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Case Report

Post-transplant lymphoproliferative disorder presented with diplopia; Diagnosis by FDG-PET/CT ☆

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ABSTRACT

Post-transplant lymphoproliferative disorder (PTLD) is a general term describing lymphoproliferative disorders that develop against the background of immunosuppression after organ transplantation, and that range from benign tumors to malignant lymphoma. PTLD is relatively rare after liver transplantation, and there are few cases of post-liver transplant lymphoma with lesions in the clivus. We here describe the case of a patient who visited our hospital complaining of diplopia after a liver transplant. Fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) revealed lesions with high FDG uptake in the clivus and throughout the body, and the patient was diagnosed with lymphoproliferative disease after liver transplantation. The diplopia was thought to have been

Abbreviations: PTLD, post-transplant lymphoproliferative disorder; FDG PET/CT, fluorodeoxyglucose positron emission tomography/computed tomography; MRI, magnetic resonance imaging; EBV, Epstein-Barr virus; DNA, deoxyribonucleic acid; CyA, cyclosporine; MMF, mycophenolate mofetil; FLAIR, fluid-attenuated inversion recovery; EBER, EBV-encode RNA; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B-cell; WHO, World Health Organization; Pola-R-CHP, polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone; Pola-R-PSL, polatuzumab vedotin, rituximab, and prednisone; CMR, complete metabolic response; SUV max, maximum standardized uptake value; MIP, maximum intensity projection.

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caused by the clivus lesion infiltrating into the abducens nerve. In patients after organ transplantation, care must be taken to watch for onset of PTLD, and FDG-PET/CT is thought to be useful for its diagnosis.

Introduction

Post-transplant lymphoproliferative disorder (PTLD) is a general term describing lymphoproliferative disorders that develop against the background of immunosuppression after organ transplantation, and that range from benign tumors to malignant lymphoma [1]. Although the development of PTLD after liver transplantation is relatively rare, when it does occur it threatens the graft and the life prognosis of the transplant recipient [2]. Fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) is often used to diagnose PTLD, and most PTLD lesions are reported to be FDG-avid [3]. PTLD lesions may infiltrate the abducens nerve, causing diplopia [4]. Based on our search of the relevant literature, there have been few reports of post-liver transplant malignant lymphoma involving the clivus. Here, we report a case of post-liver transplant lymphoproliferative disorder with a clivus lesion with high FDG uptake, which was diagnosed following diplopia.

Case report

The patient is a woman in her 70s who underwent a liver transplant for B-type liver cirrhosis 4 years prior to presentation at our hospital with a complaint of diplopia and dizziness. She was admitted and underwent examination. Although she complained of diplopia in all directions, neurological examination revealed no obvious abnormalities. Brain stem infarction was suspected, but no obvious acute cerebral infarction was found on head magnetic resonance imaging (MRI). The patient's symptoms subsequently improved slightly, and she was discharged from our hospital. One month later, blood tests revealed a significant increase in lactate dehydrogenase (1,848 U/L). This result suggested PTLD, and additional blood tests showed elevated soluble interleukin-2 receptor (1,216 U/mL) and Epstein-Barr virus (EBV)-DNA levels (4.71 log IU/mL). At the time, she was being managed with chronic immunosuppression via the combination of cyclosporine (CyA) (75 mg/day) and mycophenolate mofetil (MMF) (320 mg/day). FDG-PET/CT showed FDG uptake in the left side of the skull, skull base, and mandible (Fig. 1A-D). FDG uptake was observed in the clivus (Fig. 1C, D), which was presumed to be the cause of the diplopia. In addition, diffuse mild FDG uptake was observed in the dorsal sides of both lungs (Fig. 1E), and lesions with high FDG uptake were also found in the left axillary lymph nodes, right ovary, sacrum, right tibia, and right calcaneus. These findings suggested malignant lymphoma. Re-evaluation of the brain MRI from a month earlier revealed a lesion in the clivus with mildly high signal on fluid-attenuated inversion recovery (FLAIR) and restricted diffusion (Fig. 2A–C), findings consistent with lymphoma.

A bone marrow biopsy revealed atypical cells with enlarged, irregular nuclei within normal marrow (Fig. 3A). The atypical cells were CD20-positive (Fig. 3B), CD3-negative, and EBV-encode RNA (EBER)-negative on immunohistochemistry, suggesting the infiltration of diffuse large B-cell lymphoma (DLBCL), a nongerminal center B-cell (non-GCB) subtype. The final diagnosis was post-liver transplant lymphoproliferative disorder (DLBCL non-GCB type, stage IV) as per the World Health Organization (WHO) 5th edition classification: Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation, lymphomas arising in immune deficiency / dysregulation [5].

Chemotherapy was started immediately. Pola-R-CHP (polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone) therapy was started first, and was then changed to Pola-R-PSL (polatuzumab vedotin, rituximab, and prednisone) therapy. Tapering of immunosuppressants was also performed. During hospitalization, the patient developed adrenal insufficiency and had difficulty eating, but chemotherapy could be continued with a reduced dosage. After 3 courses of chemotherapy, the lesions with FDG uptake had almost disappeared and the patient was considered to have achieved a complete metabolic response (CMR). Currently, Pola-R-PSL therapy is being continued and the immunosuppressant is CyA 75 mg/day; the MMF has been discontinued.

Discussion

The imaging findings of PTLD are diverse and are mainly classified into lymph node involvement and extranodal involvement [3]. PTLD lesions are FDG-avid on FDG-PET/CT, and the median standardized uptake value (SUV) max is 17.4, with a sensitivity of 89% and specificity of 89% [6]. PTLD lesions often occur in the grafted organ, and after liver transplantation, they often occur in the grafted liver [7]. In addition, central nervous system lesions in PTLD are often found in the basal ganglia and subcortical white matter [8]. In this case, lesions were observed throughout the body, including the clivus, but the lesions in the grafted liver were not obvious. Regarding clivus lesions, malignant lymphoma lesions are rarely seen in the clivus [4], and based on our search of the relevant literature, there have been few reports of clivus lesions in PTLD. Other differential diagnoses for clivus lesions include metastatic tumors, chordomas, meningiomas, and ectopic pituitary adenomas [9]. FDG-PET/CT revealed systemic lesions including the clivus and was able to diagnose PTLD, suggesting that FDG-PET/CT can be successfully used for PTLD diagnosis.

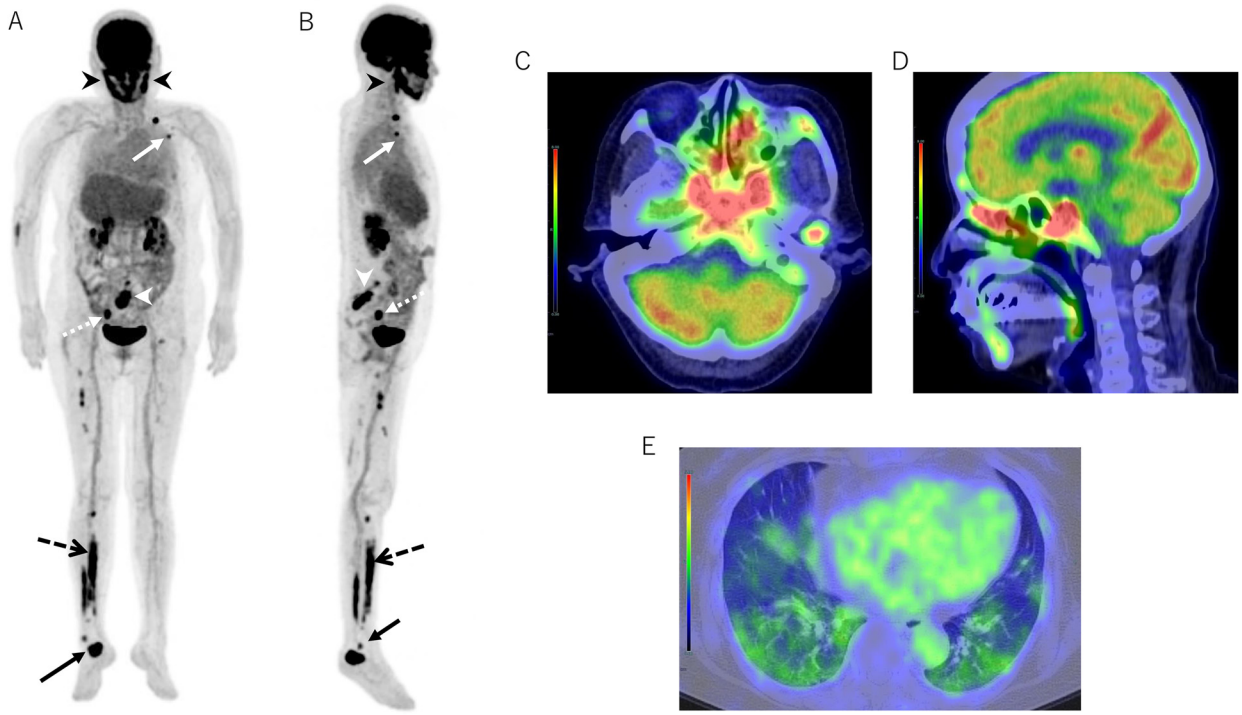

Fig. 1 – FDG-PET/CT images. (A and B) Maximum intensity projection (MIP) in the early phase. (A) Frontal view. (B) Lateral view: a diffuse FDG uptake of the mandible (black arrowhead), a slight diffuse uptake of both lungs, and focal FDG uptakes in the left axillary lymph nodes (white arrow), right ovary (white dotted arrow), sacrum (white arrowhead), right tibia (black dotted arrow), right calcaneus (black arrow) and so on. (C and D) Fused CT and FDG PET image (mediastinal window) in the early phase. (C) Axial image. (D) Sagittal image: a high FDG uptake in the skull base (arrow), with standardized uptake value SUVmax of 16.1. (E) Fused axial CT and FDG PET image (parenchymal window) in the early phase: a diffuse mild FDG uptake in both lungs, with SUVmax of 3.2.

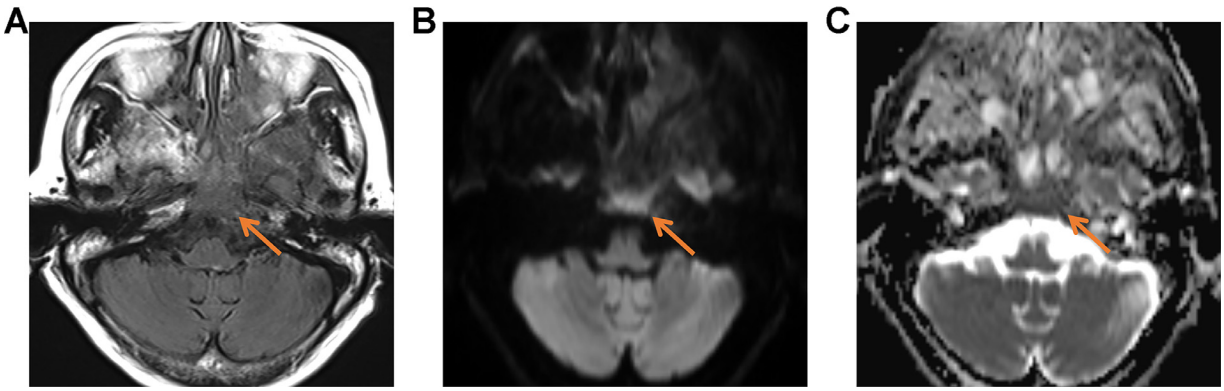

Fig. 2 – MRI images. (A) Axial fluid-attenuated inversion recovery (FLAIR) revealed a high signal intensity mass in the clivus (arrow). (B) Axial diffusion-weighted imaging showed a high signal intensity mass (arrow), and (C) the axial apparent diffusion coefficient indicated a low signal intensity mass (arrow), so there was diffusion restriction.

The clivus has a structure called the canal of Dorello, and the abducens nerve penetrates the dura mater, passes through the canal of Dorello, runs into the cavernous sinus, and finally distributes into the orbit [4]. In our patient, the clivus lesion caused diplopia due to abducens nerve invasion (Figs. 4 and 1D), which prompted the patient to seek medical attention.

PTLD is a general term for lymphoproliferative diseases associated with immunodeficiency after organ transplantation. These diseases range from hyperplastic lesions of plasma cells (benign tumors) to malignant lymphoma [1]. Many cases are associated with reactivation of EBV, so regular monitoring of serum EBV-DNA levels is recommended after transplantation [10]. The incidence rate following organ transplantation is highest at approximately 20% for the small intestine, versus only 1%-2.8% for the liver. There are 2 peak periods of onset: 1 year after transplantation (early stage) and 4-5 years

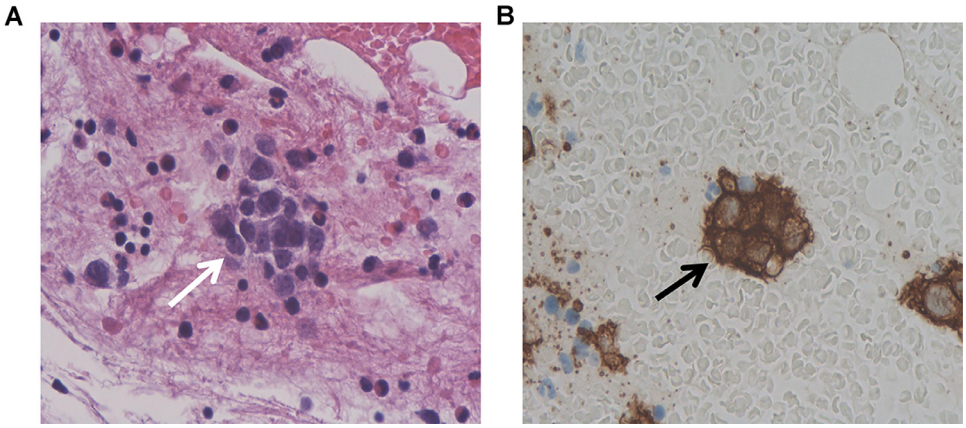

Fig. 3 – Histological findings of bone marrow. (A) Hematoxylin and eosin staining, 200 x magnification: atypical cells with enlarged, irregular nuclei within normal marrow (white arrow). (b) CD 20 immunohistochemical stain: positive (black arrow).

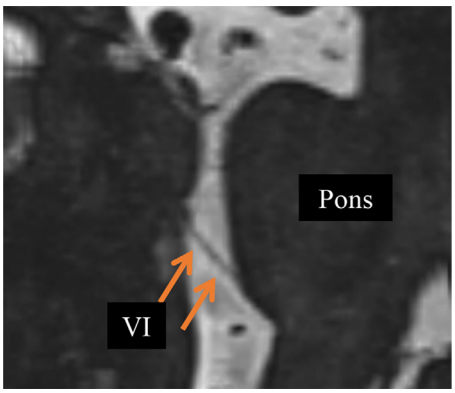

Fig. 4 – Image of the clivus. Sagittal MRI 3D basiparallel anatomic scanning depicts the abducens nerve (arrow) exiting the pons and entering the clivus.

after transplantation (late stage) [7,11]. The classification of PTLD was revised in the 2022 WHO classification (5th edition), and the method of classifying lymphomas associated with immunodeficiency, including PTLD, was changed significantly. PTLD is now classified first by histological type, and then subclassified by the etiology of immunodeficiency and the presence or absence of viral infection.

Pathologically, the lymphocytes that proliferate in early-onset PTLD are B cells at various stages of differentiation and exhibit polyclonal proliferation. In contrast, late-onset PTLD is less EBV-related, exhibits monoclonal tumor growth [12], and often has DLBCL-type histology [13]. Our patient was a late-onset case related to liver transplantation, and bone marrow biopsy revealed type DLBCL. At the time of diagnosis of PTLD, the blood EBV-DNA level was high at 4.71 log IU/mL, and initially it was thought to be EBV-related; however, the biopsied tissue was EBER-negative.

In this case, because the patient had central nervous system symptoms and the disease was in an advanced stage, treatment was prioritized over a biopsy of the clivus lesion, and tissue examination was limited to a bone marrow biopsy. After 3 courses of chemotherapy, the lesions with FDG uptake by FDG-PET/CT had almost entirely disappeared, which was considered consistent with a diagnosis of malignant lymphoma.

Conclusion

We report a case of PTLD that presented with diplopia and was diagnosed by FDG-PET/CT. FDG-PET/CT can clearly depict lesions throughout the body, including the clivus, and is thought to be helpful in the differentiation of patients who complain of diplopia after transplantation.

Author contributions

All authors provided final approval of the submitted version.

Patient consent

Informed consent was obtained from the patient for the publication of this report and any accompanying images.

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