Συζήτηση Περίπτωσης

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Πανεπιστημιακό Γενικό Νοσοκομείο ΑΤΤΙΚΟΝ

Ασθενής

- Μετά από μεταμόσχευση νεφρού
- Λεμφαδενοπάθεια
- Πυρετός
- Θετική PCR-EBV

Spectrum of Histopathologic Diagnosis of Lymph Node Biopsies After Liver and Kidney Transplant

Table 2. Patient Demographics and Characteristics

Characteristic	PTLD	Kaposi	Metastatic	Reactive	Infectious	Amyloid	Dermatopathic	Castleman	Kikuchi	Sea Blue Histiocytosis	Hemangioma
No. of patients	7	2	1	8	6	4	2	1	1	1	1
Mean age at first transplant (y)	26.21	24.5	23	30.8	38.5	30	20	48	35	50	28
Mean age at biopsy (y)	32.5	26.5	42	38.6	42.1	35.5	20	48	53	50	28
Sex (male/female)	4/3	1/1	0/1	8/0	2/4	3/1	1/1	1/0	1/0	1/0	1/0
Transplanted organ											
Liver	3	0	0	0	0	0	1	0	0	0	0
Kidney	4	2	1	8	6	4	1	1	1	1	1
Immunosuppressive therapy (%)											
Tacrolimus	57	0	0	25	17	0	50	0	100	0	0
Cyclosporine	43	100	100	62.5	83	75	50	0	0	100	100
Steroid	0	0	0	12.5	0	25	0	100	0	0	0
Average duration (mo)	75.2	26.5	234	102	42	68.5	3	0	223	0	0
Fever (%)	72	0	0	37.5	83	25	100	0	100	100	0
Night sweats (%)	14	0	0	0	33	0	0	0	0	100	0
Weight loss (%)	43	0	0	0	17	25	50	0	0	0	0
Lymphadenopathy detection (%)											
Palpable	86	100	0	12.5	50	0	0	0	0	0	0
Radiographic	14	0	100	37.5	33	0	50	0	100	100	0
Incidental	0	0	0	50	17	100	50	100	0	0	100
Localization type (%)											
Localized	57	0	100	100	67	50	50	0	0	0	100
Generalized	43	100	0	0	33	50	50	100	100	100	0
Mean lymph node size (cm)	2.37	3.75	1.8	2.67	2.53	2.5	2	6	1.4	2.2	2.3

Experimental and Clinical Transplantation (2015) Suppl 1: 177-182

Spectrum of Histopathologic Diagnosis of Lymph Node Biopsies After Liver and Kidney Transplant

Table 4. Histopathologic Diagnosis of Lymphadenopathy in 34 Solid-Organ Transplant Patients Undergoing Lymph Node Biopsy

Histopathologic Diagnosis	Number (%)
Total	34 (100%)
Malignant lymph node group	10 (29%)
PTLD	6 (17%)
Kaposi sarcoma	2 (6%)
Papillary thyroid carcinoma	1 (3%)
PTLD and Kaposi sarcoma	1 (3%)
Benign lymph node group	24 (71%)
Reactive	8 (24%)
Tuberculous lymphadenitis	6 (17%)
Amyloid lymphadenopath	4 (12%)
Dermatopathic lymphadenopathy	2 (6%)
Castleman's Disease and amyloid lymphadenopathy	1 (3%)
Kikuchi-Fujimoto disease	1 (3%)
Sea blue histiocytosis	1 (3%)
Hemangioma	1 (3%)

Experimental and Clinical Transplantation (2015) Suppl 1: 177-182

Infection in Solid-Organ Transplant Recipients

Nosocomial, technical (donor or recipient)	Activation of latent infection (relapsed, residual, opportunistic)	Community-acquired

Dynamic assessment of risk of infection

Common Infections in Solid-Organ Transplant Recipients

<1 Month

Infection with antimicrobial-resistant species:
- MRSA
- VRE
- Candida species (non-albicans)

Aspiration
Catheter infection
Wound infection
Anastomotic leaks and ischemia
Clostridium difficile colitis

Donor-derived infection (uncommon):
- HSV, LCMV, rhabdovirus (rabies), West Nile virus, HIV, *Trypanosoma cruzi*

Recipient-derived infection (colonization):
- Aspergillus, pseudomonas

1–6 Months

With PCP and antiviral (CMV, HBV) prophylaxis:
- Polyomavirus BK infection, nephropathy
- *C. difficile* colitis
- HCV infection
- Adenovirus infection, influenza
- *Cryptococcus neoformans* infection
- *Mycobacterium tuberculosis* infection

Anastomotic complications

Without prophylaxis:
- Pneumocystis
- Infection with herpesviruses (HSV, VZV, CMV, EBV)
- HBV infection
- Infection with listeria, nocardia, toxoplasma, strongyloides, leishmania, *T. cruzi*

>6 Months

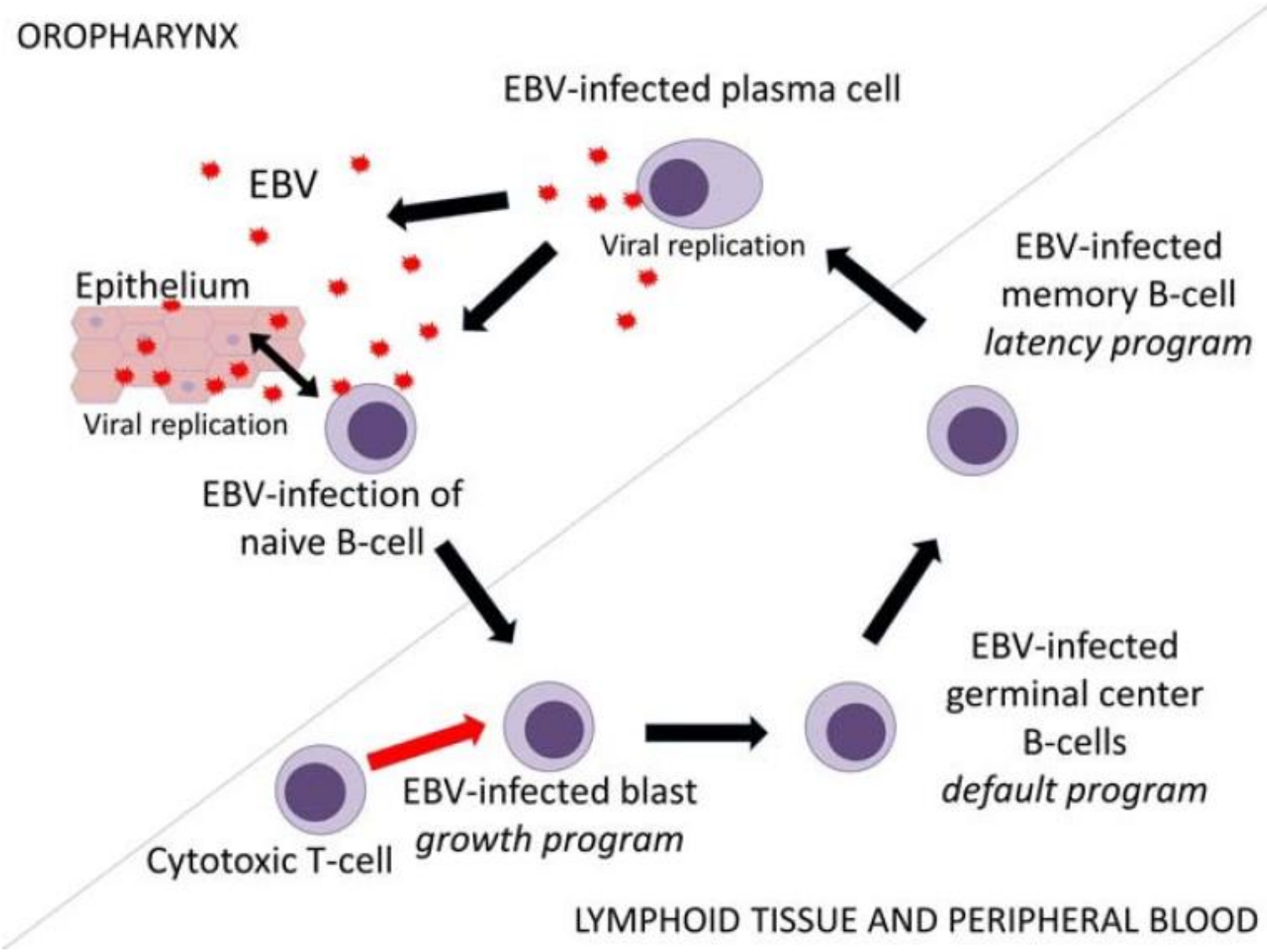
Community-acquired pneumonia, urinary tract infection
Infection with aspergillus, atypical molds, mucor species
Infection with nocardia, rhodococcus species
Late viral infections:
- CMV infection (colitis and retinitis)
- Hepatitis (HBV, HCV)
- HSV encephalitis
- Community-acquired (SARS, West Nile virus infection)
- JC polyomavirus infection (PML)
- Skin cancer, lymphoma (PTLD)

N Engl J Med 2007;357:2601-14.

Επιδημιολογία-Κλινικά σύνδρομα

- Μετάδοση με στοματικές εκκρίσεις αλλά και με αίμα, η μεταμόσχευση ανθρώπινων ιστών
- 90% των ενηλίκων έχουν μολυνθεί
- Μετά την πρωτολοίμωξη ο ιός παραμένει σε λανθάνουσα κατάσταση σε μνημονικά Β-λεμφοκύτταρα
- Ασυμπτωματική λοίμωξη
- Σύνδρομο λοιμώδους μονοπυρηνώσεως

EBV – life cycle



EBV – latency programs

Table 1 Epstein-Barr virus-driven lymphoproliferative disorders are linked with particular Epstein-Barr virus latency programs

Latency	Expressed *EBV* gene products	Normal B-cell stage	Associated disease
III (growth)	EBER1-2, EBNA1-6, LMP1, LMP2A-B	Activated B lymphoblast	PT-DLBCL AIDS-related lymphoma Acute infectious mononucleosis
II (default)	EBER 1-2, EBNA1, LMP1- 2A	B-cell undergoing the GC reaction	PT-DLBCL Classical Hodgkin lymphoma
I	EBER 1-2 , EBNA1	Memory B-cell	(PT-) Burkitt lymphoma (PT-) PBL

Ανοσοεπαρκή άτομα

- Σημαντικό ποσοστό από τα κυκλοφορούντα CD8+ T cell έχουν ειδικότητα έναντι EBV-specific epitopes με σκοπό τον έλεγχο της λοίμωξης
- Περίπου 0.2% το 2% με ειδίκευση έναντι lytic epitopes
- Περίπου 0.05% το 1% με ειδίκευση έναντι latent epitopes

Epstein-Barr Virus–Positive Posttransplant Lymphoproliferative Disease After Solid Organ Transplantation: Pathogenesis, Clinical Manifestations, Diagnosis, and Management

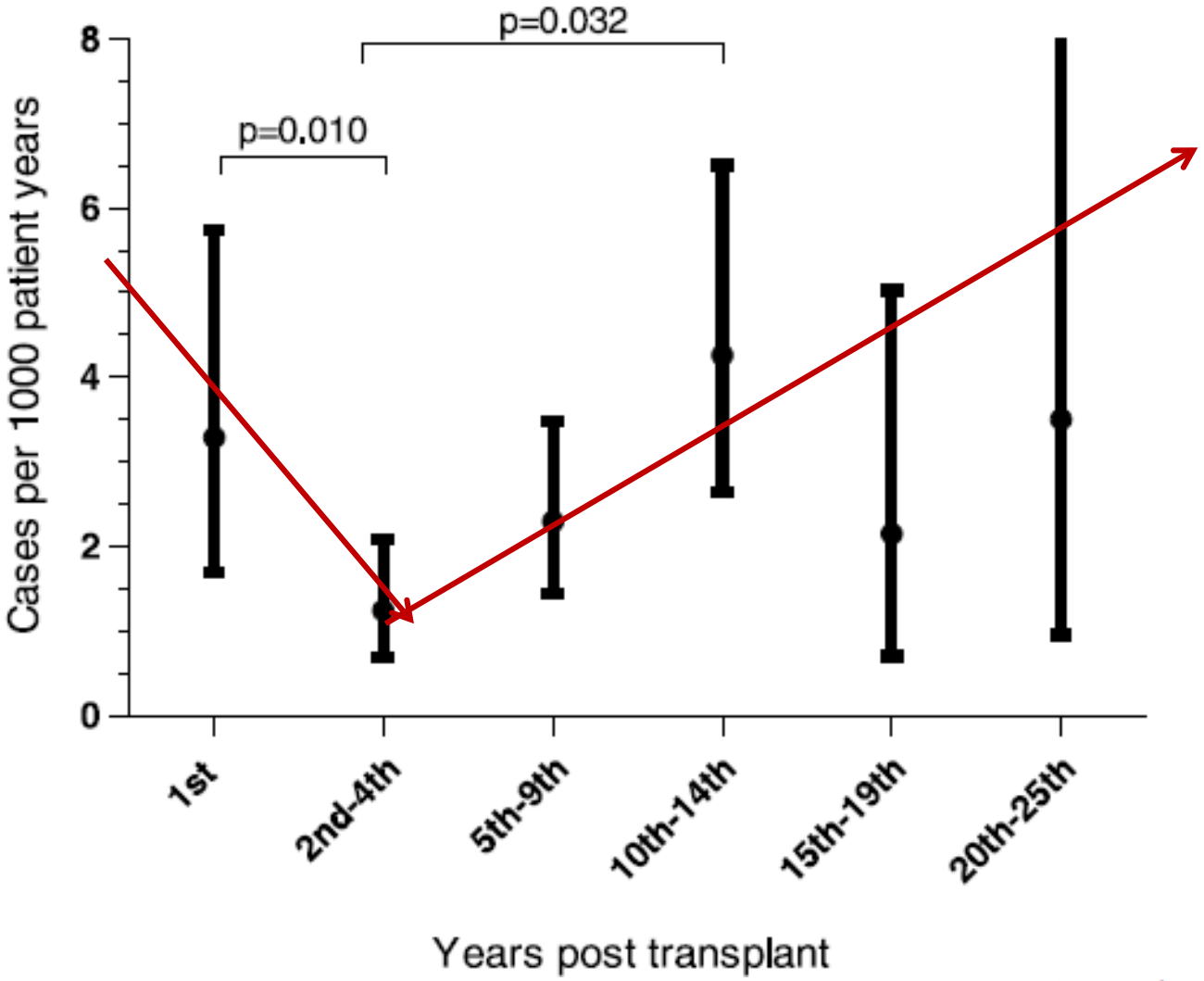
WHO classification of PTLD

WHO classification	Subcategories
Early lesions	Plasmacytic hyperplasia
	Infectious mononucleosis-like lesion
Polymorphic PTLD	To be classified according to the type of lymphoma they resemble
Monomorphic PTLD	B cell neoplasms
	DLBCL
	Burkitt lymphoma
	Plasma cell myeloma
	Plasmacytoma-like lesions
	Other
	T cell neoplasms
	Peripheral T cell lymphoma, not otherwise specified
	Hepatosplenic T cell lymphoma
	Other
Classical Hodgkin lymphoma-type PTLD	

Latency –III Growth program

Latency – I, II

Epidemiology of Posttransplantation Lymphoproliferative Disorder in Adult Renal Transplant Recipients



Transplantation 2013;95: 470–478

Epidemiology of Posttransplantation Lymphoproliferative Disorder in Adult Renal Transplant Recipients

- Early onset (≤1 year): 15%
  - ✓ Nearly 100% EBV+
- Late onset (>1 year): 85%
  - ✓ 50%-80% EBV+
- Very late onset (>10 years): 30%

Transplantation 2013;95: 470–478

Post-transplant lymphoproliferative disorders

Early lesions

- Plasmacytic hyperplasia
- Infectious mononucleosis-like lesion

Polymorphic post-transplant lymphoproliferative disorder (PTLD)

Monomorphic PTLD*

- Diffuse large B cell lymphoma‡
- Burkitt lymphoma‡
- Plasma cell myeloma‡
- Plasmacytoma-like lesion‡
- Others‡
- T cell neoplasms§
- Peripheral T cell lymphoma, NOS§
- Hepatosplenic T cell lymphoma§
- Others§

Classic Hodgkin lymphoma-like PTLD

Response to Rituximab-Based Therapy and Risk Factor Analysis in Epstein Barr Virus–Related Lymphoproliferative Disorder After Hematopoietic Stem Cell Transplant in Children and Adults: A Study From the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation

Table 1. Frequency of Posttransplant Lymphoproliferative Disorder and Hazard Risk Related to Type of Transplant

Type of Donor	Number of Allogeneic HSCT	No. of PTLDs	Frequency, %	Hazard Ratio (95% CI)	*P* Value
MFD	1902	22	1.16	1.00	
MMFD/haplo	455	13	2.86	2.47 (1.17–5.17)	.015
MUD	1762	70	3.97	3.43 (2.07–5.74)	<.001
MMUD	347	39	11.24	9.72 (5.53–17.17)	<.001
Total	4466	144	3.22	2.79 (1.74–4.50)	<.001

- **Μέσος χρόνος εμφάνισης: 2-4 μήνες μετά την μεταμόσχευση**
- **Early onset disease (≤100 days): 75% των ασθενών**
- **1ος μήνας: 6% των ασθενών**
- **> 6ος μήνα: 11% των ασθενών**
- **>12ος μήνα: 4% των ασθενών**

Epstein-Barr Virus and Posttransplant Lymphoproliferative Disorder in Solid Organ Transplantation

Table 2: Presenting symptoms and signs in patients with lymphoproliferative disorder

Symptoms/complaints	Signs
Swollen lymph glands	Lymphadenopathy
Weight loss	Hepatosplenomegaly
Fever or night sweats	Subcutaneous nodules
Sore throat	Tonsillar enlargement
Malaise and lethargy	Tonsillar inflammation
Chronic sinus congestion and discomfort	Signs of bowel perforation
Anorexia, nausea and vomiting	Focal neurologic signs
Abdominal pain	Mass lesions
Gastrointestinal bleeding	
Symptoms of bowel perforation	

Διάγνωση

- Επαγρύπνηση για την έγκαιρη διάγνωση
- EBV-DNA με Quantitative PCR σε:
  1. Ολικό αίμα
  2. Μονοπύρηνα περιφερικού αίματος
  3. Πλάσμα
- Βιοψία και ανίχνευση EBV για EBER με
  1. FISH για ανίχνευση EBER (ιδανική μέθοδος)
  2. Ανοσοιστοχημεία για ανίχνευση EBNA, LMP
- Επιβεβαιωμένη διάγνωση
- Πιθανή διάγνωση

EBV-PTLD

- Προφύλαξη
- Pre-emptive monitoring and treatment
- Θεραπεία διαγνωσμένης νόσου

Pre-emptive monitoring and treatment

- Σημαντική EBV-ιαιμία επιβάλλει χορήγηση Rituximab
  1. Ποιο το επίπεδο της ιαιμίας?
  2. Σε τι δείγμα (ολικό αίμα, πλάσμα μονοπύρηνα)?
- Rituximab κάθε εβδομάδα (1 – 4 δόσεις) μέχρι εξαφάνιση της ιαιμίας
- Ταυτόχρονη μείωση της ανοσοκαταστολής εάν είναι εφικτό
- Αντιικα φάρμακα και IVIgG δεν προσφέρουν θεραπευτικό όφελος

Διαφορική Διάγνωση

- EBV-related Disease
  - ✓ Other
  - ✓ PTLD
- Non-EBV related Disease (EBV-reactivation without clinical significance)
- PCR-EBV: 44.401×10^3 U/ml

Διευκρίνηση

- Σε τι δείγμα πραγματοποιήθηκε η PCR-EBV?
  1. Ολικό αίμα?
  2. Πλάσμα?

EBV PCR in the Diagnosis and Monitoring of Posttransplant Lymphoproliferative Disorder: Results of a Two-Arm Prospective Trial

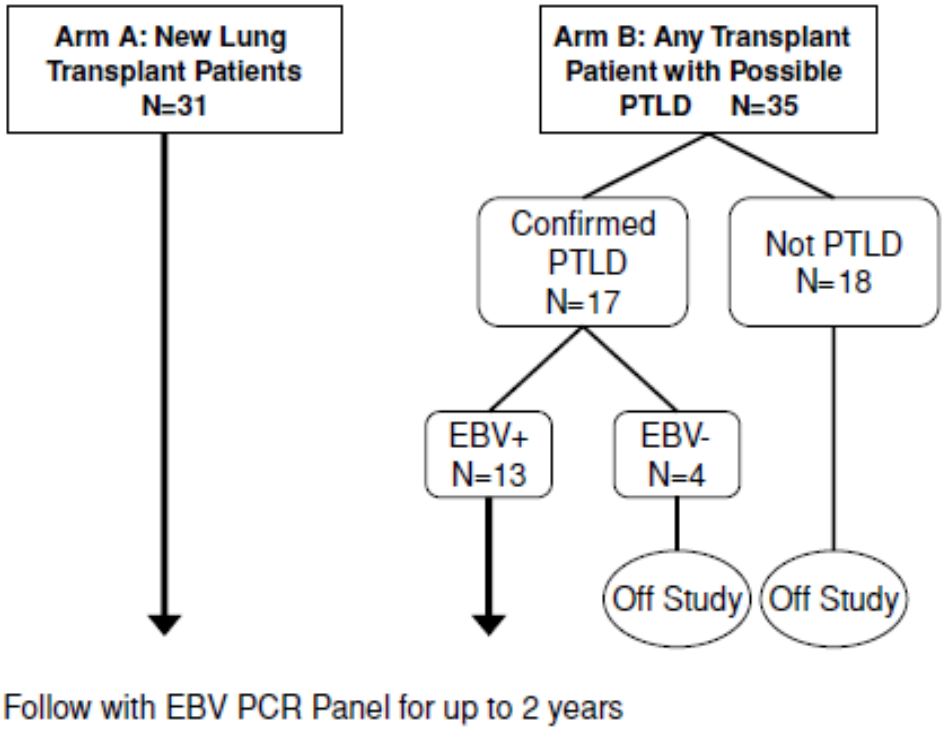


Table 2: EBV positive PTLD characteristics

Patient characteristic	All patients (n = 35)	PTLD (n = 17)	Non-PTLD (n = 18)
Age at enrollment (years)			
Median	56	55	60
Range	21–78	36–59	21–78
Gender			
Male	20 (57%)	7 (41%)	13 (72%)
Female	15 (43%)	10 (59%)	5 (28%)
Organ transplant type			
Lung	2 (6%)	1 (6%)	1 (6%)
Heart	8 (23%)	3 (18%)	5 (28%)
Liver	10 (28%)	3 (18%)	7 (39%)
Kidney	10 (28%)	7 (41%)	3 (17%)
Pancreas	1 (3%)	1 (6%)	0 (0%)
Kidney/pancreas	1 (3%)	1 (6%)	0 (0%)
Liver/pancreas	1 (3%)	0 (0%)	1 (6%)
Stem cell	2 (6%)	1 (6%)	1 (6%)

American Journal of Transplantation 2008; 8: 1016–1024

EBV PCR in the Diagnosis and Monitoring of Posttransplant Lymphoproliferative Disorder: Results of a Two-Arm Prospective Trial

Table 4: Control Arm A EBV PCR panel results

	Positive	Negative	Median copies/Ml	Range
Plasma EBV				
EBNA	0	31	0	NA
EBER	1 (3%)	30	100	100
LMP	0	31	0	NA
Intracellular EBV				
EBNA	7 (23%)	24	300	100–2800
EBER	13 (42%)	18	300	100–2300
LMP	4 (13%)	27	200	100–600

American Journal of Transplantation 2008; 8: 1016–1024

EBV PCR in the Diagnosis and Monitoring of Posttransplant Lymphoproliferative Disorder: Results of a Two-Arm Prospective Trial

Table 6: Eighteen transplant patients in Arm B with no PTLD. Initial evaluation EBV PCR results

	Positive	Negative	Median copies/mL	Range
Plasma EBV				
EBNA	0	18	0	NA
EBER	0	18	0	NA
LMP	0	18	0	NA
Intracellular EBV				
EBNA	4 (22%)	14	300	200–800
EBER	4 (22%)	14	800	200–2,200
LMP	2 (11%)	16	300	200–400

American Journal of Transplantation 2008; 8: 1016–1024

EBV PCR in the Diagnosis and Monitoring of Posttransplant Lymphoproliferative Disorder: Results of a Two-Arm Prospective Trial

Table 8: Comparison of individual EBV PCR assays

	Free Plasma EBV			Cellular EBV			
	EBNA	EBER	LMP	EBNA	EBER	LMP	Panel
Sensitivity (%)	77	46	31	77	69	46	92
Specificity (%)	100	100	100	78	78	89	72
PPV (%)	100	100	100	72	69	75	71
NPV (%)	86	72	67	82	78	70	93

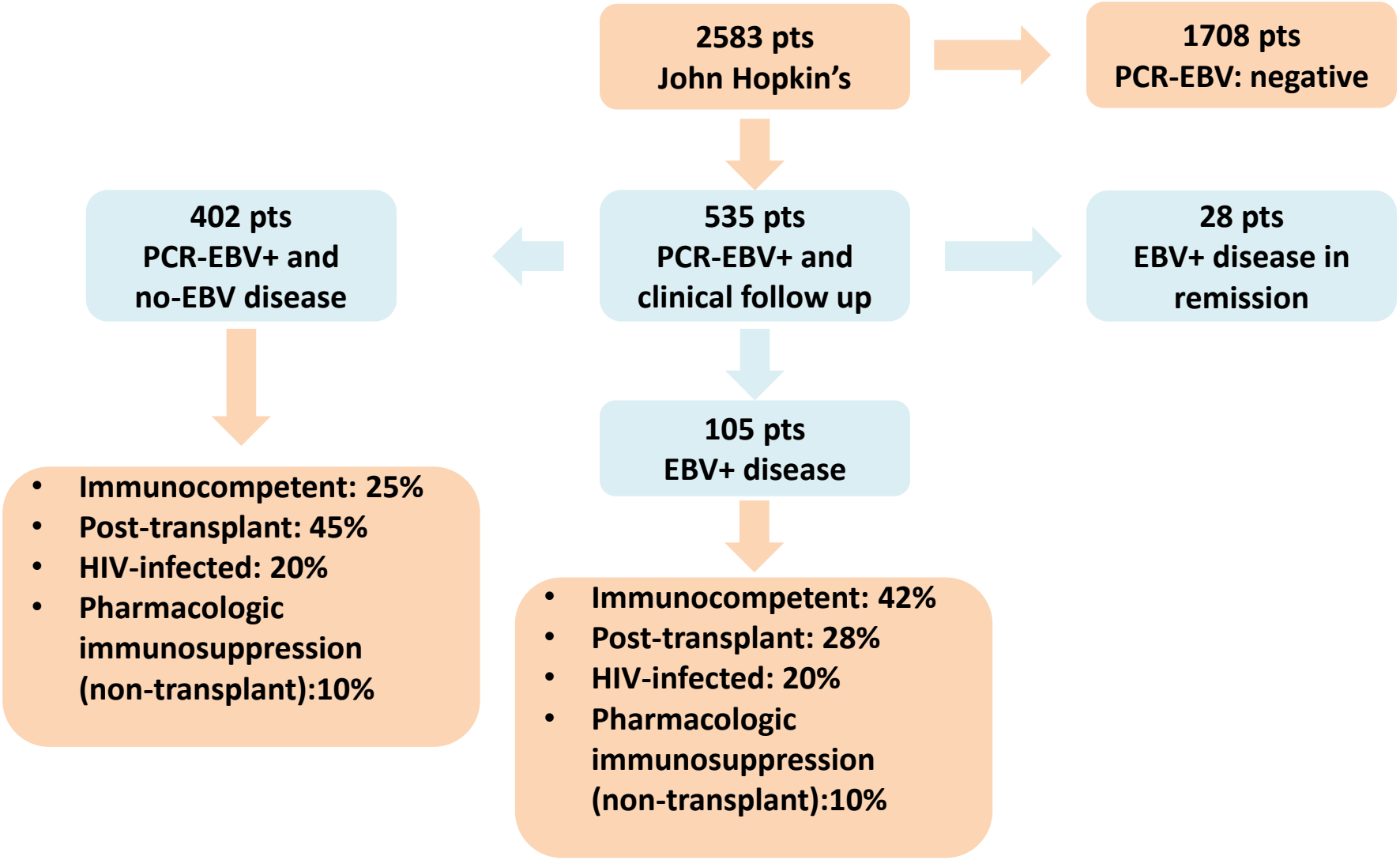
American Journal of Transplantation 2008; 8: 1016–1024

The clinical significance of EBV DNA in the plasma and peripheral blood mononuclear cells of patients with or without EBV diseases

- **Cases were grouped into 5 diagnostic categories:**
  1. Active systemic (non CNS) EBV+ disease
  2. EBV+ CNS disease
  3. Partially treated EBV+ disease
  4. EBV+ disease in remission
  5. No EBV+ disease
- **The 9 active systemic EBV+ disease groups were:**
  - ✓ IM, EBV+ HLH, biopsy-proven EBV+ PTLD, unproven EBV+ PTLD, EBV+ NHL, EBV+ HL, EBV+ lymphoproliferative disorder, EBV+ NPC, and oral hairy leukoplakia
- **The 2 EBV+ CNS diseases were:**
  - ✓ EBV encephalitis and EBV+ primary CNS lymphoma
- **No EBV+ disease, cases were further subdivided:**
  - ✓ Based on whether or not the patient was immunocompromised
  - ✓ The cause of immunocompromise (HIV, inherited, or pharmacologic)

Blood. 2016;127(16):2007-2017

The clinical significance of EBV DNA in the plasma and peripheral blood mononuclear cells of patients with or without EBV diseases



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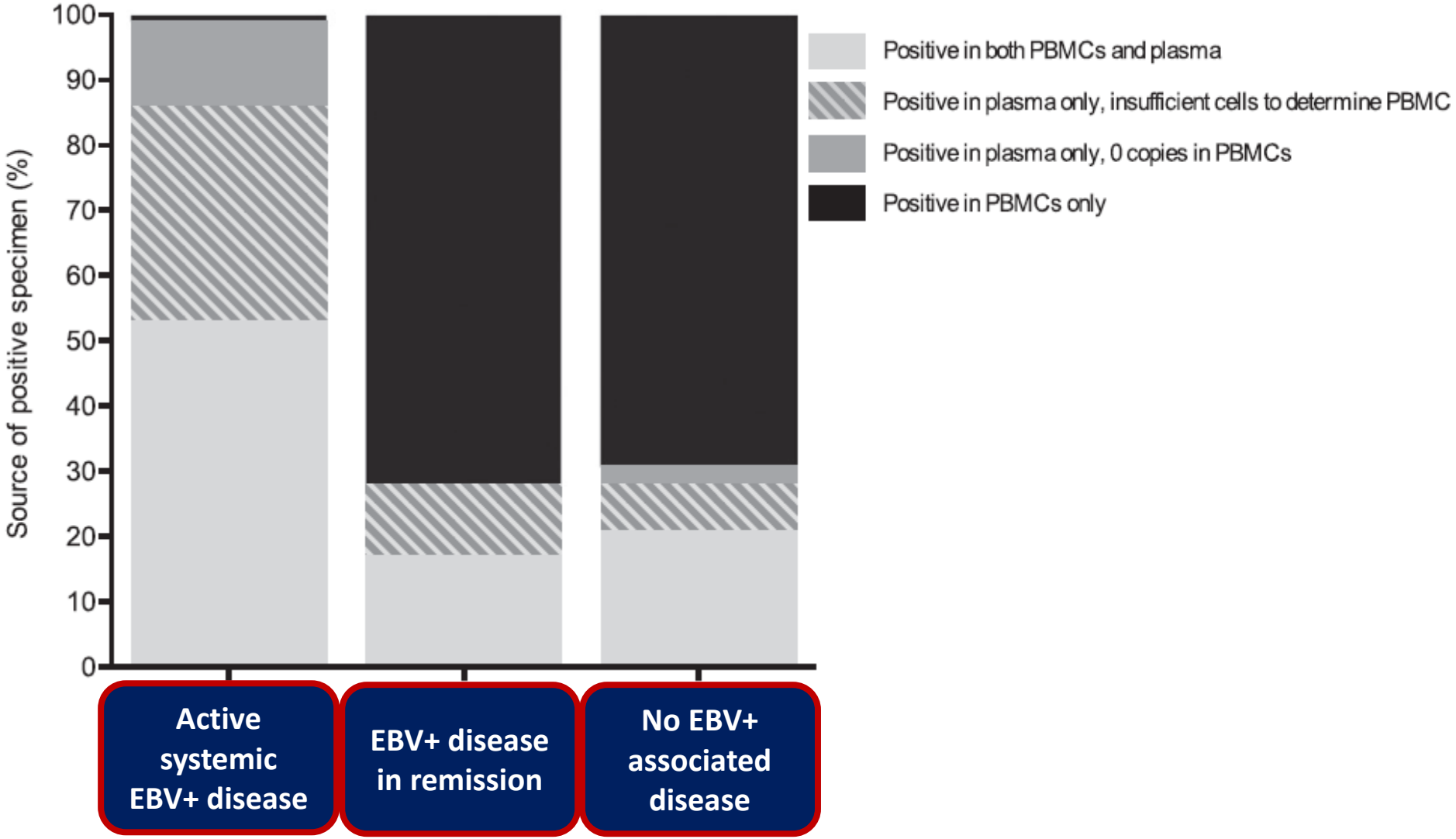
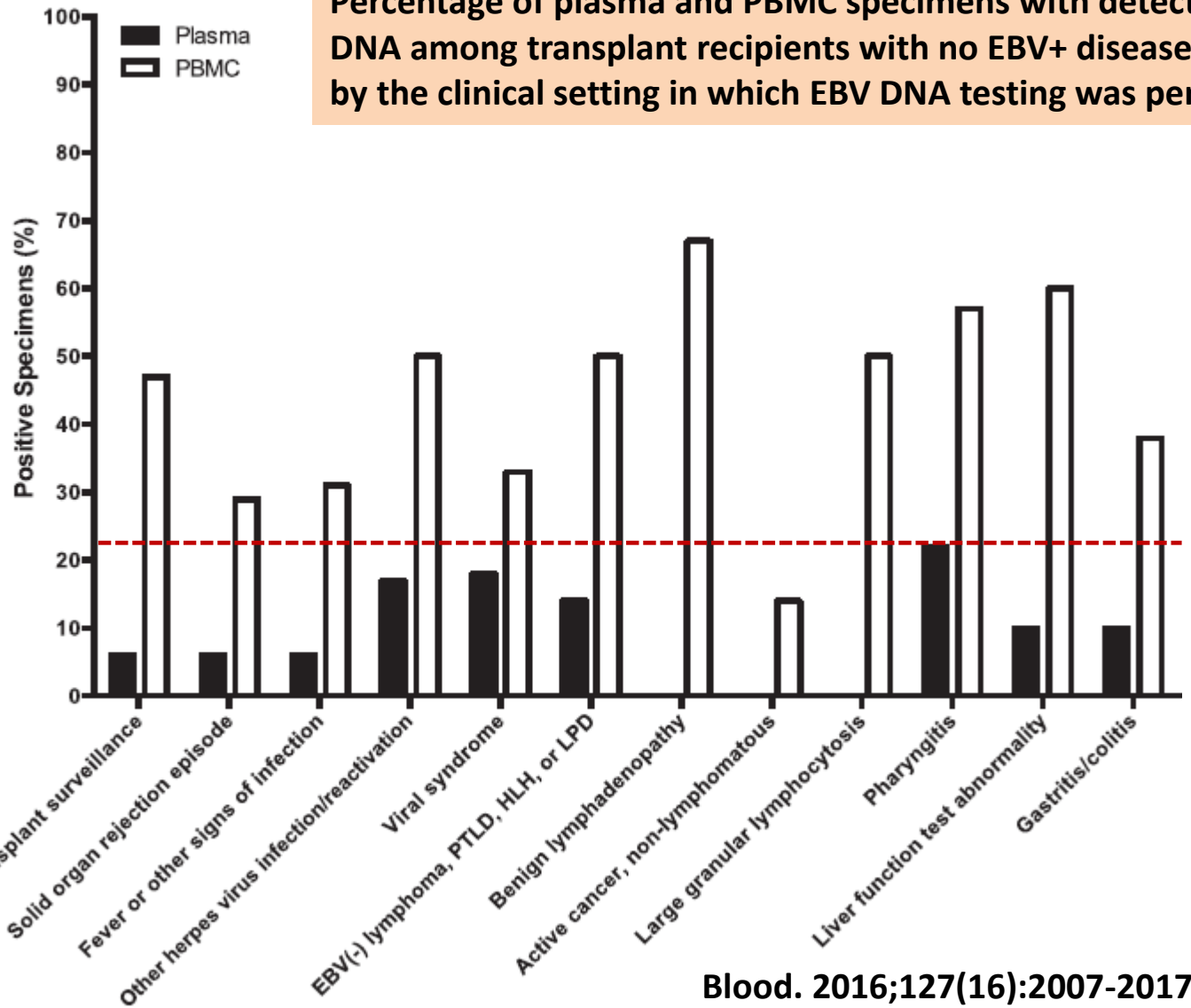


Blood. 2016;127(16)

The clinical significance of EBV DNA in the plasma and peripheral blood mononuclear cells of patients with or without EBV diseases

Percentage of plasma and PBMC specimens with detectable EBV DNA among transplant recipients with no EBV+ disease, grouped by the clinical setting in which EBV DNA testing was performed



Blood. 2016;127(16):2007-2017

The clinical significance of EBV DNA in the plasma and peripheral blood mononuclear cells of patients with or without EBV diseases

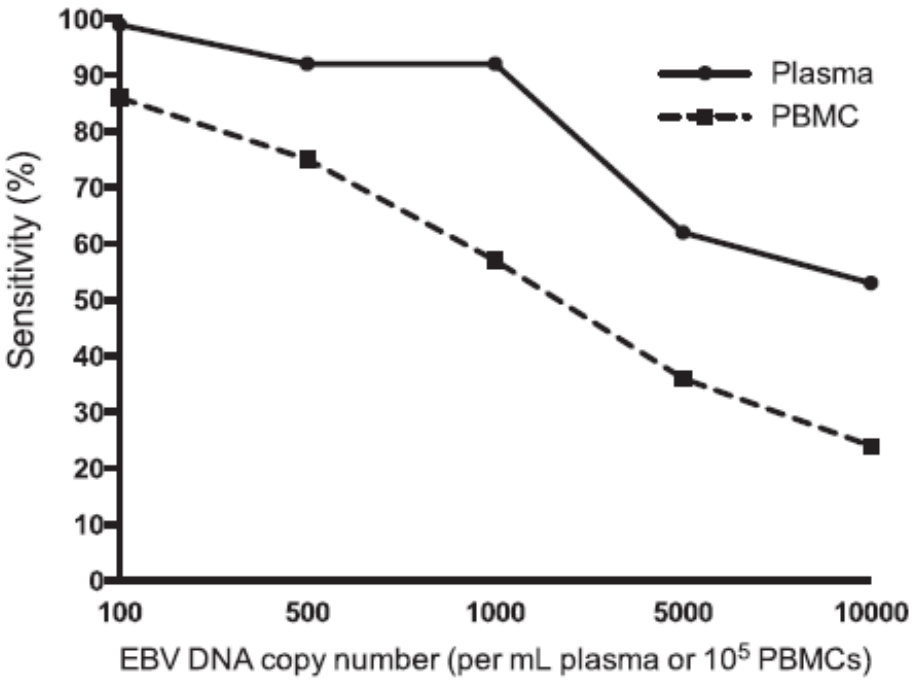
Detection of EBV DNA among patients with no current, prior, or subsequent EBV^+ disease

Diagnosis	# of patients	EBV DNA detected in plasma n (%)	EBV DNA detected in PBMCs n (%)
No EBV disease	2004	121 (6)	366 (18)
Immunocompetent	808	28 (3)	90 (11)
Transplant recipient	680	49 (7)	161 (24)
On pharmacologic immunosuppression	312	14 (4)	37 (12)
HIV-infected	178	29 (16)	78 (44)
Primary immunodeficiency	26	1 (4)	0 (0)

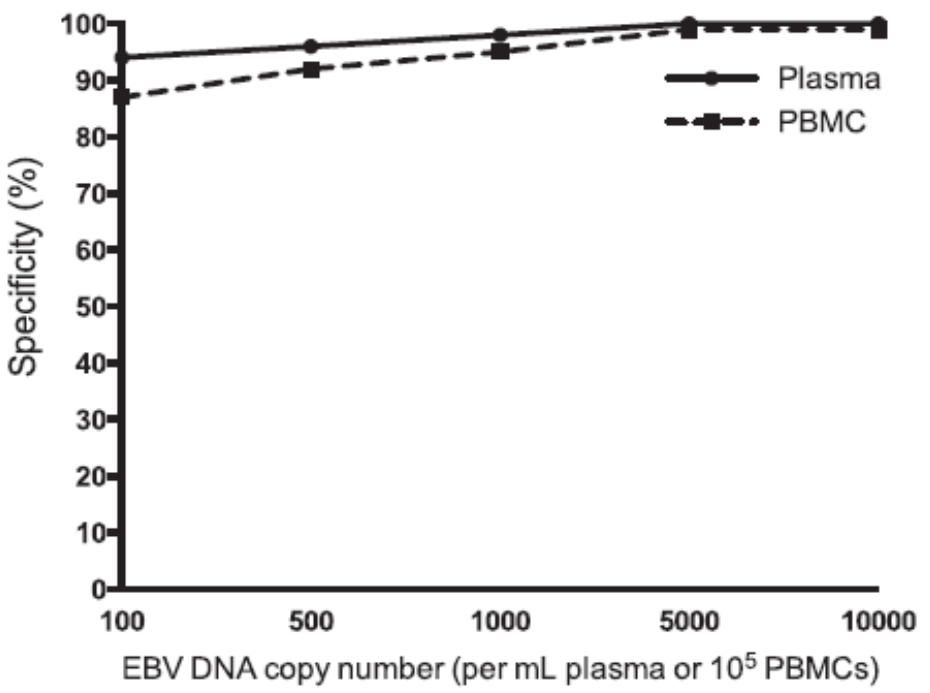
Blood. 2016;127(16):2007-2017

The clinical significance of EBV DNA in the plasma and peripheral blood mononuclear cells of patients with or without EBV diseases

Sensitivity for EBV+ disease diagnosis



Specificity for EBV+ disease diagnosis



Blood. 2016;127(16):2007-2017

Διαφορική Διάγνωση

- **EBV-related Disease**
  - ✓ **Other**
  - ✓ **PTLD**
- Non-EBV related Disease (EBV-reactivation without clinical significance)
- ***PCR-EBV: 44.401x10³U/ml***

Διαφορική Διάγνωση

Epstein-Barr virus–associated B-cell lymphoproliferative diseases

Disease
Infectious mononucleosis
Chronic active Epstein-Barr virus of B-cell type
Epstein-Barr virus–positive diffuse large B-cell lymphoma
Epstein-Barr virus mucocutaneous ulcer
Diffuse large B-cell lymphoma associated with chronic inflammation
Lymphomatoid granulomatosis

EBV-associated T-cell and NK cell lymphoproliferative diseases

Disease
EBV-associated hyperinflammatory syndrome
EBV-associated hemophagocytic lymphohistiocytosis
CAEBV-type T/NK cell disease
Systemic chronic active EBV infection of T cell or NK cell type
Cutaneous forms of CAEBV
Severe mosquito bite allergy
Hydroa vacciniforme-like lymphoproliferative disease
Malignant T/NK cell disease
Systemic EBV-positive T-cell lymphoma
Extranodal NK/T cell lymphoma, nasal type
Extranasal NK/T cell lymphoma
Aggressive NK cell leukemia
EBV-positive nodal NK/T cell lymphoma (provisional)

Σύνδρομο λοιμώδους μονοπυρηνώσεως

1. Πρωτολοίμωξη από EBV
2. Σε παιδιά η λοίμωξη είναι συνήθως ασυμπτωματική
3. Σύνδρομο λοιμώδους μονοπυρηνώσεως εμφανίζεται όταν η πρωτολοίμωξη αφορά εφήβους ή νέους ενήλικες
4. 95% άνω των 40 ετών έχουν εκτεθεί στο παρελθόν στον EBV
5. Ποιο το προηγούμενο EBV status του ασθενούς (EBV-IgG)?

Chronic active EBV infection (CAEBV)

- CAEBV was defined as:
  1. A severe progressive illness of more than 6 months duration usually with fever, lymphadenopathy, and splenomegaly that either began as a primary EBV infection or was associated with markedly elevated antibody titers to EBV viral capsid antigen (VCA> 1:5,120) or early antigen (EA>1:640), or markedly elevated EBV DNA in the blood,
  2. Infiltration of tissues (e.g. lymph nodes, lungs, liver, central nervous system, bone marrow, eye, skin) with lymphocytes,
  3. Elevated EBV DNA, RNA or proteins in affected tissues, and
  4. Absence of any other immunosuppressive condition

EBV-associated Hemophagocytic Lymphohistiocytosis (EBV-HLH)

- EBV λοίμωξη
- Αιμοφαγοκυτταρικό σύνδρομο
- Κριτήρια για την διάγνωση

EBV-associated diseases

- EBV-encephalitis
- EBV-myelitis
- EBV-hepatitis
- EBV-pneumonitis

Διαφορική Διάγνωση

Table 2. Classification of Post-Transplantation Lymphoproliferative Disorder (PTLD) by the World Health Organization (WHO).*

Characteristic	Nondestructive PTLD†	Polymorphic PTLD	Monomorphic PTLD	Hodgkin's Lymphoma–like PTLD
Underlying architecture	Nondestructive	Destructive	Destructive	Destructive
Composition	Plasma cells, small lymphocytes, immunoblasts	Complete spectrum of B-cell maturation	Fulfills specific WHO criteria for NHL; mantle-cell and follicular NHL are not considered PTLD	Fulfills specific criteria for classic Hodgkin's lymphoma
Immunohistochemical features	No diagnostic value	Mixture of B cells and T cells	Monoclonal population 90% DLBCL, mostly CD20+ (majority ABC type)	CD20–, CD30+; most cases CD15+
EBV association	Almost 100%	>90%	Both EBV-positive and EBV-negative	>90%
Clonality	No in most cases	Variable	Yes	Yes
Molecular genetic findings	None	Variable (BCL6 somatic hypermutations)	Differences between EBV-positive (genomic stable) and EBV-negative (similar to DLBCL in immunocompetent patients)	No information available
Clinical features	Mostly early PTLD	Variable	Both early and late PTLD	Possible increase in incidence of late-onset Hodgkin's lymphoma after allogeneic HSCT

Πιθανή διάγνωση

Early lesions

- Plasmacytic hyperplasia
- Infectious mononucleosis-like lesion

Polymorphic post-transplant lymphoproliferative disorder (PTLD)

Monomorphic PTLD*

- Diffuse large B cell lymphoma‡
- Burkitt lymphoma‡
- Plasma cell myeloma‡
- Plasmacytoma-like lesion‡
- Others‡
- T cell neoplasms§
- Peripheral T cell lymphoma, NOS§
- Hepatosplenic T cell lymphoma§
- Others§

Classic Hodgkin lymphoma-like PTLD

Διαγνωστική εξέταση

- FNB σε block παραορτικών λεμφαδένων (max diam 4.5cm) υπό την καθοδήγηση CT