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A case of delayed primary-CNS post-transplant lymphoproliferative disorder in a patient with concurrent metastatic colorectal malignancy

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ABSTRACT

Introduction: Post-transplant lymphoproliferative disorders (PTLD) are a complication of immunosuppression following organ transplantation. Due to their heterogeneous presentation, diagnosis of PTLD can be challenging.

Case Report: In this case report, we present a patient with metastatic colon cancer, with remote history of multivisceral organ transplant 20-years prior, who presented with altered mental status and was diagnosed with primary central nervous system PTLD.

Conclusion: This case illustrates the importance of continued suspicion of PTLD long after transplantation in solid-organ transplant recipients, even in the setting of multiple comorbidities.

Keywords: Immunosuppression, Lymphoproliferative disorders, Neoplasms, Organ transplantation

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INTRODUCTION

Post-transplant lymphoproliferative disorders (PTLDs) represent a spectrum of conditions characterized by lymphoid proliferation in patients on immunosuppression following organ transplant [1]. These conditions vary from benign, polyclonal pathologies including infectious mononucleosis to such malignancies as Burkitt lymphoma, with a collective incidence of 3.2% in solid-organ transplant recipients. The type of organ transplant imposes a pronounced difference in PTLD incidence, with kidney transplant recipients (0.5–2.5%) and pancreatic transplants (0.5–5.0%) having the lowest incidence of PTLD, compared to incidences of ~20% among multiorgan and intestinal transplant recipients. Epstein–Barr virus (EBV) seronegativity prior to transplantation multiplies risk by a factor of 10 to 75 (5–12 fold in adult cohorts); thus, an EBV-seronegative patient with an EBV-seropositive donor is at highest risk of PTLD. Further risk factors include the mode of immunosuppression after transplant, with increased risk associated with tacrolimus, anti-thymocyte globulin, and azathioprine [1–3].

Diagnosis of PTLD is typically made according to histopathological examination. The World Health Organization (WHO) 2017 classification scheme for PTLD outlines six distinct categories of PTLD, including three types of nondestructive PTLDs (plasmacytic hyperplasia, infectious mononucleosis-like PTLD, and florid follicular hyperplasia), nearly all of which are EBV-associated, as well as polymorphic PTLD (90% EBV association), monomorphic PTLD (~50% association), and classic Hodgkin's lymphoma-like PTLD (>90% association). Timing of PTLD onset is highly variable, with early-onset PTLD in particular associated with

EBV positivity and graft involvement (as opposed to extranodal disease) [1]. Extranodal PTLD most commonly affects the gastrointestinal (GI) tract, and infrequently affects the central nervous system (CNS, 5–20%) [1]. To identify sites of involvement, 18F-fluorodeoxyglucose (FDG) positron-emission tomography combined with computed tomography (PET-CT) is noted to have high sensitivity and discriminatory capacity [4]. Once diagnosed, PTLDs can be accurately staged according to criteria germane to the lymphoma associated with the presentation. Post-transplant lymphoproliferative disorders can subsequently be managed via reduced immunosuppression, chemotherapy including rituximab treatment, and/or surgery and radiotherapy [5]. Rituximab treatment, administered as monotherapy or in conjunction with chemotherapy, has in particular become a mainstay of treatment for patients with nondestructive PTLDs or diffuse large B-cell lymphomas refractory to reduced immunosuppression [6].

Here, we describe the case of a multivisceral organ transplant recipient with a recent history of colorectal adenocarcinoma who presented with altered mental status and was subsequently diagnosed with primary CNS PTLD concurrent with metastatic colorectal cancer affecting the liver. Her case illustrates the challenges associated with diagnosis of a rare disorder in the setting of multiple prior malignancies.

CASE REPORT

A 62-year-old woman presented with subacute onset of confusion and acute nausea and vomiting. Her past medical history included basal cell carcinoma of the scalp, orthostatic hypotension from autonomic dysfunction, and type-1 diabetes mellitus, for which she received a kidney transplant 24-years prior and a pancreas transplant 20-years prior. She has since been treated with tacrolimus and mycophenolic acid.

Six months prior to admission, she was diagnosed with a deep-vein thrombosis and pulmonary embolism and was started on apixaban. She subsequently developed a GI bleed and a diagnostic colonoscopy revealed colon cancer. After a transverse colectomy, her cancer was classified as a stage I malignancy. Computed tomography (CT) scan of the brain, performed during staging, showed findings consistent with age-related atrophy and potential small-vessel ischemic disease. Shortly thereafter, she began to experience worsening confusion, including forgetfulness and disorientation to time and place. Two months prior to her admission, magnetic resonance imaging (MRI) was performed, showing no abnormalities or lesions of the brain aside from diffuse cerebral atrophy, with electro-encephalography (EEG) showing generalized slowing, which was attributed to an encephalopathy of likely toxic-metabolic etiology.

Progressive cognitive decline prompted inpatient admission. On presentation, a CT-scan of her abdomen showed an ill-defined hepatic mass, with follow-up MRI demonstrating a 2.5 cm 2.6 cm hypovascular enhancing lesion in the lateral segment of the left hepatic lobe and a 1 cm × 0.8 cm hypovascular lesion in the anterior right hepatic segment. Repeat CT of the head showed hypoattenuated areas in the left frontal and right-parietal lobes, and MRI of the head with contrast showed multifocal, heterogeneously enhancing lesions in the left inferior frontal lobe, right anterior and posterior temporal lobe, and corpus callosum (Figure 1).

Differential diagnosis for her CNS lesions included PTLD, metastatic disease, or progressive multifocal leukoencephalopathy (PML). Lumbar puncture was performed and CSF studies were notable only for markedly elevated protein (155 mg/dL). Cytological analysis and flow cytometry of cerebrospinal fluid (CSF) was not concerning for malignancy, with slide review showing monocytes and lymphocytes of occasional plasmacytoid morphology.

Serum studies detected EBV viral antigen, with viral load quantified as 93.8 IU/mL—findings that were in themselves not strongly indicative of a particular etiology to the patient's condition.

Serum JC virus was also negative, reducing the likelihood of PML. A biopsy of the patient's liver lesions was subsequently performed and was consistent with metastatic colorectal adenocarcinoma. This raised suspicion of metastatic disease to the brain as well, though brain metastasis in colon cancer is rare, occurring in 1–3% of patients with metastatic colorectal malignancies [7]; and the irregular rim-enhancement of lesions noted on brain imaging was atypical of metastatic disease. Repeat brain MRI showed significant interval progression of brain lesions, with cerebral edema and mass effect concerning for lymphoma or a multifocal glioblastoma, in addition to metastasis (Figure 2).

Stereotactic brain biopsy was performed and on pathology exam, large lymphoid cells were identified, with no evidence of metastatic cells. These lymphoid cells were positive for CD45, CD20, PAX5, CD21, CD30, BCL6, MUM1, BCL2, and EBER(ISH), while negative for CD5 and CD10. Myc positivity was 20%, and Ki67 was positive in 40% of cells. These findings were consistent with a diagnosis of EBV+ monomorphic PTLD, favoring a diffuse large B-cell lymphoma (DLBCL) of activated B-cell (ABC) immunophenotype. Whole-body PET-CT was then performed and showed no FDG signal involvement beyond the brain and the two liver lesions identified as metastatic colon cancer, confirming a diagnosis of primary CNS PTLD (Figure 3).

Treatment was subsequently initiated, prioritizing management of PTLD over the liver metastasis due to the rapid progression of her brain disease. She was initiated on a course of high-dose methotrexate, rituximab, and temozolomide [8], as well as dexamethasone to treat vasogenic edema from her lesions. Acyclovir was also initiated [9], and her prior immunosuppressant regimen of tacrolimus, mycophenolate mofetil, and prednisone

was held. Her treatment course was complicated by hyponatremia and hypokalemia attributed to a syndrome of inappropriate antidiuretic hormone (SIADH), and treated using salt tablets, with furosemide dosed to increase free water clearance. During her second 15-day rituximab/methotrexate cycle, repeat brain MRI showed that her four dominant supratentorial intra-axial masses were decreased in size with substantially decreased vasogenic edema. Her EBV viral load was further found to be undetectable (Figure 4A).

During this admission, her liver metastases were found to have progressed. She began to complain of nausea with vomiting and diffuse abdominal pain. She was found to have a 13 cm long-segment intussusception. She underwent emergency small bowel resection and exploratory laparotomy with concern for a malignant lead point; final pathology revealed tubulovillous adenoma with extensive high-grade dysplasia and pyloric metaplasia. Since she resumed a normal diet and bowel function, with progress followed on an outpatient basis; her liver lesions have been treated between rounds of rituximab infusion by transarterial chemoembolization and radioablation, with MRI abdomen during her fifth rituximab infusion showing response in liver disease (Figure 4B).

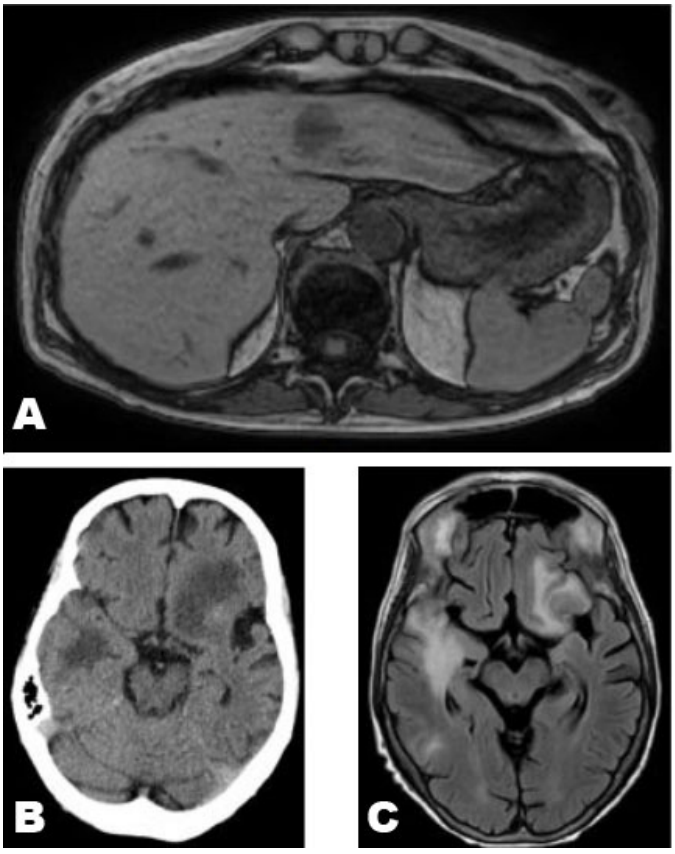

Figure 1: Initial imaging findings. (A) MRI abdomen showing liver lesions concerning for metastatic disease. (B) CT head showing hypoattenuated areas in the left frontal and right-parietal lobes. (C) Axial T2-Flair images showing heterogeneously enhancing lesions in the left inferior frontal lobe, right anterior and posterior temporal lobe, and corpus callosum on presentation.

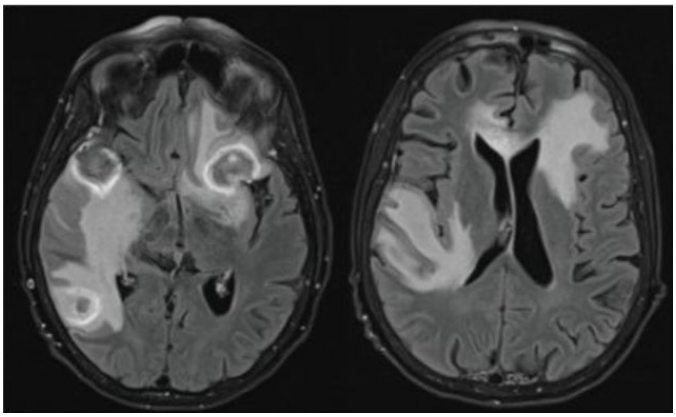

Figure 2: Stealth MRI showing interval enlargement of all four dominant intra-axial masses.

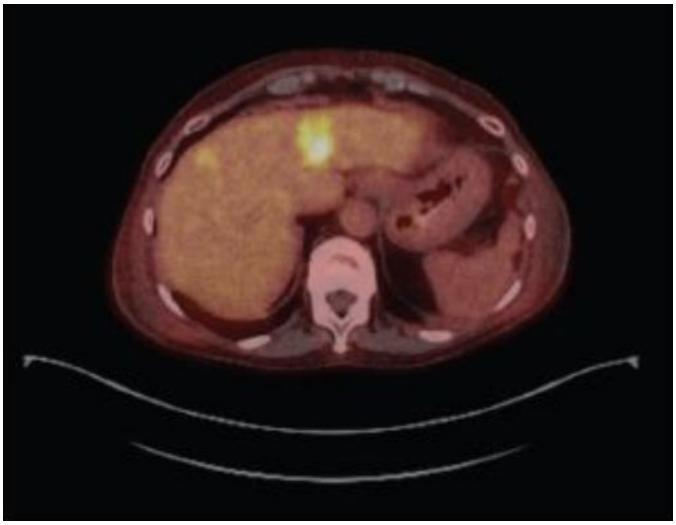

Figure 3: PET imaging showing FDG uptake in the two liver lesions identified as metastatic colon cancer.

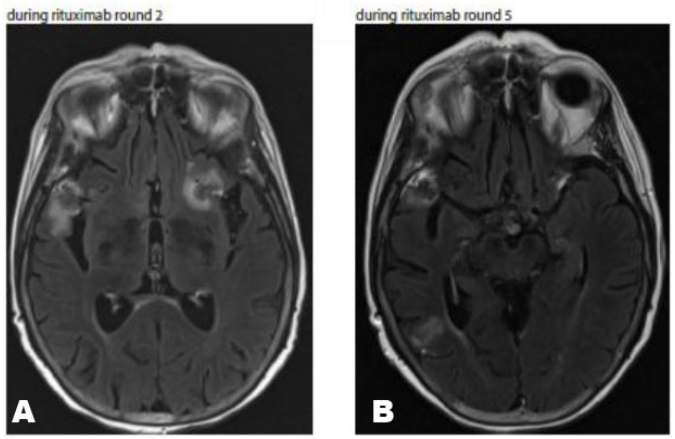

Figure 4: T2-weighted MRI images re-demonstrating supratentorial intra-axial masses, decreased after (A) one and (B) four rounds of chemotherapy with substantial decrease in previously noted surrounding vasogenic edema.

DISCUSSION

Post-transplant lymphoproliferative disorder represents an established complication of solid-organ transplantation; nonetheless, identification and diagnosis of PTLD can be challenging in patients. Central nervous system-PTLDs in particular are rare, with a retrospective study identifying these to account for only 7% of PTLD cases [8]. As such, there is a relative paucity of reports on CNS-PTLD patients. This case illustrates the complicated path to diagnosis of a delayed presentation of PTLD in a patient with multiple malignancies.

Alone, brain lesions in immunosuppressed patients have a broad differential diagnosis, including degenerative, structural, infectious, and malignancy. The patient described presented with altered mental status and ring-enhancing lesions, which often occur in PTLD [10, 11], but are nonetheless nonspecific; moreover, nonspecific CSF abnormalities were of low-yield; in keeping with extant data describing only rare definitively abnormal CSF cytology and flow cytometry results in PTLD. Thus, while immediately proceeding to biopsy is controversial in PTLD workup [12, 13], brain biopsy was ultimately the only method of ascertaining this patient's pathology, given a picture further complicated by her metastatic colorectal adenocarcinoma.

This case exemplifies many of the characteristic features of CNS-PTLD, which is commonly associated with kidney and multivisceral transplant, tacrolimus administration, EBV positivity, as well as monomorphic B-cell origin [12]. However, though CNS-PTLDs do often present late, this patient's presentation with PTLD multiple decades after organ transplantation is atypical [11].

Treatment for our patient sought to achieve a balance between adequate management of rapidly progressing CNS lesions, and a background of metastatic malignancy. The former was ultimately prioritized, with ablation of liver metastasis and identification of other metastatic/primary sites occurring during breaks in lymphoma treatment. Central nervous system-PTLDs are commonly treated with a combination of immunosuppression reduction, rituximab, and (in EBV-positive patients) antiviral therapy [12]. Notably, while rituximab treatment does have demonstrated utility in CNS-PTLD [14, 15], limited CNS penetration of the drug is a noted concern [16], though in this instance, did yield clinical improvement. Whole brain radiotherapy, while a typically viable option for patients with CNS-PTLD [17, 18], was ultimately deferred in this instance due to toxicity.

CONCLUSION

This report demonstrates a unique presentation of PTLD, with late presentation of isolated CNS-PTLD as a second malignancy. While there is no standardized treatment of CNS-PTLD, she ultimately improved with rituximab treatment. This case presentation is representative of the importance of continued suspicion of PTLD long after transplantation in solid-organ transplant recipients, even in the setting of multiple comorbidities. It is our hope that this can be used as a reference for treating other patients with CNS PTLD.

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Author Contributions

Vinay Ayyappan – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Nichole Smith – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Ye Tian – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Jean Miller – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Data Availability
All relevant data are within the paper and its Supporting Information files.