



THE UNIVERSITY OF TEXAS

MD Anderson  
~~Cancer Center~~

# Blastic Plasmacytoid Dendritic Cell Neoplasm with *DNMT3A* and *TET2* mutations (SH2017-0314)

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# Clinical Presentation

- 71 year old man presented in June, 2015 with skin rash.
- Bone marrow core biopsy, aspirate smears, and skin biopsy were initially diagnosed as acute myeloid leukemia (AML).
  - Cytogenetic studies showed normal male karyotype, 46, XY[11].
  - FISH was negative for *CBFB/MYH1* rearrangement.
  - Real-time PCR was negative for *PML-RARA* and *RUNX1-RUNX1T1* fusion transcripts.
  - PCR was negative for *FLT3-ITD*, *FLT3-D835*, or *NPM1* mutations.

# Clinical Presentation

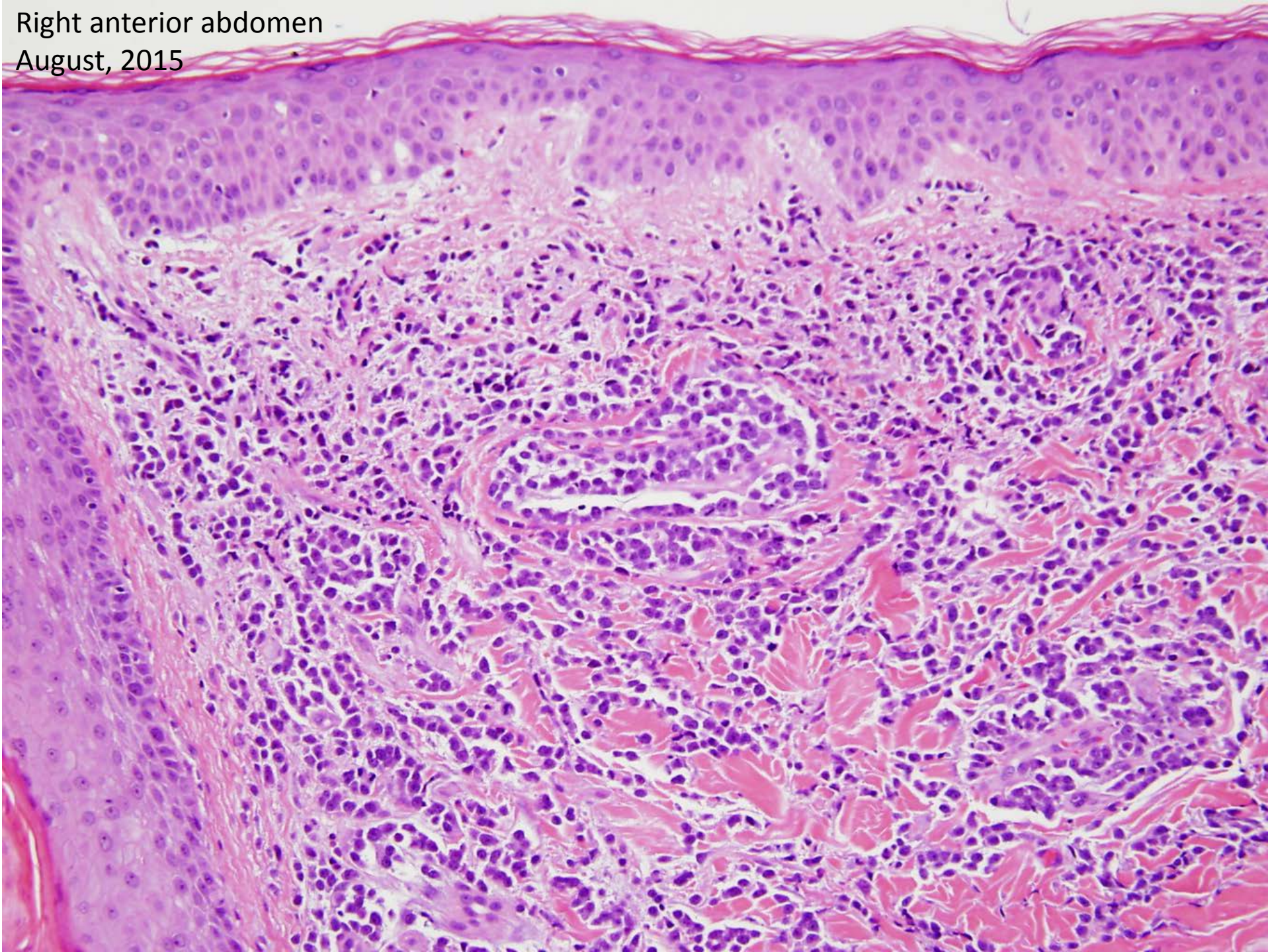
- Patient received multiple AML-based chemotherapy regimens
  - 7+3 induction chemotherapy (Daunorubicin and Cytarabine) with remission
  - Azacitidine, Pioglitazone, ATRA
  - Cytarabine
  - FLAG-IDA (Fludarabine, Cytarabine, Idarubicin and G-CSF)
- Patient received radiation for skin lesions.
- He was referred to our institution in June, 2016 for further treatment options.



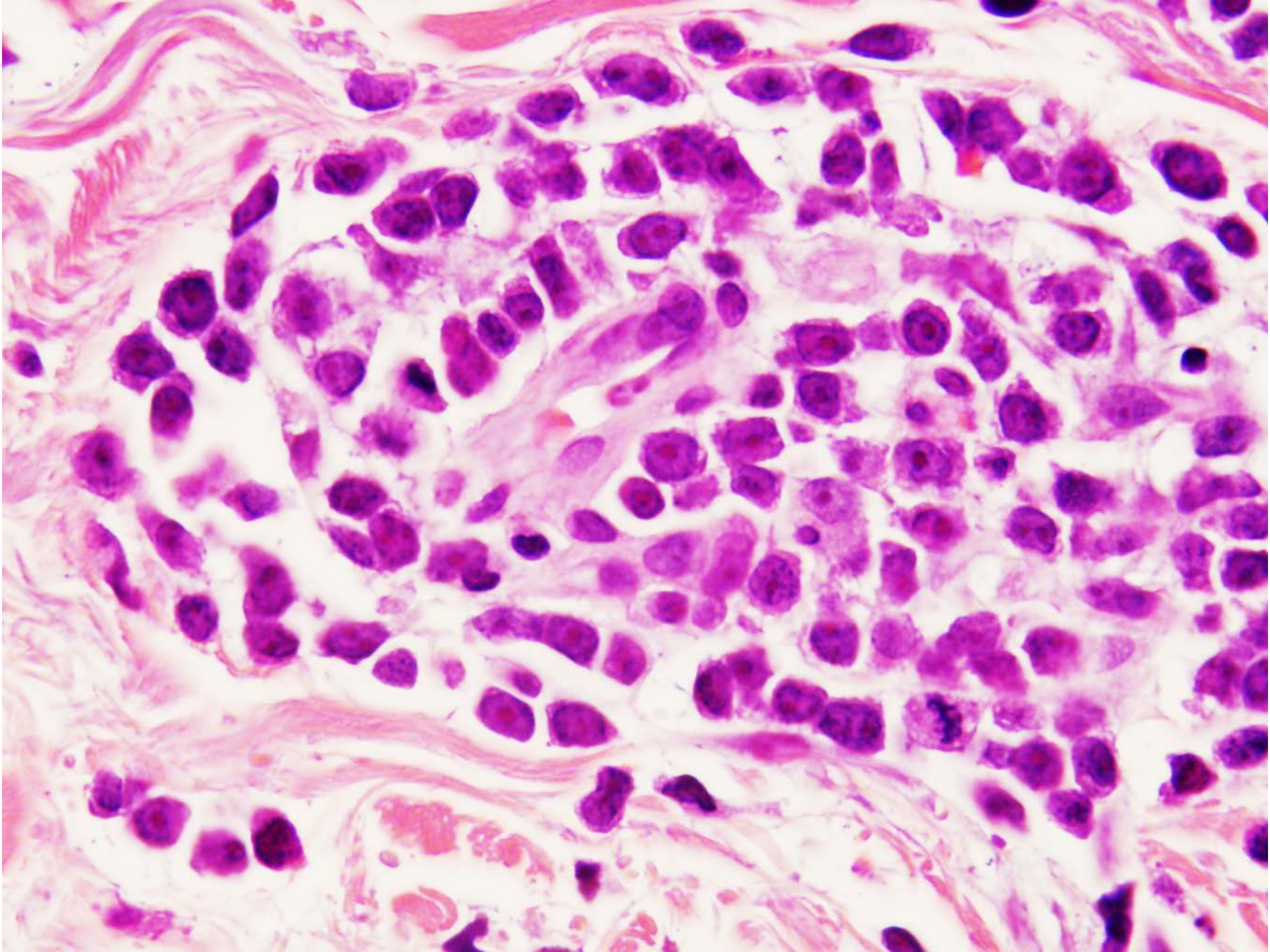
SKIN LESIONS



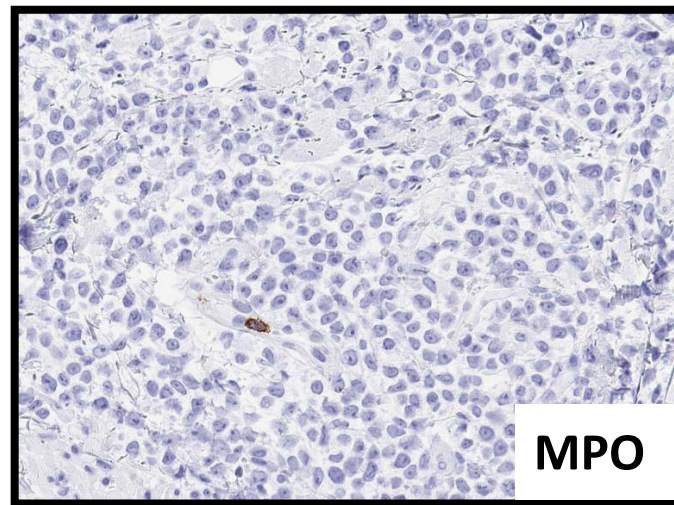
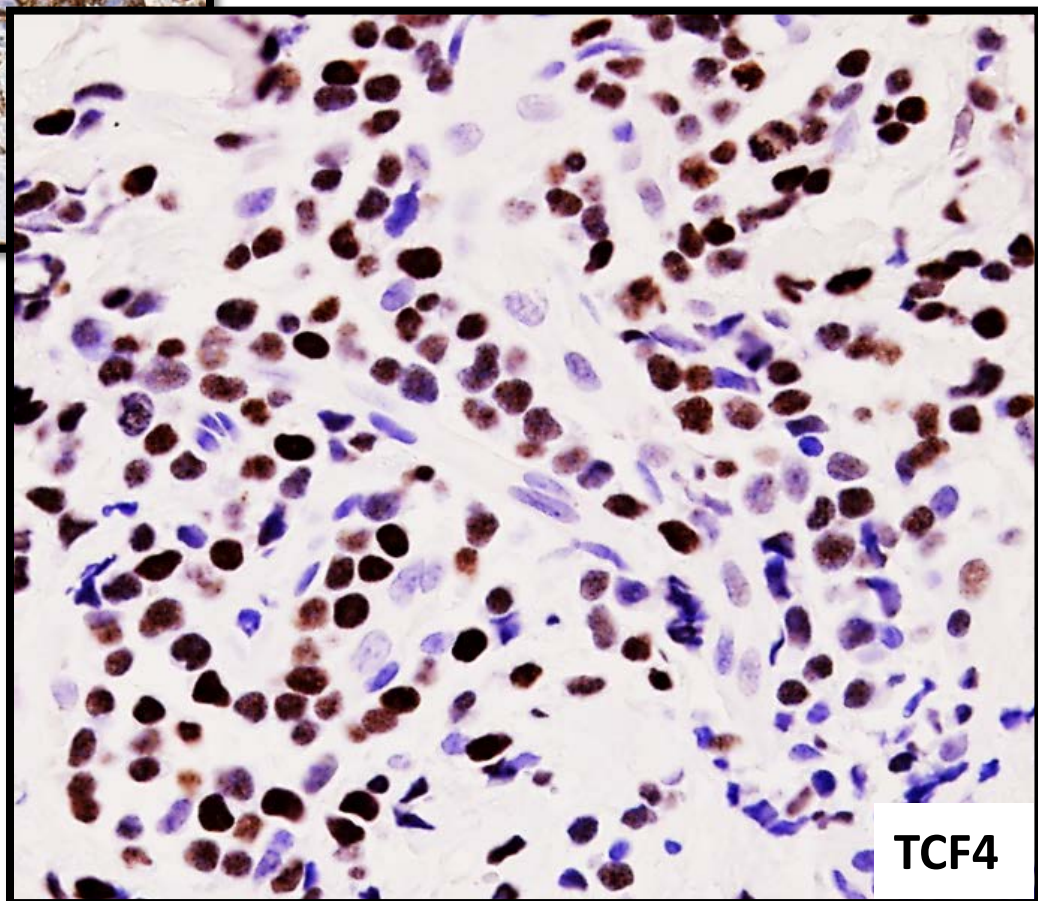
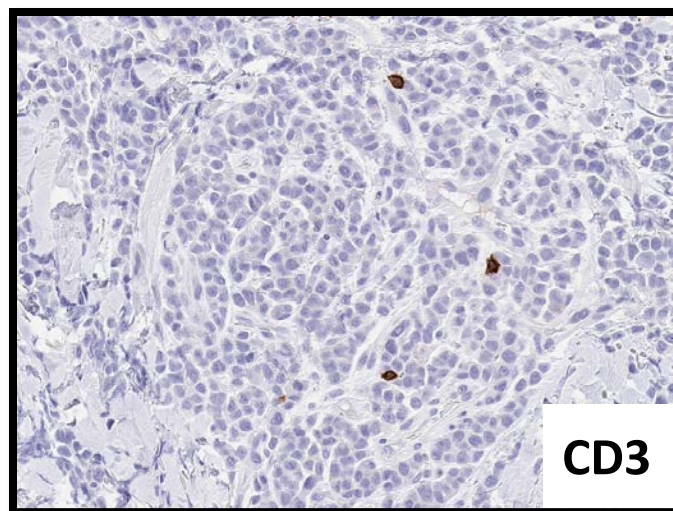
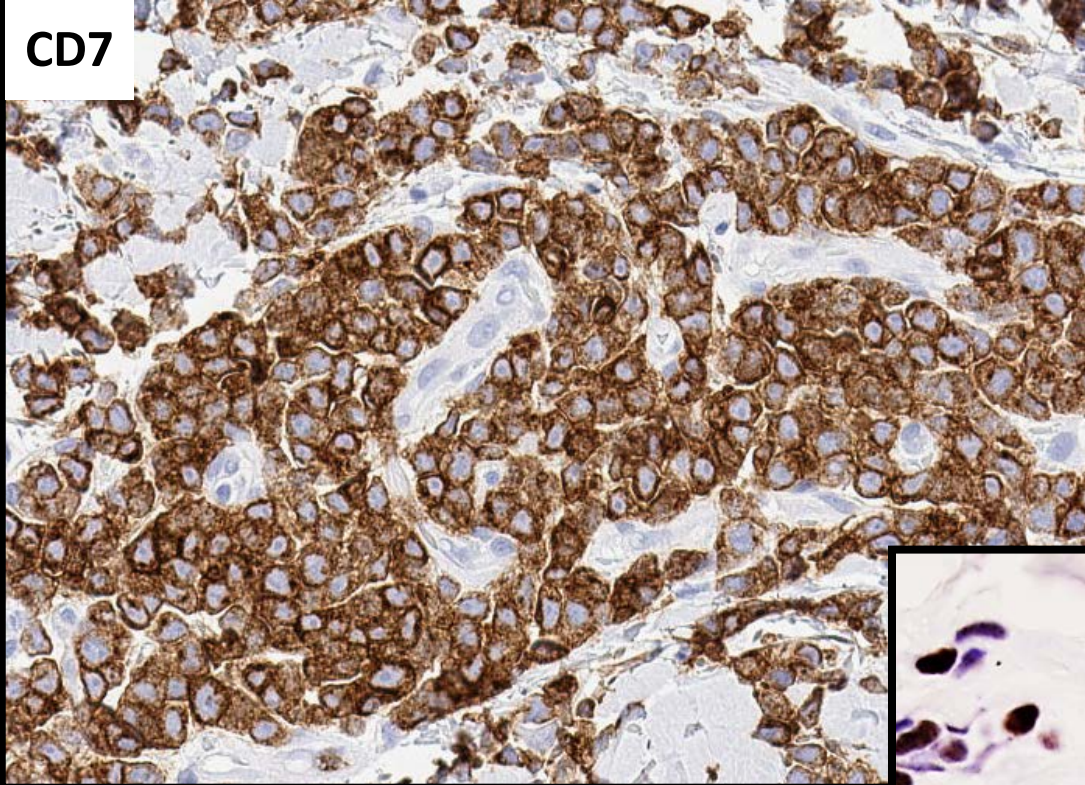
Right anterior abdomen  
August, 2015







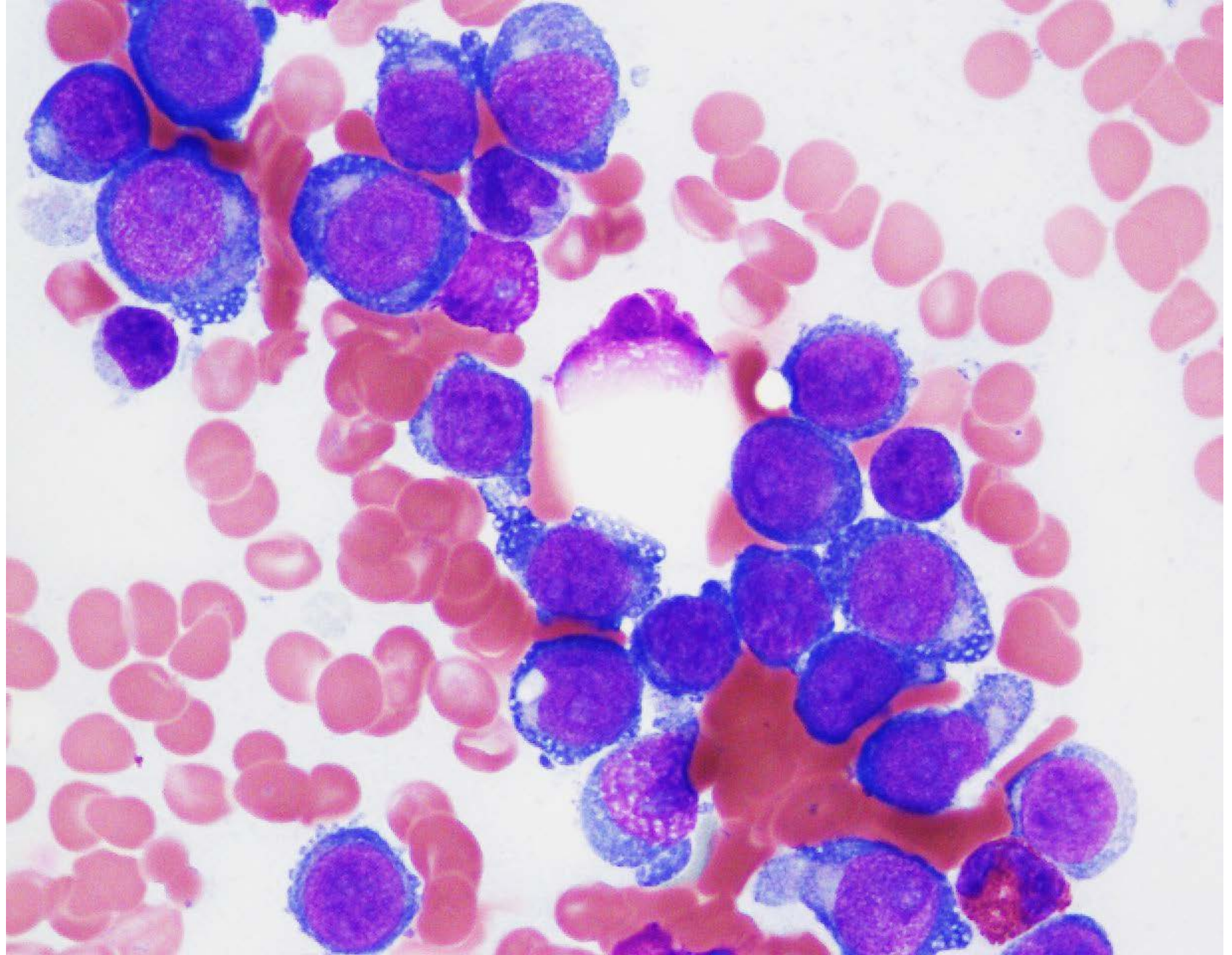




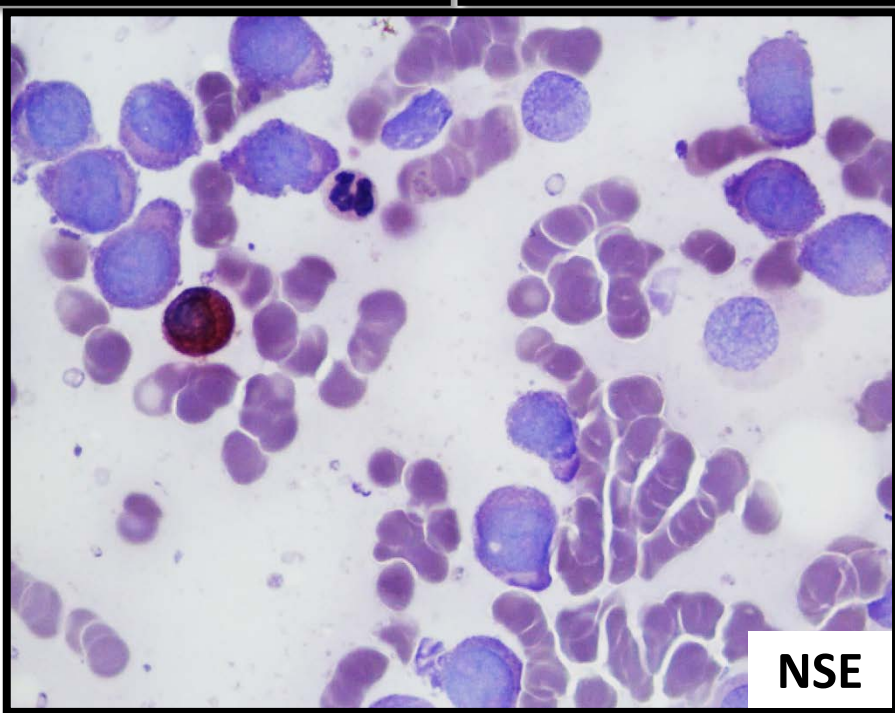
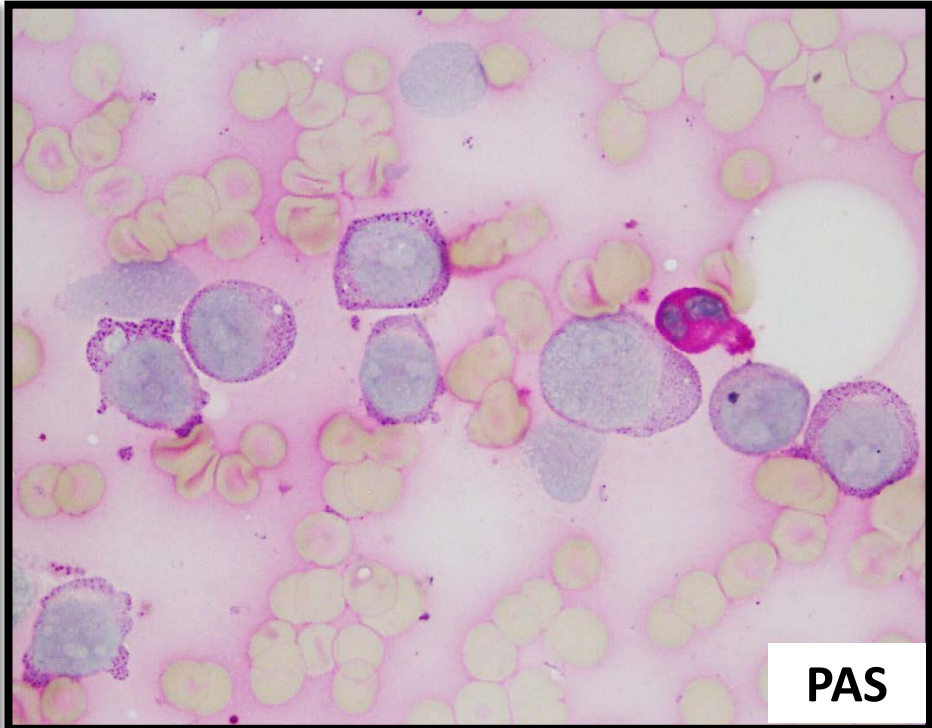
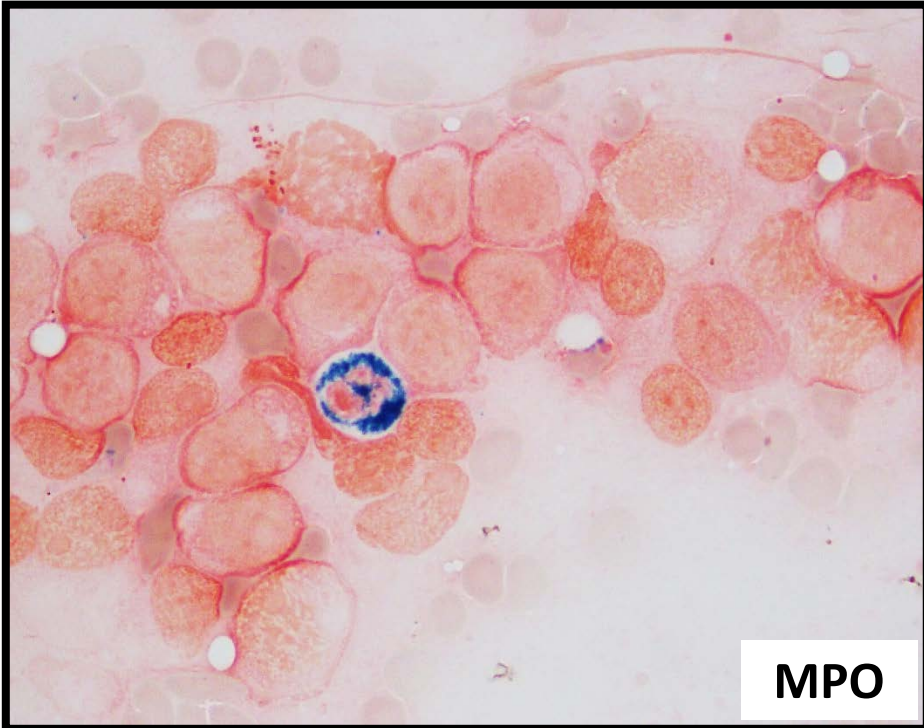
# Immunophenotypic profile of skin lesions

- **Positive:**
  - TCF4, CD123, CD43, CD7, and TdT (partial)
- **Negative:**
  - CD3, MPO, CD117, CD34, CD15, CD33, lysozyme, and CD56

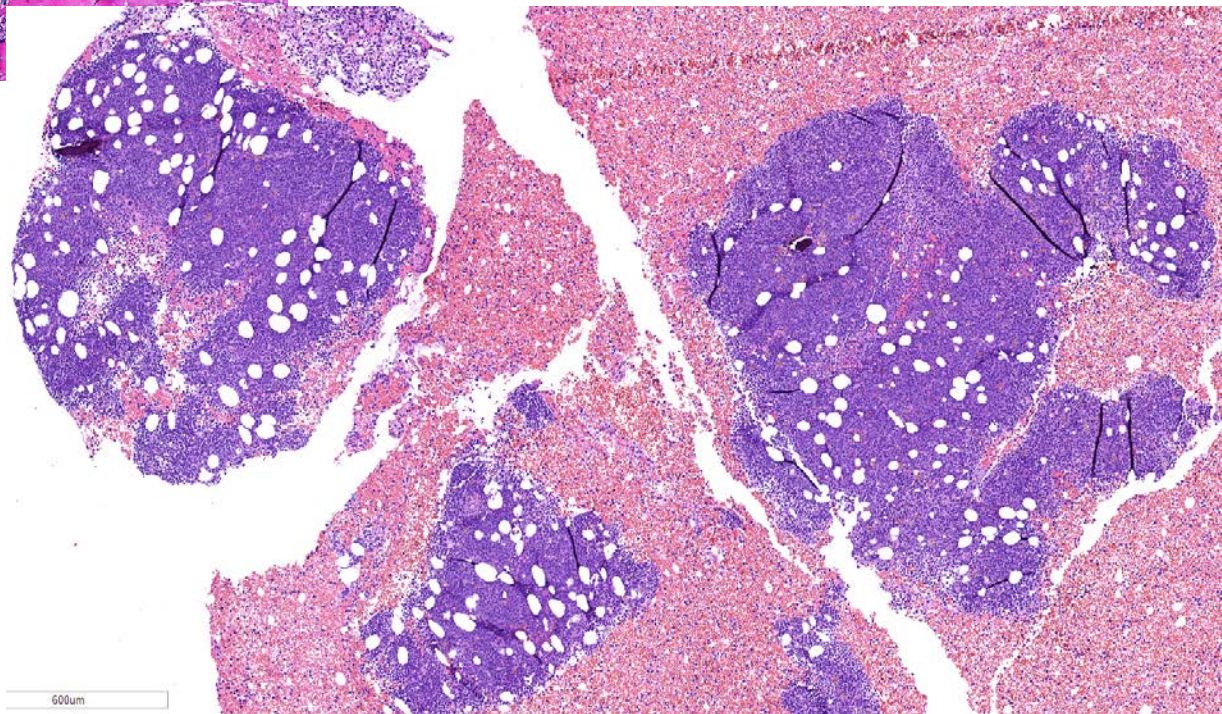




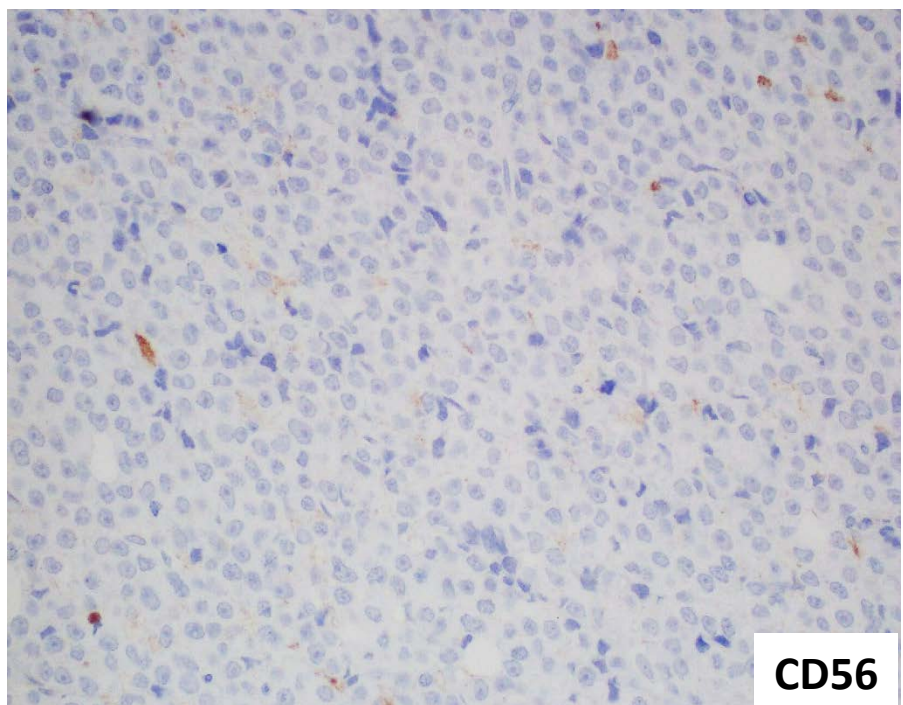
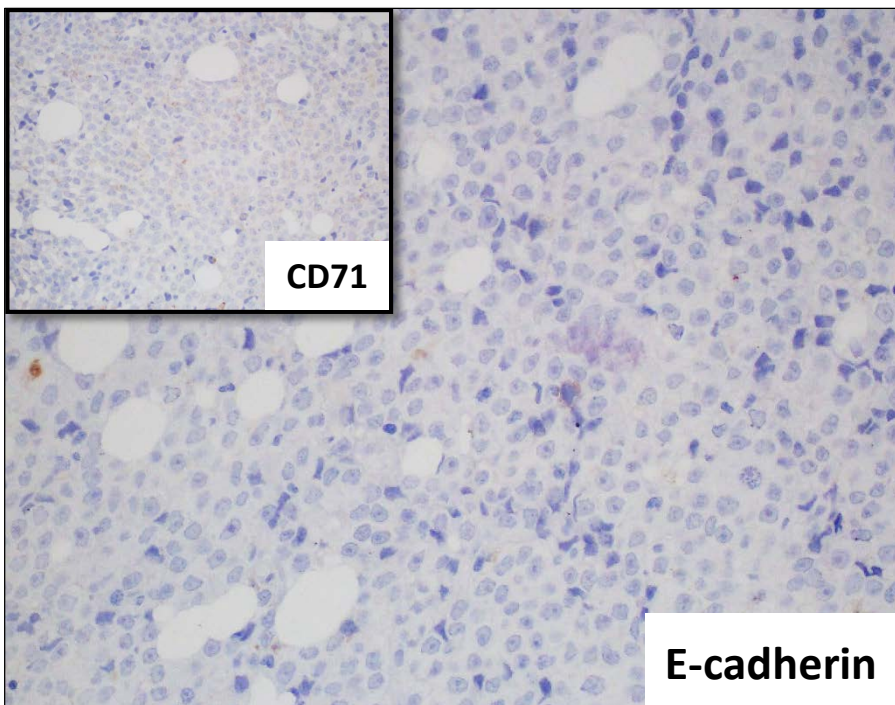
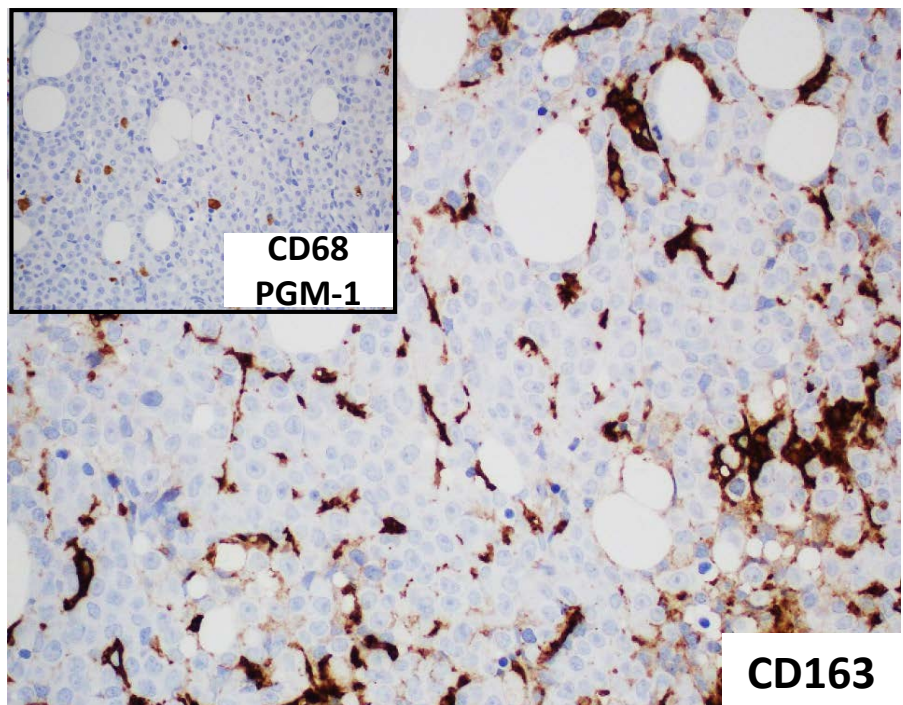
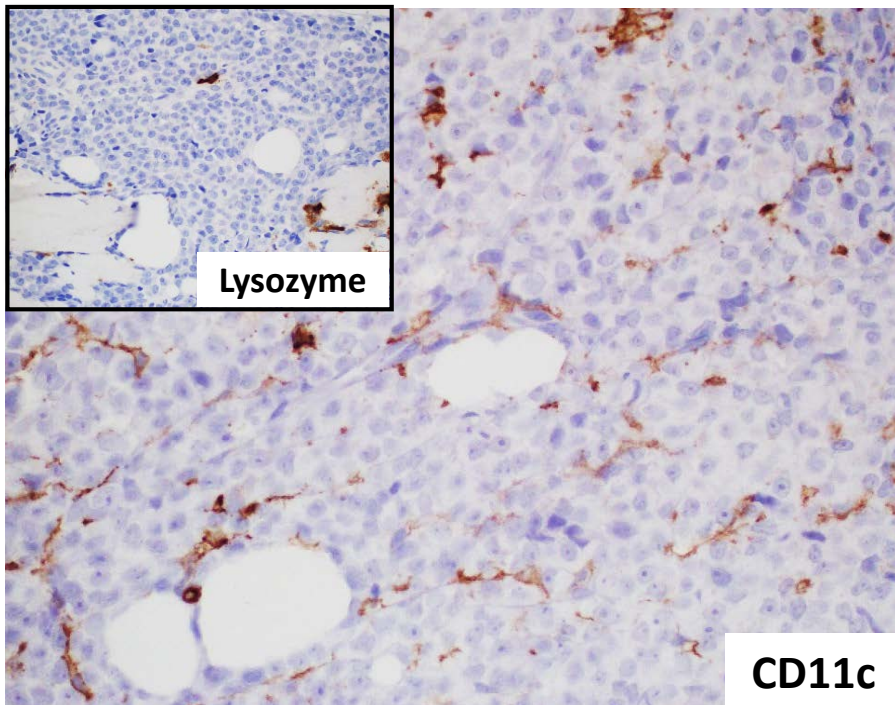




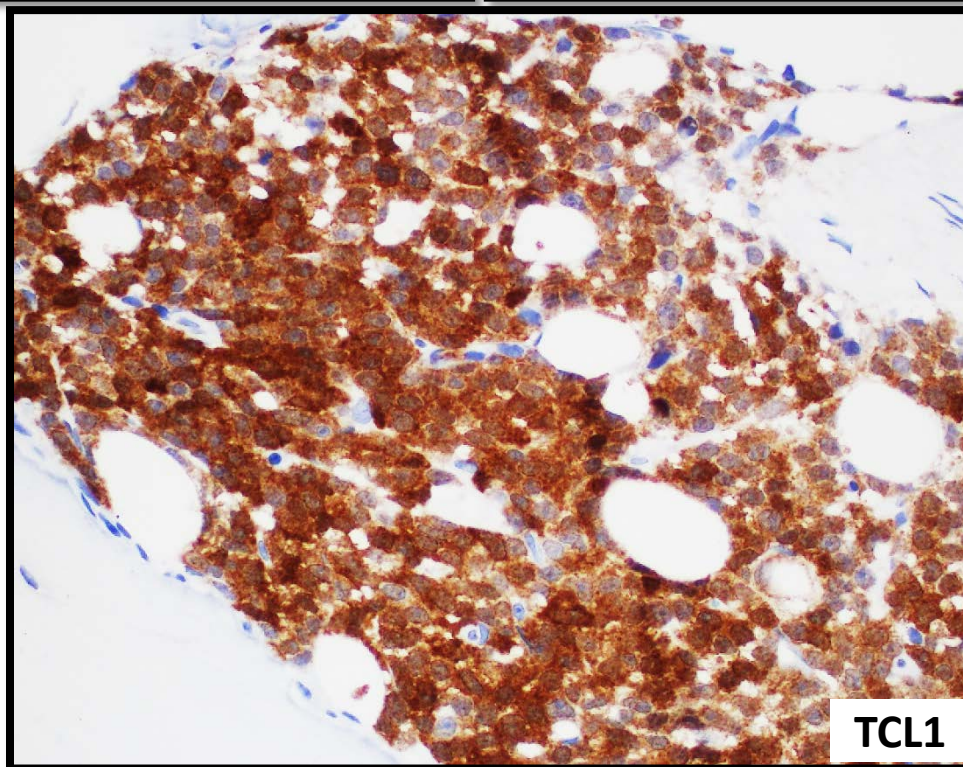
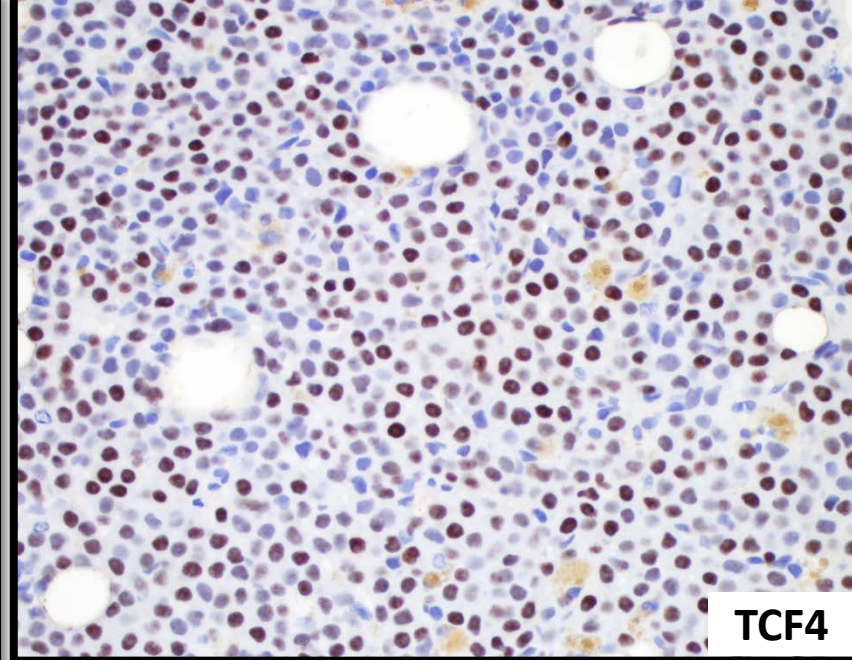
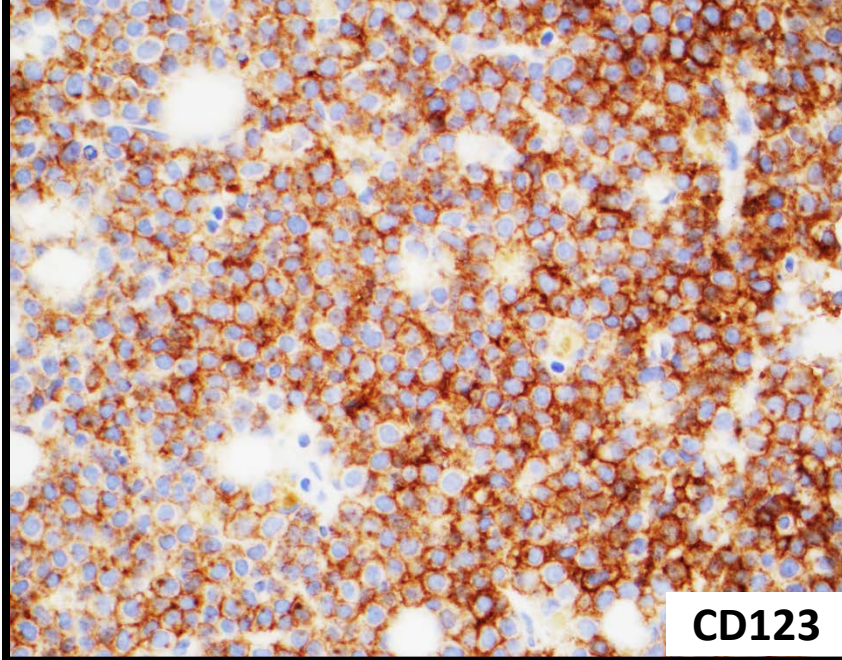




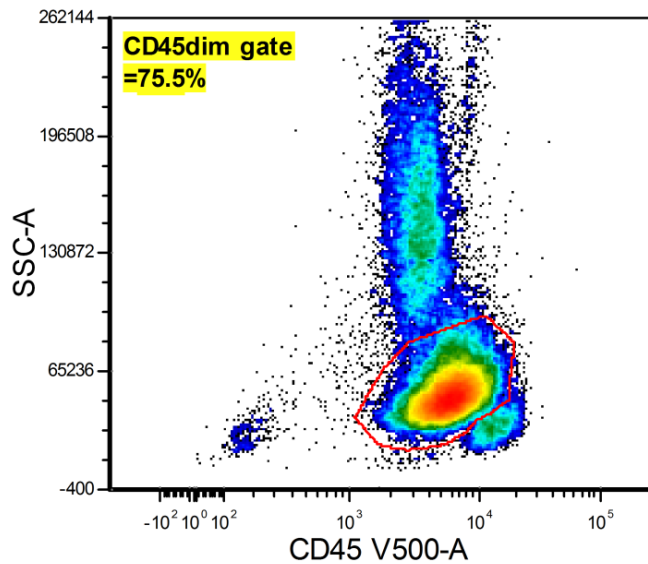




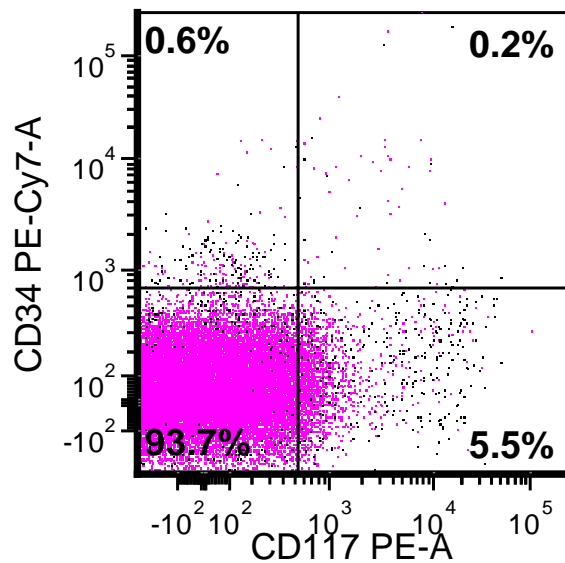




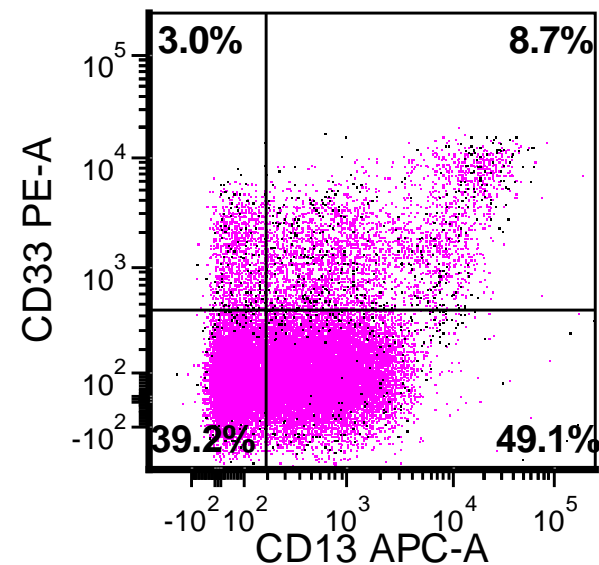
Singlet F + S



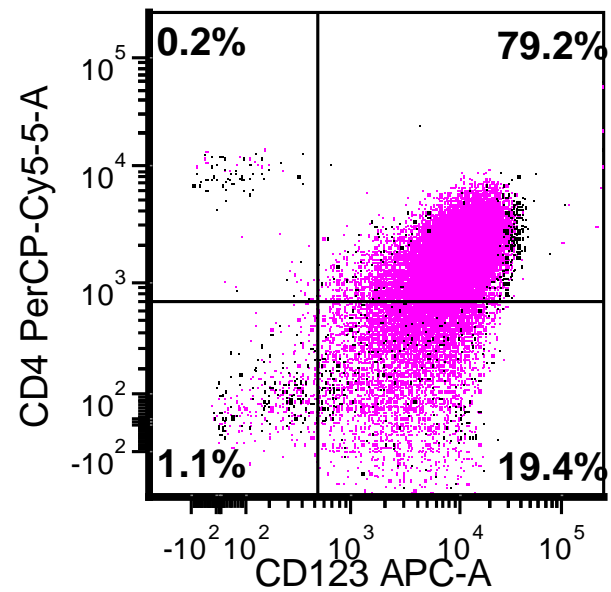
Perm-CD45 dim gate



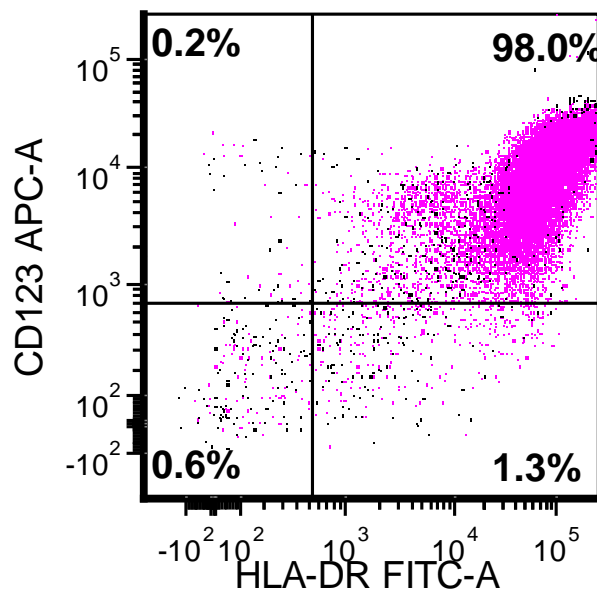
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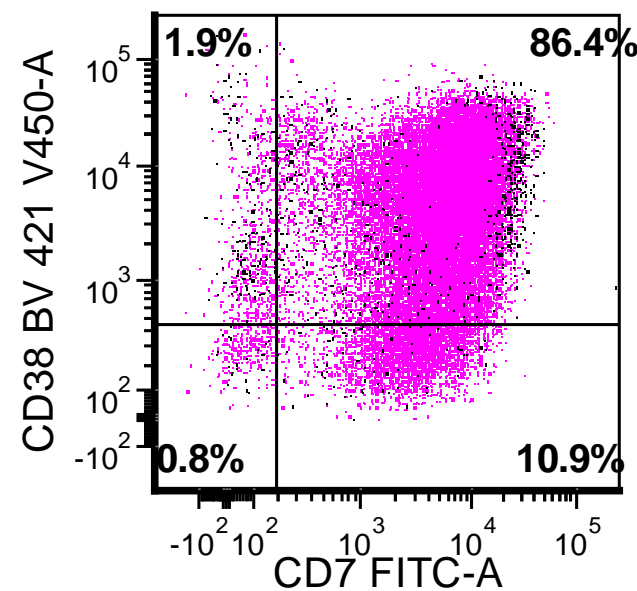
Perm-CD45 dim gate



Perm-CD45 dim gate

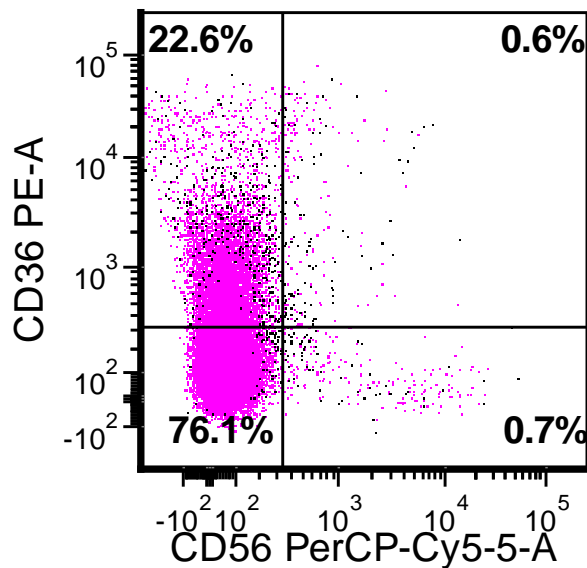


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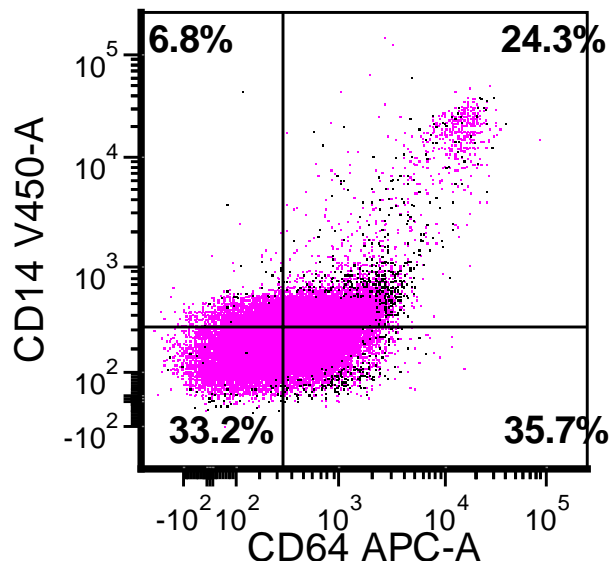




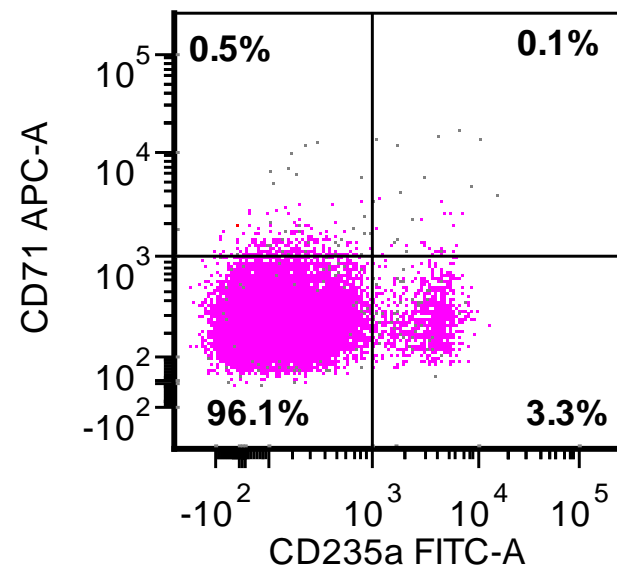
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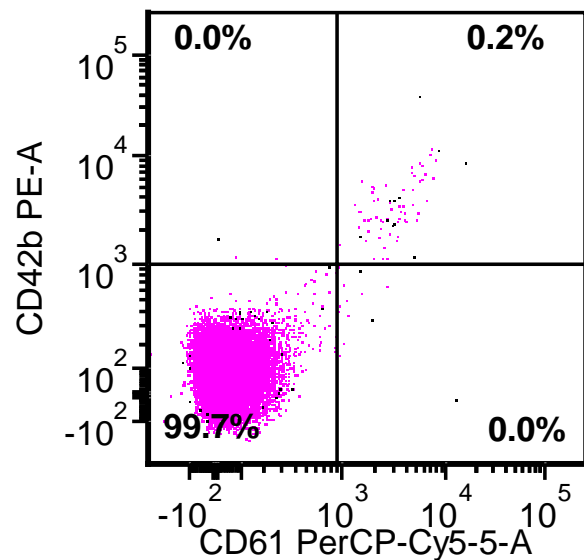
Perm-CD45 dim gate



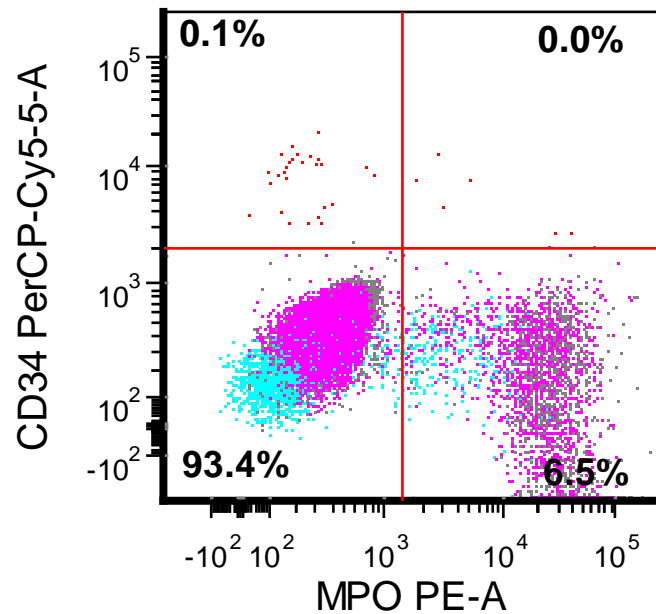
CD45dim clean gate



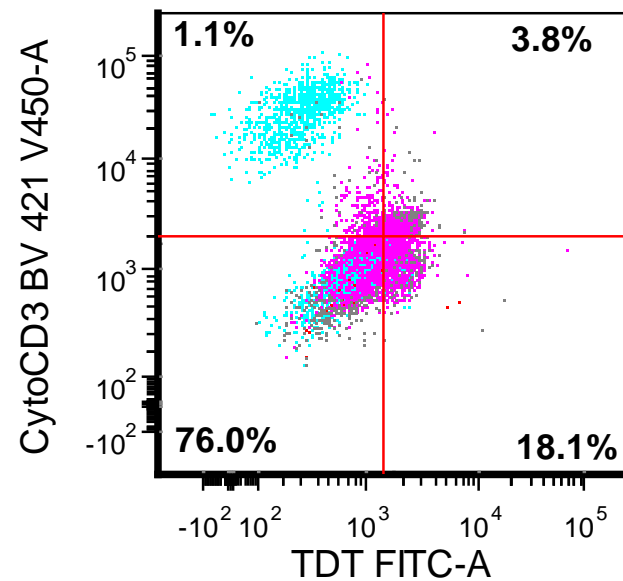
CD45dim clean gate



CD45dim and lymph



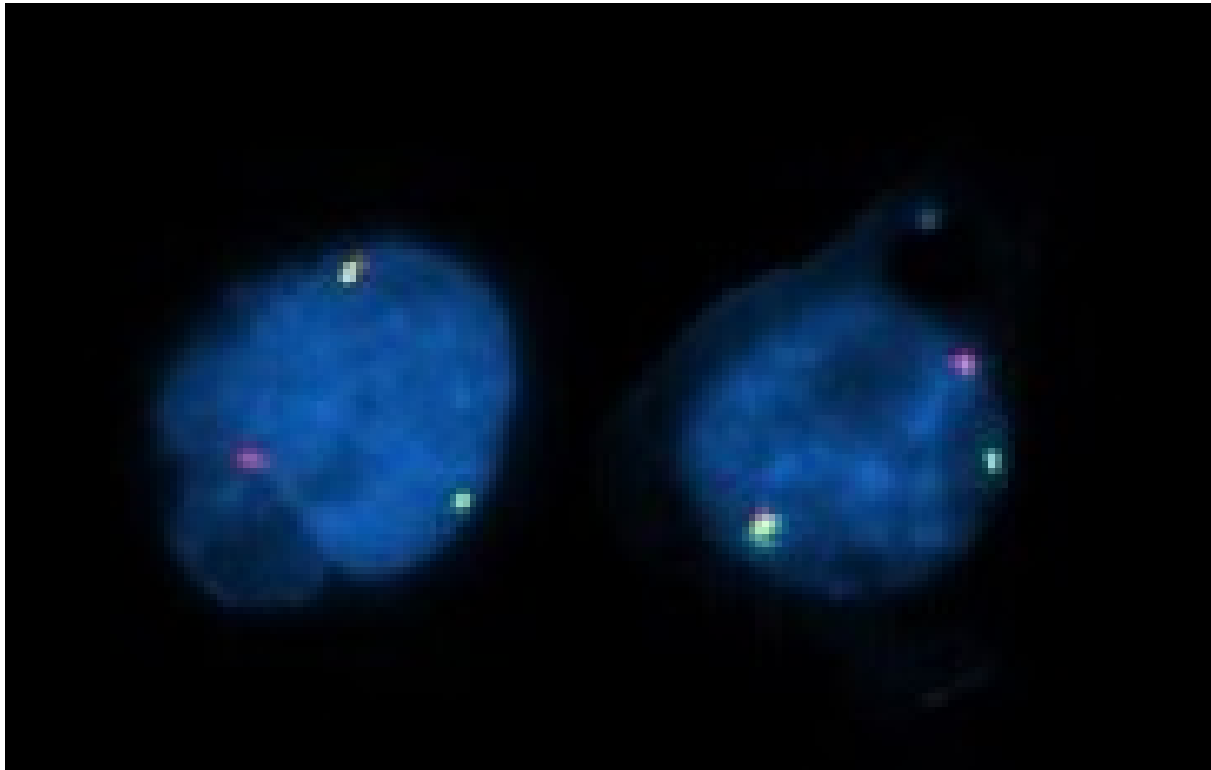
CD45dim and lymph



# Cytogenetic/FISH Studies

46,XY,t(6;8)(p21;q24.3)[5]/47,idem,+18[11]/46,XY[4]

MYC rearrangement detected in 90% of the cells





# Molecular Studies

<i>ABL1</i>	<i>EGFR</i>	<i>GATA2</i>	<i>IKZF2</i>	<i>MDM2</i>	<i>NOTCH1</i>	<i>RUNX1</i>
<u><i>ASXL1</i></u>	<u><i>EZH2</i></u>	<i>HRAS</i>	<u><i>JAK2</i></u>	<i>MLL</i>	<u><i>NPM1</i></u>	<b><u><i>TET2</i></u></b>
<i>BRAF</i>	<i>FLT3</i>	<u><i>IDH1</i></u>	<u><i>KIT</i></u>	<u><i>MPL</i></u>	<u><i>NRAS</i></u>	<u><i>TP53</i></u>
<b><u><i>DNMT3A</i></u></b>	<i>GATA1</i>	<u><i>IDH2</i></u>	<u><i>KRAS</i></u>	<i>MYD88</i>	<i>PTPN11</i>	<i>WT1</i>

Gene	Exon	Nucleotide change	Amino acid change	Mutation	VAF(%)
<b><i>DNMT3A</i></b>	23	c.2645G>A	p.R882H	Missense	38.1
<b><i>TET2</i></b>	11	c.4893T>G	p.Y1631	Nonsense	35.8

# Proposed and Panel Diagnosis

Blastic plasmacytoid dendritic  
cell neoplasm (BPDCN)



# Treatment and Follow-up

- Patient treated with cobimetinib and venetoclax.
- End of cycle bone marrow was not done since patient developed tumor lysis syndrome and sepsis, and missed multiple doses.
- He died after 6 weeks from his admission.

# Discussion

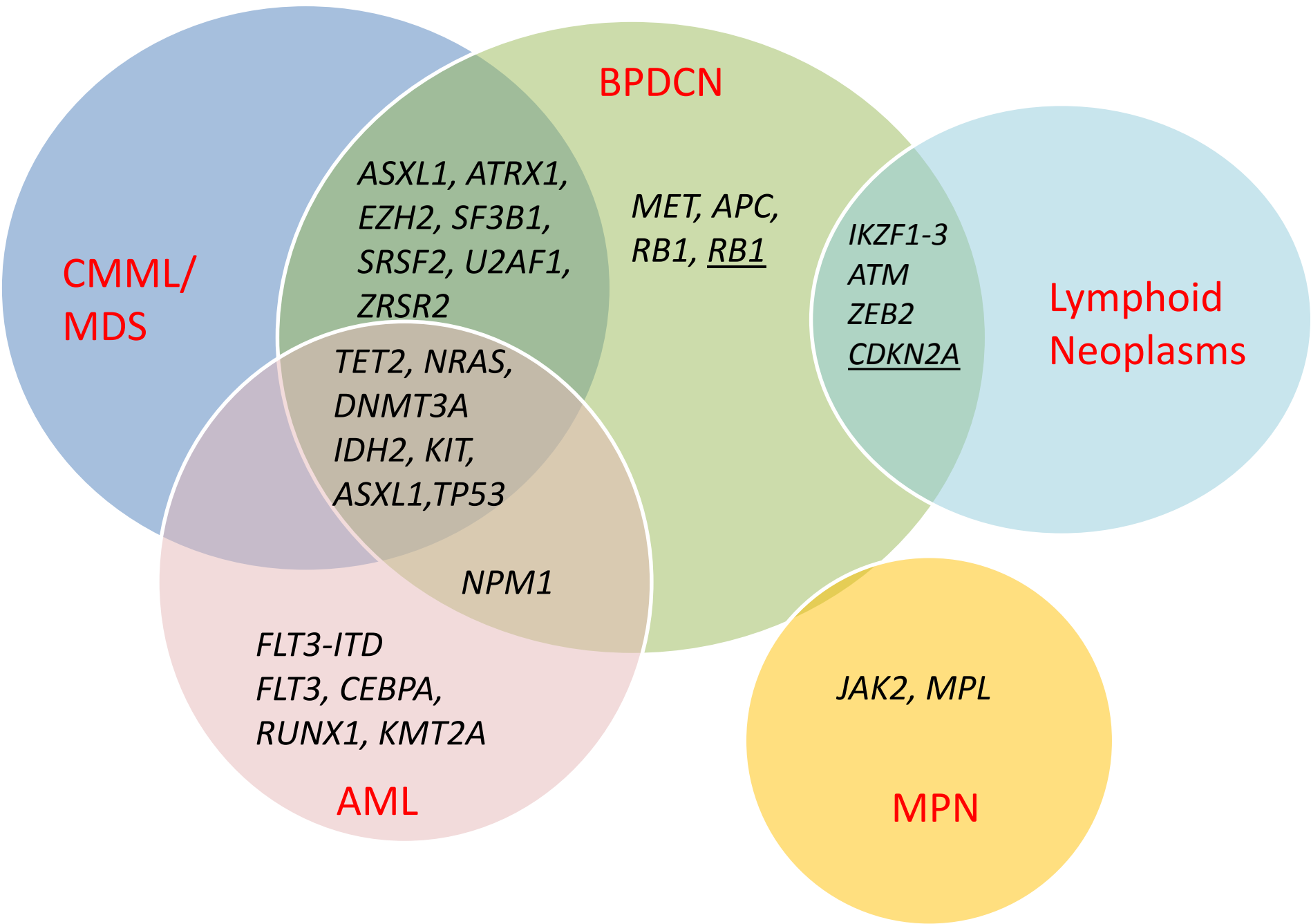
- ❖ Mutational spectrum of BPDCN
- ❖ Genetic abnormalities of BPDCN vs AML



Pathway	Genes
Chromatin Remodeling	<i>ASXL1, ATRX, EZH2</i>
DNA Methylation	<i>TET2, DNMT3A, IDH2, IDH1, TET1</i>
Transcript Factor	<i>ZEB2, ETV6, IKZF3, HOXB9, IKZF1, IKZF2, RUNX</i>
Splicing	<i>SF3B1, SRSF2, U2AF1, ZRSR2</i>
RAS/MAPK	<i>NRAS, KRAS, BRAF</i>
Nucleophosmin	<i>NPM1</i>
Protein Kinase	<i>MET, KIT, RET, FLT3, FLT3-ITD, JAK2</i>
Tumor Suppressor	<u><i>CDKN2A</i></u> , <i>TP53, APC, RB1, <u>RB1</u>, <u>TP53</u>, PTEN, VHL</i>
Ubiquitination	<i>CBLB, CBLC, UBE2G2</i>
DNA Damage Response	<i>ATM, MLH1</i>

Size of font, relative proportion of the mutations; blue font, recurrent mutations; black font, genetic alterations occurred once; underline: deletions

A Stenzinger et al. Oncotarget (2014); J Menezes et al. Leukemia (2014); F Jardin et al. Br J Haematol. (2011); K Alayed et al. Am J Hematol (2013)





# Discussion

- ❖ Mutational spectrum of BPDCN
- ❖ Genetic abnormalities of BPDCN vs AML

# Recurrent chromosomal/copy number changes in BPDCN

Chromosome region	Change	Candidate genes (proteins)
<b>9p21.3</b>	Loss	<i>CDKN2A</i> (p16 <sup>INK4a</sup> , p14 <sup>ARF</sup> ), <i>CDKN2B</i> (p15 <sup>INK4b</sup> ), <i>MTAP</i>
<b>9q12-9q34.3</b>	Loss	<i>CDC14B</i> , <i>DBC1</i> , <i>SYK</i>
<b>12p13.2-p13.1</b>	Loss	<i>CDKN1B</i> (p27 <sup>KIP1</sup> ), <i>ETV6</i>
<b>13q11- q31.1</b>	Loss	<i>RB1</i> , <i>LATS2</i> , <i>KPNA3</i>
<b>15q11.2–q26.3</b>	Loss	*
<b>7p12.2</b>	Loss	<i>IKZF1</i>
<b>17p</b>	Loss	<i>TP53</i>
<b>4q34.1-4q34.2</b>	Loss	*
<b>5q21, 5q32–q35.2</b>	Loss	<i>SMAD5</i> , <i>MSH3</i>
<b>6q23.3–q27</b>	Loss	<i>PARK2</i>
<b>19p13.3–p13.4</b>	Loss	*
<b>3p22.2–p21.1</b>	Loss	<i>PTPN23</i>
<b>7p22.3–p22.1</b>	Loss	<i>MAD1L1</i>
<b>21q22.3</b>	Loss	*

\*Candidate genes are not mentioned, because losses included large parts of chromosomes and hundreds of genes. Blue font, most frequent genetic alterations.

D Leroux et al. Blood (2002); R Dijkman et al. Blood (2007); F Jardin et al. Leukemia (2009), T Wiesner et al. J Invest Dermatol (2009), M Lucioni et al. Blood (2011)



## BPDCN

*ATRX1, EZH2, SF3B1,  
SRSF2, U2AF1, ZRSR2,  
IKZF1-3, ATM, MET, RB1,  
ZEB2, APC, CDKN2A*

*9p21.3(CDKN2A/CDKN2B)  
13q13.1-q14.3 (RB1),  
12p13.2-p13.1 (CDKN1B),  
13q11-q12 (LATS2)  
7p12.2 (IKZF1)  
17p (TP53)*

*MYC*

## AML

*FLT3-ITD  
FLT3, CEBPA,  
RUNX1, KMT2A*

*t(8;21)(q22;q22)  
inv(16)(p13.1q22) or  
t(16;16)(p13.1;q22)  
t(15;17)(q22;q12)  
t(9;11)(p22;q23)  
t(6;9)(p23;q34)  
inv(3)(q21q26.2) or  
t(3;3)(q21;q26.2)  
t(1;22)(p13;q13)*

*NPM1,  
ASXL1*

*TET2, NRAS,  
...DNMT3A  
IDH2, KIT,  
TP53*

*t(11;19)  
(q23;p13.3)  
(KMT2A-  
MLLT1)*

# Thank You!

Blastic plasmacytoid dendritic cell  
neoplasm (BPDCN)