GITMO
GRUPPO ITALIANO PER IL TRAPIANTO DI MIDOLLO OSSEO, CELLULE STAMINALI EMOPOIETICHE E TERAPIA CELLULARE

MALATTIA LINFOPROLIFERATIVA POST-TRAPIANTO

FAD SINCRONA
4 dicembre 2024

con il patrocinio di: S·I·T·O· SOCIETÀ ITALIANA DEI TRAPIANTI D'ORGANO E DI TESSUTI

Definizione, epidemiologia, patogenesi del PTLD

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Post-transplantation lymphoproliferative diseases (PTLD) are a **heterogeneous** group of **rare lymphoproliferative diseases** that represent a **serious complication** of allogeneic transplants (in SOT and HSCT) with an incidence of **about 1%** of transplants, which they reach due to the state of induced immunosuppression.

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Transplant Proc. 1969 March ; 1(1): 106–112.

Malignant Lymphomas in Transplantation Patients

First description of 5 cases in 1969

I. Penn, **W. Hammond**, **L. Brettschneider**, and **T. E. Starzl**
From the Departments of Surgery and Pathology, University of Colorado School of Medicine and the Veterans Administration Hospital, Denver, Colorado.

- Recipients of SOT or allogeneic HCT have an increased risk of EBV-associated cancers[1]
- PTLD accounts for 21% of cancers after SOT[2]
- Increasing incidence due to:[3]
  - Growing number of transplants
  - Older age of donors and recipients
  - Use of new immunesuppressive agents
  - Greater use of haploidentical HCT
  - Increased awareness of PTLD and improved diagnostic tools

EBV, Epstein–Barr virus; HCT, hematopoietic cell transplantation; PTLD, post-transplant lymphoproliferative disorder; SOT, solid organ transplantation.
1. Cohen JI. N Engl J Med. 2000;343:481–92; 2. Dierickx D, et al. N Engl J Med. 2018;378:549–62; 3. Fujimoto A, et al. Cancers (Basel). 2020;12:328

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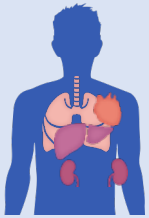
Epidemiology:

EBV+ PTLD in allogeneic HCT patients

19,806[1]
allogeneic HCT in the EU in 2021[1]

- Incidence of PTLD: 0.8–4%[2]
- Almost 100% of PTLD cases are associated with EBV[3,4]
- Typically arises <1 year after transplant[4]

EBV+ PTLD in SOT patients



27,952[5]
SOT patients in the EU in 2022[5]

- Incidence of PTLD : 1–33%[2]
- ~60% of PTLD cases are associated with EBV[6]
- >50% cases arise after >1 year after transplant[4]

Patients with relapsed or refractory EBV+ PTLD that have received at least one previous treatment are considered ultra-rare haemopathies[7]

EBV, Epstein Barr virus; HCT, haematopoietic cell transplant; PTLD, post-transplant lymphoproliferative disease; SOT, solid organ transplant.

1.Passweg JR et al. BM 2023;58:647–658; 2. Fujimoto A, et al. Cancers (Basel). 2020;12:328; 3. Styczynski J et al. Haematologica 2016;101(7):803–811; 4. Dierickx D et al. Curr Opin Oncol 2022;34(5):413–421; 5; EDQM –Newsletter Transplant 2023;28:19; 6. Vergote VKJ. et al. Transpl Int 2022;35:10707; 7. DeStefano CB. et al. British Journal of Haematology 2018;182:330–343.

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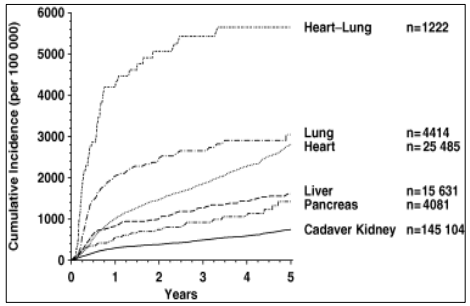
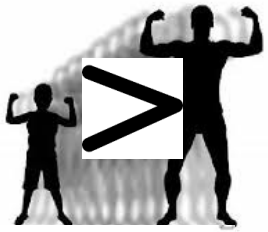
Risk Factors:

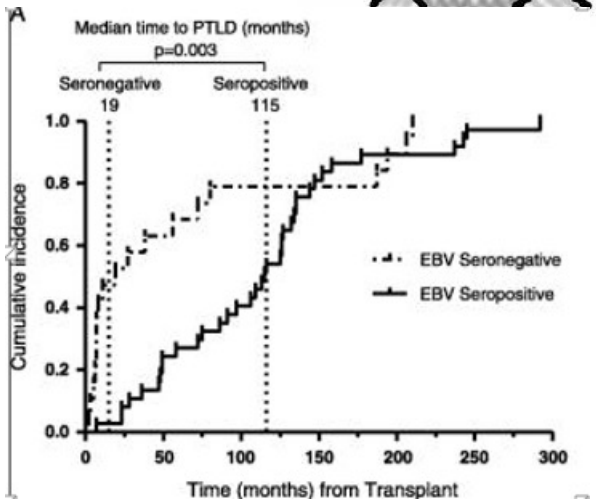
1. Organ type



Allogeneic HSCT
Selective T-cell depletion methods
Use of ATG therapy (prevention/therapy)
Two HLA antigen–mismatched siblings, or unrelated donors, accompanied by selective T-cell depletion methods or ATG therapy
Age 50 years or older at allogeneic HCT

2. EBV





Opelz G, et al. Am J Transpl 2003;4:222-30
Landgren O, et al. Blood 2009;113:4992-5001
Shahinian VB, et al. Transplantation 2003;75:851-6
Dharnidharka VR, et al. Am J Transplant 2012;12:976-83
Morton M, et al. Transplantation 2013;95:470-80

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Risk Factors:

3. Immune suppression

EBV

Increased risk associated with ATG, OKT3, tacrolimus, azathioprine, new agents (e.g., belatacept in EBV-negative transplant recipient)
Controversial degree of risk associated with alemtuzumab, cyclosporine, mTOR inhibitors
No increase in risk associated with mycophenolate mofetil, basiliximab, daclizumab

Early spike: Induction
EBV

Late wave:
Cumulative immune suppressive intensity

50-70%

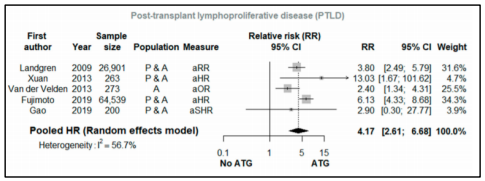
Combination maintenance therapy

SOT Induction regimen Different doses Episodes of rejection

HSCT Conditioning regimen aGVHD

Maintenance therapy

cGVHD



Early spike:
Conditioning
EBV

Late wave:
Cumulative immune suppressive intensity

> 95%

Dierickx D, Habermann TM. N Engl J Med 2018;378:549-62
Enok Bonong PR, et al. Vaccines (Basel) 2021;19:288

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Risk Factors SOT:

Early PTLD
Primary EBV infection
Type of organ transplanted (intestine > lung>heart > liver>pancreas > kidney)
Polyclonal anti-lymphocyte antibodies[a]
Young recipient age (ie, infants and young children)
Late PTLD
Duration of immunosuppression
Type of organ transplanted
Older recipient age (ie, adults)

Allen et al, Clinical Transplantation. 2019

Risk Factors HCT:

Type of Donor
T-cell depletion regimens
Age at transplant
Early PTLD
High-intensity immunosuppression in the peri-transplant induction phase
Late PTLD
Cumulative immunosuppressant burden in the following years
Other weak risk factors:
Previous exposure to immunosuppressants as a treatment of the primary disease
Use of RIC regimens
Splenectomy
Highly oncogenic variant protein LMP-1 in donors
Untreated HCV infection in recipients, reactivation of other viruses

Clerico M et al, J Clin Med 2022

WHO Classification

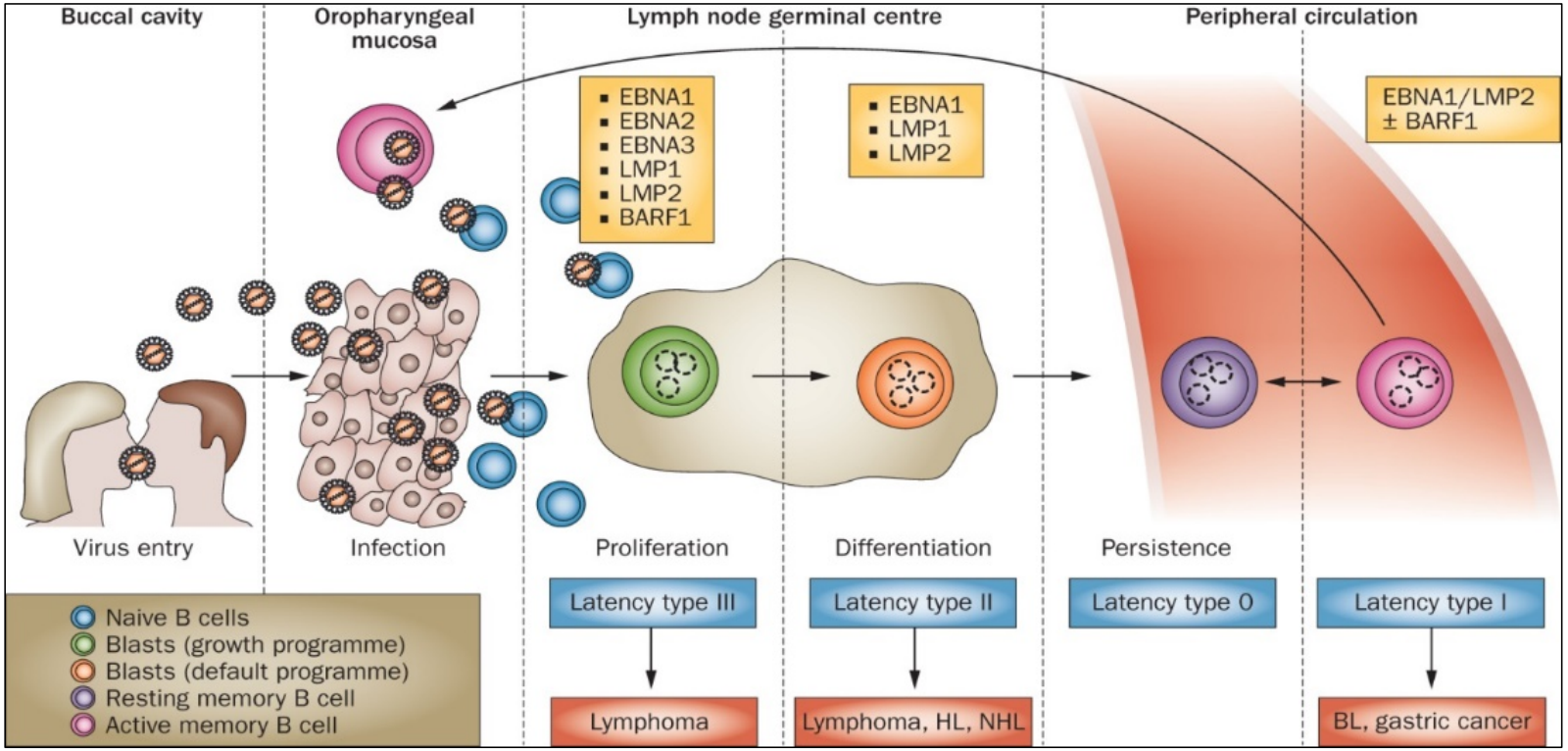
The WHO recognises distinct histological subtypes of PTLD[1]

	% of EBV+ disease
Non-destructive PTLD (21%)[1,2] • Plasmacytic hyperplasia • Infectious mononucleosis-like PTLD • Florid follicular hyperplasia	Most cases
Destructive PTLD (79%)[1,2] • Polymorphic PTLD • cHL PTLD / cHL-like PTLD	>90%
• Monomorphic PTLD (DLBCL, Burkitt lymphoma, plasma cell neoplasms, T-cell/ NK-cell lymphomas)	Variable %

cHL, classical Hodgkin lymphoma; DLBCL, Diffuse large B-cell lymphoma; EBV, Epstein-Barr virus; NK, natural killer; PTLD, post-transplant lymphoproliferative disorder; WHO, World Health Organisation.

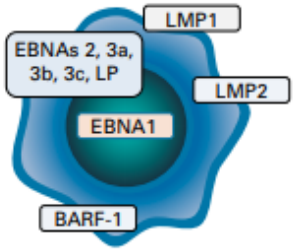
1. Atallah-Yunes S et al. Br J Haematol 2023;201:383–395; 2. Liu Y et al. Cancers 2023;15(3):976.

Pathogenesis: EBV role



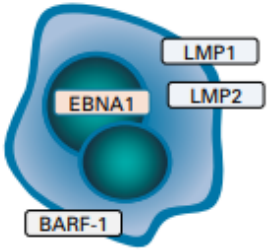
Tsurumi T, et al. Rev Med Virol 2005;15:3-15; Bollard CM, et al. Nat Rev Clin Oncol 2012;9:510-9; Taylor GS, et al. Annu Rev Immunol 2015;33:787-821

Pathogenesis: EBV role



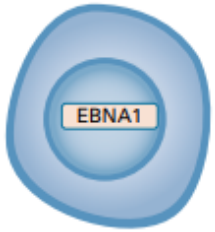
Latency III

Type of Lymphoma	EBV Frequency (%)
PTLD post HSCT	> 95
PTLD post SOT	95 in first year 70-80 after 1 year
NHL associated with primary immunodeficiency	> 95
Primary CNS lymphoma	> 95
Methotrexate-induced lymphoma	> 95



Latency II

Type of Lymphoma	EBV Frequency (%)
Hodgkin lymphoma	30-40
NK-T lymphoma	> 95
PTLD post SOT (late)	70-80
Aggressive NK lymphoma	30-60
T, B, and NK cell CAEBV	> 95
Lymphatoid granulomatosis	80-95
Angioimmunoblastic lymphoma	> 80
T-cell rich B-cell lymphoma	20
DLBCL and ALCL	10-30



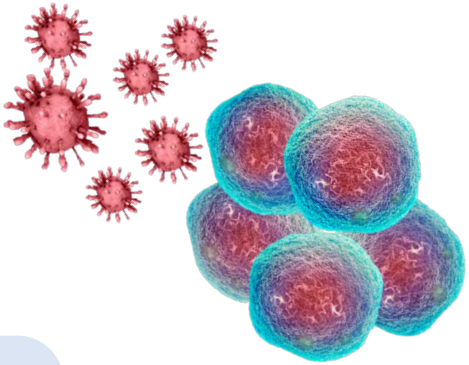
Latency I

Type of Lymphoma	EBV Frequency (%)
Burkitt's	30-60
Primary effusion lymphoma	> 90

Heslop HE, et al. J Clin Oncol 2021;39:514-24

How a latent infection reactivates

- Latent EBV can become reactivated in patients with **dysfunction or suppression of the host immune system** after transplantation[1]
- Once reactivated B-cells may transform and rapidly proliferate, causing a range of neoplasms attributable to the dysregulated proliferation of infected B-cells[1]



The incidence of EBV reactivation post-allogeneic HCT ranges from 0.1–63%[2]
Impacted by transplant type, antiviral agents, monitoring protocol, and assay sensitivity

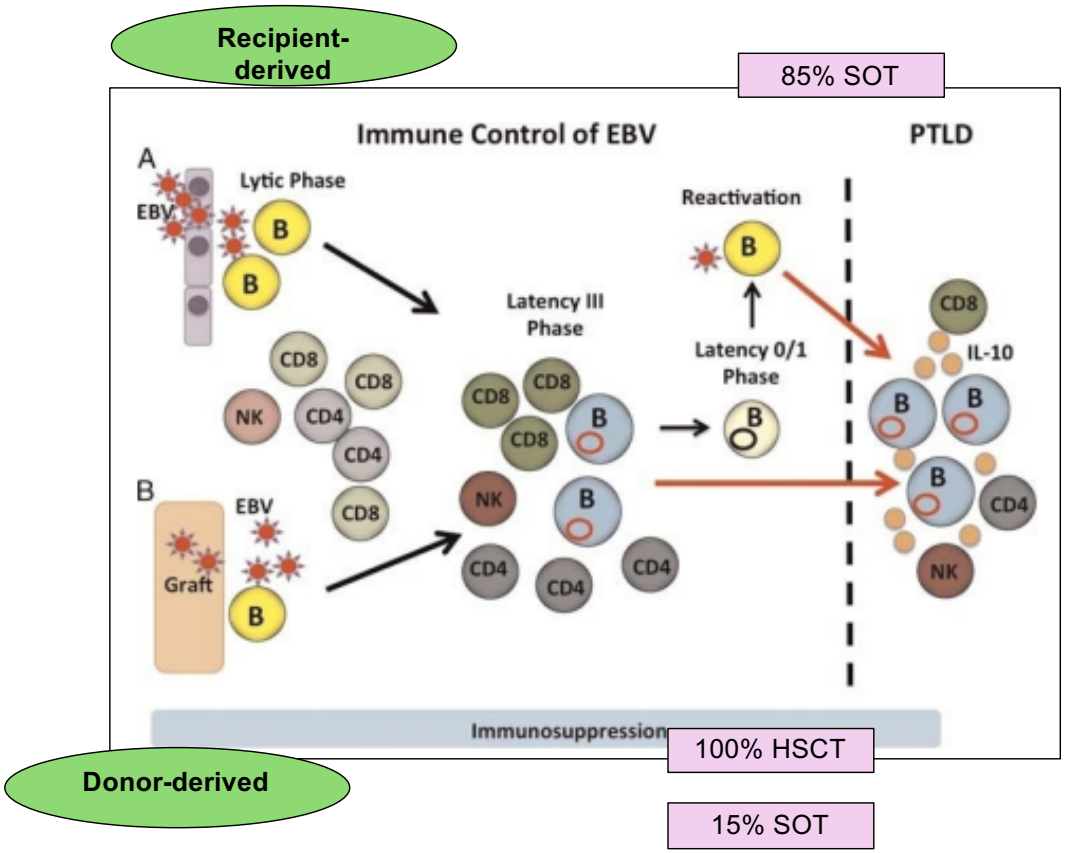
The incidence of EBV reactivation post-SOT ranges from 13–48%[3]
Impacted by immunosuppressive regimes and analytical techniques

Recipients of SOT or allogeneic HCT have an increased risk of EBV-associated cancers such as PTLD[4]

EBV, Epstein-Barr virus; HCT, haematopoietic cell transplantation; PTLD, post-transplant lymphoproliferative disorder; SOT, solid organ transplant.

1. Fujimoto A, et al. Cancers (Basel). 2020;12:328; 2. Ru Y, et al. BMT 2020;55:1754–1762; 3. Blazquez-Navarro A, et al. Transpl Int; 2021;34:1680–1688. 4. Cohen JI. N Engl J Med. 2000;343:481–492.

PTLD origin



Olagne J, et al. Am J Transplant 2011;11:1260-9
Kinch A, et al. Am J Transplant 2014;14:2838-45
Martinez O, Krams SM. Transplatation 2017;101:2009-16

EBV+ PTLD: clinical presentation

Factor	Clinical presentation
Heterogeneity[1]	• Heterogeneous (from incidental asymptomatic findings to fulminant presentation), including organ failure and spontaneous tumour lysis
Symptoms[2]	• **Most common:** lymphadenopathy and fever • **Rare (EBV end-organ disease):** encephalitis/myelitis, pneumonitis, hepatitis, and hemophagocytic lymphohistiocytosis
Target organs[2]	• **Frequently:** lymph nodes • **Rarely:** CNS, GI tract, lungs, liver
Progression[3]	• After HCT, PTLD often progresses rapidly and is more frequently at an advanced stage than after SOT

CNS, central nervous system; EBV, Epstein–Barr virus; GI, gastrointestinal; HCT, haematopoietic cell transplantation; PTLD, post-transplant lymphoproliferative disorder; SOT, solid organ transplantation.
1. Dierickx D, et al. N Engl J Med. 2018;378:549–562; 2. Styczynski J, and Giebel S. EBMT Handbook 2019; Chapter 45; 3. Fujimoto A, et al. Cancers (Basel). 2020;12:328.

EBV+ PTLD: diagnosis

- Diagnosis must be based on symptoms and/or signs consistent with PTLD together with detection of EBV[1]
- Definitive diagnosis requires non-invasive and invasive techniques[1,2]

Non-invasive diagnostic methods[1,2]

- Quantitative determination of EBV-DNA-emia
- Imaging: CT or PET-CT* or MRI**

Currently the method of choice for **early detection and monitoring progression and response to treatment** of EBV+ PTLD starting no later than 4 weeks after HCT[1]

Longer monitoring recommended in patients considered to have poor T-cell reconstitution, with severe GvHD, after haplo-HCT, with the use of TCD, after conditioning with ATG/alemtuzumab, or in those having experienced an early EBV reactivation[1]

* For avid structures, localised in the lymph nodes, spleen, liver, gastrointestinal tract, skin, lungs, bone, bone marrow.
** In central nervous system disease and non-avid histologies.

ATG, anti-thymocyte globulin; CT, computed tomography; EBV, Epstein–Barr virus; GvHD, graft-versus-host disease; HCT, haematopoietic cell transplantation; MRI, magnetic resonance imaging; PET-CT; positron emission tomography–computed tomography; PTLD, post-transplant lymphoproliferative disorder; TCD, T-cell depletion.

1. Styczynski J, and Giebel S. EBMT Handbook 2019; Chapter 45; 2. Samant H, et al. Posttransplant Lymphoproliferative Disorders. StatPearls 2023.

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Invasive diagnostic methods[1,2]

- **Biopsy:** of the lymph node and/or other suspected sites → **Currently key to diagnose PTLD**
- Endoscopy: when GI symptoms present
- Histological examination
  a) Detection of viral antigens or *in situ* hybridisation for EBV-encoded RNA transcripts
  b) Immunohistochemistry
  c) Flow cytometry for B-cell, T-cell, and plasma cell lineage-specific antigens

EBV, Epstein–Barr virus; GI, gastrointestinal; PTLD, post-transplant lymphoproliferative disorder.
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Thank you for your attention!!

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