

## Case Report

# Posttransplant Lymphoproliferative Disease (PTLPD)-Central Nervous System (CNS) Involvement in a Case With Liver Transplantation: Case Report and Review of the Literature

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### Abstract

Post transplant lenfoproliferative diseases (PTLPD) are generally seen in cases with solid organ transplantation (SOT) and relatively less commonly after stem cell transplantation and related with EBV infection, in 70-90% of the cases. Most commonly occurs within one year of transplantation although this entity may develop later than 4-6 years. Here a case with PTLPD with CNS involvement has been reported and literature has been reviewed.

**Keywords:** Post transplant lymphoproliferative disease, liver transplantation

**Cite This Article:** Kakci M, Paydas S, Acikalin A, Kuran S. Posttransplant Lymphoproliferative Disease (PTLPD)-Central Nervous System (CNS) Involvement in a Case With Liver Transplantation: Case Report and Review of the Literature. *EJMA* 2022;2(1):13–16.

PTLPDs are heterogenous lymphoid proliferations occurring due to pharmacologic immune suppression after organ or cell transplantations. These proliferations have a wide range from benign polyclonal lymphoid collections to aggressive lymphomas originating from T, B and plasma cells.<sup>[1]</sup> Lymphoproliferative disorders (LPDs) developing primary immune deficiency are LPD, HIV associated lymphomas, PTLPD and LPD developing at primary immune deficiency background.<sup>[2]</sup>

PTLPD has been defined firstly at 1968.<sup>[3]</sup> PTLPDs developing at immune deficiency background after transplantation and there are 4 subtypes: 1-polymorphic, 2-monomorphic, 3-early lesion, 4-classical Hodgkin lymphoma like type.<sup>[2]</sup>

Solid organ transplant recipients are more commonly affected when compared to recipients of a hematopoietic stem cell transplant.<sup>[4]</sup> PTLPD is the most common cause of cancer-related mortality in patients with SOT.<sup>[3]</sup> The most important risk factors for PTLD are ongoing immunosuppressive therapy, duration of immunosuppression, and status of EBV infection.<sup>[4]</sup>

Clinical manifestations are heterogeneous, non-specific, and highly variable. PTLD can present as a localized or disseminated disease. Malaise, fatigue, fever, and a mononucleosis-like picture are some presenting features of PTLD. B-symptoms of fever, night sweats, and weight loss, as well as lymphadenopathy, are frequent manifestations. PTLD develops rapidly and may cause compressive symptoms.<sup>[4]</sup>

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**Submitted Date:** December 10, 2021 **Accepted Date:** January 20, 2022 **Available Online Date:** January 20, 2022

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## Case Report

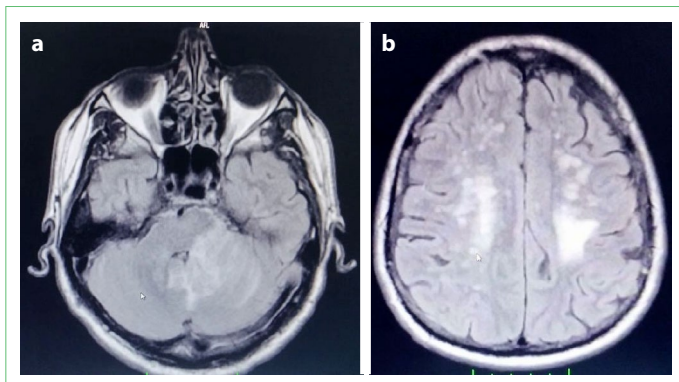
55 year-old-man admitted to the hospital with one week of fever, cough, sputum, headache and difficulty in writing. He had the history of liver transplantation from related living donor and had been treated by mycophenolate mophetile (2X100 mg/day) for 18 months, everolimus a few months and then tacrolimus for 2 years. Physical exam showed fever (37.8°C) and he had been treated by tazobactam piperacillin and moxifloxacin combination. Cranial MRI spectroscopy showed bilateral parietal and left cerebellar lesions compatible with metastatic lesions (Fig. 1a, b). Systemic staging with CT and PET/CT scanning did not show extracranial lesion. Hydrocephalus developed in a short time and ventriculo-peritoneal shunt was performed and cerebellar mass was excised. Histopathologically mass was reported as PTLPD-polymorphic type: shows a full range of B cell maturation antigens and may be polyclonal and involve T cells and plasma cells. Immune-histochemically LMP-EBV, CD20, LCA, Pax5 and CD30 were found to be positive and CD15 was negative (Fig. 2 a-c). Bone marrow biopsy was reported as normal hematopoiesis. Rituximab and methotrexate containing regimen was planned but he died due to opportunistic infection.

## Discussion

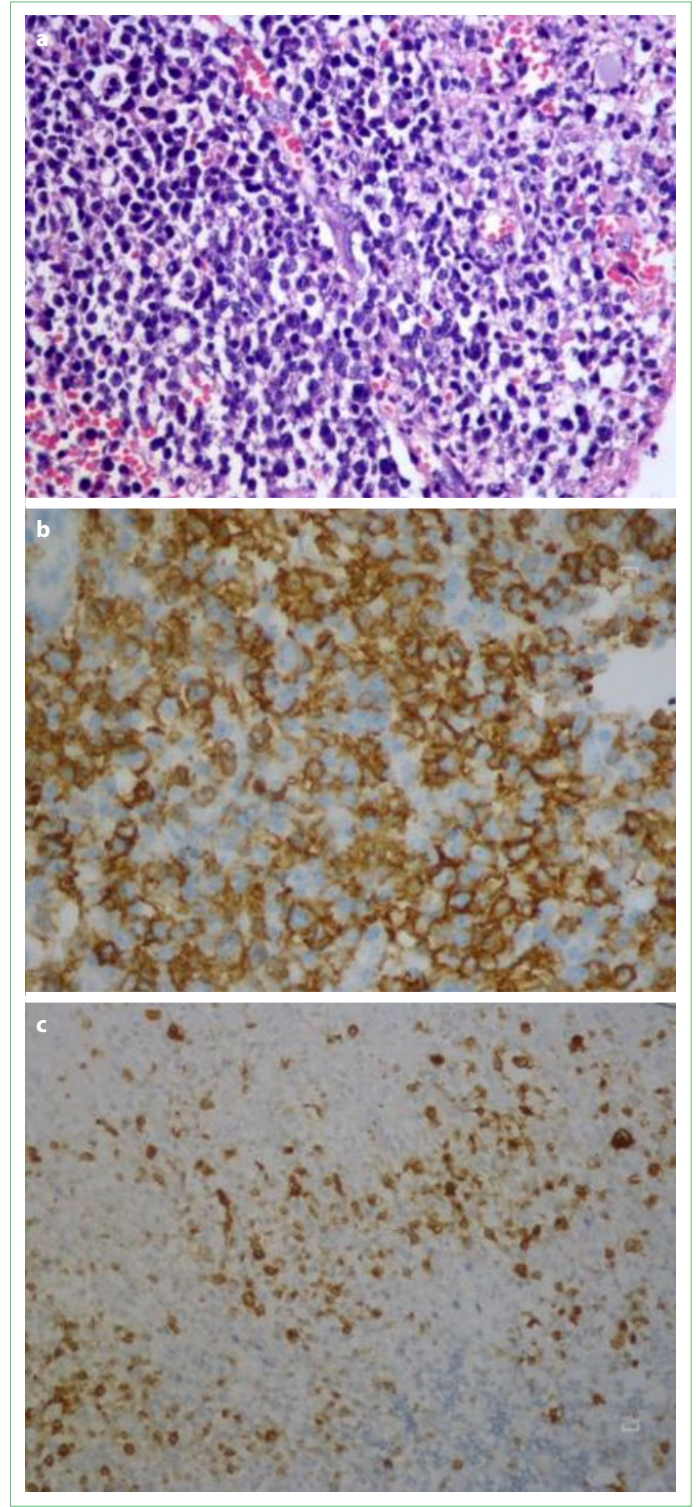
Immune suppressive drugs used to prevent rejection after SOTs cause complications ranging from infections to malignant diseases. The most common malignancies are lymphoid neoplasias frequently B cell lymphomas.<sup>[5-9]</sup> Polymorphic PTLPDs show all stages of B cell maturation and may be polyclonal and also may contain T cells and plasma cells.<sup>[6]</sup> In contrast,

monomorphic type contains one type of monoclonal transformed B cells.<sup>[8]</sup> The presence of EBV in tumor tissue is associated with tumor histology: EBV is generally posi-

tive in polymorphic type while negative in monomorphic type and this is the background of the difference of these 2 types of PTLPD. Clinical presentations and genetic characteristics are different in subtypes: early lesions are generally



**Figure 1.** (a) Mass lesion in the left occipital lobe. (b) Multiple mass lesions in the right frontal periventricular location and left parietal location.



**Figure 2.** (a) Variable sized atypical lymphoid cells (Hematoxyline and eosine, x400). (b) CD20 positivity in atypical cells (Immunohistochemistry, x400). (c) LMP-EBV antibody positivity in large atypical cells (Immunohistochemistry, x200).

polymorphic and late lesions are monomorphic and these two entities are different. EBV serologic status during organ transplantation has a role in the development of PTLPD subtype. EBV positive PTLPD occurs more frequently in EBV seronegative patients.<sup>[11-13]</sup> Conditions causing PTLPD change according to the immune suppression and transplantation protocols and it has been found increased EBV negative monomorphic subtype in recent years.<sup>[8]</sup> PTLPD risk changes according to the aggressivity of immune suppressive regimens and risk may be decreased by de-escalation of immune suppressive drugs. However the intensity of treatment and timing of cessation of immune suppression are not clear enough. At this point multidisciplinary approach and risk benefit ratio are important points.<sup>[1,8,11]</sup>

Primary CNS lymphoma is 1% of all lymphomas. Post transplant primary CNS lymphoma is a very rare entity and has been detected in 2-7% in autopsy series.<sup>[14]</sup> The majority of PCNS-PTLDs are B-cell non-Hodgkin lymphomas, 20- to 120-fold higher incidence of lymphomas/PTLD have been reported in cases with SOT. Age, type of transplantation and intensity of immunosuppression are the most significant risk factors. Although PTLPDs typically occur in the first year post-transplant period, late recurrences of EBV+ PTLPD are common and 40% of cases are diagnosed later than 6 years after SOT. PTLPD in our case was detected at 4<sup>th</sup> year of transplantation. Isolated CNS involvement of PTLD is uncommon, about 100 patients have been reported so far. Presenting signs and symptoms of PCNS-PTLD are similar to intracranial mass lesions as in our case. MRI is the preferred imaging as in our case. Multifocal supratentorial involvement is more frequent but periventricular region may be involved and may cause to hydrocephalus as in our case. Diagnosis is based on biopsy to confirm the diagnosis and also to exclude opportunistic infections. Surgical resection is the treatment of choice but this may be possible in the minority of the cases. Surgery can not be performed in cases with multicentric disease as in our case and poor prognostic indicator. Other treatment options are reduction of immunosuppression, whole-brain radiotherapy, and systemic chemotherapy with/without rituximab. Although reduction of immunosuppression alone is useful in cases with early systemic polyclonal PTLPD this is not sufficient in cases requiring rapid disease control as in our case. Autologous or allogeneic EBV-specific cytotoxic T-lymphocytes (CTL) may be useful but it requires time and is not appropriate in cases requiring urgent treatment. Mortality is as high as 50%.<sup>[3]</sup> Another strategic question is the therapeutic approach in cases with developing organ dysfunction after cessation of immune suppressive drugs.

## Disclosures

**Informed Consent:** Written informed consent was obtained from the parents of the patient for the publication of the case report and the accompanying images.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

**Authorship Contributions:** Concept – S.P.; Design – M.K., S.P.; Supervision – M.K., S.P.; Materials – M.K., S.K.; Data collection and/or processing – M.K., S.P., S.K., A.A.; Analysis and/or interpretation – M.K.; Literature search – M.K., S.P.; Writing – M.K., S.P.; Critical review – M.K., S.P.

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