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Rare Case of Extracranial Metastases in a Patient with IDH-Mutant Glioblastoma

Rishan Thimma Sudarsan[1] Vishnu Ramanujan[2] Adhithyan Rajendran[3] Sadiya Shafi[4] Sushma Patil[4] Siddhartha Ghosh[5] Rakesh Jalali[1]

[1] Department of Radiation Oncology, Neuro-Oncology Cancer Management Team, Apollo Proton Cancer Centre, Chennai, Tamil Nadu, India
[2] Department of Orthopedic Oncology, Apollo Proton Cancer Centre, Chennai, Tamil Nadu, India
[3] Department of NeuroRadiology, Apollo Proton Cancer Centre, Chennai, Tamil Nadu, India
[4] Department of NeuroPathology, Apollo Proton Cancer Centre, Chennai, Tamil Nadu, India
[5] Department of Neurosurgery, Apollo Hospitals, Chennai, Tamil Nadu, India

Address for correspondence Rakesh Jalali, MBBS, MD, Department of Radiation Oncology, Apollo Proton Cancer Centre, Taramani, Chennai, Tamil Nadu 600041, India (e-mail: rjalali@apollohospitals.com).

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Abstract

Rishan Thimma Sudarsan

Glioblastoma are known for its aggressive intracranial course of disease, where the overall survival is less than 18 months. Of late, the World Health Organization has reclassified and renamed secondary glioblastomas as isocitrate dehydrogenase (IDH)-mutant grade 4 astrocytomas, which is relatively better than its IDH wild-type counterpart; however, overall survival remains poor. In such tumors, metastases outside the craniospinal neuraxis is very rare, and does sometimes present with symptoms which create a diagnostic dilemma and arriving at such diagnosis is still challenging even for the best of the clinicians worldwide. Herewith, presenting a rare case scenario, where a grade 4 astrocytoma that has transformed from a low-grade glioma, presenting with bone metastases, its workup, treatment, and various possible mechanisms underlying such a rare event, and the need of such clinical scenario especially long-term survivors to be wary of distant metastases.

Keywords

- astrocytoma
- extracranial
- glioblastoma
- IDH
- metastases

Introduction

Glioblastomas are malignant brain tumors associated with rapid progression with unfavorable prognosis. Isocitrate dehydrogenase (IDH) wild-type primary glioblastomas are usually MGMT unmethylated tumors, with overall median survival less than 18 months. Secondary glioblastomas

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(grade 4 astrocytomas, as per the World Health Organization [WHO] 2021 classification)[1] are usually IDH-mutant and most of them are MGMT methylated tumors. Despite being a tumor with highly aggressive behavior, extracranial metastases are exceedingly rare. We report a rare case of a young man with IDH-mutant glioblastomas presenting with extracranial metastases.

Case Report

A 39-year-old male, evaluated in 2010 for history of headache, underwent magnetic resonance imaging (MRI) of brain with contrast which showed a right parietal lesion suggestive of a low-grade glioma. He underwent surgery for the same with histopathology reported as diffuse astrocytoma, grade II, post which he received adjuvant radiotherapy without concurrent chemotherapy in 2010. He was on follow-up till 2015, when he developed recurrence on the right parietal region, for which he underwent right parietal craniotomy and excision of the lesion; histopathology of the same was reported as diffuse astrocytoma, grade II, IDH1 positive, MGMT methylated. He underwent adjuvant chemoradiation to a total dose of 41.4 Gy in 23 fractions along with concurrent temozolomide followed by adjuvant temozolomide in 2015 and was on regular follow-up.

In October 2020, he again developed seizures and an MRI of the brain showed recurrence in the right parietal region at the same site (►Fig. 1A, B). He underwent a redo right parietal awake craniotomy and gross total excision of the lesion. Histopathology was reported as glioblastoma with primitive neuroectodermal tumor (PNET) pattern, WHO grade IV with IDH1-mutant ATRX loss, p53 positive, Ki67 of 65%, brisk mitotic activity with a count of 30 to 32/10 high power field, and large areas of necrosis. He then underwent reirradiation using image-guided intensity-modulated proton beam therapy to a total dose of 55.8 CGE in 31 fractions during December 2020 along with 140 mg of concurrent temozolomide. His follow-up MRI showed excellent response with no residue, and he completed eight cycles of adjuvant temozolomide till December 2021.

In October 2021, he started complaining of pain in the right hip region, local imaging (X-ray) did not reveal any abnormality. However, MRI of the same picked up a thin hairline fracture without any associated soft tissue

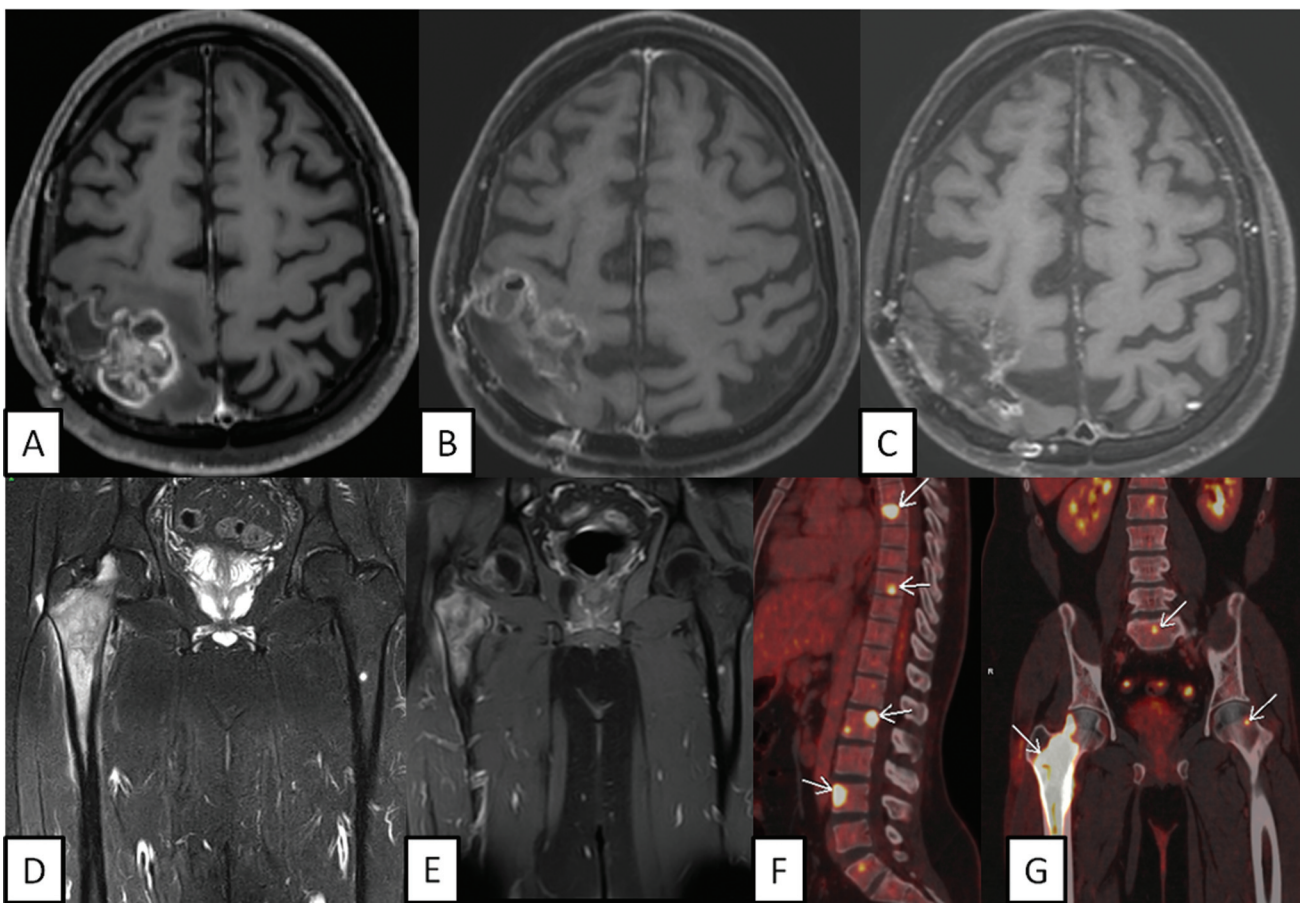

Fig. 1 (**A**) Presurgery contrast T1 magnetic resonance imaging (MRI) in October 2020—heterogeneously enhancing mass lesion with necrotic areas seen involving the right parietal lobe region favoring high-grade glioma likely grade 4 astrocytoma. (**B**) Postsurgery contrast T1 MRI November 2020—complete excision of the mass lesion with postoperative changes seen. (**C**) Recent contrast T1 MRI—no significant residual or recurrent tumor mass seen. (**D**) (Short-tau inversion recovery [STIR] coronal sequence MRI) STIR hyperintense large mass lesion seen at right proximal femur. (**E**) T1 postcontrast T1 fat saturated (FS) showing heterogeneously enhancing lesion at right proximal femur. Small lesion at left femur shaft. (**F**) Multiple fluorodeoxyglucose (FDG) avid lesions in positron emission tomography-computed tomography (PET-CT) at dorsolumbar vertebra. (**G**) Multiple FDG avid lesions in PET-CT in bilateral proximal femur.

component, and subsequent positron emission tomography-computed tomography (PET-CT) scan showed localized uptake and was managed conservatively. He was pain-free till December 2021 when he reported to the emergency room with severe pain (pain score of 7/10), plain X-ray of local part done did not reveal any abnormality, but MRI of both the hip joints showed altered signal intensity in the subtrochanteric area of the right femur, with intramedullary skip lesions noted 5 cm distal to the main lesion with avulsion fracture of lesser trochanter (►Fig. 1D, E). A CT-guided biopsy of the right femoral lesion done showed marrow infiltrating lesion arranged in diffuse sheets interspersed with septae, positive for glial fibrillary acidic protein, synaptophysin, CD56, IDH1 positive, and ATRX loss highly suggestive of metastases from a high-grade glioma. PET-CT scan done subsequently showed intense fluorodeoxyglucose (FDG) avid ill-defined lytic lesion with cortical erosion in proximal shaft of the right femur (standard uptake value 31.3), with foci of abnormal intramedullary skip lesions in the right femur, proximal shaft of the left femur, multiple dorsal and lumbar vertebrae, iliac bones, and right third rib (►Fig. 1F, G). MRI brain with contrast, MR spectroscopy, and perfusion studies along with spine screening (►Fig. 1C) did not reveal any abnormality and showed only postoperative cavity with treatment-related changes. In view of severe pain and need for mobilization, he then underwent prosthetic replacement of the right proximal femur in January 2022, and subsequent histopathology from main sample also confirmed the immunohistochemistry findings of metastases from high-grade glioma favoring glioblastoma (►Fig. 2). In view of PET-CT showing multiple FDG avidity at bony areas, and patient being asymptomatic for the same, palliative radiotherapy was deferred, and was discussed extensively in our neuro-oncology multidisciplinary tumor board (MDT) as well as national MDTs and was planned for single-agent lomustine (CCNU) and to consider palliative radiotherapy later. He is at present asymptomatic, completed one cycle of single-agent lomustine, and is able to take care of his daily day-to-day activities.

Discussion

IDH-mutant glioblastomas (previously known as secondary glioblastomas and renamed as grade 4 astrocytomas at

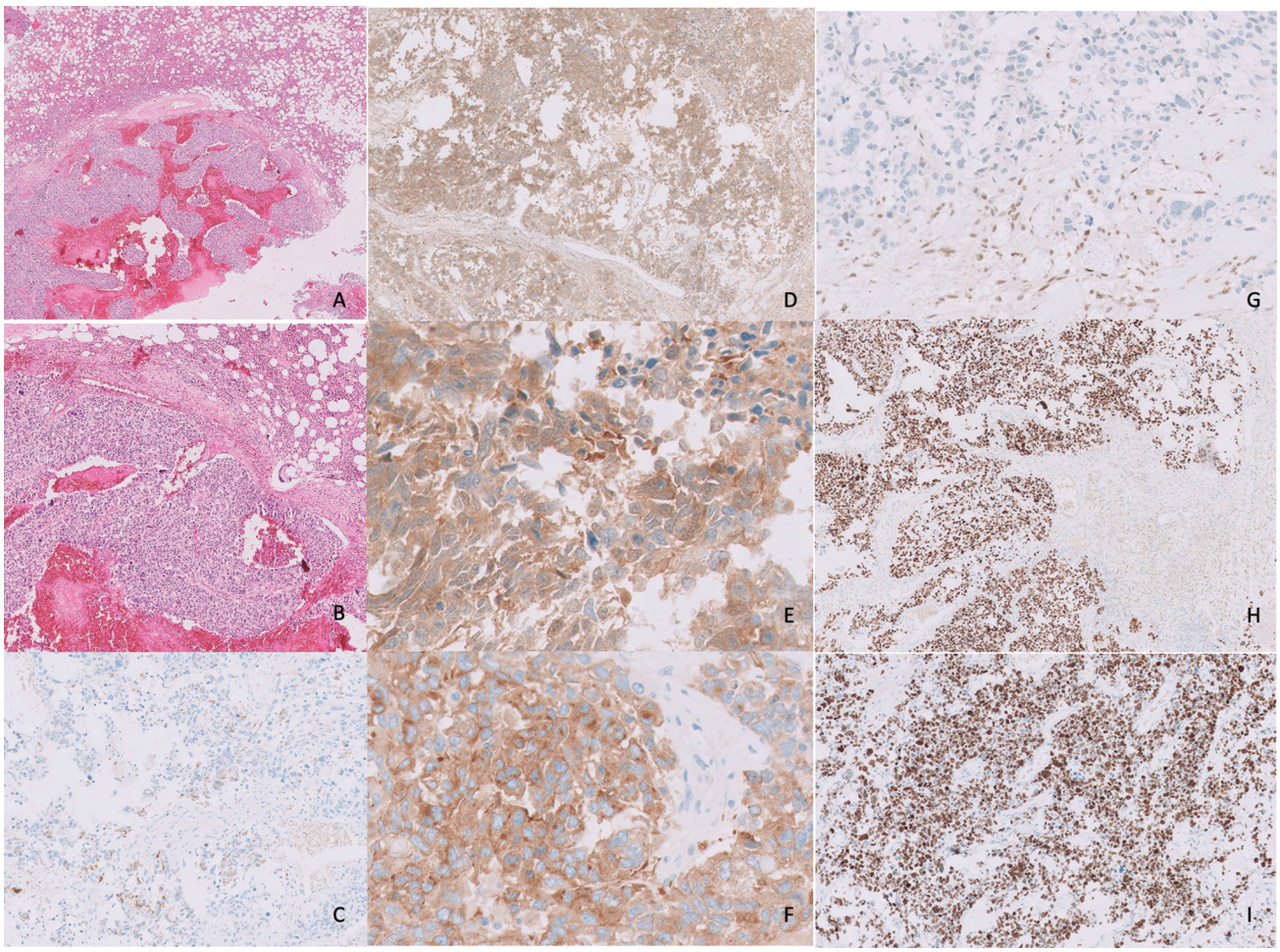

Fig. 2 Histopathology of right femur. (**A**) Hematoxylin and eosin (H&E) low power showing tumor tissue with normal bone marrow cells. (**B**) H&E high power showing tumor tissue with normal bone marrow cells. (**C**) Glial fibrillary acidic protein (GFAP) positive suggesting glial lineage. (**D**) Isocitrate dehydrogenase (IDH) 1 low power (mutant) suggesting metastases from glial neoplasm. (**E**) IDH1 high power (mutant) suggesting metastases from glial neoplasm. (**F**) Synaptophysin positive showing positivity for primitive neuroectodermal tumor (PNET) pattern. (**G**) ATRX loss. (**H**) P53 positive. (**I**) Ki67 high indicating aggressiveness of the tumor.

present) are rare compared to de novo primary glioblastomas, manifest in younger patients, and usually progress from low-grade diffuse astrocytomas.[2] Extracranial metastases from glioblastoma are extremely rare but can affect 0.4 to 0.5% of all patients with glioblastomas. This can be attributed to rapid intracranial progression of the disease leading to poor overall survival, thereby not having sufficient time for dissemination, lack of favorable cerebral environment for extracranial tumor cell spreading, and absence of neural stroma for metastatic cells to adhere and multiply. The most common sites of metastases so far noted are lymph nodes, lung, and bone; liver, soft tissue, and skin can also be involved. Among bone metastases, spine (73%) is the most common site, followed by ribs (23%), sternum (18%), skull (14%), and acetabulum (9%).[2] Mean time between diagnoses of metastases and death is about 12 months, with better prognosis to lymph nodes and worse to lungs and liver. Exact pathogenesis of extracranial spread is not understood but is hypothesized to be invasion through venous system or directly through dura and breakdown of blood–brain barrier favoring diffusion through systemic circulation. Also, recent studies have demonstrated the existence of lymphatic system in meninges, called "glymphatic system," which can be attributed to disease spread.[3] It is also postulated that predilection for bone metastases may come from both tumor-derived and extracellular niche-derived cues, where glioblastoma cells express same hematopoietic stem cell proteins that are critical for growth within the bone marrow, including stromal cell-derived factor 1 alpha (SDF-1α), C-X-C chemokine receptor 4 (CXCR4), osteopontin (OPN), and cathepsin K (CATK). Glioblastoma cells are also thought to recruit bone marrow-derived progenitor cells that support tumor-associated angiogenesis including hypoxia-inducible factor-1α and vascular endothelial growth factor, which are known to increase glioma aggressiveness and invasion.[4]

Treatment of extracranial metastases varies widely, with no consensus due to the rarity of the tumors and paucity of available literature. They are based on symptomatology such as palliative radiotherapy and/or chemotherapy.[5] Progressive systemic involvement in the absence of intracranial progression, leads to a conundrum of clinical diagnoses. Initial favorable histopathological and molecular pattern can increase the likelihood of systemic spread from a glioblastoma. In our patient, we reviewed the histopathology comparing with the previous histopathology of the craniotomy specimen in 2020, where we did find the PNET pattern to be common in both the samples thereby confirming the clinical diagnosis. Our initial working diagnosis was toward a granulomatous/tuberculous etiology, with myelodysplasia also being thought of; however, after careful histopathological, clinical, and radiological correlation, extracranial metastases were confirmed and treated accordingly.

Conclusion

Long-term survivors of IDH-mutant glioblastomas without any intracranial disease presenting with systemic symptoms should warrant the thought of extracranial metastases in the differential diagnosis, as these tumors are known to cause systemic spread; however, treatment paradigm remains futile and managed as per palliative care principles. Further molecular analysis can throw more light on treatment of such tumors.

Conflict of Interest

None declared.

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