Case Report

Rare Cases of Extracranial Metastases from High-grade Glioma Detected on FET PET-CT with Histopathological Confirmation

Abstract

Extracranial metastasis from high-grade glial tumors is an extremely rare condition with its reported incidence being <1%. The most common sites reported in the literature are leptomeninges and spinal cord, followed by the liver, lung, and skeletal system. Its low incidence is thought to be related to the intrinsic aggressive biology of the tumor, thus reducing median overall survival in patients. As there is lack of knowledge about the mechanism of extracranial spread of glioma cells, its diagnosis and management remain a major challenge. We report two cases of extracranial metastases from glial tumors to cervical nodes and postoperative site involving preauricular region detected on F18 Fluoro ethyl tyrosine (FET) positron emission tomography–computed tomography and later on confirmed with histopathology Fluoro ethyl tyrosine.

Keywords: *Extracranial, FET positron emission tomography–computed tomography, glioma, metastases*

Indraja Devidas Dev, Ayushi Sahay[1], Ameya D. Puranik, Nilendu C Purandare, Archi Agrawal, Sneha Shah, Sayak Choudhury, Suchismita Ghosh, Venkatesh Rangarajan

Department of Nuclear Medicine and Molecular Imaging, Tata Memorial Hospital and Advanced Center for Training, Research and Education in Cancer, Tata Memorial Center, Homi Bhabha National Institute, [1]Department of Pathology, Tata Memorial Center, Homi Bhabha National Institute, Mumbai, Maharashtra, India

Introduction

High-grade glioma (WHO Grade 3 and 4) is the most common and aggressive primary central nervous system tumor. In spite of rigorous treatment with surgical resection, chemotherapy, and radiotherapy, its overall survival remains poor with a range of 12–15 months.[1] Primary reasons for poor survival are inherent infiltrative nature of the tumor with increased risk of local progression and insensitivity for chemoradiotherapy.[2]

Extracranial metastasis is an extremely rare condition, especially in those cases where there is no disruption of blood–brain barrier due to surgical manipulations, which is thought to be the primary mechanism for extracranial seeding of tumor cells.[3]

However, in last decades, there is a steady increase in the detection rates of extracranial metastases due to better imaging modalities, leading to early diagnosis with incidence of 0.4%–1%.[4] The most documented cases of extracranial metastases involve leptomeningeal spread to the spine, although metastases to the liver, skin, spleen, lungs, peritoneum, and lymph nodes may also occur.[5]

We report two cases of extracranial metastases to cervical nodes and postoperative craniotomy site detected on 18F FET positron emission tomography–computed tomography (PET-CT) and confirmed with histopathology.

Case reports

First case

A 17-year-old male patient presented with recurrent episodes of seizures and forgetfulness. Contrast-enhanced magnetic resonance imaging (MRI) of the brain revealed a large mass in the left frontal lobe. The patient underwent stereotactic biopsy which revealed a glioblastoma, CNS WHO Grade 4 [Figure 1a and b]. The tumor was IDH-wild type, and MGMT was unmethylated. The tumor was negative for histone mutations (H3.3 and H3.1) as well. Further, the patient received whole brain radiation therapy with concurrent temozolomide (TMZ). Subsequently, the patient presented with pain and swelling in the left neck cervical region 3 months after receiving 2 cycles of adjuvant TMZ. Ultrasound revealed discrete nodes in the left cervical Level II and V region. Clinically, it was thought to be lymphadenitis; hence, the patient received antibiotics for 2 weeks.

Address for correspondence:
Dr. Ameya D. Puranik, Department of Nuclear Medicine and Molecular Imaging, Tata Memorial Center, Dr. E Borges Road, Parel, Mumbai - 400 012, Maharashtra, India.
E-mail: ameya2812@gmail.com

Received: 14-03-2024
Revised: 10-05-2024
Accepted: 11-05-2024
Published: 17-08-2024

Access this article online

Website: www.ijnm.in

DOI: 10.4103/ijnm.ijnm_34_24

Quick Response Code:

How to cite this article: Dev ID, Sahay A, Puranik AD, Purandare NC, Agrawal A, Shah S, *et al.* Rare cases of extracranial metastases from high-grade glioma detected on FET PET-CT with histopathological confirmation. Indian J Nucl Med 2024;39:216-9.

However, there was increase in the swelling, and the patient additionally developed imbalance and difficulty in walking. In view of high suspicion of recurrent disease, the patient was referred for FET PET-CT. Maximum intensity projection (MIP) of the head and neck [Figure 2a] revealed no significant FET localization in the brain with intense FET localization in the left cervical region. Corresponding fused transaxial PET-CT images revealed no significant FET localization in hypodense cavity involving the left frontal lobe, which was suggestive of no evidence of active glial tumor [Figure 2b]. The small focus of low-grade uptake in the left frontal lobe seen on FET PET-CT corresponds with posttreatment changes and the T/w ratio was <2.5. There was intense FET uptake in enlarged two cervical nodes at Level II and V region [Figure 2c and d]. Biopsy was taken from these nodes, which revealed a high-grade glial tumor [Figure 1c and d].

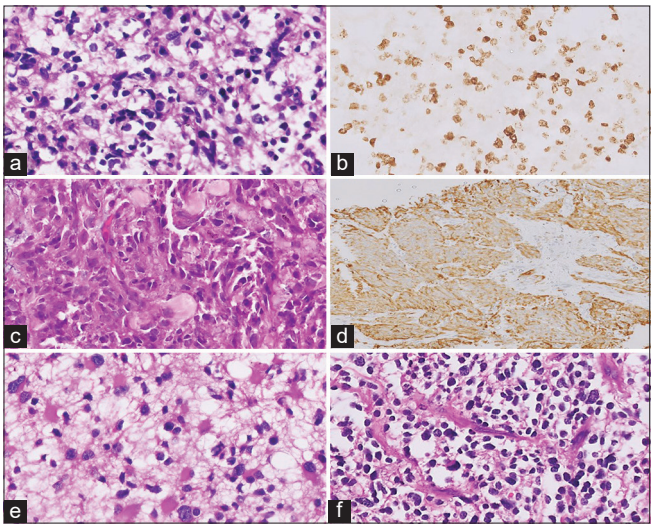

Figure 1: Histopathological correlate. Photomicrographs showing (a) left frontotemporal high-grade astrocytoma (case 1), with marked nuclear pleomorphism, mitotic activity, and high MIB1 labeling index (b). The left neck swelling of the same patient (c) revealed a similar high-grade astrocytic tumor, with nuclear pleomorphism, positive for glial fibrillary acid protein (d). The right frontal lesion in the second case showed an astrocytoma, histologically corresponding to CNS WHO Grade 3 (e). The tumor showed ATRX loss and was positive for p53. IDH mutation was confirmed on sequencing (IDH1R132G). The right preauricular biopsy of the patient revealed high-grade glial tumor (f) with similar morphology and immunoprofile

Second case

A 34-year-old female patient presented with complains of occasional headache and loss of consciousness; MRI brain revealed a well-defined lesion in the right frontal lesion. Gross total resection was performed and histopathology reports revealed and IDH-mutant WHO Grade III astrocytoma [Figure 1e]. The patient received WBRT with concurrent TMZ and adjuvant 22 cycles of TMZ. There was small residual disease present at postoperative site. The patient presented with recurrence after 3 years, for which she underwent redo excision. Histopathology was suggestive of WHO Grade IV glioma for which she received Re Radiation and chemotherapy with TMZ and bevacizumab. Follow-up MRI revealed posttreatment changes in the right frontal region with small enhancing soft tissue at the right preauricular region, which was suspicious for scar site deposit. Hence, the patient was referred for FET PET-CT and biopsy. Regional MIP [Figure 3a] revealed two foci in the brain and one discrete focus in the right preauricular region. Corresponding fused transaxial images revealed no FET uptake at necrotic hypodensity involving the right frontal lobe with two distinct foci FET uptakes seen at the dura involving the left frontal lobe suggestive of leptomeningeal enhancement confirmed on MRI [Figure 3b]. Another focus of intense FET uptake seen in the soft tissue lesion in the right preauricular region [Figure 3c]. Its biopsy revealed metastatic deposit from high-grade glial neoplasm [Figure 1f].

Discussion

Early diagnosis and prompt management of high-grade glial tumors is the biggest challenge that is faced worldwide. In spite of advances in surgical approach, and development of highly potent systemic therapies, the survival remains poor with a range of 12–15 months.[1] This is due to the fact that >90% of the patients with high-grade glial tumors

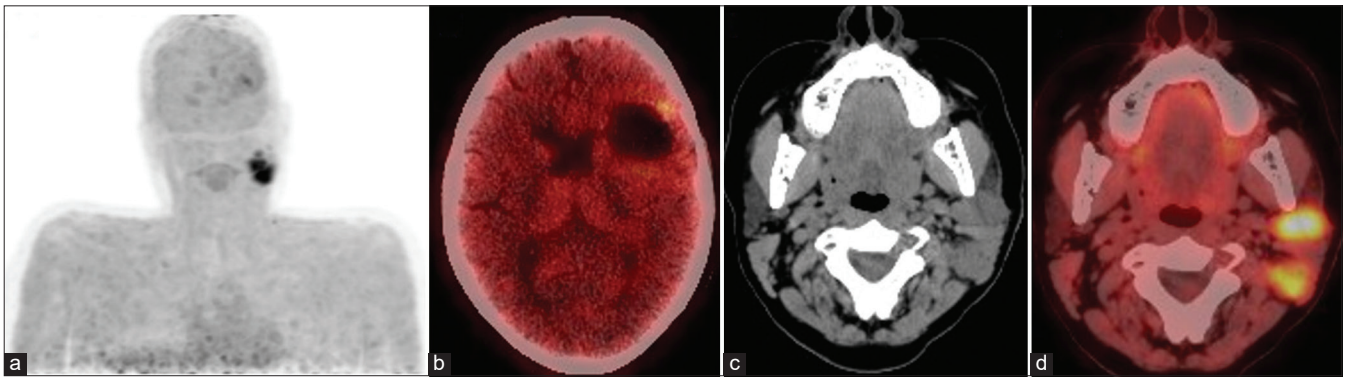

Figure 2: CNS WHO Grade 4 Glioma with metastases to cervical nodes. Maximum intensity projection (a) depicts normal background FET uptake in brain with intense FET uptake in the left cervical region. Corresponding fused positron emission tomography–computed tomography (PET-CT). (b) Image showing no FET uptake in postoperative resection cavity involving the left frontoparietal region. (c) Two discrete left Level II cervical nodes and corresponding fused transverse PET-CT image. (d) Intense focal FET localization in the left Level II cervical nodes

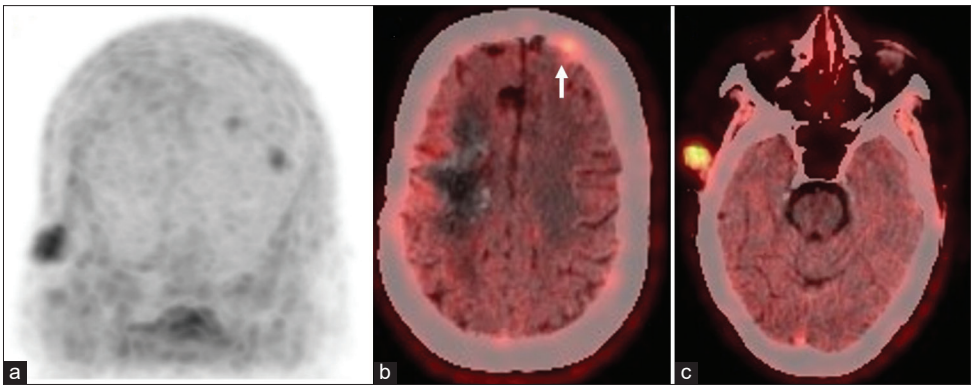

Figure 3: CNS WHO Grade 3 Glioma with metastatic preauricular deposit. Maximum intensity projection. (a) Two foci of FET uptake in the left frontal region with one discrete focus of FET uptake in the right preauricular region. Fused transverse positron emission tomography–computed tomography image show focal FET uptake in the left frontal lobe. (b: white arrow) Suggestive of leptomeningeal involvement. (c) Intense focal FET uptake in metastatic soft tissue deposit involving the right preauricular region

develop recurrence in the due course of treatment. Primary reason for recurrence is the presence of residual tumor cells in the postoperative tumor bed.

Initially, it was believed that extracranial metastases from primary central nervous system tumors do not occur due to intrinsic biological obstacles that prevent tumor cells from infiltrating and surviving beyond the neural environment. These obstacles may include the presence of impermeable blood–brain barrier that prevent tumor cell infiltration and secondly, absence of lymphatic system in the central nervous system that would cause systemic dissemination. However, there is steady rise in the rate of extracranial metastases with involvement of various organs such as spinal cord, liver, lung, skeletal system, lymph nodes etc.[6-8] The most common intracranial tumor showing extracranial metastasis is glioblastoma, which is high-grade astrocytoma on histology, followed by oligodendroglioma, medulloblastoma, etc.[9] Histologically, the morphology at the extracranial sites may be more anaplastic with higher degenerative atypia than that the primary, however evidence of glial differentiation, and matching immunohistochemical and genetic profile helps in confirmation of metastasis. The exact mechanism is still unclear but disruption of blood–brain barrier due to surgical exploration/chemoradiotherapy with resultant seeding of glial tumor cells into the extra neural environment is thought to be the primary cause.[3,10] Overall survival in such cases reduces to <6 months.[11]

Regional contrast-enhanced MRI is the standard investigation done for the diagnosis and treatment response assessment for glial tumors. However, the sensitivity and specificity of MRI to detect early recurrence drops significantly in posttreatment settings. To overcome this drawback, PET-CT with amino acid radiopharmaceuticals like FET, FDOPA is routinely performed and is now recommended by RANO group as the uptake of radiopharmaceuticals is independent of integrity of blood–brain barrier and is directly proportional to the expression of L amino acid transporters; thus, reflecting the tumor proliferation.[12,13]

In our cases. 18F FET PET-CT was performed as there was a clinical and radiological dilemma between the posttreatment changes and early recurrence.

First case had cervical node which was suspicious for metastasis and in second case there was a clinicoradiological dilemma between early recurrence and posttreatment changes at local site with suspicion of scar site deposit from glioma. Hence, FET PET-CT was performed.

In both cases, FET PET-CT has outperformed in detecting the extracranial metastases as well as detected the local recurrence in primary tumor site. All three patients were explained about the guarded prognosis and referred for palliative treatment.

Few cases of extracranial metastases detected using FDG PET-CT have been reported.[14] Our cases are unique as the extracranial sites were detected on 18F FET PET-CT and later confirmed by histopathology.

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.

Financial support and sponsorship

Nil

Conflicts of interest

There are no conflicts of interest.

References

1. DeAngelis LM. Brain tumors. N Engl J Med 2001;344:114-23.
2. Buckner JC. Factors influencing survival in high-grade gliomas. Semin Oncol 2003;30:10-4.
3. Frank S, Kuhn SA, Brodhun M, Mueller U, Romeike B,

Kosmehl H, *et al.* Metastatic glioblastoma cells use common pathways via blood and lymphatic vessels. Neurol Neurochir Pol 2009;43:183-90.

4. Kurdi M, Baeesa S, Okal F, Bamaga AK, Faizo E, Fathaddin AA, *et al.* Extracranial metastasis of brain glioblastoma outside CNS: Pathogenesis revisited. Cancer Rep (Hoboken) 2023;6:e1905.
5. Sun Q, Xu R, Xu H, Wang G, Shen X, Jiang H. Extracranial metastases of high-grade glioma: The clinical characteristics and mechanism. World J Surg Oncol 2017;15:181.
6. Lun M, Lok E, Gautam S, Wu E, Wong ET. The natural history of extracranial metastasis from glioblastoma multiforme. J Neurooncol 2011;105:261-73.
7. Amitendu S, Mak SK, Ling JM, Ng WH. A single institution experience of the incidence of extracranial metastasis in glioma. J Clin Neurosci 2012;19:1511-5.
8. Piccirilli M, Brunetto GM, Rocchi G, Giangaspero F, Salvati M. Extra central nervous system metastases from cerebral glioblastoma multiforme in elderly patients. Clinico-pathological remarks on our series of seven cases and critical review of the literature. Tumori 2008;94:40-51.
9. Mondin V, Ferlito A, Devaney KO, Woolgar JA, Rinaldo A. A survey of metastatic central nervous system tumors to cervical lymph nodes. Eur Arch Otorhinolaryngol 2010;267:1657-66.
10. Ueda S, Mineta T, Suzuyama K, Furuta M, Shiraishi T, Tabuchi K. Biologic characterization of a secondary glioblastoma with extracranial progression and systemic metastasis. Neuro Oncol 2003;5:14-8.
11. Vertosick FT Jr., Selker RG. Brain stem and spinal metastases of supratentorial glioblastoma multiforme: A clinical series. Neurosurgery 1990;27:516-21.
12. Albert NL, Weller M, Suchorska B, Galldiks N, Soffietti R, Kim MM, *et al.* Response assessment in neuro-oncology working group and European Association for Neuro-Oncology recommendations for the clinical use of pet imaging in gliomas. Neuro Oncol 2016;18:1199-208.
13. Cui M, Zorrilla-Veloz RI, Hu J, Guan B, Ma X. Diagnostic accuracy of pet for differentiating true glioma progression from posttreatment-related changes: A systematic review and meta-analysis. Front Neurol 2021;12:671867.
14. Johansen MD, Rochat P, Law I, Scheie D, Poulsen HS, Muhic A. Presentation of two cases with early extracranial metastases from glioblastoma and review of the literature. Case Rep Oncol Med 2016;2016:8190950.