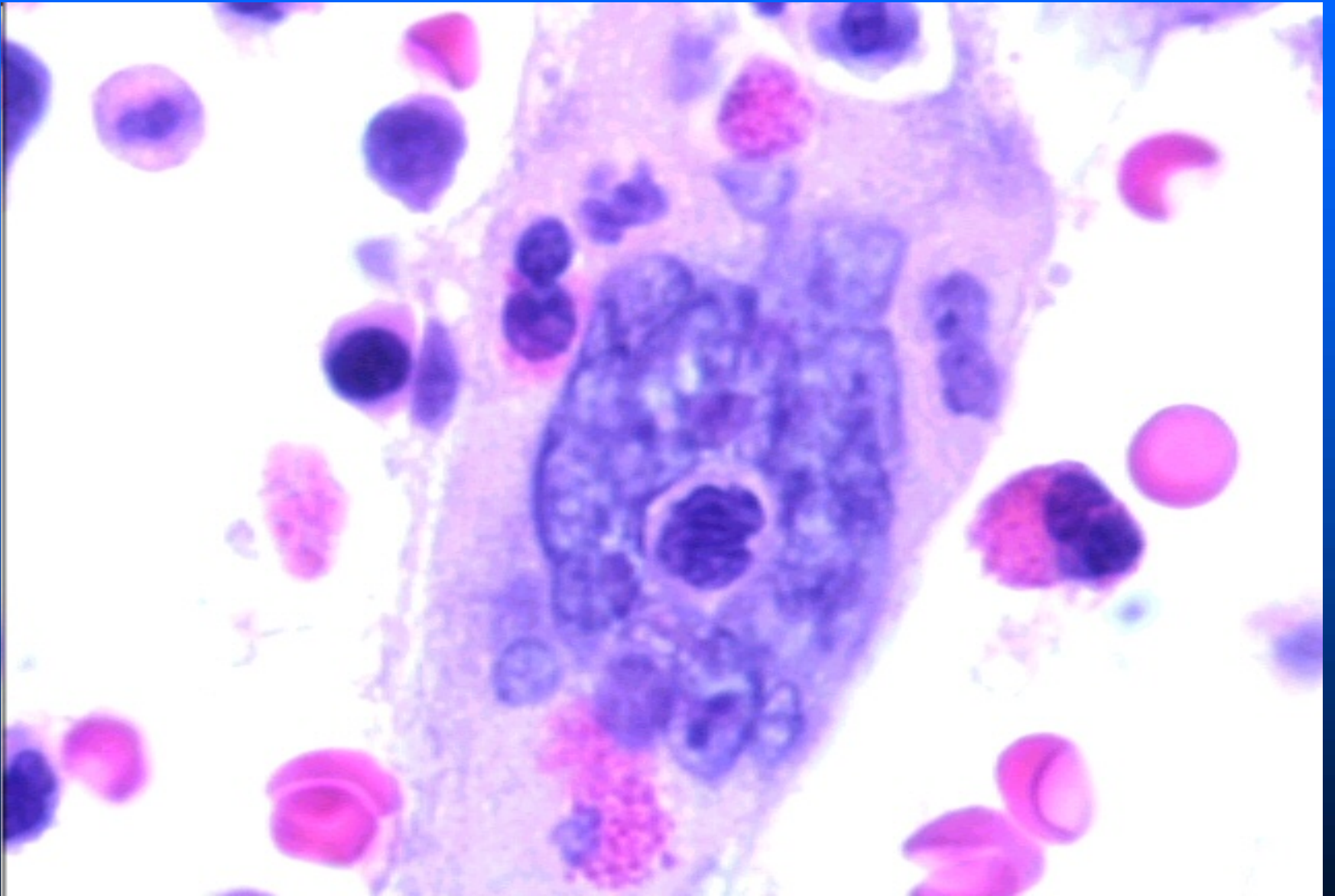


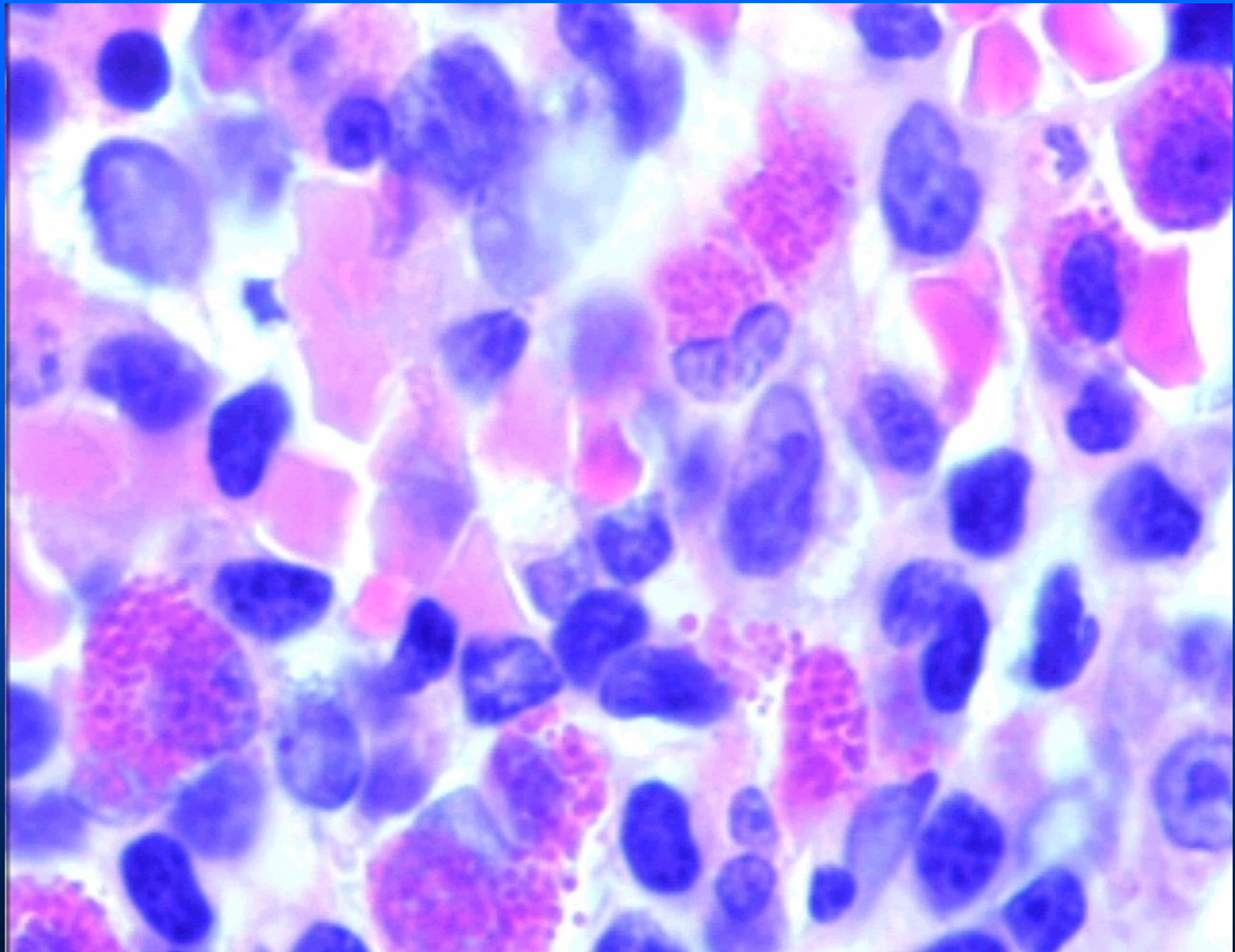


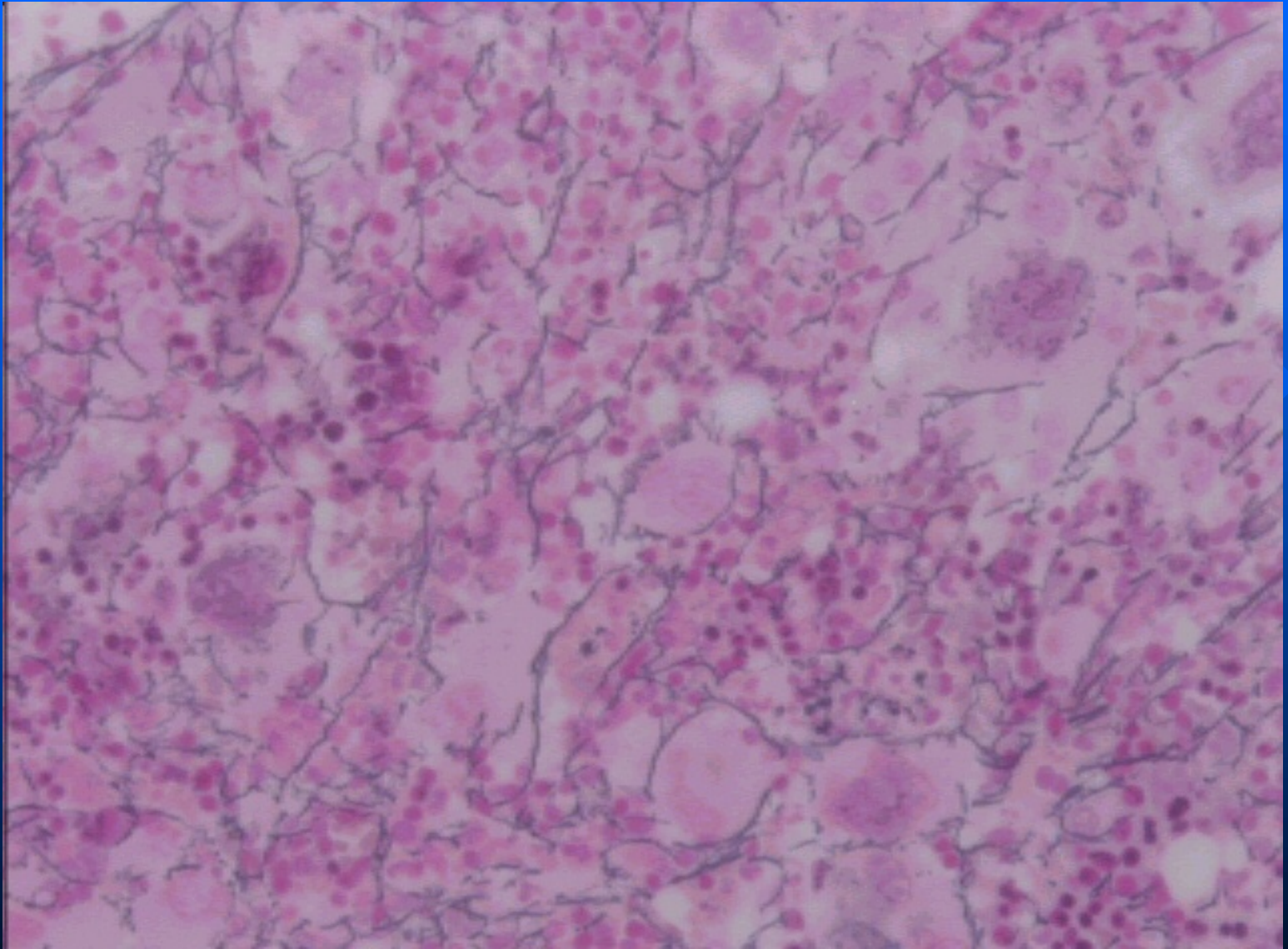


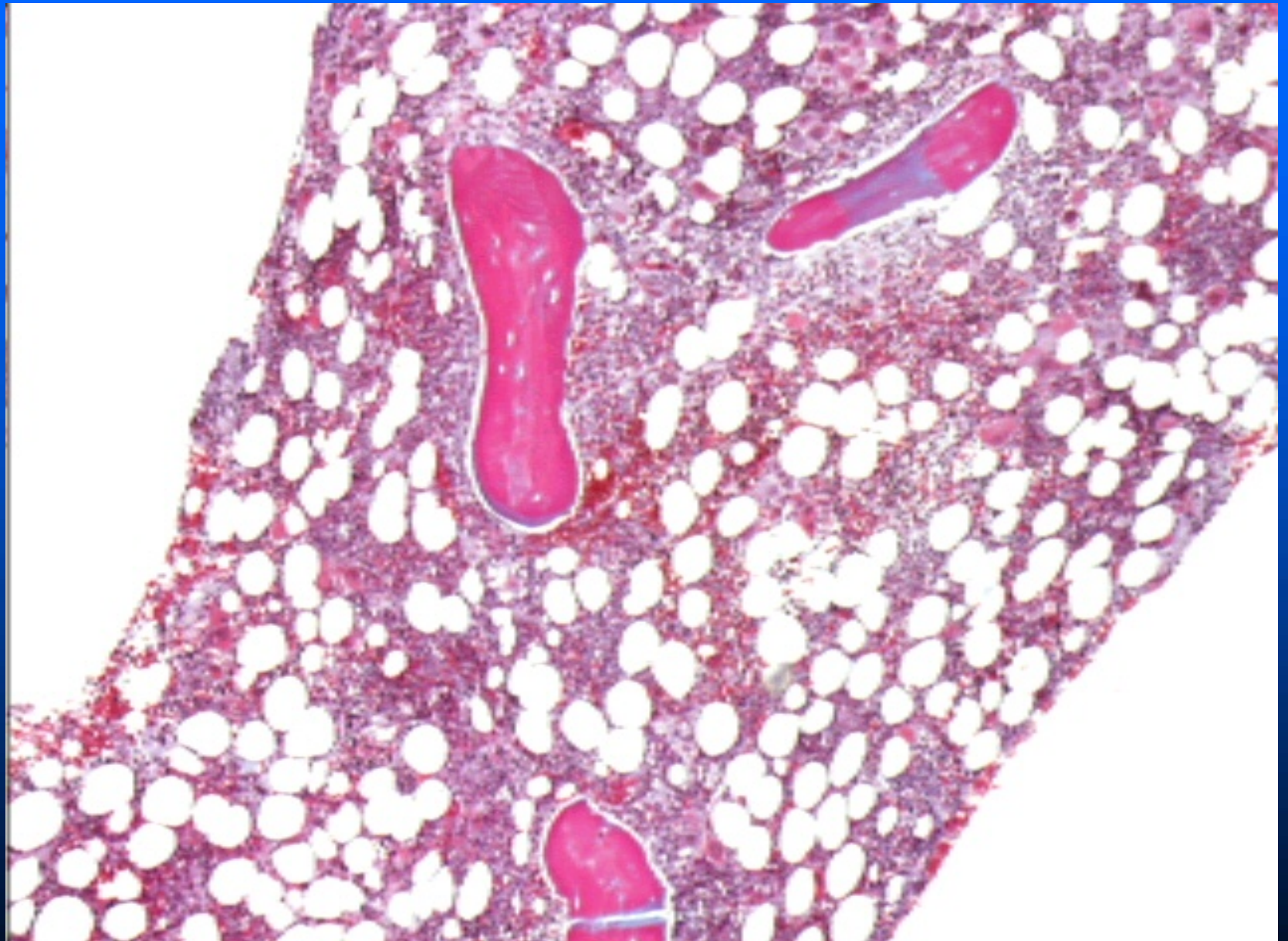












Iron Studies

- Storage Iron was decreased in the core and clot section.
- Few non-ringed sideroblast were identified in the aspirate smear.
- NO ringed sideroblast were identified.

Ancillary Studies

■ Molecular Studies:

-Negative for BCR/ABL fusion transcripts.

■ Cytogenetics:

-Normal Karyotype

Diagnosis

- Chronic Myeloproliferative disorder with bone marrow and peripheral findings most consistent with Essential Thrombocythemia.
- Depleted marrow iron stores.
- Mild leukocytosis due to mild absolute neutrophilia
- Absolute reticulocytosis in the absence of anemia.

Essential Thrombocythemia(ET)

WHO Classification of CMPD's

- 1: Chronic Myelogenous Leukemia
- 2: Chronic Neutrophilic Leukemia
- 3: Chronic Eosinophilic Leukemia
- 4: Polycythemia Vera
- 5: Chronic Idiopathic Myelofibrosis
- 6: **Essential Thrombocythemia**
- 7: Chronic Myeloproliferative disease, Unclassifiable

ET...Introduction

- Clonal Hematopoietic stem cell disorder characterized by proliferation in the bone marrow of Megakaryocytic lineage.
- Characterized by sustained thrombocytosis in the peripheral blood and increased number of large, mature megakaryocytes in the bone marrow, and clinically, by episodes of thrombosis and/or hemorrhage.

ET,....Epidemiology

- Exact incidence is not known but it is estimated to be 1-2.5 per 100,000 individuals annually.
- Most Pt.'s are 50-60y's age, no major predilection for any sex. However, the data shows a second peak in disease occurrence in 30 years of age with preference in women.

Clinical Features

- >50% Pt's are asymptomatic & markedly elevated platelet count is discovered incidentally on a routine complete blood examination.
- 20-25% present with manifestations of vascular occlusion or hemorrhage. Micro vascular occlusion may lead to TIA, digital ischemia with paresthesias and gangrene.
- ET may be cause of splenic and hepatic vein thrombosis. Modest splenomegaly found in 50% of pt' and mild hepatomegaly in 15% at Dx.

WHO Diagnostic Criteria

POSITIVE CRITERIA:

- 1: Sustained platelet count > 600K
- 2: Bone Marrow Biopsy specimen showing proliferation mainly of megakaryocytic lineage with increased numbers of enlarged, mature megakaryocytes.

EXCLUSION CRITERIA:

- 1: No Evidence of of CML
 - No Philadelphia chromosome and no BCR/ABL fusion gene

WHO Diagnostic Criteria

2: No evidence of Polycythemia Vera (PV)

- Norm red cell mass or Hb <18.5

- Stainable iron in marrow

3: No Evidence of Myelodysplastic Syndrome

- No del(5q), t(3;3)(q21;q26), inv(3)(q21q26)

- No significant granulocytic dysplasia, few if any micromegakaryocytes

WHO Diagnostic Criteria

4: No evidence of Chronic Idiopathic Myelofibrosis

- Collagen fibrosis absent
- Reticulin fibrosis minimal

5: No evidence that thrombocytosis is reactive due to:

- Underlying inflammation or infection
- Underlying neoplasm
- Prior splenectomy

ET

- Etiology:

- Cause of ET is unknown at this point of time. Rare Familial cases have been reported in the Literature.

- Immunophenotype:

- No aberrant phenotype has been described.

ET

- Genetics:
 - No Specific cytogenetic or molecular genetic abnormality is known at the current time. No Ph chromosome or BCR/ABL fusion gene; and cytogenetic and molecular genetic studies should always be done to exclude CML.

ET

■ Prognosis:

- ET is an indolent disorder, with long symptoms free intervals and occasionally interrupted by life-threatening thromboembolic or hemorrhagic episodes.
- Median survival times of 10-15 years are commonly reported. Transformation to AML or MDS occurs in $> 5\%$ of Pts.

ET... What's new

- Recently, three independent research groups from both sides of Atlantic, USA, UK and Italy published their results in a period of 6 weeks which points towards discovery and confirmation of an *acquired genetic mutation may explain the origins of ET, PV, and IMF myeloproliferative (MPD) disorders.*

“The Loss of heterozygosity (LOH) on the short arm of chromosome 9 (9pLOH) in myeloproliferative disorders suggest that 9p harbors a mutation that contributes to the cause of clonal expansion of hematopoietic cells in these diseases.”

9pLOH region was detected Fluorescent micro satellite PCR tech., noted that this region harbored the Janus Kinase 2 (JAK2) gene.

It was noted that in patients with 9pLOH, JAK2 had a homozygous G-T transversion, causing Phenylalanine to be substituted for Valine at position 617 of JAK2, leading to “V617F” mutation.

- The V617F is a somatic mutation that leads to “gain of function” JAK2 gene which is actually a tyrosine kinase .(Just Another Kinase)

- Tyrosine kinases are enzymatic proteins referred as cellular "switches" involved in cellular signaling pathways and regulate key cell functions such as proliferation, differentiation, anti-apoptotic signaling. Unregulated activation of these proteins, by mutations can lead to various forms of cancer as well as benign proliferative conditions. Indeed, more than 70% of the known oncogenes and proto-oncogenes involved in cancers, actually code for different Tyrosine kinases.

Results

- Frequency of “V617F” mutation of JAK2
....in MPD's

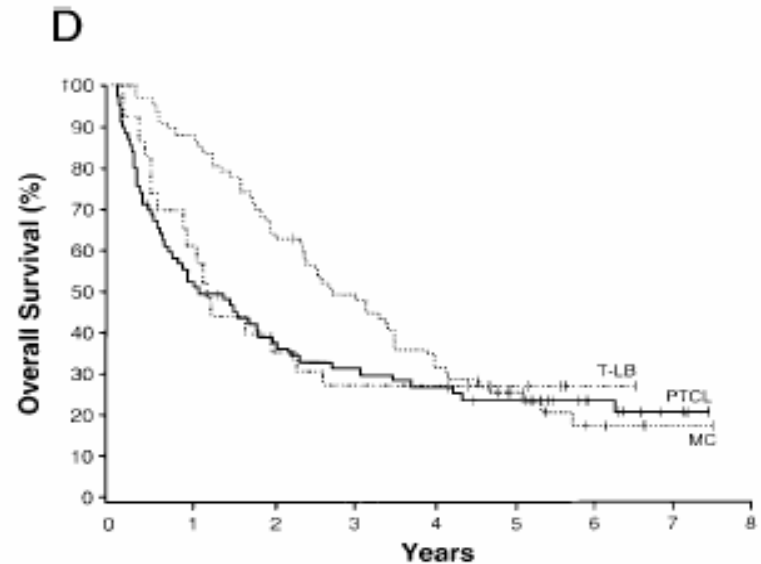
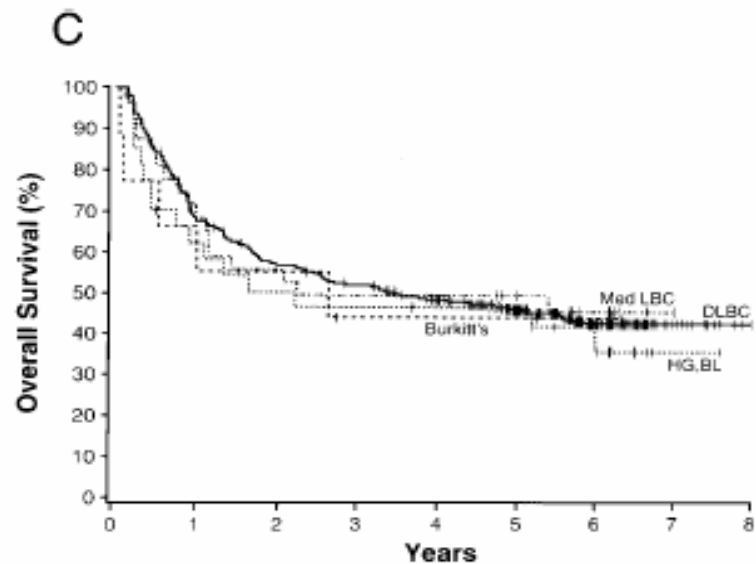
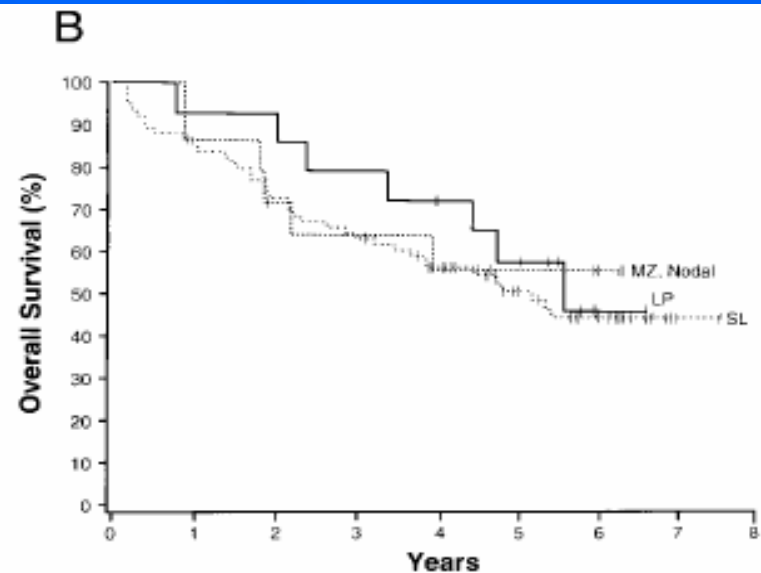
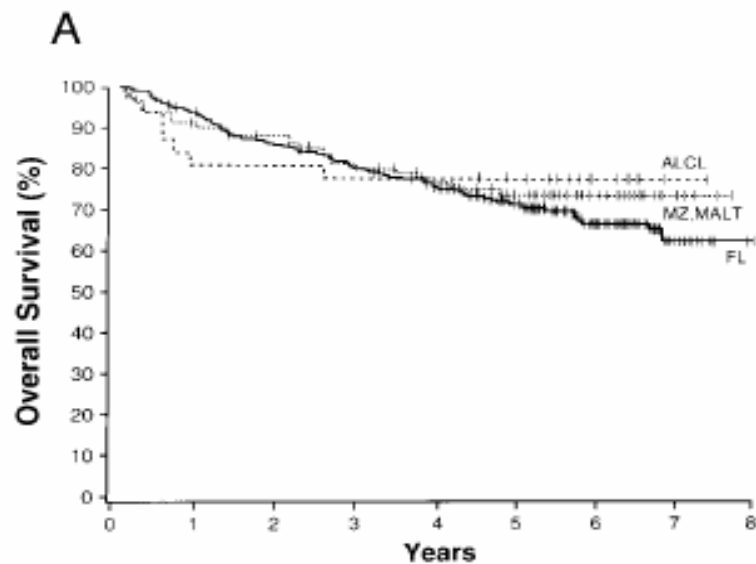
PV (65%)

IMF (57%)

ET (27%)

THANK YOU !!!

A Clinical Evaluation of the International Lymphoma Study Group Classification of Non-Hodgkin's Lymphoma



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