2017 CST-Astellas Canadian Transplant Fellows Symposium

EBV Post Transplantation Implications and Approach to Management

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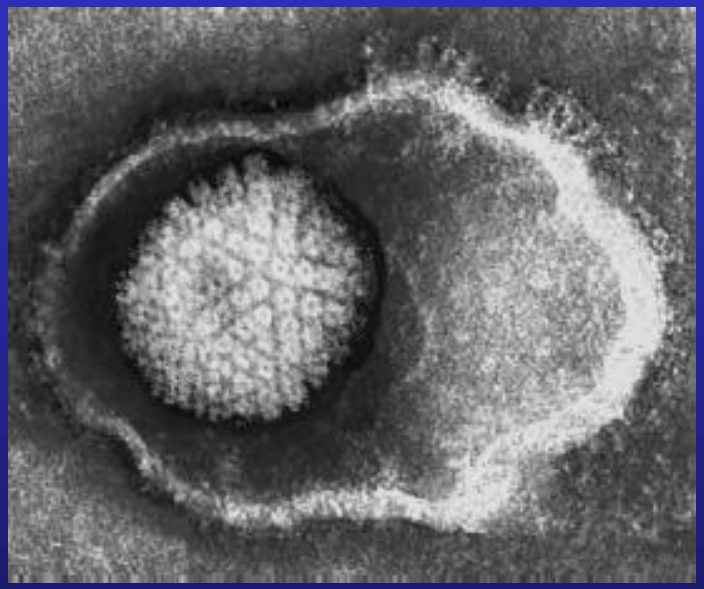
EBV AND PTLD



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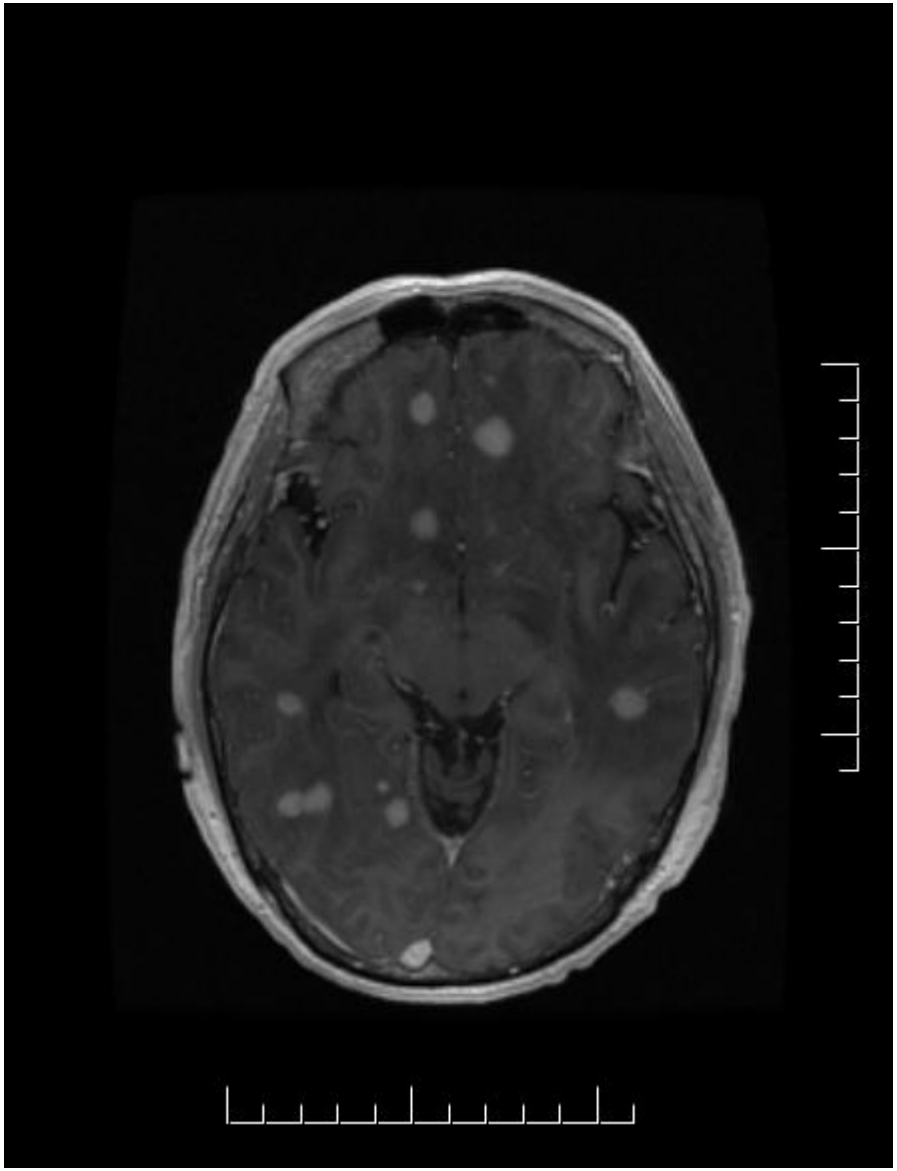
MULTI-ORGAN TRANSPLANT/ INFECTIOUS DISEASES

- **Disclosures: Consulting, Honoraria or research support Astellas, Chimerix, Roche, Qiagen**
- **Objectives:**
  - **To describe risk factors for and presentation of EBV infection/disease**
  - **To describe EBV prevention and treatment**
  - **To describe new developments related to EBV**

CASE

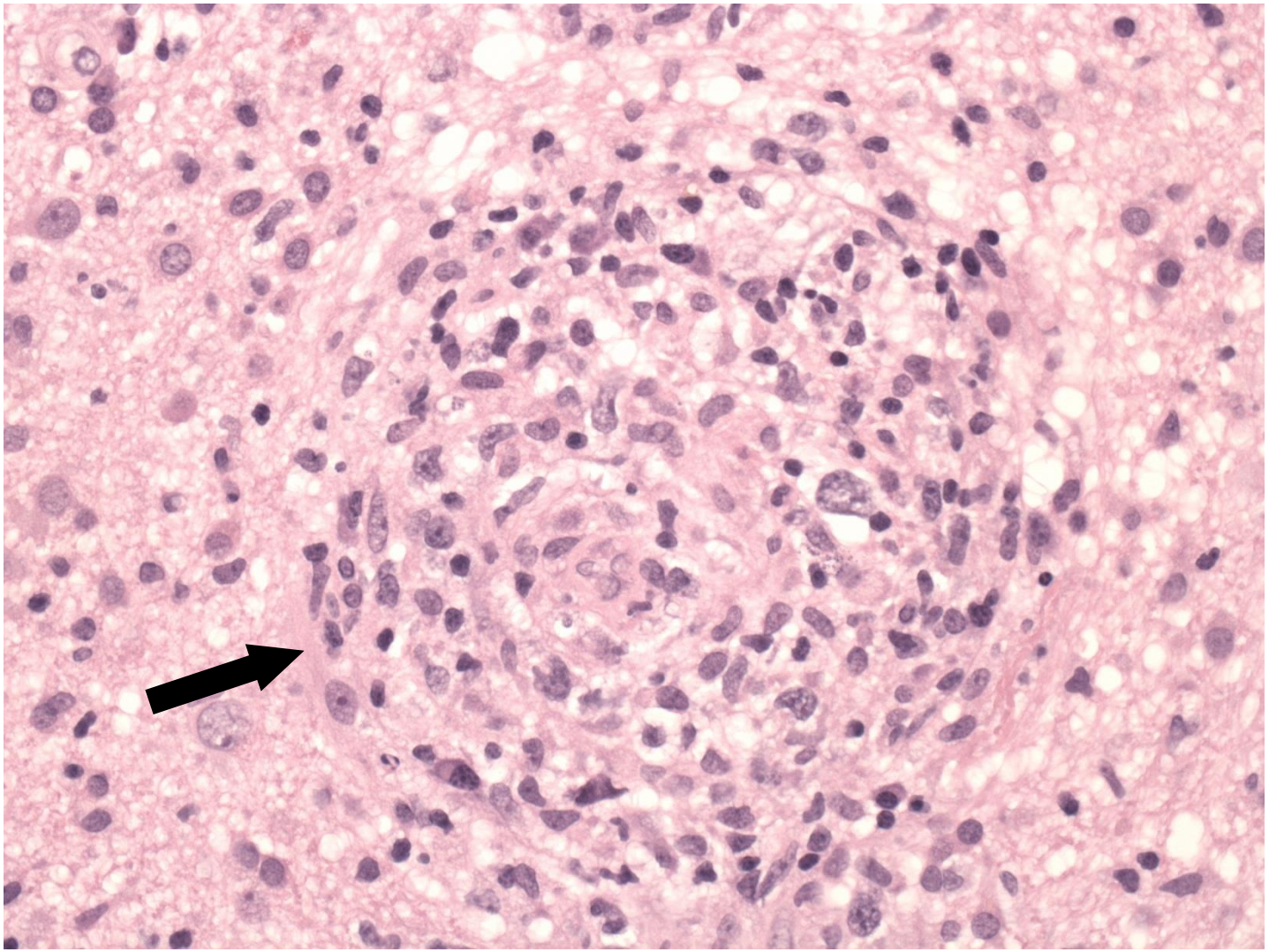
- 57 y/o man originally from China
- Kidney transplant 28 years ago w/ baseline creat 200 umol/L (2.3 g/dL) – on Mycophenolate/Pred/CsA
- Presented with dizziness, fever, confusion w/ falls
- CSF 62 WBC/µL (90% lymphs), inc protein
- All other CSF micro neg (viral, AFB, fungal, crypto Ag)
- MRI done



What tests would You do?

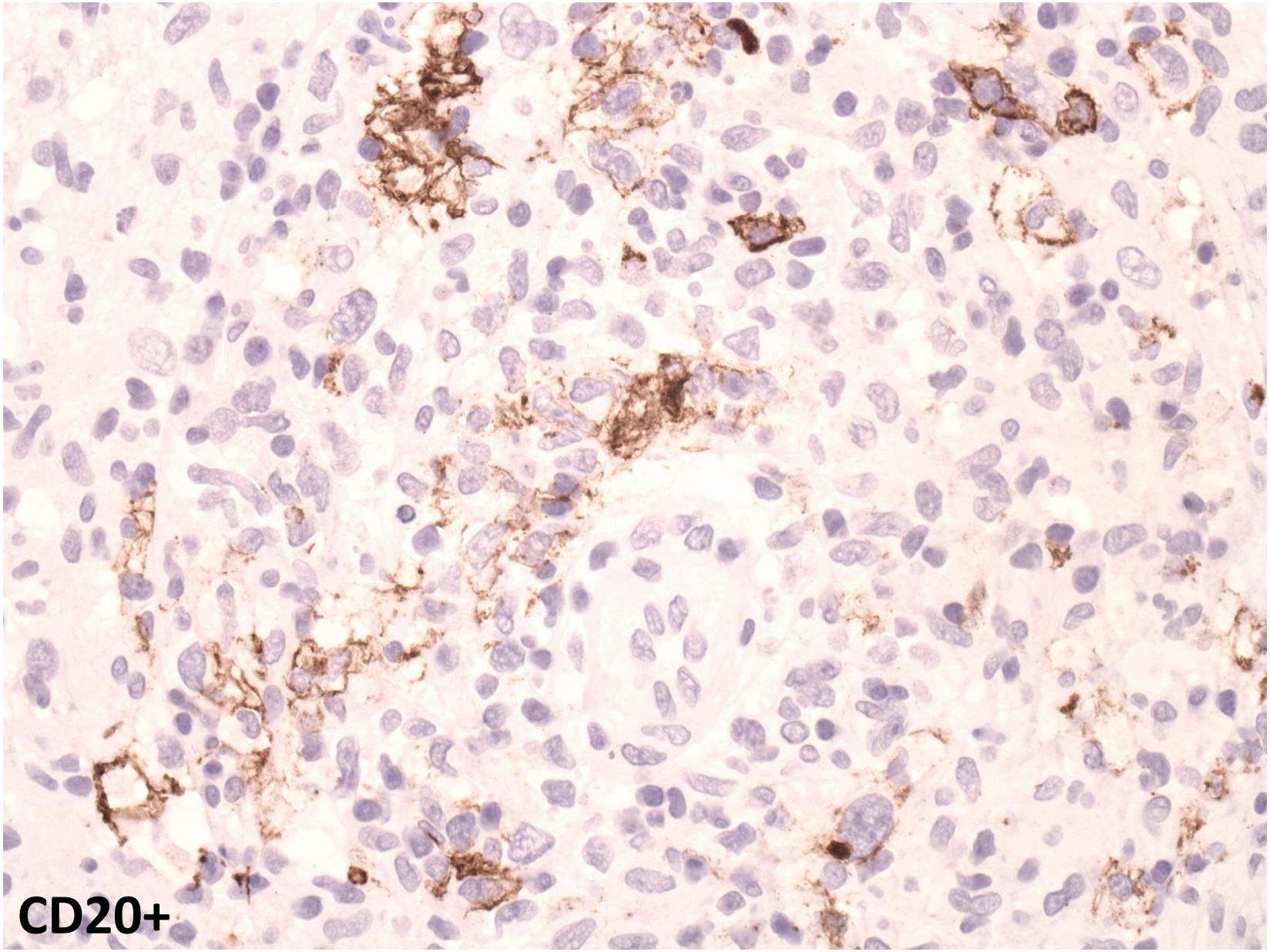
What is differential Dx?

Brain Biopsy



H&E

Courtesy: Dr. Jan Delabie, UHN pathology



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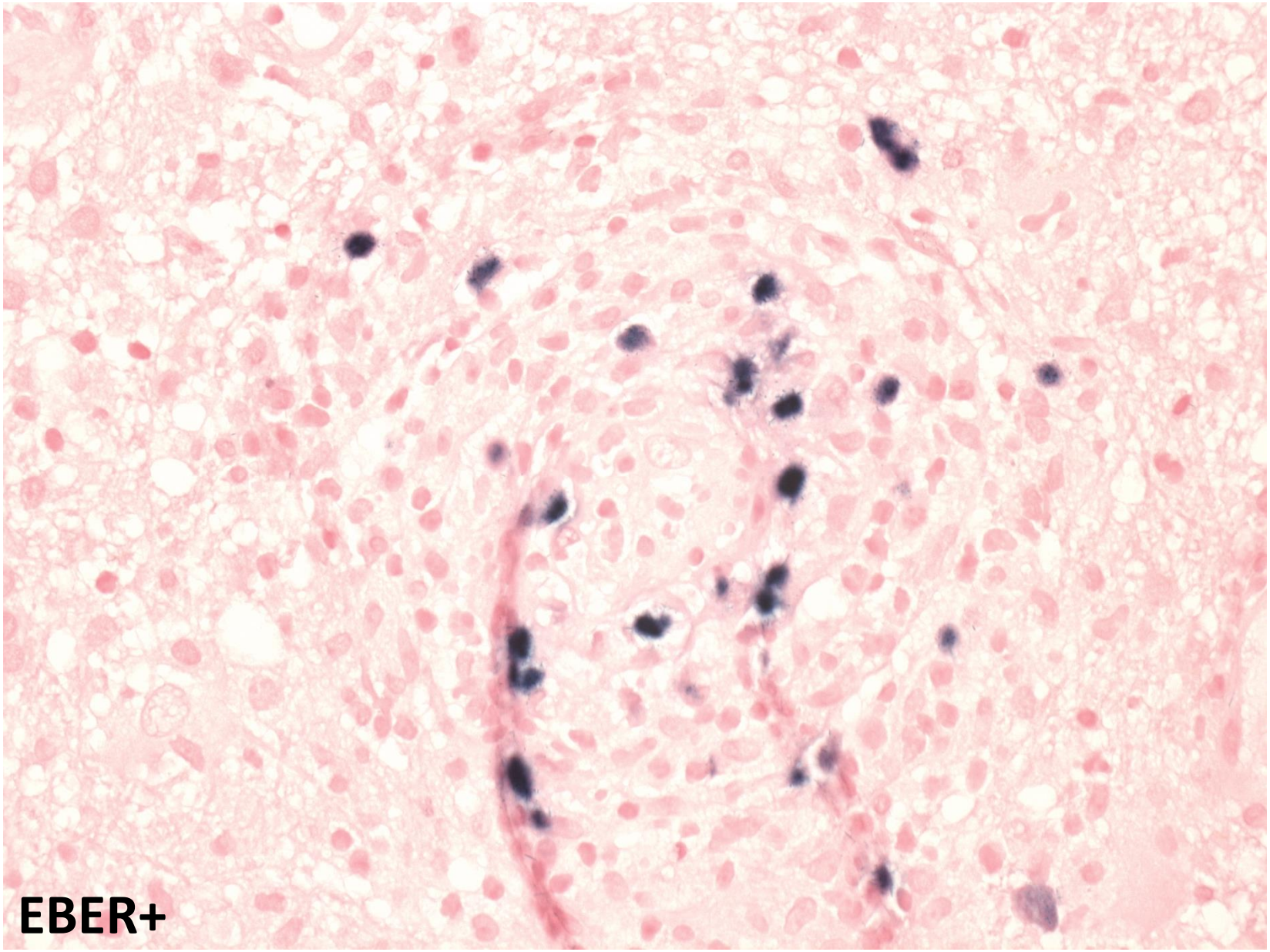


Courtesy: Dr. Jan Delabie, UHN pathology

FINAL DIAGNOSIS:

CNS PTLD: Lymphomatoid granulomatosis isolated to CNS

EBV - VIROLOGY

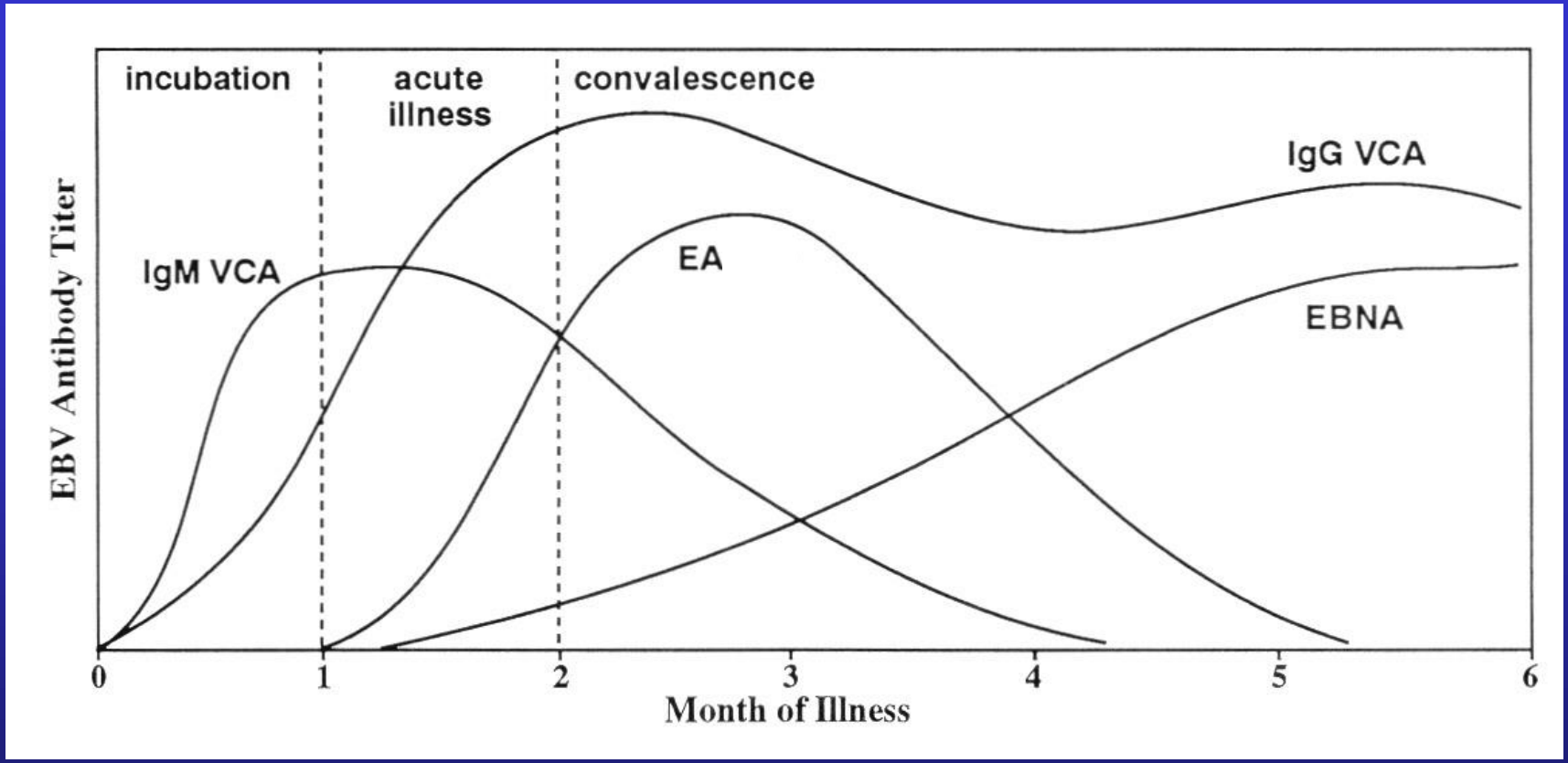
- γ-herpesvirus
- 172-kb linear DS-DNA
- Lifetime persistence

EBV Causes / Associated with

- Infectious Mononucleosis
- Forms of Cancer
  - PTLD
  - Hodgkins lymphoma
  - Burkitt's lymphoma
  - Nasopharyngeal carcinoma
  - HIV associated CNS lymphomas

EBV- IM

- Transmission primarily through saliva
- Incubation period ~ 30-50d
- Asymptomatic or IM
- Most symptoms resolve by 1 month although fatigue may persist
- Acute complications
  - Cytopenias, neurological complications, splenic rupture, airway obstruction



Johnson DH, Cunha BA. Epstein-Barr virus serology. Infect Dis Pract. 1995;19:26-27.

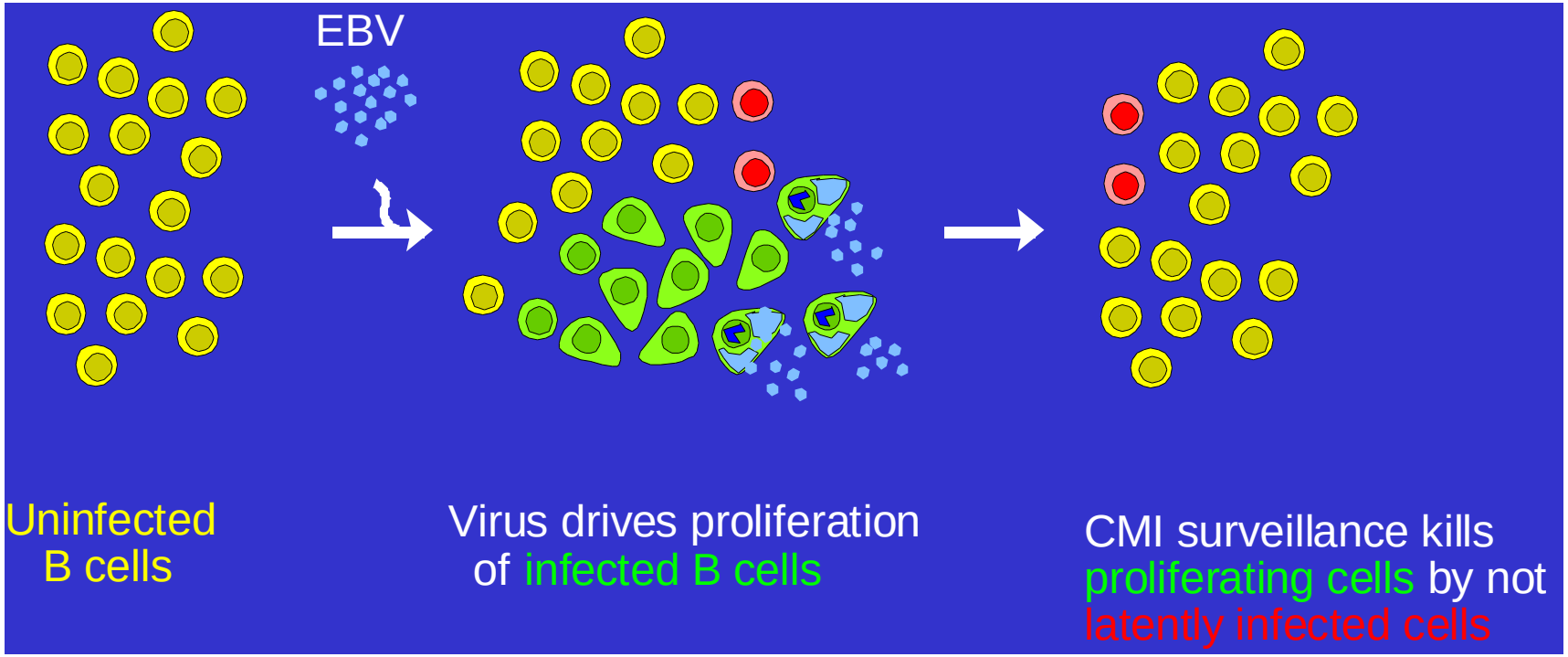
EBV

- **Lytic infection**
  - **~100 genes expressed, lysis of B-cell**
- **Latent infection**
  - **< 10 genes expressed**
  - **LMP 1,2, EBNA 1,2,3, EBER, BCRF, BHRF, BARF**
  - **Evades host immune response**
  - **Latent gene products drive B-cell proliferation**

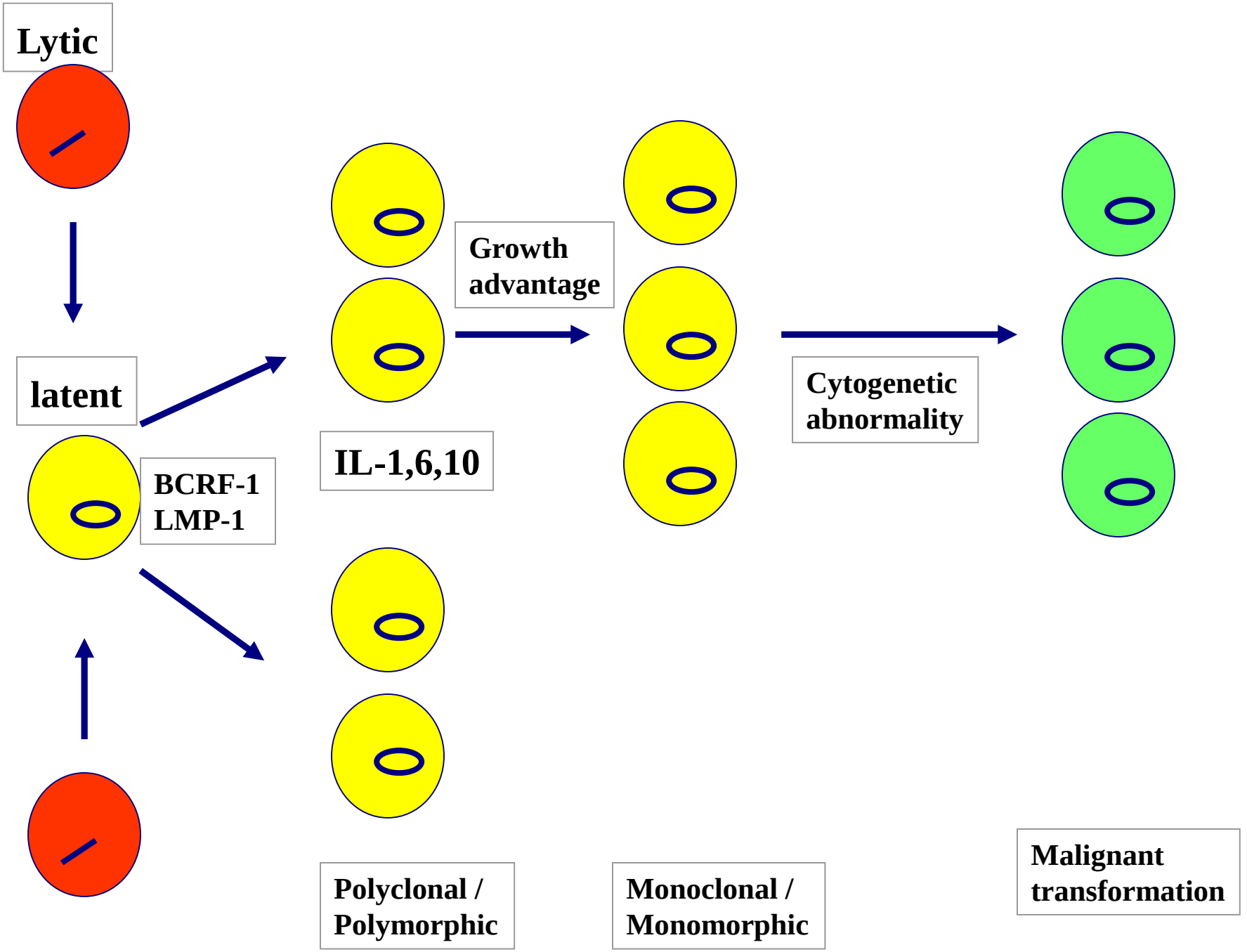
TABLE 1. EXPRESSION OF EBV LATENT GENES IN DISEASE.*

PATTERN OF LATENCY	EBNA-1	EBNA-2	EBNA-3	LMP-1	LMP-2	EBER	DISEASE
Type 1	+	−	−	−	−	+	Burkitt's lymphoma
Type 2	+	−	−	+	+	+	Nasopharyngeal carcinoma, Hodgkin's disease, peripheral T-cell lymphoma
Type 3	+	+	+	+	+	+	Lymphoproliferative disease, X-linked lymphoproliferative disease, infectious mononucleosis
Other	±	−	−	−	+	+	Healthy carrier

Normal Proliferation & Control of EBV



Courtesy M. Green; UPMC


Lytic
latent
BCRF-1
LMP-1
IL-1,6,10
Growth advantage
Cytogenetic abnormality
Polyclonal / Polymorphic
Monoclonal / Monomorphic
Malignant transformation

PTLD

- An abnormal proliferation of B-cells driven by EBV
  - May be polyclonal or monoclonal
  - (occasional tumors are T-cell, NK cell)

- Overall frequency
  - 3-5% of HSCT (unrelated donors higher risk)
  - 1-20% of SOT (EBV D+/R- & lung transplants highest risk)

PTLD

Viral Infection

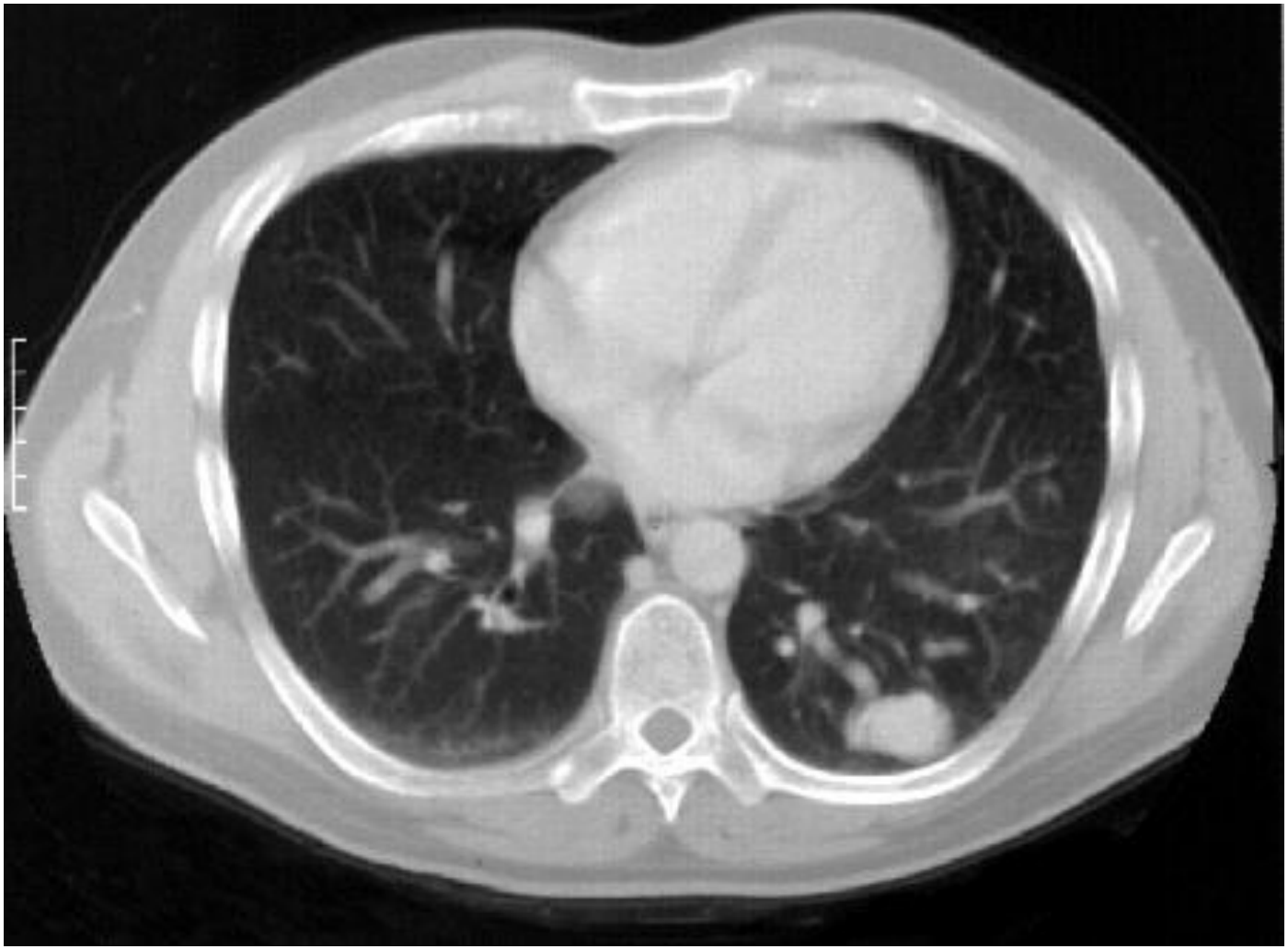
Tumor

PTLD – Clinical Presentation

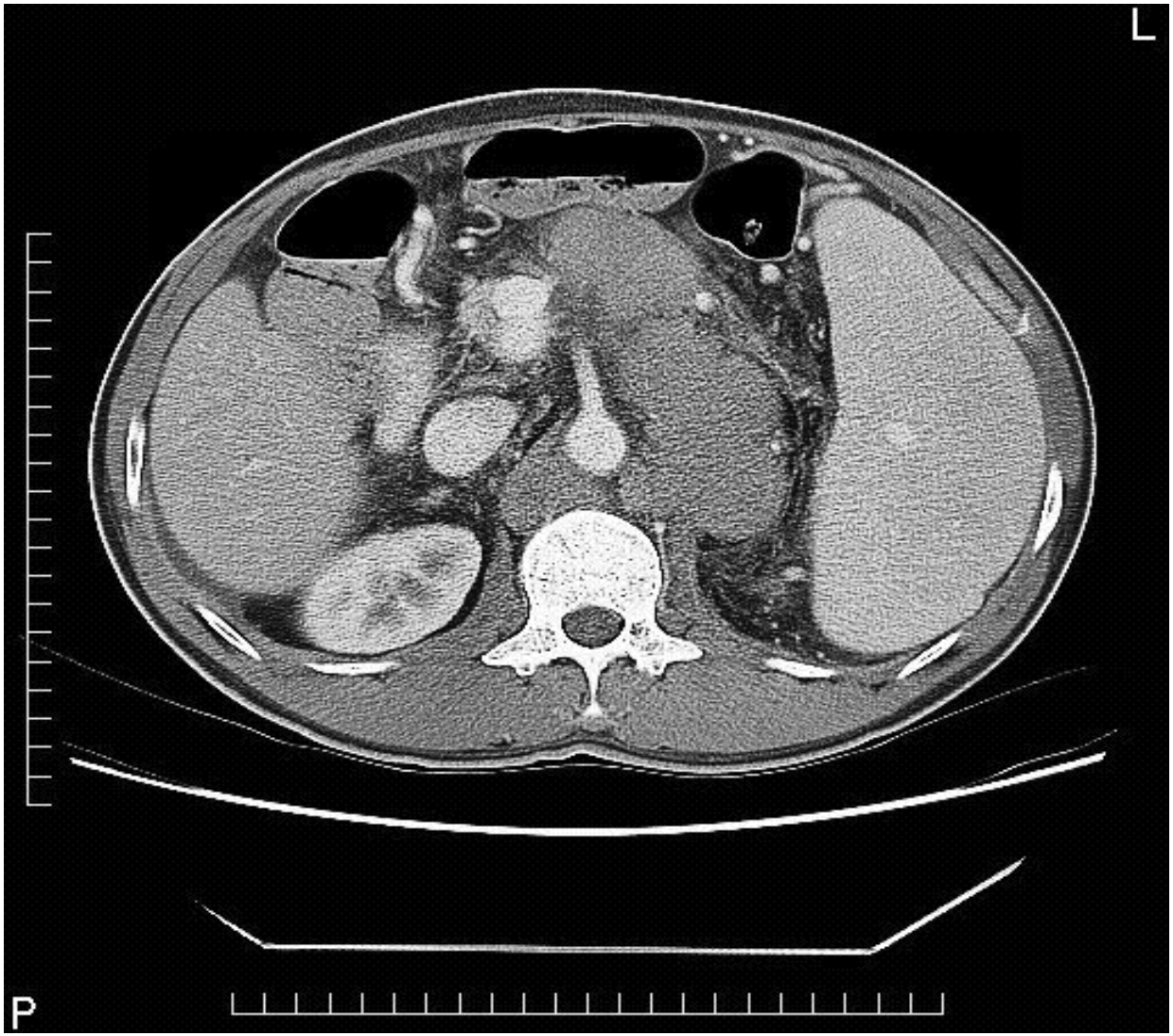
FUO	Allograft involvement	Extra allograft disease
• Lymph-adenopathy • Pancytopenia	• Lymphocytic infiltrate in graft mimics rejection	• CNS lymphoma • Other organs

- PTLD can clinically resemble other infectious diseases – need tissue!

Lung transplant patient EBV D+/R-

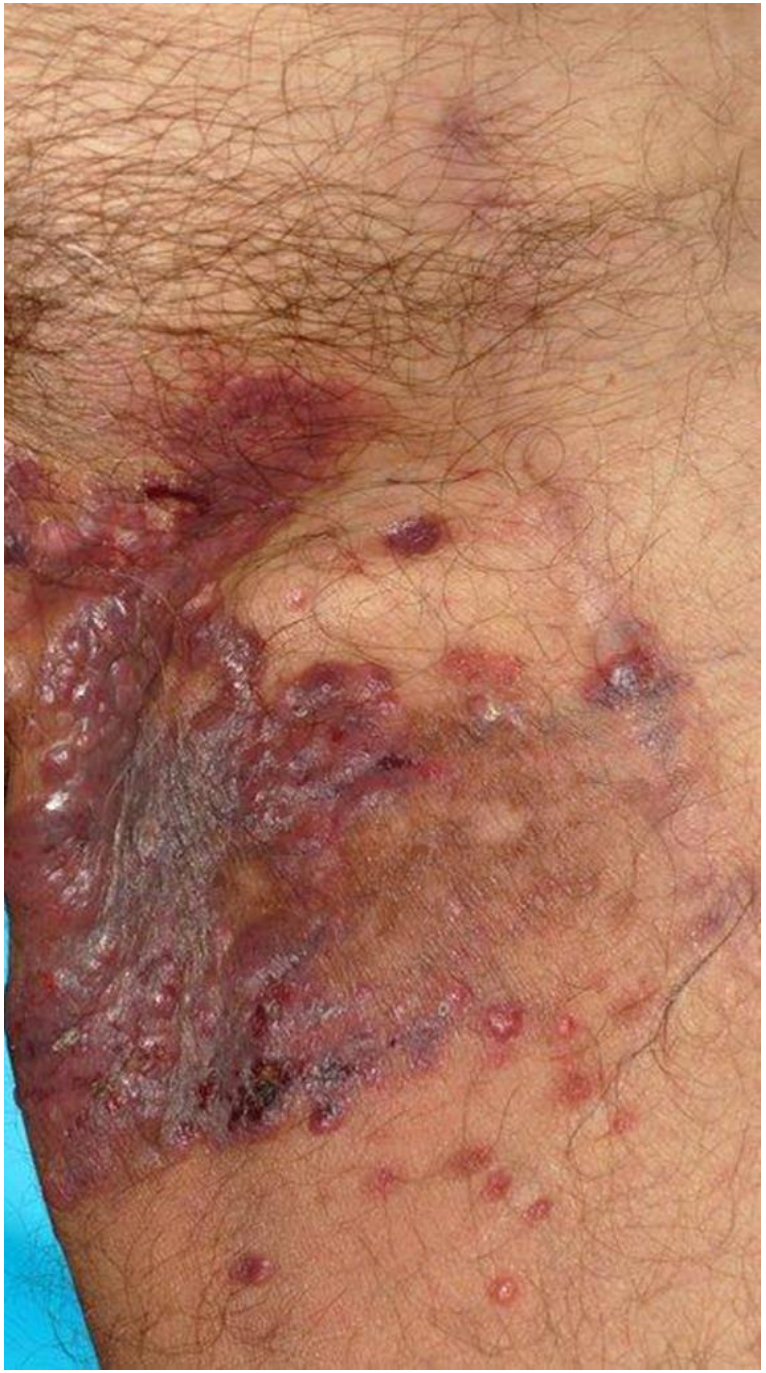


Pyrexia of Unknown Origin in kidney transplant



74 y.o. man
Heart transplant
12 years ago
Rash in groin
and upper thigh

Biopsy: T-cell
lymphoma



Case

- **28 year old female DM**
- **CMV D+/R-**
- **EBV D+/R-**
- **The patient receives a SPK transplant**
  - **Induction with Thymoglobulin 5mg/kg**
  - **On Tac/pred/MMF**
  - **At 3 months the patient has an episode of Acute rejection and given pulse steroid and thymoglobulin 3mg/kg**

What is this patients risk of PTLD?

- Low?
- Moderate?
- High?

RISK FACTORS FOR PTLD

- EBV serology
  - 1-5% incidence in R+ vs. 20-30% in R-
- Intensity of Immunosuppression
  - ATG
- Type of transplant
  - Small bowel > lung > heart > liver, kidney
- Herpesvirus interactions

Early vs. Late PTLD

Early (<1 year)	Late (>1 year)	
EBV D+/R- (primary infection)	Mean 7-10 years post-transplant	
Pediatrics	Older age	
ATG	Duration of immunesuppression	
Type of organ transplanted	Type of organ transplanted	
Donor origin	Recipient origin	
Disease within the graft	CNS lymphoma and GI tract	

EBV and PTLD

Table 1: Patient demographic and clinical characteristics

	EBV-negative PTLD (n = 58)	EBV-positive PTLD (n = 118)	p
Patient characteristics			
Patient sex: n (%)			0.74
Male	35 (60)	75 (64)	
Female	23 (40)	43 (36)	
Age at transplant: years, median	51	50	0.32
(range)	(1–76)	(0.2–71)	
Age at PTLD: years, median	56	56	0.16
(range)	(18–77)	(15–83)	
Time from transplant to PTLD, years, median	4.8	2.1	0.008
(range)	(0.02–19)	(0.03–36)	
Time from transplant to PTLD: n (%)			<0.001
First year	9 (16)	49 (43)	
Beyond first year	49 (84)	66 (57)	
Unknown	0	3	

Luskin et al., AJT 2015

Can EBV viral load predict PTLD

- **EBV viral load is negative in EBV-negative PTLD (approx. 20-40% cases)**
- **EBV PCR has good sensitivity for EBV-positive PTLD**
- **Viral loads are variable between labs so no standard cut-off value**

Preiksaitis et al. Am J Trans 2010

Pathologic classification of PTLD

- Early lesions
  - Plasmacytic hyperplasia
  - Infectious mononucleosis-like lesion
- Polymorphic PTLD
- Monomorphic PTLD (classify according to the lymphoma they resemble)
- B cell neoplasms
- Diffuse large B cell lymphoma
- Burkitt lymphoma
- Plasma cell myeloma
- Plasmacytoma-like lesion
- Other: T cell neoplasms Peripheral T cell lymphoma, NOS , Hepatosplenic T cell lymphoma, Classical Hodgkin lymphoma-type PTLD

Staging

- CT chest and abdomen
- PET scan if available (good for follow-up of lesions)
- MRI head (suggested by some experts)

Prognosis

Poor prognosis if:

- T cell or NK cell PTLD
- EBV-negative
- Recipient origin
- Multiple sites
- CNS disease

Therapy for PTLD

Depends on pathology but reduction in IS is first step:

- **Polymorphic – reduction of IS alone may work**
- **Monomorphic – if CD20+, rituximab**
  - **T-cell origin – CHOP chemotherapy**
  - **Mixed T/B – CHOP-R**
- **CNS – intrathecal methotrexate**

Other Strategies for PTLD

- **Antivirals – Ganciclovir for EBV viremic patients**
  - **Might be beneficial for lytic virus**
  - **Does not effect latent phase because antivirals target polymerase**
  - **Might help reduce co-infection with CMV (risk factor for PTLD)**

PREVENTION OF PTLD IN EBV D+/R-

Case

- **28 year old female DM**
- **CMV D+/R-**
- **EBV D+/R-**
- **The patient receives a SPK transplant**

Questions

- **What are your suggestions?**
  - **Related to immunosuppression?**
  - **Related to antiviral prophylaxis?**
  - **Do you have any other suggestions?**

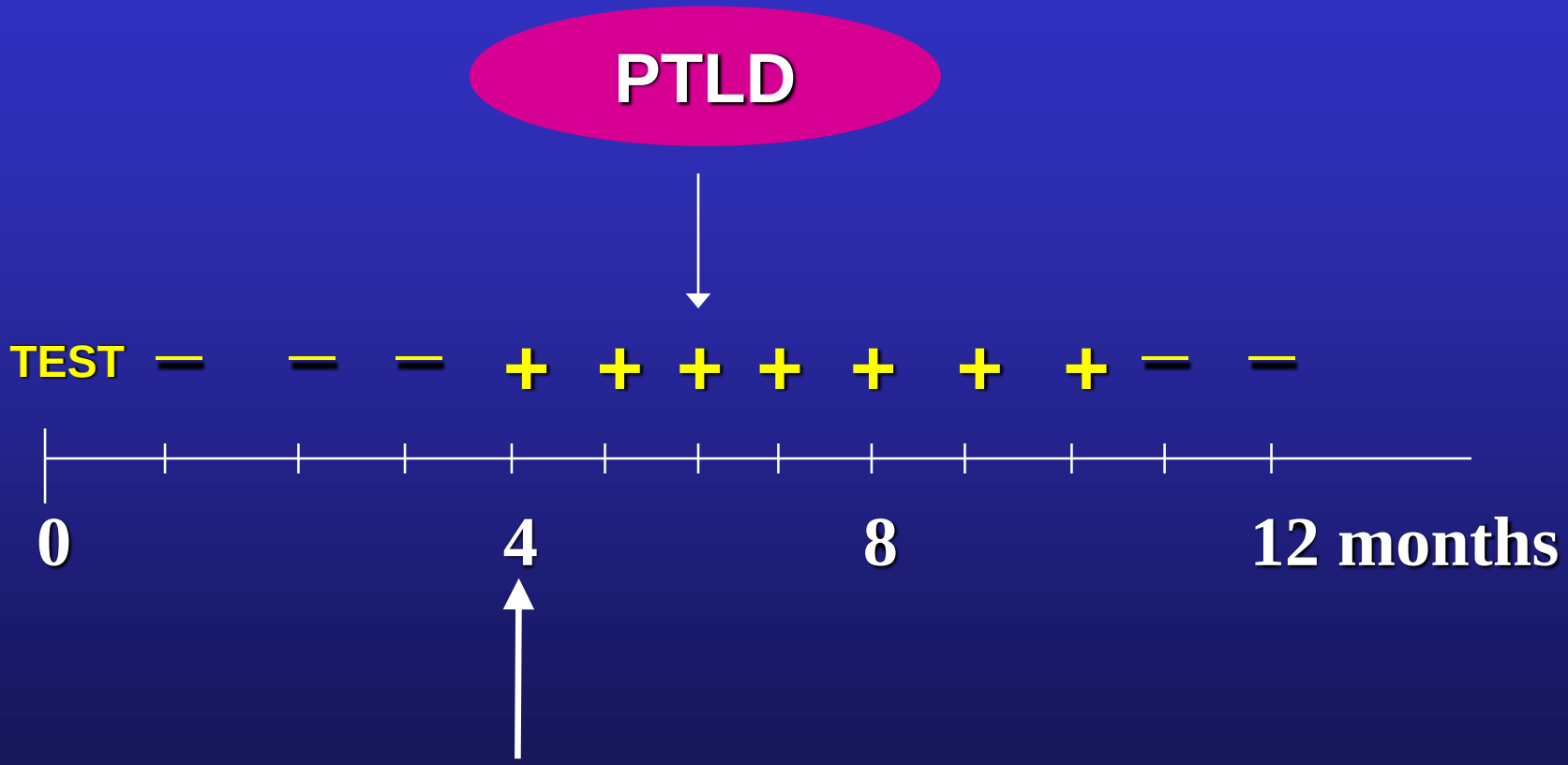
Prevention of PTLD in EBV D+/R-

- **EBV viral load monitoring with reduction of immunosuppression for high viral loads** ***(Kumar et al. ATC abstract 2015)***
  - **?at what level of DNAemia do we intervene**
- **Antivirals (val)ganciclovir for 3 months in EBV D+/R-** ***(Funch et al. AJT 2005)***
- **Pre-emptive Rituximab** ***(van Esser et al. Blood 2004)***
- **Adoptive Immunotherapy** ***(Savoldo et al. Blood 2006)***

ANTIVIRAL PROPHYLAXIS?

- Ganciclovir / Valganciclovir 10X more potent in vitro than Acyclovir
- However not effect against latent virus.
- Not proven to be effective for PTLD prevention
- Prevents CMV, may decrease lytic EBV replication

PRE-EMPTIVE THERAPY



What do I do about a positive test?

- You are doing EBV viral load every two weeks on a D+/R- patient on valgan x 3 months. At week 14, the viral load is 5000 copies/mL
- What are the options?
  - Wait for next viral load
  - Decrease immunosuppression
  - Antiviral therapy
  - Pre-emptive rituximab
  - Adoptive immunotherapy

Pre-EMPTIVE RITUXIMAB

- Monoclonal anti-CD 20 antibody
- TCD allo-HSCT recipients with EBV viral loads > 1000 copies/ml
  - 17 patients of whom 15 given pre-emptive rituximab – one dose
  - Viral load ranged from 1150 to > 1,000,000 copies
- 14/15 had complete clearance of EBV from blood and no PTLD.

Van Esser at al; Blood 2004

Adoptive immunotherapy

- Successful ex-vivo generation of EBV-CTLs from 33 of 35 high-risk SOT recipients
- Infused EBV-CTLs in 12 of the recipients who had persisting high EBV-DNA load and/or localized PTLD.
- Infusion increased the number of EBV-responsive T cells in the circulation + transient increase in plasma EBV-DNA suggestive of lysis of EBV-infected cells, although there was no consistent decrease in virus load in PBMCs.
- None of pre-emptively treated patients developed PTLD.

Savoldo et al. Blood 2006

Preventing PTLD: Summary

- Optimize immunosuppression
  - Avoid ALG, minimize overall immunosuppression
- Prophylaxis
  - Antiviral prophylaxis could be considered for high-risk
  - Ganciclovir ?better than acyclovir (also prevents CMV)
- Pre-emptive therapy
  - Monitor viral loads (e.g. monthly x 12 months in D+/R-)
  - Reduce immunosuppression if persistently elevated viral load
  - If this fails, other strategies may be considered (?antivirals, rituximab, adoptive immunotherapy)

Thank you!