CORSO EDUCAZIONALE

GRUPPO LINFOMI IN PAZIENTI CON IMMUNODEFICIT

Milano, Best Western Hotel Madison
29 maggio 2026

L’infezione cronica da EBV (CAEBV): inquadramento diagnostico-terapeutico

Federico Erbella
IRCCS Ospedale San Raffaele, Milano

Disclosures of Federico Erbella

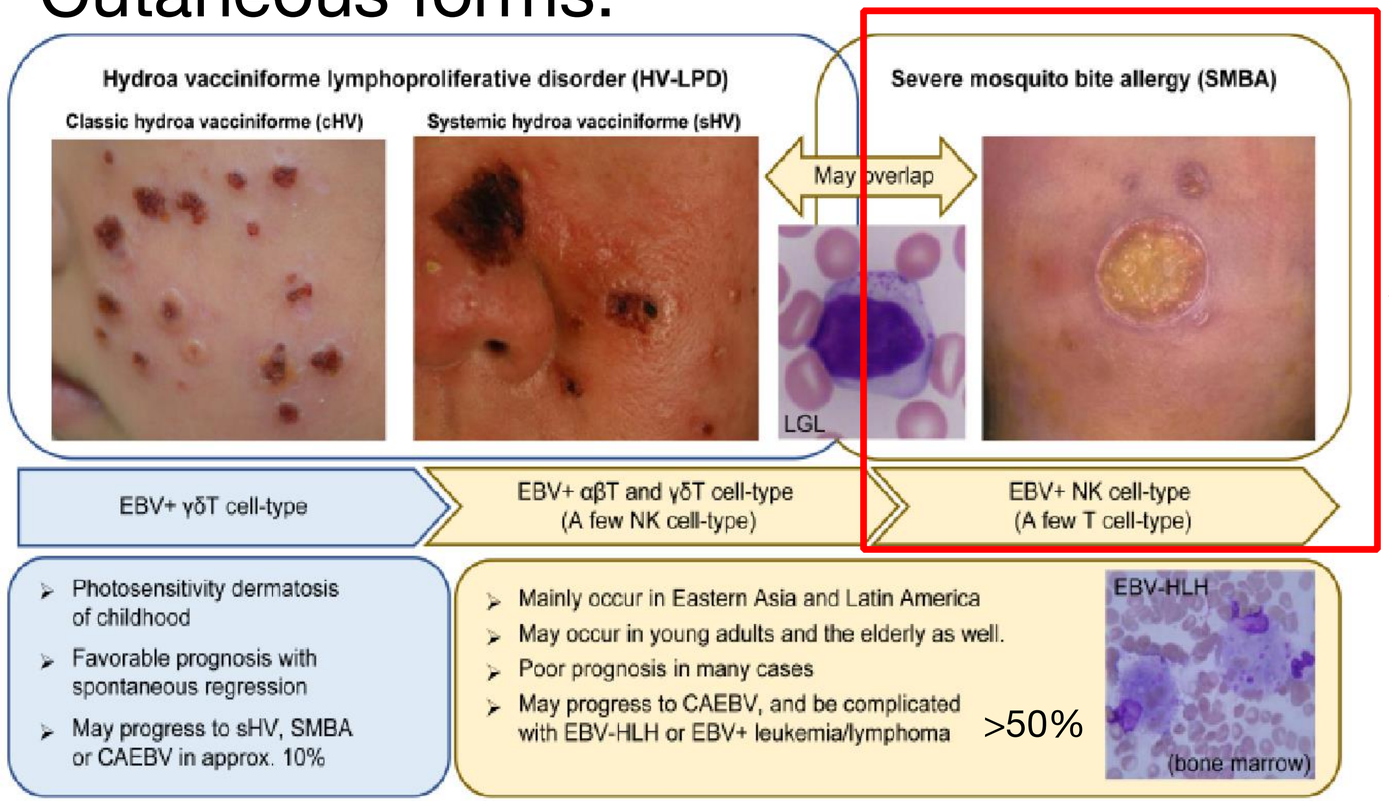
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AbbVie	**x**						**x**
Takeda						**x**	
Roche	**x**						**x**
Janssen	**x**						**x**
Astrazeneca						**x**	
Kite							**x**

Current definitions:

EBV-associated T and NK cell LPD WHO 2017	EBV-associated T and NK cell LPD 2022 international consensus classification
EBV+ T and NK cell LPD in childhood	EBV+ T and NK cell LPD in childhood
• Chronic active EBV infection -Cutaneous form	
Hydroa vacciniforme-like LPD	• Hydroa vacciniforme LPD ▪ *Classic form:* indolent, self-limited, more common in whites ▪ *Systemic form:* mild to severe disease, systemic symptoms (fever, lymphadenopathy, liver involvement), more common in Asia and Latin America. Treatment similar to CAEBV disease
Severe mosquito bite allergy	• Severe mosquito bite allergy
-Chronic active EBV infection, systemic form	• Chronic active EBV disease ▪ Systemic disease ▪ Only of T and NK cell type ▪ B cell type is excluded
• Systemic EBV+ T cell lymphoma of childhood	• Systemic EBV+ T cell lymphoma of childhood
Extranodal NK/T cell lymphoma, nasal type	Extranodal NK/T cell lymphoma, nasal type ▪ New genetic findings ▪ Intravascular EBV+ NK cell lymphoma might be a related disease
Aggressive NK cell leukemia	Aggressive NK cell leukemia ▪ Rare cases of EBV-negative are recognized, most common in non-Asians
Primary EBV+ nodal T and NK cell lymphoma, variant of PTCL, NOS	*Primary EBV+ nodal T/NK cell lymphoma* ▪ More common in elderly and/or immunodeficient patients ▪ Lack nasal involvement ▪ Characteristic genetic findings

Quintanilla-Martinez L, et al. Virchows Archiv, 2023

Cutaneous forms:



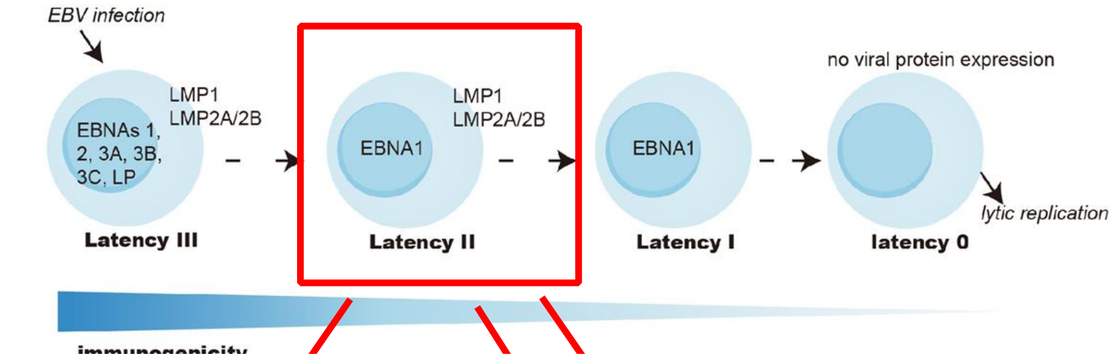
Classic:
->white
-Localized papulo-vesicular eruptions on sun-exposed skin and no systemic symptoms
-Increased recurrence in spring and summer
-Spontaneous remission during adolescence and clearing after photoprotection
-Rarely progressive to systemic disease

Systemic:
->Asians and Hispanics
-Skin lesion in sun-exposed and non-exposed areas, and edema of face and lips
-Fever and organ involvement

Erythema, bullae, ulcers, and scarring in the sites of mosquito bites and vaccine injection, accompanied with fever and general malaise (moderate and severe form)
EBV+NK LGL > 30% on PB
High risk of progression to HLH or lymphoma

Tokura Y, et al., J Am Acad Dermatol, 2001; Hirai Y, et al. J Dermatol, 2023; Yamada et al., Allergology Int, 2021

Systemic CAEBV: pathogenesis

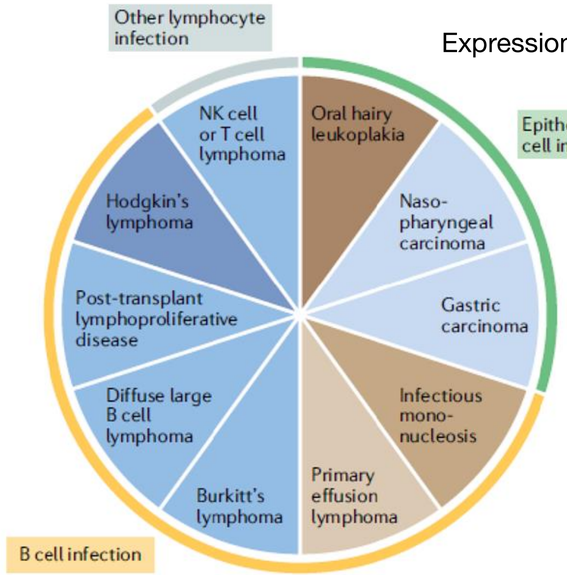


PTLD and HIV+ LPD | NK/T cell lymphomas/HL/DLBCL | Burkitt lymphoma | Healthy carriers

NF-κB, JAK/STAT, and PI3K-AKT-mTOR pathways activation

MAPK and WNT/β-catenin signaling

Expression of EBV lytic genes (BZLF1, BRLF1)



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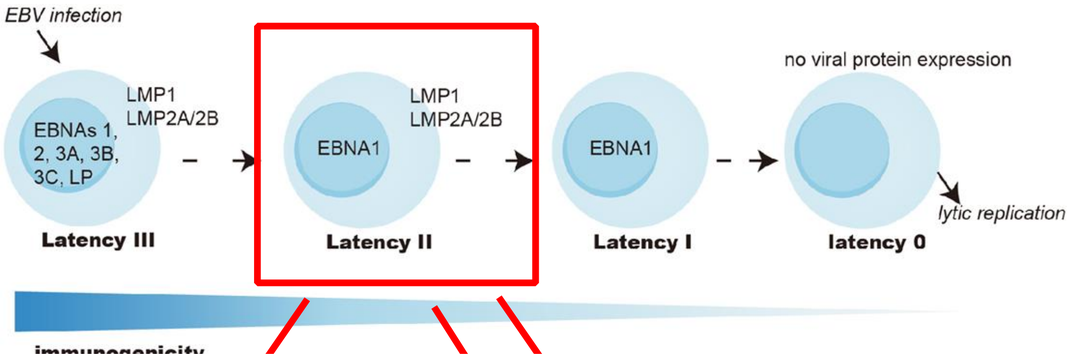

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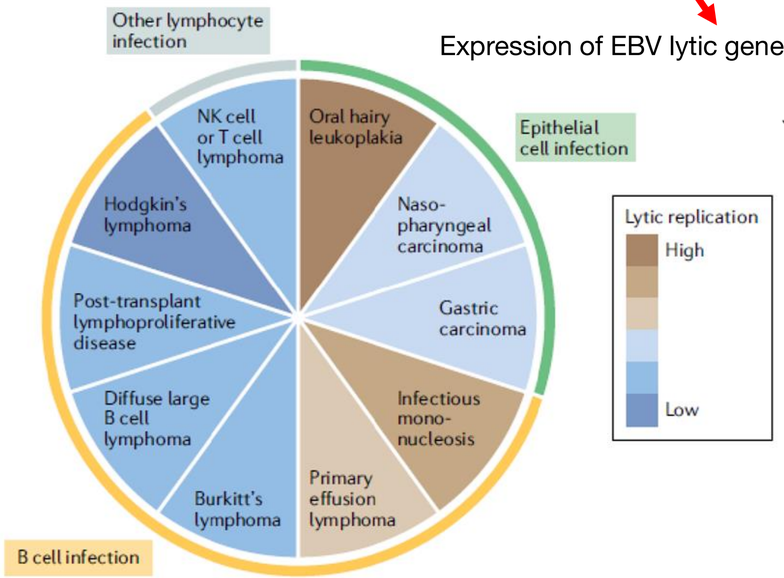
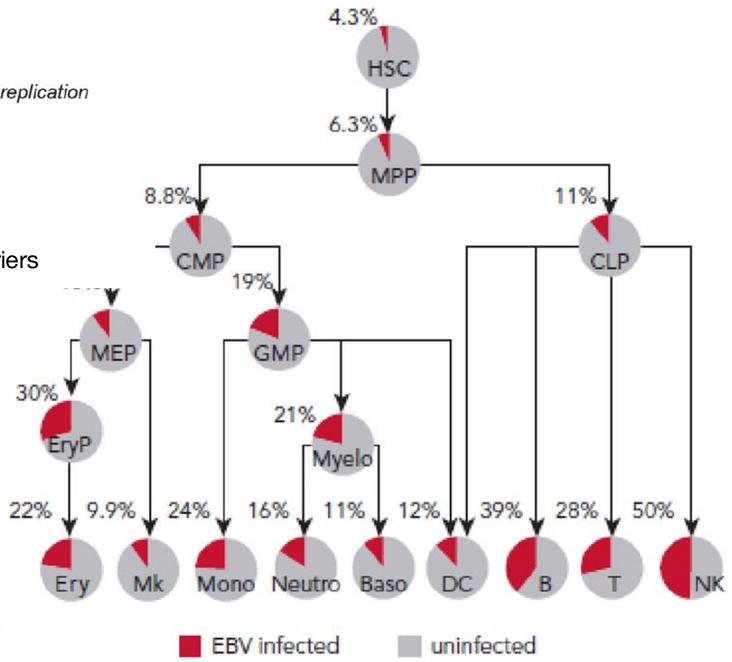
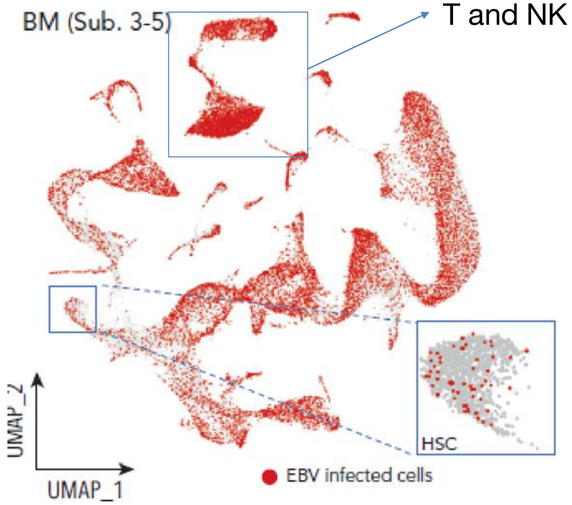


EBV infection of HSC or lymphoid progenitor cell with higher differentiation rate





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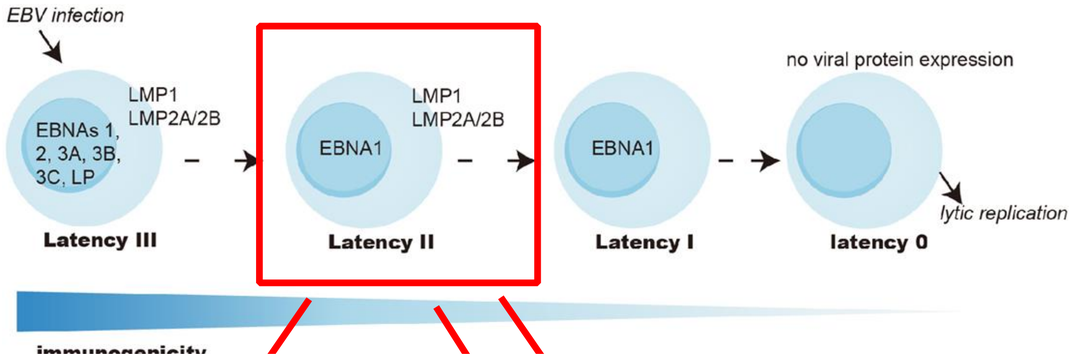

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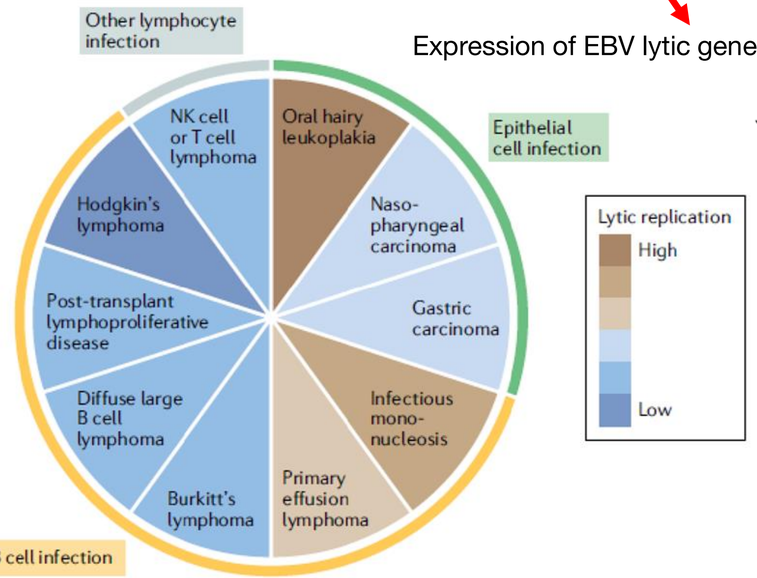

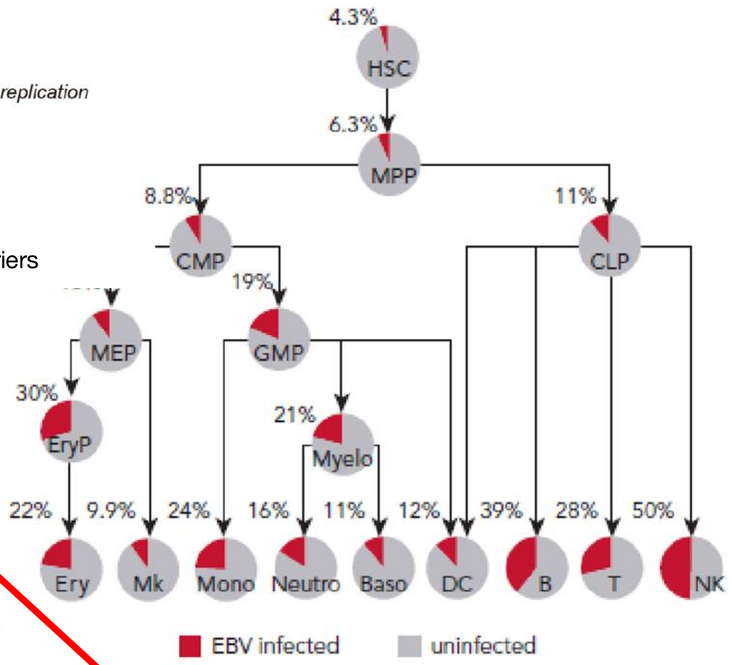

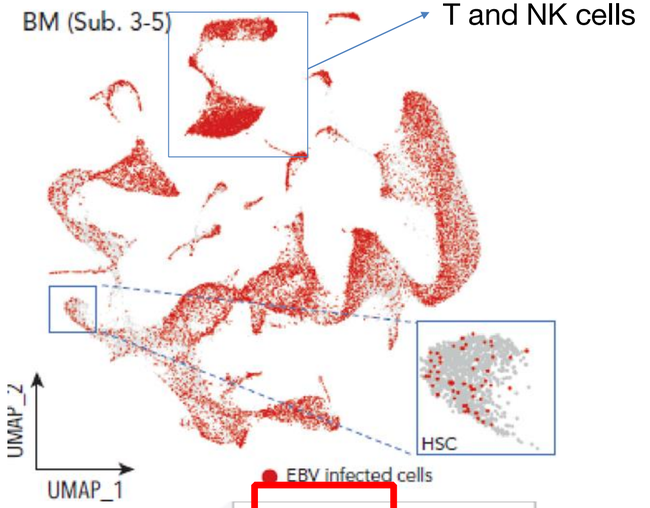

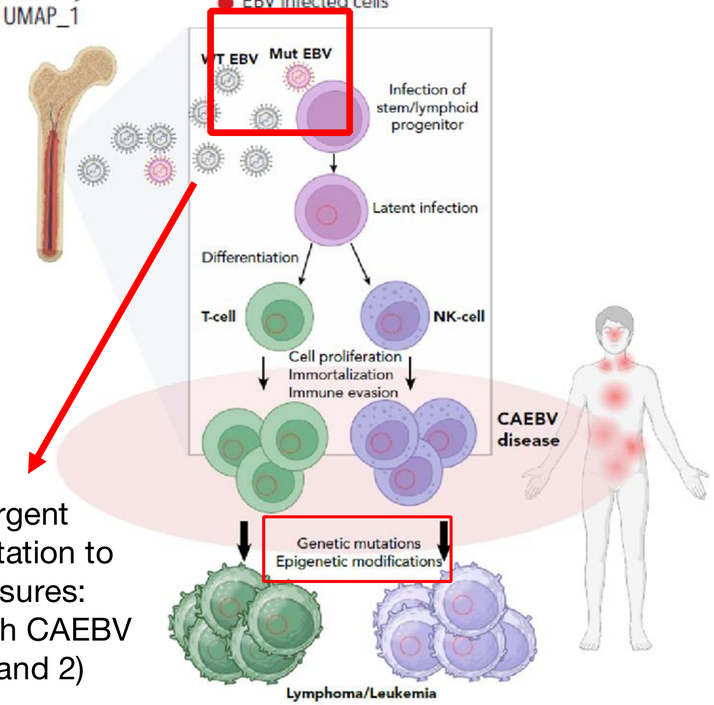

geographical variation of convergent mutations in EBV genome as adaptation to population-specific immune pressures:
↑ ↑ deletions in genomes of pts with CAEBV (e.g. BART microRNA clusters 1 and 2)

Münz C, Nature, 2019; Thiri Khine H, et al. Blood, 2021; Wang J, et al. Blood, 2024; Kimura H and Cohen JI, Blood, 2026

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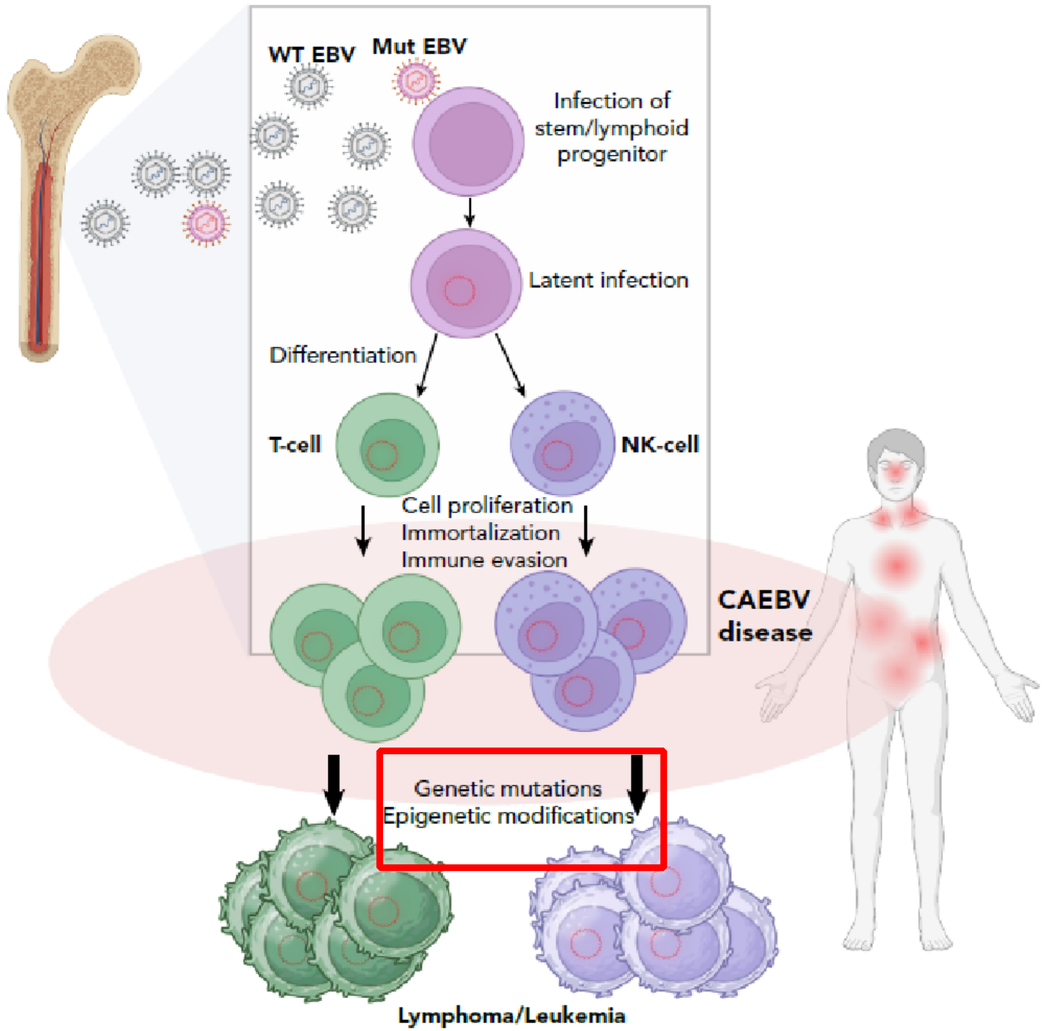

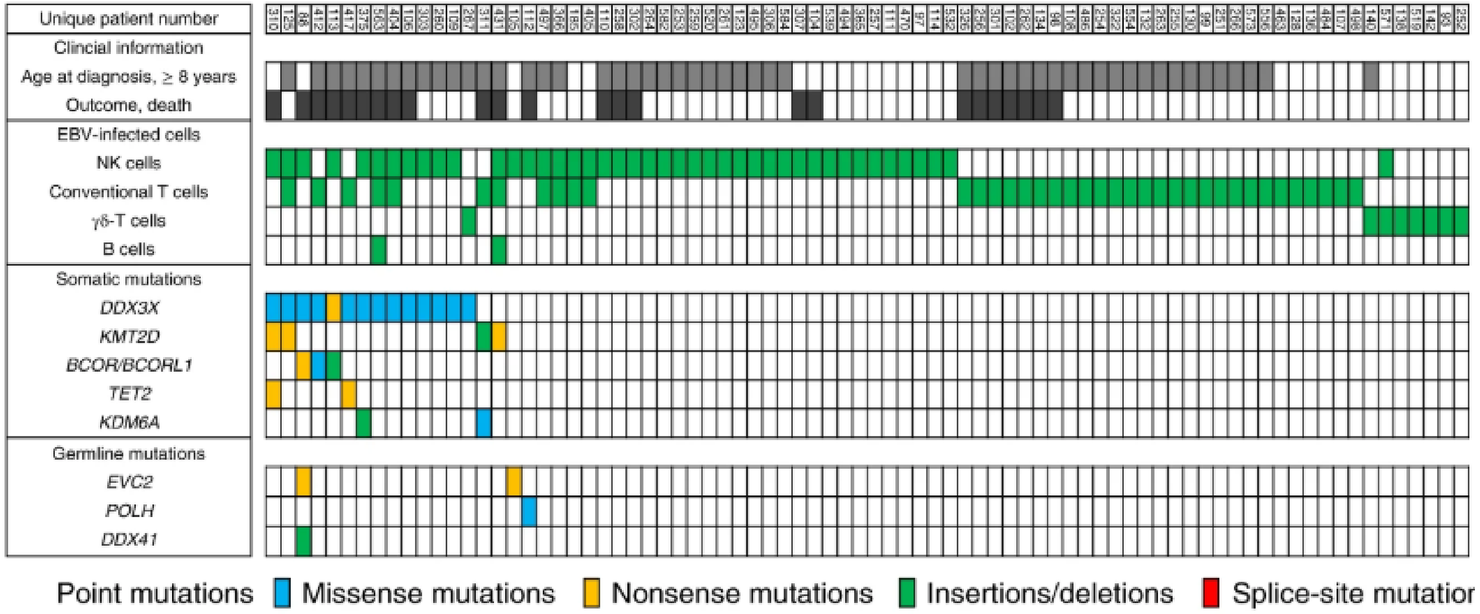

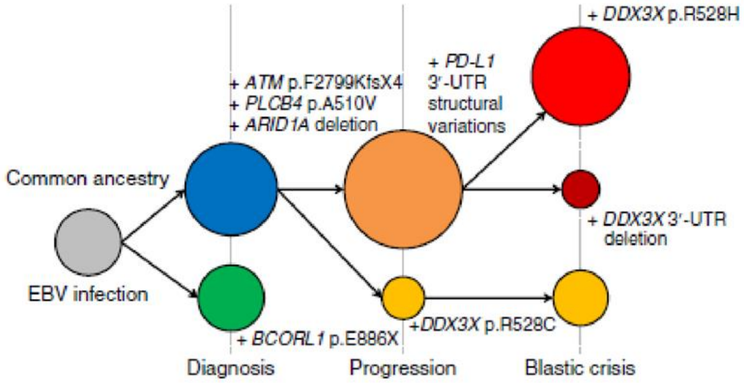

DDX3X mut in 87.5% (14/17) of pts carrying somatic mutations (29%)

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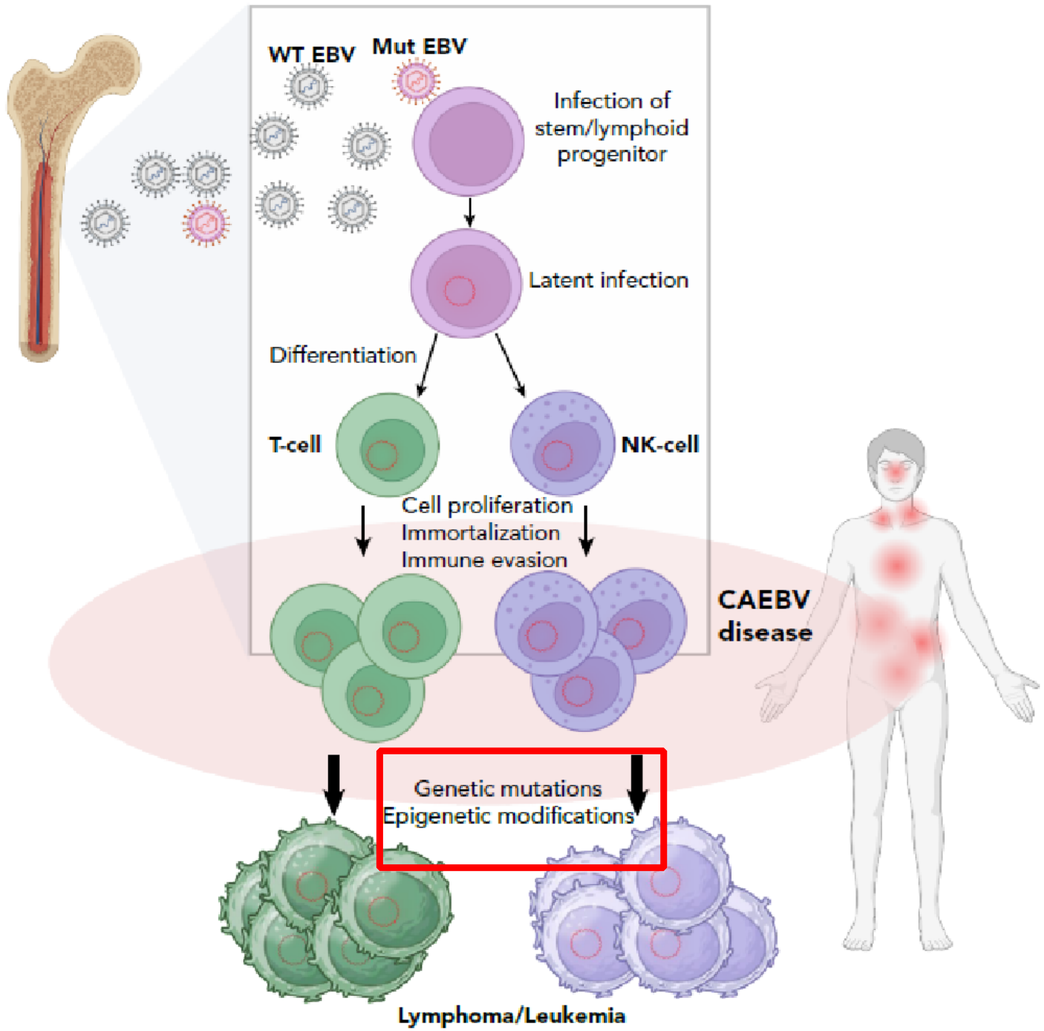

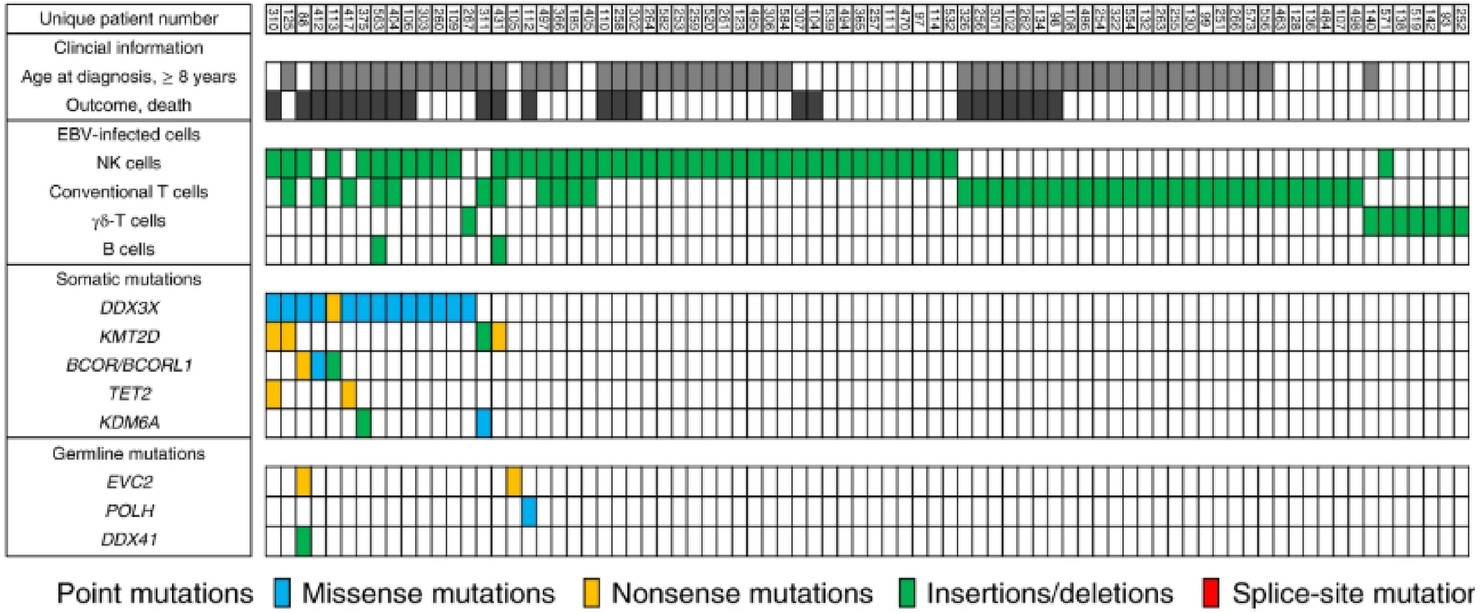

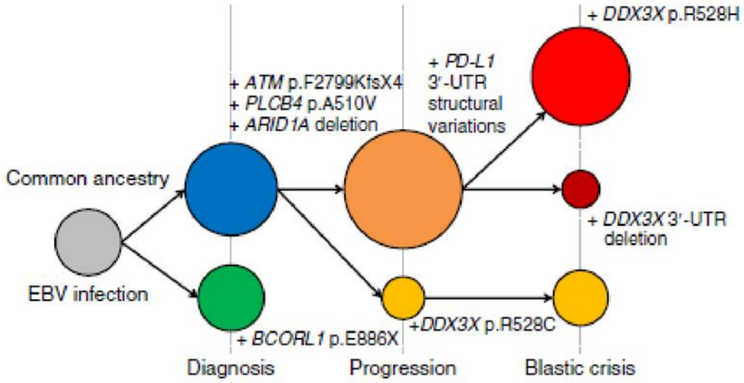

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Neoplastic disease?

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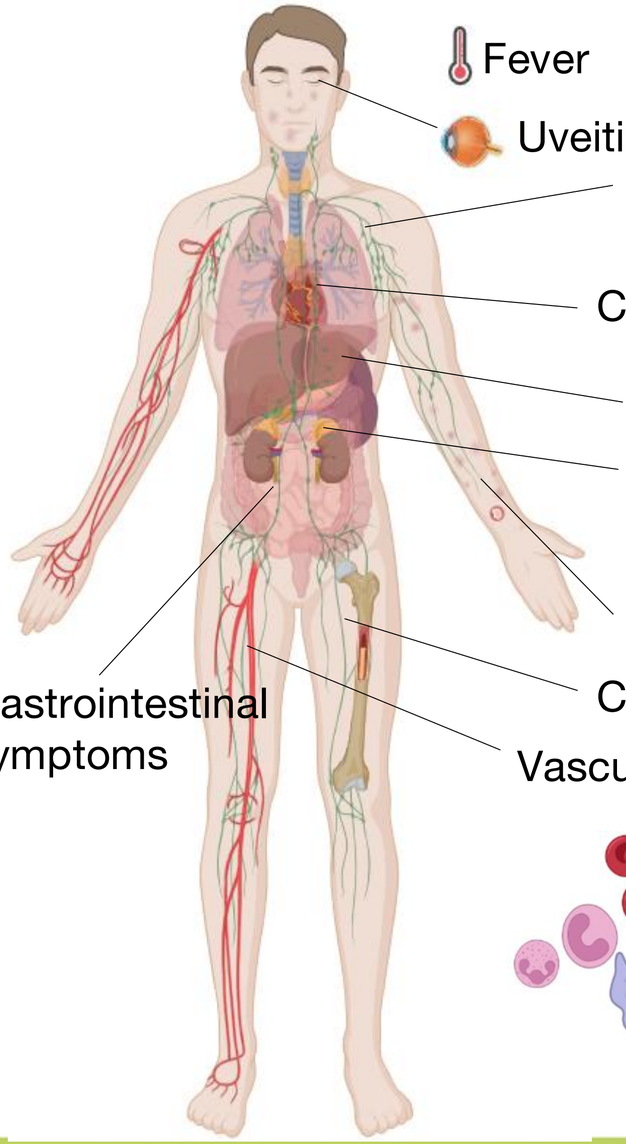
Quintanilla-Martinez L, et al. Virchows Archiv, 2023

Systemic CAEBV: clinical presentation and diagnosis



	N = 100, n (%)
Male/female, n	53/47
Age, range (median), y	1-78 (21)
EBV-infected cell type	
CD4	25 (25)
CD8	13 (13)
CD56	28 (28)
γδT	3 (3)
CD56⁻ NK	2 (2)
Others	26 (26)
NA	5 (5)*
Clinical presentation	
Fever	85 (85)
Hepatosplenomegaly	64 (70)
Lymphadenopathy	48 (53)
Cardiac dysfunction	8 (9)
Aneurysm	8 (9)
Gastrointestinal symptom	7 (8)
Neurological symptoms	7 (8)
Vasculitis	6 (7)
Uveitis	4 (4)
HLH	24 (26)
SMB	25 (25)
HV-like eruption	9 (9)
Neutropenia (<1000/μL)	14 (16)
Anemia (<9 g/dL)	12 (14)
Plts <10 × 10^4/μL	27 (30)
High ALT (>128 U/L)	27 (31)
High sIL-2R (>2400 U/mL)	17 (27)

Characteristics	Outside Asia (N = 57)	Japan (N = 100)
Age, y	14 (mean)	21 (median)
Race, %		
Hispanic or Asian	49	100
White	39	0
Native American	12	0
Female sex, %	56	47
EBV-infected cell type, %		
T cell	65	53
NK cell	18	34
NK and T cell	14	13
EBV load in whole blood	5.7 million copies/mL	50 000 copies/μg DNA
Anemia, %	63	14
Thrombocytopenia, %	63	30
HLH, %	58	26
NK- or T-cell lymphoma, %	40	22
Hydroa vacciniforme LPD, %	3.5	9
Vascular involvement, %	3.5	16
Survival rate, %	47 at 24 mo*	58 at 3 y

Elderly (>45y):
85% F (vs 75% M in childhood)
Mostly CD8+
No vascular/cardiac involvement
↑ **risk of lymphoma**

Yonese I, et al. Blood Adv, 2020; Davila Saldana BJ, et al., Blood Adv 2021; Kimura H and Cohen JI, Blood, 2026

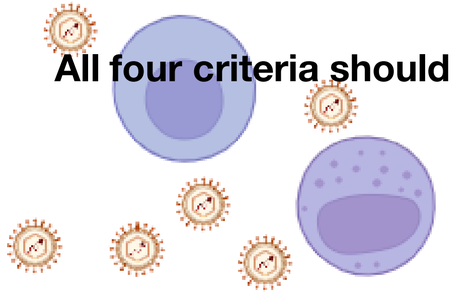
Systemic CAEBV: diagnostic criteria

Updated guidelines for chronic active Epstein–Barr virus disease

Jun-ichi Kawada[1] · Yoshinori Ito[2] · Koichi Ohshima[3] · Masaki Yamada[4] · Shinsuke Kataoka[1] · Hideki Muramatsu[1] · Akihisa Sawada[5] · Taizo Wada[6] · Ken-ichi Imadome[4] · Ayako Arai[7] · Keiji Iwatsuki[8] · Shouichi Ohga[9] · Hiroshi Kimura[10] · The Committee for Guidelines for the Management of Chronic Active EBV Disease, Related Disorders (the MHLW Research Team in Japan)

1. Persistent or recurrent infectious mononucleosis-like symptoms for more than 3 months;
2. Detection of an increased number of EBV genomes in peripheral blood and/or affected tissues;
3. Detection of EBV-infected T or NK cells in peripheral blood and/or affected tissues;
4. Chronic illness that cannot be explained by other known disease processes at the time of diagnosis (immunodeficiencies, rheumatic diseases, lymphoma/ leukemia).

All four criteria should be met before CAEBV can be diagnosed



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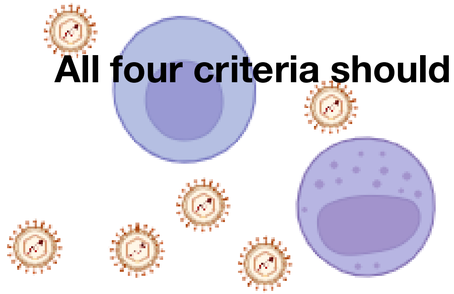

- >10,000 IU/mL (4.0 log IU/mL, or >10^2.5 cp/μg DNA) of EBV DNA is detected in whole-blood samples using real-time PCR.
- EBER in situ hybridization for the detection of EBV-positive cells in tissues.

Kawada JI, et al. Int J of Hematology, 2023

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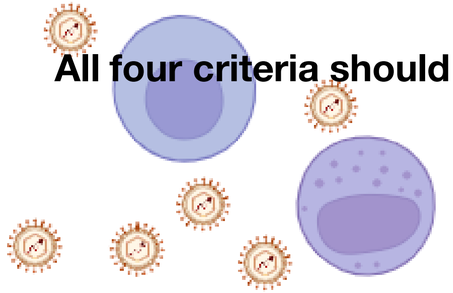

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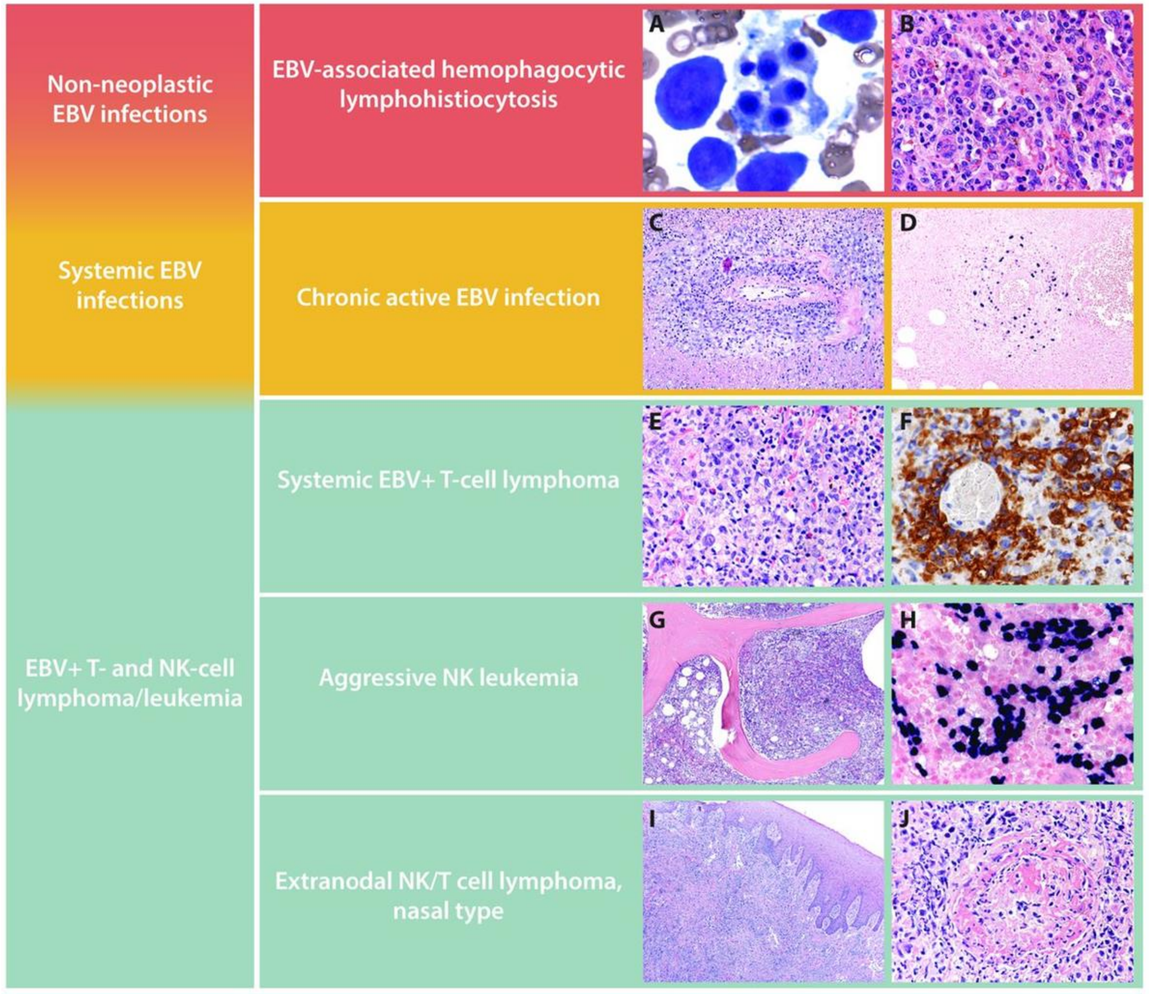
Differential diagnosis

Kawada JI, et al. Int J of Hematology, 2023

CAEBV-associated lymphoproliferative disorders: DD



Disease	Localization	Age	Infected cell lineage	Clonality	Clinical features	Notes
EBV-HLH	Systemic	All ages (primary: children; secondary: any age)	T (CD8 >> CD4) > NK	Polyclonal	Fever, cytopenia, hypercytokinemia; variable severity	May present as part of CAEBV disease, ANKL, or with primary infection
Systemic EBV-positive T-cell lymphoma of childhood	Systemic (multiorgan)	Children, young adults	T (CD8 >> CD4)	Monoclonal	Aggressive disease with a fulminant course resulting in multiorgan failure and death	Distinction from severe EBV-HLH is often difficult
ENKTL	Extranodal (nasal/upper aerodigestive tract)	Adults (40-70 y)	NK > T	Monoclonal	Extranodal mass (typically in nasal cavity) with necrosis and angioinvasion	May evolve from CAEBV disease or severe mosquito bite allergy
ANKL	Systemic (bone marrow, liver, and spleen)	Young to middle-aged adults	NK	Monoclonal	Leukemia-like symptoms and blood picture with a fulminant course	May evolve from CAEBV disease or severe mosquito bite allergy

Other EBV-associated LPD, secondary HLH **...**

Fernandez-Pol S, et al. Haematologica, 2018; Kimura H and Cohen JI, Blood, 2026

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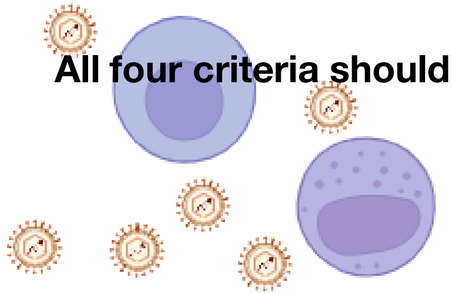

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Determination of the infected cell-type

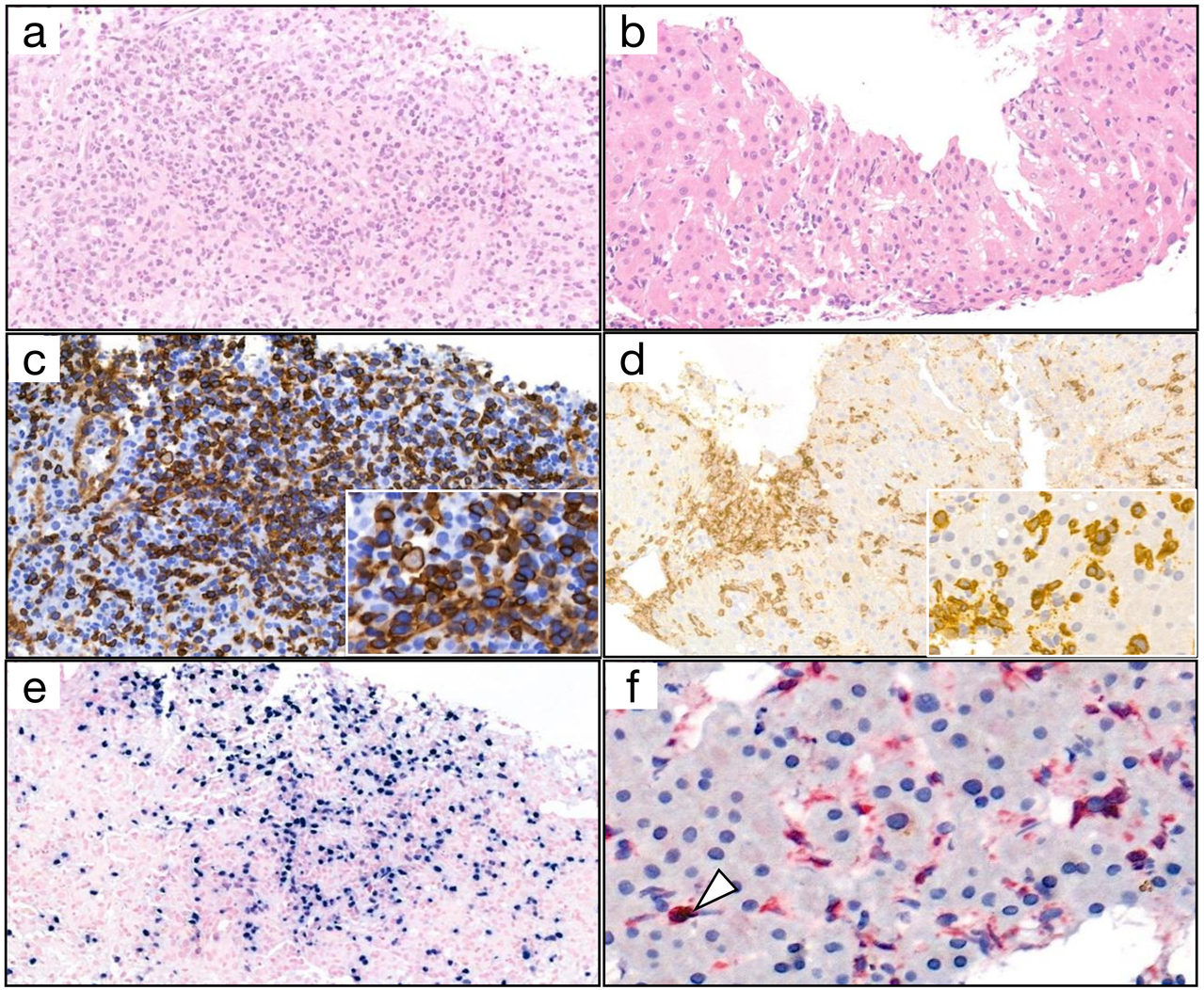
Kawada JI, et al. Int J of Hematology, 2023

Systemic CAEBV: determination of the infected cell-type

Pathology:

- few to moderate numbers of scattered EBER+ small T lymphocytes without atypia
- > CD3+,CD4+, TIA1 and granzyme B (<CD8+ or NK)
- HLH
- TCR clonality (70%)
- Double stainings with CD3/EBER and CD20/EBER

Limits: target tissue required, few infiltrating cells



Dojcinov S and Quintanilla-Martinez L, Am J Clin Pathol 2023; Erbella F,…Ponzoni M, Ferreri AJM, Blood ICT, 2026.

Systemic CAEBV: determination of the infected cell-type

EBVDNA by real-time PCR on B, T, and NK cells isolated from PBMCs by means of magnetic-activated cell sorting

Limits: frequent contamination of the T or NK cell or non–B cell fraction by either infected B cells or plasma EBV DNA

Flow-FISH assay: flow cytometry with antibody-based staining of surface markers in combination with EBERs:

1-surface staining (CD3, CD4,..)
2-intracellular staining with fluorochrome-conjugated EBER-FISH probe
3-flow cytometry

Limits: expensive and time-consuming (2-days experiment)

Fournier B, et al. J Exp Med, 2020.

Systemic CAEBV: determination of the infected cell-type

EBVDN… …m PBMCs by means of magn…

Limits: …cell fraction by either …

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Rapid identification and characterization of infected cells in blood during chronic active Epstein-Barr virus infection

Benjamin Fournier[1,2], David Boutboul[3], Julie Bruneau[2,4], Charline Miot[5], Cécile Boulanger[6], Marion Malphettes[3], Isabelle Pellier[5], Bertrand Dunogué[7], Benjamin Terrier[7], Felipe Suarez[8], Stéphane Blanche[9], Martin Castelle[9], Sarah Winter[9], Henri-Jacques Delecluse[10], Thierry Molina[2,4], Capucine Picard[1,2,11], Stephan Ehl[12], Despina Moshous[2,9], Lionel Galicier[3], Vincent Barlogis[13], Alain Fischer[2,9,14,15], Bénédicte Neven[2,9], and Sylvain Latour[1,2]

Highly sensitive detection of Epstein-Barr virus-infected cells by EBER flow FISH

Dan Tomomasa[1] · Kay Tanita[1,2] · Yuriko Hiruma[3] · Akihiro Hoshino[2,4] · Ko Kudo[5] · Shohei Azumi[6] · Mitsutaka Shiota[7] · Masayoshi Yamaoka[8] · Katsuhide Eguchi[9] · Masataka Ishimura[9] · Yuka Tanaka[10] · Keiji Iwatsuki[11] · Keisuke Okuno[12] · Asahito Hama[13] · Ken-Ichi Sakamoto[14] · Takashi Taga[14] · Kimitoshi Goto[15,16] · Haruka Ota[17] · Akihiro Ichiki[17] · Kaori Kanda[18] · Takako Miyamura[19] · Saori Endo[20] · Hidenori Ohnishi[20] · Yoji Sasahara[21] · Ayako Arai[22] · Benjamin Fornier[2,23] · Ken-Ichi Imadome[24] · Tomohiro Morio[1] · Sylvain Latour[2] · Hirokazu Kanegane[4]

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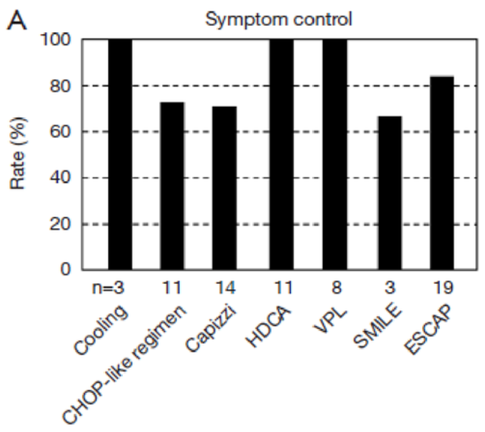
Characterizing EBV-associated lymphoproliferative diseases and the role of myeloid-derived suppressor cells

Paul J. Collins,[1,2] Christopher P. Fox,[3,4] Lindsay George,[5] Hayden Pearce,[1,2] Gordon Ryan,[1] Carmela De Santo,[1,2] Francis Mussai,[1,2] David Lewis,[6] Heather Long,[1,2] and Claire Shannon-Lowe[1,2]

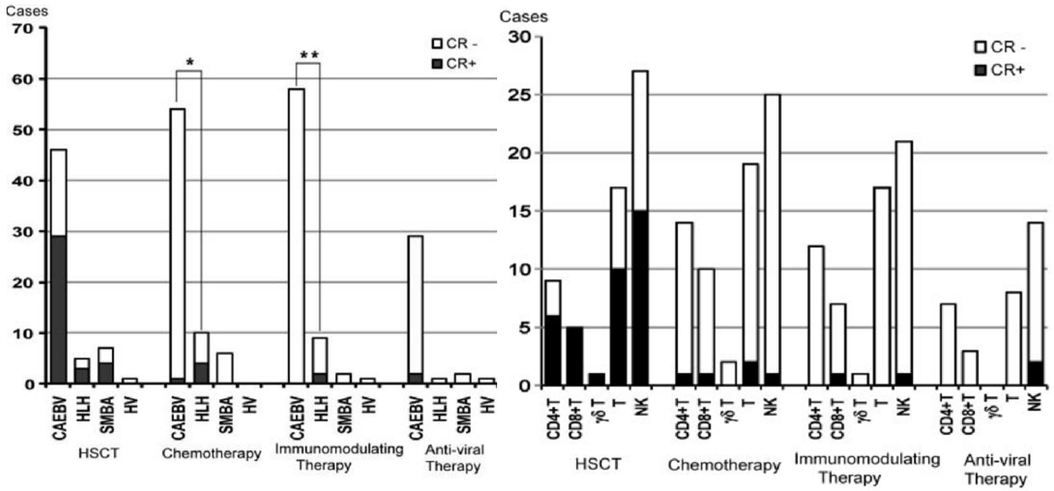
[1]Institute for Immunology and Immunotherapy, [2]Cancer Research UK Birmingham Centre, The University of Birmingham, Birmingham, United Kingdom; [3]Department of Clinical Haematology, City Campus, Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom; [4]Divison of Cancer and Stem Cells, School of Medicine, University of Nottingham, Nottingham, United Kingdom; [5]Department of Haematology, Queen Elizabeth Hospital NHS Trust, Birmingham, United Kingdom; and [6]Plymouth Hospitals NHS Trust, Derriford Hospital, Plymouth, United Kingdom

Fournier B, et al. J Exp Med, 2020.

Systemic CAEBV: treatment



Koyama M, et al. Hematol Oncology, 2004



Kimura H, et al. Blood, 2012

Regimen	n	Response, n (%)						
		Overall	PR	CR	vCR	PD	SD	NA
Cooling	35	20 (57)	14 (40)	6 (17)	0 (0)	8 (23)	3 (9)	4 (11)
Steroid+CsA	10	3 (30)	1 (10)	2 (20)	0 (0)	3 (30)	3 (30)	1 (10)
Steroid	8	2 (25)	2 (25)	0 (0)	0 (0)	2 (25)	3 (38)	1 (13)
Steroid+ETP	6	3 (50)	3 (50)	0 (0)	0 (0)	1 (17)	2 (33)	0 (0)
CHOP	23	9 (39)	6 (26)	3 (13)	0 (0)	4 (17)	7 (30)	3 (13)
ESCAP	7	1 (14)	0 (0)	1 (14)	0 (0)	1 (14)	4 (57)	1 (14)
DeVIC	10	3 (30)	2 (20)	1 (10)	0 (0)	3 (30)	4 (40)	0 (0)
L-Asp	5	3 (60)	3 (60)	0 (0)	0 (0)	1 (20)	1 (20)	0 (0)

Yonese I, et al, Blood Adv, 2020

Koyama M, Hematol Oncology, 2004; Kawa K, et al. BMT, 2011; Kimura H, et al. Blood, 2012; Suma S, et al. Rinsho Ketsueki, 2019; Yonese I, et al, Blood Adv, 2020; Sawada A, et al. Ann Lymphoma, 2021

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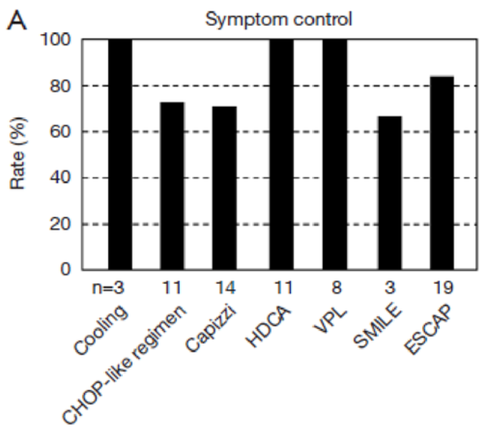

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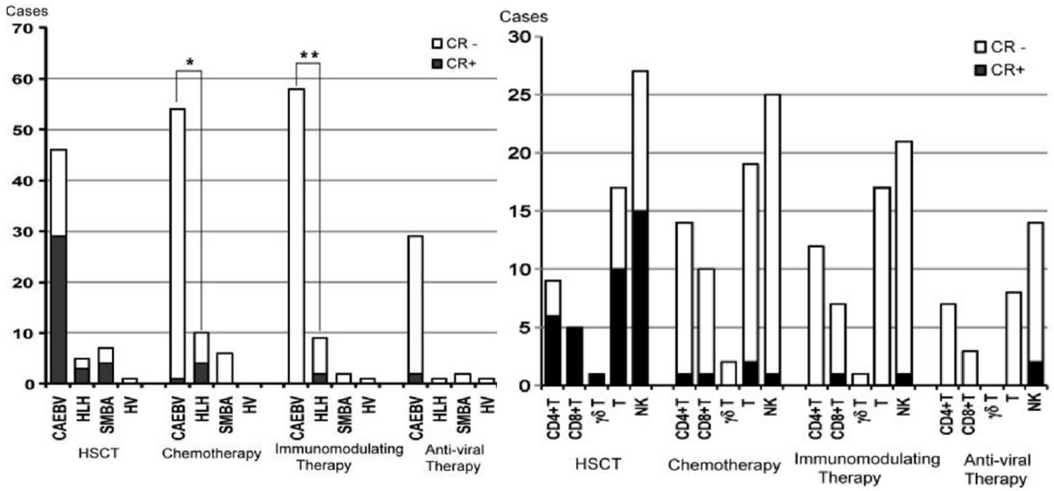

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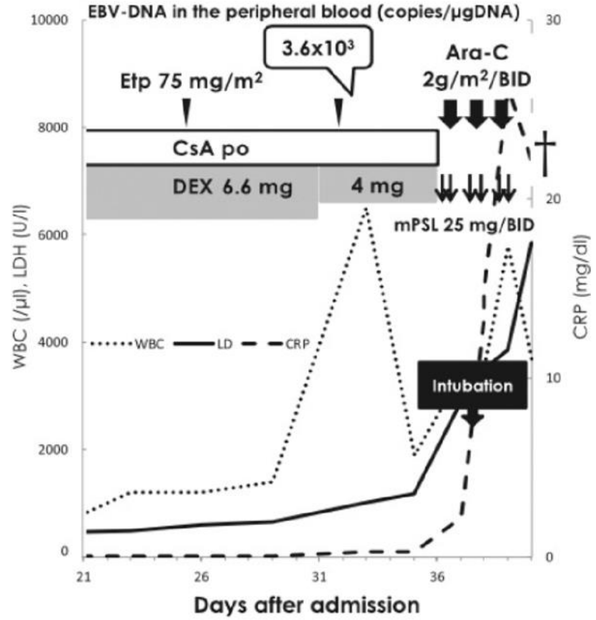

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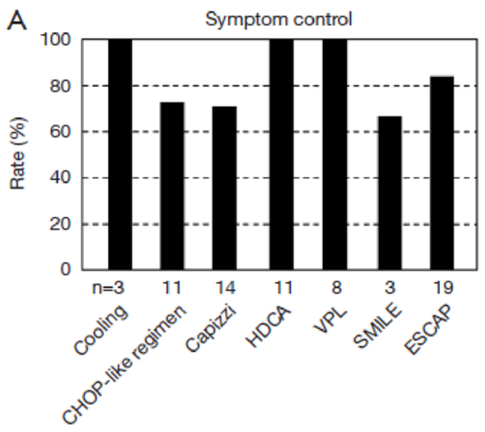

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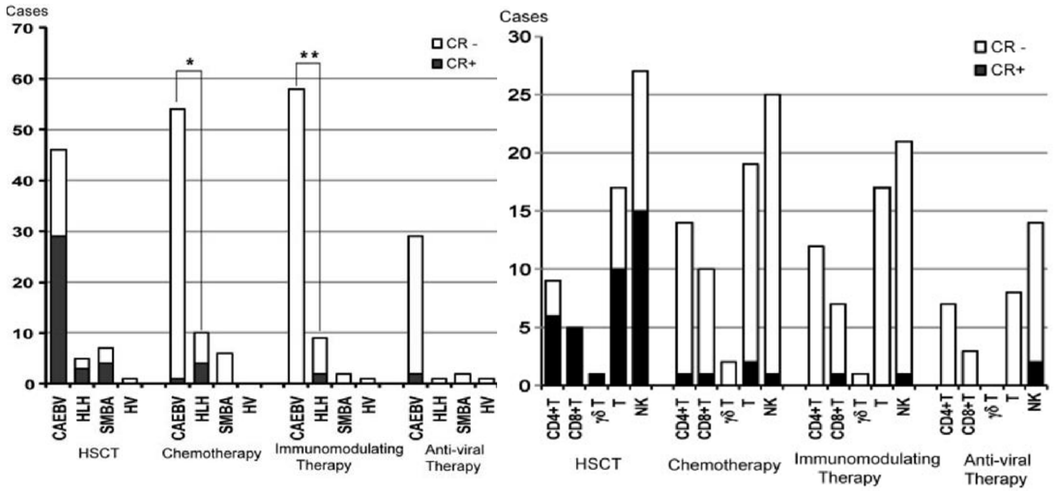

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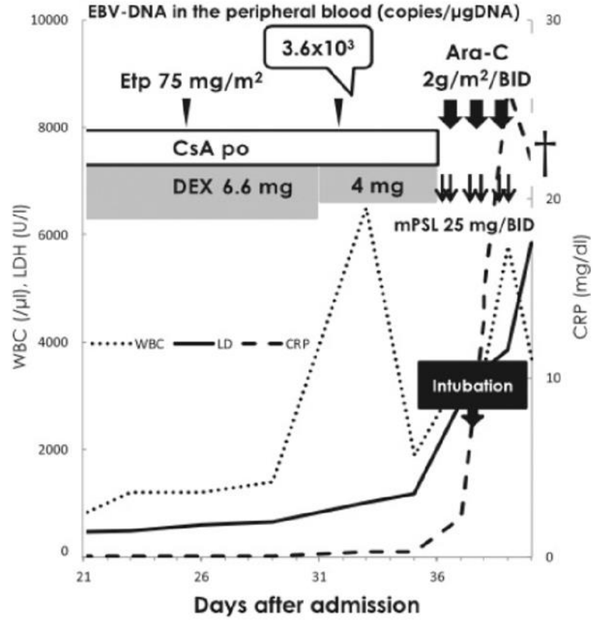

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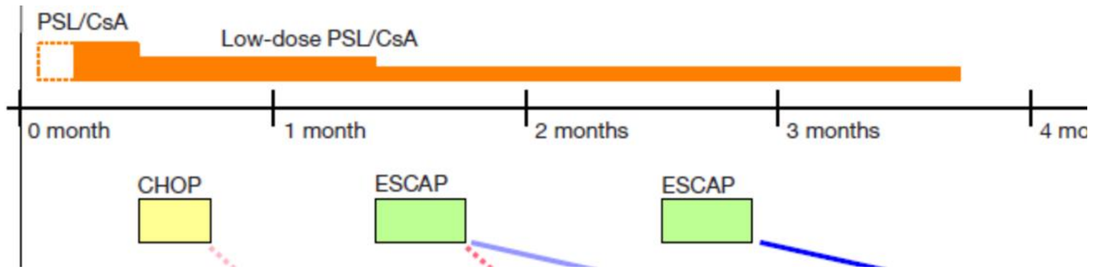

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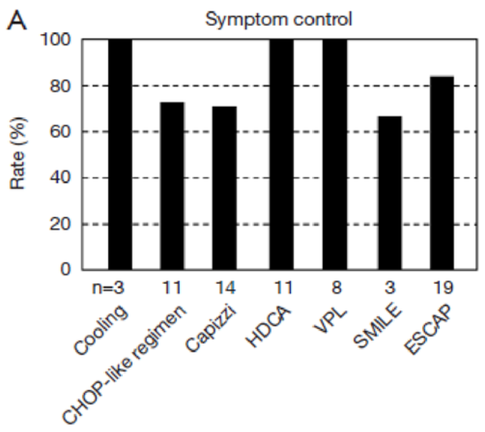

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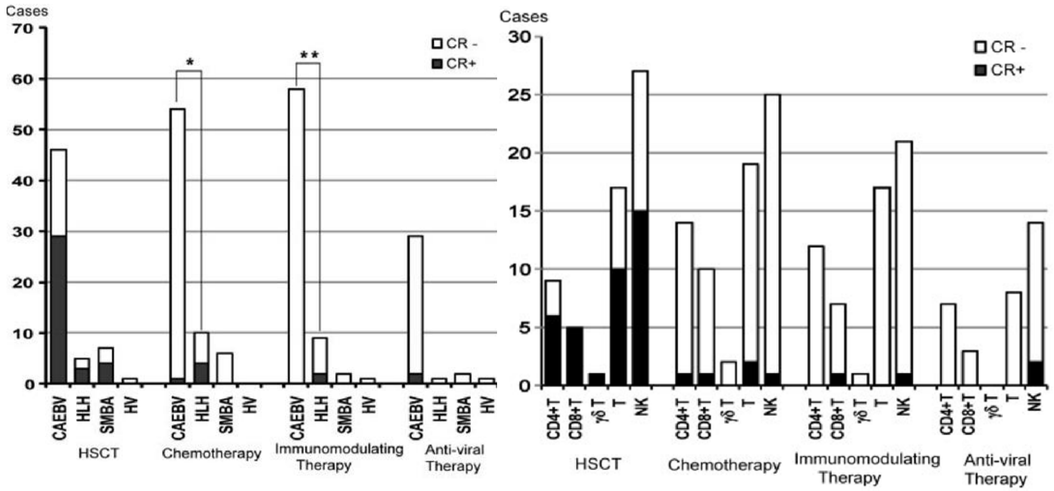

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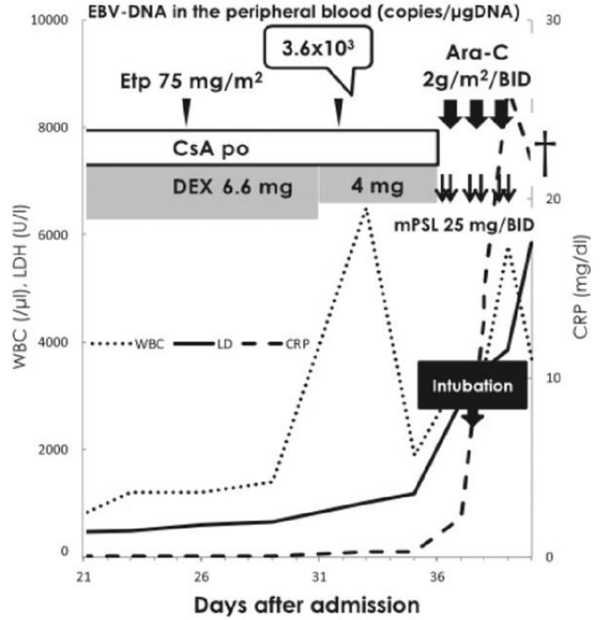
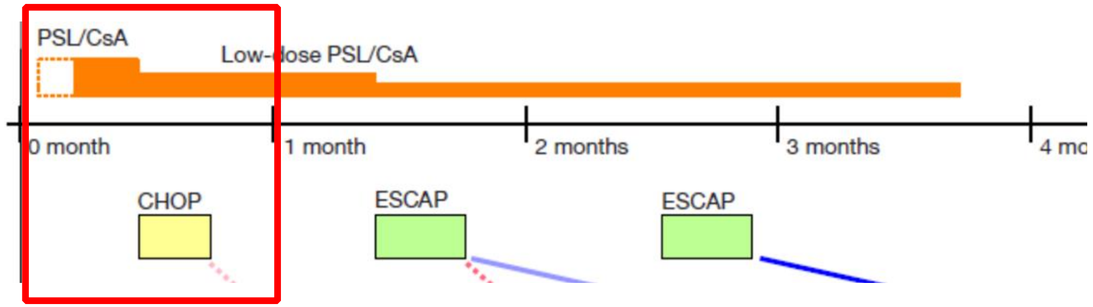


53 yo M with T-CAEBV

Step 1: Cooling

PSL	0.5–2 mg/kg/d po t.i.d. or b.i.d. (or div)
CsA	3 mg/kg/d po bis in die (or civ)
Etp	150 mg/m² weekly div

- Suppression of EBV-infected T/NK cells and hypercytokinemia
- Gradual debulking
- CsA: P-gp inhibition→anthracyclines sensibilization
- Overt HLH→ HLH-94/2004 protocol



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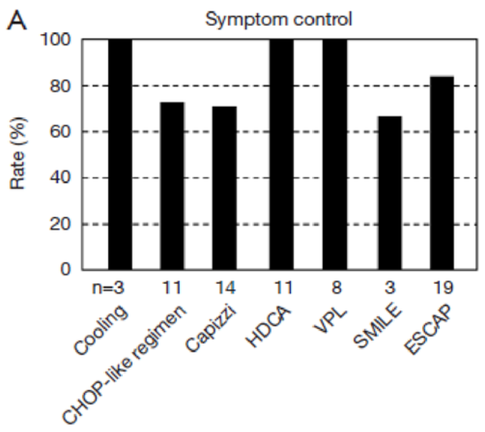

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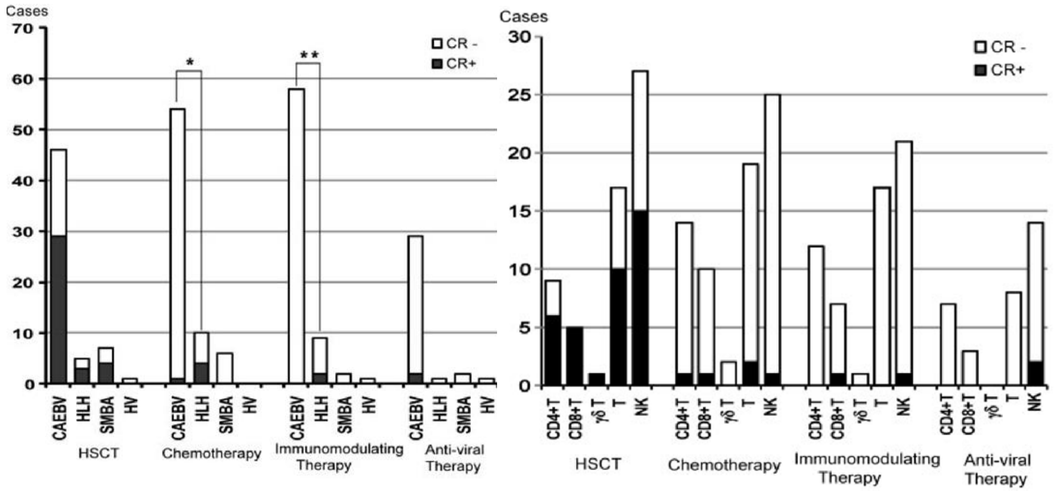

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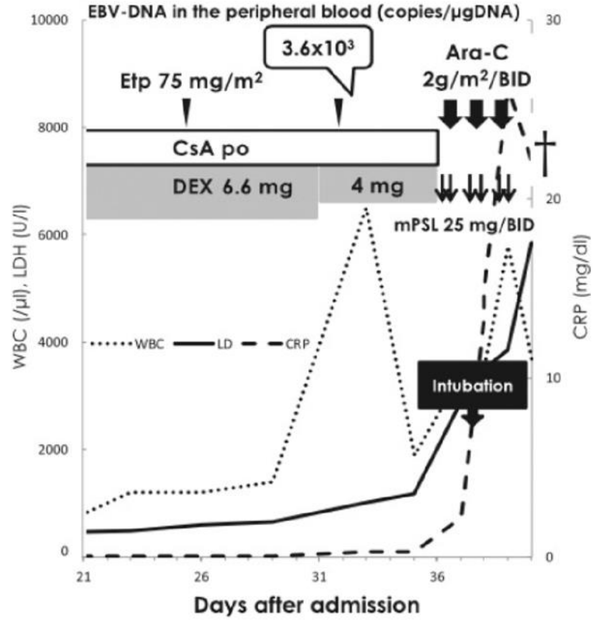

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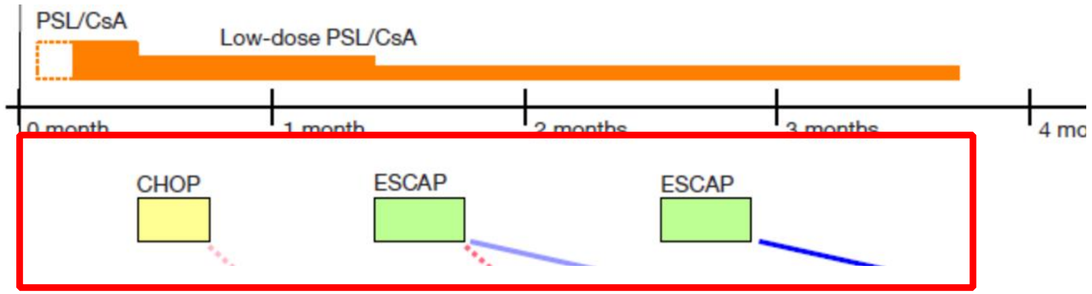
- Gradual debulking
- CsA: P-gp inhibition anthracyclines sensibilization
- Overt HLH HLH-94/2004 protocol

Step 2: cytoreduction chemotherapy with gradually increasing intensity



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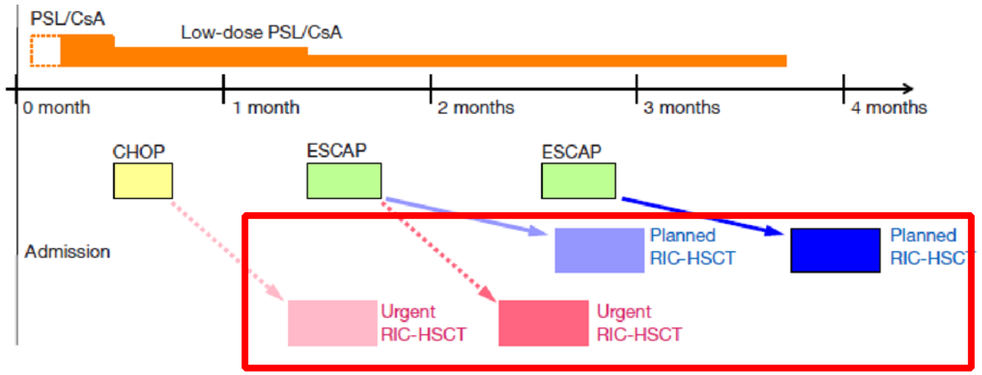
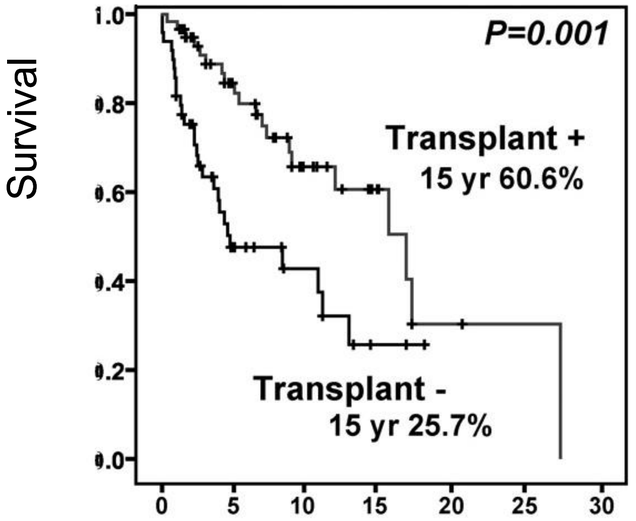
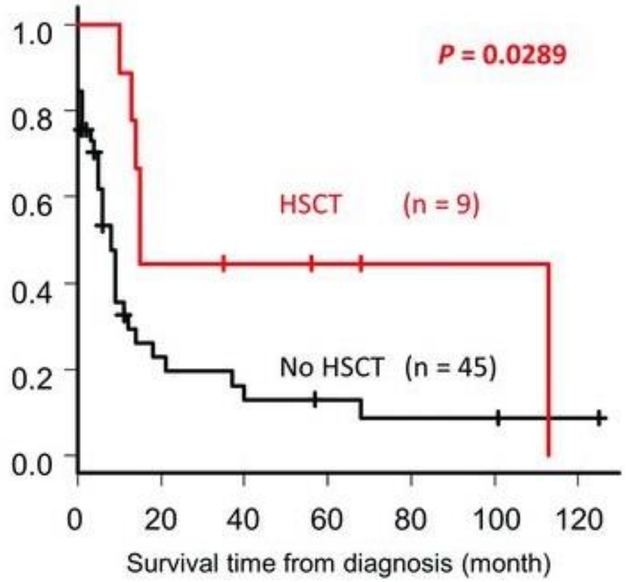
Systemic CAEBV: allogeneic transplant (step 3)





Kimura, 2012:
Children and AYA (108 cases)



Kawamoto, 2018:
Adults (54 cases)

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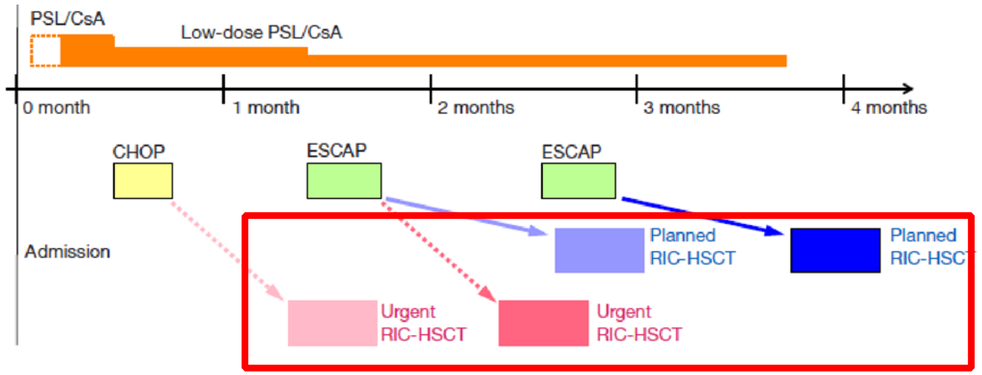
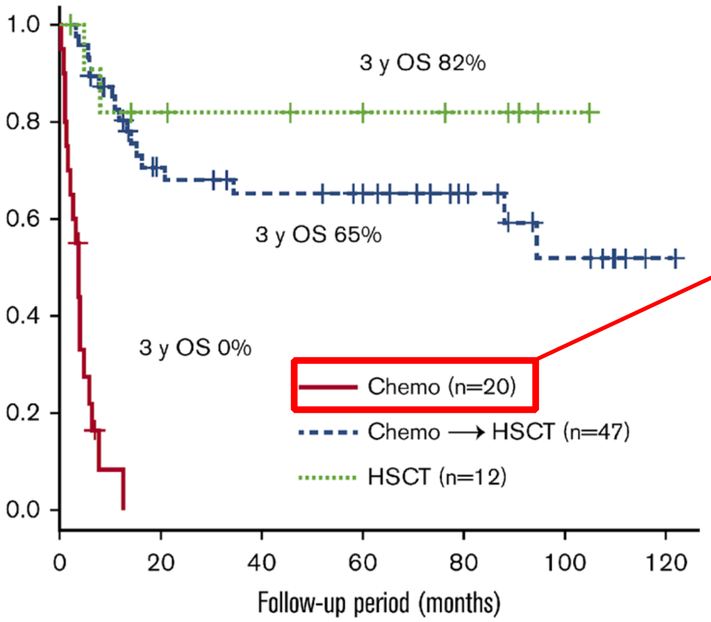
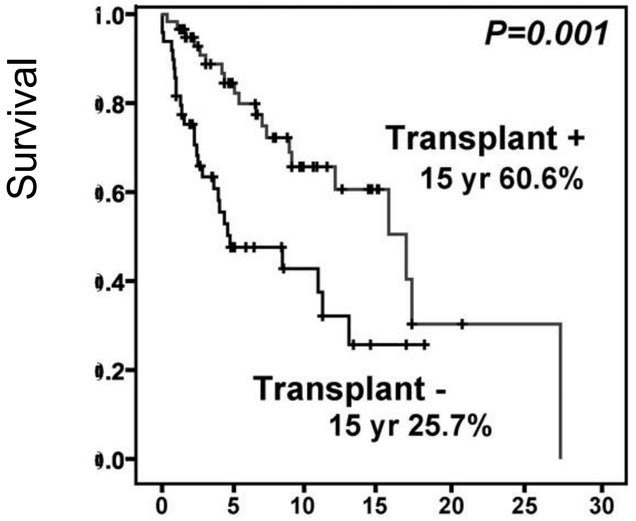




Rapidly progressive uncontrolled disease



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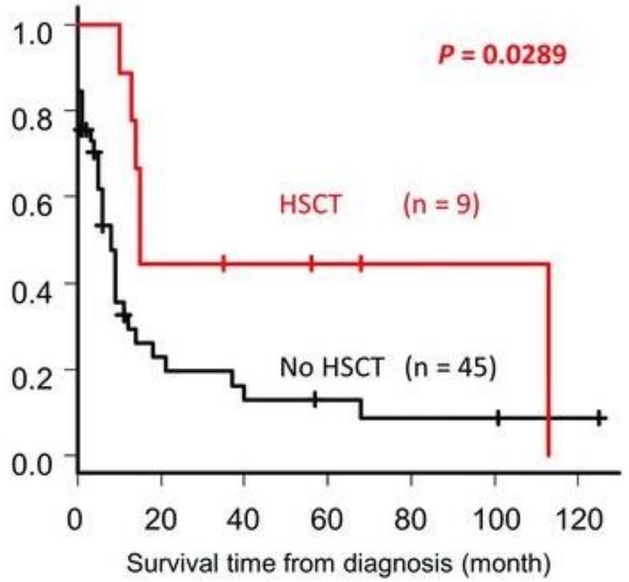

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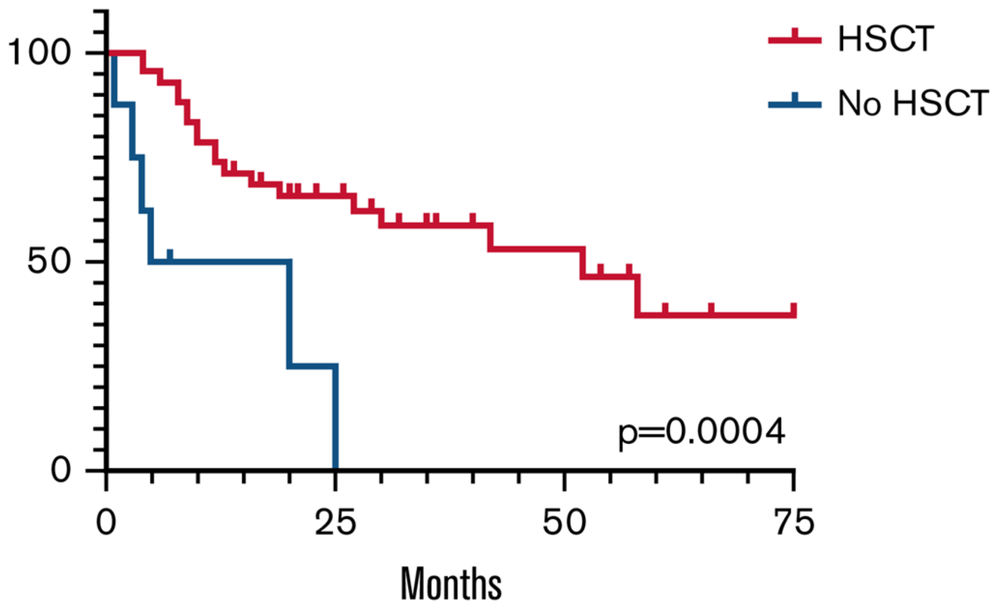
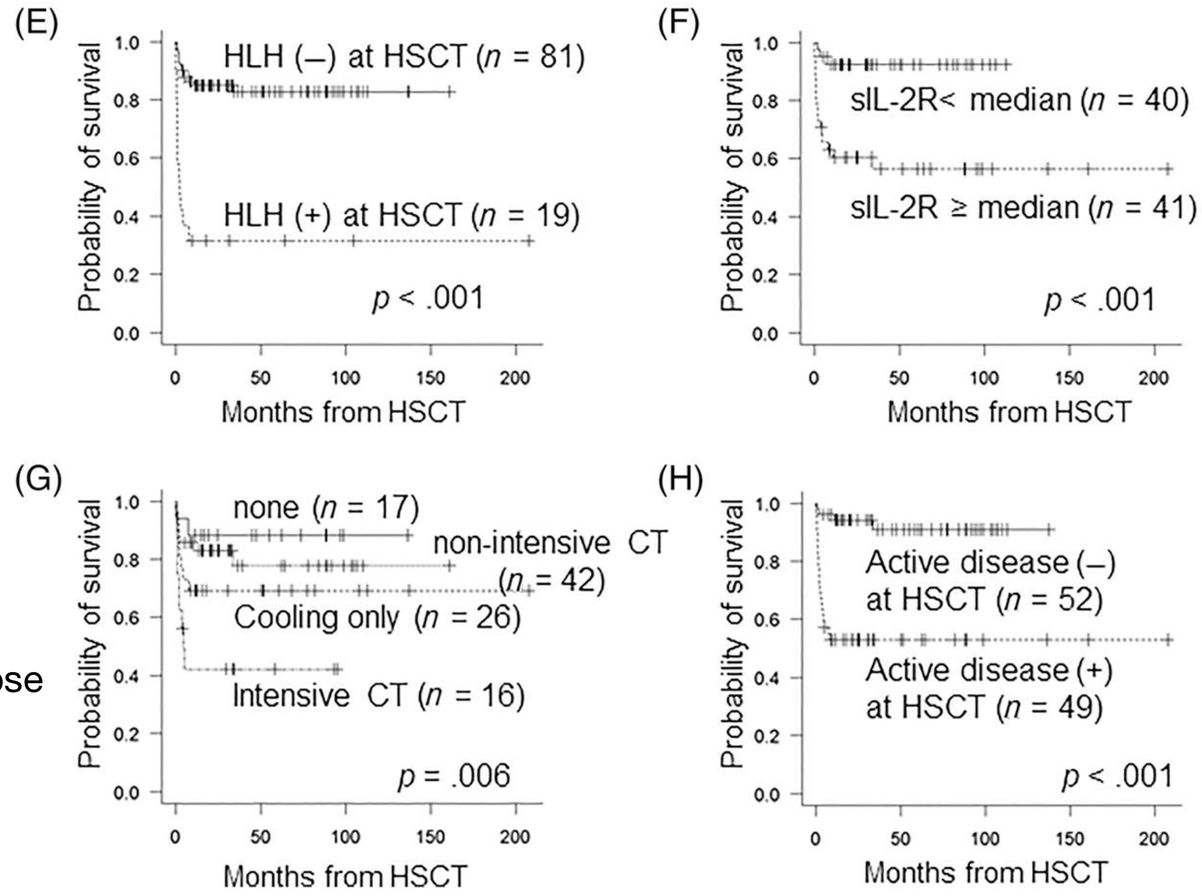


45%(20/44) died after HSCT， 75% (15/20) due to disease relapse
> 70% disease history >8 years

Predictors of survival at HSCT



Davila Saldana BJ, et al. Blood Adv, 2022; Yamamoto M, et al. Am J Hematology, 2022

Country Overview of CAEBV
Country: Italy

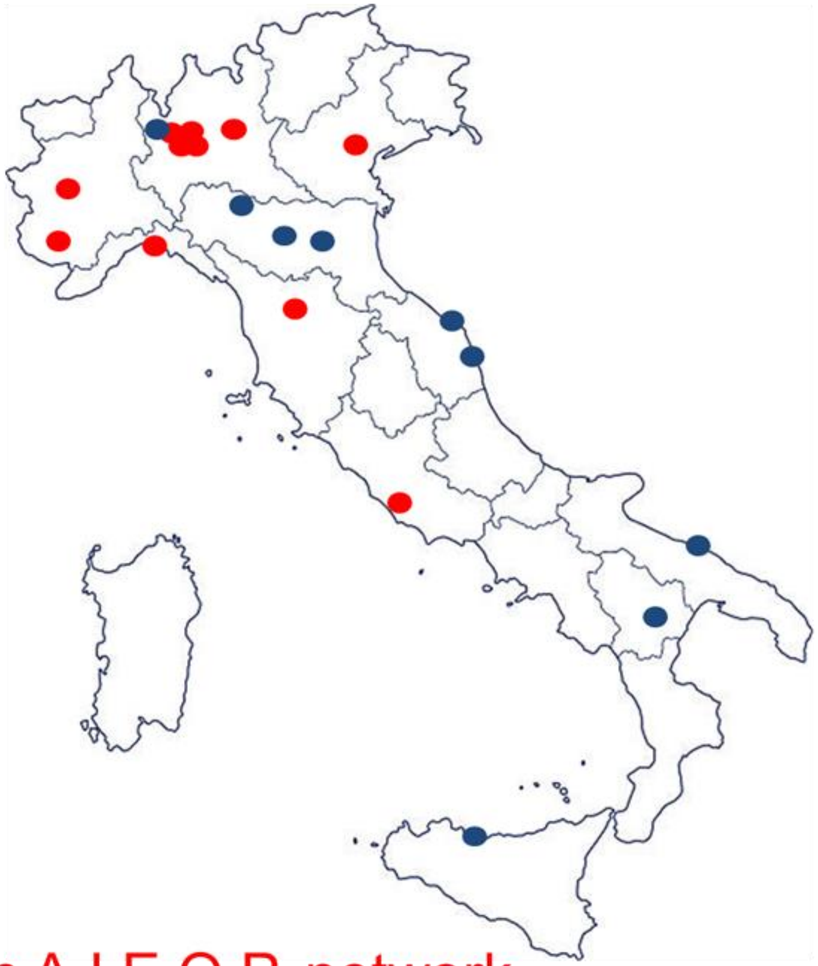
Results:

- Responses from 20 centers (11 northern, 6 middle, and 3 southern Italy) collected.

- 18 (90%) were familiar with the disease.

- 11 (58%) centers recorded at least 1 case
  → at least 15 cases identified.

- 100% interested in participating in a observational study.



collection of pediatric CAEBV cases through A.I.E.O.P. network

Thank you!

Mail contact: erbella.federico@hsr.it