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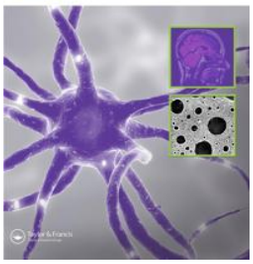

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CASE REPORT

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Metastatic glioblastoma to the lungs: a case report and literature review

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ABSTRACT

Glioblastoma is the most common malignant primary brain tumor. Despite its infiltrative nature, extra-cranial glioblastoma metastases are rare. We present a case of a 63-year-old woman with metastatic glioblastoma in the lungs. Sarcomatous histology, a reported risk factor for disseminated disease, was found. Genomic alterations of *TP53* mutation, *TERT* mutation, *PTEN* mutation, and +7/-10 were also uncovered. Early evidence suggests these molecular aberrations are common in metastatic glioblastoma. Treatment with third-line lenvatinib resulted in a mixed response. This case contributes to the growing body of evidence for the role of genomic alterations in predictive risk in metastatic glioblastoma. There remains an unmet need for treatment of metastatic glioblastoma.

Plain language summary: Glioblastoma is the most common malignant primary brain tumor. Glioblastoma can spread into healthy tissue, but metastases beyond the brain are rare. We present a case of a 63-year-old woman with metastatic glioblastoma in the lungs. We identified risk factors associated with spread beyond the brain, including factors related to tissue structure and specific molecular alterations. Treatment with third-line lenvatinib resulted in a mixed response. This case adds to the limited existing data for the use of molecular alterations to serve as risk factors for metastatic glioblastoma. Treatment options are needed for this devastating disease.

TWEETABLE ABSTRACT

Despite the infiltrative nature of glioblastoma, extra-cranial metastases are rare. Sarcomatous histology and genomic alterations of *TP53* mutation, *TERT* mutation, *PTEN* mutation, and +7/-10 are described as risk factors for the development of glioblastoma metastases. No effective treatments exist. In our metastatic glioblastoma patient, third-line lenvatinib resulted in a mixed response. #glioblastoma #metastaticglioblastoma #lenvatinib #VEGF #VEGFinhibitor.

ARTICLE HISTORY
Received 13 November 2023
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KEYWORDS
extra-neural glioblastoma; gliosarcoma; lenvatinib; metastatic glioblastoma; vascular endothelial growth factor inhibitor; VEGF

1. Background

Glioblastoma is the most commonly occurring malignant primary brain tumor [1]. Despite the infiltrative nature of glioblastoma, metastases are infrequent with an incidence of only 0.4–2.0% [2–5]. Accordingly, the rare detection of metastases has resulted in the forgoing of staging for glioblastoma [6]. However, cases are on the rise due to heightened awareness and evidence suggests that 20% of glioblastoma cases are found to have tumor-circulating cells [7–9]. Despite this finding, glioblastoma predominantly remains an intracranial disease [7–9]. There are several reasons for restricted disease dissemination beyond the brain [10]. First, shortened survival prior to the development of metastases has been postulated [10–12]. Second, the failure of tumor cells to proliferate in unfavorable extra-cranial 'soil' that lacks brain-specific growth factors may preclude the distal spread of glioblastoma cells [10–15]. Last, immunocompetency may drive circulating glioblastoma cells into dormancy and prohibit tumor development [16]. For the subset of cases in which metastases do occur, extra-cranial intra-neural drop metastases to the spine are more common than extra-neural dissemination to outside organs. Extra-neural glioblastoma metastases have been previously reported in the lung, liver, bone, lymph nodes, and spleen [12,17–25]. Prognosis remains especially poor with a median overall survival of 10.5 months and a median time from metastasis to death of 1.5 months [19]. We present a case of a 63-year-old woman with metastatic glioblastoma in the lungs. We examine possible risk factors, including genomic alterations, for the development of her extra-neural disease. We also describe her treatment response to lenvatinib monotherapy. Our case adds

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to the limited, but growing body of evidence supporting the early identification and prompt treatment for metastatic glioblastoma (Table 1).

2. Case presentation

A 63-year-old female with a past medical history of hypertension presented with expressive aphasia secondary to a left frontal heterogeneously enhancing mass with surrounding vasogenic edema (Figure 1A & B). She underwent a left frontal craniotomy for tumor resection. Postoperative brain MRI demonstrated near total resection of her enhancing tumor and persistent vasogenic edema (Figure 1C & D).

Histopathologic evaluation showed an *IDH* wildtype glioblastoma, WHO grade 4 with characteristic features of both necrosis and microvascular proliferation, which was *MGMT* unmethylated. Next-generation sequence analysis revealed mutations in *TP53* (p.R248W), *TERT* promoter (c.-124C>T), *PTEN* (p.M199del), *PDGFRA* amplification and trisomy 7/monosomy 10 (+7/-10). Her radiation planning brain MRI demonstrated significant resolution of the prior vasogenic edema, but new contrast enhancement at the posterior margin of the resection and a minimally ring-enhancing mass posterior to the resection cavity with associated T2 FLAIR hyperintensity (Figure 1E & F). During her standard 6-week course of radiation (60 Gy) and chemotherapy (temozolomide 75 mg/m^2), dexamethasone 4 mg twice daily was started for new right hemiparesis. Her post-radiation brain MRI with and without contrast showed a new 2.6 cm enhancing mass posterior to the resection cavity with surrounding vasogenic edema (Figure 1G & H) that was subsequently near totally resected with stable T2 FLAIR hyperintensity (Figure 1I & J). Histopathology confirmed residual/recurrent glioblastoma with giant cell features, and repeat sequencing showed mutations in *TP53* (p.R248W), *TERT* promoter (c.-124T>C), *PTEN* (p.Y336*), *RB1* (p.L385*), amplification of *EGFR*; and +7/-10 (Figure 2A & B). Second-line combination therapy was started with bevacizumab for steroid dependence and lomustine for tumor-directed therapy. Following 2 doses of lomustine with a dose reduction for severe neutropenia and 3 doses of bevacizumab, her brain MRI showed a second recurrence in the most recent operative bed (Figure 1K & L). Lomustine was discontinued after 2 cycles for severe neutropenia. Despite her history of hypertension, bevacizumab therapy did not require any interruptions for hypertension. Following 1 additional dose of bevacizumab, her brain MRI revealed further progressive disease (Figure 1M & N).

She subsequently developed a persistent cough. CT chest obtained to evaluate for pulmonary fibrosis instead showed multiple enhancing pulmonary masses (Figure 3A). CT imaging of her abdomen and pelvis and complete spine MRI showed no evidence of disease. Histopathologic analyses from her lung biopsy showed metastatic glioblastoma with sarcomatoid features (Figure 2C–E). Next-generation sequencing analysis demonstrated mutations in *TP53* (p.R248W), *TERT* promoter (c.-124T>C) *PTEN* (p.M199del) amplifications of *PDGFRA* and *CDK4*, focal deep deletion of *NAV3* and +7/-10 (Figure 2F). Salvage therapeutic options were restricted to oral therapies due to transportation limitations at her rehabilitation facility. She decided to proceed with lenvatinib.

Ten days later, repeat systemic imaging showed worsening pulmonary metastases and new hepatic lesions (Figure 3B). However, repeat brain MRI showed significant improvement in the enhancing tumor and T2 FLAIR hyperintensity (Figure 1O & P). Her care was transitioned to hospice and she unfortunately passed away 1.5 months after her metastatic glioblastoma diagnosis. Our patient's disease course is summarized in Figure 4. Ethical guidelines set out by the Declaration of Helsinki were followed in the preparation of this report and the patient provided written consent.

3. Discussion

Metastatic glioblastoma is a rare disease with an especially poor prognosis [2–5,19,56]. The time from metastasis to death in our patient was 1.5 months, which corroborates with the median time from metastasis to death of 1.5 months in a study conducted by Lun et al. [19]. In the aforementioned study, analyses from 88 metastatic glioblastoma cases showed a median overall survival of 10.5 months and a median time from the initial diagnosis to extra-neural metastases of 8.5 months [19]. Our patient's findings substantiate these findings with an overall survival of 10 months and a time from the initial diagnosis to extra-neural metastases of 8.5 months. Despite her shortened overall survival which should preclude tumor cells from distal spread [10–12], she developed metastatic disease. Accordingly, we assessed for additional contributory risk factors that may have predetermined her disease course. First, prior neurosurgical intervention is a described risk factor for the development of metastatic glioblastoma [57]. Our patient underwent two craniotomies with anatomic barrier compromise. However, there was no radiographic evidence of lateral ventricular violation or drop metastases with spinal dissemination. The postsurgical iatrogenic spread was unlikely to explain her metastases. Further, extra-neural metastases have been reported even in the absence of craniotomy and therefore does not account for her metastatic spread in its entirety [58–60]. Sec-

Table 1. Extra-neural glioblastoma cases.

Publication	Age/gender	Site of initial disease	EOR	Pre-metastases treatment	Site of metastases	Interval from Dx to metastases (months)	Sarcomatous component	Metastases treatment	Outcome and cause of death	Interval from metastasis to death	Interval from initial Dx to death	Ref.
Yuen et al., 2024 (present case)	63/F	L frontal	NTR	XRT, TMZ, BEV, CCNU	Lung	8.5	Y	Lenvatinib	PD	1.5	10	
Potter et al., 1983	41/M	L frontal	STR	WBRT	Submandible	11	NR	XRT, CCNU	SD at 9 month follow-up	–	–	[26]
Wallace et al., 1996	41/M	R frontal	GTR	XRT, BCNU	LN	NR	NR	XRT, chemo	Aspiration	NR	8	[27]
Beauchesne et al., 2000	54/M	R temporal	STR	XRT, etoposide	Heart, lung, bone	7	NR	–	–	2	9	[28]
Hübner et al., 2001	47/M	R cerebellum	NR	XRT, chemo	Neck and LN	10	NR	RT	PD	7	17	[29]
Allan et al., 2004	60/M	NR	STR	XRT	Scalp	12	NR	Steroids	NR	2	14	[30]
Ogungbu et al., 2005	49/F	R occipital	Resection	XRT, CCNU, procarbazine	Lung, parotid gland	7	NR	NR	NR	NR	16	[31]
Taha et al., 2005	33/M	L frontal	STR	XRT	Parotid gland	6	XRT, PCV	NR	PD	3.5	NR	[32]
Templeton et al., 2008	58/M	L frontal	GTR	XRT, TMZ	Epidural spine, lungs, bone, retroperi-toneum	5	Y	Resection, XRT, TMZ	Metastases to soft tissue and spine and PE	6	11	[33]
	47/F	R frontal	STR	TMZ	Pleura	24	NR	–	Respiratory insufficiency	24	24	
Zhen et al., 2010	25/M	R frontoparietal	GTR	Re-resection, XRT	Bone and LN	2	N	Chemo	NR	NR	NR	[34]
Armstrong et al., 2011	30/F	L frontal	STR	XRT, TMZ, sorafenib and erlotinib	Soft tissue scalp	NR	N	Irinotecan and bevacizumab	Stable for 11 months then metastases to bone	NR	NR	[35]
Kalokhe et al., 2012	72/M	R temporal and occipital	GTR	XRT, TMZ, BEV, BCNU	Lung, bone	10	NR	–	NR	9	19	[36]
	31/F	L cerebellum	GTR	Erlotinib, BEV	Bone	4	NR	RT, TMZ, BEV	PD	5	9	
Seo et al., 2012	46/M	L frontoparietal	Resection	GKRS, PCV, TMZ	Cervical LN	60	NR	Resection and unspecified aggressive treatment	PD	6	66	[37]
Blume et al., 2013	40/M	R parasagittal	STR	XRT, TMZ	Lung, LN, bone, muscle, epidura	36	NR	STR, XRT, TMZ	NR	NR	NR	[38]
Dawar et al., 2013	57/F	R temporal	GTR	XRT, TMZ	Pre-auricular region	51	NR	Mesna, adriamycin, ifosfamide, gemcitabine, docetaxel, SRS	PD	6.5	57.5	[39]

BCNU: Carmustine; BEV: Bevacizumab; BG: Basal ganglia; Chemo: Chemotherapy; CCNU: Lomustine; CSI: Craniospinal irradiation; Dx: Diagnosis; EOR: Extent of resection; F: Female; GKRS: Gamma knife radiosurgery; GTR: Gross total resection; IFN-β: Interferon-β; LM: Leptomeninges; LMD: Leptomeningeal disease; LN: Lymph node; M: Male; NR: Not reported; NTR: Near total resection; PCV: Procarbazine, CCNU, vincristine; PD: Progressive disease; PLIC: Posterior limb of internal capsule; RT: Radiation therapy; SD: Stable disease; SRS: Stereotactic radiosurgery; STR: Subtotal resection; TMZ: Temozolomide; WBRT: Whole brain radiation therapy.

Table 1. Extra-neural glioblastoma cases (cont.).

Publication	Age/gender	Site of initial disease	EOR	Pre-metastases treatment	Site of metastases	Interval from Dx to metastases (months)	Sarcomatous component	Metastases treatment	Outcome and cause of death	Interval from metastasis to death	Interval from initial Dx to death	Ref.
Lettau et al., 2013	80/NR	L temporal	GTR	XRT and TMZ	Dura	7	NR	Resection	NR	NR	NR	[40]
Romero-Rojas et al., 2013	26/M	Frontal	NR	XRT, TMZ	Parotid gland, LN, bone	NR	NR	XRT, TMZ	NR	NR	NR	[41]
Undabeitia et al., 2015	20/F	R temporal	GTR	XRT, chemo	Lung	5	NR	–	–	3	8	[42]
Anghileri et al., 2016	30/M	L central sulcus	NR	XRT, RT, re-resection, BEV	Neck	82	No	–	PD	1.5	83.5	[7]
	43/M	L frontal	GTR	XRT, TMZ, BEV, re-resection	Subcutaneous	23.5	–	–	PD	1.5	25	
Franceschi et al., 2016	70/M	NR	STR	NR	Lung, liver, bone	NR	NR	NR	NR	NR	NR	[43]
Lewis et al., 2017	47/F	L cerebellum	GTR	XRT, TMZ	Soft tissue and LM	NR	NR	CSI, TMZ, thymalfasin	Stable LMD, excision of subcutaneous mass	NR	NR	[44]
Semonetti et al., 2017	38/M	L parietal	GTR	XRT, TMZ, re-resection, BEV	Lung, LN, bone	48	NR	Etoposide, oncocarbide	Metastases to liver, intralesional hemorrhage, pleural effusion	NR	NR	[45]
Hori et al., 2018	75/F	L fronto-temporal, L BG and R frontal	STR	–	LN and pleura	2.8	NR	–	Respiratory failure	0.3	3.4	[46]
Janik et al., 2019	51/M	R temporal	GTR	XRT, TMZ	Lung	3	NR	–	NR	3.5	22.5	[47]
Tamai et al., 2019	49/M	R temporal	GTR	XRT, TMZ	Ventricle, dura, LM, lung	NR	NR	Resection, XRT, TMZ, BEV	Respiratory failure	NR	12	[48]
Houston et al., 2000	19/M	L parietal	STR	XRT, 125I brachytherapy	Bone	16	NR	RT, cisplatin, VP-16, MTX/adriamycin/vincristine/taxol	Recurrence	1	17	[49]
	32/M	L temporal	STR	XRT, BCNU, 125I brachytherapy	Scalp	6	Y	Excision	Recurrence	6	13	
	36/F	Frontal	bx	XRT, 125I brachytherapy	Neck	17	NR	Procarbazine	PD	9	26	
Hsu et al., 2020	53F	R temporo-parieto-occipital	NTR	PBRT, re-resection, Gliadel wafers, TMZ, BEV	Bone	15	Y	Resection	NR	NR	20	[50]

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Liu et al., 2020	46/M	L temporal	GTR	XRT, TMZ	Scalp	6	NR	XRT, irinotecan, TMZ	Metastases to lung after 9 months	14	20	[2]
Rossi et al., 2020	29/F	R frontal	STR	Multiple resections, XRT, TMZ	Lymphatic and bone metastases	39	NR	XRT, procarbazine, CCNU	PD and sepsis	12	48	[51]
Umphlett et al., 2020	74/F	L occipital	Resection	XRT, TMZ, SRS	Lungs, heart, breast, liver, thyroid, bowel, bone, LN	1	N	–	–	NR	12	[52]
Sickler et al., 2021	57/M	R temporal	NTR	XRT, TMZ	Bone	12	N	XRT, TMZ	NR	NR	NR	[24]
Alsardi et al., 2022	43/F	R parasagittal	GTR	XRT, TMZ, atorvastatin, BEV, multiple resections, irinotecan, re-RT	Lung, LN	59	N	Carboplatin, etoposide	NR	NR	NR	[53]
Hersh et al., 2022	46/F	L parietal	STR	XRT, TMZ	Bone	10	NR	Percutaneous microwave ablation, vertebroplasty, palliative RT, chemo	NR	NR	NR	[23]
Kumaria et al., 2022	65/M	L temporal	STR	XRT, TMZ	Lung	17	NR	–	Respiratory failure	NR	NR	[54]
Nakib et al., 2022	53/M	R PLIC and thalamus	STR	XRT, TMZ, BEV, CCNU, irinotecan	Skin	6	N	BEV	Asystole	NR	NR	[55]

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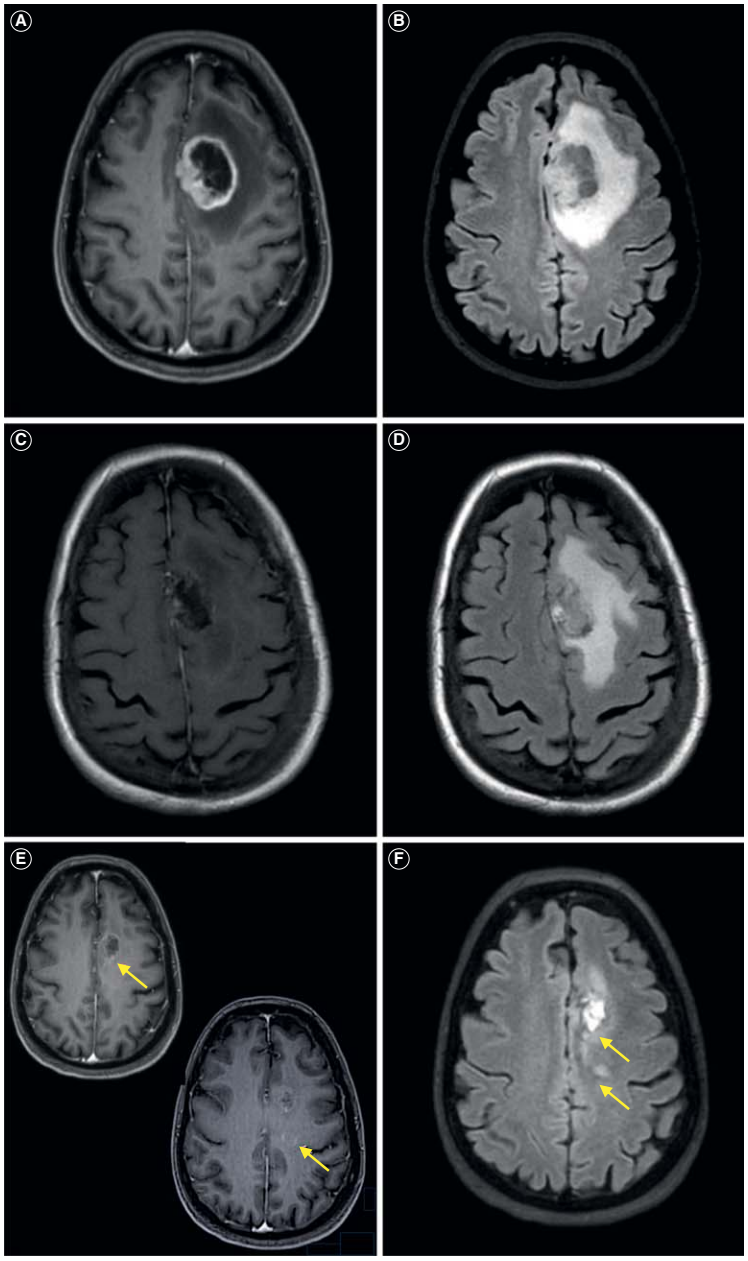
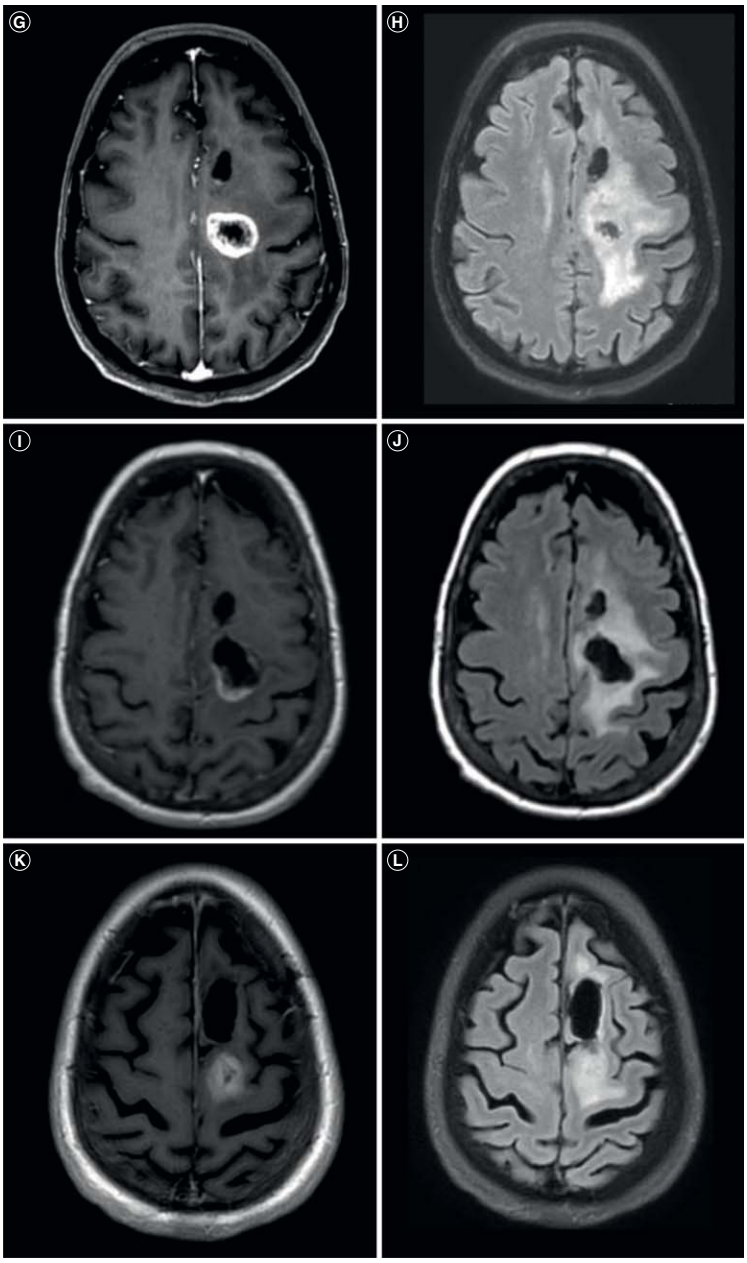


Figure 1. Patient's intracranial glioblastoma throughout the therapy course. **(A)** Preoperative axial T1 post-contrast brain MRI shows a left frontal heterogeneously enhancing mass. **(B)** Preoperative axial T2/FLAIR brain MRI shows surrounding vasogenic edema. **(C)** Postoperative axial T1 postcontrast brain MRI shows near total resection of the previously seen enhancing tumor. **(D)** Post-operative axial T2/FLAIR brain MRI shows persistent hyperintensity. **(E)** Radiation planning axial T1 post-contrast brain MRI shows interval development of contrast-enhancing lesions at the posterior margin of the resection cavity and posterior to the resection cavity (yellow arrows). **(F)** Radiation planning axial T2/FLAIR brain MRI shows hyperintensity associated with the new enhancing lesions. **(G)** Post-radiation axial T1 post-contrast brain MRI shows interval enlargement of the prior lesion posterior to the resection cavity. **(H)** Post-radiation T2/FLAIR axial brain MRI shows surrounding vasogenic edema. **(I)** Re-resection postoperative T1 postcontrast axial brain MRI shows near total resection of the prior enhancing mass. **(J)** Re-resection postoperative T2/FLAIR axial brain MRI shows improvement in the surrounding vasogenic edema. **(K)** Post 2 cycles of lomustine and 3 cycles of bevacizumab, T1 post-contrast axial brain MRI shows interval development of a contrast-enhancing mass. **(L)** Post 2 cycles of lomustine and 3 cycles of bevacizumab, T2/FLAIR axial brain MRI shows surrounding vasogenic edema. **(M)** Post 2 cycles of lomustine and 4 cycles of bevacizumab, T1 post-contrast axial brain MRI shows interval enlargement of the contrast-enhancing mass. **(N)** Post 2 cycles of lomustine and 4 cycles of bevacizumab, T2/FLAIR axial brain MRI shows surrounding vasogenic edema. **(O)** Post 10 days of lenvatinib, T1 post-contrast axial brain MRI shows an interval decrease in the previously seen contrast-enhancing mass. **(P)** Post 10 days of lenvatinib, T2/FLAIR axial brain MRI shows an interval decrease in the previously seen T2/FLAIR hyperintensity. **(Q)** Post 10 days of lenvatinib, DWI axial brain MRI shows associated abnormal signals with the aforementioned mass. **(R)** Post 10 days of lenvatinib, ADC axial brain MRI shows minimal ADC correlate along the lateral margin of the mass.



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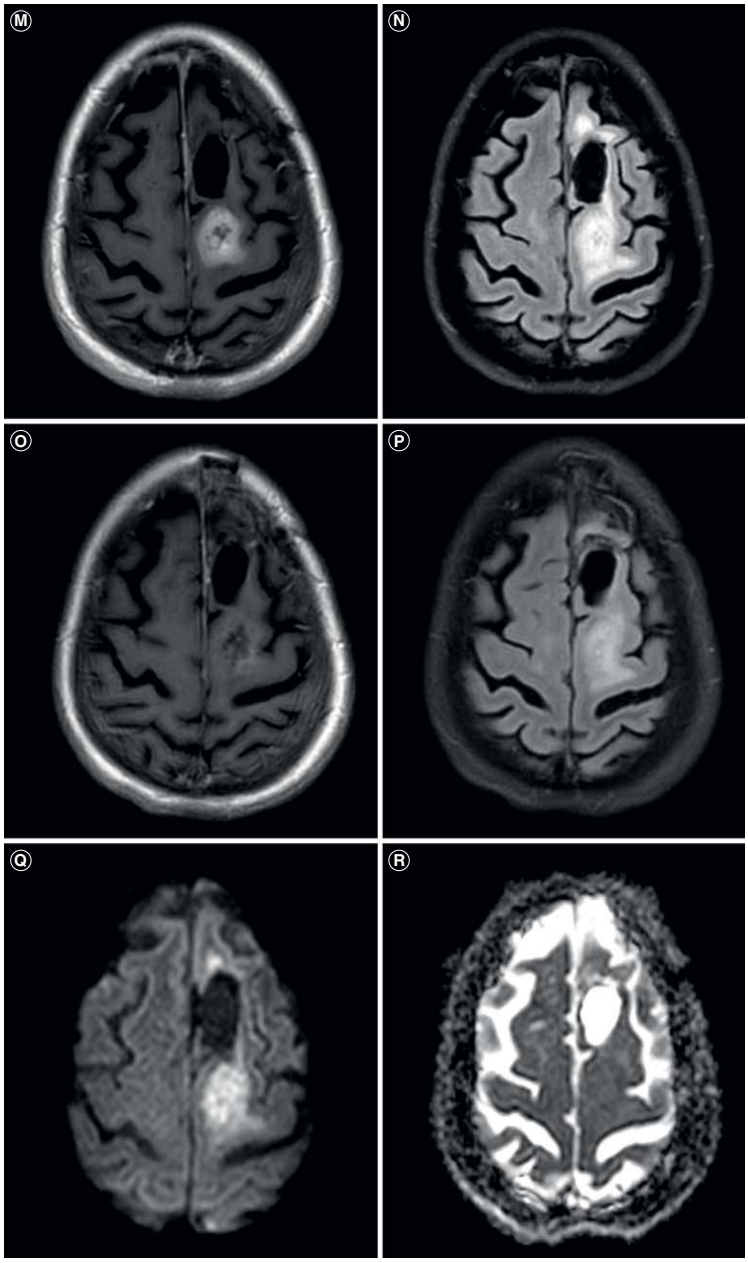

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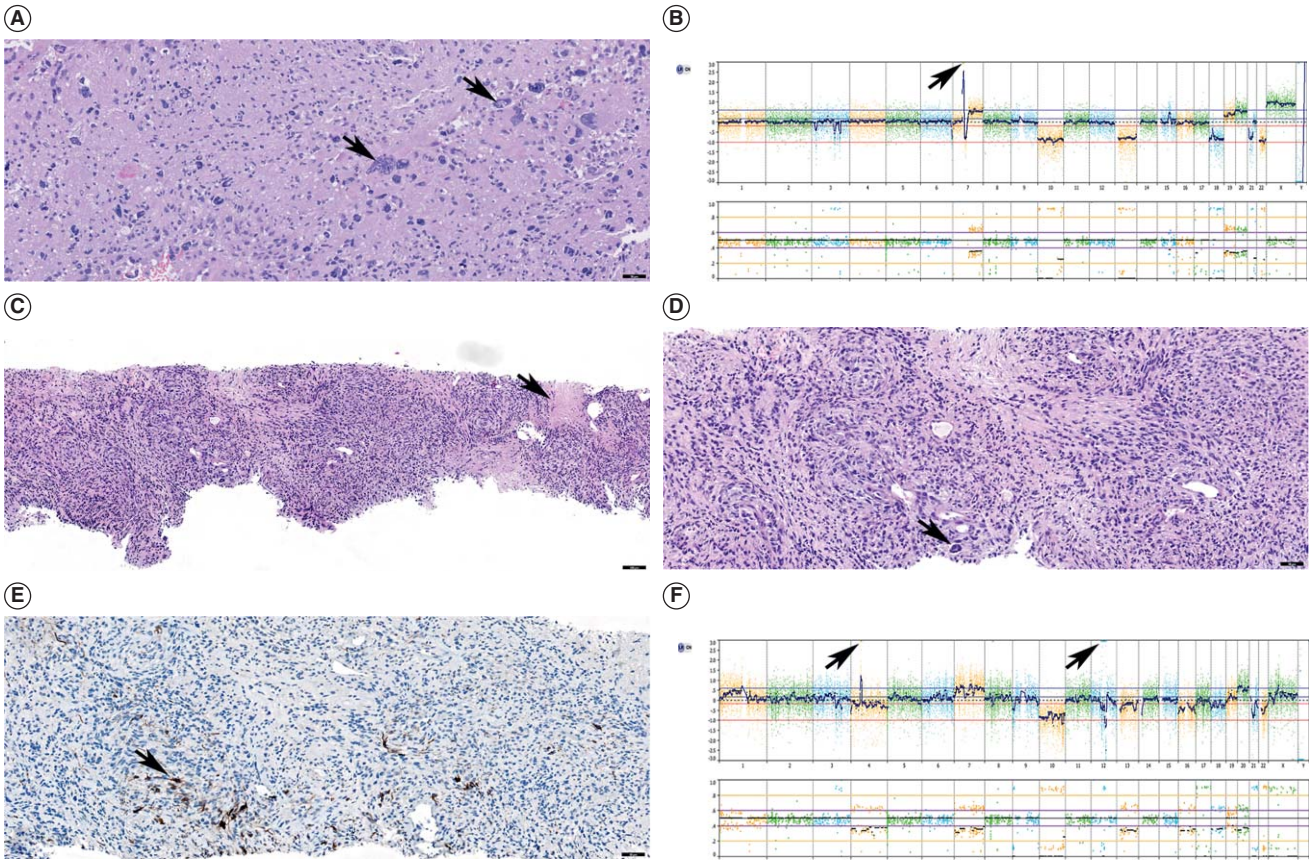

Figure 2. Patient's residual/recurrent glioblastoma patholog. **(A)** Histologic section of the residual/recurrent glioblastoma with giant cell features (black arrows), Hematoxylin and Eosin, scale bar 50 microns. **(B)** Whole genome copy number profile of residual/recurrent glioblastoma showing gains of chromosomes 7, 19 and 20, losses of chromosomes 10, 13, 18, 21 and 22 and amplification of *EGFR* on chromosome 7 (black arrow). **(C)** Histologic section of the lung mass demonstrating predominantly spindle cell neoplasm with areas of necrosis (black arrow) morphologically consistent with residual/recurrent glioblastoma with sarcomatous features. Hematoxylin and Eosin, scale bar 100 microns. **(D)** Histologic section of the lung mass demonstrating predominantly spindle cell neoplasm consistent with residual/recurrent glioblastoma with sarcomatous features, scattered multinucleated giant cells (black arrow) are present similar to the patient's intracranial tumor. Hematoxylin and Eosin, scale bar 50 microns. **(E)** Immunohistochemical stain for GFAP performed on lung mass showed scattered positive cells (black arrow), confirming the glial nature of the neoplasm. Scale bar 50 microns. **(F)** Whole genome copy number profile of lung mass showing gains of chromosomes 1p, 7 and 20, losses of chromosomes 4, 10, 13, 16, 18, 21 and 22 and amplifications of *PDGFRA* and *CDK4* on chromosomes 4 and 12, respectively (black arrows).

ond, tumor recurrence has been reported to increase the risk for metastases, which may have contributed to her metastases. Following her initial diagnosis, early progression was noted on her postradiation brain MRI. Despite standard-of-care chemoradiation, she developed a second recurrence 4 months after her initial diagnosis, followed by a rapid third recurrence in her brain and lungs 4.5 months later. Taken together, these findings suggest that her tumor had an exceptionally aggressive biology. Though the pathogenesis for metastatic glioblastoma is poorly understood, we posit that the aggressive molecular characteristics of her tumor coupled with her immunocompromised state increased her risk for the eventual rise of metastatic disease.

Our patient's aggressive tumor biology is supported by an unmethylated *MGMT* status, which portends a poorer prognosis compared with methylated *MGMT* glioblastomas [61]. However, given that the vast majority of unmethylated *MGMT* glioblastomas do not spread distally, further investigation into the pathology from her lung biopsy was warranted. The pathology revealed sarcomatous histology, which is a recognized risk factor for disease dissemination in glioblastomas [15,39,62–67]. This new histologic finding was not present in her original or recurrent intracranial tumors. Limited investigations evaluating genetic alterations in metastatic glioblastoma show that *TP53*, *TERT*, *PTEN* and *RB1* mutations are frequent alterations in metastatic glioblastoma [22,48]. Gain of chromosome 7 with loss of chromosome 10 has also been reported in metastatic glioblastoma [68,69]. Our patient's metastatic tumor carried alterations in *TP53*, *TERT*, *PTEN* and +7/-10, which were retained among her

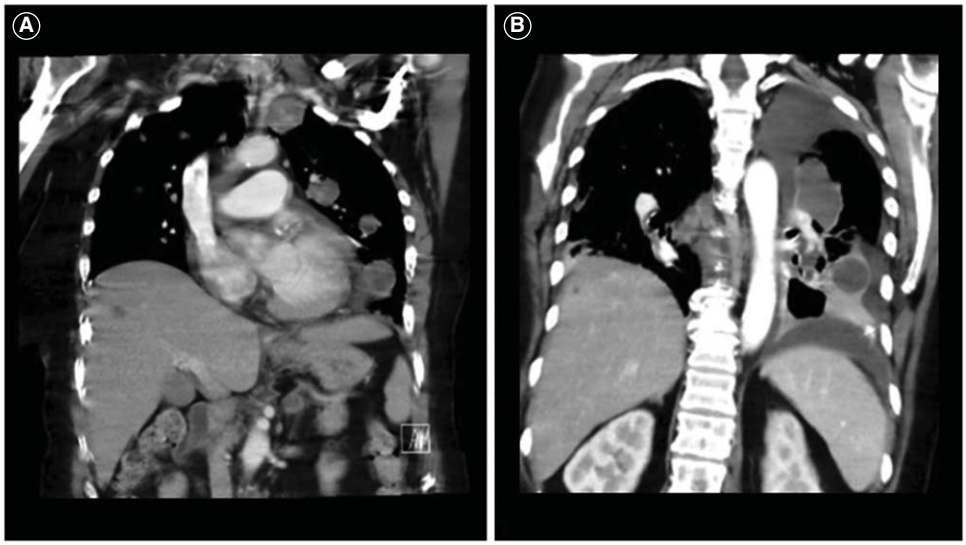

Figure 3. Patient's metastatic glioblastoma to the lungs. **(A)** Coronal computed tomography (CT) chest shows multiple enhancing pulmonary metastases. **(B)** Coronal CT chest shows further progression of pulmonary metastases and new hepatic metastases.

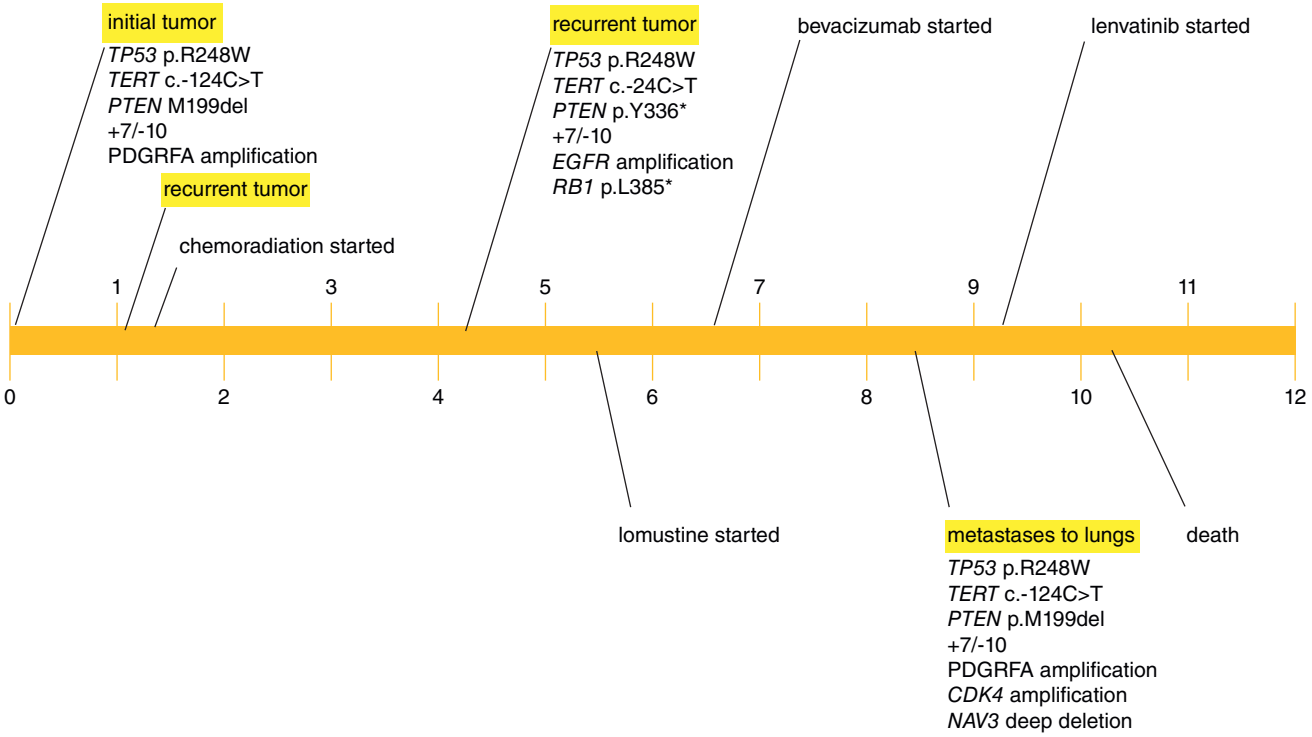

Figure 4. Patient disease course (timeline in months).

initial intracranial, recurrent intracranial and metastatic lung tumors (Figure 3). While our patient's intracranial glioblastoma and metastatic glioblastoma to the lung samples all harbored *TP53*, *TERT* promoter and *PTEN* mutations and +7/-10, these are some of the most frequent alterations in glioblastoma in adults and are not specific to metastatic tumors, or any particular histologic subtype [48].

We reason that our patient's immunocompromised state secondary to steroid dependence contributed to the development of her metastases. It is plausible that prior to the initiation of steroids, low-level latent circulating glioblastoma cells in her systemic circulation bearing no clinical consequence were controlled by her immune system. Following chronic steroid administration, dysregulated immune surveillance and immunosuppression set these previously quiescent circulating glioblastoma

cells into motion with ultimate clinical relevance presenting as respiratory distress. This is substantiated by evidence garnered from organ donor-derived glioblastoma in transplant recipients on chronic immunosuppression to prevent organ rejection [9,70,71].

Routes of dissemination have been described for metastatic glioblastoma, including direct dissemination, hematogenous spread and lymphatic meningeal spread, [3,9,19]. Hematogenous spread was the most likely route of dissemination for metastases to her lungs on several bases. First, the lung is the most common site for glioblastoma dissemination [18]. Second, glioblastoma is an infiltrative tumor that can breach the blood–brain barrier, which may allow for vascular permeation of tumor cells. Third, the lungs are the first organ to receive deoxygenated blood from the brain following the heart. Based on the sequence of vascular flow from the brain to the heart and then systemic circulation, we propose the following: the tumor cells intravasated into the intracranial veins, proceeded onward to the heart, passed through the large pulmonary artery and into the tiny pulmonary capillaries where the tumor cells likely became entrapped, extravasated out and deposited into the lungs. Direct dissemination through the cerebral spinal fluid was unlikely given that evaluation of her complete spine with MRI showed no evidence of metastatic disease.

Treatment for metastatic glioblastoma is challenging and no standard treatment exists [11,72,73]. Therapeutic options gleaned from existing literature includes bevacizumab, surgery, temozolomide rechallenge, etoposide, irinotecan, procarbazine and immunotherapy [12,72,74,75]. Despite bevacizumab and lomustine, our patient developed metastatic glioblastoma to the lungs. In a similar case of metastatic glioblastoma to the lungs, Yang et al. reported a prolonged response of 27 months with combined bevacizumab and pembrolizumab [72]. The addition of pembrolizumab to bevacizumab was considered for our patient, but transport barriers from her rehabilitation facility restricted any intravenous therapy. Based on this limitation and her lack of response to bevacizumab, lenvatinib monotherapy, an oral multi-targeted tyrosine kinase inhibitor currently under investigation for glioblastoma [76–79], was initiated. A dramatic response was observed in her intracranial tumor on her follow-up post-contrast brain MRI (Figure 1O & P). For this imaging finding, we considered pseudo-response, a widely accepted imaging alteration associated with decreased vascular permeability from antiangiogenic therapy to explain this radiographic finding [80,81]. Lenvatinib has antiangiogenic, immunomodulatory and antitumor-inhibitory effects on multiple tyrosine kinase inhibitors [82,83]. However, our patient was also treated with 4 cycles of bevacizumab, a pure *VEGF* inhibitor [81], prior to lenvatinib with no apparent pseudo-response (Figure 1K–N).

Interestingly, her systemic lung disease did not demonstrate a response to lenvatinib. We speculate that her systemic glioblastoma originated from a subset of glioblastoma cells that were more aggressive than her intracranial glioblastoma. The vast differences in the histologic and molecular features of her intracranial glioblastoma compared to her sarcomatous lung glioblastoma corroborate these findings (Figure 2).

Limitations of the study include the nature of a single case report. In addition, this study is limited by short-term follow-up due to her transition to hospice. Firm conclusions cannot be drawn about the efficacy of lenvatinib given the shortened follow-up. As standard practice, we did not assess for metastatic disease at the time of initial glioblastoma diagnosis nor prior to her respiratory symptom development. It remains unknown if asymptomatic metastatic disease developed earlier in her disease course. Furthermore, we did not assess for tumor-circulating cells.

Future investigations should be directed at evaluating the potential role of genomic alterations to inform of potential metastatic risk in glioblastoma patients. Larger cohorts and longer follow-ups investigating the use of lenvatinib may impact treatment for metastatic glioblastoma. Lastly, new symptoms in a glioblastoma patient necessitate further diagnostic evaluation as early identification of metastases can expedite treatment and may improve overall survival.

4. Conclusion

Though rare, extra-neural metastases should be considered in the differential of a glioblastoma patient with new systemic symptoms. Early evidence gleaned from metastatic glioblastoma case studies suggests that genomic alterations may play a role in predicting risk for metastatic glioblastoma. Treatment options are needed for metastatic glioblastoma and novel therapies should be investigated.

Executive Summary

- Metastatic glioblastoma is a rare phenomenon.
- Risk factors for the development of metastatic glioblastoma include gliosarcoma, surgery, tumor recurrence and prolonged survival.
- Preliminary evidence suggests that genomic alterations may play a potential role in predicting the risk of metastatic glioblastoma.
- Treatment options for metastatic glioblastoma remains an unmet need.
- Lenvatinib for glioblastoma is under investigation.

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Author contributions

CA Yuen – study concept, data collection, analysis, interpretation, manuscript drafting, revision and final approval. M Pekmezci – data collection, analysis, interpretation, manuscript drafting, revision and final approval. S Bao – data collection and final approval. X-T Kong – manuscript revision and final approval.

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Competing interests disclosure

Xiao-Tang Kong, MD received honorarium from Zai Lab for invited speeches for symposiums prior to July of 2021. The authors have no other competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript apart from those disclosed.

Writing disclosure

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Ethics approval and consent to participate

Need for ethics approval was needed.

Consent for publication

Written consent was obtained.

Data availability statement

The datasets from this study are available from the corresponding author upon reasonable request.

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