Reactive T-cell proliferations in the bone marrow including those associated with myelodysplastic syndromes

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LUND SWEDEN

MAY 28th - 31st

Layout

Physiological roles of mature bone marrow T-cells

Bone marrow T-cells in viral infections

Bone marrow T-cells in (auto)immune conditions

Bone marrow T-cells in drug reactions

Paraneoplastic bone marrow T-cell expansions

Mimickers and caveats

Layout

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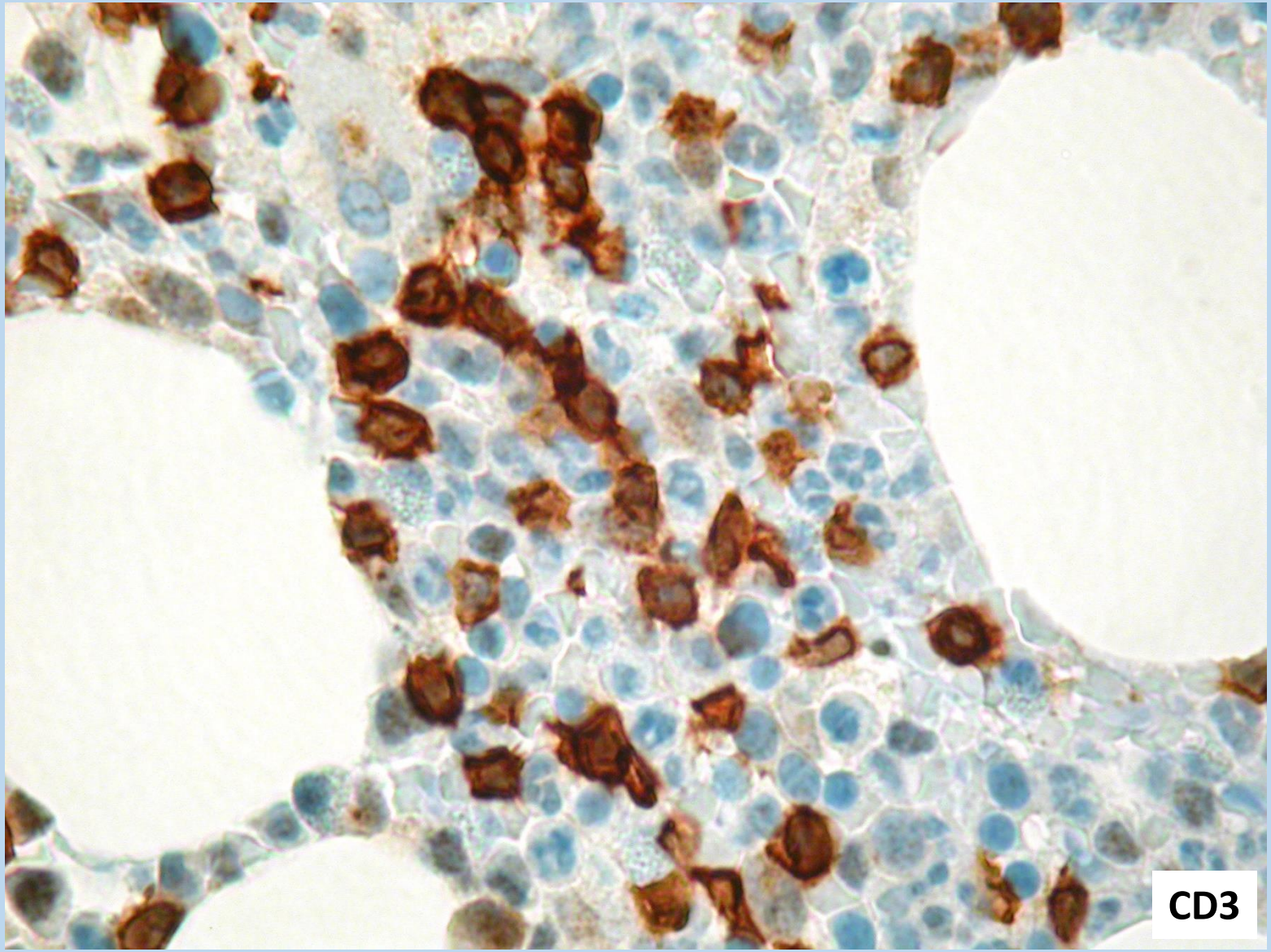
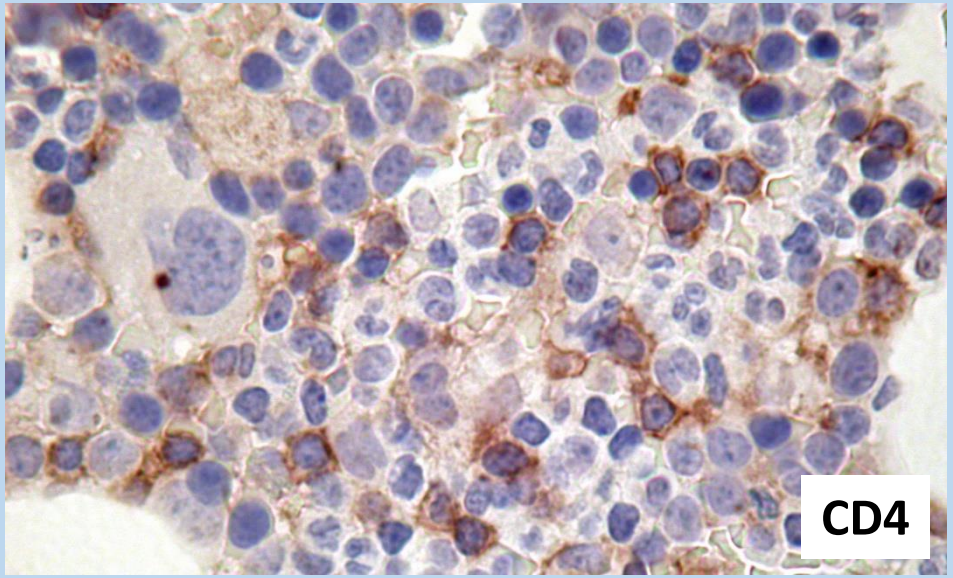
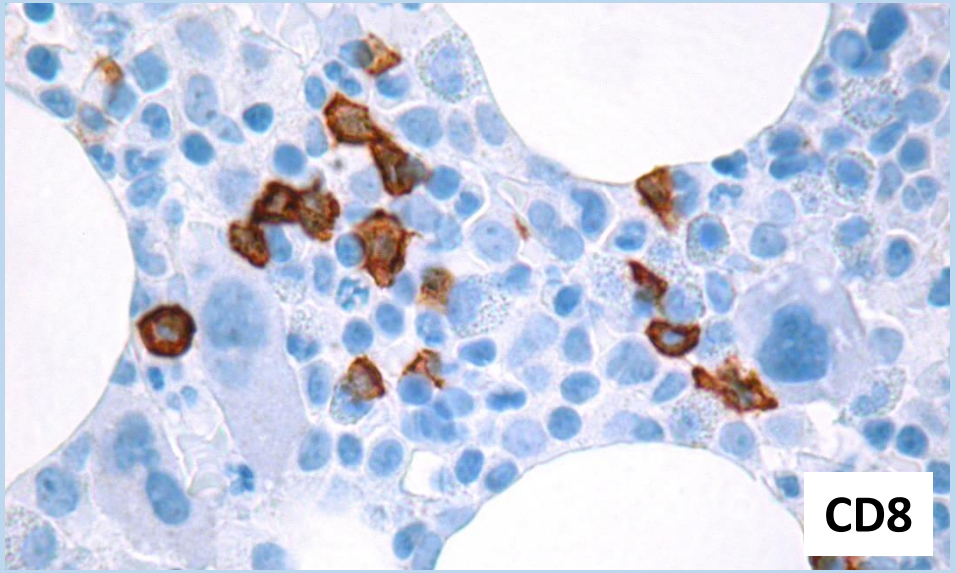
T-cells constitute 25% of the BM cells







Lymphocyte composition of the BM

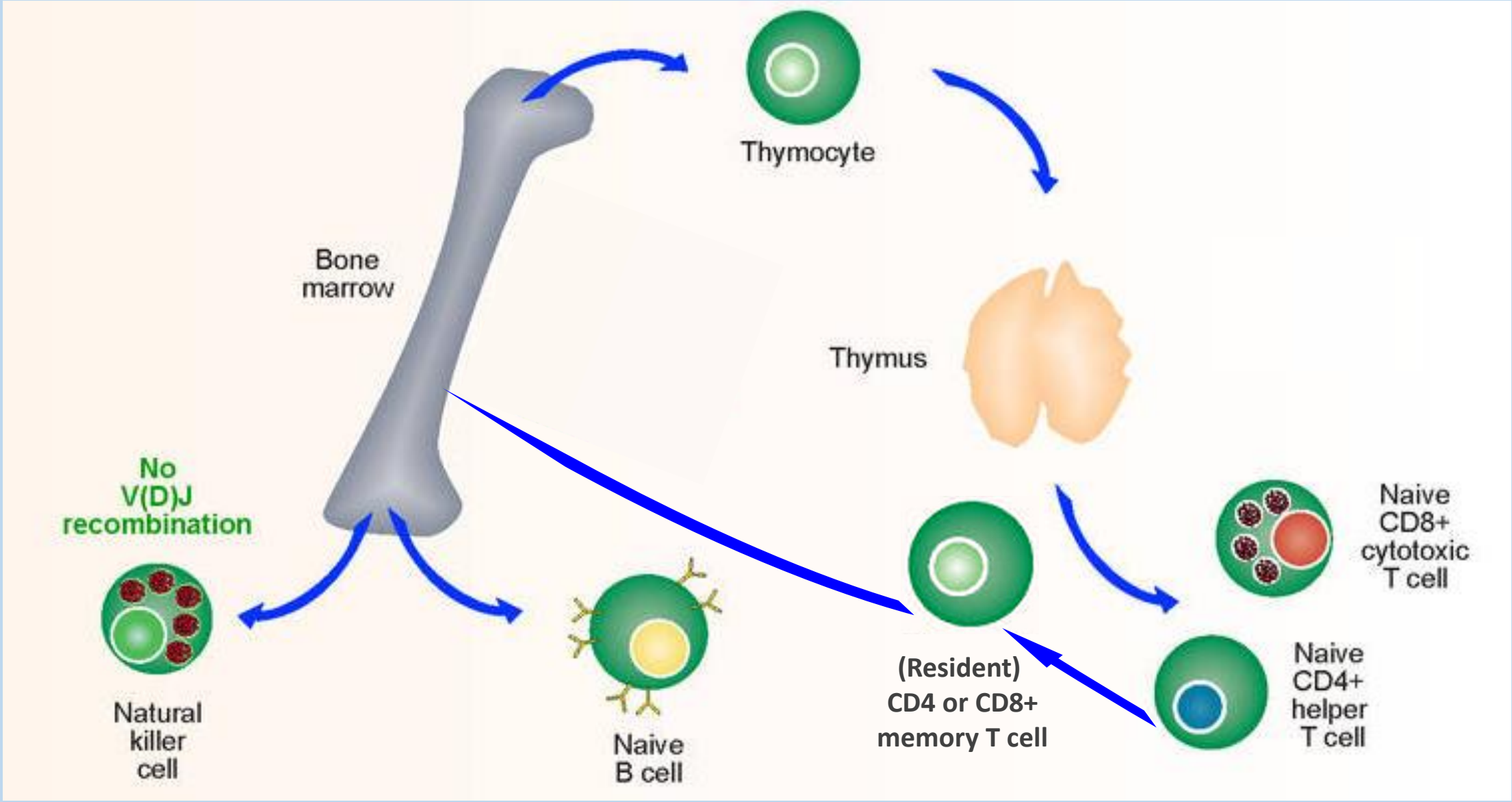
- 7-9% B-cells
- 20-25% T-cells
  - 8-9% CD4+ T-cells
  - 14-18% CD8+ T-cells
  - CD4/CD8 = 0.5-0.7
- 2-5% NK-cells
- Higher & less CD8-skewed in aspirates

Clark et al. Blood 1986;67:1660

- >50% of bone marrow T-cells express
  - CD69, early activation marker
  - HLA-DR, late activation marker
- Only 25% CD45RA+/RO- naïve T-cells
- 20% CD45RA+/RO+ recently/re-activated T-cells
- Major source of CD8+ long-lived memory T-cells

Dean et al. Immunol Let 2005;99:94
Di Rosa. Immunol Cell Biol 2009;87:20

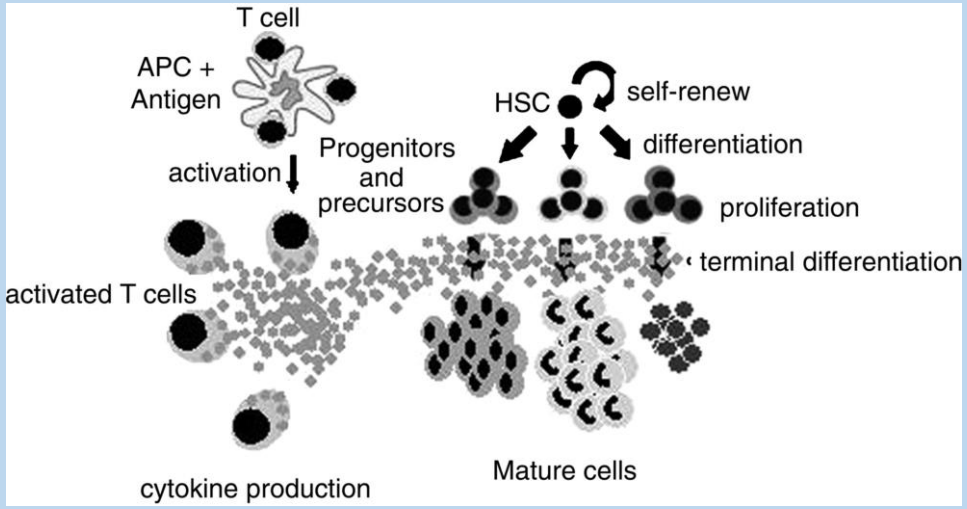
The circuit of T-cells: BM->thymus->P(B)->BM

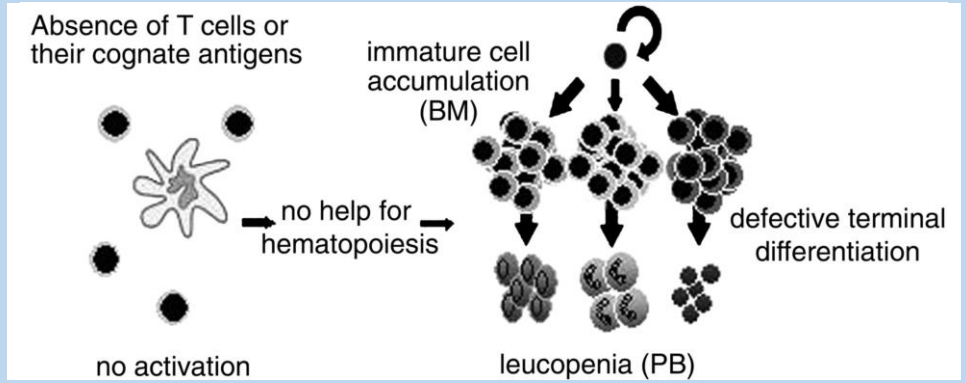


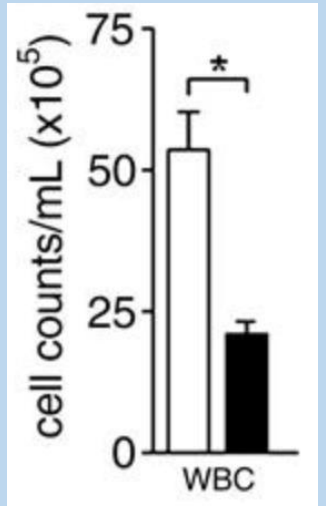
Modified from http://www.immunopaedia.org.za

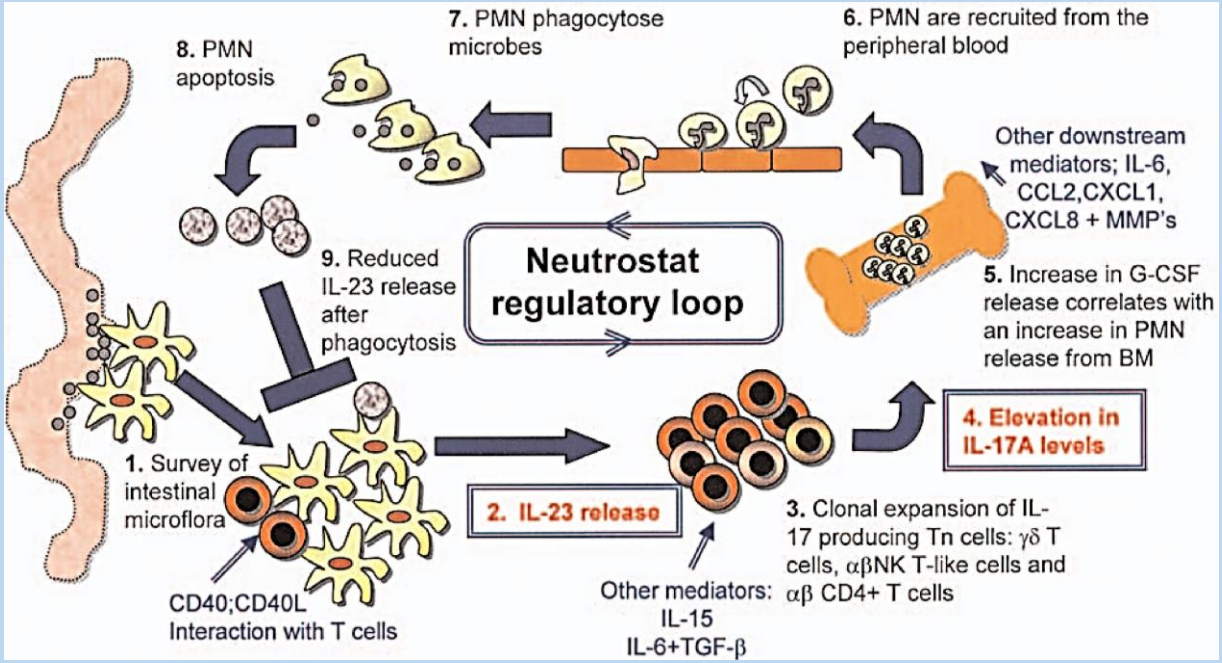
Physiological roles of BM T-cells

- Thymectomy leads to neutropenia
- T-cell infusion aid hematopoietic reconstitution
  - Attributable to CD4+ BM T-cells
  - Dependent on MHC matching
- Source of GM-CSF, IL3-6 & 13
- Granulopoiesis is Th17-cell dependent



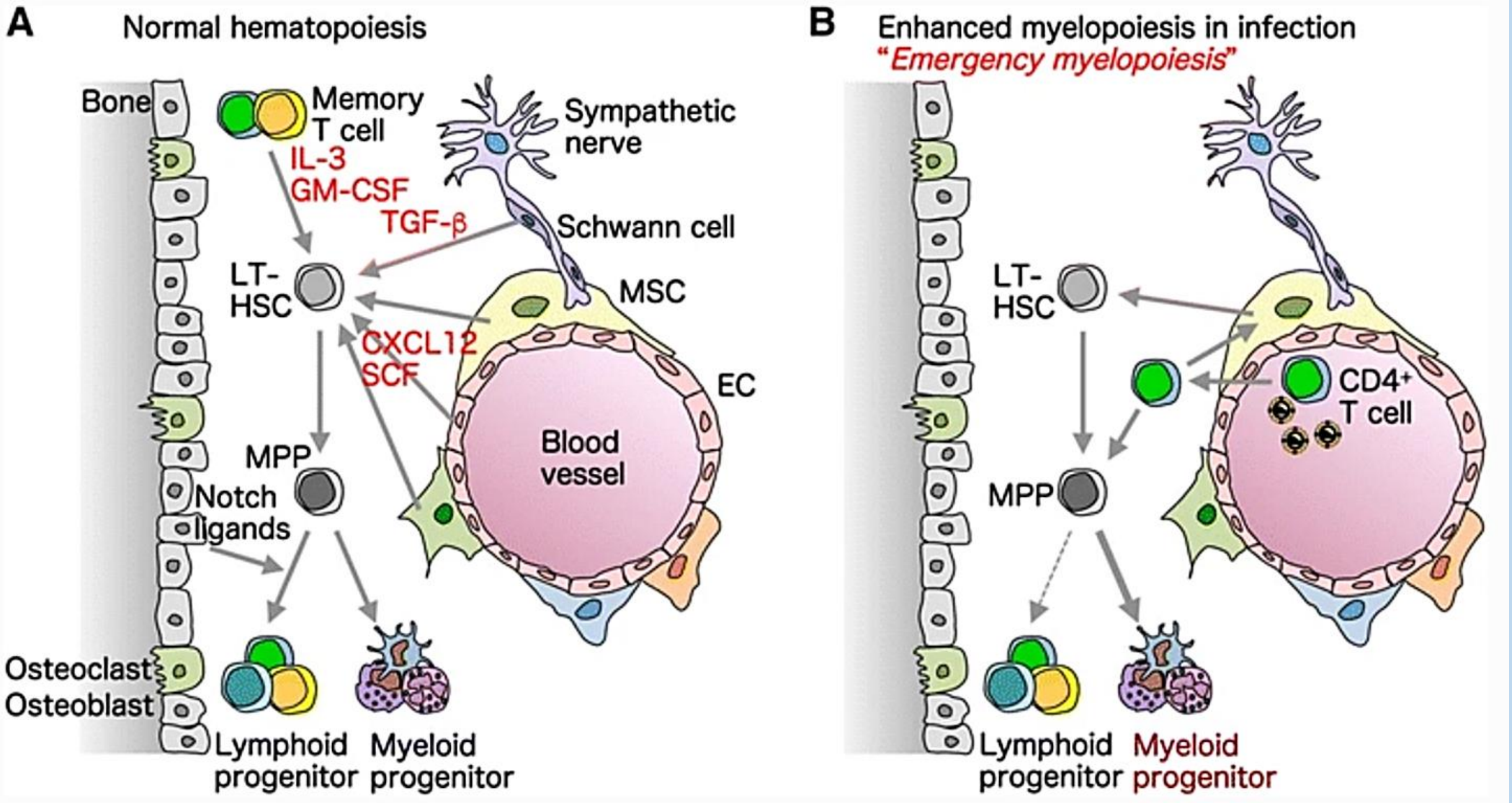






Trainin et al. Nature 1969;221:1154
Lord et al. Blood 1973; 42:395
Ilstad et al. J Immunol 1984;136:28
Schwarzenberger et al. J Immunol 2000;164:4783
Monteiro et al. Blood 2005; 15:105
Ley et al. Immunol Res 2006;34:229
Lee et al. J Immunol 2009;10:6377

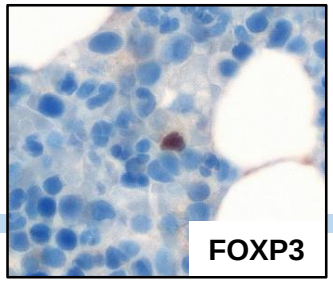
BM T-cells in emergency myelopoiesis



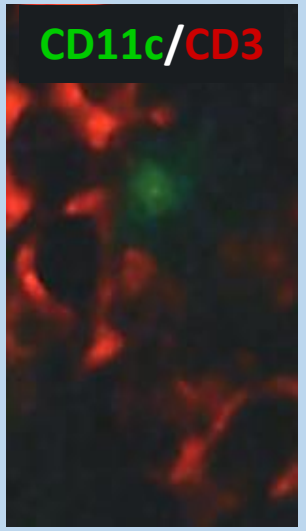
Chiba et al. Cell Mol Life Sci 2018;75:1363

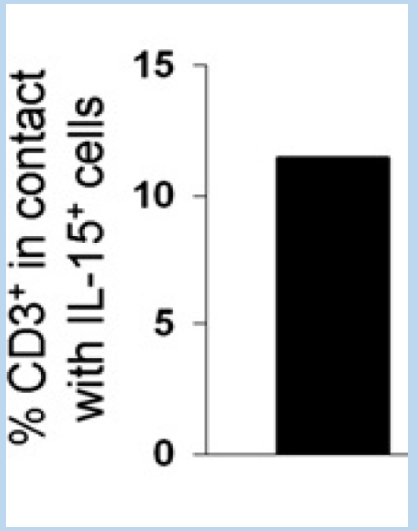
Physiological roles of BM T-cells

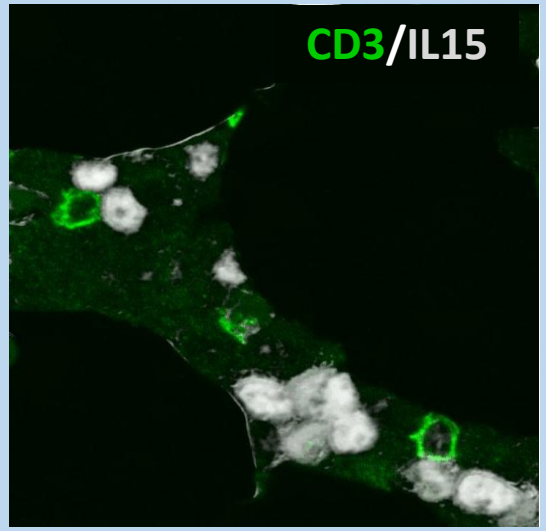
- Major cytotoxic defense against systemic blood-borne antigens with immunological memory
- T(R/E)M-cells dependent on IL15 from the BM
- Treg suppress myelopoiesis

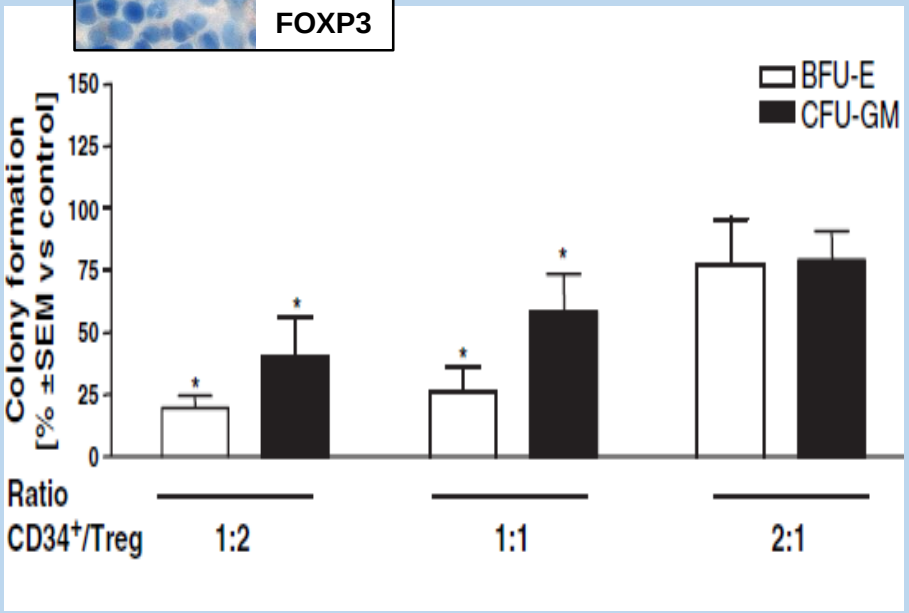


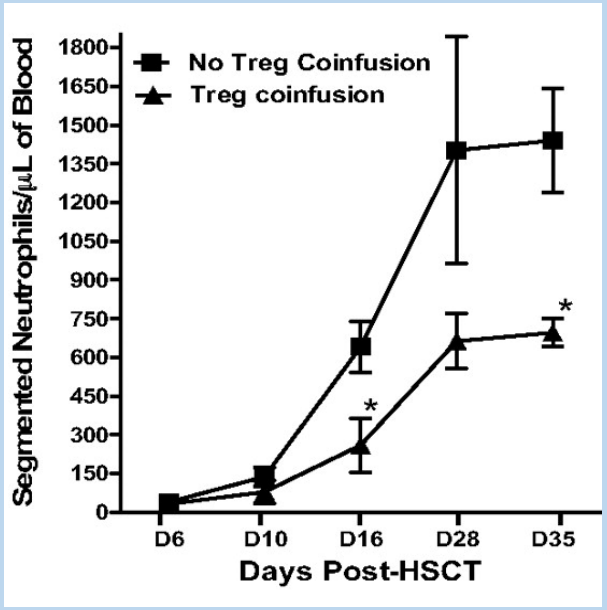
Feuerer et al. Nat Med 2003;9:1151
Salvador et al. Br J Haematol 2008;142:845
Urbieta et al. Blood 2010;115:4934
Herndler-Brandstetter et al. J Immunol 2011;186:6965

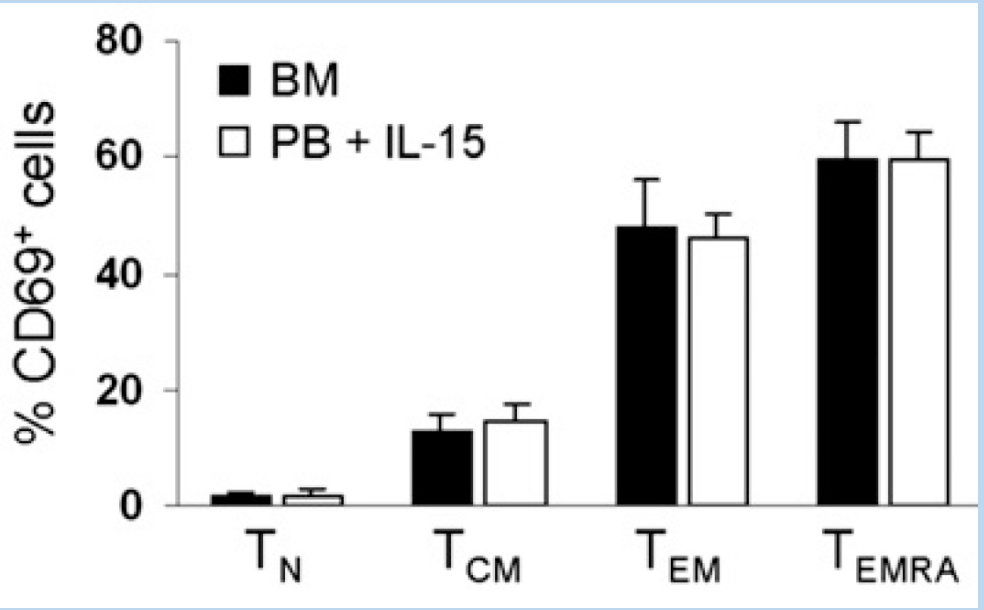












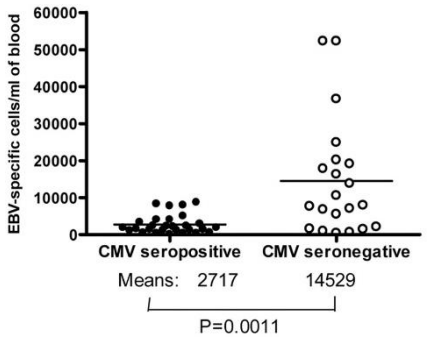
Age and CMV-related changes in BM T-cells

- Decrease of naïve T cells

CD4 T cell memory derived from young naive cells functions well into old age, but memory generated from aged naive cells functions poorly.

Haynes et al. PNAS 2003;100:15053

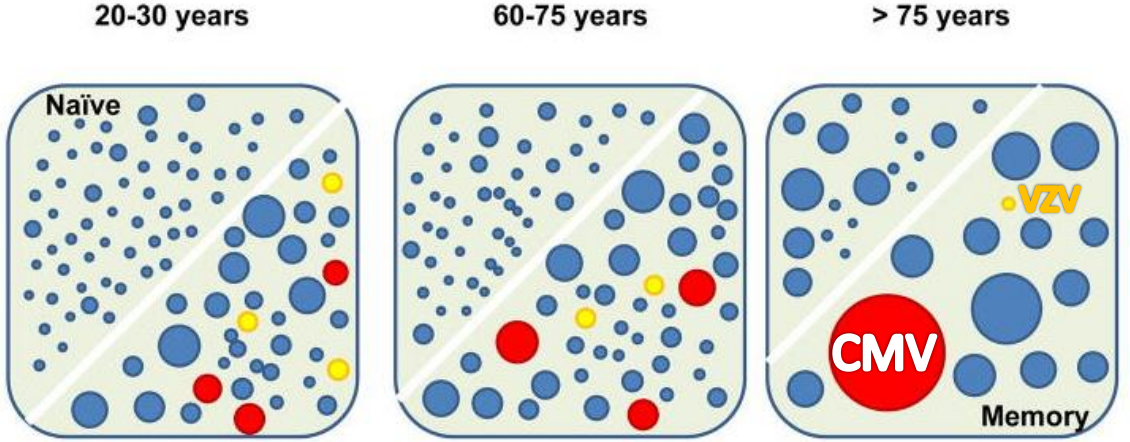
- Increase of CD4+ T_{EM}
- Increase of CD8+ T_{EMRA}
- Increase of CD8/CD57+ T cells
- Decrease in T-cell diversity due to overexpansion of CMV-specific clones
  - Decrease of EBV (VZV)-specific cells



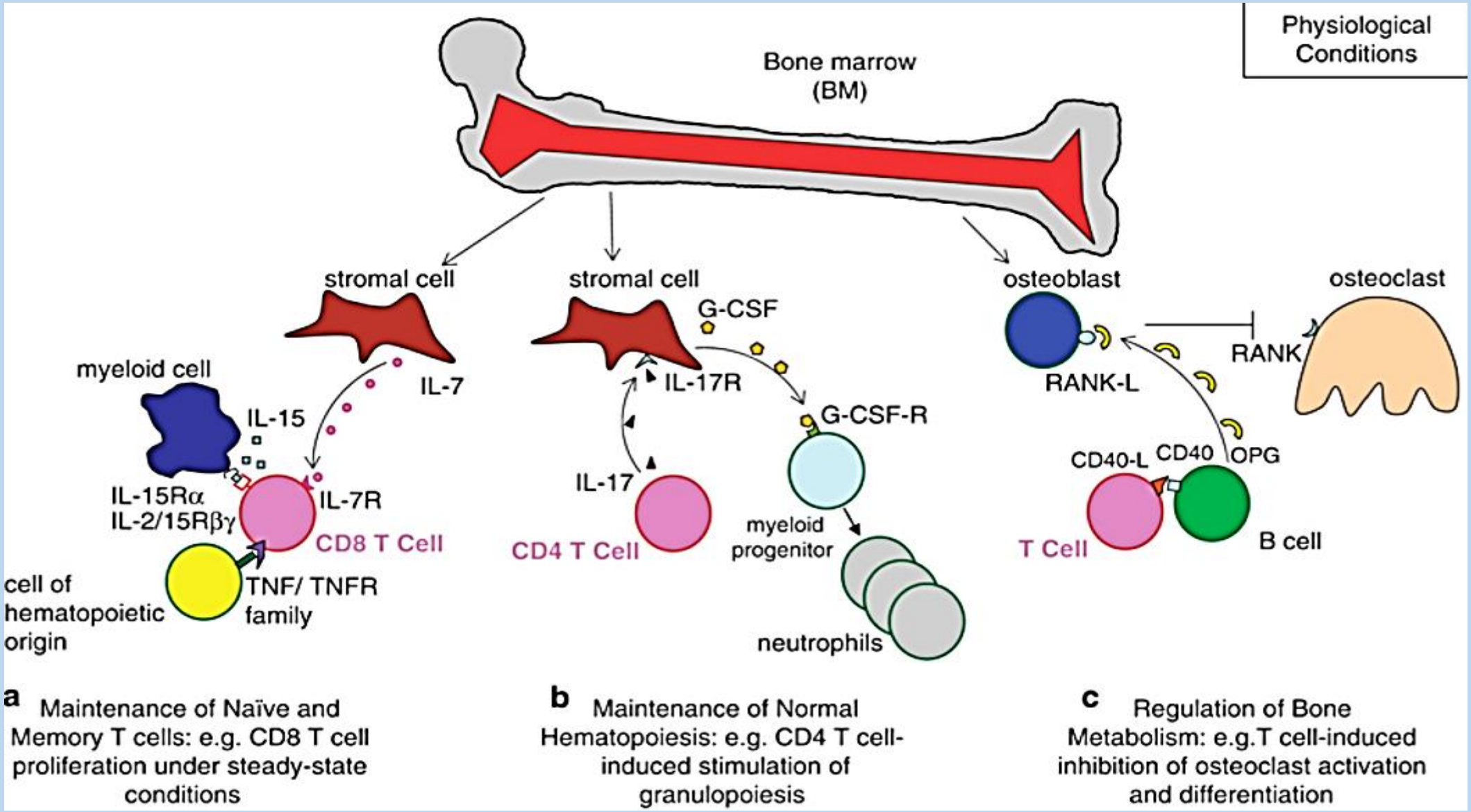
30 000 000 TCR → **300 000 TCR**

Khan et al. J Immunol 2004;173:7481
Herndler-Brandstetter et al. J Leukoc Biol 2012;91:197
Goronzy & Weyand, Nat Immunol 2013;14: 428

	Young			Elderly		
	CMV⁻	CMV⁺		CMV⁻	CMV⁺	
BM						
CD4⁺ T cells						
% T_N	39.6 ± 4	23.2 ± 3.3	$P < 0.05$	30.8 ± 3.6	21.1 ± 1.4	$P < 0.05$
% T_{CM}	29.6 ± 6	22.1 ± 5.1		33.1 ± 3.7	22.3 ± 2	$P < 0.05$
% T_{EM}	19.6 ± 5.1	42.9 ± 6	$P < 0.05$	29.9 ± 3.1	43.9 ± 3.8	$P < 0.05$
% T_{EMRA}	9.1 ± 4.9	10.4 ± 2.2		5.9 ± 3.9	12.3 ± 0.4	
% CD28⁻	2.6 ± 0.7	5.9 ± 1.5	$P < 0.05$	3.2 ± 0.5	7.5 ± 2	$P < 0.05$
% CD69⁺	11.5 ± 8.3	15 ± 2.8		13.2 ± 3.3	17.3 ± 2.8	
CD8⁺ T cells						
% T_N	38.6 ± 5.5	12.8 ± 3.6	$P < 0.01$	16.5 ± 3.5	7.1 ± 1.4	$P < 0.05$
% T_{CM}	7 ± 1.8	3.6 ± 1.1		14.9 ± 1.8	5.6 ± 2.2	$P < 0.05$
% T_{EM}	30.1 ± 5.5	34.3 ± 12		48.1 ± 6	33.4 ± 8.2	
% T_{EMRA}	22.1 ± 3.8	45.8 ± 12.3	$P < 0.05$	20.3 ± 5	52.2 ± 6.7	$P < 0.05$
% CD28⁻	17.9 ± 4.6	46.8 ± 13.3	$P < 0.05$	34.7 ± 2.6	56.8 ± 7	$P < 0.05$
% CD57⁺	5.3 ± 0.7	10.5 ± 4.2		10.2 ± 6.1	16.2 ± 2.7	
% CD69⁺	23.5 ± 15.9	29.4 ± 3.8		48.5 ± 4.6	50.8 ± 4.3	



Summary of physiologic BM T-cell functions



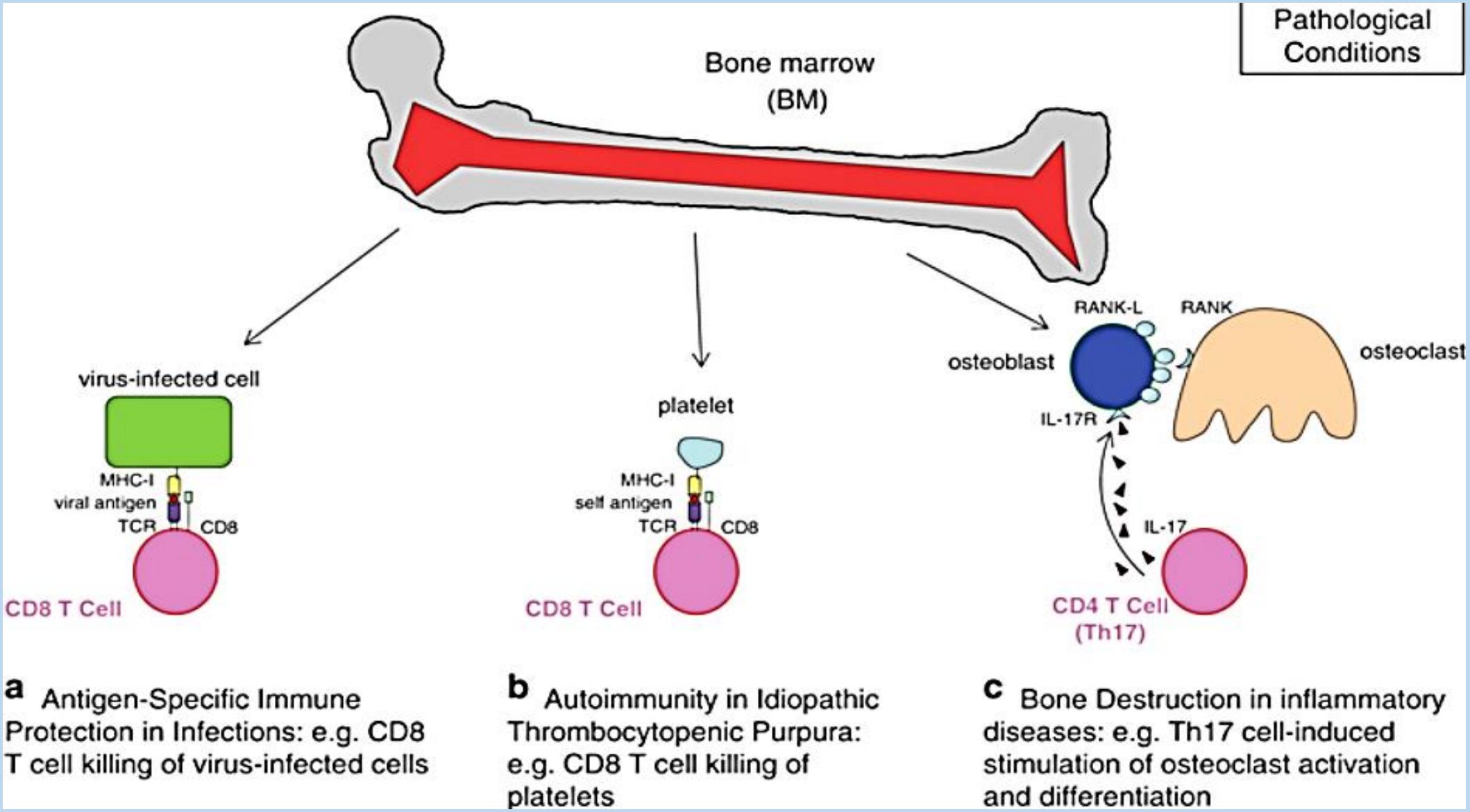
a Maintenance of Naïve and Memory T cells: e.g. CD8 T cell proliferation under steady-state conditions

b Maintenance of Normal Hematopoiesis: e.g. CD4 T cell-induced stimulation of granulopoiesis

c Regulation of Bone Metabolism: e.g.T cell-induced inhibition of osteoclast activation and differentiation

Di Rosa. Immunol Cell Biol 2009;87:20

BM T-cells in specific reactive conditions



a Antigen-Specific Immune Protection in Infections: e.g. CD8 T cell killing of virus-infected cells

b Autoimmunity in Idiopathic Thrombocytopenic Purpura: e.g. CD8 T cell killing of platelets

c Bone Destruction in inflammatory diseases: e.g. Th17 cell-induced stimulation of osteoclast activation and differentiation

Di Rosa. Immunol Cell Biol 2009;87:20

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Bone marrow T-cells in (auto)immune conditions

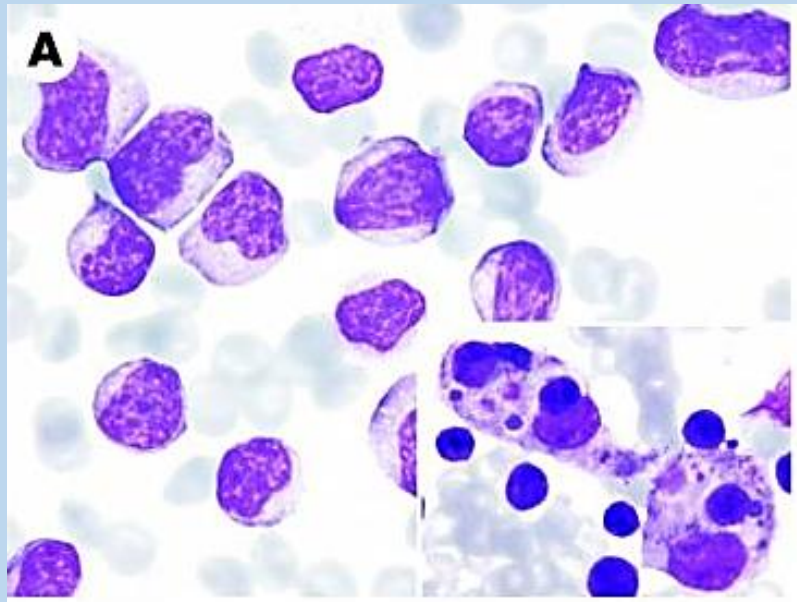
Bone marrow T-cells in drug reactions

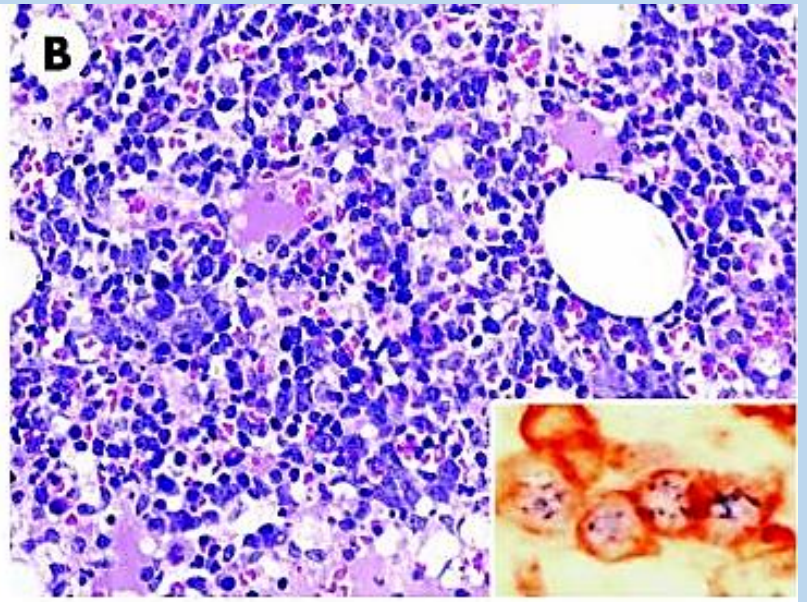
Paraneoplastic bone marrow T-cell expansions

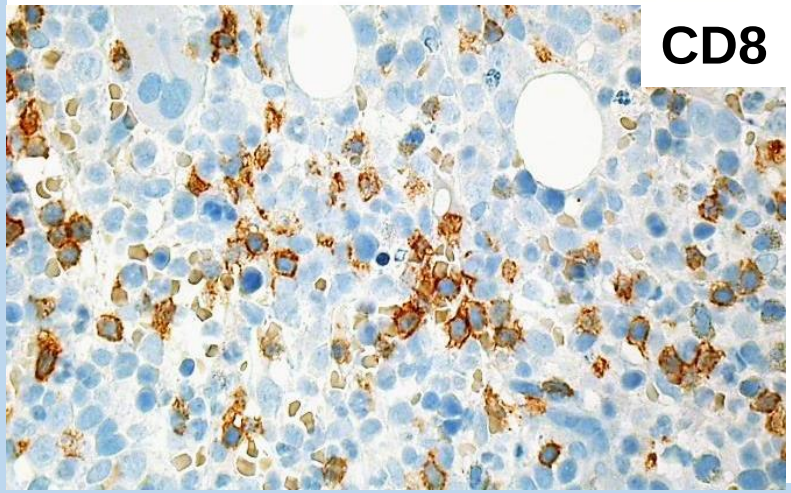
Mimickers and caveats

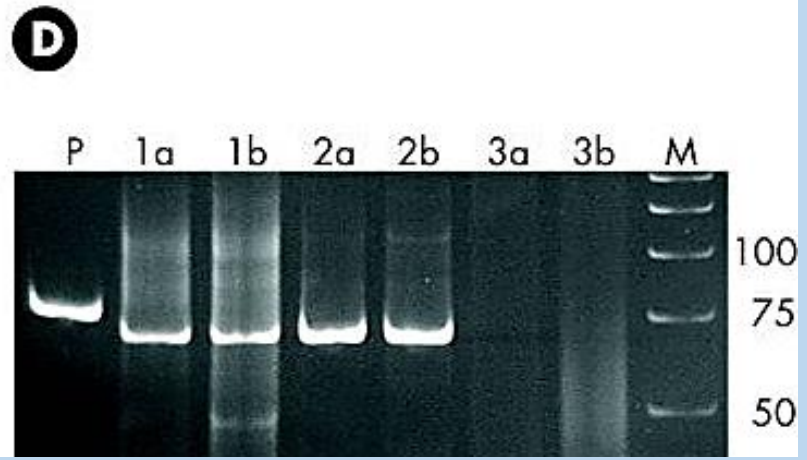
EBV

- Atypical peripheral T-cell lymphocytosis
  - CD8 skewed
- BM T-cell lymphocytosis
  - CD8 skewed
  - antigenic loss for CD5 or CD7
- Occasionally T-cell clonality
- Plasmacytosis
  - more prominent in immunocompromised
- Hemophagocytosis/HLH
- Contextual: PTLD



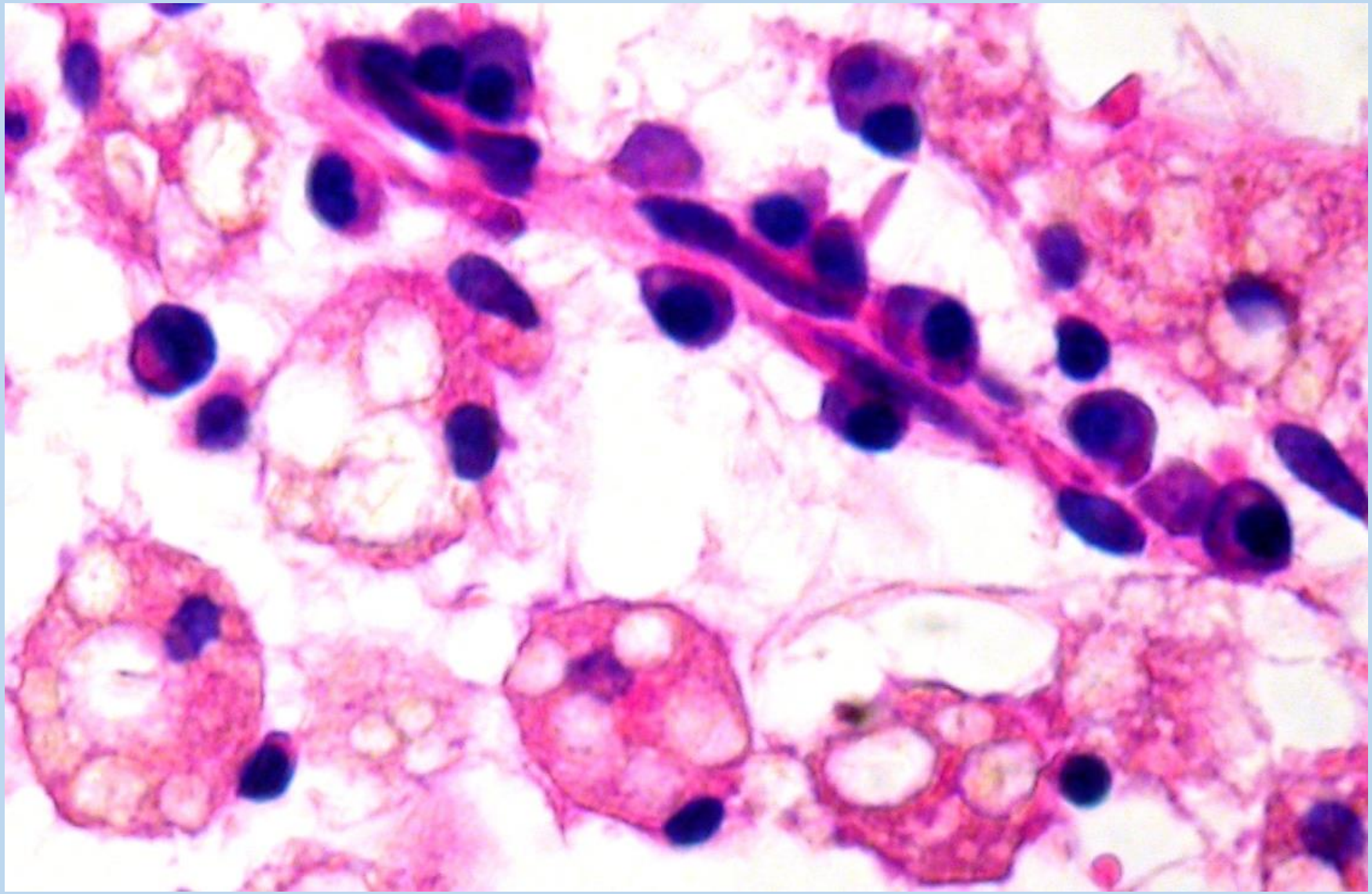


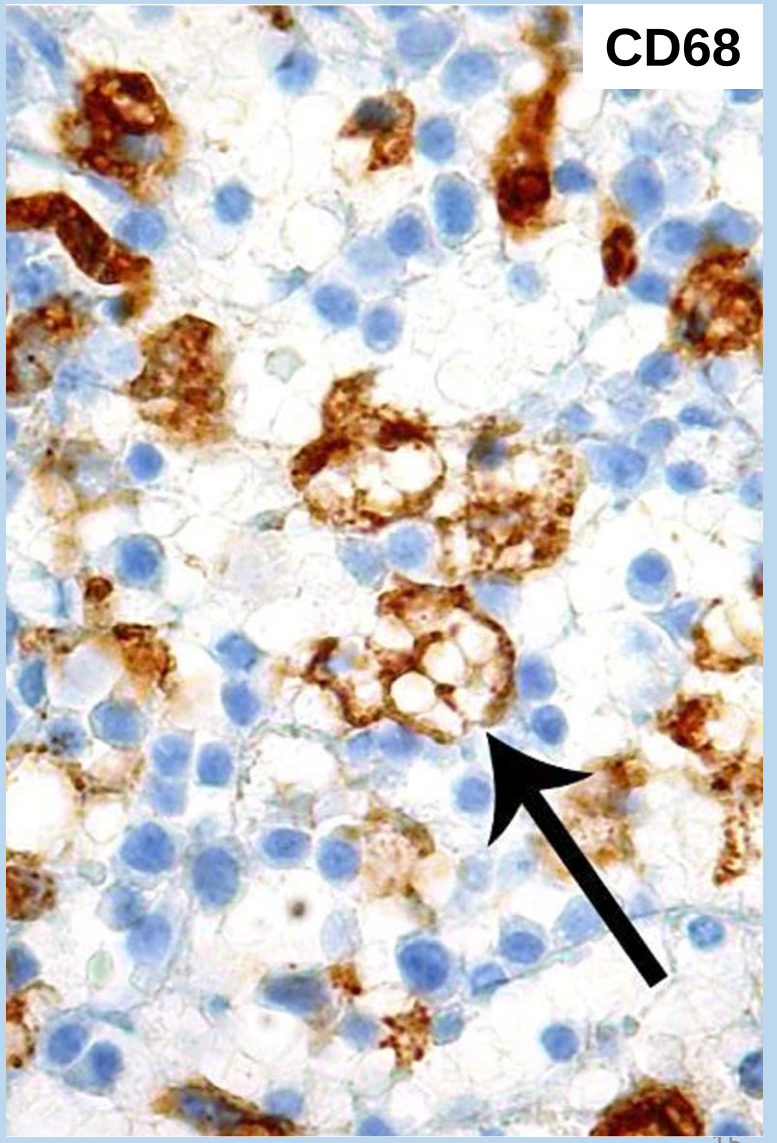




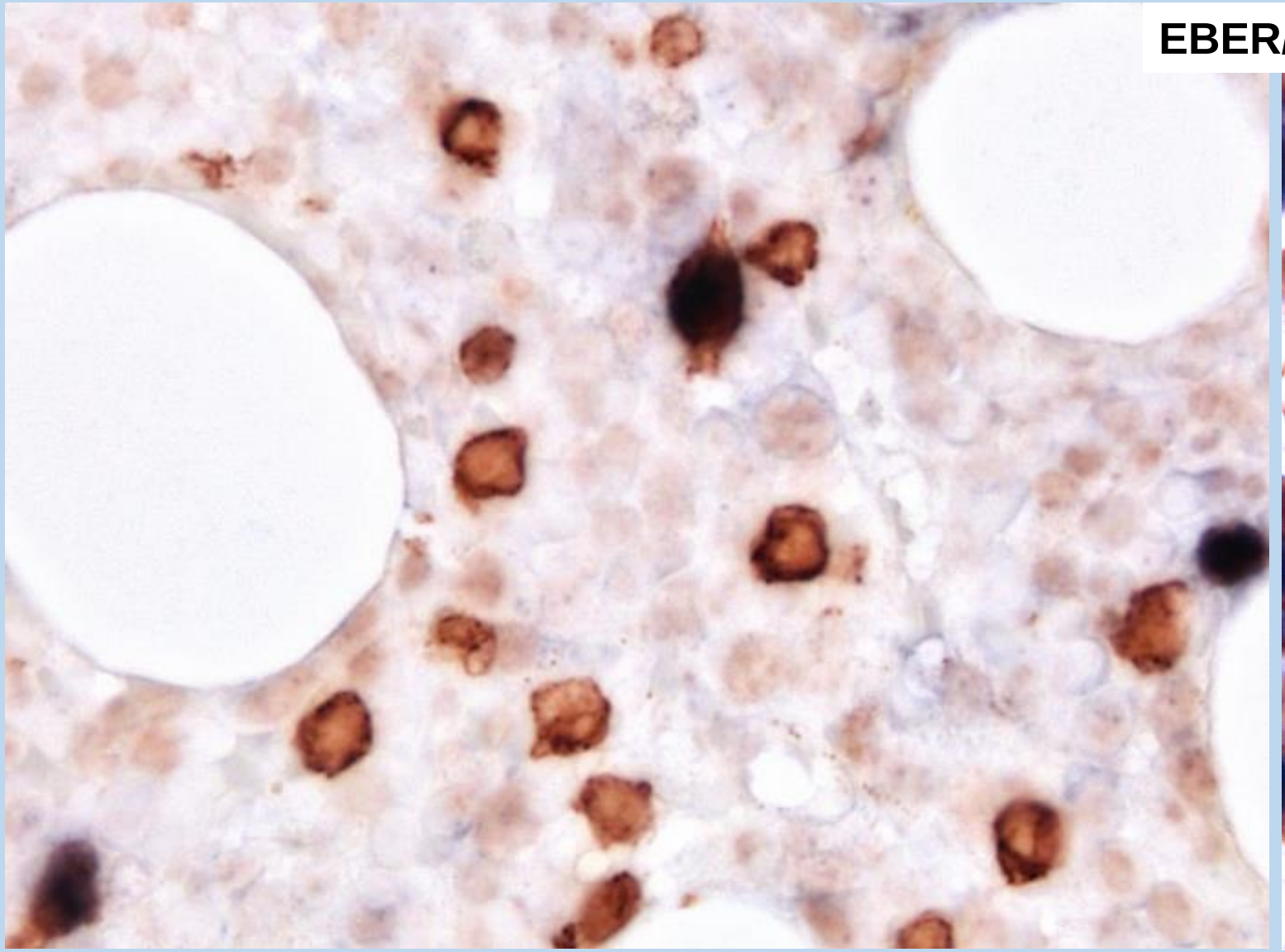
Lin et al. J Clin Pathol 2007;60:101
Daikeler et a. Ann Rheum Dis 2011;70:1338

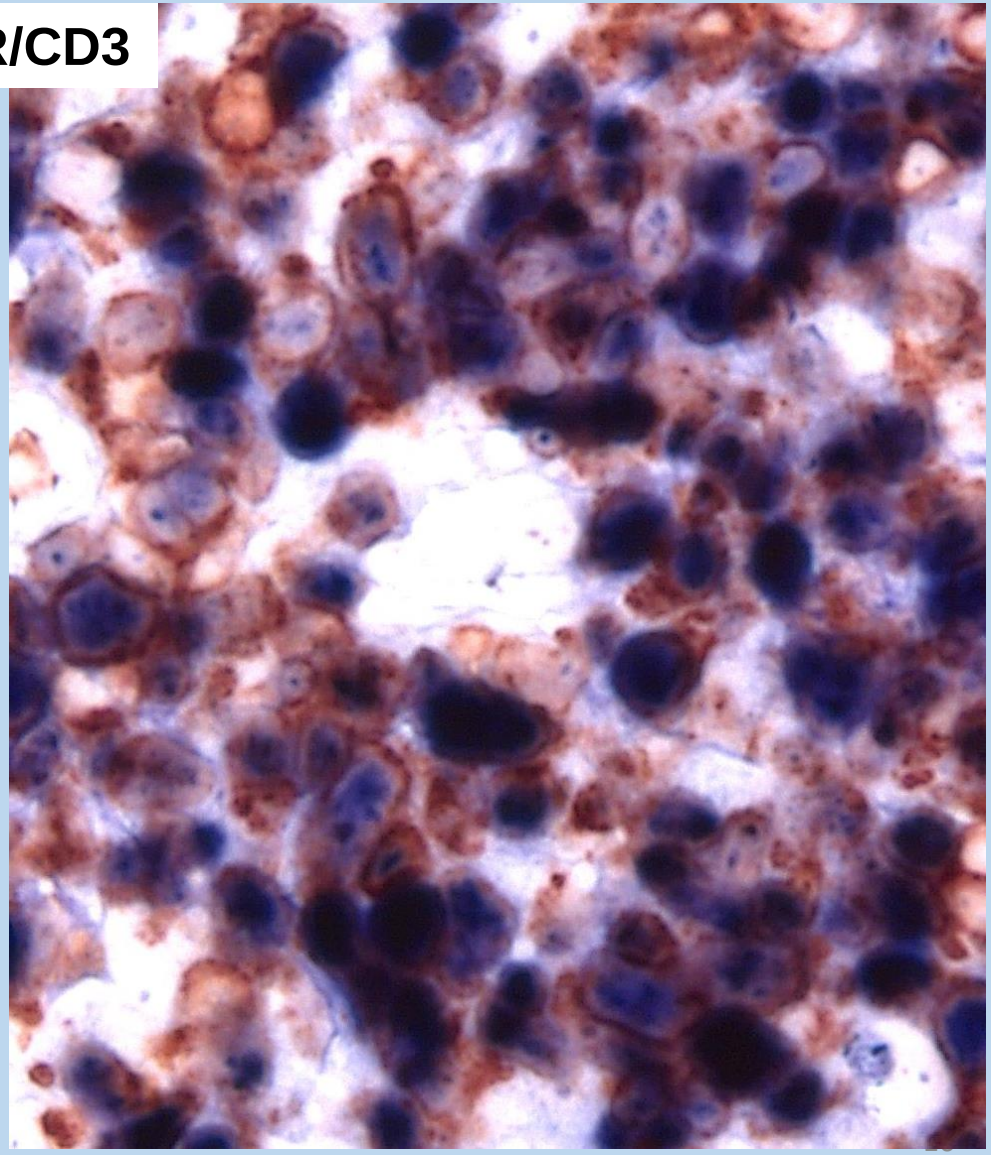
HLH: very often linked to EBV





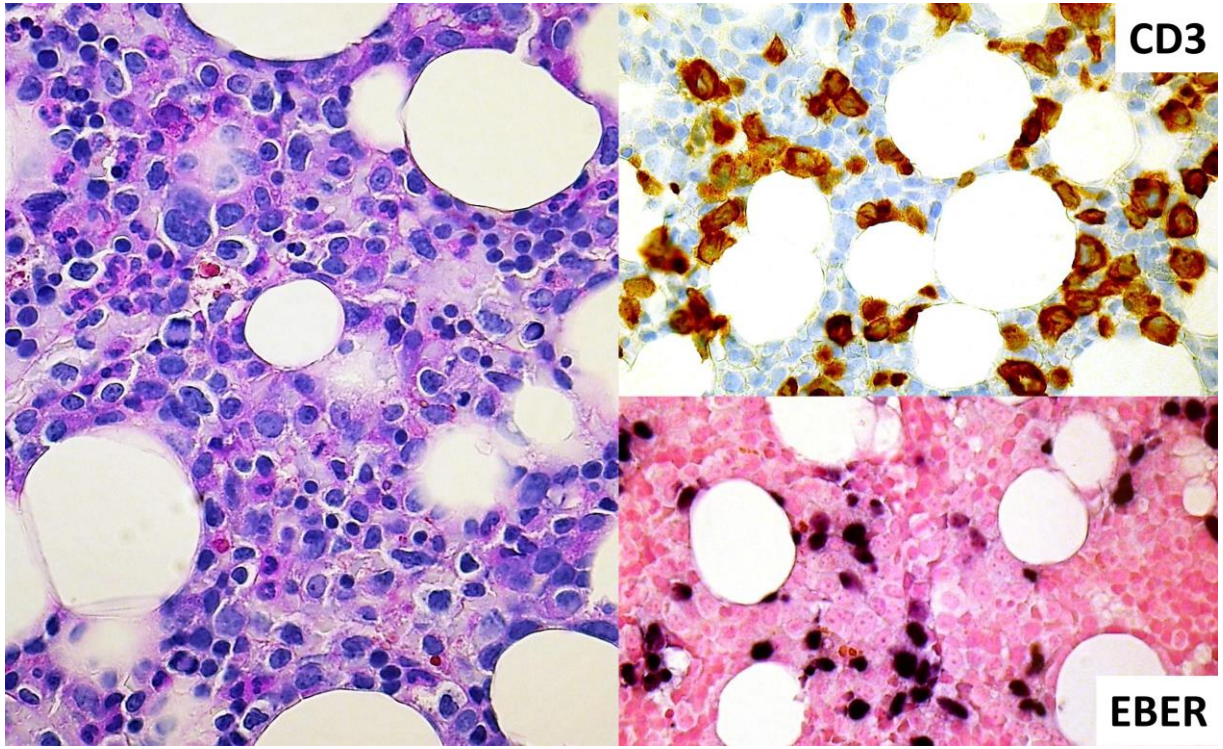
HLH: always look for EBV-infected T-cells



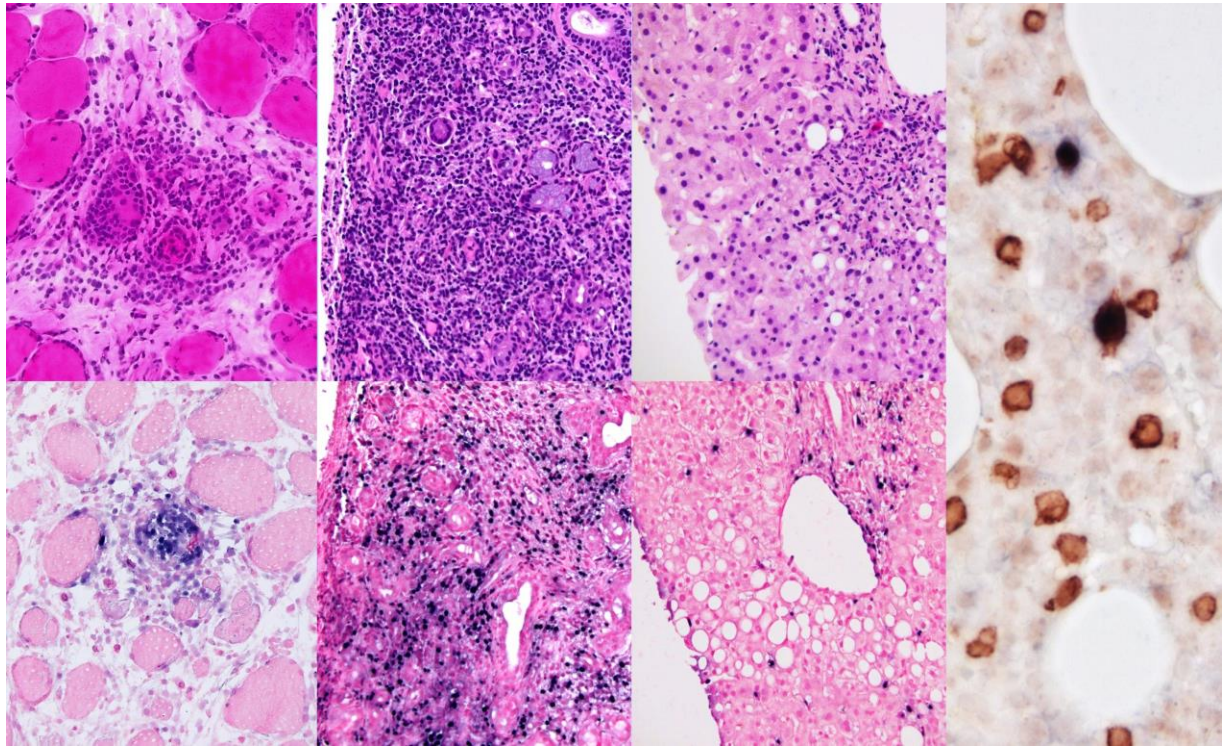


EBV-infected T-cells – harbingers of evil

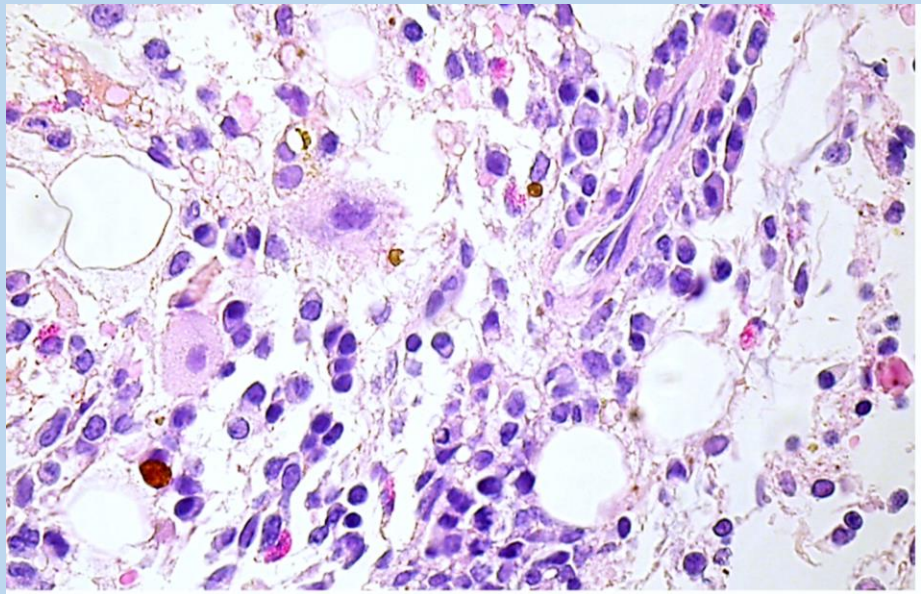
- NK/T-cell lymphoma nasal type

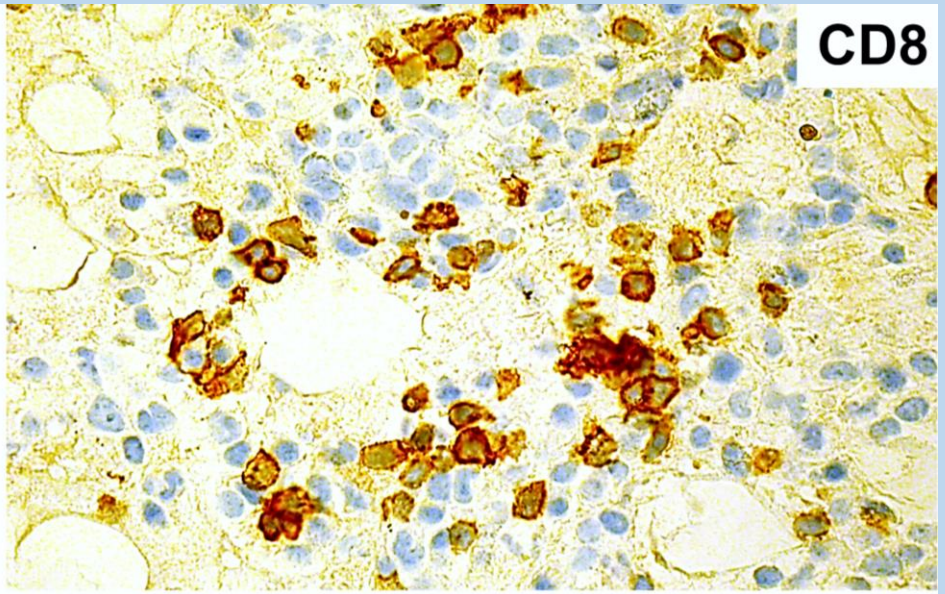


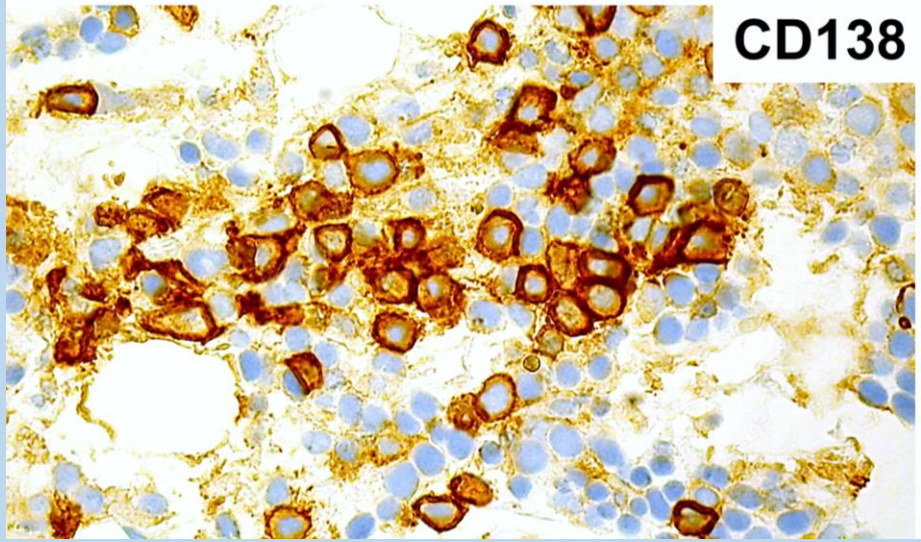
- EBV+ T/NK-cell LPD of childhood

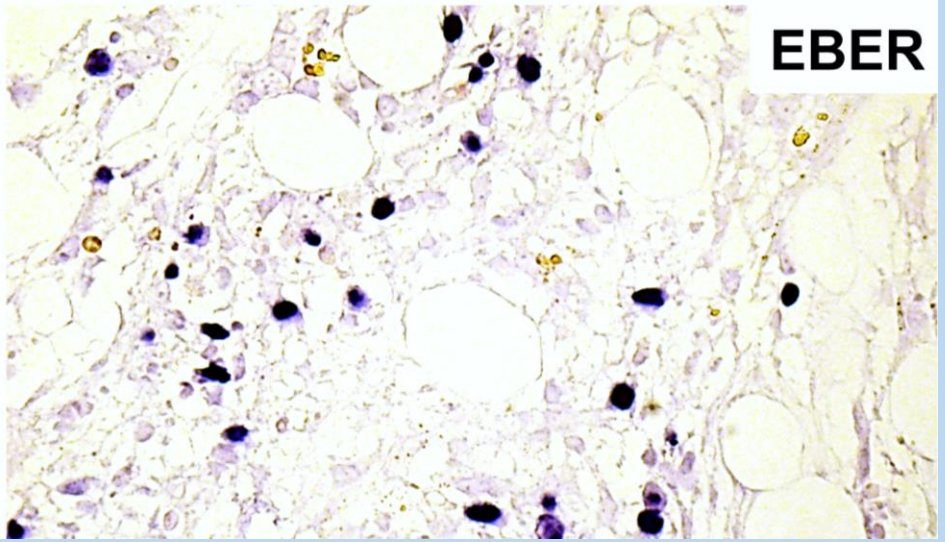


EBV in the proper context: PTLD



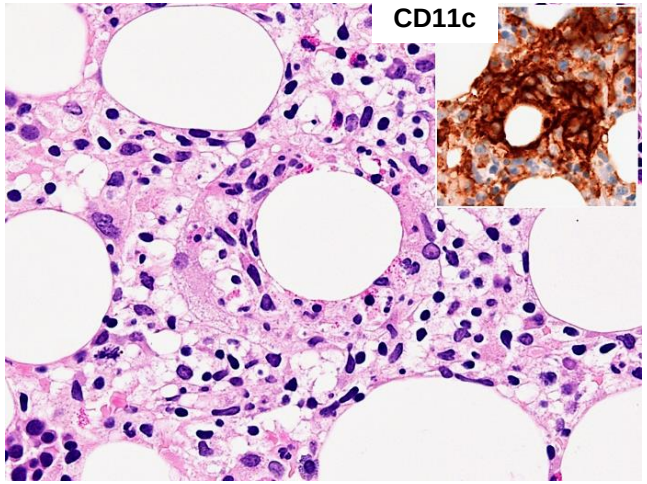


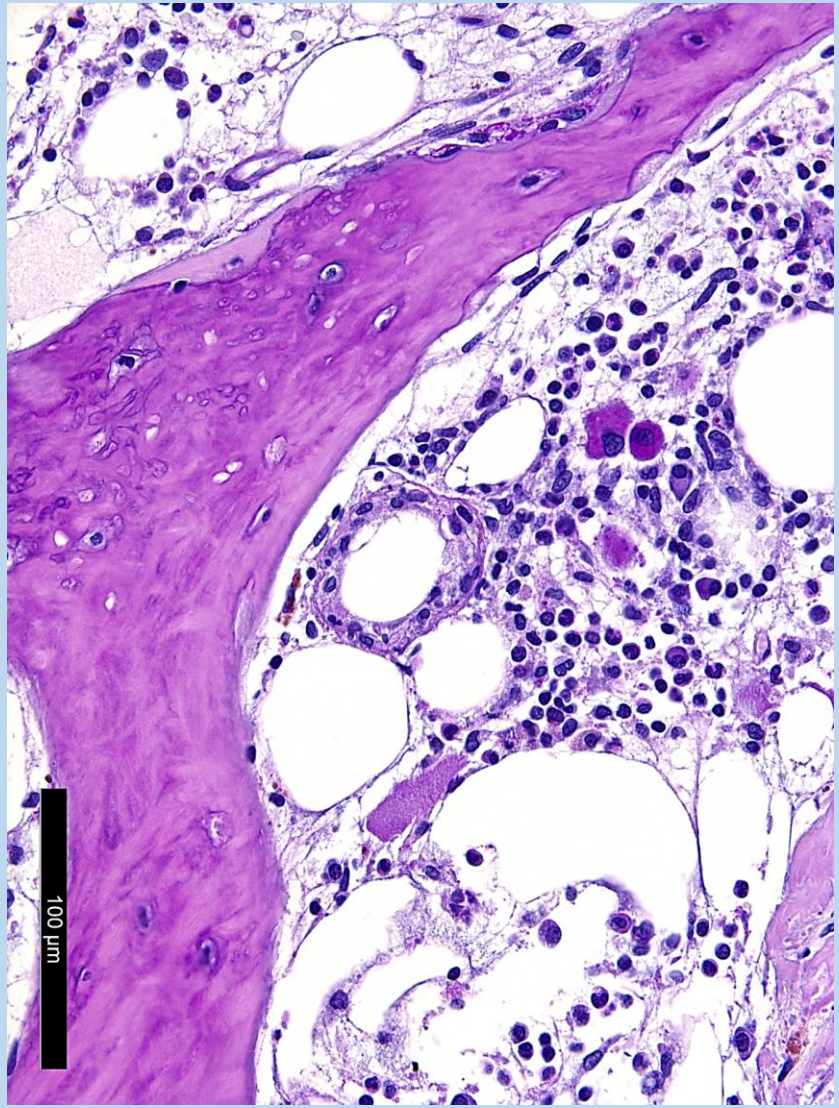


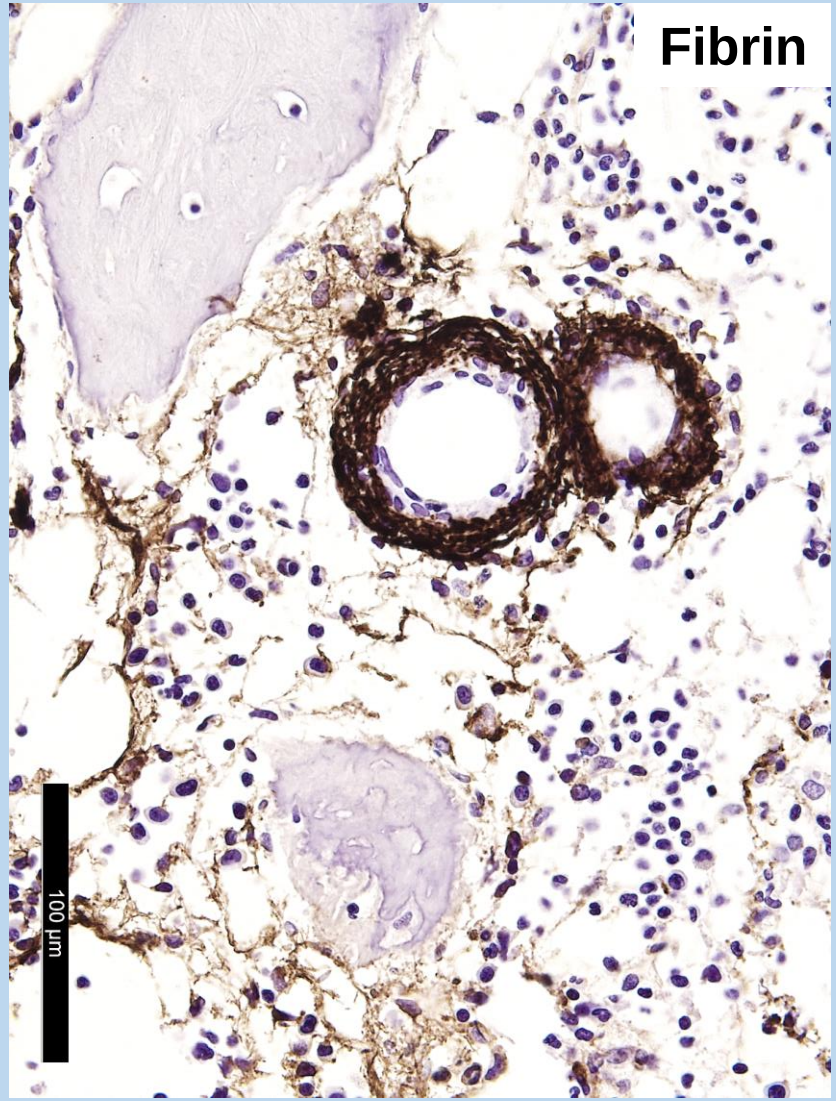


CMV

- Fibrin ring granulomas
- Bone marrow T-cell lymphocytosis (CD8 skewed)
- (T-LGL) atypical peripheral lymphocytosis in transplanted
- Occasionally T-cell clonality
- Bone marrow hypoplasia in immunocompromised

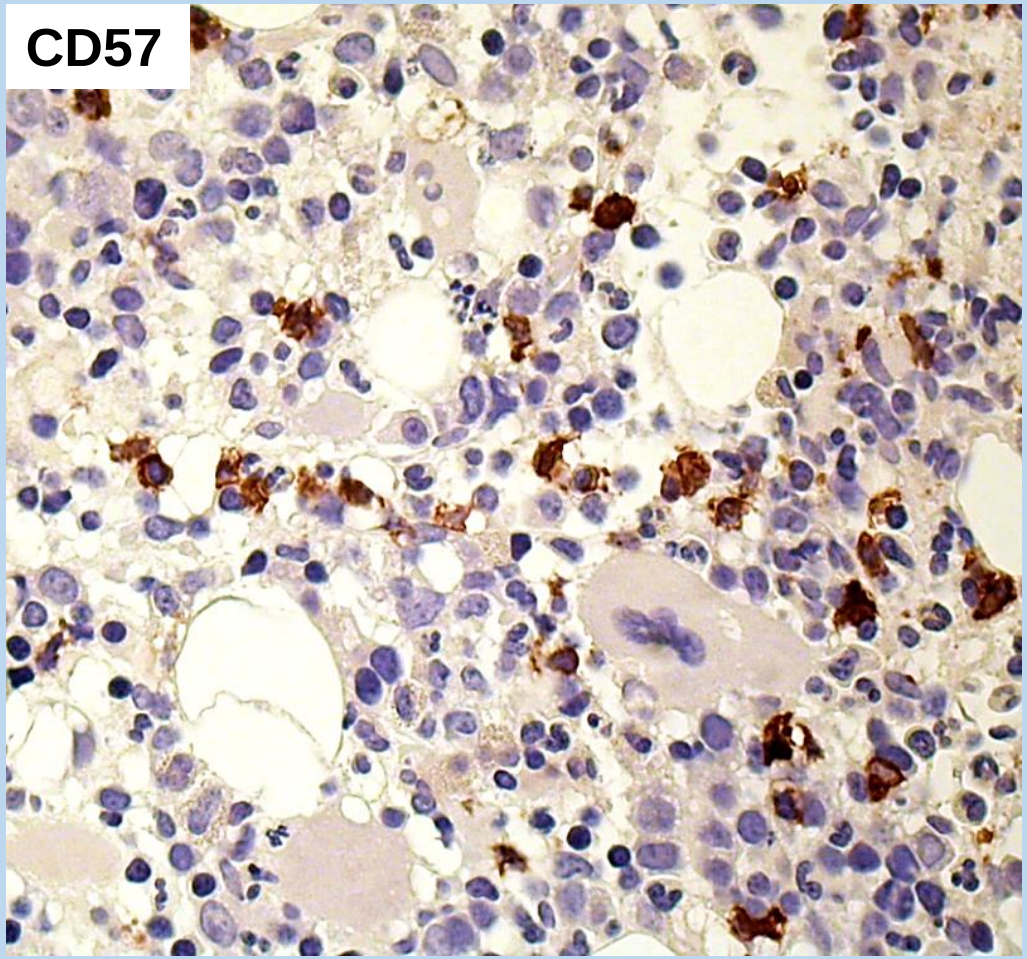


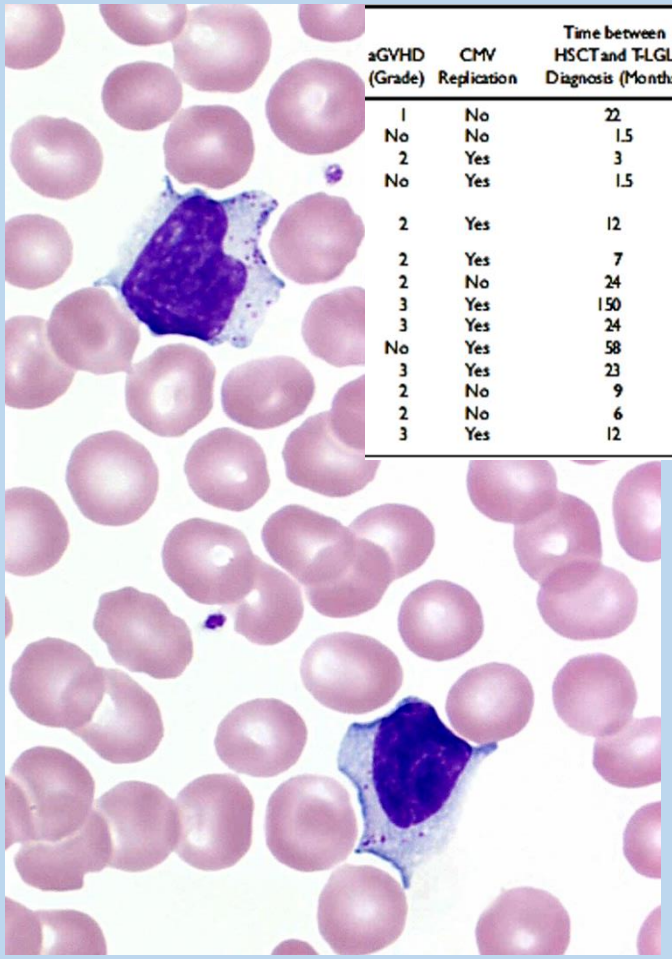




Large Granular Lymphocyte Expansion after Allogeneic Hematopoietic Stem Cell Transplant Is Associated with a Cytomegalovirus Reactivation and Shows an Indolent Outcome

See also WS case 3-5 Dr. Hock and 3-15 Dr. Amini

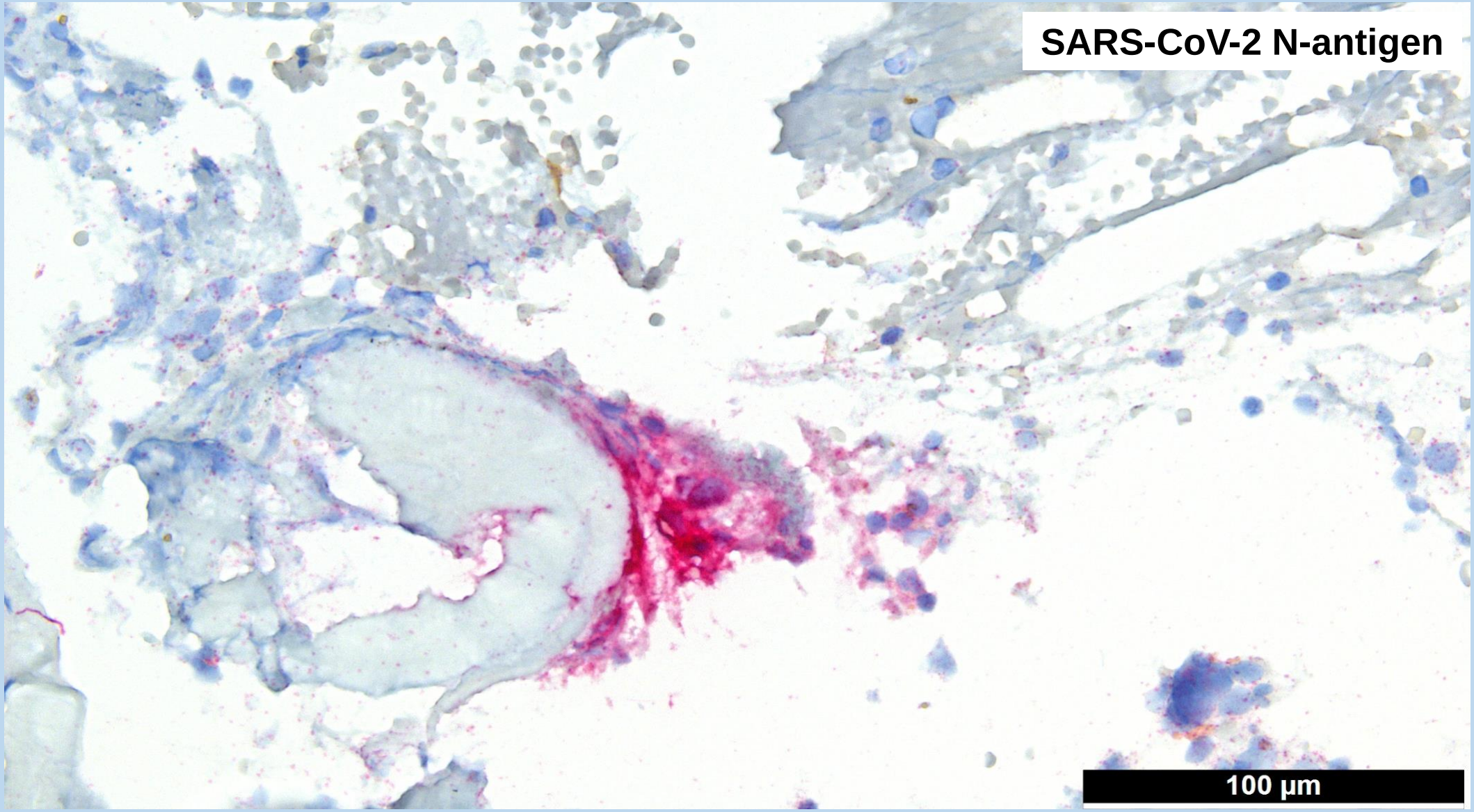




aGVHD (Grade)	CMV Replication	Time between HSCT and T-LGL Diagnosis (Months)	T-LGL Count (G/L)	Immunophenotype of T-LGL Expansion	TCR-gamma Gene Rearrangement	Alive/Dead Follow-up (Months)
1	No	22	2.130	CD2/CD3/CD5/CD7/CD8/HLADR/CD16/CD57/TCRab/CD56−	Clonal	Alive 53
No	No	1.5	2.039	CD2/CD3/CD5/CD7/CD8/HLADR/CD16/CD57/TCRab/CD56−	Clonal	Alive 61
2	Yes	3	2.652	CD2/CD3/CD7/CD8/CD16/CD57/TCRab/CT56−	Clonal	Alive 8
No	Yes	1.5	11.528 3.619	CD2/CD3/CD5/CD7/CD8/HLADR/CD57/TCRab/CD16−/CD56− and CD2/CD3/CD4/CD5/HLA-DR/CD57/TCRab/CD16−/CD56−	Clonal	Dead 18
2	Yes	12	2.109	CD2/CD3/CD5/CD7/CD8/HLADR/CD16/CD57/TCRab, CD56−	Biclonal	Alive 13
2	Yes	7	2.629	CD2/CD3/CD8/CD57 CD16/TCRab/CD56−	Polyclonal	Alive 162
2	No	24	1.252	CD2/CD3/CD5/CD7/CD8/CD57/TCRab/CD16−/CD56−	Polyclonal	Alive 146
3	Yes	150	1.934	CD2/CD3/CD8/CD57/TCRab/ CD16-/CD56−	Polyclonal	Alive 61
3	Yes	24	1.286	CD2/CD3/CD5/CD7/CD8/HLADR/CD16/CD56/CD57/TCRab	Polyclonal	Alive 86
No	Yes	58	2.168	CD2/CD3/CD5/CD7/CD8/HLADR/CD56/CD57/TCRab/CD16−	Polyclonal	Alive 71
3	Yes	23	1.692	CD2/CD3/CD5/CD7/CD8/CD16/CD57/TCRab/CD56−	Polyclonal	Alive 37
2	No	9	1.513	CD2/CD3/CD5/CD7/CD8/CD16/CD57/TCRab/CD56−	Polyclonal	Alive 29
2	No	6	2.745	CD3/CD5/CD7/CD8/HLA-DR/CD16/CD57/TCRab/CD56−	Polyclonal	Alive 3
3	Yes	12	2.086	CD3/CD4/CD56/CD57/TCRab/CD16−	Polyclonal	Alive 85

- T-LGL expansions in 5-10% of AHCT
- Mostly clinically asymptomatic
- Common in CMV reactivation and/or aGvHD
- All with detectable T-LGL increase in BM
- 65% polyclonal, 35% clonal cells
- None in need of treatment for T-LGL

The new kid on the block: COVID-19



Layout

Physiological roles of mature bone marrow T-cells

Bone marrow T-cells in viral infections

Bone marrow T-cells in (auto)immune conditions

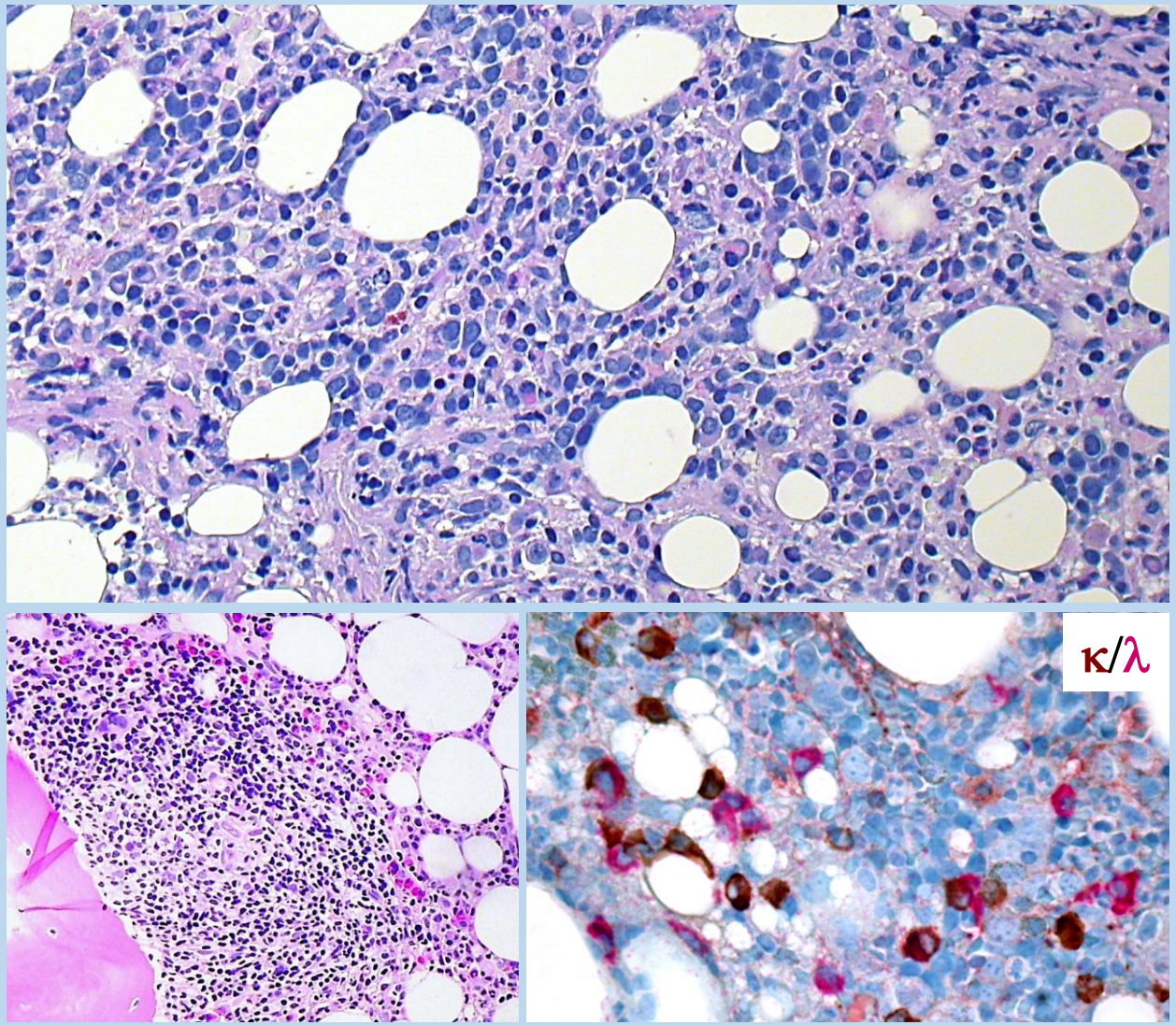
Bone marrow T-cells in drug reactions

Paraneoplastic bone marrow T-cell expansions

Mimickers and caveats

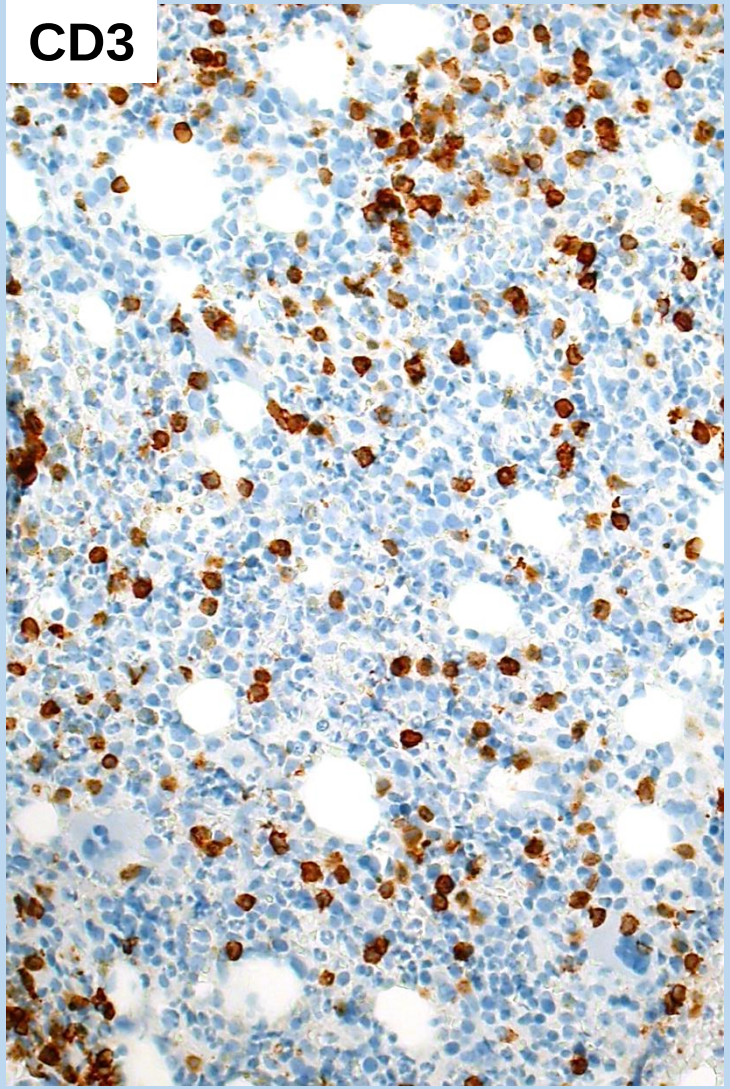
BM findings in autoimmune conditions

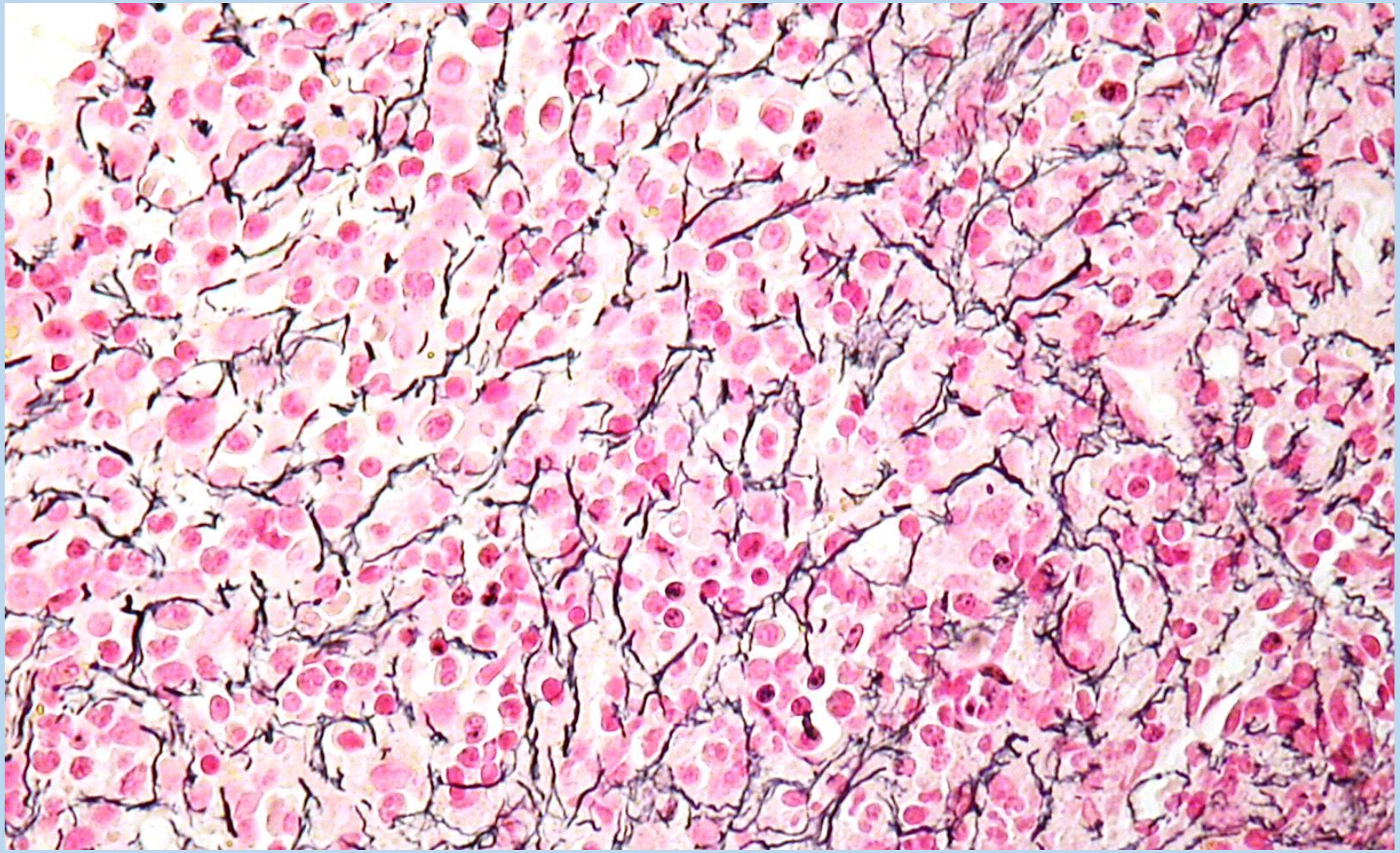
- T-cell (T-LGL skewed) lymphocytosis
- Germinal centers
- Erythro- and megakaryopoietic changes
  - Hemolysis (AIHA)
  - Peripheral platelet consumption (ITP)
  - "Anemia of chronic disease"
- Plasmacytosis



Rizzi et al. Leuk & Lymphoma 2004;45:561
Bass et al. AJCP 2001;116:211
Voulgarelis et al. Am J Hematol 2006;81:590
Prochorec-Sobieszek et al. Arthritis Res Ther 2008;10:R55

Autoimmune myelofibrosis





Clonal T-cells in autoimmune MF

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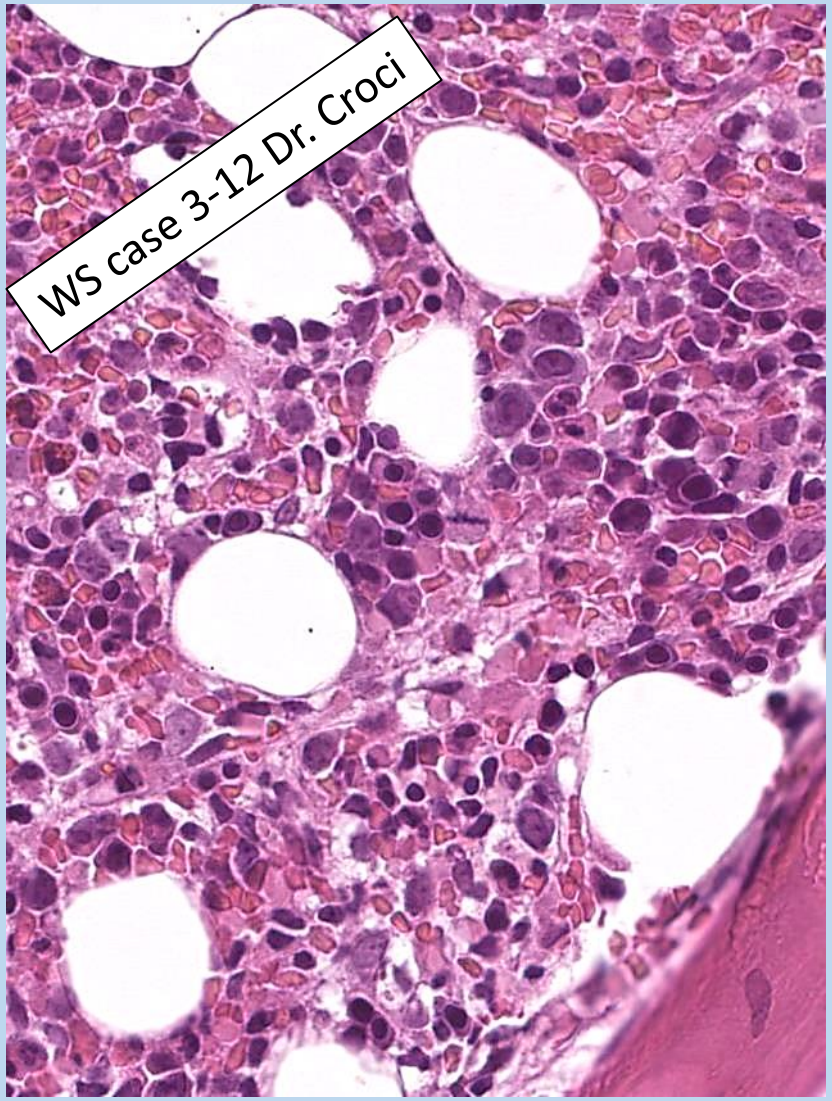

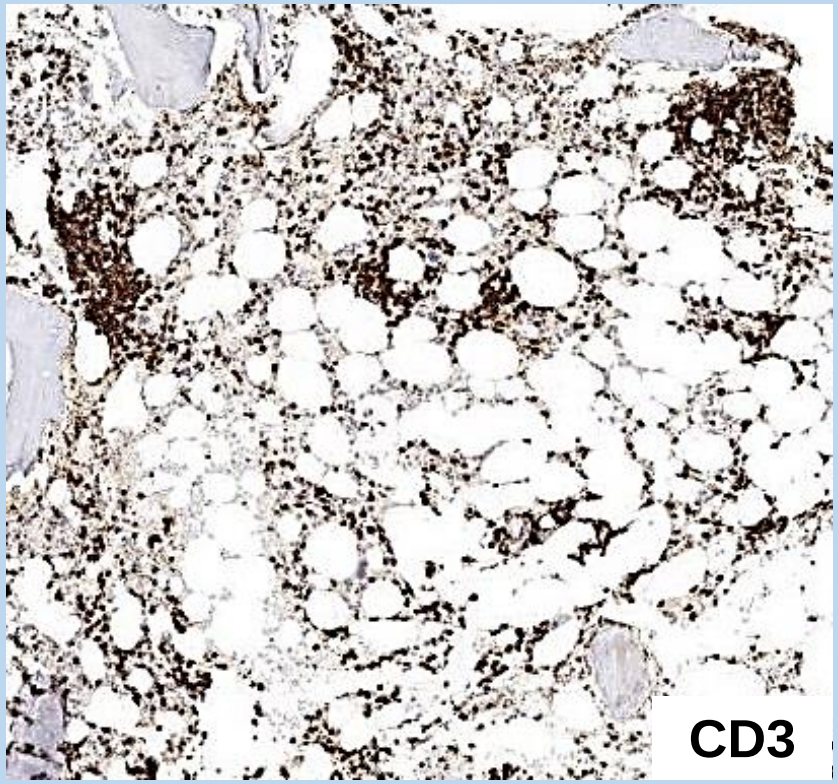

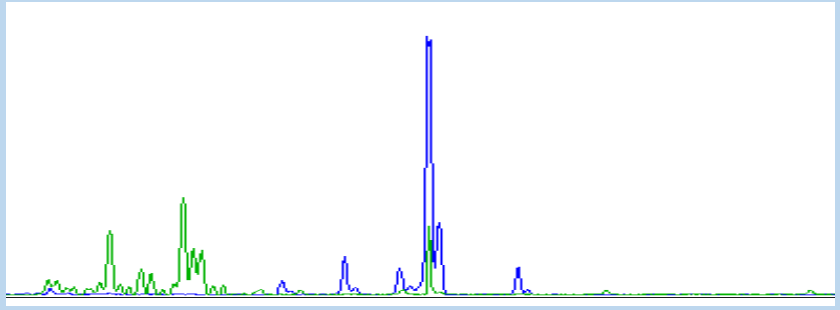

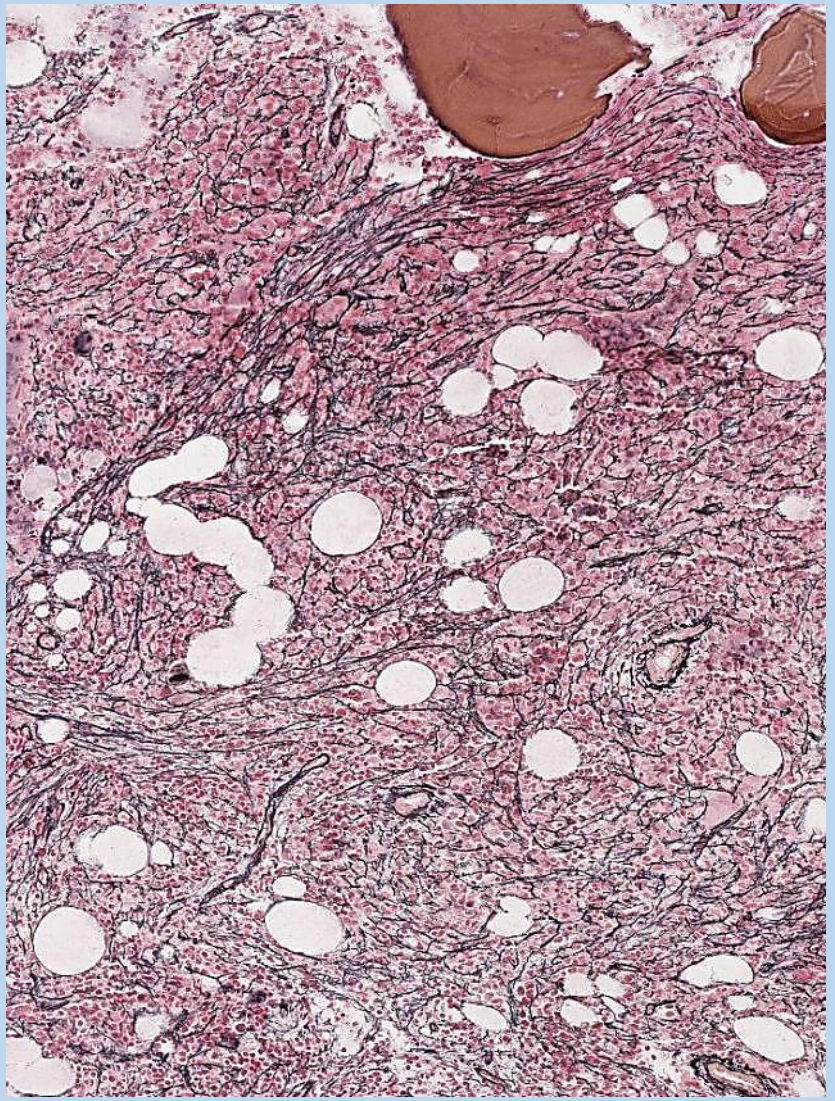

Massive CD4/CD8 DN lymphocytosis in ALPS

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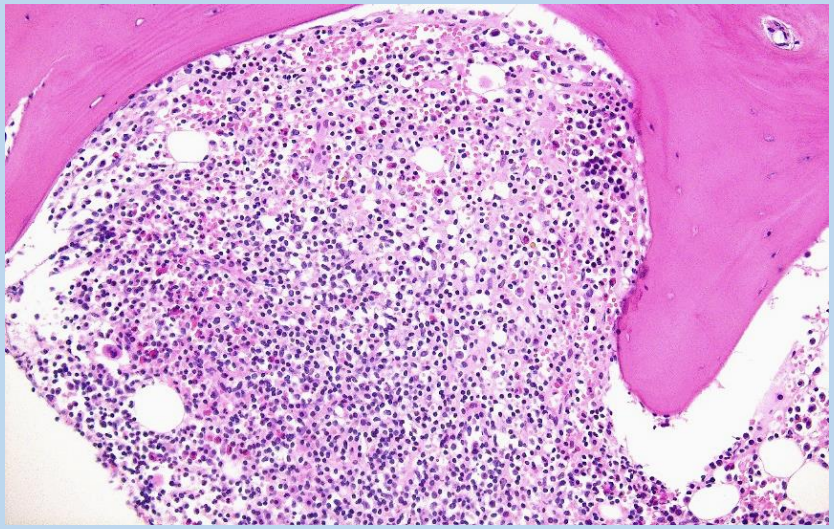
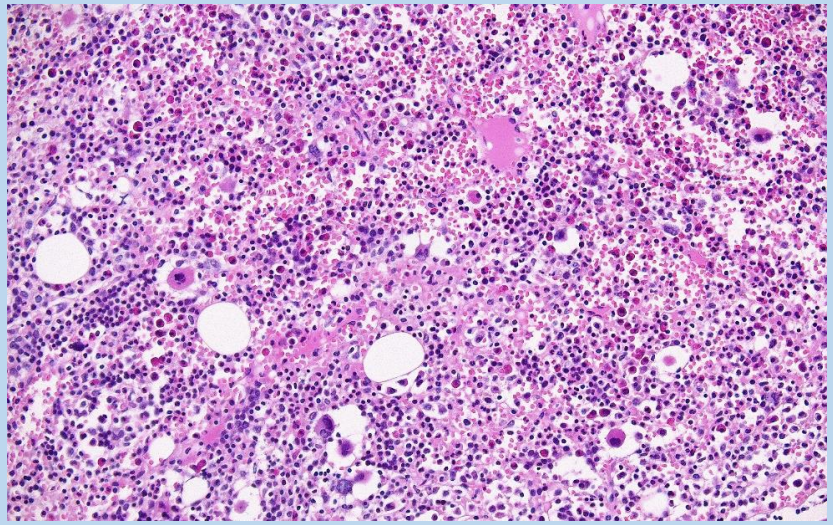
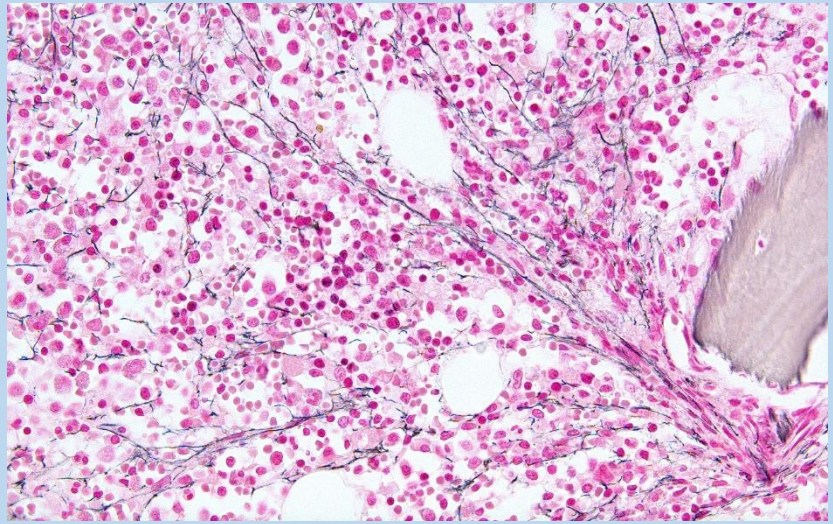
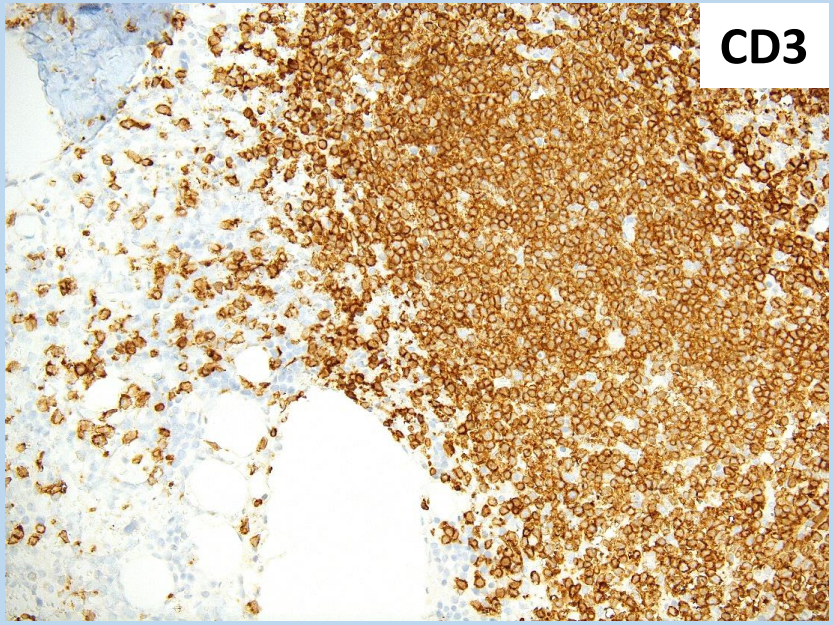
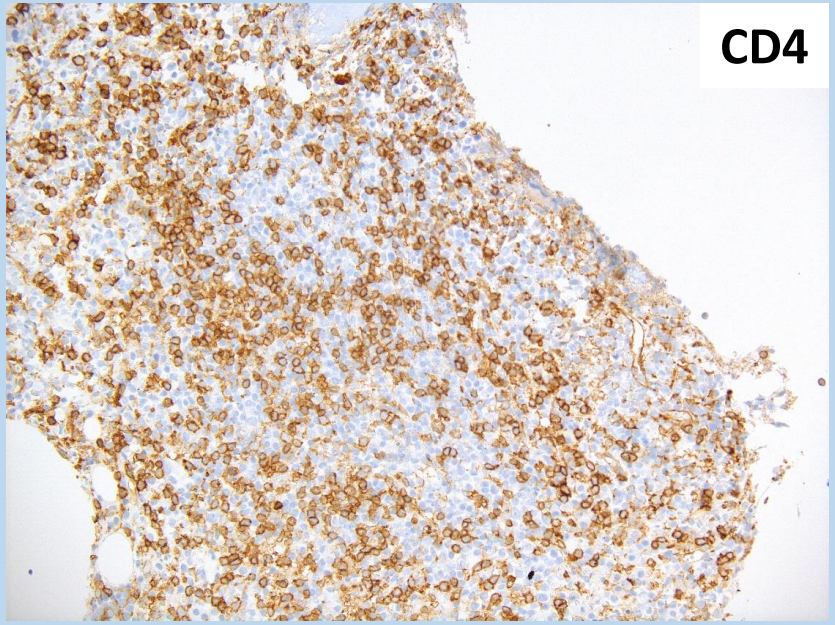
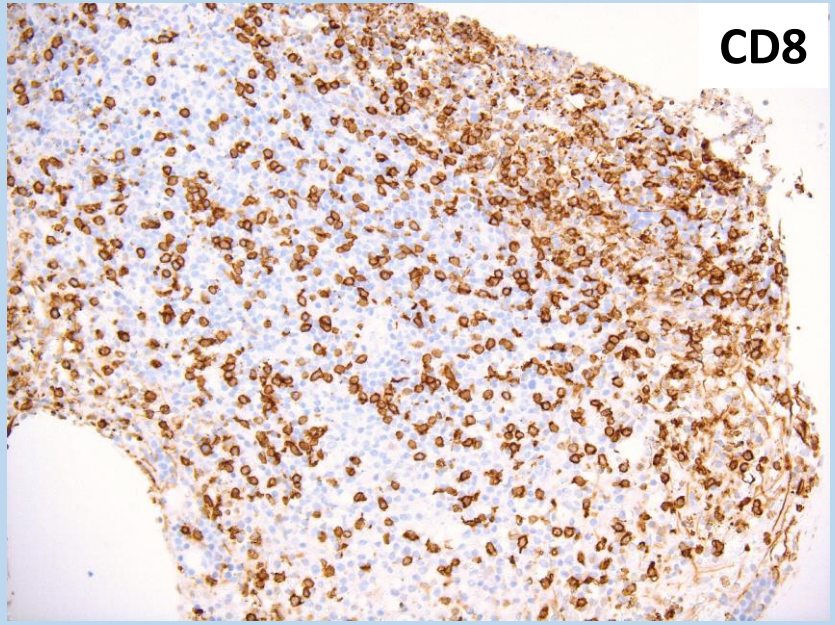










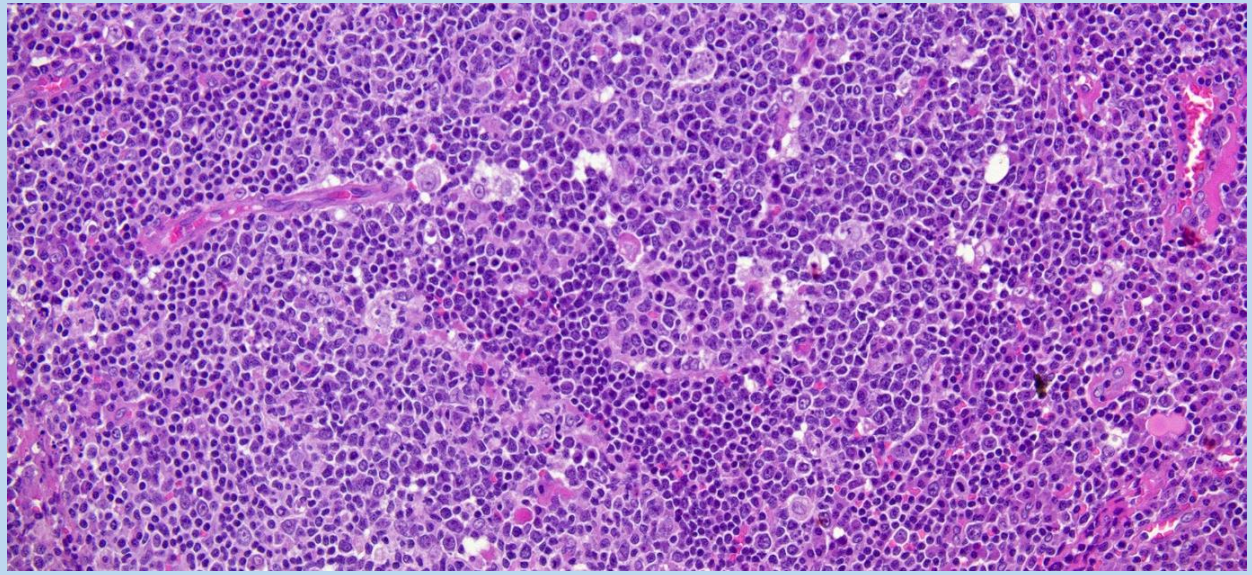


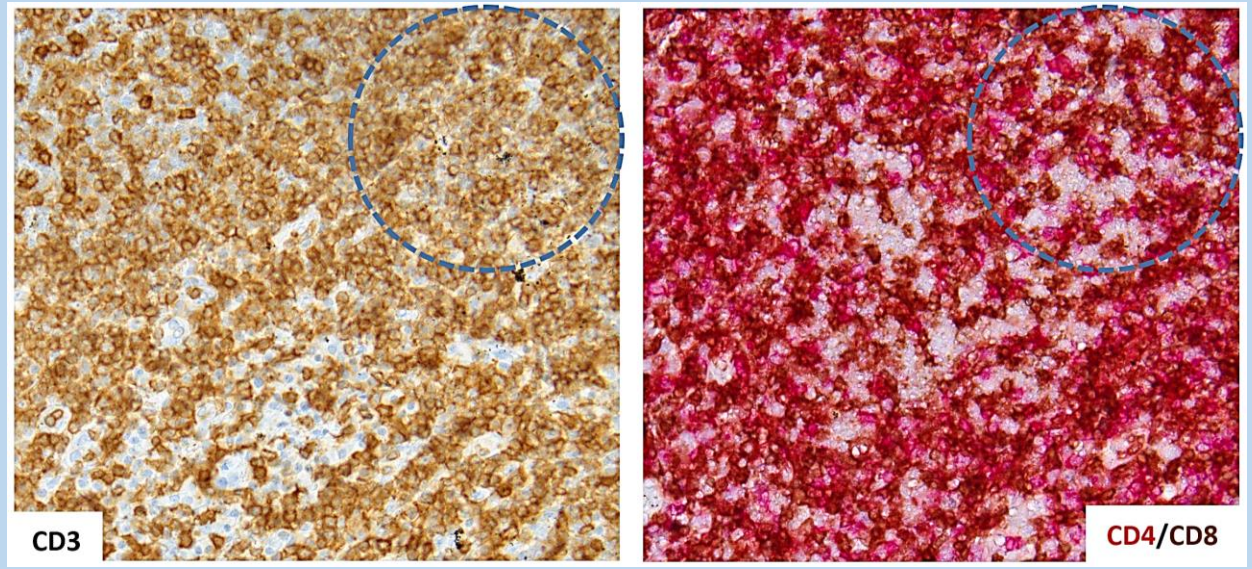
ALPS

- Disruption of FAS-mediated apoptosis due to mutations in *FAS*, *FASLG*, *FADD* or *CSP10*:
  - Disordered lymphocyte selection in the thymus
    - Occurrence of CD4/CD8 double-negatives
    - ≥2.5% of all CD3+ lymphocytes
  - Disruption of apoptosis in the GC with FH

- Symptoms:
  - Lymphadenopathy & splenomegaly
  - Pancytopenia & MF
  - CD4/CD8 double negative T cells
  - Elevation of vitamin B12
  - Hypergammaglobulinemia

- Risks:
  - Rosai-Dorfman disease-like lymphadenopathy
  - Increased risk of Hodgkin and Burkitt lymphoma

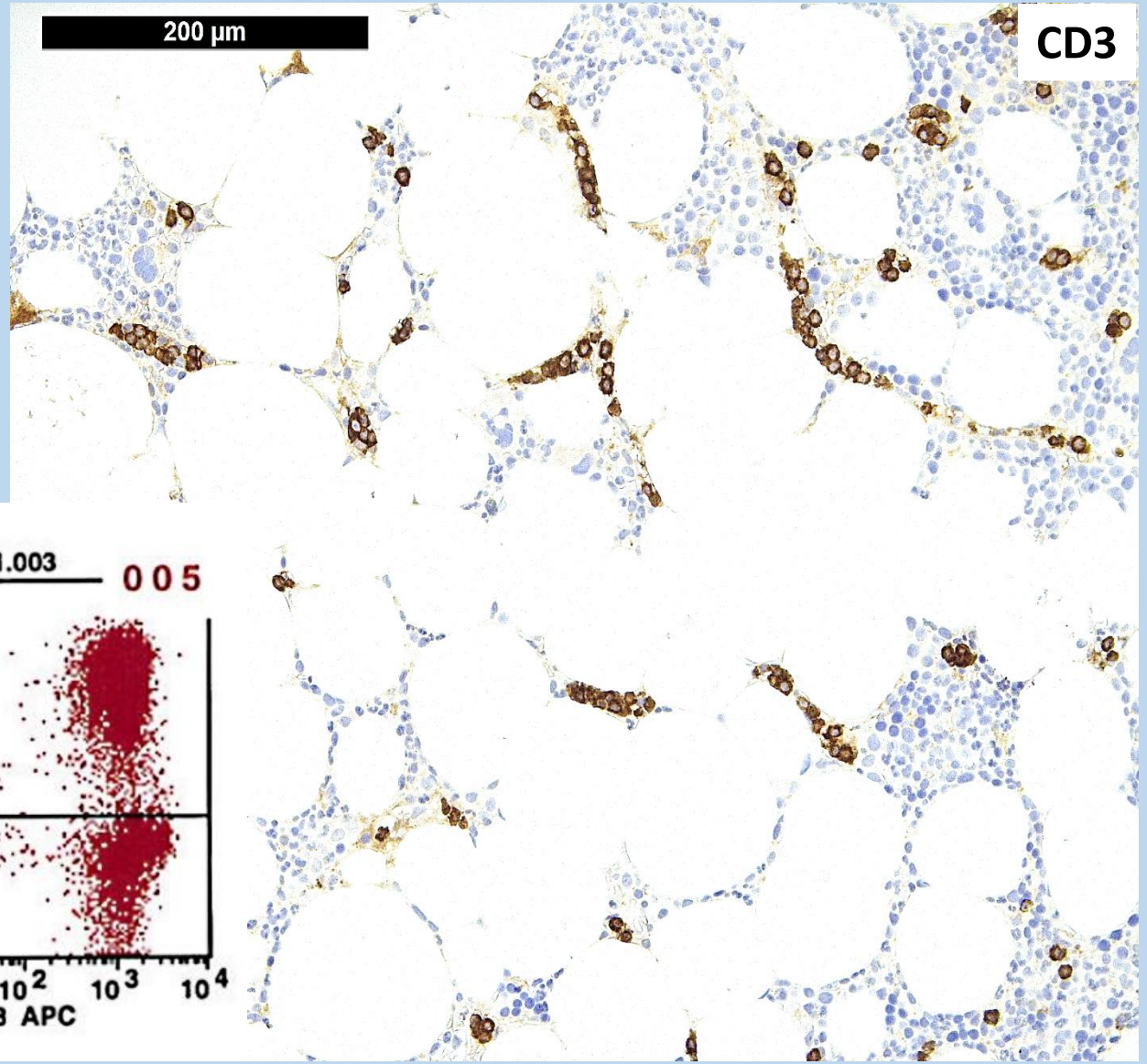


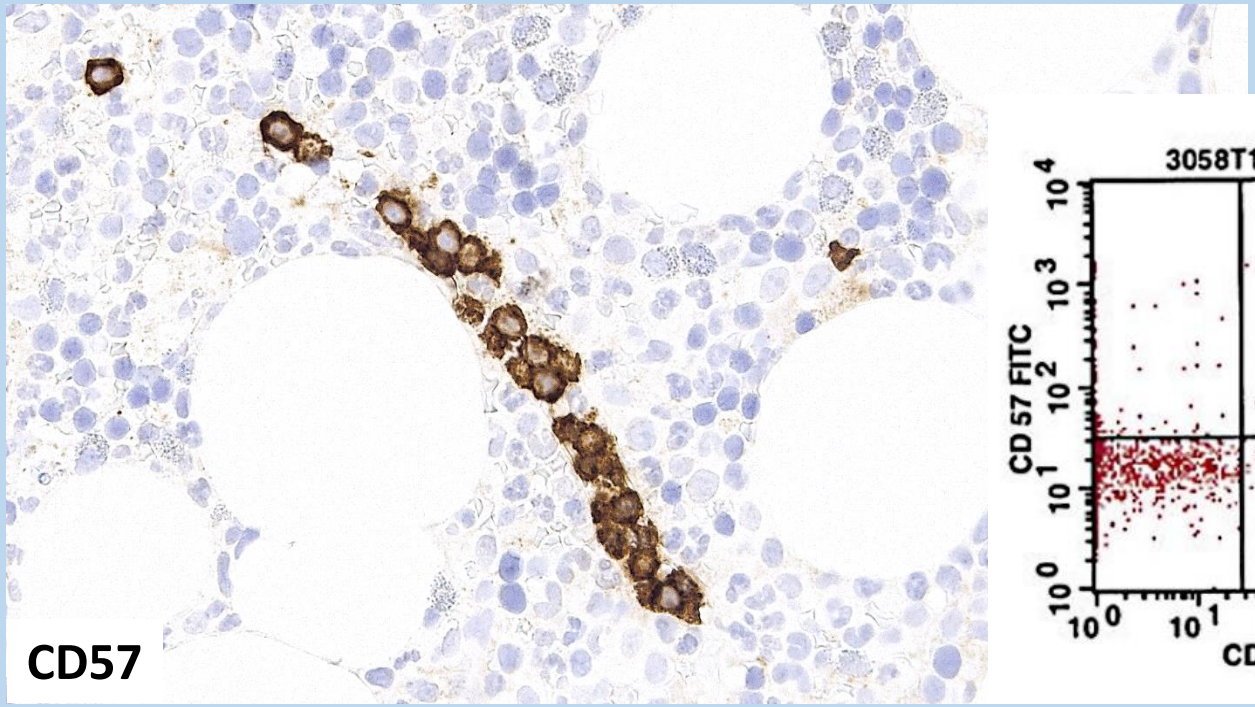


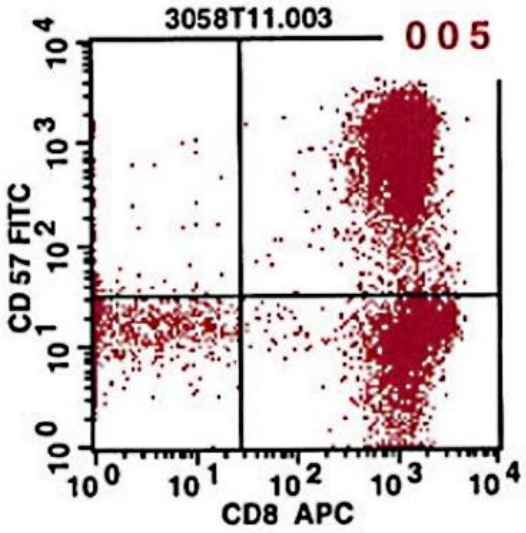
LGLs, Felty and …

- T-LGL lymphocytosis up to T-LGLL in many autoimmune disorders
- Felty syndrome
  - Rheumatoid arthritis
  - Splenomegaly & lymphadenopathy
  - Neutropenia

Arthritis Res Ther 2008;10:R55

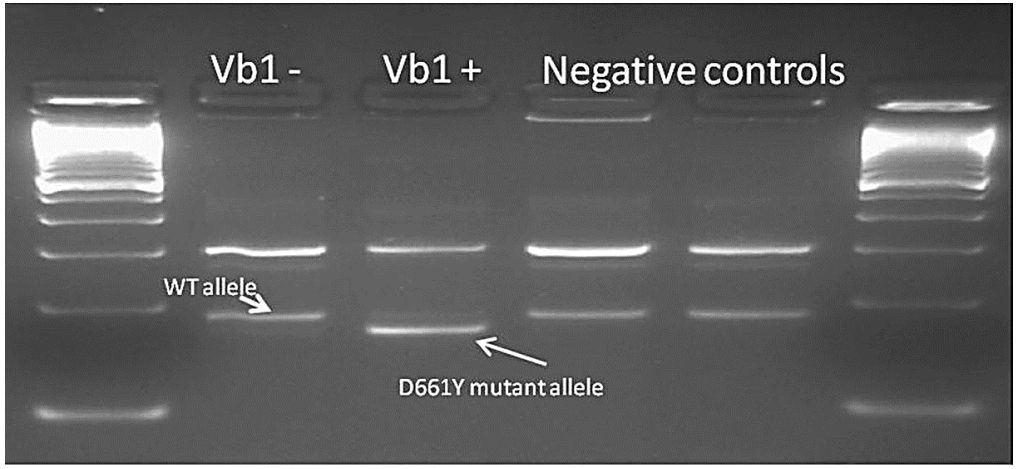


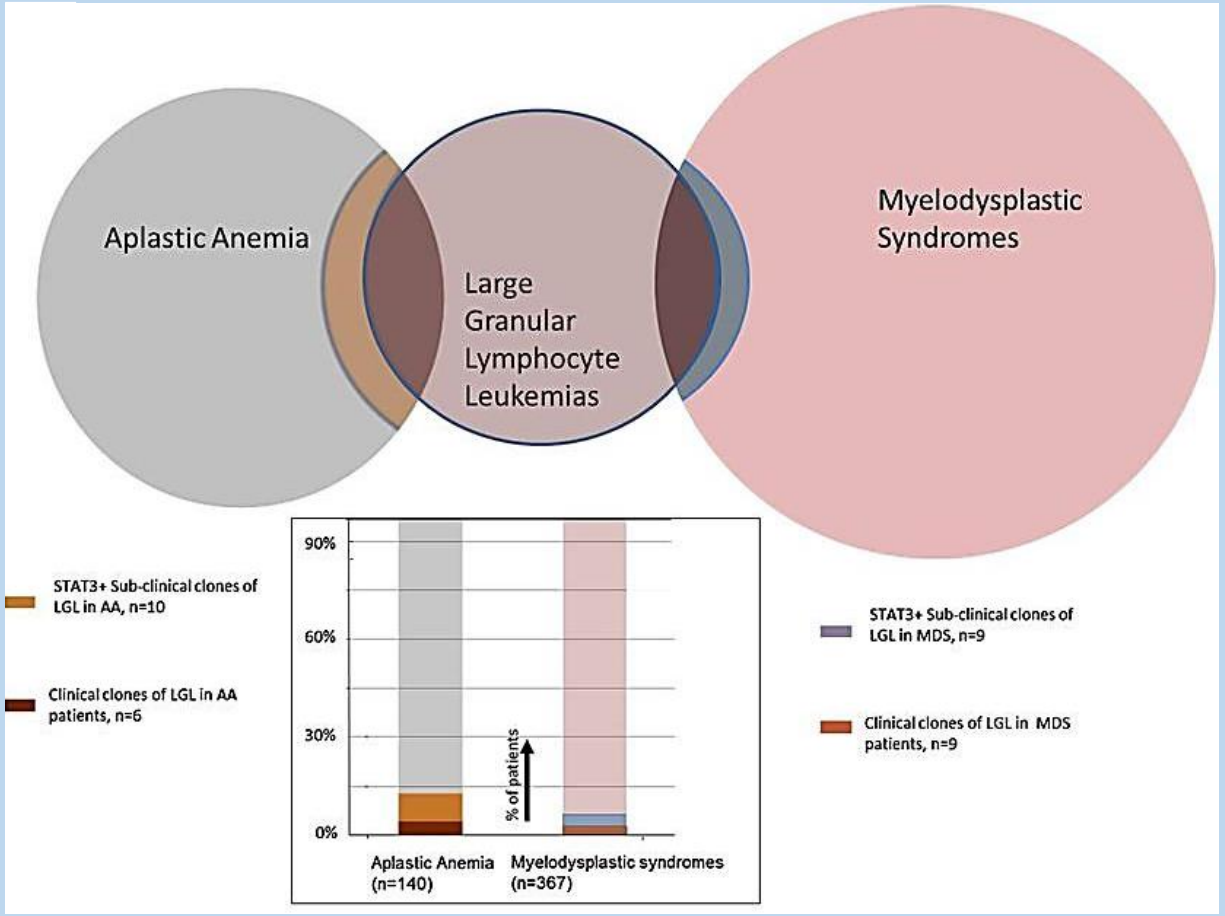




…the missing link to AA – MDS… ?

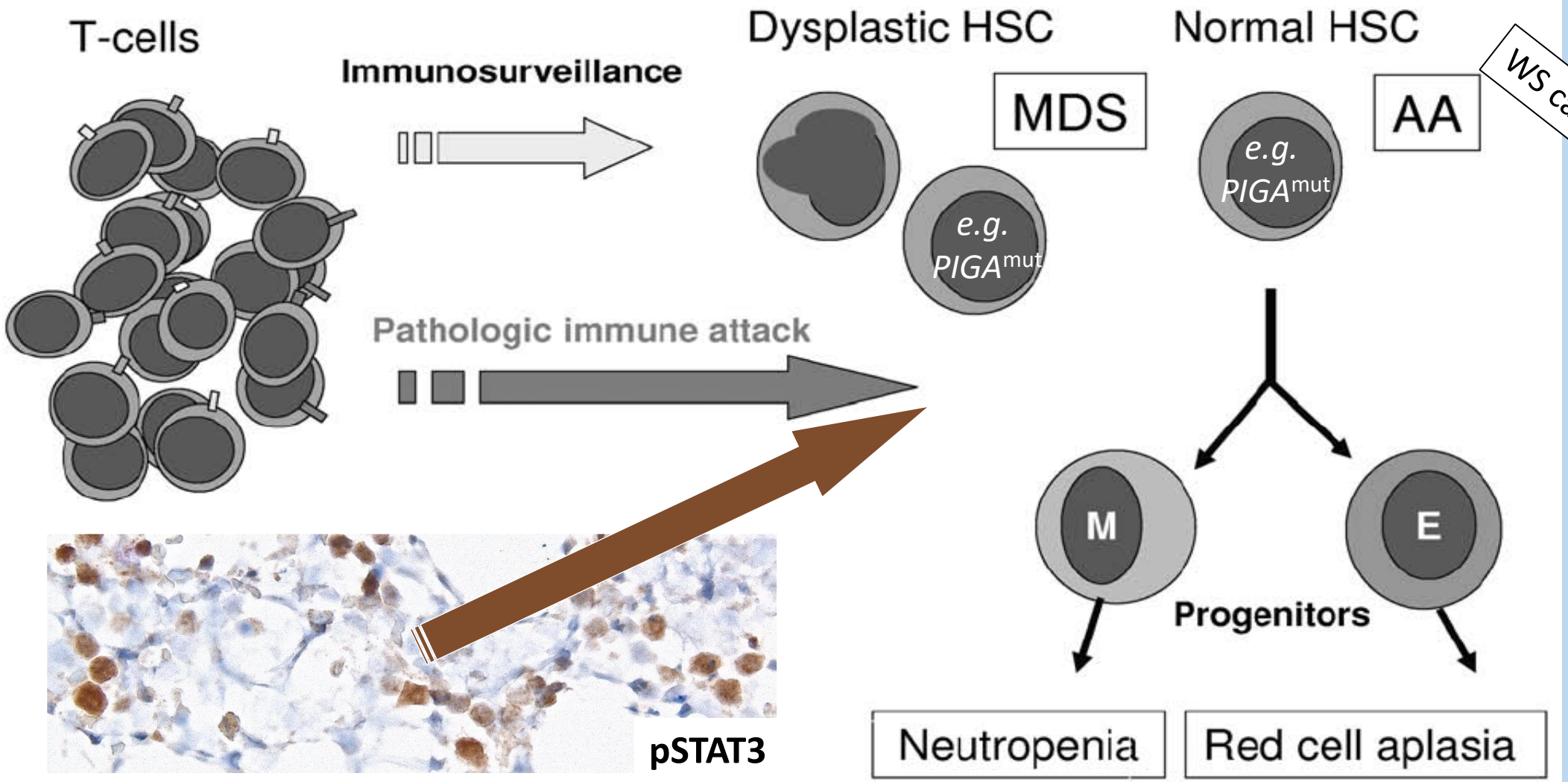
- Associations with T-LGL and chronic NK LPD
  - 5% T-LGLL present as AA
    - *Go et al. Semin Hematol 2003*
  - 7% AA display *STAT3*^{mut} CD57+ T-cell clones
    - *STAT3* mutants in 75% HLA-DR15+ (vs. 44%)
    - *Jerez et al. Blood 2013*





AA anemia as a collateral damage

- Of unapparent T-LGLL or imminent MDS



Maciejewski et al. Folia Histochem Cytobiol 2007;45:5

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Physiological roles of mature bone marrow T-cells

Bone marrow T-cells in viral infections

Bone marrow T-cells in (auto)immune conditions

Bone marrow T-cells in drug reactions

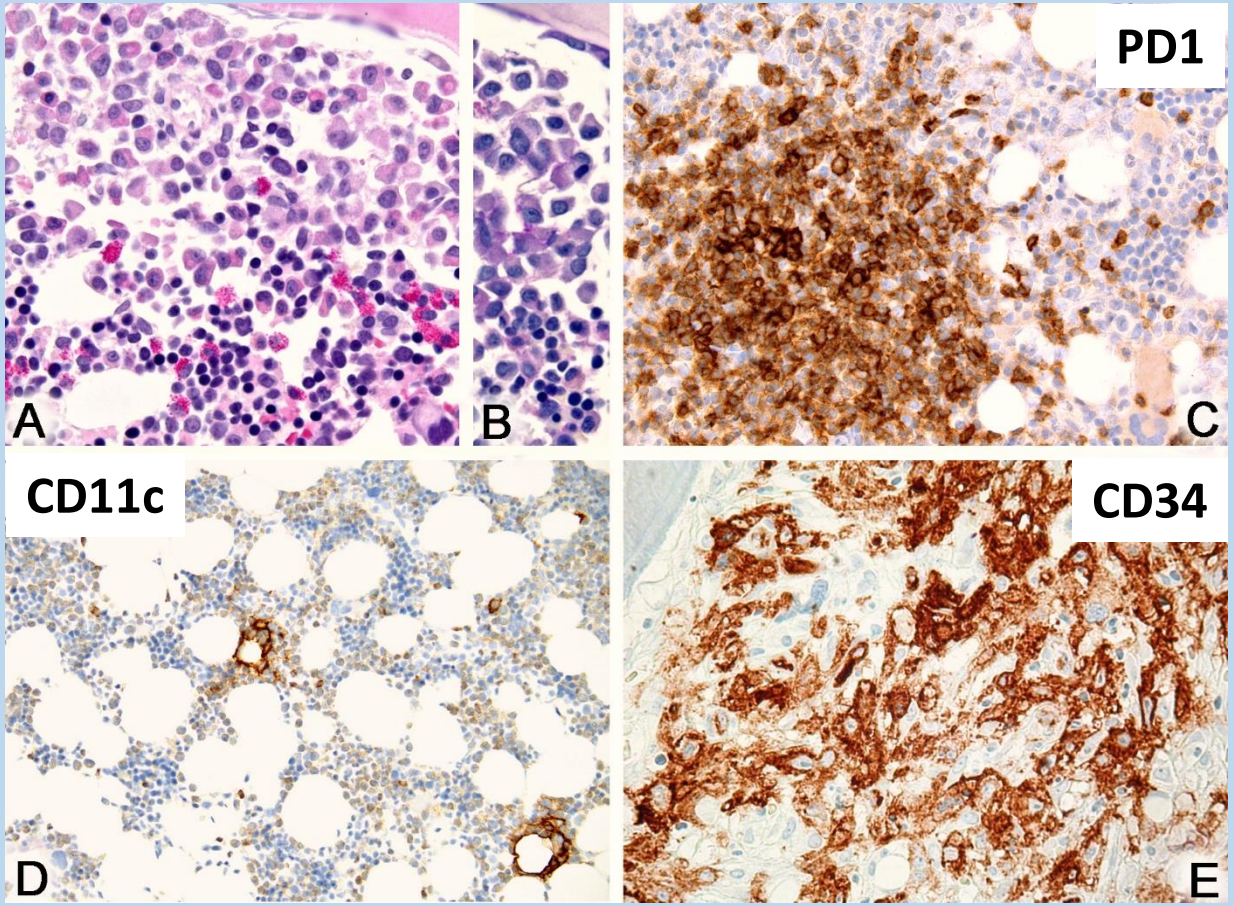
Paraneoplastic bone marrow T-cell expansions

Mimickers and caveats

BM T-cell proliferations due to drugs

- Associated drugs
  - Allopurinol & Co.
  - Rituximab (Alemtuzumab)
  - Imatinib
  - HBV immunization
- Patterns
  - CD4-skewed T-cell increase (PD-1!), occasionally clonal
  - Myelopoietic dysmaturation
  - Eosinophilia
  - Granulomas

Acetaminophen
Acetazolamide/methazolamide
Allopurinol
Aminoglutethimide
Aminosalicylic acid
Amodiaquine
Beta-lactams
Calcium dobesilate
Carbamazepine
Carbimazole
Clomipramine
Clopidogrel
Clozapine
Dapsone
Diclofenac
H2-blockers
Hydantoins
Ibu-/Ketoprofen
Indomethacin
Metamizole (Aminopirine)
Methimazole/Thiamazole
Metoclopramide
Mianserin
Nimesulide
Phenothiazines
Phenylbutazone
Procainamide
Propylthiouracil
Sulfamethoxazole
Sulfasalazine
Ticlopidine
Trimethoprim
Vesnarinone



MJHID 2010;6207
Blood 2002;100:435
Hum Pathol 2008;39:194
Br J Haematol 2000;110:230
Diagnostic Bone Marrow Haematopathology, Cambridge University Press, 2021

Allopurinol induced DRESS

J Allergy Clin Immunol Pract 2016;4:1262

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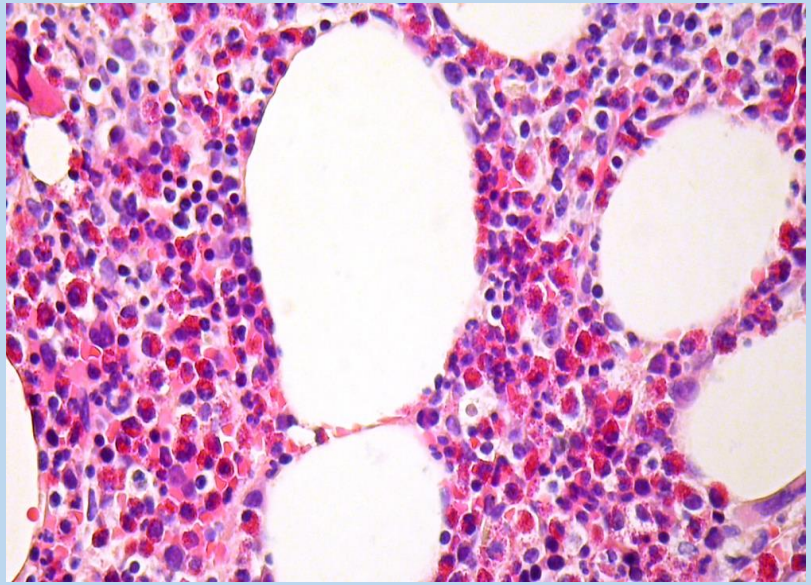
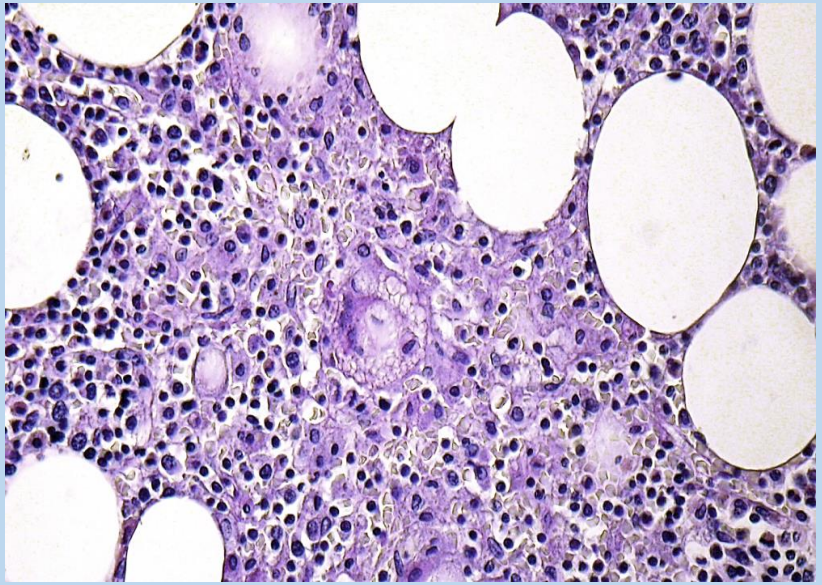
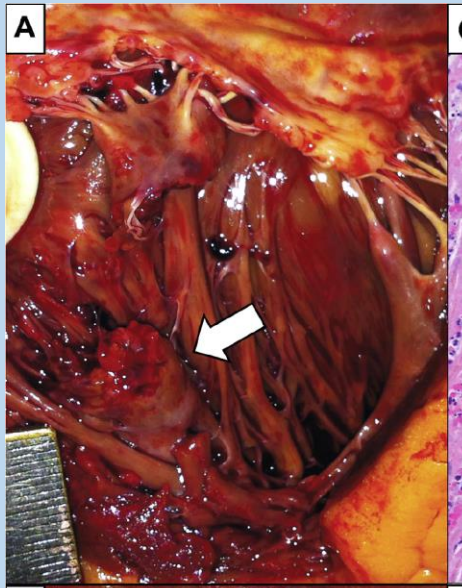
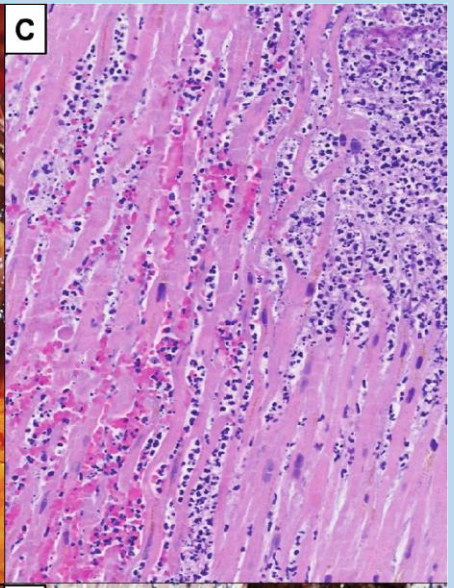
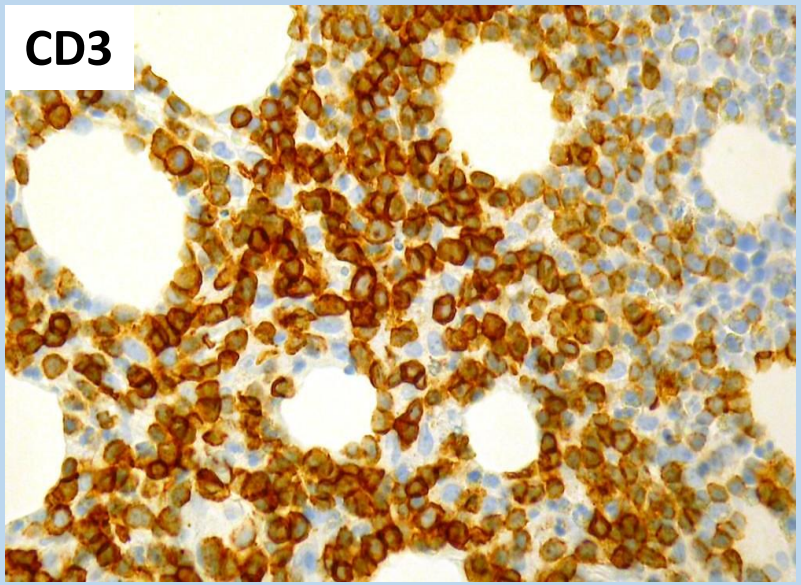
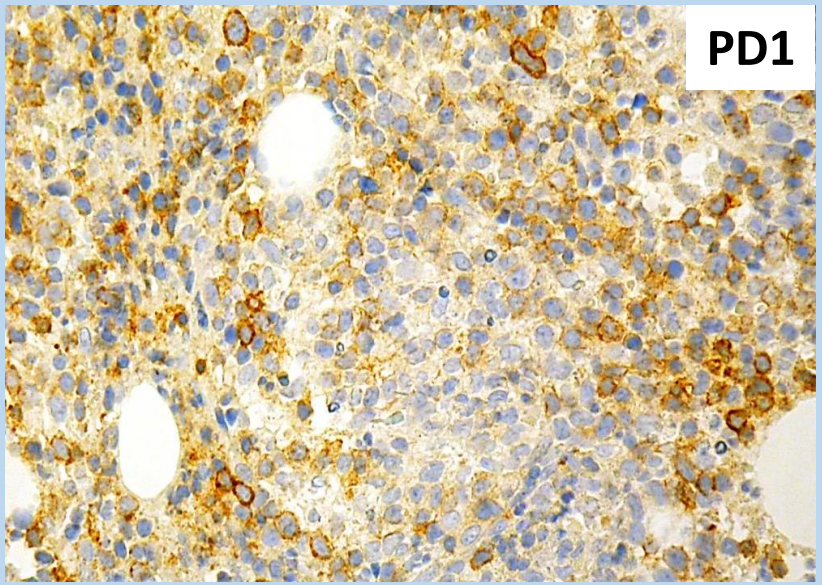


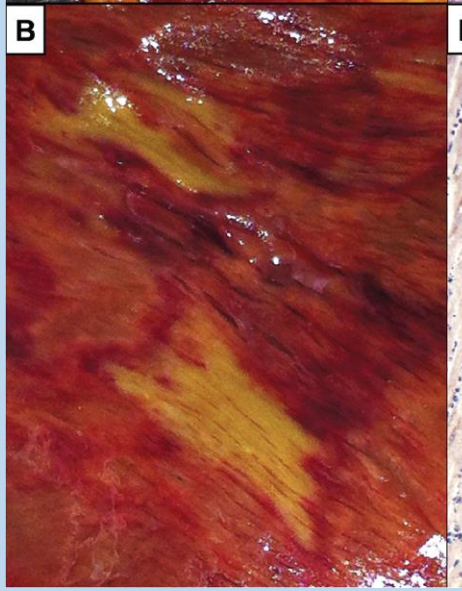


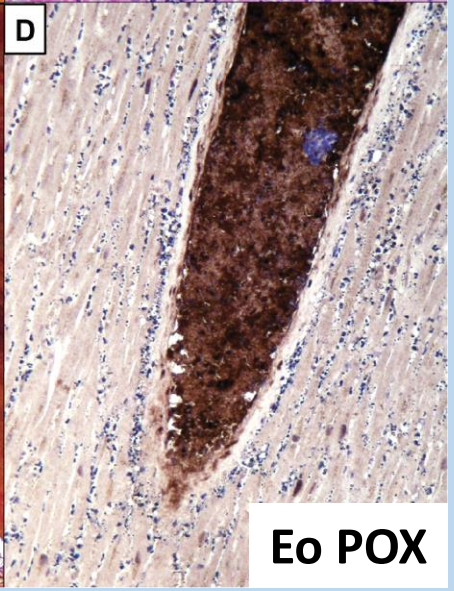




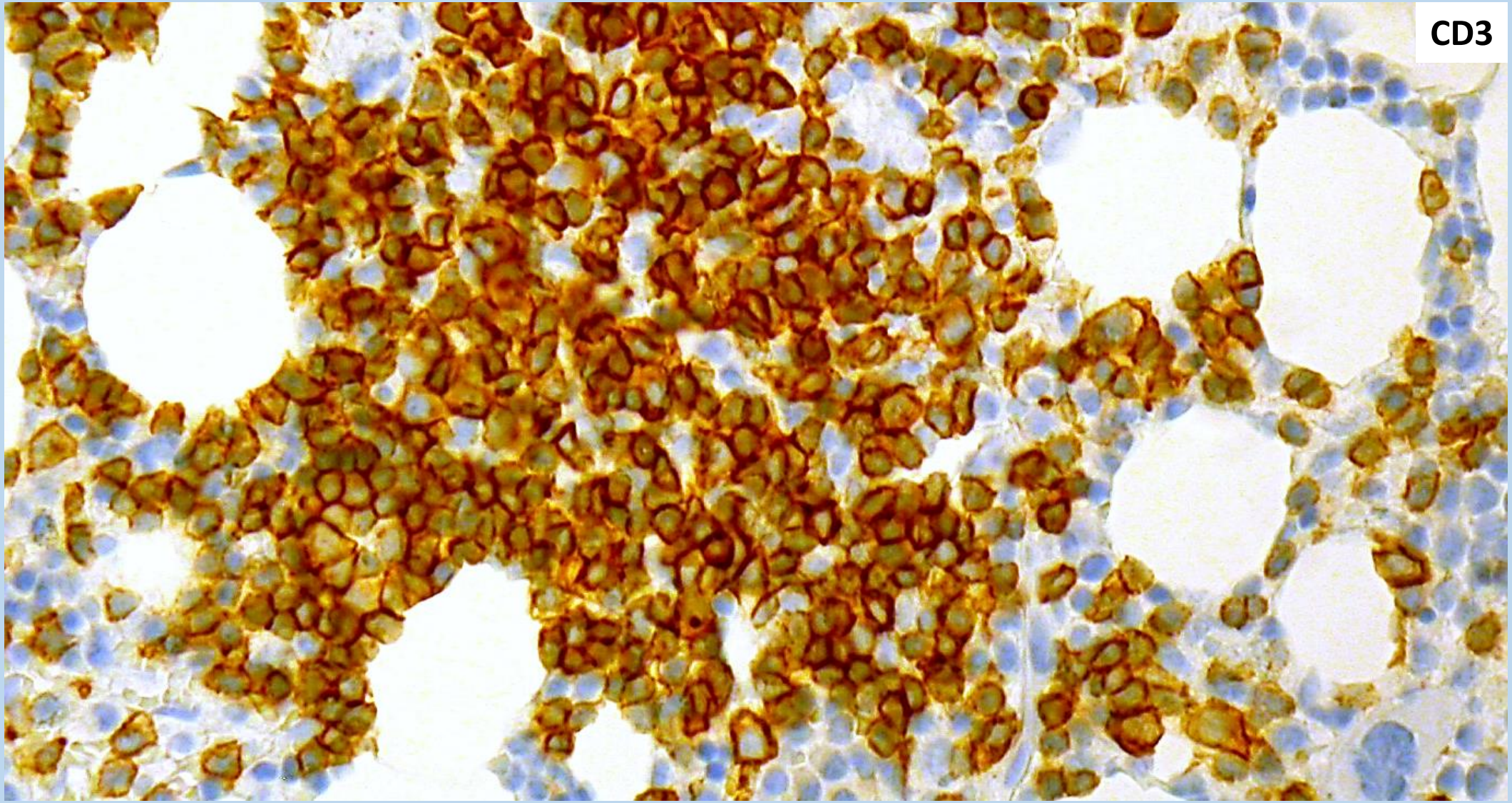








T-cell aggregate after Rituximab



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Bone marrow T-cells in viral infections

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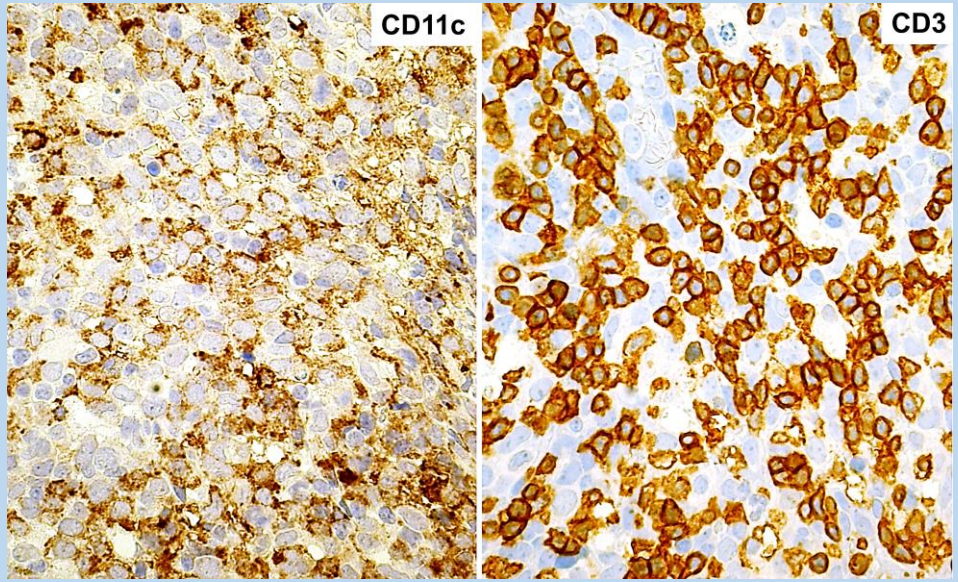
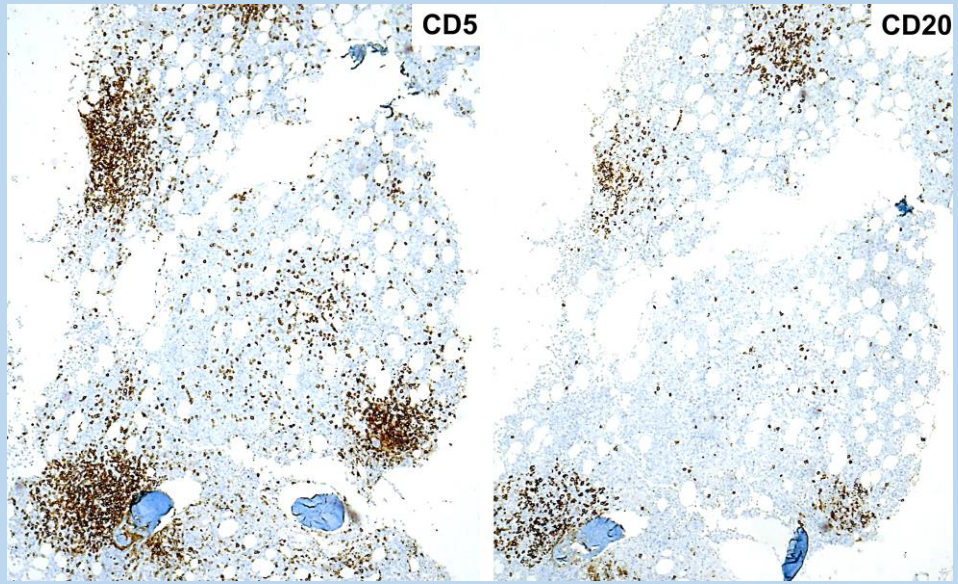
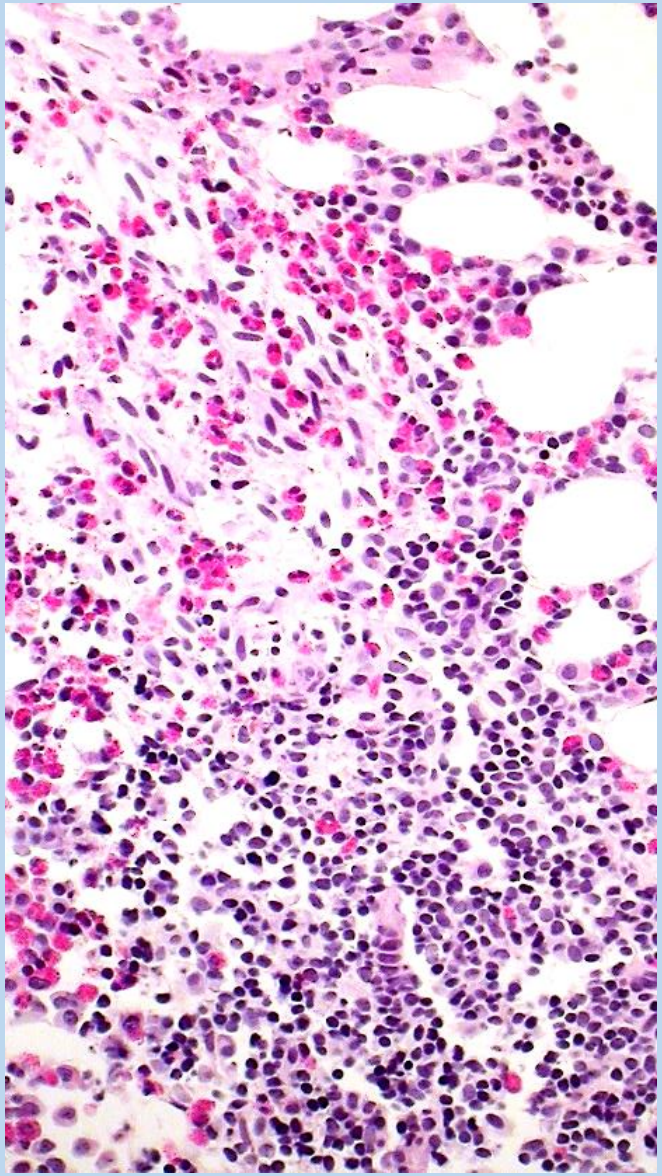
Mimickers and caveats

BM T-cells accompanying other malignancies

- AML, particularly *MLL* rearranged
- B-cell lymphomas
  - Marginal zone B-cell lymphoma
  - Lymphoplasmacytic lymphoma
  - Follicular lymphoma
- MDS
- MPN
- Systemic mastocytosis
- Thymomas

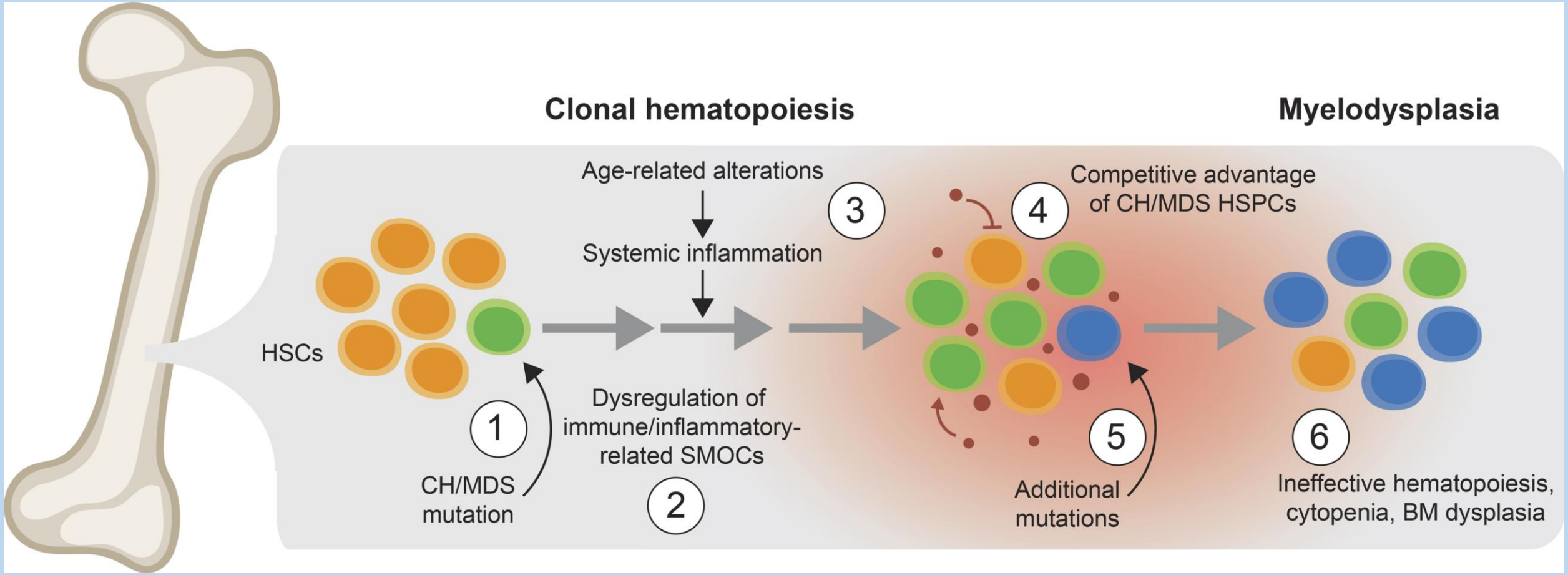






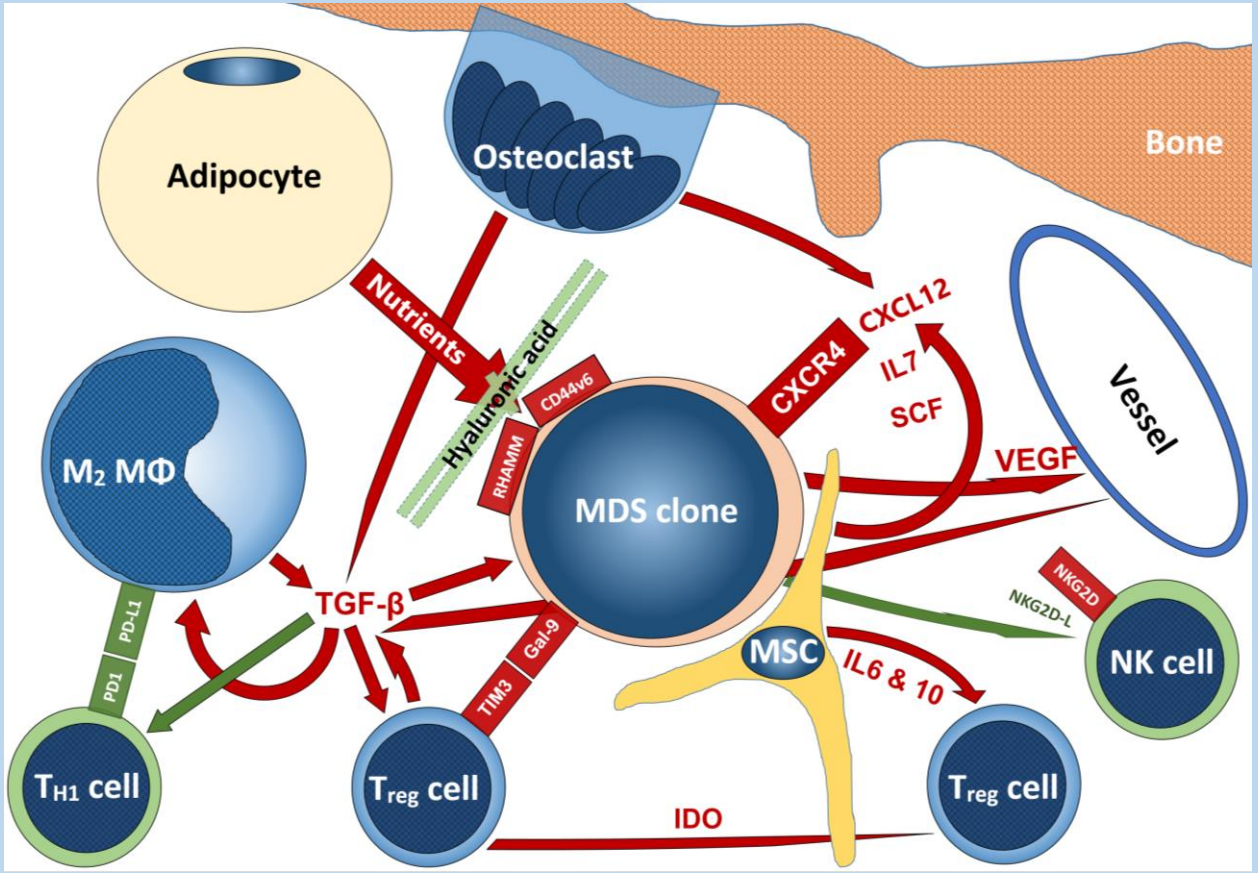
Horny et al. J Clin Pathol 2003;56:575
Magalhães et al. Leuk Res 2002;26:525
Smith et al. AJCP 1994;102:447
Cervantes et al. Br J Haematol 1988;70:279

BM T-cells in MDS



Trowbridge & Starczynowski J Exp Med 2021;218: e20201544

T-cells & immune pathways in MDS



Impaired distribution of lymphocytes among MDS compared to normal subjects.

Lymphocyte category	Low risk MDS	High risk MDS
B lymphocytes	↓	↓
Cytotoxic T lymphocytes CD8+	↑	↓
Treg	N-↓	↑
T lymphocytesTh17	↑	↓
T lymphocytes γδ	↓	↓
NK cells	↑	↓

↑: No. of cells increased; N: Normal range; ↓: No. of cells decreased.

Braun & Fenaux Best Pract Res Clin Haematol 2013;26:32
Modified from Menter & Tzankov Front Immunol 2022; 13:811144

BM “failure” in some* MDS to a part T cell-mediated / responsive to immunosuppression

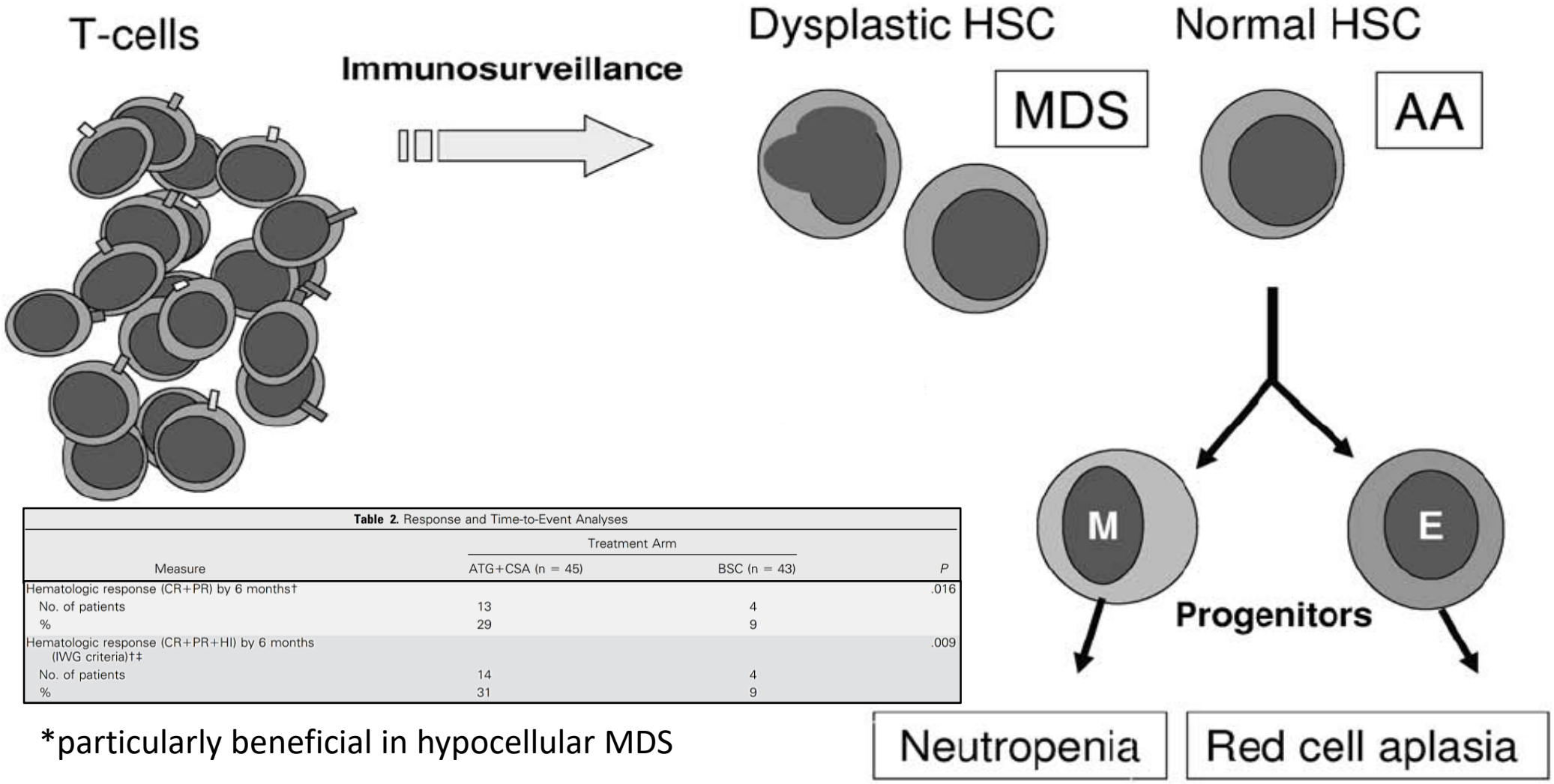


Table 2. Response and Time-to-Event Analyses

Measure	Treatment Arm: ATG+CSA (n = 45)	Treatment Arm: BSC (n = 43)	*P*
Hematologic response (CR+PR) by 6 months†			.016
No. of patients	13	4	
%	29	9	
Hematologic response (CR+PR+HI) by 6 months (IWG criteria)†‡			.009
No. of patients	14	4	
%	31	9	

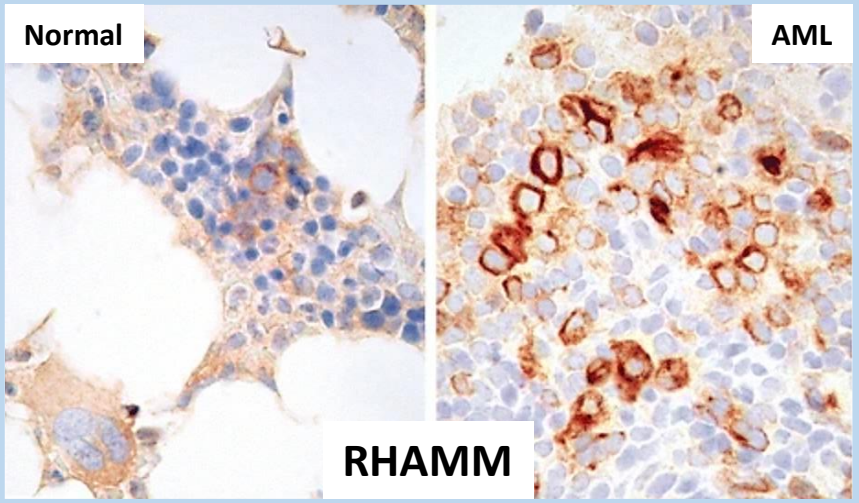
*particularly beneficial in hypocellular MDS

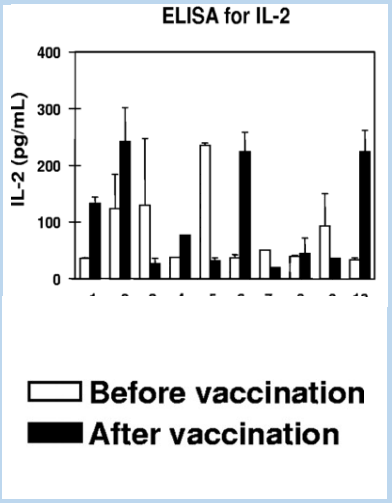
Maciejewski et al. Folia Histochem Cytobiol 2007;45:5
Passweg et al. 2011; J Clin Oncol;29:303

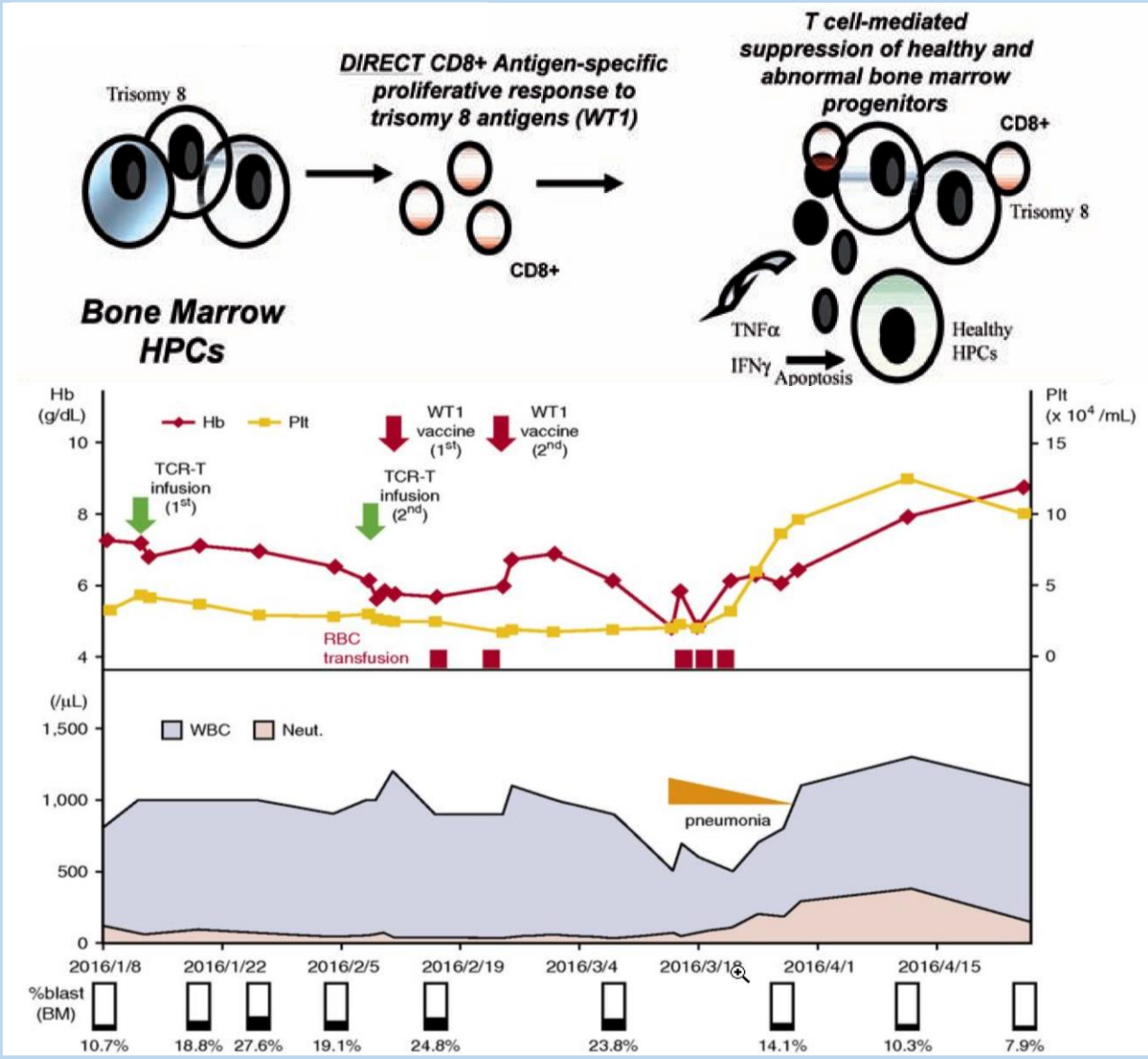
T cell-mediated “check but not mate” in MDS

- Clonally expanded CD8+ T-cells recognize aneuploid or “neoantigen”-expressing hematopoietic progenitor cells in MDS
  - WT1
    - WT1-specific TCR-T cells have the capacity to mount an immune reaction to WT1
  - RHAMM
    - Overexpressed in MDS (AML) and immunogenic

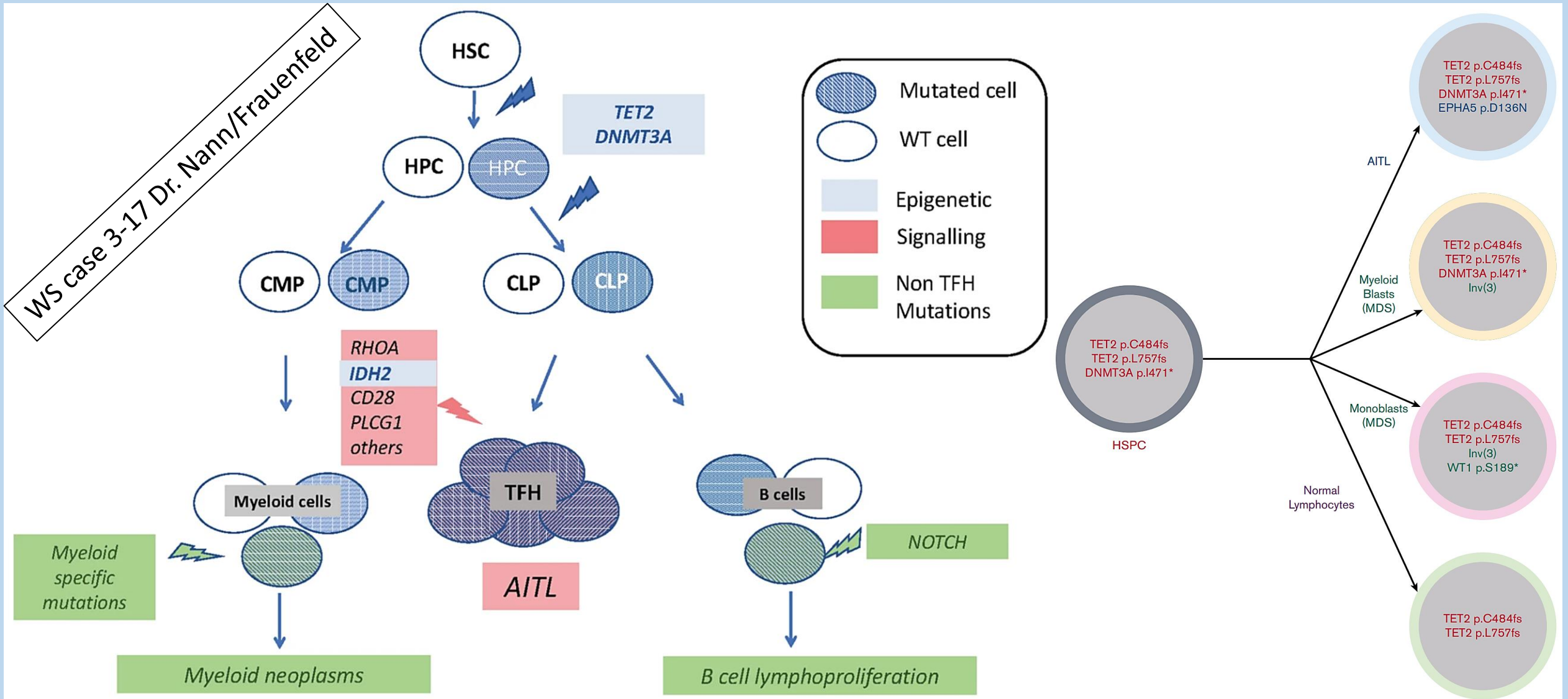
Sugimori et al. Hematol Rep 2010;2:e1
Tzankov et al. Ann Hematol 2011;90:901
Sloand et al. Blood 2011;117:2691
Tawara et al. Blood 2017;130:1985







T-cells as part of the MDS clone



Mhaidly et al. Oncogenesis 2020;9:73 & Lewis et al. Blood Adv 2020;4:2261

T-cells in the BM: roles, mimickers, caveats

- Important and poorly studied physiological roles of T-cells in the BM
- T-cell increase and CD8-skewing in viral and autoimmune diseases
  - exclude T-LGLL, HLH, TCL with HLH
- T-cell increase and CD4-skewing in adverse drug reactions
- T-cells attack, mask, accompany or are part of neoplastic diseases

Thank you!

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