CORSO EDUCAZIONALE

GRUPPO LINFOMI IN PAZIENTI CON IMMUNODEFICIT

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NUOVE CLASSIFICAZIONI DELLE PATOLOGIE LINFOPROLIFERATIVE ASSOCIATE A IMMUNODEFICIT/ IMMUNODISREGOLAZIONE

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Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Roche Ventana Diagnostics			x				

WHO5

IMMUNODEFICIENCY AND DYSREGULATION ASSOCIATED LYMPHOPROLIFERATIVE DISORDERS

recognized by the variable combination of the following parameters:

1. Histological: hyperplasia, polymorphic LPD, lymphoma
2. Presence or absence of virus: EBV, HHV8
3. Clinical/immunodeficiency setting: post-transplant, HIV, iatrogenic/autoimmune
4. Inborn errors of immunity

ICC

LARGE B-CELL LYMPHOPROLIFERATIVE DISORDERS ASSOCIATED WITH VIRAL INFECTIONS

» Immunodeficiency is not an exclusion criteria

RECOGNIZED ENTITIES

1. The effacement of the lymphnode is due to POLYMORPHIC infiltrate which does not fullfill diagnostic criteria of lymphoma
2. If distortion by EBV-positive cells of architecture does not occur, the term REACTIVATION is suggested
3. DLBCL EBV-positive NOS occurs whenever >80% B cells are positive and pursuits aggressive clinical course; it is important to make a differential diagnosis with EBV+ Hodgkin lymphoma
4. EBV-positive mucocutaneous ulcer

WHO5 IMMUNODEFICIENCY AND DYSREGULATION ASSOCIATED LYMPHOPROLIFERATIVE DISORDERS

1. EBV+ polymorphic B-cell lymphoproliferative disorder
2. EBV+ mucocutaneous ulcer
3. Fibrin-associated large B-cell lymphoma (still provisional in ICC)
4. Fluid overload-associated large B-cell lymphoma (corresponds to ICC 'HHV8-negative, **EBV-negative** primary effusion- based lymphoma)

HYPERPLASIA

- Follicular,and/or interfollicular and/or paracortical
- T-cell
- Histiocytic
- Possible presence of small clones
- EBV infection not mandatory
- HHV8+ multicentric Castleman disease

IRIS: IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

» Poorly defined germinal centres

» Non necrotizing granulomas

» Small number of plasma cells

HHV8 MULTICENTRIC CASTLEMAN DISEASE

- Prominent plasmocytosis
- Paracortical hypervascularization
- Prominent regressive germinal centres
- HHV8-positive plasmablasts in the mantle zone (possible LAMBDA light chain restriction)
- Blurring mantle zones
- Follicular lysis
- PCR shows polyclonal population

EBV+ POLYMORPHIC B-CELL LYMPHOPROLIFERATIVE DISORDER

- Variable amount of NECROSIS
- POLYMORPHISM= Co-presence of all B cell stages of differentiation (i.e,, from centroblasts to plasma cells), including RS-like cells
- CD20 may be weak or absent; further confirmatory B-cell markers are needed
- Preferential expression of NON-germinal center markers (i.e. MUM1)
- Variable amount of accomplishing T cells
- Clonality may occur

EBV+ MUCOCUTANEOUS ULCER

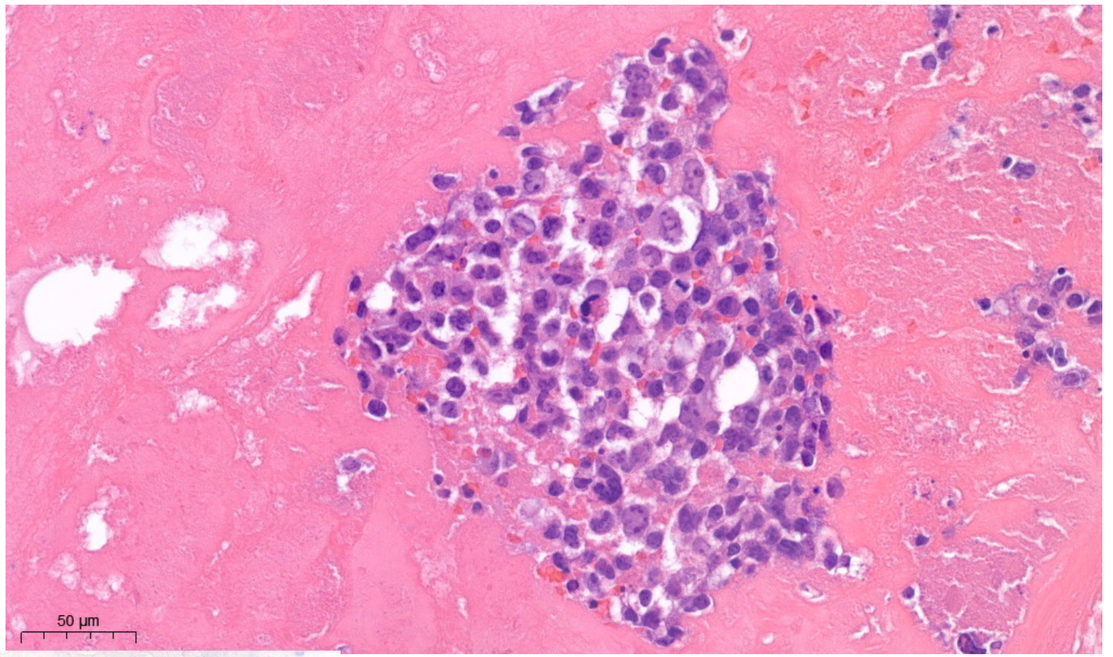
REQUIREMENT: LOCALIZED DISEASE!

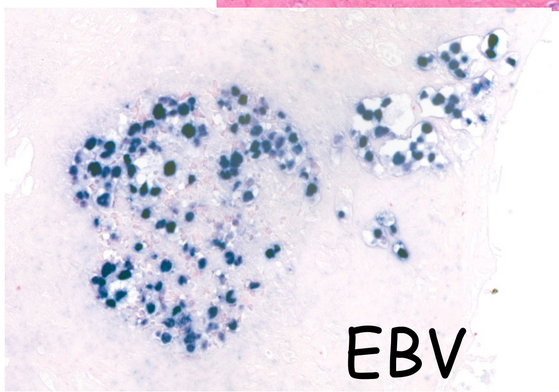
Histology:

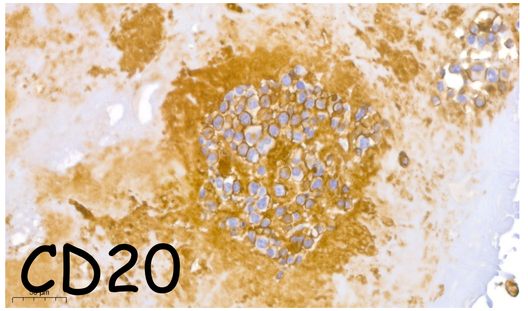
- similar to EBV+ polymorphic lymphoproliferative disorder
- scattered large atypical cells are often CD20-positive, variably positive for CD30
- Lesion is usually separated from uninvolved tissue by a 'wall' of reactive T cells
- Clonality may occur
- Mutatons in key genes for DLBCL may occur rarely (more aggressive behaviour?)

FIBRIN-ASSOCIATED LARGE B-CELL LYMPHOMA (STILL PROVISIONAL IN ICC)

- Large B cells (sometimes CD20-) embedded in clots or fibrin-rich environment (i.e,, within other tumors)
- EBV +/-
- Favourable prognosis
- No molecular characteristic features







FLUID OVERLOAD-ASSOCIATED LARGE B-CELL LYMPHOMA (CORRESPONDS TO ICC 'HHV8-NEGATIVE, EBV-NEGATIVE PRIMARY EFFUSION- BASED LYMPHOMAS')

1. Mostly centroblastic (not plasmablastic) morphology
2. Expression of at least one B-cell antigen
3. GCB cell of origin
4. better prognosis of PEL (sometimes spontaneous regression or upon drainage)

LYMPHOMAS ARISING IN IMMUNE DEFICIENCY/DYSREGULATION

- Mostly B cell lymphomas (but also T-cell lymphomas!!)
- EBV often present
- Higher amount of tumor-associated macrophages, CD8+, granzyme+, and PD1+ lymphocytes
- Most frequent histotypes: DLBCL>> plasmablastic lymphomas >> PEL << classical Hodgkin lymphomas>>EBV+ MALT lymphomas

DLBCL ARISING IN IMMUNE DEFICIENCY/DYSREGULATION

- EBV+ DLBCL show a minor degree of genetic complexity in comparison with EBV-negative ones and genetic aberrations differ between the two groups
- EBV+ are more frequently of non-GC origin
- In PTLD and HIV DLBCLs MYC rearrangement is frequent (not BCL2!) and loss of 18q23 is linked to poorer survival
- Are EBV-negative DLBCL related to immunodeficiency state or an 'incidental' finding?

EBV+ MARGINAL ZONE B CELL LYMPHOMA IN IMMUNE DEFICIENCY/DYSREGULATION

TAKE HOME MESSAGE

It may occur outside the PTLD context!

HIV-RELATED (ONLY?) HODGKIN LYMPHOMA

(at least till some years ago….)

- Increasing incidence (a role for CD4 count?)
- HAART does not seem to play a protective role against HL development
- Usually present with advanced stage disease
- Relative increase of mixed cellularity subtype
- **EBV almost constantly expressed**
- Unusual presentations may occur

HIV-RELATED HODGKIN LYMPHOMA: PECULIAR PRESENTATIONS

Isolated Bone Marrow Manifestation of HIV-Associated Hodgkin Lymphoma

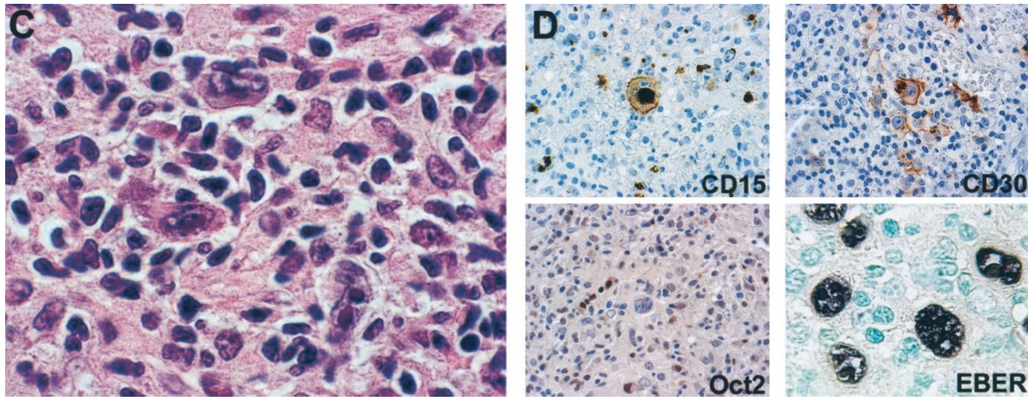
Maurilio Ponzoni, M.D., Luca Fumagalli, M.D., Giuseppe Rossi, M.D., Massimo Freschi, M.D., Alessandro Re, M.D., Maria Grazia Viganò, M.D., Massimo Guidoboni, M.D., Riccardo Dolcetti, M.D., Robert W. McKenna, M.D., Fabio Facchetti, M.D., Ph.D.

TABLE 1. Clinical Characteristics

Case No.	Age (y)/Sex	Previous Drug Abuse	Previous OI	Previous HAART	Nadir CD4	CD4 at Diagnosis	Symptoms at Presentation	Symptoms to Diagnosis (mo)	Chemotherapy (cycles)	Survival from Diagnosis (mo)
1	58/M	No	No	No	20	20	Fever, cytopenia	4	ABVD (1)	2
2	36/M	Yes	No	No	31	31	Fever, cytopenia	3	ABVD (1)	4
3	31/M	Yes	No	Yes	159	549	Fever, cytopenia	5	ABVD (6)	18 (+)
4	49/M	No	PCP	No	54	54	Fever, cytopenia	NA	ABVD (6) + G-csf	114 (+)
5	33/M	Yes	EC	No	26	104	Fever, cytopenia, asthenia	1, 5	EBV(4)+ G-csf+AZT	4
6[a]	34/M	No	No	Yes	64	86	Fever, cytopenia	1, 5	ABVD (2)	3 (+)

OI, opportunistic infections; HAART, highly antiretroviral therapy; ABVD, adriamicin, bleomicin, vinblastin, dacarbazin; EBV, epiadriamicin, bleomicin, vinblastin; AZT, zidovudine; G-csf, granulocyte colony-stimulating factor; PCP, *pneumocistis carinii* pneumonia; EC, esophageal candidiasis; NA, not available; +, alive.

[a] This patient is currently under treatment.

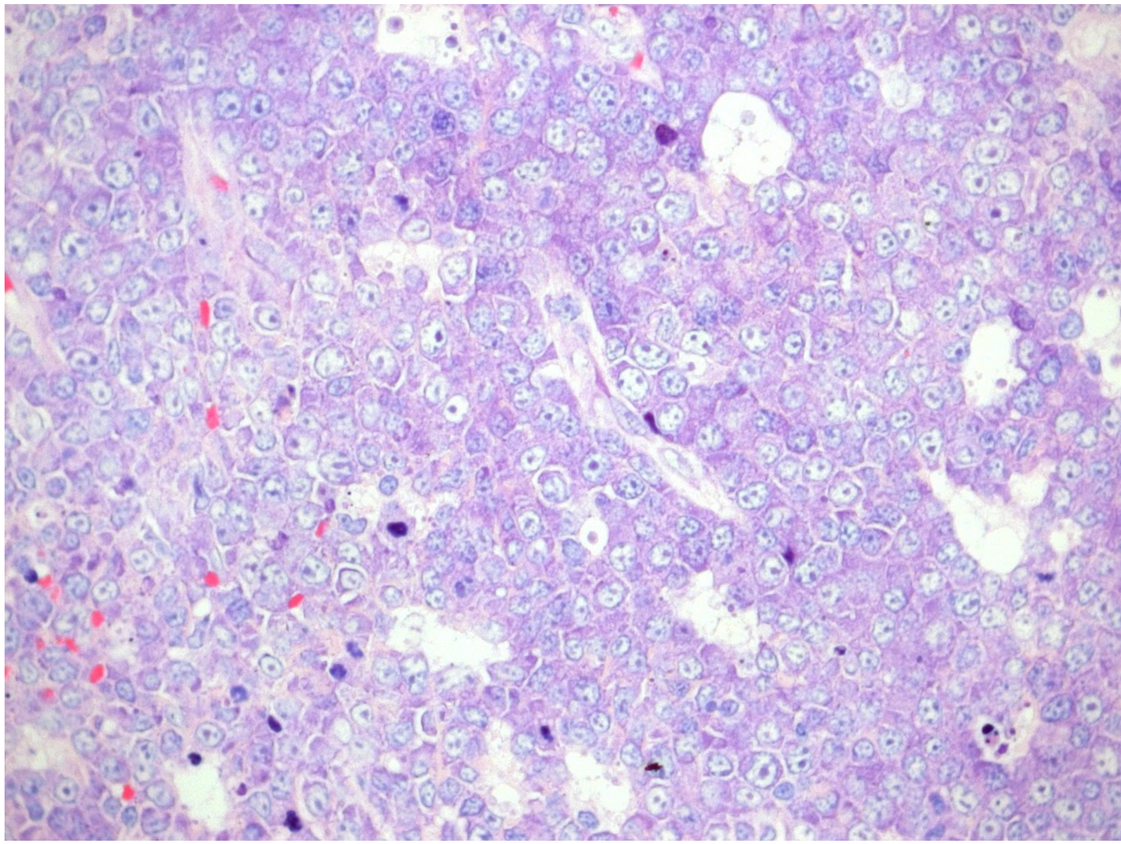


PLASMABLASTIC LYMPHOMAS

Morphology

- Frequent mitoses
- Few apoptotic cells
- Possible areas of plasmacytic differentiation
- Differential diagnosis: anaplastic and plasmablastic myeloma. Useful criteria:

1. High proliferation rate
2. Extranodal localization
3. History of immune deficiency
4. EBV
5. MM-associated translocations
6. MM-associated clinical features



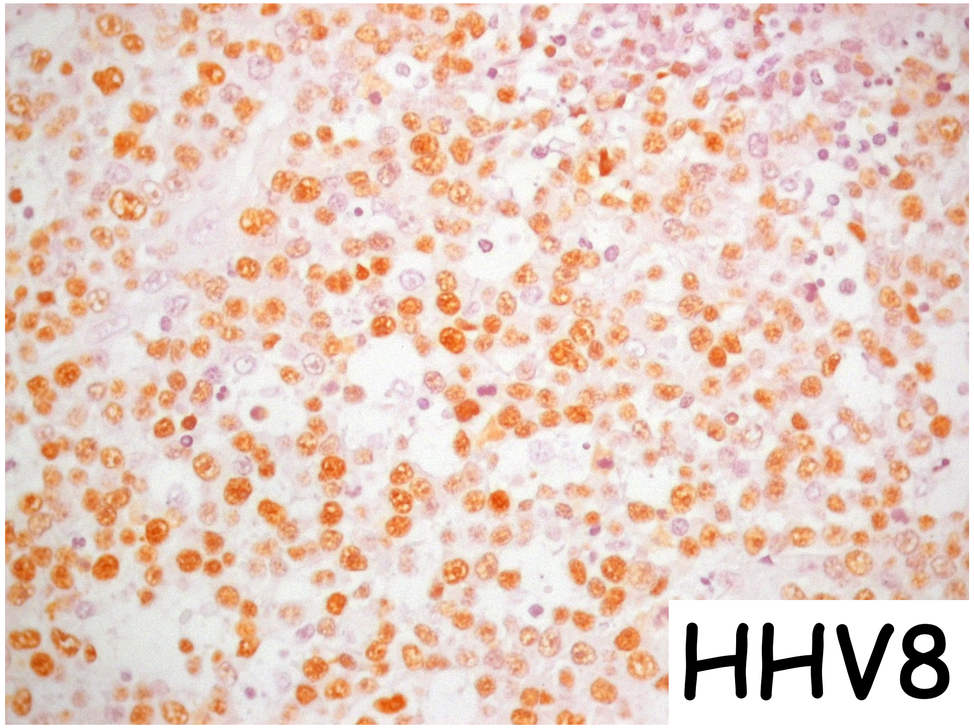
PLASMABLASTIC LYMPHOMAS

Immunophenotype

- PC phenotype (MUM1>>CD138>CD38, VS38c, XBP1)
- Cytoplasmic IgG+
- High proliferation index (40%)
- CD45-, CD19-, ALK-, CD20-, PAX5-negative (or weakly positive)
- CD79a: 40%, CD10: 20%, bcl2 and bcl6: 10%
- CD56: 25%
- EMA and CD30 possibly positive
- HHV8-negative
- Possible occurrence of T-cell markers
- The problem of differential diagnosis with anaplastic plasmacytoma

PRIMARY EFFUSION LYMPHOMAS

- Associated with HHV8, often with EBV
- Associated with Kaposi sarcoma or multicentric Castleman disease
- May have a 'solid tumor' counterpart ('extracavitary PEL') in GI tract, lung, CNS and lymph nodes



HHV8

PRIMARY EFFUSION LYMPHOMAS

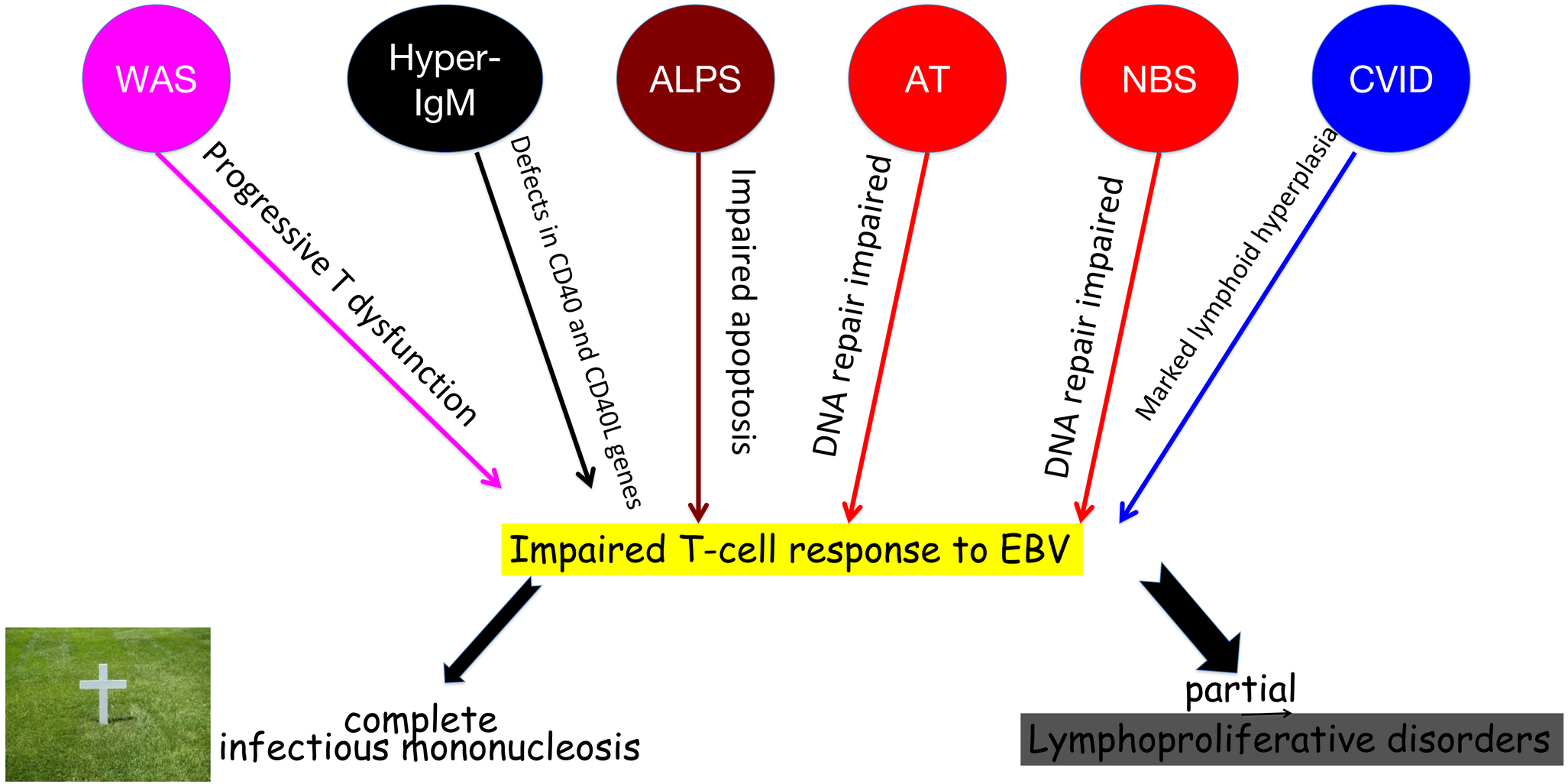
Morphology

- LARGE cells, variable immunoblastic, plasmablastic or anaplastic morphology
- Prominent nucleoli
- Basophilic cytoplasm
- Possible aberrant expression of T-cell markers (in particular extracavitary cases)

Immunophenotype

- CD45-positive
- B cell markers (CD20, CD19 and CD79a)-negative
- Immunoglobulin (surface and immunoglobulin)-negative
- Activation of PC-related markers

LYMPHOPROLIFERATIVE DISORDERS IN INBORN ERRORS OF IMMUNITY: PATHOGENESIS



PRIMARY IMMUNE DISORDERS: MOST COMMON LYMPHOPROLIFERATIVE DISORDERS

Non neoplastic

XLP: Infectious mononucleosis ± haemophagocytic syndrome clonal B-cell

CVID: expansion within GI nodular lymphoid hyperplasia

ALPS: double negative T-cells and follicular hyperplasia

hyper-IgM: absence of GC and IgM+ plasma cells

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Blood Reviews

journal homepage: www.elsevier.com/locate/issn/0268960X

Review

Immune deficiency/dysregulation -associated lymphoproliferative disorders. Revised classification and management

Antonino Carbone [a,*], Amy Chadburn [b], Annunziata Gloghini [c], Emanuela Vaccher [d], Mark Bower [e]

Blood Reviews 2024

WHO classification, 5th edition	ICC 2022
Hyperplasia arising in immune deficiency/ dysregulation distincted in - Follicular proliferation - interfollicular and paracortical proliferations Plasma-cell hyperplasia Mononucleosis-like hyperplasia - T-cell and histiocytic proliferations	Non-destructive forms distincted in - Florid follicular hyperplasia - Plasmacytic hyperplasia - Infectious mononucleosis
KSHV/HHV8 Multicentric Castleman disease (also included in tumor-like lesion with B cell predominance)	Multicentric Castleman disease (not included in this category, but included in HHV8 associated disorders)
Polymorphic lymphoproliferative disorder arising in immune deficiency/ dysregulation	Polymorphic
Epstein-Barr virus-positive mucocutaneous ulcer	Epstein-Barr virus-positive mucocutaneous ulcer (not included in this category, but included in large B-cell lymphoma)
Lymphomas arising in immune deficiency/dysregulation	Monomorphic B and T cell neoplasms, classic Hodgkin lymphoma Lymphomas associated with HIV infection Other iatrogenic immunodeficiency associated lymphoproliferative disorders
In born error of immunity-associated lymphoid proliferations and lymphomas	

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