Southern African HIV Clinicians Society

3rd Biennial Conference

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Sandton Convention Centre
Johannesburg

Our Issues, Our Drugs, Our Patients

www.sahivsoc.org
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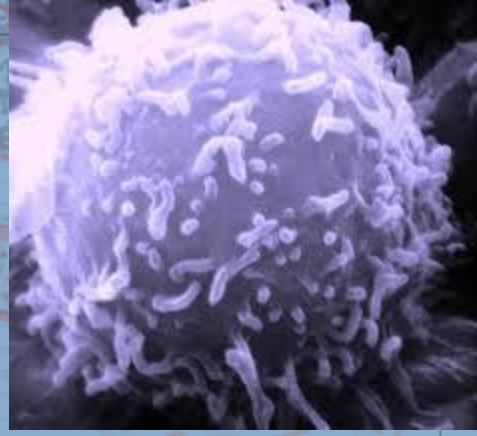


HIV ASSOCIATED LYMPHOMA

Dr N Rapiti

HIV ASSOCIATED LYMPHOMA: OVERVIEW

- Classification
- Pathogenesis
- Prognosis
- cART
- Chemotherapy/Radiotherapy/SCT
- Supportive

CASE

40 yr old male, Mr BM, p/w

- Symptomatic anemia April ’15
- Constitutional sympt

Known HIV, on HAART, CD4 800, ?VL

PTB 2008, 2013, May 2014

Clinically:

- Pale, cervical, axillary, inguinal LN 15cm hepatomegaly

Ix: BMAT=> variable celluarity, ill-defined granulomas, Z-N –ve

Axillary LN biopsy: HV CD with HHV8 LANA-1 positivity

?Mx

INTRODUCTION

- Pre-cART, HIV px 60-200x higher risk NHL
- Risk of NHL increases with declining CD4 count
- cART era incidence reduced, but still high 11-25x
- 4% with AIDS will have NHL at diagnosis
- 10% will develop during course of illness
- Pre-ART, malig→10% HIV deaths
- Post-ART, malig→ 28% HIV deaths

WHO CLASSIFICATION OF HIV LYMPHOID MALIGNANCIES

- **1) Lymphoma also in immunocompent px**

  1.1 DLBCL

  - Centroblastic
  - Immunoblastic(PCNS)

  1.2 Burkitt and Burkitt-like

  1.3 Extranodal MALT lymphoma(rare)

  1.4 PTCL(rare)

  1.5 Classical Hodgkins Dx

- **2) Lymphoma more specifically in HIV +ve px**

  2.1 PEL

  2.2 Plasmablastic lymphoma of oral cavity

  2.3 Lymph assoc HHV8+ Castleman dx

- **3) Lymphoma in other immunodef states**

  3.1) Polymorphic B cell lymphoma(rare)

CLASSIFICATION: INVOLVEMENT SITES

1. Systemic

- 80% of all ARL
  - 1.1) Small non-cleaved(Burkitt and Burkitt-like)
  - 1.2) DLBCL(centroblastic, immunoblastic plasmablastic). CD4 low

2. PCNSL: < common, CD4< 50/μL

3. PEL: rare

AETIOLOGY

- **Chronic Ag stimulation** → polyclonal B cell expansion→monoclonal B cell(circ free LC)

- **Co-infecting oncogenic viruses**:
  - EBV exp LMP1→cell prolif NFkB→bcl-2 over exp→B cell survival
  - HHV8 all PEL

- **Molecular abn**: myc, BCL6

- **Cytokine/chemokine dysreg**: IL6, IL10(EBV, HHV8 assoc lymphoma)

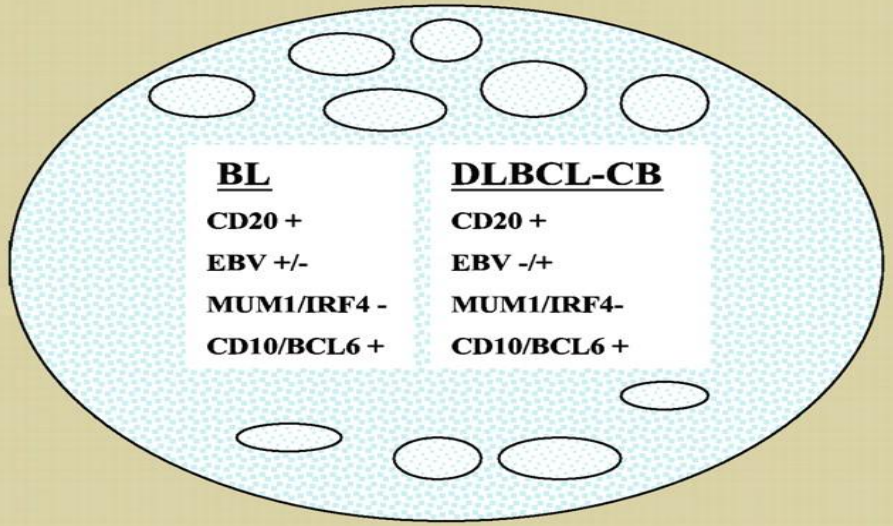
PATHOPHYSIOLOGY

HISTO		EBV	BCL-6	C-myc	p53	BCL-2	HHV 8
Burkitt		30-50%	-	100%	50-60%	-	-
DLBCL	Centroblastic	30%	20%	-	-	-	-
	Immunoblastic	90% LMP1 65-75%	-	-	-	high	-
Plasmablastic		50%	-	-	-	-	80%
PCNSL		90% LMP1 90%	Most	-		high	-
PEL		90-100%	60%	NO	-	-	100%

PATHOGENESIS:

A model for the histogenesis of HIV-associated lymphomas showing molecular and viral pathogenesis and DLBCL taxonomy.

Germinal Center	Post-Germinal Center	
Germinal Center B-cell type (GCB)	Activated B-cell type (ABC)	Plasmacytic type
Mild immunodeficiency		Severe immunodeficiency
Moderate CD4 count		Low CD4 count
Good Prognosis		Poor prognosis
Post-CART		Pre-CART



BL
CD20 +
EBV +/-
MUM1/IRF4 -
CD10/BCL6 +

DLBCL-CB
CD20 +
EBV -/+
MUM1/IRF4-
CD10/BCL6 +

DLBCL-IB
CD20 +
EBV ++/-
MUM1/IRF4 +
CD10/BCL6 -

PEL
CD20-
EBV +
KSHV/HHV8 +
MUM1/IRF4 -
CD10/BCL6 -

PB
CD20 -
EBV +
KSHV/HHV8 +
MUM1/IRF4 -
CD10/BCL6 -

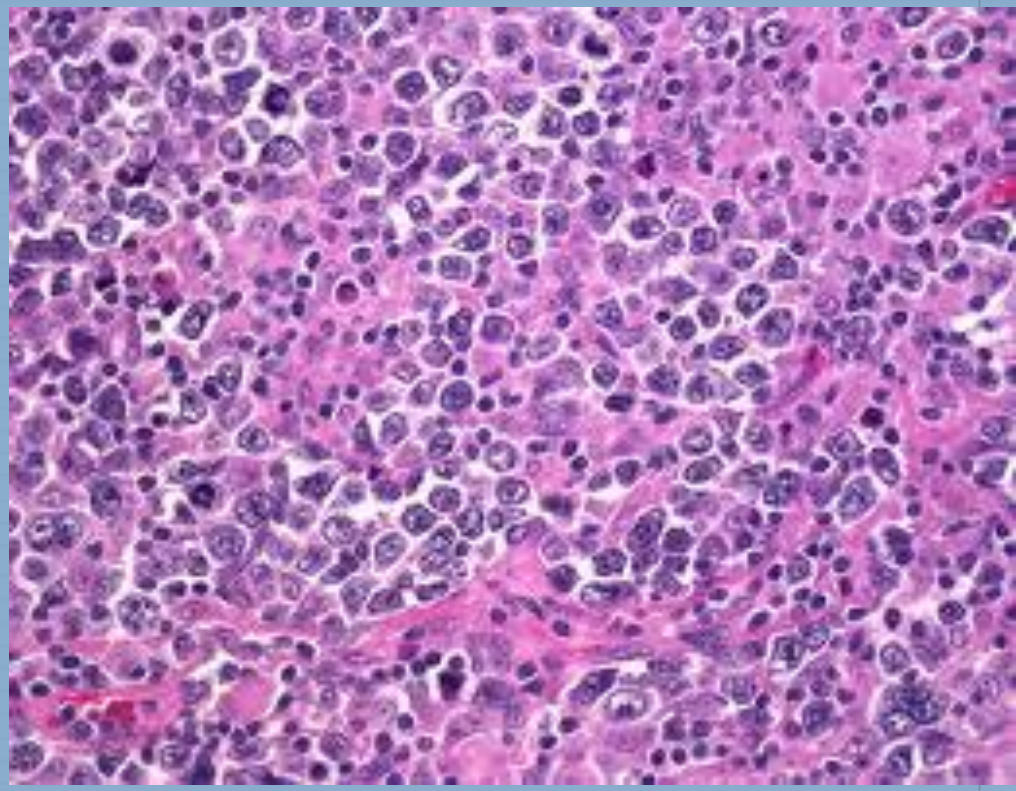
Kieron Dunleavy, and Wyndham H. Wilson Blood 2012;119:3245-3255

INVESTIGATION

- Excisional LN biopsy
- FBC, chemistry, LDH, urates
- CD4, VL, Hep B/C
- BMAT 20% involv
- LP with CSF flow
- CT staging vs PET
  - HIV nodal reactive hyperplasia
  - Lipodystrophy
  - infection
- MRI brain

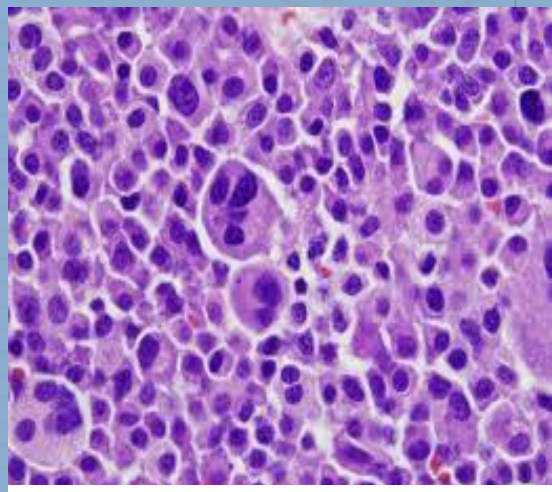
HISTOLOGY: DLBCL: Centroblastic

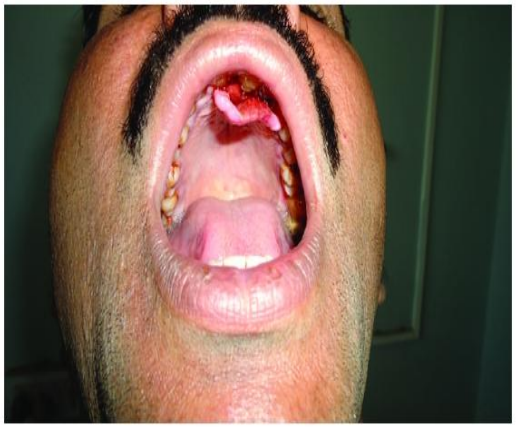
- 25% HAL
- diffuse sheets of large lymphoid cells, oval nuclei, prominent nucleoli
- GCB→ CD10, BCL6, CD20+



PLASMABLASTIC LYMPHOMA

- CD 38, 138, MUM1/IRF4 +ve
- CD20, 45 –ve
- Jaw, oral cavity, overlap with PEL
- CART appears beneficial
- ?infusional regimens
- ?Bortezomib ?Lenalidomide





PROGNOSIS

- 70% advanced dx, with B symptoms and extranodal dx
- Prognosis: IPI with CD4 count

NCCN IPI	AGE	LDH	STAGE 111/1V	ENDx	PS ≥ 2	CD4
1	40-60yr	1-3 x normal	↓	↓	↓	
2	60-75yr	>3x normal				
3	>75yr					

0-1: low
2-3: LI
4-5: HI
≥ 6: High

ANTIRETROVIRAL Rx

- Concurrent with chemo
- Interaction cytotoxics and ART
- May potentiate chemotherapy toxicity
- Highest with combinations with strong enzyme inhibitors eg Ritonavir-boosted protease inhibitors
- Integrase inhibitor containing ARV regimen suggested
- CD4 ↓ not prevented with cART, returns baseline 12/12
- No controlled studies

HAART ARL PROFILE

	PRE	POST
INCIDENCE	36.6	8.4 per 1000p/y
CD4 >200	3%(70)	21%(94)
VL(copies/ml)	264 667	35 500
% FEMALE	2%	14%
OI	83%	36%
MEDIAN S	3/12	13/12

Rx

- DLBCL: R-CHOP or R-EPOCH x 6 = SOC
- BL(good performance status): GMALL B-ALL/NHL protocol
- Plasmablastic and PEL, no standard Rx
- 1st relapse, sensitive dx, HDT with ASCT
- Resistant dx, 2nd line or palliate
- cART concurrent with bolus chemo
- Rx as for HIV-ve px

DLBCL Rx

	CHOP	R-CHOP	R-EPOCH	R-CDE
CR	48-60%	↑ 10%		
Infection +	2%	14%		
CR with R				
Infection +				
2-3yr OS				

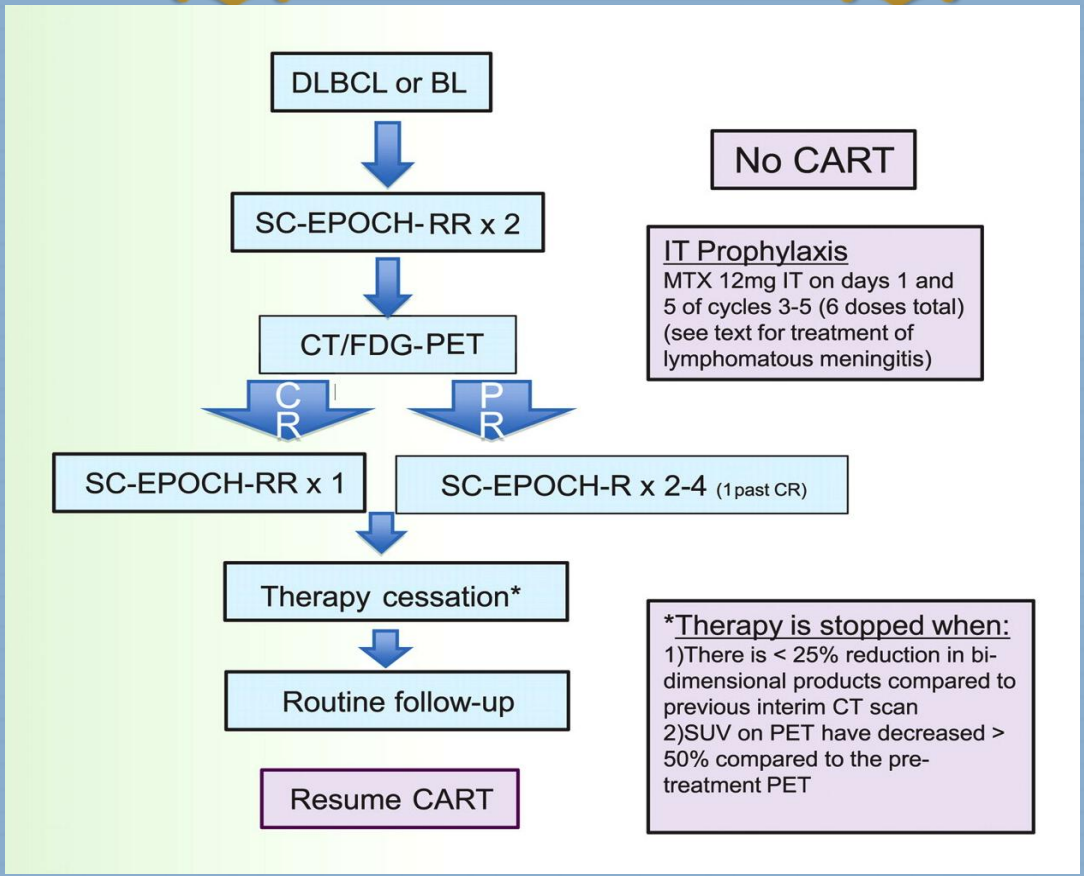
1 randomised trial c-ART era

Several prospective and Phase 2 studies CR 69-76%

2-9% mortailty with Rituximab inclusion

56-75% > than CHOP or historical controls

INFUSIONAL REGIMENS



CASTLEMANS DX AND NHL

- 18% association 1 series
- Higher predisposition in HIV px
- HDx also associted MCD
- Prospective study MCD with HIV: 60px f/u 20/12
- 23% dev NHL(incidence 14x > HIV pop)→50% plasmablastic
- CD4, VL not predictive of risk

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PLASMABLASTIC CD

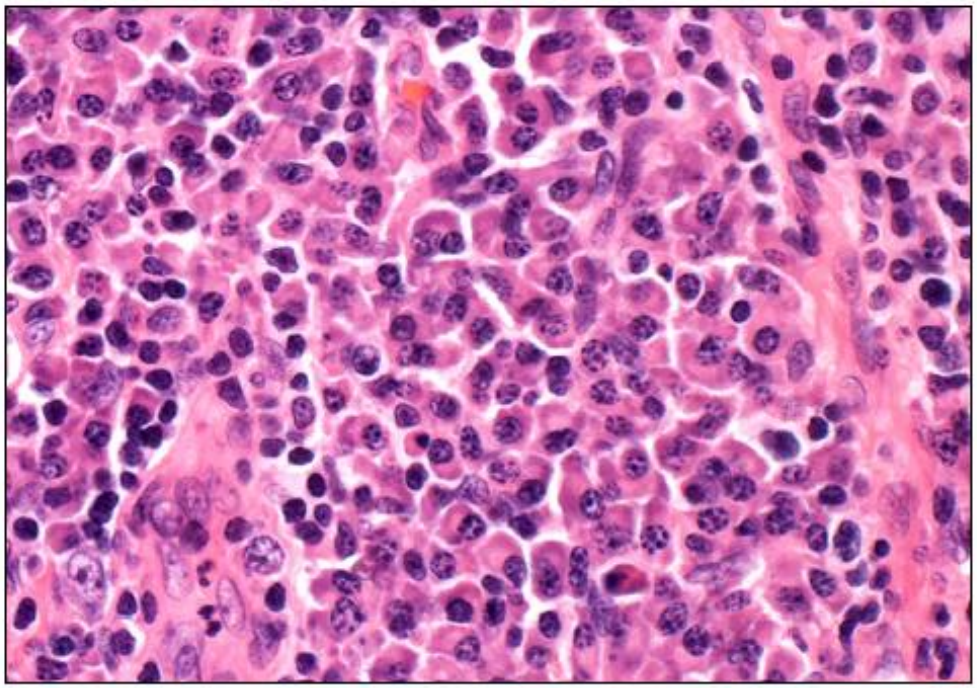
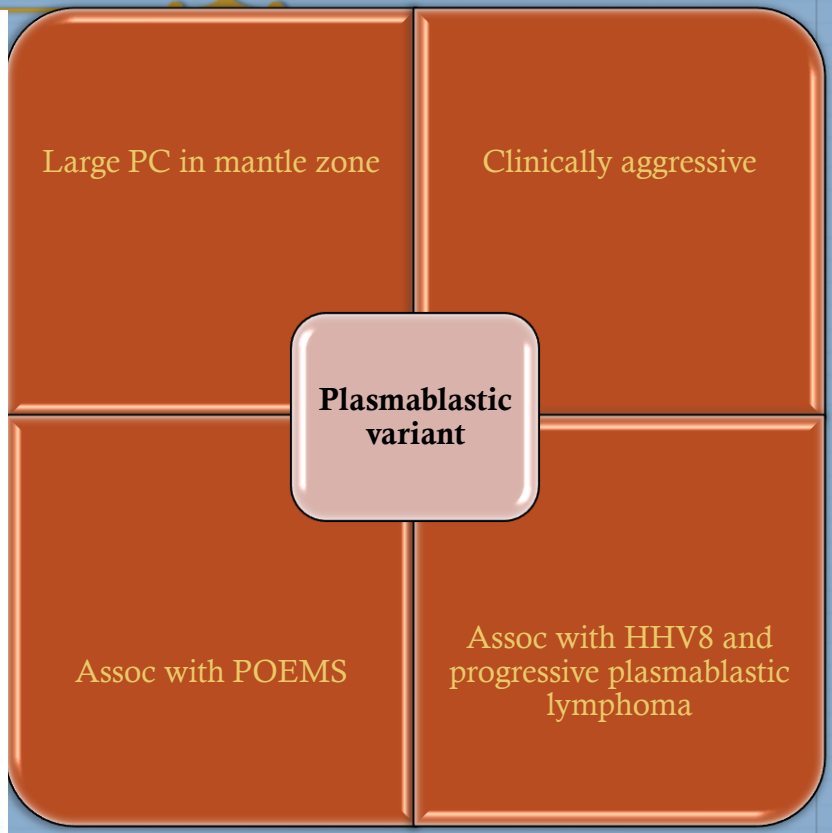
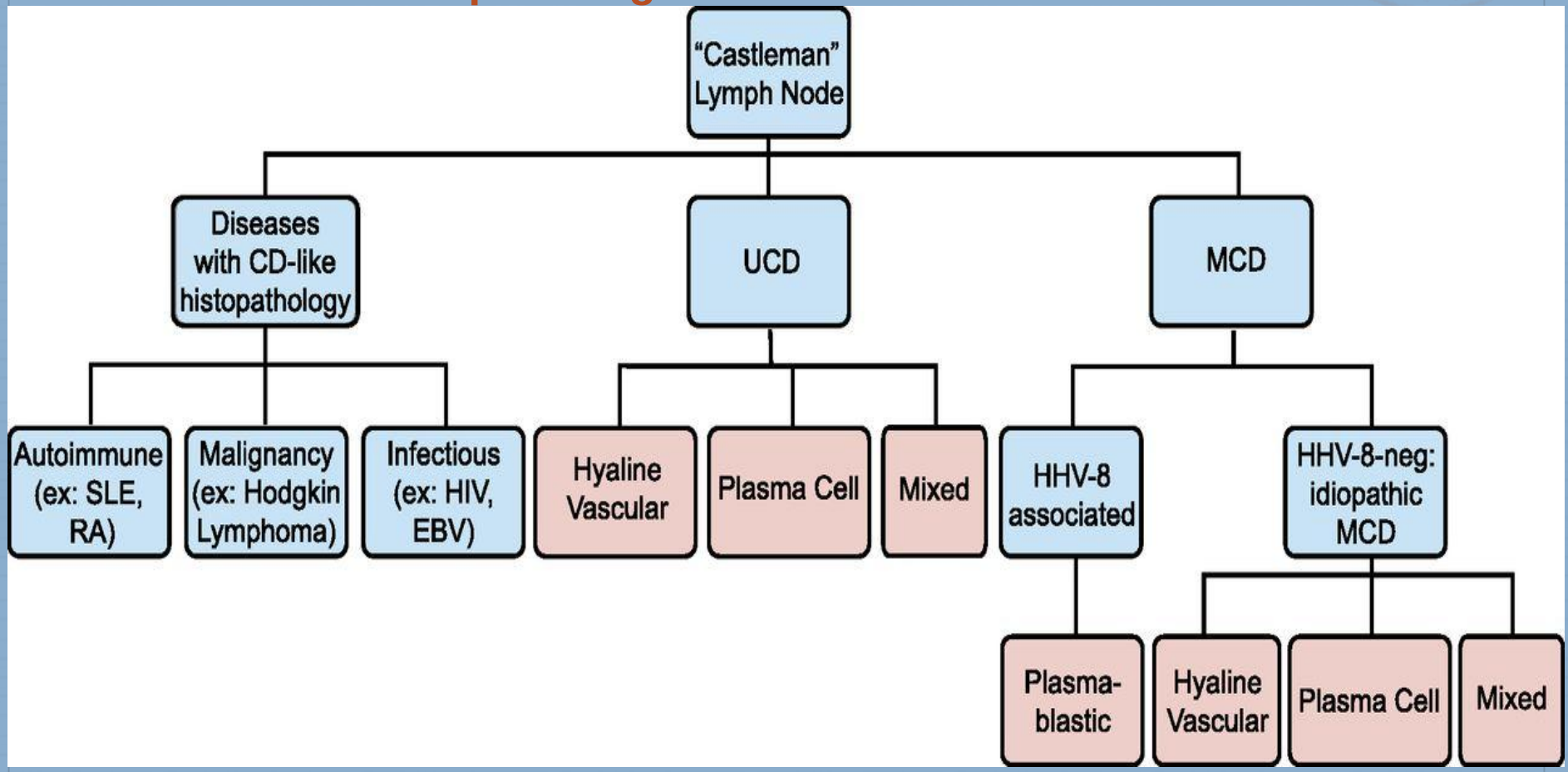


Fig. 5. Castleman disease, plasmablastic variant with large plasmablasts (immunoblasts) in the mantle zone. Original magnification

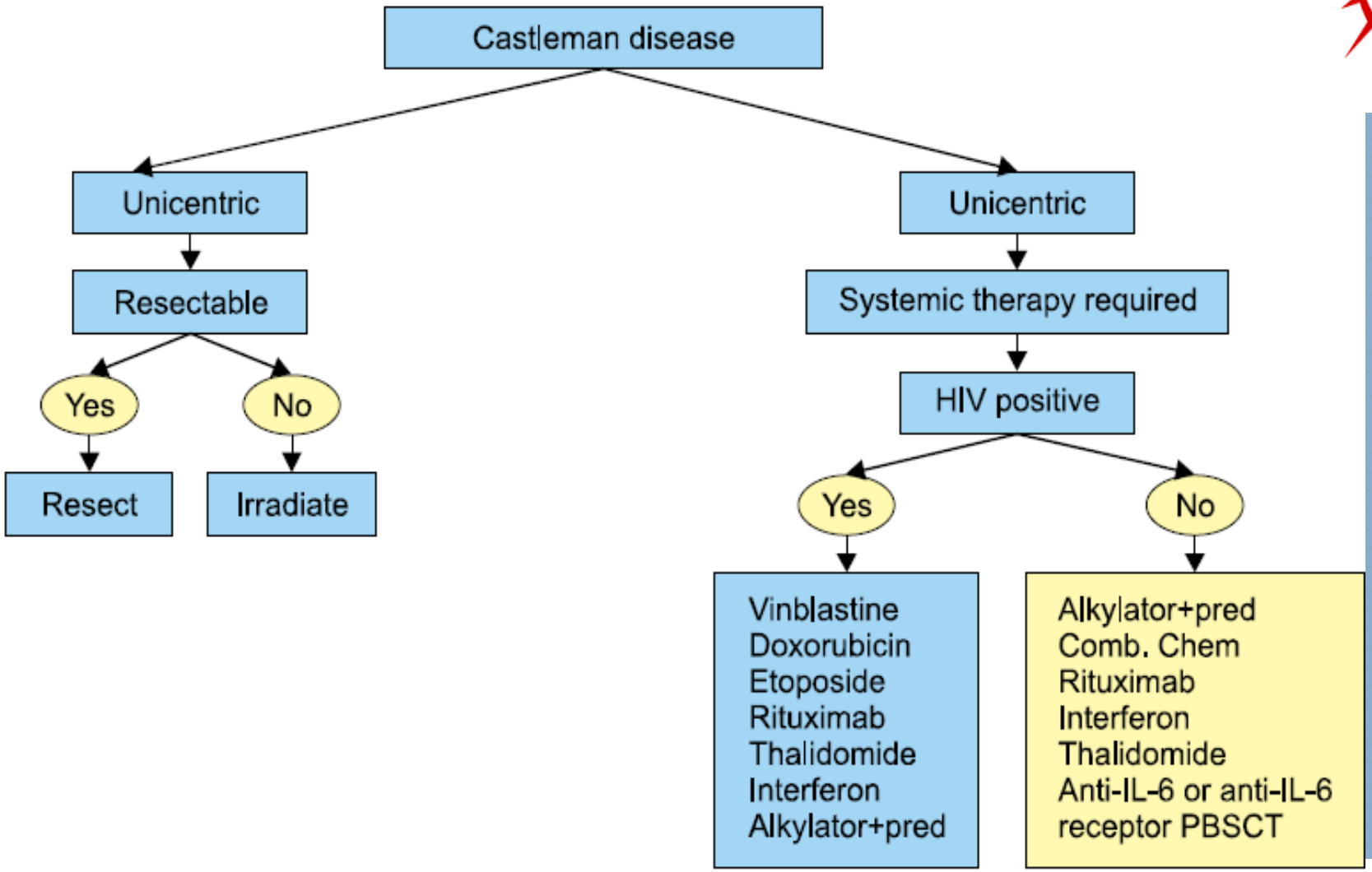


SUMMARY: Diseases with Castleman-like lymph node histopathological features



David C. Fajgenbaum et al. Blood 2014;123:2924-2933

TREATMENT


Castleman disease
Unicentric
Resectable
Yes
No
Resect
Irradiate
Unicentric
Systemic therapy required
HIV positive
Yes
No
Vinblastine
Doxorubicin
Etoposide
Rituximab
Thalidomide
Interferon
Alkylator+pred
Alkylator+pred
Comb. Chem
Rituximab
Interferon
Thalidomide
Anti-IL-6 or anti-IL-6
receptor PBSCT

FUTURE

- Practical: delayed diagnosis, concurrent pathology, clinician awareness, dx evolution
- Identify cell of origin ie. GCB verses non
  - Tailored Rx eg Bortezomib
- ID MYC +ve DLBCL, poor outcome with R-CHOP
- Monitoring risk with serum free LC
- Rx: bolus vs infusional
- Novels agent eg. Bortezomib, Lenalidomide