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Case Report

Extraneural metastases of glioblastoma: A case report and literature review

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ABSTRACT

Background: Glioblastoma (isocitrate dehydrogenase [IDH]-wildtype, WHO Grade 4) is known to have a high recurrence rate with poor management of morbidity and mortality. Metastatic spread of glioblastomas is rare with extraneural osseous spread having been reported in under 100 cases. In this report, a case of glioblastoma with widespread extraneural metastatic lesions, including distal extremities, is presented.

Case Description: A 70-year-old female presented with progressive word-finding difficulty and confusion. Brain magnetic resonance imaging (MRI) revealed a 5 × 7 cm left temporal solid and cystic mass with heterogenous contrast enhancement and significant surrounding edema. She underwent near-total tumor resection, and the pathological diagnosis was glioblastoma, (IDH-wildtype, WHO grade 4), with sarcomatous and primitive neuronal components. She received radiation therapy and temozolomide over 4 months. At 5 months postoperative, she presented with new bilateral lower extremity weakness and left facial droop. MRI and positron emission tomography scans revealed local recurrence and metastatic lesions to vertebrae, extremities, and lymph nodes.

Conclusion: Previous research into rare glioblastoma bone metastases supports the theories of spread through hematogenous routes, surgical disruption, glymphatic system, and potential genetic susceptibility. However, no literature to date can adequately explain the distal limb metastases presented in this case, which shows the necessity for further understanding of this pathology.

Keywords: Case report, Extracranial metastasis, Glioblastoma, Malignant astrocytoma, Osseous metastasis

INTRODUCTION

Malignant astrocytomas are known to be the most common primary central nervous system tumors in adults.[14] Malignant astrocytomas form only 2% of all cancers and are notorious for their disproportionate rate of disease-related morbidity and mortality. Glioblastoma (isocitrate dehydrogenase [IDH]-wildtype, WHO Grade 4), a subgroup of malignant astrocytoma, has an average survival time of 15 months despite the combination of gross total/safe resection and adjunct chemotherapy and radiation therapy.[34] Metastatic spread of glioblastoma to neuroaxis is rare. Metastasis outside of the nervous system is extremely rare and is reported in only up to 2% of all glioblastoma cases.[8,26,28,31,33,37] Furthermore, only 35% of this group have metastatic spread to osseous structures.[33] In this report, a case of glioblastoma with widespread extraneural metastatic lesions, including distal extremities, is presented. A review of current literature on ways of spread is discussed.

CASE REPORT

A 70-year-old female with a past medical history of hypertension, hyperlipidemia, and thyroidectomy for medullary thyroid cancer 26 years prior was presented to the emergency room with a 1-week history of word-finding difficulty and confusion. Brain magnetic resonance imaging (MRI) revealed a 5 × 7 cm left temporal mass with solid and cystic components, heterogenous contrast enhancement, and significant surrounding edema [Figure 1]. She underwent near-total resection of the tumor through a left frontotemporal craniotomy. The pathological diagnosis was glioblastoma (IDH-wildtype, WHO grade 4) with sarcomatous and primitive neuronal components [Figure 2]. Her recovery was uneventful, with complete improvement of neurological deficit. She then received concurrent treatment with radiation therapy and temozolomide (TMZ). This was accomplished by utilizing intensity modulation with image guidance to deliver an initial dose of 46 Gy in 23 fractions, followed by subsequent boosts, which became a total dose of 60 Gy in 30 fractions over the 6 weeks of therapy. One month later, she began adjuvant TMZ with 5-day monthly courses initiated at 260 mg, increasing to 360 mg over four cycles.

Local recurrence measuring as 5 × 5 cm cystic mass was detected on a 5-month imaging follow-up, and surgical resection was planned [Figure 3]. Meanwhile, she was presented with new symptoms of bilateral lower extremity weakness and left facial droop. Spine MRI revealed diffuse vertebral body contrast enhancement, suggesting an infiltrating process and a T3 pedicle tumor with T3-T4 epidural extension and significant cord compression. Full-body positron emission tomography scan showed active involvement of multiple lymph nodes, consistent with metastatic disease [Figure 4]. These included multiple 1 cm lymph nodes through suboccipital, supraclavicular, and mediastinal regions. There was a diffuse osseous metastatic disease with lesions involving the skull, right temporal bone, clivus, entire spine, ribs, sternum, pelvis, and distal extremities. She underwent left T3 hemilaminectomy with partial resection of the pedicle and resection of the epidural tumor. Histopathology revealed a malignant small cell neoplasm, most consistent with metastatic primitive neuronal component derived from glioblastoma, although the possibility of a metastatic carcinoma could not be completely excluded [Figure 2]. Craniotomy and resection of the recurrent tumor revealed glioblastoma (IDH-wildtype, WHO grade 4) with sarcomatous and primitive neuronal

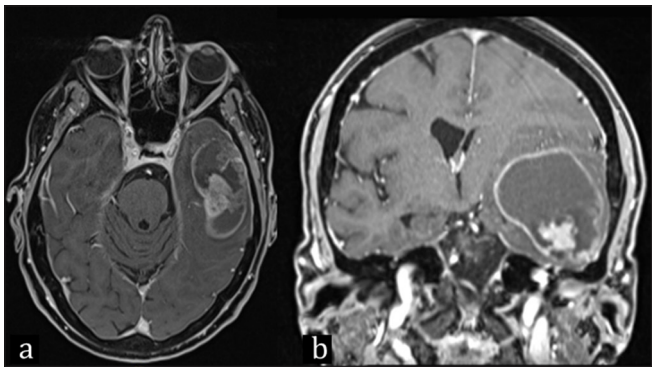

Figure 1: Preoperative magnetic resonance imaging displaying 5 × 7 cm left temporal enhancing mass with vasogenic edema and notable mass shift. (a) Axial and (b) coronal view.

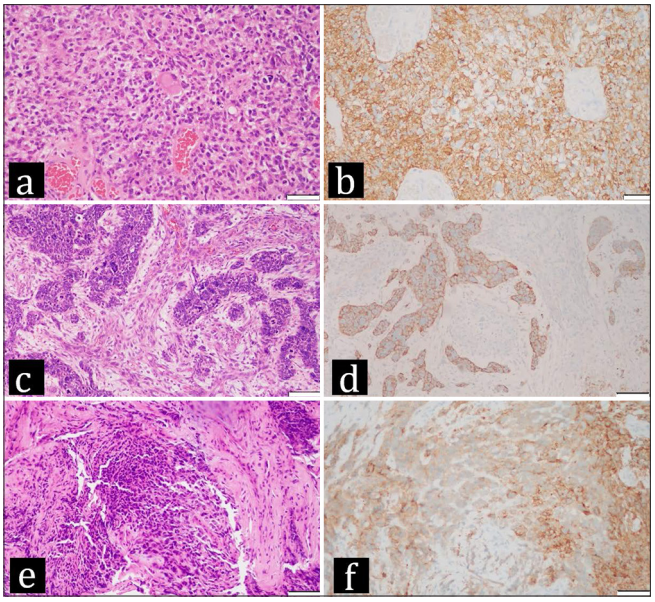

Figure 2: (a-d) Representative areas from the first resection of the brain tumor. (a) Hematoxylin and eosin (H&E) section from a region of the neoplasm that exhibits astrocytic histopathological features. The neoplastic cells, some with subtle fibrillar processes, some with eosinophilic cytoplasm, and some without obvious cytoplasm are haphazardly distributed. Nuclei are pleomorphic, and mitotic activity is present. Multifocal necrosis that is present in the neoplasm is not shown. (b) Most of the cells in the region with glial histomorphology express glial fibrillary acidic protein (GFAP), identified by the brown staining, as seen in this GFAP immunohistochemical preparation. (c) H&E section from a region of the brain tumor that consists of circumscribed nests of primitive neuronal cells with hyperchromatic blue nuclei and little visible cytoplasm distributed among spindle cells that represent a sarcomatous component within the neoplasm. (d) Synaptophysin immunohistochemistry demonstrates synaptophysin expression in the cells that are arranged in nests that represent a primitive neuronal component; the surrounding unstained cells comprise the sarcomatous component in the neoplasm. (e and f) show a representative area from the thoracic vertebral lesion, which extended into the epidural space. (e) The H&E section demonstrates abundant cells with hyperchromatic nuclei and little cytoplasm, characteristic of small blue cells. (f) Synaptophysin immunohistochemistry from the area shown in e demonstrates that these small blue cells express synaptophysin, consistent with their origin from the primitive neuronal component of the brain tumor. (a, b, e, f) - 200x magnification, scale bar = 50 microns; (c and d) - 100x magnification scale bar = 100 microns.

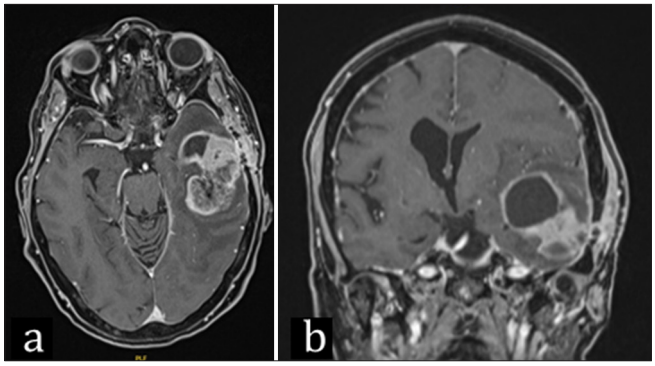

Figure 3: Brain magnetic resonance imaging showing tumor recurrence with more solid compartments and interval increase. (a) Axial and (b) coronal view.

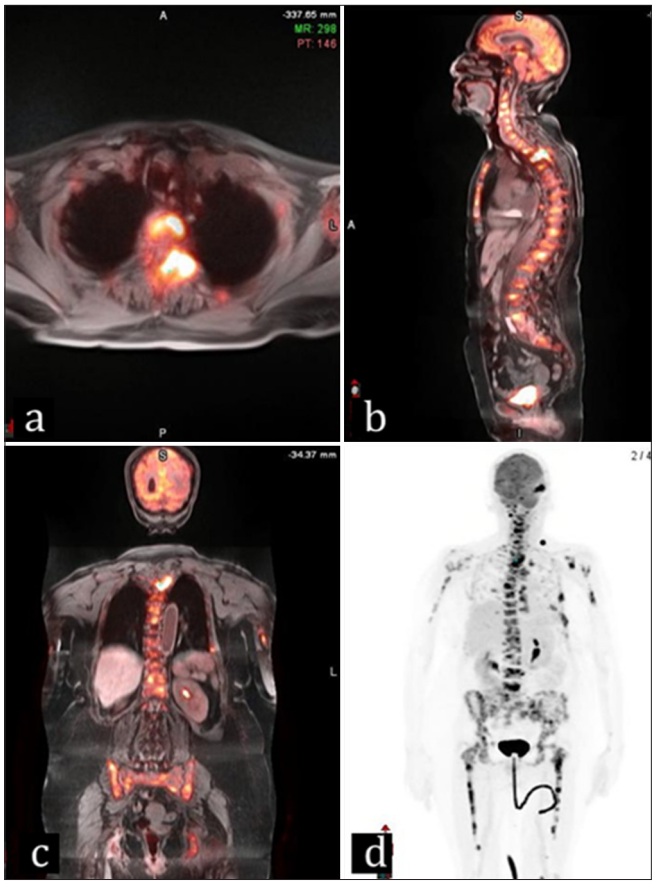

Figure 4: 7-month positron emission tomography scan with metastases seen in the tibia, humerus, left supraclavicular lymph node, mediastinal lymph nodes, suboccipital lymph nodes, skull, right temporal bone, clivus, entire spine, ribs, sternum, and pelvis. (a) Axial, (b) sagittal, (c and d) anterior view.

components. Two weeks later, she presented with progressive lower extremity weakness and generalized symptoms. Imaging showed epidural metastatic disease at T2, T3, T7, and T8 [Figure 5]. Further, the metastatic spread was visualized in cervical soft tissue, a 3.2 × 2.6 cm left supraclavicular lymph node, and a new right lung nodule. Laboratory

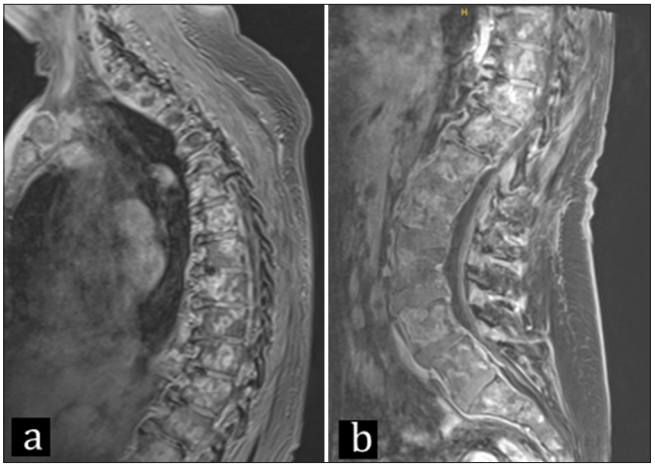

Figure 5: (a) Thoracic and (b) lumbar spinal magnetic resonance imaging with extensive metastases and bone marrow infiltration to all vertebral bodies with contrast enhancement.

results additionally showed myelophthisic smear with severe thrombocytopenia requiring transfusion and lactic acidosis. Treatment with cisplatin and etoposide was initiated; however, due to progressive worsening, withdrawal of care was requested by the family.

DISCUSSION

The case presented here represents a left temporal glioblastoma (IDH-wildtype, WHO grade 4) with a distribution of metastatic disease that has not been previously reported, both in the combination of metastases seen in the bone, soft tissue, and lymph nodes together with the spread to the distal extremities. There are several theories regarding glioblastoma spread to bone based on the limited case presentations in the literature, with many agreeing that comprehension of this pathology is limited due to the short survival time of these patients.

Strong *et al.* report many similarities between our case and previous literature, such that 24% of bone metastases occur in the thoracic region, 36% of patients receive the triad of chemotherapy, surgery, and radiotherapy, and thrombocytopenia is a common late-stage finding.[33] However, our case differs in that the majority of cases are younger men with a median survival rate of 16 months compared to this case of a 70-year-old female with an aggressive disease progression of 8 months between initial surgery and death.[33] In addition, the presentation of leg weakness as the main clinical symptom differs from the typical presentation of back or bone pain.[25] Furthermore, metastases were found here at the same time as her original tumor recurrence, and despite the widespread nature of the disease, no leptomeningeal spread was seen in brain or spine MRI.

Extensive metastatic lesions to vertebral and distal extremity bones can be explained by theories suggesting spread is surgical disruption of the original tumor area, although many studies have shown that this is not a prerequisite for metastasis.[7,21,22,25] This path overcomes the thickened basement membrane; however, the natural progression alone of glioblastomas may also disrupt the blood–brain barrier or venous structures creating a hematogenous spread to the venous plexus of vertebral bodies or red bone marrow.[7,11,17,20,33,37] Genetic markers associated with bone metastases include GFAP-positive tumors or germline mutations, although this is not consistently seen in the literature.[7,9,29,36] Additional glioblastoma metastatic genetic components have been shown by Liu *et al*., 2022 in their LASSO Cox regression, finding Insulin-like growth factor binding protein 2 gene (IGFBP2), Glucosamine (N-acetyl)-6-sulfatase gene (GNS), Limb bud-heart gene (LBH), Scavenger receptor class a member 3 gene (SCARA3), Epidermal growth factor receptor gene (EGFR), and MutL protein homolog 1 gene (MLH1) mutations to be most highly correlated to glioblastomas.[19] MutL protein homolog 1 gene (MGMT) methylation, IDH wildtype, and tumor protein p53 gene (TP53) mutations have also been linked to extraneural metastases, often with subclones of different TP53 in the metastasis compared to the original glioblastoma tumor.[6,17,20,25,27,32,37,38] Many of these hypermutated genotypes may be the result of radiation therapy that these patients often receive.[23]

In addition to the osseous spread, there were also metastases found in the lymph node, cervical soft tissue, and lungs. The newly reported glymphatic system has been speculated to play a role in the spread to these areas, such as through a recent MR imaging study by Albayram *et al*. (2022) that proved the ventral meningeal lymphatics system with a direct route between cranial nerves and cervical lymph nodes.[1,13,15] This path can additionally be caused by surgery, which serves as a route of exposure for the emissary veins connected to the lymphatic system.[2,11,33]

One of the most compelling current theories for soft tissue and organ spread is the ability of glioblastomas to avoid immune surveillance through the presence of circulating tumor cells (CTCs) in 20–39% of patients and case reports of organ donor recipients that later developed glioblastomas.[4,10,16,24,33,35] It has been shown that CTCs are correlated with decreased T-cell infiltration, which may be amplified by glioblastoma's ability to sequester T-cells and by specific hypermutations or inherited genotypes.[5,23,30] This immune surveillance is assisted by common glioblastoma expression of factors, such as C-X-C Chemokine receptor type 4 (CXCR4) and Cluster of differentiation 44 (CD44), which promote invasion and growth.[12,25] Certain gene overexpression seen in glioblastomas is similar to those in liver and lung cancer, potentially indicating why these are the most frequent sites of spread to organs.[10,33] Extraneural spread may be aided by the similarity of glioblastomas to extraneural structures, such as hematopoietic cells, or the presence of extraneural proteins, such as fibronectin and collagen.[3,18,29] This may also explain their ability to recruit similar progenitor cells for vascular tumor support or travel through nerve roots.[25,37]

There are several limitations to understanding this pathology, with a significant one being the short survival time limiting the metastases that are able to present in these cases before death. It makes understanding this spread incredibly difficult and each case an important study. It has also been postulated that this may be the reason for the lack of distal metastases seen in the literature before our reported case.[36] Some literature even reports the progression of bone metastases without cranial relapse, which displays a different path than seen in this case that is still to be researched.[8,36] This heterogeneity in disease presentation, location, and progression for glioblastomas warrants further research to supplement the current literature of only about 100 cases. The distal metastatic spread here may also represent a previously undiscovered route of metastasis.

CONCLUSION

Previous research into rare glioblastoma bone metastases supports the theories of spread through hematogenous routes, surgical disruption, glymphatic system, and potential genetic susceptibility. However, no literature to date can adequately explain the distal limb metastases presented in this case, which shows the necessity for further understanding of this pathology.

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