Spectrum of [18F]FDG PET/CT Findings in Primary Central Nervous System Lymphoma – A Pictorial Essay

Abstract

Primary central nervous system lymphoma (PCNSL) is a rare, aggressive variant of extranodal non-Hodgkin's lymphoma. Although gadolinium-enhanced magnetic resonance imaging remains the initial imaging modality of choice, a whole-body F-18 fluorodeoxyglucose (FDG) positron emission tomography–computed tomography is imperative to exclude systemic lymphomatous involvement. Furthermore, the metabolic parameter, maximum standardized uptake value (SUV_{max}) of the lesion, tumor-to-normal cerebral tissue SUV_{max} ratio, and FDG uptake patterns help in differentiating intracranial lymphomas from High-grade Glioblastoma Multiforme (HGM) and infectious lesions, and hence, consolidating the diagnosis. In this pictorial essay, we present a series of PCNSL cases, representing the different imaging characteristics and metabolic uptake patterns.

Keywords: *F-18 fluorodeoxyglucose positron emission tomography-computed tomography, non-Hodgkin's lymphoma, primary central nervous system lymphoma, tumor to normal cerebral tissue maximum standardized uptake value ratio*

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Introduction

Primary central nervous system lymphoma (PCNSL) is the exclusive lymphomatous involvement of the brain, spinal cord, cerebrospinal fluid (CSF), leptomeninges, and vitreoretina.[1] Guidelines established by the International PCNSL Collaborative Group suggest an initial imaging evaluation with gadolinium-enhanced magnetic resonance imaging (MRI), followed by CSF studies, human immunodeficiency viral serology, ophthalmological examination with slit lamp, followed by staging evaluation with computed tomography (CT) chest, abdomen, and pelvis, bone marrow aspiration, and testicular ultrasonography.[2] Although the primary role of F-18 fluorodeoxyglucose positron emission tomography-CT (FDG PET-CT) lies in excluding systemic involvement, metabolic imaging characteristics and parameters also provide additional diagnostic information. This pictorial essay is a compilation of spectrum of F-18 FDG PET-CT findings in PCNSL.

Case 1

A 38-year-old male was evaluated with an MRI brain for complaints of unilateral headache, which revealed an enhancing left frontal lesion with mass effect. Later, a left frontal parasagittal craniotomy and decompression was performed. Postoperative histopathological examination (HPE) was suggestive of lymphoproliferative disorder and immunohistochemistry (IHC) was suggestive of diffuse large B-cell lymphoma (DLBCL), with an MIB-1 index of 95%. The ophthalmic examination was normal. CSF cytology was normal. A whole-body F-18 FDG PET-CT showed intensely avid multiple iso-to-hyperdense lesions in the left frontal lobe, in the region of genu and body of corpus callosum, causing significant perilesional edema and another similar lesion in the left cerebellum [Figure 1]. Received eight cycles of R (rituximab) – methotrexate (MTX), procarbazine, and vincristine regimen, followed by whole brain radiotherapy (WBRT).

Learning point

In the case of PCNSL, the main role of F-18 FDG PET-CT is to rule out systemic involvement. Although the current NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for evaluation of PCNSL, recommends either a whole-body

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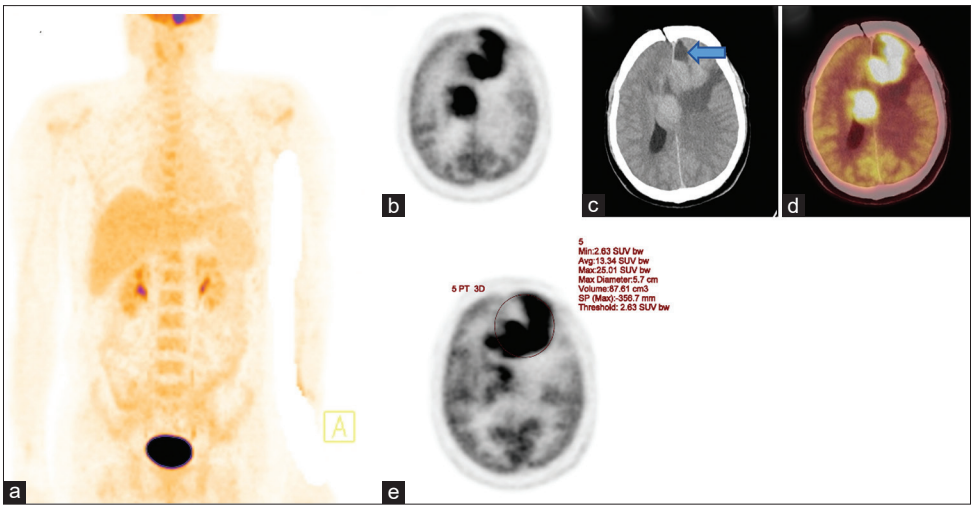

Figure 1: (a) F-18 fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET-CT) maximum intensity projection image of whole body showing homogenous bone marrow uptake in vertebrae– Reactive change. (b) F-18 FDG PET, (c) Axial noncontrast CT and (d) fused F-18 FDG PET-CT showing intense FDG avid hyperdense lesion involving left frontal lobe and genu of corpus callosum, with adjacent disproportionate perilesional edema and maximum standardized uptake value (SUV_{max}) of 25.01. Another hyperdense lesion was noted in left frontal lobe, compressing left lateral ventricle and midline shift to right, with SUV_{max} of 20.5. The frontal lesion shows well-defined intralesional hypodensity indicative of postoperative change (blue arrow). (e) F-18 FDG PET showing intense FDG avid left frontal lesion, with max. SUV of 25.01

CT with bone marrow biopsy or a F-18 FDG PET-CT for staging evaluation, in a meta-analysis by Park *et al*., in 2020, concluded that F-18 FDG PET-CT had better diagnostic yield when compared to whole-body CT.[3,4]

The tumor demonstrates hypercellularity with high nuclear/cytoplasmic ratio, thus it is characterized by intense tumoral FDG uptake. The FDG uptake is more homogenous as the tumor is rarely associated with hemorrhage, necrosis, or calcifications.[5] A study published in 2011 by Makino *et al*. demonstrated that a maximum standardized uptake value (SUV_{max}) of >12 helps in differentiating PCNSL from other neoplastic lesions such as high-grade glioblastoma multiforme, with a sensitivity of 100% and specificity of 71.4%.[6] In another study, Kawai *et al*., put forth a semiquantitative analysis, where the SUV_{max} of PCNSL lesion is on average 2.5 times greater than that of contralateral normal gray matter.[7] The high FDG avidity of PCNSL lesions may provide useful diagnostic information in differentiating it from High grade Glioblastoma Multiforme (HGM) and infectious lesions. This case demonstrates a typical PCNSL with hyperdense lesions confined to CNS, that are intensely FDG avid, with max. SUV of 25.0 and tumor-to-normal (T/N) ratio of 2.55. The lesion is associated with disproportionate perilesional edema due to compression of blood vessels.

Case 2

A 35-year-old male, a known case of IgA nephropathy, postrenal transplant, and on immunosuppressant therapy for 2 years, presented with complaints of headache. MRI brain showed enhancing altered signal intensity lesions in the right frontal lobe and cerebellum. Subsequently, an F-18 FDG PET-CT was performed, which showed two hyperdense lesions with few central hypodense areas in the right frontal lobe and cerebellum [Figure 2]. Later, the patient underwent craniotomy and tumor excision of the right frontal lobe lesion, and postoperative HPE and IHC were suggestive of DLBCL.

Learning point

The incidence of PCNSL in posttransplant patients, under immunosuppressant therapy, is estimated to be around 7%. In patients with immunocompromised status, PCNSL has an atypical presentation, characterized by multifocal heterogeneous lesions, frequently associated with necrosis or hemorrhage.[8] Due to the atypical characteristics, the FDG uptake is lower compared to typical PCNSL lesions. Similarly, in this case, the SUV_{max} of the frontal lesion is 8.57 and that of the cerebellar lesion is 10.39, with a T/N ratio of 1.8.

A study conducted by Hustinx *et al*. concluded that apart from atypical radiographic features, other factors such as corticosteroid use, patient's plasma glucose level, associated inflammation, and age of the patient may also lead to variations in SUV_{max} value in primary brain tumors. Hence, F-18 FDG PET-CT should always be reported with caution.[9]

Case 3

A 64-year-old male presented with headache not relieving on medication. MRI brain showed enhancing altered signal intensity lesion in the interventricular region. Subsequently, a right parietal craniotomy and excision of the tumor were performed and postoperative HPE and IHC were suggestive of DLBCL. A whole-body F-18 FDG PET-CT was performed, which showed two intensely FDG avid

hyperdense lesions in the interventricular region and left frontal lobe [Figure 3].

Learning point

Usual sites of involvement include frontal lobes (20%–43%), basal ganglia (13%–20%), brainstem and/or cerebellum (9%–13%), and infrequently in the spinal cord (1%–2%).[5]

This case represents a rare site of involvement in the brain, located in the interventricular region extending into the posterior horn of both lateral ventricles.

Case 4

A 61-year-old female was initially evaluated for complaints of inability to recognize persons, behavioral change, headache, and urinary incontinence. MRI brain with contrast showed heterogeneous enhancing lesion involving bilateral frontal lobes, raising a suspicion of glioma. A whole-body F-18 FDG PET-CT showed FDG avid heterogeneous density lesion in bilateral cerebral parenchyma [Figure 4]. A differential diagnosis of Glioma and PCNSL was made. Burr hole and excision biopsy of tumor, with subsequent

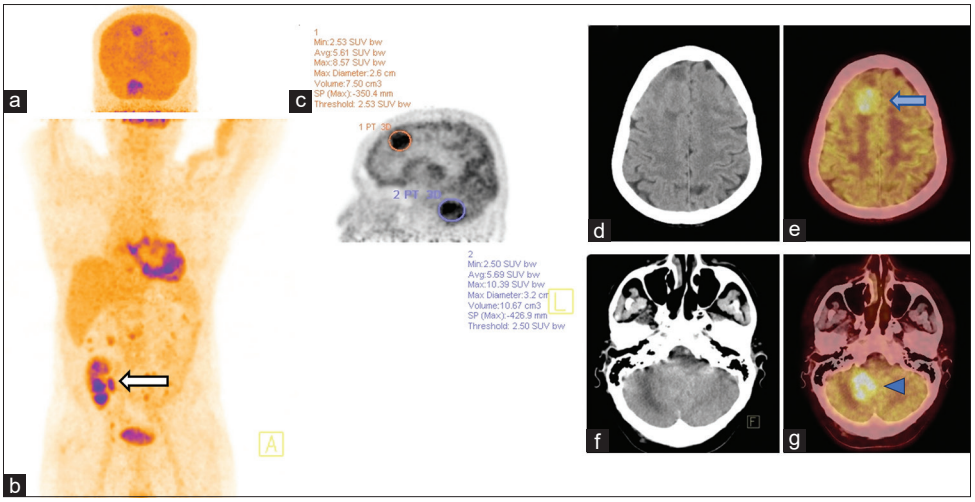

Figure 2: F-18 fluorodeoxyglucose positron emission tomography–computed tomography (FDG PET-CT) maximum intensity projection image of (a) head showing abnormal FDG concentration in right cerebral and cerebellar hemispheres and (b) of whole body showing FDG clearance through the transplanted kidney in right renal fossa (white arrow). (c) Sagittal F-18 FDG PET showing maximum standardized uptake value of frontal (orange) and cerebellar (purple) lesions. (d and f) Axial non-contrast CT and (e and g) fused F-18 FDG PET-CT showing FDG avid heterogenous density lesion in the right frontal lobe (blue arrow), and another hyperdense lesion in the right cerebellum (blue arrowhead)

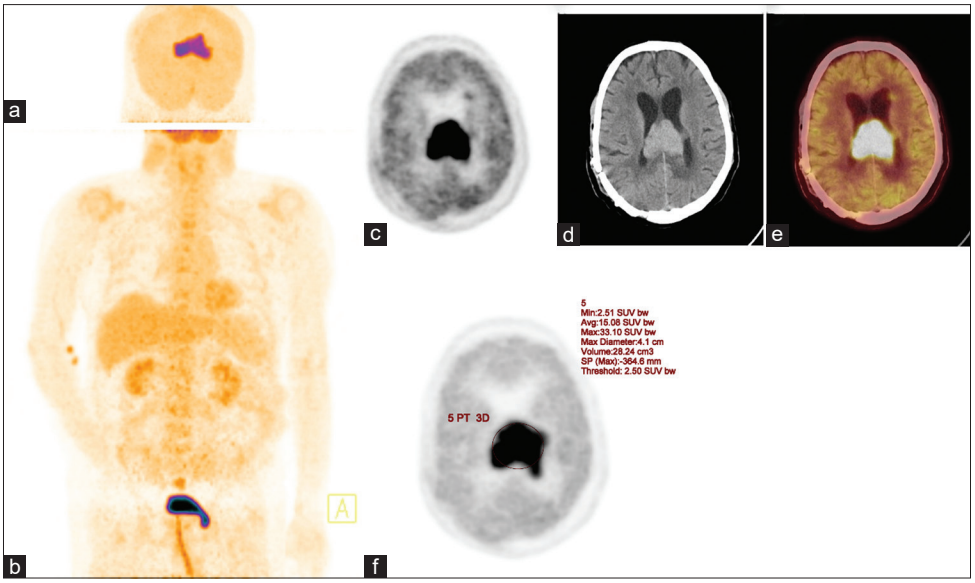

Figure 3: F-18 fluorodeoxyglucose positron emission tomography–computed tomography (FDG PET-CT) maximum intensity projection image of (a) head and (b) whole body showing abnormal FDG concentration in the interventricular region extending laterally on either sides, with no abnormal FDG concentration in rest of the body.(c) 18-F FDG PET. (d) Axial noncontrast CT and (e) fused F-18 FDG PET-CT showing intense FDG uptake in a lobulated hyperdense lesion in the interventricular region, obliterating posterior horn of bilateral lateral ventricles and associated with disproportionate perilesional edema. (f) 18-F FDG PET showing intense FDG avidity in the lesion (maximum standardized uptake value 33.10), when compared to surrounding normal brain parenchyma

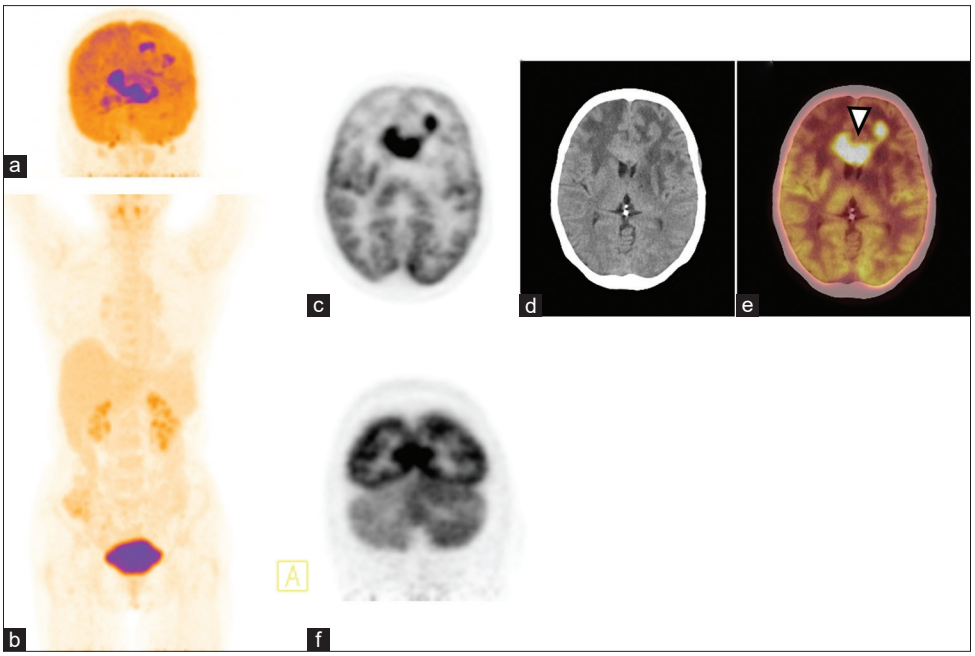

Figure 4: F-18 fluorodeoxyglucose positron emission tomography–computed tomography (FDG PET-CT) maximum intensity projection image of (a) head and (b) whole body showing abnormal FDG concentration in the brain in the midline. (c) F-18 FDG PET (d) Axial noncontrast CT and (e) fused F-18 FDG PET-CT showing intense FDG avid heterogenous density lesion in left frontal lobe, involving centrum semiovale, crossing midline through genu and body of corpus callosum to involve right frontal lobe giving the classical "butterfly pattern" (arrowhead) (f) Note made of cross cerebellar diaschisis

HPE and IHC, showed evidence of DLBCL. The patient received six cycles of single-agent rituximab and high-dose MTX.

Learning point

One of the classical imaging findings of PCNSL is the "butterfly pattern" or "mirror image." The lesion symmetrically involves white matter of both hemispheres, usually the frontal lobes, by crossing the midline, through the corpus callosum, which is illustrated in this case. However, it is not specific to PCNSL, as high-grade gliomas also exhibit a similar pattern of brain parenchymal involvement.[10]

Case 5

A 77-year-old female, with a history of hypertension and hypothyroidism, presented with a history of excessive sleepiness, bladder and bowel incontinence, hypnopompic hallucinations, and weakness of left upper and lower limbs. MRI brain showed enhancing lesions in the right frontal lobe, right thalamus, midbrain with optic nerve sheath enhancement, and possible diagnoses included demyelination – neuromyelitis optica and vasculitis. The patient improved symptomatically after treatment with methylprednisolone and a repeat MRI showed reduction of all lesions. Three months after treatment with steroids, the patient again presented with similar complaints. MRI brain showed nodular lesions in the periventricular location of the bilateral frontal region, right thalamus, and septum pellucidum of the brain stem. A whole-body F-18 FDG PET-CT showed intensely avid lesions in the left anterior periventricular white matter and right thalamus and a provisional diagnosis of lymphoma was made [Figure 5]. Subsequently, a right craniotomy and excision of the frontal lesion was performed and postoperative HPE and IHC were suggestive of DLBCL.

Learning point

It is common for PCNSL to present initially as inflammatory demyelinating lesions, with similar disease course and response to corticosteroids. Thus, adding to the difficulty in diagnosis during the initial stages. These multifocal, steroid-responsive lesions mimicking demyelination, are termed "sentinel lesions," which may undergo malignant transformation in the due course to form lymphomatous lesions. Certain features which should raise the clinical suspicion of PCNSL, include advanced age, disproportionate perilesional edema, worsening of symptoms, and radiographic features of lesion despite adequate treatment with corticosteroids and the absence of spinal cord involvement. Demyelinating lesions show a relatively lower FDG uptake on F-18 FDG PET-CT, which can potentially differentiate it from lymphomatous lesions.[11,12]

The lesions on F-18 FDG PET-CT showed a high FDG avidity, with SUV_{max} of 26.7, thereby making PCNSL the probable differential. As the lesion is located in the right thalamus, diffuse areas of hypometabolism are noted in the right cerebrum and left cerebellar hemisphere, delineating the corticospinal tract.

Case 6

A 43-year-old male presented with progressive weakness of the bilateral lower limbs, associated with paraesthesia, and

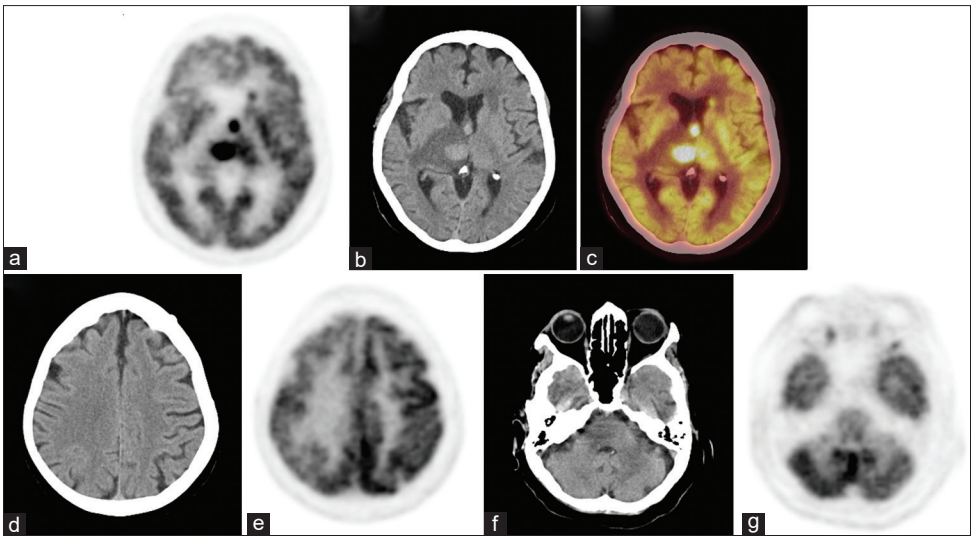

Figure 5: (a) F-18 fluorodeoxyglucose positron emission tomography (FDG PET), (b) Axial noncontrast computed tomography (CT) and (c) fused F-18 FDG PET-CT showing intense FDG uptake in an isodense lesion in the interventricular region, abutting anterior horn of left lateral ventricle. Another FDG avid isodense lesion is noted in the right thalamus and associated with disproportionate perilesional edema, with maximum standardized uptake value of 26.7. (d and e) Axial noncontrast CT and F-18 FDG PET showing diffuse decreased metabolism in the right cerebral hemisphere. (f and g) Axial noncontrast CT and F-18 FDG PET showing diffuse decreased metabolism in the left cerebellar hemisphere– indicative of "crossed cerebellar diaschisis"

urinary and fecal incontinence. He reported a history of fall from his bike, 2 weeks prior to the onset of symptoms. He was initially evaluated with an MRI spine which showed clumped and thickened nerve roots of cauda equina with homogenous postcontrast enhancement. A possibility of ependymoma was considered. The patient underwent L1-S1 laminectomy and decompression. Postoperative HPE was suggestive of lymphoproliferative disorder and IHC showed positive for LCA and CD 20 and a diagnosis of high-grade B-cell lymphoma was made. F-18 FDG PET-CT was performed that showed a metabolically active ill-defined soft-tissue density lesion in the spinal canal extending from D-10 to S2 vertebral levels [Figure 6]. Received six cycles of rituximab (R) – cyclophosphamide, doxorubicin, vincristine, prednisolone regimen, and with high-dose MTX, followed by involved site radiation therapy.

Learning point

Neurolymphomatosis is an infrequent manifestation of extranodal non-Hodgkin's lymphoma, characterized by infiltration of nerves by lymphomatous cells, which include spinal nerve roots, nerve plexus, cranial, and peripheral nerves. As the predominant subtype is DLBCL, F-18 FDG PET-CT serves as a good diagnostic tool, with a sensitivity of 87.5%. This is a case of neurolymphomatosis involving the nerve roots of cauda equina.[13]

Case 7

A 57-year-old female, known diabetic, developed acute-onset memory disturbances and was evaluated with a MRI brain plain study, which revealed a space-occupying lesion in the left frontal lobe with perilesional vasogenic edema and MR spectroscopy showed elevated choline, reduced NAA, and increased choline–creatinine ratio,

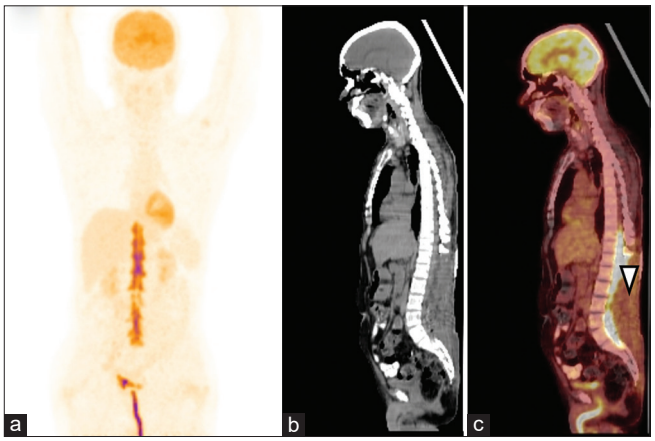

Figure 6:F 18 fluorodeoxyglucose positron emission tomography–computed tomography (FDG PET CT) (a) maximum intensity projection image showing abnormal FDG avidity in vertebral column. (b) Sagittal non contrast CT and (c) fused F 18 FDG PET CT showing metabolically active ill defined soft tissue density lesion in the spinal canal extending from D 10 to S2 vertebral levels, with maximum standardized uptake value of 7.1. Note made of post laminectomy status extending from L1 to S1 vertebrae. Mild FDG avid soft tissue density noted in the midline in the paravertebral region, extending from L1 to S1 vertebral level, indicative of postoperative changes (arrowhead)

which was suggestive of neoplastic origin. The patient later underwent craniotomy and lesion excision. Postoperative HPE showed evidence of DLBCL. A F-18 FDG PET-CT was performed for staging evaluation, which revealed an intensely avid hyperdense lesion involving the left frontal lobe and anterior body of the left corpus callosum, with disproportionate perilesional edema [Figure 7]. Received six cycles of rituximab and high-dose MTX and later underwent posttreatment follow-up with F-18 FDG PET-CT. The scan revealed non-FDG avid diffuse gliotic changes in the left frontal lobe region, suggestive of complete response.

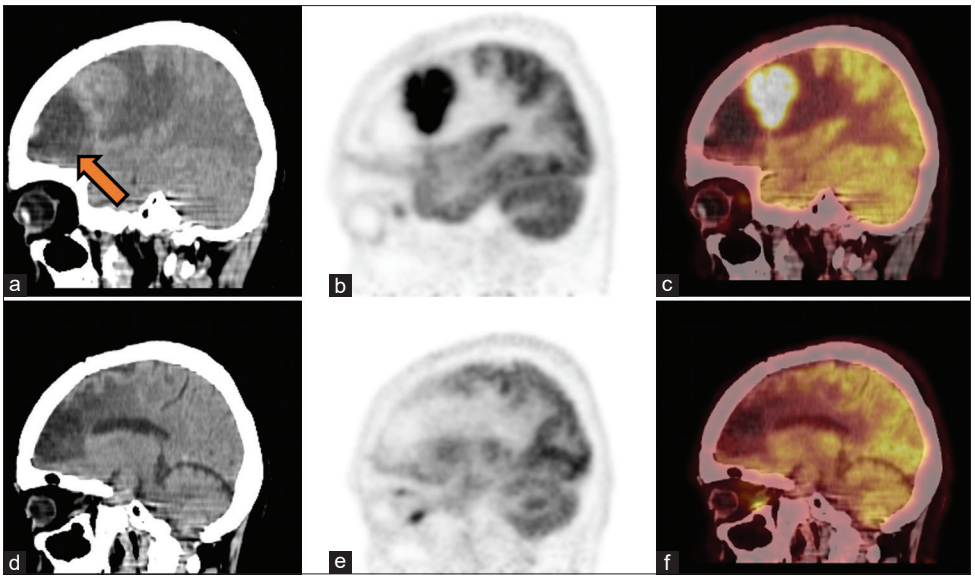

Figure 7: (a) Axial noncontrast computed tomography (CT). (b) F 18 fluorodeoxyglucose positron emission tomography (FDG PET) and (c) fused F 18 FDG PET CT showing intense FDG uptake in a hyperdense lesion in the left frontal region, associated with disproportionate perilesional edema. Note made of non FDG avid postoperative collection anterior to the lesion.(orange arrow). (d) Axial noncontrast CT. (e) F 18 FDG PET and (f) fused F 18 FDG PET CT showing complete resolution of lesion on follow up scan

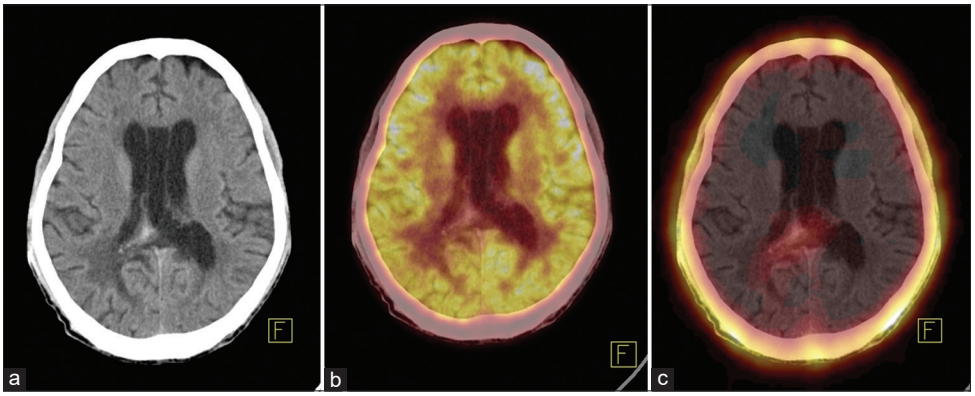

Figure 8: (a) Axial noncontrast computed tomography (CT). (b) fused F-18 fluorodeoxyglucose positron emission tomography (FDG PET) CT and (c) Tc-99 m GHA fused single photon emission CT showing mild FDG avid and GHA avid well-defined intra-axial isodense lesion in the splenium of the right corpus callosum with foci of calcifications within and surrounding perilesional edema. Suggestive of residual lymphomatous lesion

Case 8

A 44-year-old male, known case of PCNSL of DLBCL type, received treatment with six cycles of rituximab + high-dose MTX, followed by WBRT. A F-18 FDG PET-CT and Tc-99 m glucoheptonate (GHA) (Tc-99 m GHA) fused single photon emission CT was done for evaluating disease status, that showed a mildly FDG avid and GHA avid lesion in the splenium of the right corpus callosum, which is indicative residual lesion [Figure 8].

Conclusion

The primary role of F-18 FDG PET-CT in PCNSL is to exclude systemic involvement. However, parameters such as SUVmax and T/N ratio help in increasing the sensitivity of diagnosis. Moreover, in cases with atypical presentation and radiographic features, F-18 FDG PET-CT helps in consolidating the diagnosis and management.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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