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Isolated primary CNS lymphoma after liver transplantation for autoimmune hepatitis: a case report

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Abstract

Post-transplantation primary central nervous system lymphoma (PT-PCNSL) is a rare neoplasm that occurs in immunocompromised patients. It can manifest months or years after transplantation, presenting with various neurological symptoms. A 64-year-old woman, who had received a liver transplant due to autoimmune hepatitis, presented with generalized weakness, headache, and confusion. Further investigation revealed multiple ring-enhancing lesions in the right frontal and temporoparietal regions on brain MRI. A brain biopsy confirmed the diagnosis of PT-PCNSL. This case underscores the importance of considering PT-PCNSL in the differential diagnosis of contrast-enhancing brain lesions in post-transplant patients. Timely recognition of PT-PCNSL is crucial for appropriate management and improved outcomes. To the best of our knowledge, this report describes the first instance of isolated CNS lymphoma in a liver transplant recipient, due to autoimmune hepatitis, successfully brought to complete remission with a rituximab-methotrexate regimen.

Keywords Neurology, Lymphoma, Posttransplant lymphoproliferative disorder, PTLD

Introduction

Primary Central Nervous System Lymphoma (PCNSL) is a distinct and rare type of extranodal, high-grade non-Hodgkin B-cell lymphoma that originates within the CNS. In contrast, secondary CNS lymphoma refers to non-Hodgkin lymphoma that originates elsewhere in the body and subsequently spreads to the CNS. The precise causes of CNS lymphoma remain unclear, but a key risk factor is immunodeficiency, whether it's congenital or acquired [1].

Posttransplant lymphoproliferative disorder (PTLD) encompasses a spectrum of findings, ranging from abnormal lymphoid hyperplasia to lymphomas, which arise following solid organ, stem cell, or bone marrow transplantation. Primary CNS PTLD denotes the exclusive involvement of the central nervous system in PTLD, without any concurrent systemic PTLD manifestations [2]. Although PTLDs are the second most common cancer in transplanted patients, PCNSL is a rare presentation of these disorders [3]. In transplant patients, the most common patients are kidney transplant recipients, while the occurrence of PCNSL after liver transplantation is extremely rare [4].

Patients with CNS lymphoma typically present with cognitive impairment as the most common symptom. This is often accompanied by gait disturbances, focal

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neurological deficits, signs of increased intracranial pressure, and seizures. The detection of lesions through imaging highlights the importance of thorough imaging studies for diagnosis [5]. Magnetic resonance imaging (MRI) with contrast is the principal diagnostic tool for PCNSL. It is particularly effective in identifying the characteristic isointense or hypointense lesions associated with this condition [6].

We present a rare case of PCNSL that occurred months after receiving a liver transplant. The diagnosis was confirmed through a brain biopsy, and treatment was administered using a rituximab-methotrexate regimen.

Case presentation

A 64-year-old woman, who had a liver transplant 18 months earlier for autoimmune hepatitis and was on mycophenolate and tacrolimus, experienced a week of generalized weakness, headaches, confusion, and disorientation. The headache was bitemporal, constant, and of mild intensity, with no known factors that worsened or alleviated the condition.

The patient was confused. Fundoscopic examination revealed papilledema. The neurological evaluation showed left-sided hemiparesis, left-sided sensory changes, and left-sided pyramidal signs. Additionally, the patient demonstrated visuospatial deficits and loss of sensation on the right side of the body.

Laboratory tests, including C-reactive protein, and erythrocyte sedimentation rate, showed normal results. However, gamma-glutamyl transferase levels and platelet counts were elevated. Tests for CMV IgM, Hepatitis B & C, HIV, and Toxoplasma gondii returned nonreactive results, with the CMV IgG test also being negative.

Due to the range of neurological signs and symptoms reported, an initial brain CT without contrast was performed before transferring the patient to our institution, showing the absence of hemorrhage. Subsequently, after referral, an MRI scan was ordered, revealing multiple ring-enhancing lesions, primarily located in the right frontal lobe, temporoparietal regions, and left parietal lobe, with the largest measuring 2.7 cm in maximal diameter. These lesions were associated with moderate vasogenic edema. Figure 1 illustrates these MRI findings.

Given the suspicion of toxoplasmosis, the patient was started on sulfadiazine and pyrimethamine, and blood cultures were collected. As the patient's clinical condition deteriorated, an urgent craniotomy and brain biopsy were carried out to determine whether the lesions were due to toxoplasmosis, lymphoma, brain abscess, or other pathologies.

The brain biopsy revealed diffuse infiltrates of closely packed intermediate to large mononuclear cells with scant cytoplasm. Additionally, a perivascular infiltrate composed of atypical lymphoid cells and a widespread infiltrate of neoplastic intermediate to large lymphocytes tested positive for the B-cell marker CD20. Histologic findings are shown in Figs. 2, 3, 4, 5 and 6.

The patient was diagnosed with CNS PTLD, specifically high-grade diffuse large B-cell lymphoma (DLBCL) of the activated B-cell phenotype. Treatment was initiated with a regimen of systemic rituximab and methotrexate. Following the completion of eight cycles of high-dose rituximab-methotrexate, the patient's clinical status improved. A follow-up brain MRI 14 months later showed improved imaging findings (Fig. 7). As of this report's publication date, the patient remains alive and in complete remission with a normal neurological examination.

Discussion

Autoimmune hepatitis is a chronic liver condition resulting from an autoimmune attack on liver cells. It is characterized by persistent hepatocellular inflammation and necrosis, which, if left untreated, can lead to liver cirrhosis and ultimately may require a liver transplant [7].

PTLDs are life-threatening lymphoproliferative diseases that occur in patients after solid organ transplantation [8]. The most common cause of PTLD in the vast majority of patients is Epstein-Barr virus (EBV) infection. PTLD clinical presentation is non-specific and highly variable; it could range from localized to disseminated disease. Presenting features include fatigue, malaise, fever, night sweats, and weight loss. In addition to lymphadenopathy, PTLD tends to grow rapidly, which causes compressive symptoms in the structures around the tumor [9].

The initial work-up for PTLD includes a comprehensive metabolic panel, uric acid, LDH, EBV quantitative PCR, and EBV serologies for previously seronegative patients. Suspected PTLD warrants a CT or MRI with contrast, and histopathology confirms the diagnosis. CNS-PTLD may be indicated by positive EBV PCR in CSF, but definitive diagnosis often requires a biopsy. Management involves a multidisciplinary approach tailored to histology, staging, immunosuppression, and patient health, with options including surgery, radiation, rituximab, chemotherapy, immunochemotherapy, and stem-cell transplantation. Radiotherapy is effective for localized PTLD [9–11].

PCNSL is a rare, high-grade non-Hodgkin B-cell lymphoma, with approximately 90% of cases being diffuse large B-cell type. It affects 2–7% of heart, liver, and lung transplant recipients, and up to 2% of renal transplant recipients, with the highest frequency occurring in the first year after heart or lung transplantation. Most patients present with localized neurologic symptoms, commonly cognitive impairment, related to a singular brain lesion, typically in the supratentorial region [5, 12, 13].

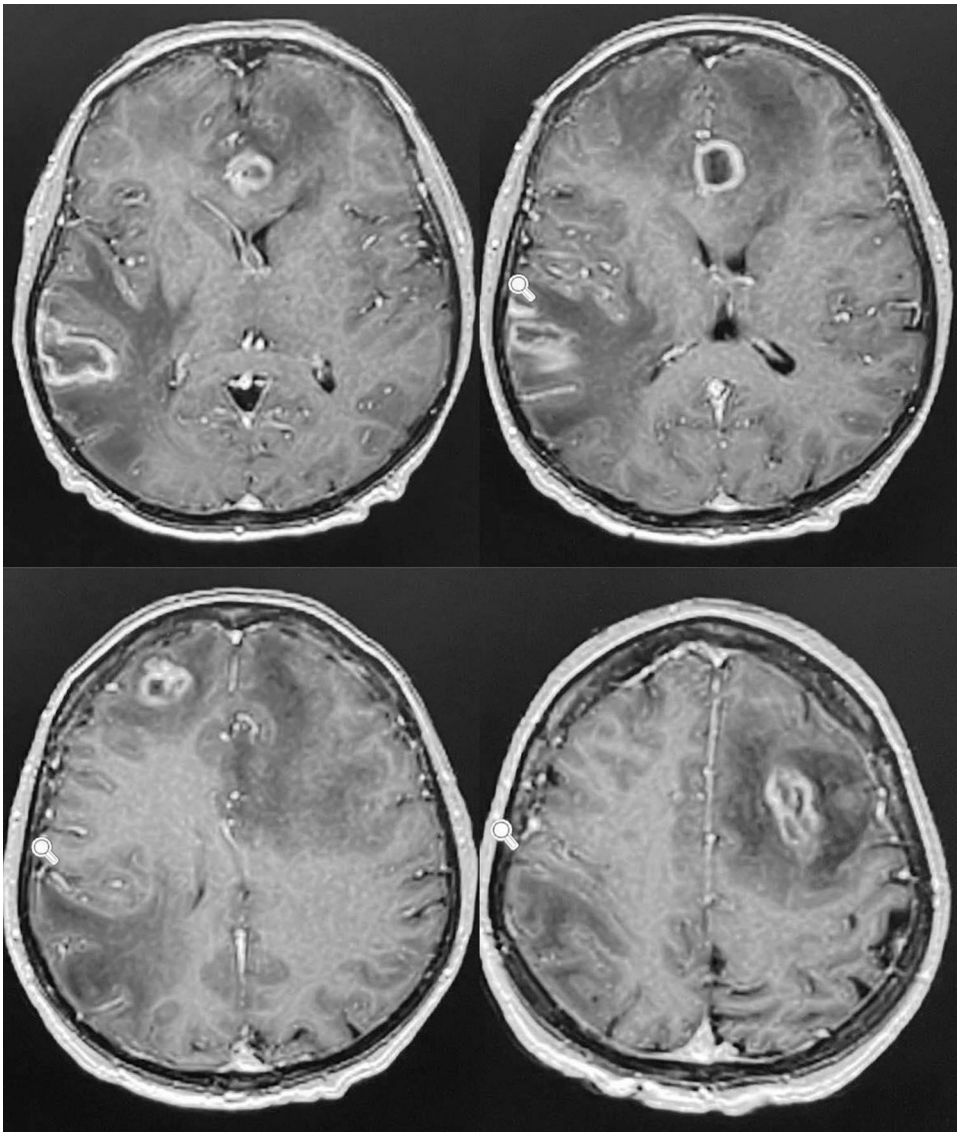

Fig. 1 This series of axial T1-weighted MRI images with contrast enhancement shows a large, irregular, heterogeneously enhancing mass predominantly in the right frontal and temporoparietal regions. The mass involves the midline structures, causing significant vasogenic edema and a midline shift. In addition, a distinct enhancing lesion is noted in the left parietal lobe. The lesions demonstrate heterogeneous enhancement with areas of necrosis

MRI with IV contrast is the primary diagnostic tool, revealing characteristic isointense or hypointense lesions on T1-weighted imaging and isointense or hyperintense lesions on T2 sequences, often with homogenous enhancement. Other modalities, like diffusion-weighted MRI and PET, help distinguish PCNSL from other brain lesions. Although less sensitive, CT can detect hyperattenuating tumors with linear enhancement features. Biopsy, particularly stereotactic, remains the gold standard for diagnosis [6, 14].

Treatment options include surgery, reduced immunosuppression, radiation, and chemotherapy, with methotrexate-based regimens, often combined with rituximab, proving the most effective. Despite these treatments, the prognosis for PT-PCNSL remains poor, underscoring the need for continued research to improve outcomes [15, 16].

A retrospective study by Abu-Shanab et al. found an increased incidence of PTLD in patients with autoimmune liver disease [17]. There have been very few cases reported so far of PTLD with only CNS involvement [18]. In our review of the English literature from 1981 to 2024, using a combination of relevant terms linked by AND and OR in PubMed and Google Scholar, no cases were found of liver transplant recipients because of autoimmune hepatitis having isolated CNS involvement at the time of diagnosis, to the best of our knowledge. This positions our case as the first of its kind, where isolated

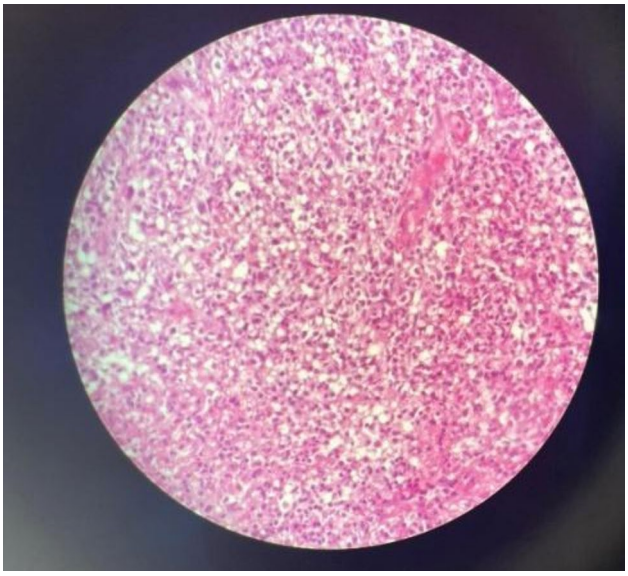

Fig. 2 Diffuse infiltrate of closely packed intermediate to large mononuclear cells with scant cytoplasm

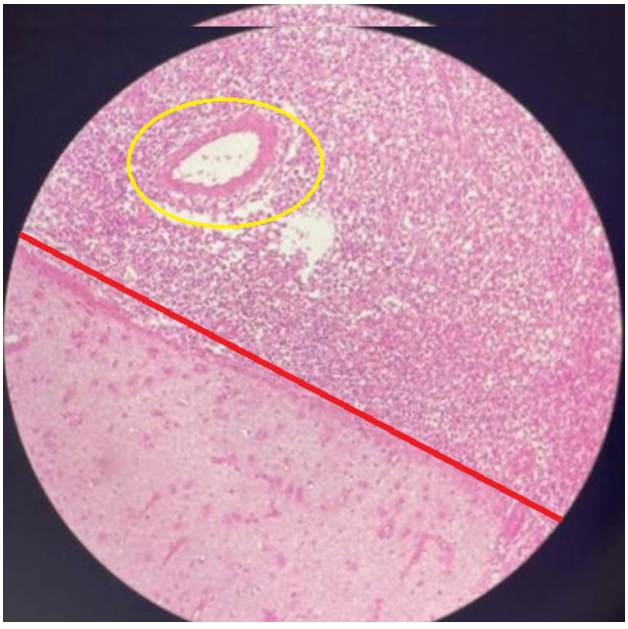

Fig. 3 Perivascular infiltrate of atypical lymphoid cells (yellow circle) with surrounding brain tissue (below the separating red line)

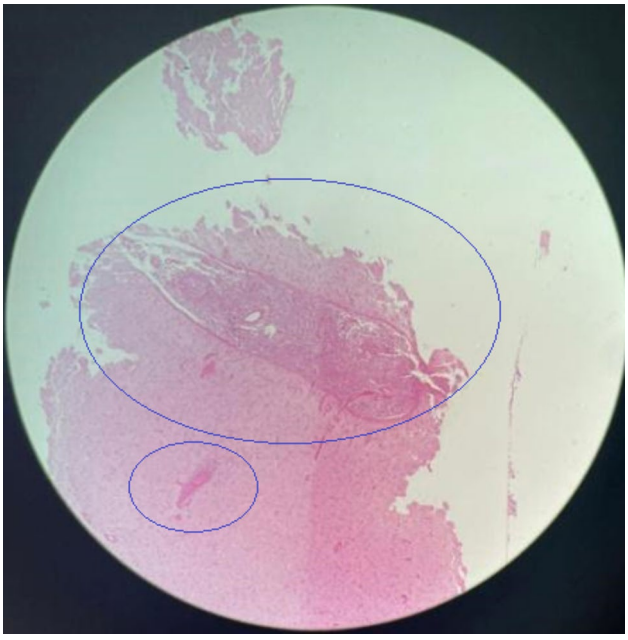

Fig. 4 Other areas of brain parenchyma show edema and reactive neurons (blue circles)

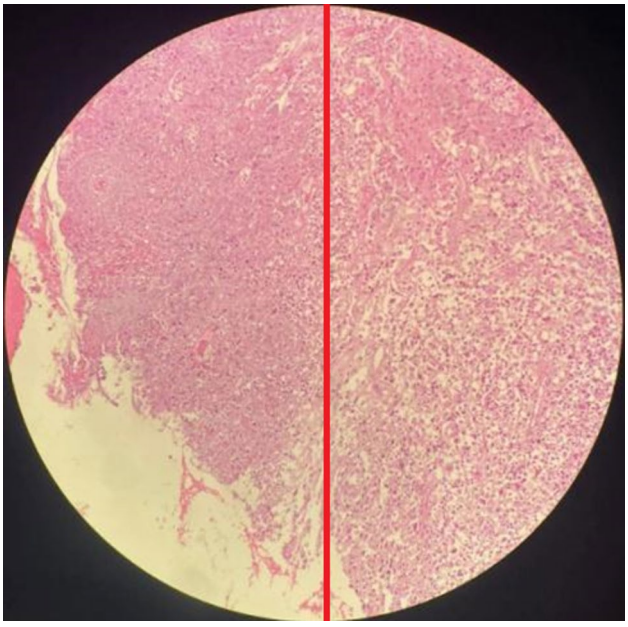

Fig. 5 Diffuse infiltrate of neoplastic intermediate to large lymphocytes (right side of the separating red line) with background inflammation and necrosis (left side of the line)

CNS lymphoma in a liver transplant recipient due to autoimmune hepatitis was successfully treated to complete remission with a rituximab-methotrexate regimen.

Given the rarity of PTLD affecting the CNS, specific survival rates are hard to find. A case series of 84 patients from 1997 to 2010 reported a median overall survival of 17 months. More recent data indicate an improved median overall survival of 4 years, likely attributable to enhanced understanding of immunosuppression management, the employment of rituximab, advances in radiological techniques, and better supportive care [19].

Because of its scarcity and possible severity, PT-PCNSL necessitates close observation and prompt treatment to protect patient health. Improving knowledge and developing new methods of diagnosis and therapy are crucial

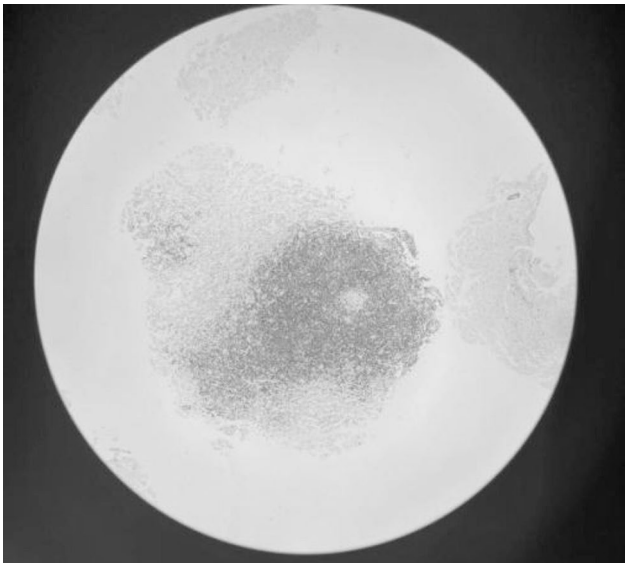

Fig. 6 Neoplastic lymphocytes positive for the B cell marker CD20 on immunohistochemical staining (brown colored)

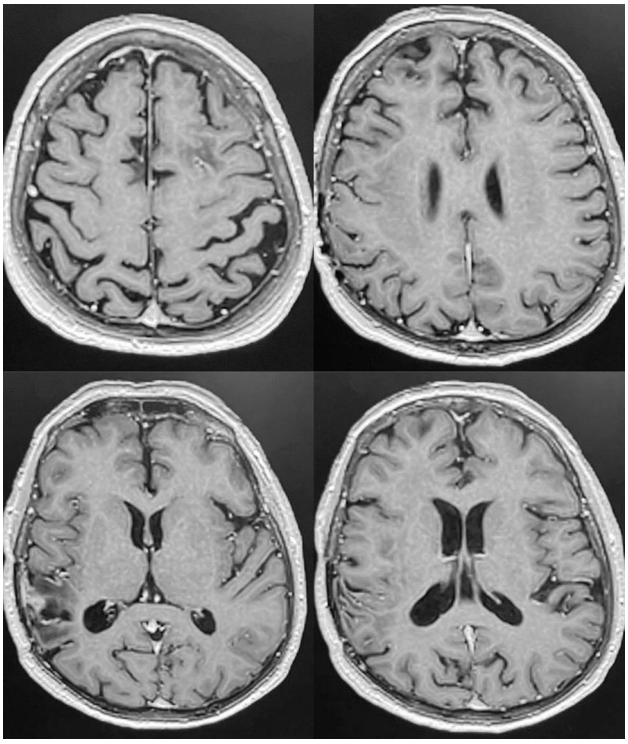

Fig. 7 Improved imaging findings (reduction in size of lesions and edema) on follow-up axial brain MRI with IV gadolinium at 14 months

for improving results and fine-tuning approaches to managing PT-PCNSL in transplant recipients.

Conclusion

This report documents the first case of isolated primary CNS lymphoma in a liver transplant recipient with autoimmune hepatitis, effectively treated with a rituximab-methotrexate regimen. It highlights the importance of including PT-PCNSL in the differential diagnosis for post-transplant patients who present with neurological symptoms and multiple ring-enhancing lesions on imaging. This contribution offers significant insights into handling a rare yet severe liver transplantation complication, underscoring the importance of prompt intervention in similar cases.

Author contributions

The following authors were responsible for the drafting of the text, sourcing, and editing of clinical images, investigation results, and critical revision for important intellectual content: Alaa Zayed, A.Shubietah, Qusay Abdoh, and A.Sarama. The following authors gave final approval of the manuscript: Alaa Zayed, A.Sarama and A.Shubietah. The following authors made the revision and addressed reviewers' comments: Alaa Zayed and A.Shubietah.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval

Ethical approval is exempt/waived at our institution.

Informed consent

Written informed consent for the publication of this case report was obtained from the patient.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Competing interests

The authors declare no competing interests.

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