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Case Report

Glioblastoma beyond the Brain: A Case Series Demonstrating Systemic Metastatic Potential

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Keywords

Glioblastoma · Extracranial metastases · Systemic dissemination · IDH-wild-type glioblastoma · Gliosarcoma · PD-L1 · *TP53* · Case series

Abstract

Introduction: Glioblastoma (GBM) is an aggressive primary brain tumor that rarely metastasizes outside the central nervous system, with reported rates of extracranial dissemination below 2%. Increasing survival and improved diagnostic capabilities may contribute to more frequent detection of this phenomenon. ***Case Presentation:*** We describe a retrospective case series of 3 consecutive patients with histopathologically confirmed IDH-wild-type GBM who developed extracranial metastases at our institution. Clinical, radiological, pathological, and molecular data were extracted from medical records. Histopathological confirmation of metastatic disease was achieved in 2 of three patients, and an independent second-opinion pathology review was obtained for 1 case. Patient 1 (55-year-old man) developed cervical lymph node metastasis within 6 months of initial resection despite *MGMT* promoter methylation; the recurrent tumor contained a primitive neuroectodermal tumor-like component, immunophenotypically supported by diffuse Ki-67 positivity (~100%) and expression of synaptophysin, chromogranin, CD56, and NSE. Patient 2 (56-year-old man) developed rapid systemic dissemination to bone, lung, liver, and the interatrial septum approximately 18 months after diagnosis; the metastatic tumor displayed mesenchymal (gliosarcoma-like) differentiation with co-expression of GFAP, SMA, and h-caldesmon, PD-L1 SP263 CPS 10/TPS 10%, retained mismatch-repair proteins, and a clinically significant *TP53* c.833C>G (p.Pro278Arg) mutation identified by NGS. Patient 3 (48-year-old woman) survived 61 months despite unfavorable molecular markers, with late leptomeningeal and multiorgan dissemination. Overall survival was 8, 22, and 61 months for patients 1, 2 and 3, respectively. ***Conclusions:*** This series illustrates three distinct biological trajectories of extracranial GBM

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dissemination and supports the concept that prolonged survival, repeated surgical interventions, and specific molecular features (mesenchymal differentiation, PD-L1 expression, *TP53* mutation) may unmask systemic metastatic potential in IDH-wild-type GBM. Clinicians should maintain a high index of suspicion for extracranial dissemination in long-term GBM survivors and in patients with atypical systemic symptoms; targeted use of whole-body 18F-FDG PET/CT and histopathological confirmation of suspicious lesions are essential for accurate diagnosis.

Introduction

Glioblastoma (GBM) is the most common and biologically aggressive primary malignant brain tumor in adults, comprising nearly half of all high-grade gliomas [1]. Despite advances in neurosurgical techniques, radiotherapy, and systemic therapies, prognosis remains poor, with median overall survival typically 14–18 months even with maximal safe resection, concurrent radiotherapy with temozolomide, and adjuvant chemotherapy [2]. This outcome reflects extensive intratumoral heterogeneity, diffuse infiltrative growth, metabolic adaptability, and marked resistance to both cytotoxic and targeted agents.

Historically, GBM has been regarded as a malignancy confined to the central nervous system (CNS). Extracranial metastases were long considered exceptional, with estimated frequencies between 0.2% and 2% [3]. However, these figures likely underestimate the true incidence due to the short survival of most patients, the absence of routine systemic imaging in clinical follow-up, and declining autopsy rates [4]. As survival improves in select patients – supported by refined surgical approaches, more precise radiotherapy delivery, antiangiogenic agents, and exploratory immunomodulatory therapies – reports of extracranial dissemination are becoming increasingly frequent [5].

The mechanisms by which GBM escapes the CNS remain incompletely understood. Surgical disruption of natural barriers may facilitate tumor cell access to systemic circulation [6]. GBM is characterized by highly invasive and migratory phenotypes [7, 8], with stem-like tumor cells contributing to resistance and dissemination [9]. Mesenchymal transition and extracellular matrix remodeling enhance invasiveness and support extraneural survival [7, 8]. Molecular determinants such as *IDH*-wild-type status, *TERT* promoter mutations, *EGFR* alterations, and mismatch-repair deficiency have been associated with highly invasive, treatment-resistant phenotypes [10]. Immunologic factors are also implicated: PD-L1 upregulation, T-cell exhaustion, corticosteroid-induced immunosuppression, and antiangiogenic therapy can create permissive conditions for tumor escape and systemic dissemination [8, 11]. The discovery of functional dural lymphatic vessels provides a plausible anatomic route for drainage of tumor cells toward cervical lymph nodes [12]. Leptomeningeal involvement may further serve as an intermediary step, as tumor cells entering the cerebrospinal fluid can potentially reach systemic circulation through arachnoid granulations and spinal outflow pathways [13].

Reported extracranial metastatic sites include bone, lung, liver, lymph nodes, mediastinum, myocardium, and soft tissues [14]. Certain histologic and molecular patterns may modify metastatic risk: primitive neuroectodermal tumor (PNET)-like components have been linked to highly aggressive behavior and a greater propensity for dissemination [15, 16], *MGMT* promoter methylation predicts response to temozolomide, but its prognostic significance may be overridden by adverse biological features, and PD-L1 expression has been associated with immune escape and metastatic potential [15, 17].

Novelty of the Present Series

Although individual reports of extracranial GBM metastasis have been published, comparative descriptions integrating modern molecular characterization (including *TP53* sequencing, PD-L1 SP263 status, and mismatch-repair assessment) with detailed clinicopathological correlation across distinct metastatic trajectories remain scarce. The present case series contributes three complementary novel observations: (i) histopathologically confirmed cervical lymph node metastasis with a PNET-like immunophenotype in a patient with *MGMT*-methylated GBM; (ii) rapid multiorgan dissemination – including the rarely reported interatrial septum – in a tumor that acquired mesenchymal (gliosarcoma-like) differentiation, PD-L1 SP263 CPS 10/TPS 10%, and a clinically significant *TP53* c.833C>G (p.Pro278Arg) mutation with independent second-opinion pathology confirmation; and (iii) late leptomeningeal and multiorgan dissemination after >5 years of survival despite the absence of favorable molecular markers. A comparative summary of previously published cases versus the present series is provided in Table 1.

Diagnostic and Methodological Framework

Imaging

Brain MRI was performed on 1.5 T or 3 T scanners and included contrast-enhanced T1-weighted, T2-weighted, FLAIR, diffusion-weighted (DWI/ADC), susceptibility-weighted (SWI), and dynamic contrast-enhanced perfusion sequences. Whole-body 18F-FDG PET/CT was performed approximately 60 min after intravenous administration of 3–4 MBq/kg of 18F-FDG. In patient 2, a complementary 18F-FET PET/CT was obtained to differentiate recurrence from radiation necrosis. Spine MRI with contrast was performed when systemic symptoms or PET/CT findings suggested osseous or leptomeningeal involvement.

Criteria for Extracranial Metastasis

A diagnosis of extracranial GBM metastasis required: (i) imaging evidence of a lesion outside the CNS in a patient with histopathologically confirmed IDH-wild-type GBM; (ii) histopathological confirmation of the extracranial lesion whenever feasible; and (iii) exclusion of a second primary malignancy, supported by glial-lineage immunoprofile (GFAP positivity), absence of organ-specific markers (e.g., TTF1 for primary lung carcinoma; EMA, pancytokeratin for carcinomas), and preserved IDH-wild-type status. In patient 2, an independent second-opinion review of brain and lung specimens by a US-based pathology consultation service further supported the diagnosis of metastatic GBM.

Immunohistochemistry and Molecular Analysis

IHC was performed on a Ventana BenchMark Ultra autostainer with marker panels tailored to the clinical scenario (GFAP, Olig2, S-100, synaptophysin, chromogranin, CD56, NSE, Ki-67, p53, EGFR, PTEN, INI-1, H3K27me3, SMA, h-caldesmon, desmin, MyoD1, myogenin, STAT6, HMB45, Melan-A, tyrosinase, SOX10, CD99, TLE1, FLI-1, EMA, DOG1, CD117, CD34, ERG, pancytokeratin (AE1/AE3), CK18, TTF1, vimentin, MMR proteins, and PD-L1 SP263). PD-L1 expression was reported as Tumor Proportion Score (TPS) and Combined Positive Score (CPS). In patient 2, targeted next-generation sequencing of >50 cancer-related genes (KAPA HyperPETE LC Fusion Panel/KAPA HyperChoice, Roche; Illumina NextSeq 2000) was performed on the lung metastasis. This case series adheres to the CARE 2016 guidelines; a completed CARE checklist is provided as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000553017).

Table 1. Comparative summary of previously reported extracranial GBM cases vs. the present series

Study (year)	*N*	Sites	Molecular profile reported	Key finding	Comparison with present series
Beauchesne et al. [3] (2011)	~30 (review)	Bone, lung, liver, LN	Not systematically reported	First systematic review questioning rarity of extracranial GBM	Provides historical baseline (<2%); our series adds molecular detail (TP53, PD-L1, MMR, H3K27me3)
Lun et al. [4] (2011)	109 (review)	Bone, lung, LN, liver	Limited (IDH/MGMT in subset)	Natural history; ~6 months median OS after metastasis	Confirms aggressive course; our patient 2 illustrates similar trajectory with modern molecular workup
Pietschmann et al. [5] (2015)	88 (IPD meta-analysis)	Multiple	IDH-wt majority; MGMT variable	Identified prognostic factors after extracranial metastasis	Our series adds NGS-confirmed TP53 mutation and PD-L1 SP263 quantification
Ray et al. (2015) [14]	Review	All sites	Mostly IDH-wt; rare PNET-like	Cataloged reported metastatic sites and proposed mechanisms	We provide histopathologically confirmed PNET-like cervical LN metastasis (patient 1) and gliosarcoma-like lung metastasis (patient 2)
Present series (patients 1–3)	3	Cervical LN; bone/lung/liver/heart; LM+multiorgan	IDH-wt all; MGMT-methylated (1), unmethylated (2, 3); PNET-like IHC (1); GFAP+/SMA+/h-caldesmon+ + PD-L1 SP263 CPS 10/TPS 10 + TP53 c.833C>G (2); expanded markers not available (3)	3 distinct metastatic trajectories (early PNET-like nodal; rapid multiorgan mesenchymal; late LM+systemic in long-term survivor)	–

Case Presentations

Case 1: Cervical Lymph Node Metastasis following Multiple Resections

A 55-year-old man presented with new-onset seizures, and brain MRI demonstrated a right temporoparietal mass. He underwent gross total resection, and histopathology confirmed WHO grade IV, IDH-wild-type GBM. The patient declined adjuvant chemoradiotherapy. Two months later, local recurrence was detected and a second craniotomy was performed. A third resection within 6 months of diagnosis demonstrated GBM with a prominent PNET-like component. MGMT promoter methylation was detected.

During radiotherapy planning, right-sided cervical lymphadenopathy was identified. Core needle biopsy of the lymph node revealed extensively necrotic tumor tissue with viable neoplastic cells; immunohistochemistry demonstrated tumor cell expression of GFAP (single

cells), focal weak pancytokeratin, synaptophysin (single cells, weak), chromogranin (single cells, weak), CD56, NSE, CK18 (focal weak) and INI-1 (retained nuclear expression), with a Ki-67 labeling index of approximately 100% in the viable component. EMA, vimentin, S-100, and TTF1 were negative. This immunophenotype was considered consistent with the PNET-like component of GBM, supporting metastatic dissemination of the primary brain tumor rather than a second primary neoplasm.

The patient subsequently underwent focal chemoradiotherapy (60 Gy in 30 fractions; concurrent temozolomide 75 mg/m^2/day during radiotherapy) to the postoperative cavity and involved cervical lymph nodes but was later lost to follow-up. Overall survival from initial diagnosis was approximately 8 months.

Despite the presence of *MGMT* promoter methylation – typically associated with more favorable prognosis and improved response to temozolomide – this patient experienced early disease progression and developed extracranial metastases within 6 months. The PNET-like component, known to correlate with highly aggressive and metastatic tumor behavior and immunophenotypically confirmed on the cervical lymph node biopsy, may have counteracted the prognostic advantage of MGMT methylation and contributed to early systemic dissemination [14, 16].

Case 2: Rapid Systemic Dissemination with PD-L1 Positivity and Acquired Mesenchymal Differentiation

A 56-year-old man underwent microsurgical resection of a left parietal mass; histopathology confirmed WHO grade IV, IDH-wild-type GBM with 1p/19q co-deletion not detected, *MGMT*-unmethylated, p53 positivity in approximately 90% of tumor cells, and a Ki-67 labeling index of 70%. He received concurrent chemoradiotherapy (60 Gy in 30 fractions with concurrent temozolomide) followed by 6 adjuvant cycles of temozolomide (days 1–5 of a 28-day cycle).

Approximately 1 year after initial diagnosis, follow-up imaging demonstrated tumor recurrence (confirmed by 18F-FET PET/CT), and a second resection was performed. The recurrent tumor was IDH-wild-type with diffuse GFAP, EGFR and p53 expression, PTEN loss, and a Ki-67 index of 45%. The patient subsequently received re-irradiation to the postoperative cavity (45 Gy in 25 fractions). Within 3 months, he developed progressive back pain and sensory deficits.

Spine MRI and whole-body 18F-FDG PET/CT (Fig. 1) revealed widespread metastatic disease involving the thoracic spine, both lungs, the interatrial septum, and the liver. Stereotactic body radiotherapy (SBRT; 30 Gy in 5 fractions of 6 Gy) was delivered to the T3–T5 vertebral region with symptomatic improvement. Progressive intracranial disease was treated with stereotactic radiosurgery (20 Gy in 5 fractions of 4 Gy, with a simultaneous integrated boost of 25 Gy in 5 fractions of 5 Gy).

CT-guided transthoracic lung biopsy (Fig. 2) revealed a hypercellular spindle-cell neoplasm with marked atypia, brisk mitotic activity (8 mitoses per mm^2) and coagulative necrosis. Tumor cells showed diffuse strong GFAP, SMA, and h-caldesmon positivity with weak membranous CD99, while Olig2, S-100, synaptophysin, pancytokeratin, EMA, TTF1, and a broad sarcoma/melanoma panel were negative. INI-1 and H3K27me3 were retained, and all 4 mismatch-repair proteins (MLH1, PMS2, MSH2, MSH6) were retained. PD-L1 (SP263) demonstrated CPS 10 and TPS 10%. These findings were consistent with metastatic GBM exhibiting mesenchymal (gliosarcoma-like) differentiation, confirmed by an independent second-opinion review (American Society of Telepathology). Targeted next-generation sequencing on the lung metastasis identified a clinically significant *TP53* c.833C>G (p.Pro278Arg) somatic variant. Overall survival from initial diagnosis was approximately 22 months.

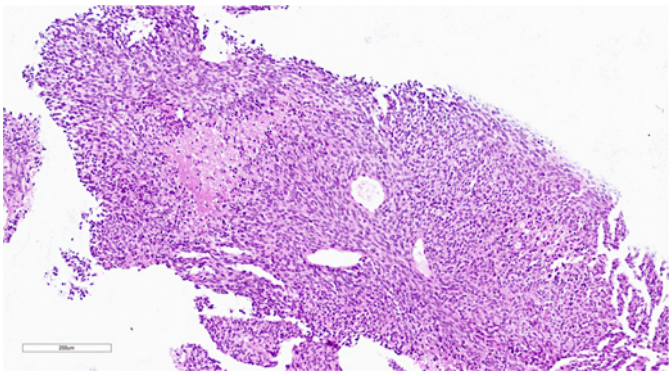

Fig. 1. 18F-FDG PET/CT (patient 2) demonstrating widespread systemic metastases. Maximum-intensity projection (MIP) and selected fused axial slices show hypermetabolic lesions involving the thoracic spine (T3–T5), both lungs, the interatrial septum, and the liver, consistent with disseminated extracranial disease. The T3 vertebral lesion corresponds to the site subsequently treated with SBRT (30 Gy in 5 fractions). Annotations: yellow arrows indicate osseous metastases; red arrows indicate pulmonary metastases; blue arrow indicates the interatrial septal lesion; green arrow indicates the hepatic lesion.

This case illustrates aggressive systemic dissemination in an IDH-wild-type, *MGMT*-unmethylated tumor that acquired mesenchymal differentiation, with co-occurrence of PD-L1 positivity and *TP53* mutation in the metastatic compartment. The mesenchymal/gliosarcoma-like immunophenotype (GFAP+/SMA+/h-caldesmon+) is consistent with literature suggesting that mesenchymal transition predisposes to extraneural metastasis, while PD-L1 positivity supports an immunoevasive microenvironment that may have facilitated both local recurrence and distant spread [14, 16, 18].

Case 3: Long-Term Survival Followed by Late Systemic Dissemination

A 48-year-old woman underwent resection of a right frontal tumor; histopathology identified WHO grade IV, IDH-wild-type, *MGMT*-unmethylated GBM. Expanded molecular profiling (*TERT* promoter mutation status, *EGFR* amplification, ATRX status, and quantitative Ki-67) was not performed at the time of initial diagnosis and could not be retrospectively retrieved. She received concurrent chemoradiotherapy (60 Gy in 30 fractions with concurrent oral temozolomide 75 mg/m^2/day, in accordance with the Stupp protocol) and 2 cycles of adjuvant temozolomide (150 mg/m^2/day on days 1–5 of a 28-day cycle) that were discontinued due to grade 4 hematologic toxicity (thrombocytopenia). Five months later, radionecrosis required reoperation. She subsequently received bevacizumab at the standard recurrent-GBM dose (10 mg/kg intravenously every 2 weeks) for approximately 2.5 years.

Approximately 3 years after diagnosis, she developed respiratory failure secondary to leptomeningeal dissemination and required prolonged inpatient supportive management. Subsequent imaging revealed osseous metastases involving T1–T2 vertebrae and lesions in the lungs, mediastinum, and left atrium. She died of multiorgan failure. Overall survival from initial diagnosis to death was approximately 61 months.

Despite the absence of favorable molecular markers (MGMT-unmethylated), this patient experienced unusually long survival exceeding 5 years. The eventual development of leptomeningeal involvement and multiorgan metastases supports the hypothesis that prolonged survival may unmask rare metastatic patterns in GBM that would otherwise remain clinically undetected.

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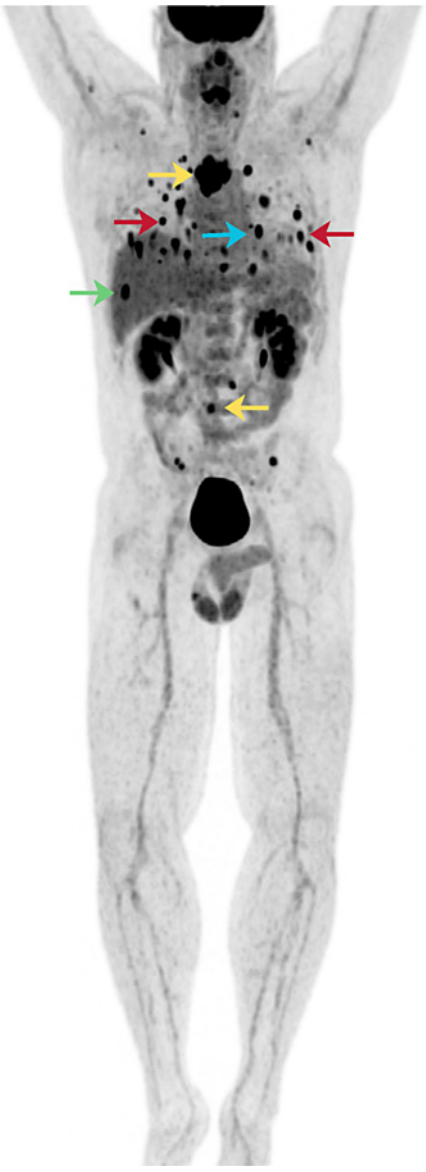

Fig. 2. Histopathological confirmation of extracranial GBM metastasis in the lung (patient 2; CT-guided transthoracic core biopsy). Hematoxylin and eosin stain, original magnification ×200 (scale bar 100 μm). The image shows a densely cellular spindle-cell neoplasm composed of atypical glial cells with pleomorphic, hyperchromatic nuclei, brisk mitotic activity (8 mitoses per mm^2) and areas of coagulative necrosis.

Overall survival from initial diagnosis to death was 8 months (patient 1), 22 months (patient 2), and 61 months (patient 3), illustrating the marked heterogeneity of disease course and outcomes observed in this series. The clinical event timelines for all 3 patients are presented in Table 2.

Discussion

The traditional view of GBM as a strictly intracranial malignancy has been challenged by increasing reports of extracranial dissemination [3, 19]. Our series of 3 cases contributes to this evolving understanding, offering clinico-pathological insights into a rare but clinically meaningful pattern of disease spread.

Table 2. Clinical event timelines for patients 1–3

Milestone (months from diagnosis)	Patient 1	Patient 2	Patient 3
Demographics; tumor molecular profile	55-year-old male; IDH-wt, MGMT-methylated; PNET-like component on third resection	56-year-old male; IDH-wt, 1p/19q intact, MGMT-unmethylated; p53 90%, Ki-67 70%	48-year-old female; IDH-wt, MGMT-unmethylated; expanded markers not available
Initial diagnosis and first surgery (month 0)	Right temporoparietal mass; gross total resection; chemoradiotherapy declined	Left parietal mass; microsurgical resection	Right frontal tumor; resection
Concurrent chemoradiotherapy	Not performed initially (declined)	60 Gy in 30 fractions + concurrent temozolomide (months ~1–3)	60 Gy in 30 fractions + concurrent temozolomide 75 mg/m^2 (Stupp protocol)
Adjuvant temozolomide	Not given	Six cycles (5 days every 28 days), months ~3–8	Two cycles (150 mg/m^2, days 1–5/28 d); discontinued, grade 4 thrombocytopenia
Repeat surgery/re-treatment	Two further craniotomies within 6 months (months 2 and 6); third resection confirmed PNET-like component	Second resection at ~month 13 (PTEN loss, EGFR+, Ki-67 45%); re-irradiation 45 Gy/25 fractions (~months 14–15)	Reoperation for radionecrosis at month 5
Antiangiogenic therapy	Not given	Not given (recurrent disease treated with re-RT)	Bevacizumab 10 mg/kg q2w, months ~7–37 (~2.5 years)
Recognition of extracranial dissemination	Cervical lymph node metastasis identified at month 6 during radiotherapy planning	Multiorgan dissemination identified at month ~18 (T3–T11 spine, lung, liver, interatrial septum)	Leptomeningeal dissemination at month ~36 (respiratory failure); subsequent T1–T2 bone, lung, mediastinum, left atrium lesions
Palliative interventions	Focal chemoradiotherapy 60 Gy/30 Fr + concurrent TMZ to the resection cavity and involved cervical lymph nodes	SBRT to T3–T5 (30 Gy in 5 fractions of 6 Gy); SRS to brain metastases (20 Gy in 5 fractions + SIB 25 Gy/5 fractions)	Inpatient supportive management
Outcome (overall survival)	Death at month 8 (OS 8 months)	Death at month 22 (OS 22 months)	Death from multiorgan failure at month 61 (OS 61 months)

Case-Specific Mechanistic Interpretation

Each patient in our series illustrates a distinct putative mechanism of extracranial spread, allowing case-specific linkage to the biology of GBM rather than purely generic discussion of dissemination routes.

Patient 1 – Surgical Disruption and PNET-Like Differentiation

This patient underwent 3 consecutive craniotomies within 6 months. Repeated surgical disruption of the blood-brain barrier and of the dural lymphatic vessels in the surgical bed provides a plausible anatomic route for tumor cell drainage into cervical lymph nodes

Table 3. Proposed mechanisms of extracranial dissemination illustrated by the three cases

Patient	Proposed mechanism	Key molecular and pathological features	Metastatic sites
1	Surgical disruption of dural lymphatic drainage with PNET-like differentiation overriding MGMT methylation prognostic advantage	≥3 craniotomies within 6 months; IDH-wt, MGMT-methylated; PNET-like component (Syn+, Chrom+, CD56+, NSE+, GFAP single cells+, Ki-67 ~100%, INI-1 retained); EMA, vimentin, S-100, TTF1-negative	Cervical lymph nodes
2	Mesenchymal (gliosarcoma-like) transition combined with PD-L1-mediated immune escape and TP53 mutation in the metastatic compartment	IDH-wt, MGMT-unmethylated, p53 90%, Ki-67 70% (primary); recurrence EGFR+, PTEN loss, Ki-67 45%; lung metastasis GFAP+/SMA+/h-caldesmon+, Olig2–, INI-1 and H3K27me3 retained, MMR retained, PD-L1 SP263 CPS 10/TPS 10%, TP53 c.833C>G (p.Pro278Arg) somatic variant	Thoracic vertebrae (T3–T11), bilateral lungs, liver, interatrial septum
3	Leptomeningeal dissemination via cerebrospinal fluid outflow pathways unmasked by prolonged survival under multimodal therapy including extended bevacizumab	IDH-wt, MGMT-unmethylated; bevacizumab ~2.5 years; expanded molecular profiling not available (acknowledged in section 4.5)	Leptomeningeal compartment; thoracic vertebrae (T1–T2), lungs, mediastinum, left atrium

[6, 11]. The detection of a PNET-like component on the third resection, immunophenotypically supported on the cervical LN biopsy by co-expression of synaptophysin, chromogranin, CD56, NSE, and GFAP with ~100% Ki-67, is consistent with an aggressive, primitive-neuronal-like phenotype with documented metastatic propensity [14, 16]. The presence of MGMT methylation in this case underscores that PNET-like differentiation can override otherwise favorable molecular predictors.

Patient 2 – Immune Evasion and Mesenchymal/Gliosarcoma-Like Transition

The metastatic lung specimen demonstrated 3 biologically convergent features: acquired mesenchymal differentiation (GFAP+/SMA+/h-caldesmon+), PD-L1 SP263 expression (CPS 10/TPS 10%), and a clinically significant *TP53* c.833C>G (p.Pro278Arg) somatic mutation. Mesenchymal transition is known to facilitate invasion and extravasation, while PD-L1 upregulation has been implicated in T-cell exhaustion and immune escape in GBM [11, 15, 17]. Together, these features support a model in which mesenchymal-immune cross-talk created permissive conditions for hematogenous and lymphatic dissemination to bone, lung, liver and the interatrial septum – the latter being a rarely reported metastatic site.

Patient 3 – Prolonged Survival and Leptomeningeal Dissemination

Despite unfavorable molecular markers, this patient survived 61 months with multimodal treatment including prolonged bevacizumab maintenance. Late development of leptomeningeal dissemination provides a plausible pathway for systemic spread via

cerebrospinal fluid outflow [13], and the bone, mediastinal, pulmonary, and left atrial deposits are consistent with a late-stage permissive systemic environment unmasked by extended survival. Table 3 summarizes the proposed mechanisms across the 3 patients.

Molecular Profiling and Metastatic Potential

Under the 2021 WHO Classification of CNS tumors (CNS5), comprehensive molecular characterization (*IDH*, *TERT* promoter, *EGFR* amplification, +7/−10 status, *CDKN2A/B* deletion, ATRX, *TP53*, Ki-67) is required for formal subtype assignment [20]. *TP53* mutations are common in IDH-wild-type GBM and have been linked to mesenchymal subtype and aggressive behavior – features that converge in patient 2 and most closely associate with extraneural dissemination [10]. The remaining markers were not uniformly available in our series, restricting formal subtype assignment in patients 1 and 3.

Practical Clinical Recommendations

When to Suspect

Clinicians should suspect extracranial dissemination in long-term GBM survivors who present with atypical systemic symptoms (bone pain, dyspnea, hepatic or cardiac findings, unexplained lymphadenopathy), particularly after multiple resections, or with high-risk molecular features (PD-L1 positivity, PNET-like or mesenchymal differentiation).

Imaging and Biopsy

Whole-body ^{18}F-FDG PET/CT with image-guided tissue confirmation should be performed whenever feasible; pathology workup should include a glial-lineage immunoprofile combined with markers excluding common primary mimics, complemented by targeted NGS and PD-L1 SP263 when clinically actionable.

Therapeutic Considerations

Therapeutic approaches in our cases were primarily palliative. SBRT to spinal metastases produced meaningful symptomatic relief in patient 2, consistent with its established role in osseous oligometastases [21]. Bevacizumab and experimental immunotherapies offered transient stabilization but did not prevent eventual widespread dissemination, in line with published findings demonstrating improved progression-free but not overall survival with bevacizumab in GBM [22]. The uniformly fatal outcomes highlight the unmet need for systemic strategies – including immune-checkpoint blockade in PD-L1-positive disease – although prospective evidence in GBM remains limited [11, 19].

Limitations

This series is limited by its retrospective nature and small sample size. Comprehensive molecular profiling was uneven across cases – most complete in Patient 2 (NGS, PD-L1, MMR, H3K27me3), limited by necrosis in patient 1, and not feasible retrospectively in patient 3 – which restricts formal WHO CNS5 subtype assignment. Histopathological confirmation of all metastatic deposits was not possible (notably in patient 3), postmortem autopsy data were unavailable, and the patient perspective could only be partially captured retrospectively.

Future Directions

Future progress will depend on multi-institutional registries and prospective data collection. Routine systemic surveillance in long-term survivors, integration of cerebrospinal fluid-based liquid biopsy, and comprehensive molecular profiling at recurrence and

metastasis may enable earlier recognition of extracranial disease. Studies investigating systemic immunotherapy – particularly in cases with PD-L1 expression or leptomeningeal dissemination – represent a promising frontier for improving outcomes [17, 23–25].

Conclusions

Although extracranial metastasis of GBM remains rare, it is being reported with increasing frequency in patients who experience prolonged survival and receive aggressive multimodal therapy. This case series adds to the expanding evidence that GBM can, under specific biological and clinical conditions, transcend the confines of the CNS. Three biologically distinct trajectories – early PNET-like nodal dissemination, rapid multiorgan mesenchymal/PD-L1-positive spread with *TP53* mutation, and late leptomeningeal/systemic dissemination in a long-term survivor – illustrate the heterogeneous metastatic potential of IDH-wild-type GBM. Clinicians should maintain a high index of suspicion for atypical systemic symptoms in long-term survivors, and pathologists should consider extended IHC and molecular panels in suspected metastatic specimens. Continued research into the molecular and immunologic mechanisms driving systemic dissemination – and the development of targeted therapeutic strategies – remains an urgent priority [18, 23–25].

Statement of Ethics

This study was conducted in accordance with the principles of the Declaration of Helsinki. According to institutional regulations, Ethics Committee approval was not required for this retrospective case series. Written and informed consent was obtained from each patient or their legal representatives for publication of the details of their medical cases and any accompanying images.

Conflict of Interest Statement

The authors have no relevant financial or nonfinancial interests to disclose.

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Author Contributions

N.S., K.T., I.L., and M.T. contributed to the study conception and design. The first draft of the manuscript was written by K.T. and I.L. Images and pathology review were prepared by M.T. The final revised version of the manuscript was prepared by K.T., incorporating all reviewer comments. All authors commented on previous versions and read and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to patient privacy and institutional regulations but are available from the corresponding author upon reasonable request.

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