Case Report,

**Skeletal Metastases in a Treated Case of WHO Grade IV Glioma without Relapse of Primary Tumor: A Rare Entity**

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**Abstract:**
Glioblastoma is the most common primary malignant brain tumor of the adult; representing 12-15% of all intracranial tumors in adults. It usually has very dismal prognosis with the mean age of survival after diagnosis being approximately 14.6 months despite treatment. However, extracranial metastases are rare in the case of glioblastoma. We report a case of a 37-year-old female who had right frontal lobe glioblastoma for which she underwent surgery in December 2019 followed by radiotherapy. Imaging studies done for the response assessment shows complete remission of the tumor. In January, 2021 she developed a low backache and pain in her right hip. Imaging performed for the same revealed multiple new-onset lesions in the bones. HPE eventually proved the lesions to be metastatic glioblastoma.

**Keywords:** Metastatic Glioblastoma multiforme, extra-cranial metastases.

**Introduction:**
The most common primary malignant intracranial tumor in adults is glioblastoma multiforme, constituting 12-15 % of all intracranial tumors in adults (1). IDH wild type (primary) GBM occurs in the elderly population and arises de novo. IDH mutant (secondary) GBM occurs in younger patients and has a better prognosis (2). GBM are high-grade tumors with a very poor prognosis. The mean age of survival is 14.6 months after the diagnosis (1). Death usually occurs due to the progression of the local disease and its complications. Extracranial spread of disease is very rare which can be attributed to short survival time and blood-brain barrier. Metastasis is comparatively more common in younger patients due to the longer survival of the patient (3). Here, we report a post-operative case of glioblastoma multiforme in complete remission with new onset bony metastasis which is a very rare entity.

**Case History:**
A 37-year-old female had complaints of dizziness, headache, and episodes of abnormal body movement which she developed in 2019. CE-MRI of the brain performed for these complaints revealed a space-occupying lesion in the right frontal lobe. Wide margin excision of the lesion was done in December 2019 which showed WHO Grade IV Glioblastoma Multiforme. The patient was further offered adjuvant radiotherapy. Follow up MRI done after a year showed complete remission of the disease. She recently presented to our institution with the chief complaints of low backache and pain in her right hip since January 2021. CE-MRI Pelvis and Spine was done for the patient’s current complaints along with CE-MRI Brain for status of primary disease. CE-MRI pelvis and spine showed a large lobulated lytic expansile lesion in the right iliac blade showing hypointense signal on T1WI, heterogeneously hyperintense signal on T2WI and STIR images (Images 1A, 1B and 1C). The lesion was showing infiltration into the right gluteus minimus and iliacus muscles. It showed diffusion restriction and heterogeneous post-contrast enhancement (Images 2A and 2B). Multiple similar signal intensity lesions were also seen in the sacrum, bilateral innominate bones, visualized part of bilateral femurs, and vertebral bodies.
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Figure 1A, 1B and 1C: Axial T1WI (1A), Axial T2WI (1B) and Axial STIR (1C) images showing lytic expansile T1 hypointense and T2/STIR hyperintense lesion in right iliac blade. The lesion is also showing extension into right gluteus minimus and iliacus muscles.

Figure 2A and 2B: Axial DWI (2A), Axial post-contrast (2B) images. The lesion shows restricted diffusion with heterogeneous post-contrast enhancement; also extending to involve right gluteus minimus and iliacus muscles.

Figure 3A, 3B, 3C, 3D, 4A and 4B: Axial post-contrast (3A), Coronal post-contrast (3B), axial DWI (3C) and Axial STIR (3D) images showing multiple similar signal intensity lesions in bilateral innominate bones, sacrum and visualized part of bilateral femurs. Creeping brain MRI was also done which showed no recurrent primary lesion with post-operative changes in the form of encephalomalacia and gliosis (Images 5A, 5B and 5C).

Figure 4A and 4B: Sagittal post-contrast images of lumbosacral (4A) and cervico-dorsal (4B) spine showing multiple well-defined enhancing lesions scattered in multiple vertebral bodies.
With the suspicion of skeletal metastases, US examination of neck was performed for evaluation of thyroid which was unremarkable. Clinical examination of breasts also showed no obvious palpable lesion. CECT thorax and abdomen was further performed which further demonstrated that the mass in right iliac blade was causing endosteal scalloping with cortical thinning (Images 6A, 6B, 7A and 7B). There were areas of cortical breach with infiltration into adjacent gluteus minimus and iliacus muscles. Rest of the visualized organs were unremarkable with no evidence of any obvious primary malignancy. guided biopsy was done from the lesion in the right iliac blade which revealed atypical cells having a high nucleocytoplasmic ratio, moderate eosinophilic cytoplasm, and hyperchromatic nuclei. Immunohistochemistry showed GFAP and p53 positivity and loss of expression of ATRX. Hence, diagnosis of bony metastases from glioblastoma multiforme was made. Palliative treatment was given to the patient for pain management.
Discussion:
Glioblastoma multiforme is the most common malignant brain tumor (4). There are two types: IDH wild type and IDH mutant. Most of the glioblastoma (90%) occurs de novo and is IDH wild type (5). They occur in the elderly and have a poorer prognosis. IDH mutant glioblastomas are rarer and progress from diffuse or anaplastic astrocytoma. They usually occur in younger patients and have a better prognosis as compared to the IDH wild type.

Patients with glioblastoma usually present with seizures, focal neurological deficit, and altered mental status. The patient may present with a headache due to increased intracranial pressure. It is a relentlessly progressive disease with a dismal prognosis. The mean age of survival is 14.6 months. Death usually occurs due to the local progression of the disease and its complications. Brain to brain metastases and CSF dissemination are common in glioblastoma, however, the extracranial spread is very rare, occurring in about 0.2 to 0.4% cases (6). Low incidence of distant metastasis in intracranial tumors is attributed to 1. Rapid progression of disease leading to death and low survival rate, hence there is less time for systemic dissemination of the disease. 2. Thick dura mater, basement membrane, and blood-brain barrier prevents spread of the disease outside CNS. 3. Inability of glial cells to proliferate in the outside stroma. 4. Absence of lymphatics in the brain (3).

However, few cases are reported of systemic dissemination of the disease. Mechanisms of GBM metastasis are not yet fully elucidated, but the direct invasion of the tumor cells into the veins, dura mater, or breakdown of the blood-brain barrier could lead to the dissemination of the disease (3). Few studies have shown the presence of a lymphatic system in the meninges which is known as the lymphatic system and drains into the deep cervical group of lymph nodes (7). The tumor can spread through this lymphatic system into the neck nodes which is a common site of metastasis. Few studies have shown that ventriculoperitoneal shunting or surgery can also increase the risk of metastasis of tumors (2). The bones, lymph nodes, and lungs are the most common affected sites. In bones, the spine is the most commonly affected site (4). The awareness of the presence of extracranial metastasis can help in the early initiation of palliative treatment for the patient.

In summary, we had a post-operative post-radiotherapy case of glioblastoma with osseous metastasis proven by HPE. The patient was managed conservatively for pain.

Abbreviations:

Conflict Of Interest:
The authors have no conflict of interest to disclose.

References:
