

## CASE REPORT

# [<sup>18</sup>F]Fluorothymidine PET imaging in the diagnosis of leptomeningeal involvement with diffuse large B-cell lymphoma

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### Abstract

The diagnosis of leptomeningeal carcinomatosis remains difficult despite improvement in central nervous system (CNS) imaging and cytologic examination of the cerebral spinal fluid. False-negative results are common, providing obstacles in assessing both prophylactic and therapeutic efforts. As a result of increased survival of patients with a variety of systemic neoplasms it is likely that central nervous involvement will need to be addressed more often. This article presents a patient with a diffuse large B-cell lymphoma with polymorphic features. Imaging using <sup>18</sup>F-labeled fluorodeoxythymidine (FLT) proved useful in demonstrating both parenchymal and leptomeningeal CNS involvement. The potential for FLT to identify proliferative tissue may make it uniquely suitable for detection of CNS malignant disease.

**Keywords:** Leptomeningeal disease; lymphoma; PET imaging; fluorothymidine; FLT.

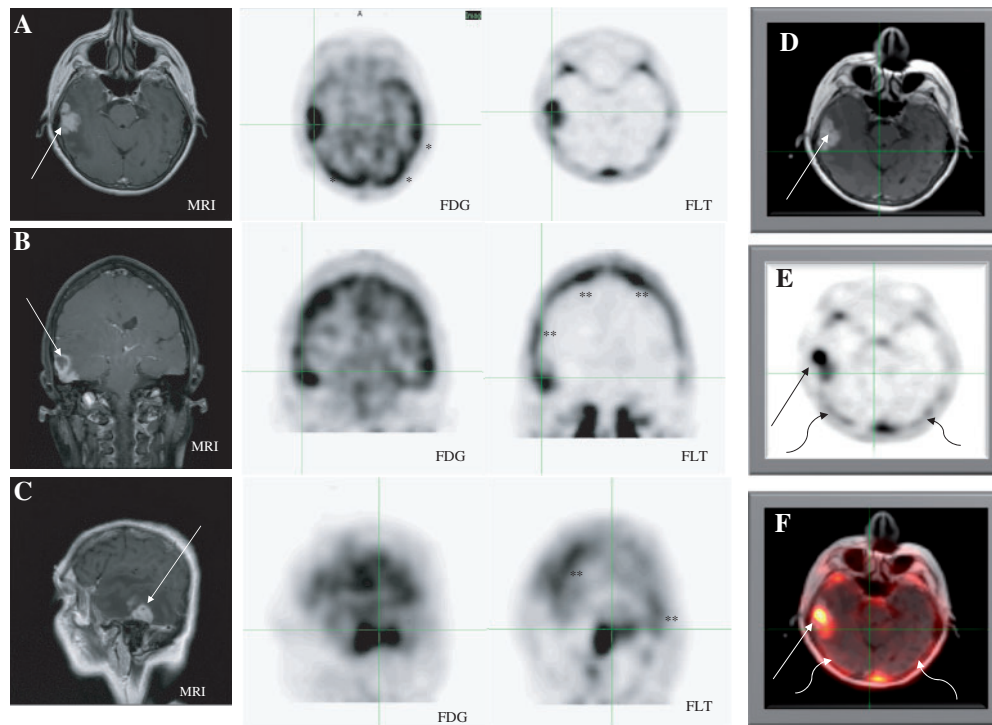
### Introduction

The diagnosis of leptomeningeal carcinomatosis remains difficult despite improvement in central nervous system (CNS) imaging and cytologic examination of the cerebral spinal fluid (CSF)<sup>[1–5]</sup>. False-negative results are common, providing obstacles in assessing both prophylactic and therapeutic efforts<sup>[6–12]</sup>. As a result of increased survival of patients with a variety of systemic neoplasms, it is likely that central nervous involvement will need to be addressed more often<sup>[13]</sup>. Since toxicity and survival outcomes of novel treatments for CNS disease require diagnostic accuracy, the search for more specific and sensitive techniques is necessary. We describe a patient with a diffuse large B-cell lymphoma with polymorphic features. Imaging using <sup>18</sup>F-labeled fluorodeoxythymidine (FLT) proved useful in demonstrating both parenchymal and leptomeningeal CNS

involvement. The potential for FLT to identify proliferative tissue may make it uniquely suitable for detection of CNS malignant disease.

### Clinical case presentation

A 58-year-old woman presented to the hospital with right upper quadrant abdominal pain, thought to be related to cholecystitis. During evaluation, the patient was noted to have a renal mass and nephrectomy was performed secondary to concern of possible renal carcinoma. Pathology was suspicious for lymphoproliferative disorder, but not diagnostic. Symptomatically, she was noted to have headaches, absence of neck stiffness and photophobia. The patient underwent positron emission tomography (PET) imaging with [<sup>18</sup>F]fluorodeoxyglucose (FDG), and was noted to have liver, lung, mediastinal and temporal lobe mass uptake by FDG. Magnetic resonance imaging



**Figure 1** (A) Corresponding axial views of MRI, FDG, and FLT images show the tumor (arrow, crosshairs). The intense cortical uptake of FDG in normal brain (\*) and the lack of FLT uptake in normal brain is also noted. (B) Corresponding coronal views show tumor (arrow, crosshairs). Again the cortical FDG uptake in normal brain is seen. FLT shows extensive meningeal enhancement (\*\*). (C) Corresponding sagittal views show tumor (arrow, crosshairs) and FLT meningeal uptake (\*\*). (D) Preoperative MRI shows the temporal lobe mass (arrow). (E) Preoperative FLT show both the temporal lobe mass (straight arrow) and distant meningeal enhancement (curved arrows). (F) Fusion image of MRI/FLT identifies uptake in the temporal lobe mass (straight arrow) and along meningeal sites (curved arrows).

(MRI) confirmed a temporal lobe mass. Neuroradiologic examination did not show evidence of leptomeningeal involvement or any other abnormal enhancement. Examination of the CSF was negative for malignant cells. The patient was enrolled in an imaging trial to evaluate the use of FLT in patients with brain tumors, and underwent imaging preoperatively. Fig. 1 delineates the tumor in all images and highlights the advantage of FLT over MRI and FDG for imaging meningeal tumor infiltration.

The patient subsequently underwent neurosurgical resection of the temporal lobe lesion. Intraoperatively, meningeal thickening suspicious for tumor involvement was also noted and biopsied. As seen in Fig. 2, pathology revealed diffuse large B-cell lymphoma, with polymorphic features, which was confirmed by outside review.

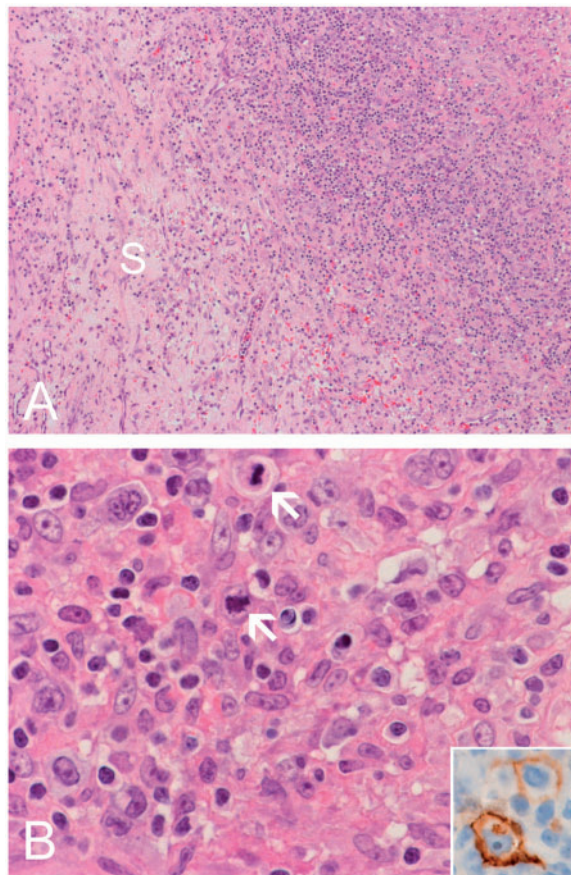
Secondary to poor renal function, the patient could not undergo high-dose methotrexate therapy, and received cyclophosphamide, rituximab, vincristine, adriamycin, and dexamethasone for 3 cycles, with vincristine dropped after cycle 3 secondary to neuropathy. The patient was treated with one dose of methotrexate intrathecally (IT) following the first cycle of chemotherapy. Secondary to a low glomerular filtrate rate of 35 ml/min, she developed

severe grade IV pancytopenia, and was unable to receive further IT therapy until cycle 7. She is now in complete remission, with 8 cycles planned secondary to poor transplant ability, and the aggressive nature of the original disease. Post-therapy imaging is planned using the FLT protocol.

## Discussion

The current diagnosis of CNS malignancy generally includes a combination of clinical symptoms, MRI imaging, and lumbar puncture with cytologic examination<sup>[7]</sup>. Gadolinium-enhanced MRI is the preferred imaging method to detect meningeal carcinomatosis<sup>[5]</sup>. However, problems of specificity exist, with inability to differentiate inflammatory, infectious and malignant processes<sup>[9]</sup>. Flow cytometry analysis has also increased sensitivity for detecting abnormal cells obtained by lumbar puncture<sup>[6]</sup>. However, both MRI and cytology are non-diagnostic in a significant number of cases<sup>[1,2]</sup>.

PET imaging using FDG is widely used for staging of lymphoma and other malignancies. Despite general diagnostic efficacy, its usefulness in detecting CNS abnormalities is limited by high levels of glucose utilization in the



**Figure 2** Pathology of the temporal lobe mass shows diffuse large B-cell lymphoma with polymorphic features confirmed by outside review. (A) and (B) denote stromal tissue (S), and involved meningeal tissue infiltrated by a population of mitotically active (arrow) large atypical lymphocytes with prominent nucleoli. These large lymphocytes are CD20 positive (insert).

brain. FLT offers 2 potential advantages for tumor imaging. Its intracellular trapping by thymidine 1 kinase directs specificity to proliferating cell populations. In addition, its independence from glucose uptake makes it attractive for CNS imaging. FLT is being evaluated in the staging of a variety of solid and hematologic tumors<sup>[11]</sup>. In high-grade glioma, FLT uptake has been correlated with proliferative rate as measured by Ki67 staining<sup>[10]</sup>.

CNS malignancies carry significant morbidity and mortality by virtue of location and the toxicity of treatment. Although lymphomas often respond to therapy, CNS prophylactic regimens have uncertain long-term benefits<sup>[3]</sup>.

Selecting patients for clinical trials of prophylaxis or possible therapeutic efforts will require more accurate techniques to identify malignant involvement of the CNS. In addition to current standards of MRI and flow cytometry, this case illustrates that FLT imaging may be a useful imaging modality to enhance early diagnosis of leptomeningeal disease. Accurate diagnosis of leptomeningeal disease is necessary to improve outcomes in further trials of prophylactic and therapeutic CNS disease management.

## Conflict of interest

Funding for FLT production was obtained from the US Qualified Therapeutic Discovery Program (QTDP) with special permission from the US FDA using a Drug Master File number issued to Midwest Medical Isotopes, Oklahoma City. All other authors have no conflict of interest.

## Acknowledgements

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