Posted on 14 Jun 2024 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.171837914.47947867/v1 — This is a preprint and has not been peer-reviewed. Data may be preliminary.

Monomorphic post-transplant lymphoproliferative disorder with plasmablastic differentiation: a challenge for diagnosis and treatment

Jinjun Cheng[1], Sarah Harney[1], Keri Toner[1], Paige Kube[1], Metin Ozdemirli[2], and Birte Wistinghausen[1]

[1]Children's National Hospital
[2]MedStar Georgetown University Hospital

June 14, 2024

Abstract

Post-transplant lymphoproliferative disorder (PTLD) is a significant complication of solid organ transplantation due to the lifelong immunosuppression (IS), ranging from non-malignant lymphoproliferations to lymphomas. Plasmablastic lymphoma (PBL), a rare and aggressive lymphoma, usually presenting in immunocompromised individuals has been rarely reported in the post-transplant setting. Here we summarize the clinical and pathological features of two children with PBL and history of solid organ transplant.

Monomorphic post-transplant lymphoproliferative disorder with plasmablastic differentiation: a challenge for diagnosis and treatment

Authors: Jinjun Cheng, MD PhD[1,3,4*], Sarah Harney, MD[2], Keri Toner, MD[2,3,4], Paige Kube, MD[2], Metin Ozdemirli, MD[5], Birte Wistinghausen, MD [2,3,4*]

1. Department of Pathology and Laboratory Medicine, Children's National Hospital, Washington, DC

2. Center for Cancer and Blood Disorders. Children's National Hospital, Washington, DC

3. Center for Cancer and Immunology Research, Children's National Hospital, Washington, DC

4.The George Washington University School of Medicine and Health Sciences, Washington, DC.

5. Department of Pathology, MedStar Georgetown University Hospital, Washington, DC.

***Correspondence to:**

Jinjun Cheng, MD, PhD

Pathology and Laboratory Medicine Division

Children's National Hospital

Room 1629, 111 Michigan Avenue NW

Washington, DC 20010-2970

Telephone: 202-476-4311

Fax: 202-476-4030

Posted on 14 Jun 2024 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.171837914.47947867/v1 — This is a preprint and has not been peer-reviewed. Data may be preliminary.

Email: jcheng2@childrensnational.org

Birte Wistinghausen, MD

Center for Cancer and Blood Disorders

Children's National Hospital

111 Michigan Ave NW

Washington, DC 20010

Tel: 202-476-2800

Fax: 202-476-5685

Email: bwistingha@childrensnational.org

Word Count: 1200

Abstract count : 64

Tables: 1

Figures: 1

Running title: Pediatric post-transplant plasmablastic lymphoma

Key words: PTLD, Rituximab, EBV, PBL, DLBCL, PEL

List of abbreviations:

Abbreviation	Full term
PTLD	Posttransplant lymphoproliferative disorder
IS	Immunosuppression
EBV	Epstein Barr Virus
DLBCL	Diffuse large B cell lymphoma
PBL	Plasmablastic lymphoma
PEL	Pleural effusion lymphoma
PT	Post transplant
COG	Children Oncology Group
WHO	World Health Organization
ICC	International consensus classification

Monomorphic post-transplant lymphoproliferative disorder with plasmablastic differentiation: a challenge for diagnosis and treatment

Abstract

Post-transplant lymphoproliferative disorder (PTLD) is a significant complication of solid organ transplantation due to the lifelong immunosuppression (IS), ranging from non-malignant lymphoproliferations to lymphomas. Plasmablastic lymphoma (PBL), a rare and aggressive lymphoma, usually presenting in immunocompromised individuals has been rarely reported in the post-transplant setting. Here we summarize the clinical and pathological features of two children with PBL and history of solid organ transplant.

Background

Post-transplant lymphoproliferative disorder (PTLD) includes a heterogeneous spectrum of disorders, ranging from non-malignant lymphoproliferations to lymphomas.[1-5] The clinical presentation of PTLD is variable, usually but not always depending on the location and histopathology.[4,6] The vast majority of pediatric PTLD

Posted on 14 Jun 2024 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.171837914.47947867/v1 — This is a preprint and has not been peer-reviewed. Data may be preliminary.

are Epstein Barr virus (EBV)-positive, CD20 positive B-cell lymphoproliferations.[6] However, rare subtypes of PTLD have created diagnostic and treatment challenges.[4]

A few cases of plasmablastic lymphoma (PBL),a rare lymphoma associated with immunodeficiency, have been reported in adult solid organ transplant (SOT) recipients.[7-13] PBL after SOT (PT-PBL) in children accounts for a minor fraction of pediatric PTLD; and limited pathological and molecular data have been reported.[4,11,12,14] Moreover, it can be difficult to diagnostically differentiate PBL from plasma cell myeloma with plasmablastic morphology,[14,15] while the treatments of these two diseases could be different. Here we report two pediatric cases of PBL post SOT and summarize their clinical, genetic and pathological features.

Case reports:

The first patient is a 14-year-old male with a history of kidney transplant one year prior, who presented with chest pain and shortness of breath and was found to have near-complete opacification of the left hemithorax with rightward mediastinal shift and moderate pleural effusion. Laboratory studies revealed an elevated uric acid, Lactate Dehydrogenase (LDH), and EBV DNA in peripheral blood. The flow cytometry analysis of pleural fluid confirmed a monoclonal B-cell population with high forward scatter, CD20 rarely dim+, CD45+, CD19+, CD2 dim+, and kappa light chain restriction. Concurrent cytological evaluation revealed a large B-cell neoplasm with plasmablastic morphology and high Ki67 proliferation rate, positive for LMP1, PAX5, BCL2, CD19, MUM1, CD38, kappa light chain, while negative for CD20, CD10, BCL6, HHV8, ALK1, and MYC. The cytogenetics identified a complex karyotype, while Fluorescence in situ hybridization (FISH) studies were negative for*MYC* , *BCL6* and *BCL2* rearrangements, positive for gains of *BCL6* , *MYC* , *BCL2* and *IGH* . These findings were consistent with an EBV positive monomorphic PTLD. The patient was initially treated with rituximab monotherapy but developed disease progression. He was switched to chemoimmunotherapy with bortezomib, cyclophosphamide, dexamethasone, and daratumumab. Repeat Positron emission tomography - computed tomography (PET/CT) scan showed near resolution of the pleural/pericardial effusions and lesions after two cycles of chemoimmunotherapy. He received an additional four cycles of this regimen but relapsed while on therapy with recurrence of his pericardial effusion and mediastinal disease as well as new intra-abdominal and skeletal disease. Interestingly, the relapsed lymphoma showed similar plasmablastic morphology with acquired expression of cytoplasmic CD3, which was not seen in the original diagnostic lymphoma. CD30 was positive on 2-3% of tumor cells. The morphology and immunophenotype are consistent with PT-PBL. Patient received six cycles of etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin (EPOCH) with rituximab and remains in remission two months after completion of therapy.

The second patient, a 9-year-old male who received heart transplant within the first year of life, presented with intestinal obstruction after a prolonged prodrome of feeding intolerance. A 4 cm mass in small bowel causing intussusception was surgically removed. The histology showed a large B-cell neoplasm with plasmablastic morphology and nearly 100% Ki67 proliferation rate, positive for variable PAX5, variable CD38, cytoplasmic CD3, and CD30; while negative for CD20, HHV8, ALK1, and EBER (Figure 1). The FISH was negative for *MYC* -rearrangement. Polymerase Chain Reaction (PCR) studies were positive for IgH clonal rearrangement while negative for T-cell receptor (TCR) clonal rearrangement. Concurrent flow cytometry identified a surface kappa light chain restricted B cell population, negative for CD19, CD20 and surface CD3. The findings were diagnostic for PT-PBL. Patient received chemotherapy with EPOCH and the addition of bortezomib. He achieved a partial response but eventually died of disease approximately 5 months after the PBL diagnosis.

Discussion:

We report two unique pediatric cases of monomorphic PTLD. They both occurred after solid organ transplant, with the first patient presenting with isolated pleural and pericardial effusions and the second with intestinal obstruction. Both cases showed aberrant cytoplasmic CD3 expression (negative TCR-gene clonal rearrangement by PCR), variable B cell antigen loss, kappa or lambda light chain restriction, EBV positive or negative, high Ki67 proliferation rate and plasmablastic morphology, consistent with PBL.[11,12,14,16] Al-

Posted on 14 Jun 2024 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.171837914.47947867/v1 — This is a preprint and has not been peer-reviewed. Data may be preliminary.

though*MYC* -rearrangement has been identified in up to 50-70% of PBL,[9,11,16-19] both of our cases were negative for*MYC* rearrangement by FISH.

An in depth literature search revealed three additional reported pediatric cases of PT-PBL.[11] Similar to our second patient, these three reported PT-PBLs (cases 4-6, Table-1) were EBV negative, occurring at least 9 years after original solid organ transplant and involving intestine.[11] Prior studies have shown that gastrointestinal tract (including oropharynx) is one of the most common sites of PBL,[11,16,20] while bone marrow involvement appears uncommon.

Our first case is a unique PT-PBL case with isolated pleural/pericardial effusion. We searched the literature and identified three adult patients with effusion-based PT-PBL (cases 1-3, Table-1).[21] The morphology and immunophenotype of effusion-based monomorphic PTLD are varied. The tumor cells often show large size, prominent nucleoli, and variable cytoplasm, resembling immunoblasts or plasmablasts. Depending on the expression of HHV8, effusion based monomorphic PTLD is divided into two categories. Absent expression of CD20 is common in effusion based monomorphic PTLD,[22,23] which has been reported with poor prognosis. Our first case was negative for HHV8 and CD20. Given the EBV positivity, our first case also resembles the new entity of "fluid overload-associated large B-cell lymphoma (FO-LBCL)" in World Health Organization (WHO) 5$^{\text{th}}$ edition[24].

There are scarce genetic studies of PT-PBL. MYC deregulation, due to copy number alteration, translocation or somatic mutations of certain signaling pathway genes is the well-recognized pathobiological mechanism for the development of PBL.[11,25-27] A recent study of 11 childhood and adult patients with PT-PBL reveals some unique genetic features of PT-PBLs.[11] For instance, mutations in epigenetic modifiers were identified in up to 70% of PT-PBL, followed by DNA damage response and repair pathway genes (64%), mitogen-activated protein kinase (MAPK) pathway genes (55%), NOTCH signaling pathway genes (45%), JAK-STAT signaling pathway genes (36%).[11] However, genomic research focusing on childhood PT-PBL is absent thus far.

The treatment of PT-PBL is a challenge.[28] The use of treatment regimens developed for immunocompetent individuals is often complicated by the reduced chemotherapy tolerance of transplant recipients.[4] The outcomes of PT-PBL patients appear variable. Leeman-Neill et al [11] reported two patients with EBV negative PT-PBL with *MYC* -rearrangement achieving a durable remission, while many other patients appear to have poor outcome. Moreover, the effusion-based monomorphic PTLD patients have poor response to chemotherapy.[8,29-31] Our first patient did not respond to rituximab, the accepted first line therapy for pediatric EBV+ CD20+ PTLD. However, this patient's lymphoma initially responded to chemotherapy with addition of daratumumab, a CD38 monoclonal antibody but relapsed a few months later. He successfully achieved remission with EPOCH-based chemotherapy. Our second patient was treated up front with EPOCH-based chemotherapy with addition of bortezomib but after initial partial response progressed and the parents withdrew further care.

In summary, we report two pediatric PT-PBL, who showed unusual pathology and variable treatment response to aggressive chemotherapy. It is well known that EBV positive PTLD has a more favorable outcome which may have contributed to the difference in outcome in our patients. It is important to recognize this rare subtype of monomorphic PTLD. Future collaborative studies are required to understand the biology and best treatment of this devastating disease in children.

Reference:

1. Swerdlow SH CE, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. . *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Revised Fourth Edition.* Vol 2. Lyon, France: IARC/WHO Press; 2017.

2. Campo E, Jaffe ES, Cook JR, et al. The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee. *Blood.* 2022;140(11):1229-1253.

3. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. *Leukemia.* 2022;36(7):1720-1748.

Posted on 14 Jun 2024 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.171837914.47947867/v1 — This is a preprint and has not been peer-reviewed. Data may be preliminary.

4. Rubinstein J, Toner K, Gross T, Wistinghausen B. Diagnosis and management of post-transplant lymphoproliferative disease following solid organ transplantation in children, adolescents, and young adults. *Best Pract Res Clin Haematol.* 2023;36(1):101446.

5. Cheng J, Wistinghausen B. Clinicopathologic Spectrum of Pediatric Posttransplant Lymphoproliferative Diseases Following Solid Organ Transplant. *Arch Pathol Lab Med.* 2023.

6. Wistinghausen B, Gross TG, Bollard C. Post-transplant lymphoproliferative disease in pediatric solid organ transplant recipients. *Pediatr Hematol Oncol.* 2013;30(6):520-531.

7. Ramadas P, Williams M, Duggan DB. Plasmablastic Lymphoma or Plasmablastic Myeloma: A Case of Post-Transplant Lymphoproliferative Disorder. *Case Rep Hematol.* 2021;2021:4354941.

8. Lambe JS, Oble DA, Nandula SV, et al. KHSV(-) EBV(-) post-transplant effusion lymphoma with plasmablastic features: variant of primary effusion lymphoma? *Hematol Oncol.* 2009;27(4):203-210.

9. Zimmermann H, Oschlies I, Fink S, et al. Plasmablastic posttransplant lymphoma: cytogenetic aberrations and lack of Epstein-Barr virus association linked with poor outcome in the prospective German Posttransplant Lymphoproliferative Disorder Registry. *Transplantation.* 2012;93(5):543-550.

10. Morscio J, Dierickx D, Nijs J, et al. Clinicopathologic comparison of plasmablastic lymphoma in HIV-positive, immunocompetent, and posttransplant patients: single-center series of 25 cases and meta-analysis of 277 reported cases. *Am J Surg Pathol.*2014;38(7):875-886.

11. Leeman-Neill RJ, Soderquist CR, Montanari F, et al. Phenogenomic heterogeneity of post-transplant plasmablastic lymphomas. *Haematologica.* 2022;107(1):201-210.

12. Choudhuri J, Pan Z, Yuan J, et al. CD138- Plasmablastic Lymphoma: A Multi-institutional Study and Review of the Literature. *Arch Pathol Lab Med.* 2023;147(6):643-654.

13. Migliavacca M, Assanelli A, Ponzoni M, et al. First Occurrence of Plasmablastic Lymphoma in Adenosine Deaminase-Deficient Severe Combined Immunodeficiency Disease Patient and Review of the Literature. *Front Immunol.* 2018;9:113.

14. Pan Z, Chen M, Zhang Q, et al. CD3-positive plasmablastic B-cell neoplasms: a diagnostic pitfall. *Mod Pathol.* 2018;31(5):718-731.

15. Chen BJ, Yuan CT, Yang CF, et al. Plasmablastic myeloma in Taiwan frequently presents with extramedullary and extranodal mass mimicking plasmablastic lymphoma. *Virchows Arch.* 2022;481(2):283-293.

16. Zhou T, Cheng J, Karrs J, et al. Clinicopathologic and Molecular Characterization of Epstein-Barr Virus-positive Plasmacytoma. *Am J Surg Pathol.* 2022;46(10):1364-1379.

17. Chang CC, Zhou X, Taylor JJ, et al. Genomic profiling of plasmablastic lymphoma using array comparative genomic hybridization (aCGH): revealing significant overlapping genomic lesions with diffuse large B-cell lymphoma. *J Hematol Oncol.* 2009;2:47.

18. Laurent C, Fabiani B, Do C, et al. Immune-checkpoint expression in Epstein-Barr virus positive and negative plasmablastic lymphoma: a clinical and pathological study in 82 patients. *Haematologica.*2016;101(8):976-984.

19. Montes-Moreno S, Martinez-Magunacelaya N, Zecchini-Barrese T, et al. Plasmablastic lymphoma phenotype is determined by genetic alterations in MYC and PRDM1. *Mod Pathol.* 2017;30(1):85-94.

20. Fu Z, Wang H, Lauwers GY, et al. Primary plasmablastic lymphoma of the gastrointestinal tract: A series of 13 HIV-negative cases and a review of literature. *Ann Diagn Pathol.* 2023;67:152204.

21. Nessim Kostandy E, Wan D, Imseis E. Rare Case of Pediatric Post-transplant Lymphoproliferative Disorder Presenting With Pleural Masses Complicated by Pleural Effusions. *ACG Case Rep J.*2023;10(9):e01158.

Posted on 14 Jun 2024 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.171837914.47947867/v1 — This is a preprint and has not been peer-reviewed. Data may be preliminary.

22. Gisriel SD, Yuan J, Braunberger RC, et al. Human herpesvirus 8-negative effusion-based large B-cell lymphoma: a distinct entity with unique clinicopathologic characteristics. *Mod Pathol.*2022;35(10):1411-1422.

23. Teruya-Feldstein J, Chiao E, Filippa DA, et al. CD20-negative large-cell lymphoma with plasmablastic features: a clinically heterogenous spectrum in both HIV-positive and -negative patients.*Ann Oncol.* 2004;15(11):1673-1679.

24. Di Napoli A, Soma L, Quintanilla-Martinez L, et al. Cavity-based lymphomas: challenges and novel concepts. A report of the 2022 EA4HP/SH lymphoma workshop. *Virchows Arch.* 2023.

25. Liu Z, Filip I, Gomez K, et al. Genomic characterization of HIV-associated plasmablastic lymphoma identifies pervasive mutations in the JAK-STAT pathway. *Blood Cancer Discov.* 2020;1(1):112-125.

26. Ramis-Zaldivar JE, Gonzalez-Farre B, Nicolae A, et al. MAPK and JAK-STAT pathways dysregulation in plasmablastic lymphoma.*Haematologica.* 2021;106(10):2682-2693.

27. Witte HM, Kunstner A, Hertel N, et al. Integrative genomic and transcriptomic analysis in plasmablastic lymphoma identifies disruption of key regulatory pathways. *Blood Adv.* 2022;6(2):637-651.

28. Vergote VKJ, Deroose CM, Fieuws S, et al. Characteristics and Outcome of Post-Transplant Lymphoproliferative Disorders After Solid Organ Transplantation: A Single Center Experience of 196 Patients Over 30 Years. *Transpl Int.* 2022;35:10707.

29. Sultana S, Salihi SA, Tandon N, et al. Post-transplant Lymphoproliferative Disorder Presented in a Form of Primary Effusion Lymphoma with t (8; 14). *Ann Clin Lab Sci.* 2017;47(3):344-348.

30. Ohori NP, Whisnant RE, Nalesnik MA, Swerdlow SH. Primary pleural effusion posttransplant lymphoproliferative disorder: Distinction from secondary involvement and effusion lymphoma. *Diagn Cytopathol.*2001;25(1):50-53.

31. Hoffmann H, Schlette E, Actor J, Medeiros LJ. Pleural posttransplantation lymphoproliferative disorder following liver transplantation. *Arch Pathol Lab Med.* 2001;125(3):419-423.

Table-1. Post solid organ transplant plasmablastic lymphoma in literature.

Case No.	Age/gender	Graft	Time to PTLD (yr)	Location	Tumor cell morphology
Case 1[8]	60-yr male	liver, kidney	0.6	Pleural effusion	Plasmablastic
Case 2[29]	63-yr male	liver	11	Ascites, splenomegaly	Plasmablastic
Case 3[31]	57-yr male	liver	2.0	Pleural effusion	Large tumor cells
Case 4[11]	12-yr-female	heart	10	Small intestine, pleura	Plasmablastic
Case 5[11]	15-yr-male	heart	10	Small intestine	Plasmablastic
Case 6[14]	22-yr-female	kidney	17	Small intestine	Large tumor cells

Abbreviation: PTLD, post-transplant lymphoproliferative disorder; TCR, T-cell gene rearrangement; EBV, Epstein Barr virus; CHOP, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate and the steroid hormone prednisone. EPOCH, etoposide phosphate, prednisone, vincristine sulfate (Oncovin), cyclophosphamide, and doxorubicin hydrochloride (hydroxydaunorubicin). ASCT, autologous stem cell transplant. N/A, not available.

Figure 1: Pathology features of plasmablastic lymphoma post solid organ transplant. A-B, the H&E section of intestinal mass (H&E, A, 20X; B, 400x) and the touch imprint (C, Diff-Quick stain,1000x) shows a diffuse infiltrate of plasmablastic tumor cells. By immunohistochemical stain, the tumor cells are negative for CD20 (not shown); positive for patchy CD79a (D, 200X), CD30 (E, 200X), cytoplasmic CD3 (F, 200X), high Ki67 proliferation rate (G, 200X); negative for EBER in situ hybridization (H, 200X). Most tumor cells are negative for CD138 (I, 200x).

Posted on 14 Jun 2024 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.171837914.47947867/v1 — This is a preprint and has not been peer-reviewed. Data may be preliminary.