Chronic eosinophilic leukemia, not otherwise specified

SH2017-0300

Geetha Jagannathan, MD; Jerald Gong, MD; Zi-Xuan Wang, PhD; Stephen C. Peiper, MD; Guldeep Uppal, MD

Thomas Jefferson University

Philadelphia

Clinical Presentation

Clinical history

- Previously well 49 -year- old man
- Presented with a 3 week h/o progressive shortness of breath and nosebleeds
- Recent loss of appetite, weight loss of 20 lbs.
- Fatigue and night sweats

Social history

- Frequent tick exposure
- Pet cats- wife had a h/o Bartonella infection

Past medical history

- Splenectomy for trauma

- 7 years ago

Physical examination

- Bilateral mobile non-tender inguinal lymphadenopathy (5-7cm)
- No hepatomegaly

Laboratory Workup and Imaging

Complete blood count and differential count		
WBC	250 B/L	↑
Hb	7.6 g/dL	↓
Platelet	22 B/L	↓
Absolute eosinophil count	32.5 B/L	↑

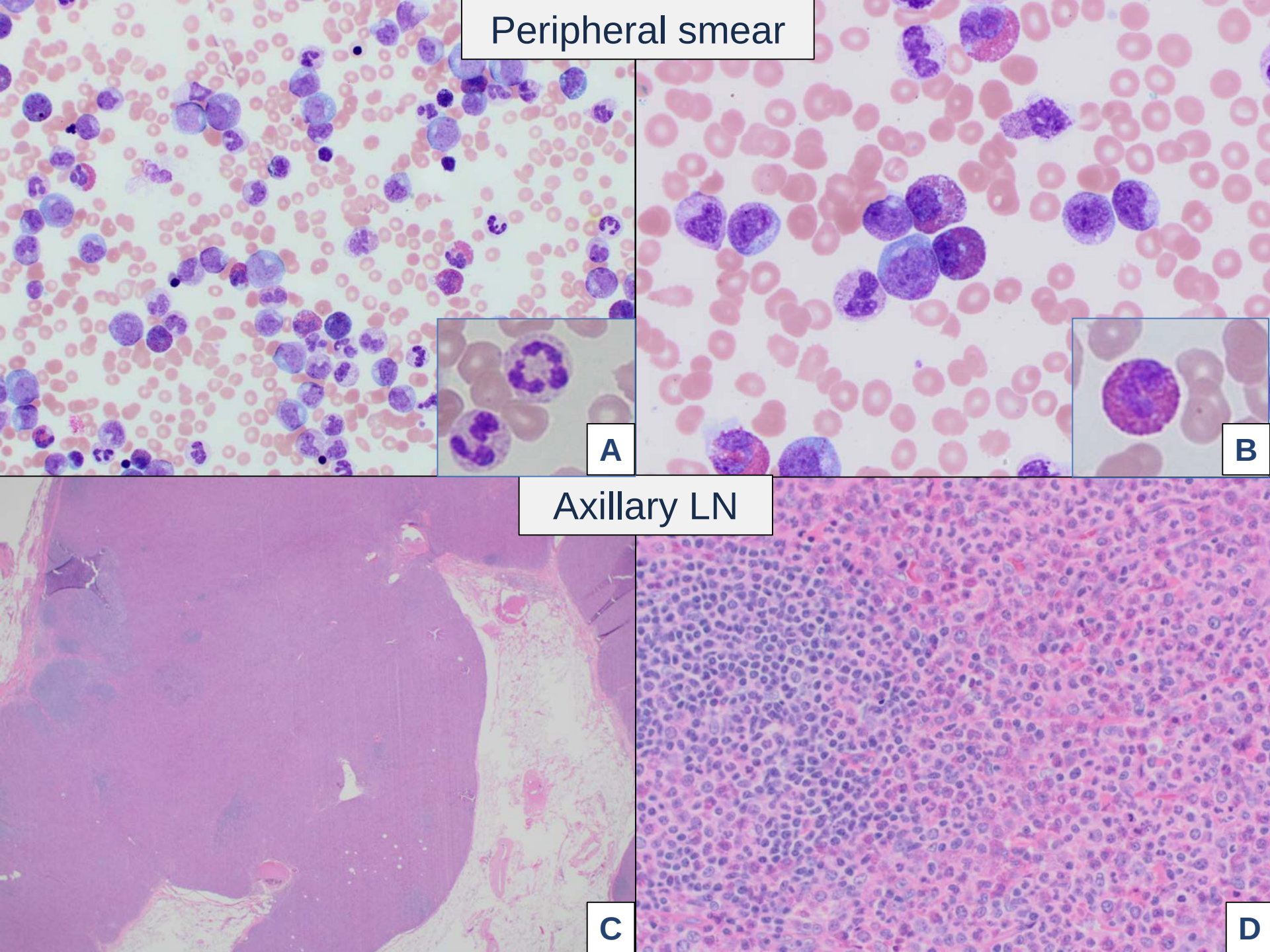
Neutrophils	22%	Eosinophils	13%
Bands	14%	Basophils	0%
Metamyelocytes	9%	Monocytes	1%
Myelocytes	24%	Lymphocyte	5%
Promyelocytes	11%	Blasts	1%

Serology

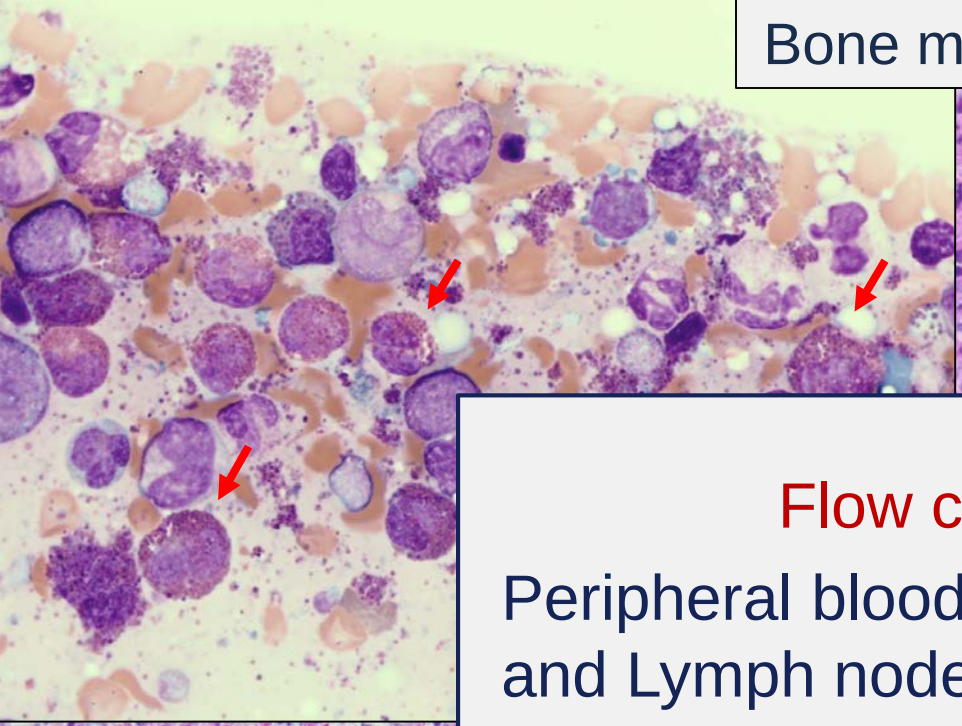
Infectious etiology was excluded

CT chest and abdomen

Diffuse lymphadenopathy involving the axilla, mediastinum and upper abdomen


Peripheral smear
A
B
Axillary LN
C
D

Bone marrow



F

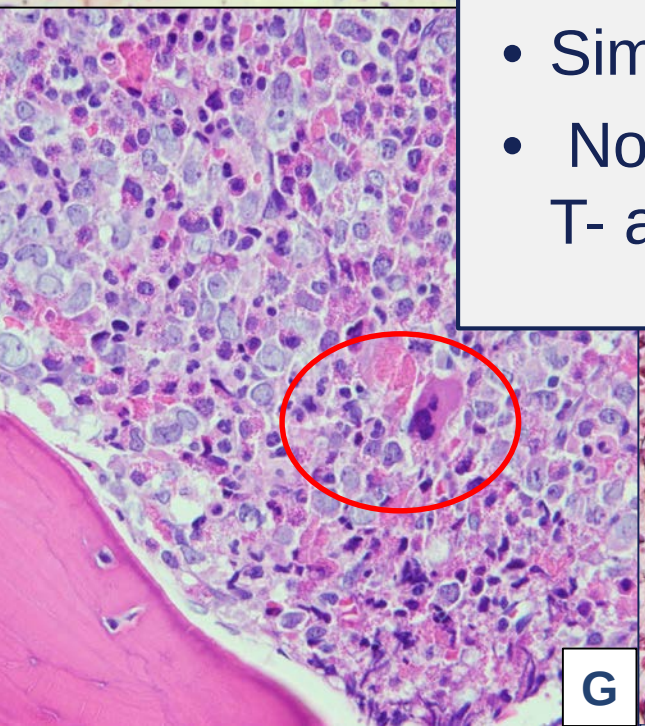
Flow cytometry

Peripheral blood, bone marrow and Lymph node

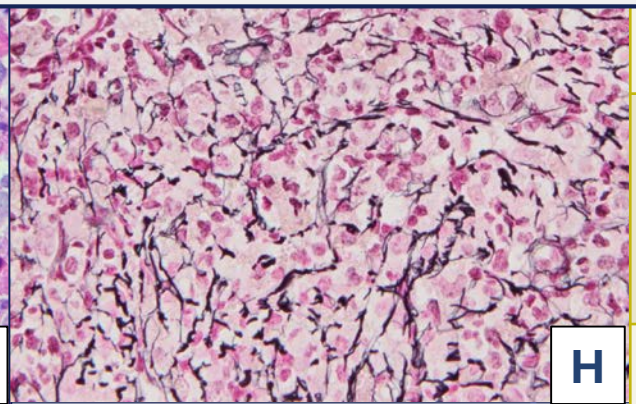
- Similar findings
- No phenotypic abnormalities of T- and B-lymphocytes

erential count

ils/ rs	33%
nils	3%
Bands	16%
Myelocytes	23%
Meta/ Promyelocytes	13%
Blasts	3%



G



H

Cytogenetics and Molecular Studies

NEGATIVE

Karyotyping:

Normal male karyotype 46, XY

Quantitative RT-PCR:

Negative- *BCR/ABL* and *PML/RARA*

FISH:

Normal patterns in

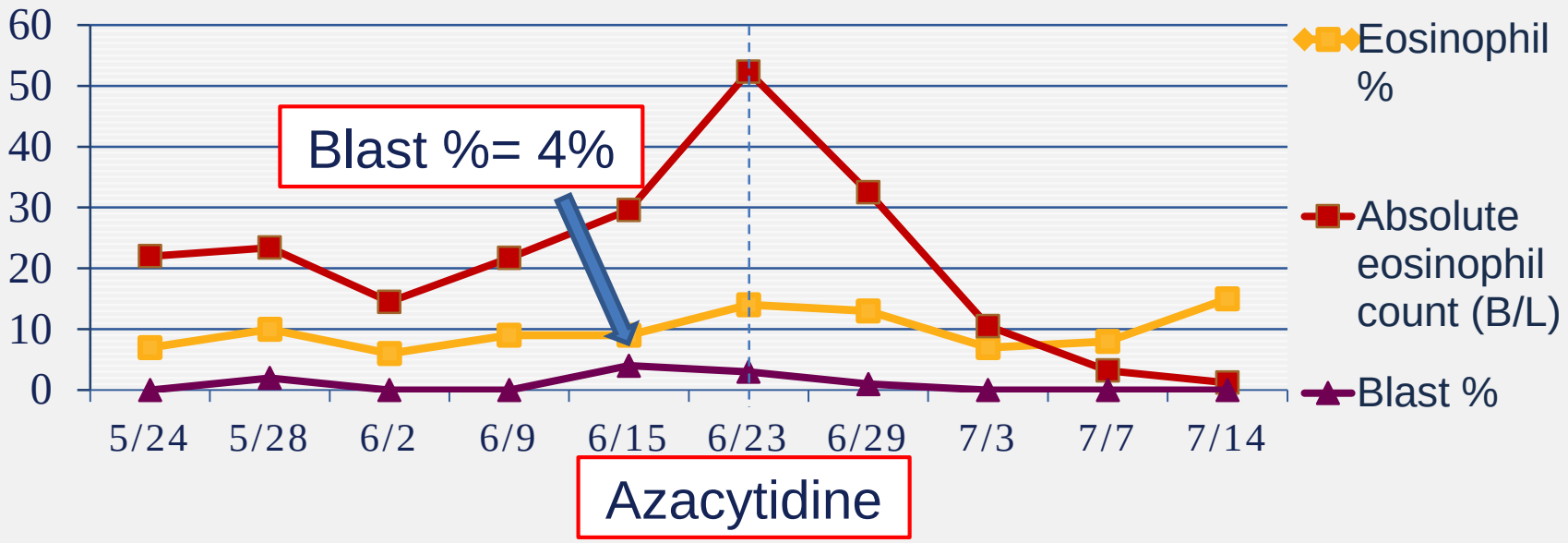
- MPN, MDS panel
- Eosinophilia panel: *PDGFRA, PDGFRB*, and *FGFR1*
- AML panel, ALL panel

POSITIVE

Next generation sequencing:

- 48 gene Illumina TruSightTM Myeloid Sequencing Panel
- ***ASXL1* - allele frequency of 49.60%**
  - c. 1927delG
  - p.G645fs*58 (Frameshift)
  - Mutation ID: COSM1180918
- No mutations in the remaining 47 genes including *JAK2, MPL, CALR,CSF3R* and *SETBP1*

- Predominantly granulocytic leukocytosis with absolute eosinophilia, bicytopenia
- Eosinophilic proliferation- BM and LN
- No significant dysplasia
- NGS: Pathologic *ASXL1* mutation



Chronic eosinophilic leukemia, NOS

Chronic Eosinophilic Leukemia, NOS

- Persistent clonal eosinophilia
- Male predominance, median age at diagnosis: 6th decade
- Aggressive disease with high risk of acute transformation (AT)

Helbig et al, 2012:

- 10 cases
- Median disease specific survival: 22 months (range:1.6-41.9)
- 50% transformed
- Median time to AT: 20 months
- Median time from AT to death: 2 months

Wang et al, 2016:

- 6 cases
- Median disease specific survival: 14.4 months (range: 1.0 - 120.1)
- 50% transformed

Helbig G et al, American Journal of Hematopathology(2012); 87:643-645
Sa A Wang et al; Modern Pathology(2016) 29, 854-864

Chronic Eosinophilic Leukemia, NOS

Diagnostic criteria

1	Eosinophil count ≥ 1.5 B/L
2	• Clonal cytogenetic or molecular genetic abnormality OR • blasts >2% in peripheral blood OR • blasts >5% in bone marrow
3	Blast count in peripheral blood or bone marrow <20%
4	No *BCR-ABL1* fusion gene or other myeloproliferative neoplasms (PV, ET, PMF) or MDS/MPN (CMML or aCML)
5	No rearrangement of *PDGFRA, PDGFRB, FGFR1* or *PCM1-JAK2*
6	No *inv*(16)(p13q22) or t(16;16)(p13;q22) or other feature diagnostic of AML

WHO classification of tumors of hematopoietic and lymphoid tissues, 2008

Idiopathic Hypereosinophilic Syndrome (IHES)

Differs from CEL, NOS:

- Absence of increased blasts
- Lack of evidence of clonal genetic abnormality

Diagnostic criteria

1	Persistent eosinophilia ≥ 1.5 B/L for at least 6 months
2	Hypereosinophilia related tissue damage
3	R/o reactive eosinophilia
4	R/o AML, MPN, MDS, MPN/MDS and systemic mastocytosis
5	R/o cytokine-producing immunophenotypically-aberrant, T-cell population

Mutational Spectrum of CEL,NOS and IHES

- 6 CEL, NOS and 51 HES cases tested for mutations associated with myeloid neoplasms by NGS
- Pathologic mutations found in 50% CEL, NOS and 28% HES (HES/NGS+)

ASXL1	43%	*NOTCH1*	14%
TET2	36%	*DNMT3A*	7%
EZH2	29%	*NRAS*	7%
SETBP1	22%	*JAK2*	7%
CBL	14%	*GATA2*	7%

CEL,NOS	HES/NGS+	HES/NGS –
Older Short survival	Heterogenous A subset resembled CEL, NOS	Younger Symptoms of eosinophil activation

Sa A Wang et al; Modern Pathology(2016) 29, 854-864

Differential diagnosis

CEL, NOS	CML	aCML
Myeloproliferative neoplasm characterized by a predominance of granulocytes at different stages of maturation		
• Absolute eosinophilia • Mild eosinophilic dysplasia • Charcot-Leyden crystals	• Thrombocytosis, monocytosis • Absolute basophilia • Hypolobated megakaryocytes	• Granulocytic dysplasia • May have dysplasia in other cell lineages • Typically lack eosinophilia
• *ASXL1,TET2, EZH2*	• Reciprocal translocation t(9;22) resulting in *BCR-ABL1* fusion gene	• Mutations-*SETBP1* and *CSF3R* • Also described in CEL, NOS and HES

Sa A Wang et al; Modern Pathology(2016) 29, 854-864

Final Panel Diagnosis: Chronic Eosinophilic Leukemia, NOS

Jefferson
HEALTH IS ALL WE DO