



Case report

Gliosarcoma with osteosarcomatous component: A case report and short review illustration



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ABSTRACT

Background: Gliosarcoma (GS) represents a rare variant of glioblastoma in the central nervous system, characterized by biphasic histopathological features of gliomatous and sarcomatous components. Here, we present an unusual case of GS, which also demonstrated osteosarcomatous differentiation.

Case presentation: A 65-year-old female patient underwent gross total resection (GTR) of the right temporal lobe lesion. Subsequently received 60 Gy external beam radiation therapy and chemotherapy. Postoperative histopathological analysis indicated that the sarcomatous portion of the typical fibrosarcoma pattern mingled with areas of osteoid structure. The molecular pathological analysis demonstrated IDH1/2 wild-type and MGMT promoter island methylated phenotype. Target Enrichment Sequencing (TES) was performed on the gliomatous and sarcomatous components of the tumor tissues. TERT promoter, RB1, NF1, TP53 mutations and copy number variations (CNVs) on chromosome 7, 10q, 11q, 12, 13, 17 and 22 were observed in gliomatous and fibrosarcomatous mixed tumor tissue; While we found TERT promoter, RB1, TP53 mutations and CNVs on chromosome 2q, 3q, 7, 8, 9, 10, 11, 12, 13, 15, 16, 17, 18, 19 and 22 in osteosarcomatous component. Noteworthy, EGFR amplification was not observed in both gliomatous/fibro-sarcomatous and osteosarcomatous components.

Conclusions: Integrated with histopathology, molecular pathology, and genomic alteration analysis, we report a case of GS with an extremely rare histopathologic phenotype of osteosarcomatous differentiation, who also suffered lung multi-metastases. Additionally, synthesizing the literature review, our study of this unusual differentiation of GS into osteosarcoma may provide novel insight into the natural history of GS.

1. Background

Gliosarcoma (GS) represents a rare type of malignant neoplasm in the central nervous system (CNS) [1], comprising both gliomatous and sarcomatous components. In 2016 WHO classification of tumors of CNS, GS was defined as a subtype of IDH wild-type glioblastoma multiforme (GBM) [2]; While GS was not listed in the 2021 WHO classification, but referred to as a classic variant of GBM [3]. GS was originally described

by Stroebe in 1895. And in 1955, Feigin [4] defined GS as a variant of GBM, characterized by a neoplastic transformation in the proliferating vessels. Hence, we sometimes referred to GS as “Feigin’s tumor”. It was estimated that GS accounted for approximately 2% of GBM [5,6].

The gliomatous component in GS usually exhibits a typical feature of glioblastoma, or occasionally shows oligodendroglial characteristics [7, 8]. While sarcomatous component is most frequently represented by a fibrosarcoma. However, other patterns resembling angiosarcoma [9],

Abbreviations: GS, Gliosarcoma; GTR, Gross total resection; TES, Target Enrichment Sequencing; CNVs, Copy number variations; CNS, Central nervous system; GBM, Glioblastoma multiforme; pGS, Primary GS; sGS, Secondary GS; MRI, Magnetic resonance imaging; CT, Computed tomography; TKI, Tyrosine kinase inhibitor; SATB2, Special AT-rich sequence-binding protein 2; MSP, Methylation-Specific PCR; LOH, Loss of heterozygosity; TMB, Tumor mutation burden; EMT, epithelial to mesenchymal transition.

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rhabdomyosarcoma [10], or pleomorphic sarcoma [11] can also be encountered. Cases of GS with osteosarcomatous components are extremely rare. To date, only quite a few cases of GS consisting of osteosarcomatous differentiated components have been reported, previously [1,12–18]. This specific type of GS can be divided into two subtypes: primary GS (pGS) and secondary GS (sGS). The pGS with osteosarcomatous component was de novo, and the diagnosis was confirmed after the initial operation [1,12,19–21]. Additionally, there was no history of radiotherapy and no history of another organ osteosarcoma. While the sGS with osteosarcomatous component always shared a history of external beam radiation therapy after intracranial malignant neoplasm surgery [16,18]. It was speculated that the osteosarcomatous component might arise as a radiation-induced malignance transformation, which was consistent with previous reports, post-irradiation GS accounted for a considerable proportion of total GS [6,15].

In this article, we report a case of GS with osteosarcomatous component. Due to the exceeding rare incidence of this type of mesenchymal differentiation in GS, we conducted a comprehensive analysis of this case, by integrating conventional histopathology, molecular pathology, and Target Enrichment Sequencing (TES) data. Furthermore, a thorough literature review was performed to deep insight into the etiology and pathological characteristics of GS with this specific mesenchymal component.

1.1. Case presentation

A 65-year-old female patient with a history of more than 10 days

holo-cranial headache, drowsiness, gait imbalance, muscle power weakness of left limbs, and other neurological deficits were excluded. T2 weighted magnetic resonance imaging (MRI) of the brain revealed a massive inhomogeneous lesion located in the right temporal lobe, measuring $4.8 \times 3.6 \times 4.3$ cm in dimension, with extensive peri-tumoral edema extending up to parietal cortex (Fig. 1A, B). Contrast-enhanced MRI exhibited a right temporal lobe irregular rosette enhancing mass (Fig. 1C, D). Computed tomography (CT) scan revealed scattered calcific density lesions abutting right middle skull base (Fig. 1E).

We operated upon the patient after the full preoperative planning, and postoperative MRI revealed that the tumor was totally resected (Fig. 2A, B). During the surgery, it was observed that the bulk of intratemporal lobe tumor tissue was very similar to gliomatous tissue with invasive growth, and abundant blood supply under the surgical microscope. But nearly 1/3 of the tumor tissue abutting the middle cranial fossa dura was hard, well-demarcated, and closely adhere to the dura mater, resembling meningiomas (Fig. 1F). The patient was given a course of external beam radiation therapy with a total of 60 Gy, subsequently. Reviewed MR scan 11 months after the surgery, enhanced-T1 weighted imaging showed novel nodular enhancements bordering on right middle cranial fossa dura (Fig. 2C), which was consistent with tumor recurrence. CT imaging revealed calcific density lesions located in the recurrent area (Fig. 2E). Subsequent sequential or alternating administrated temozolomide, Anlotinib (tyrosine kinase inhibitor, TKI), and Camrelizumab (a PD-1 inhibitor). A reviewed MR scan 2 months after the novel protocol implementation revealed that the gross tumor volume (GTV) of the recurrent tumor regressed significantly (Fig. 2D). However, calcific lesions showed poor response for novel adjuvant

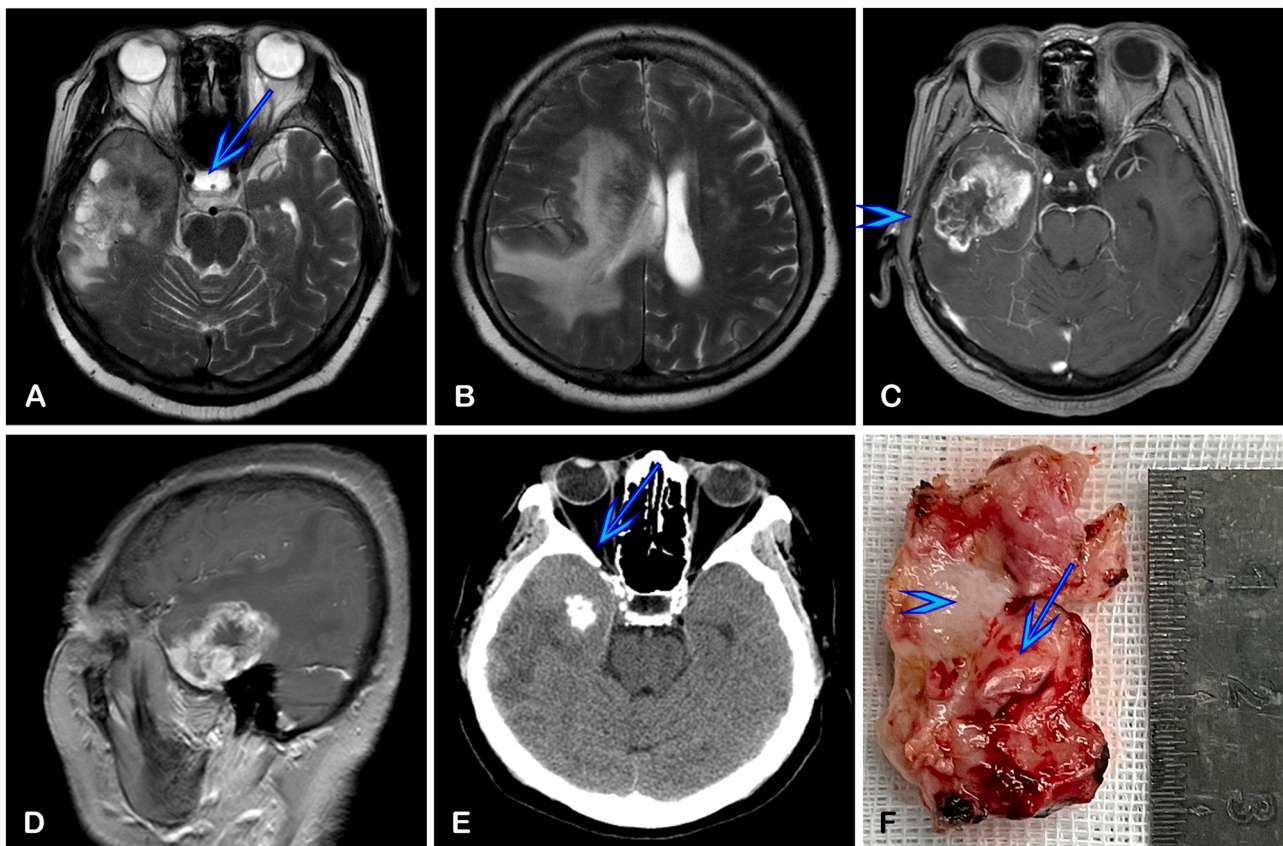


Fig. 1. Preoperative neuroradiological and intraoperative images. (A, B) T2-weighted MRI revealed an inhomogeneous lesion in the right temporal lobe, with extensive peri-tumoral edema extending up to frontal-parietal lobe; (C, D) Enhanced T1-weighted MR images irregular rosette enhancing mass; (E) Plain CT (axial) showed patchy-calcified lesions in right temporal lobe; (F) The excised tumor tissue image revealed calcified component (firm tumor tissue) and soft tumor tissue. The blue arrow represents calcified lesion, and the blue arrowhead represents soft tumor tissue. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

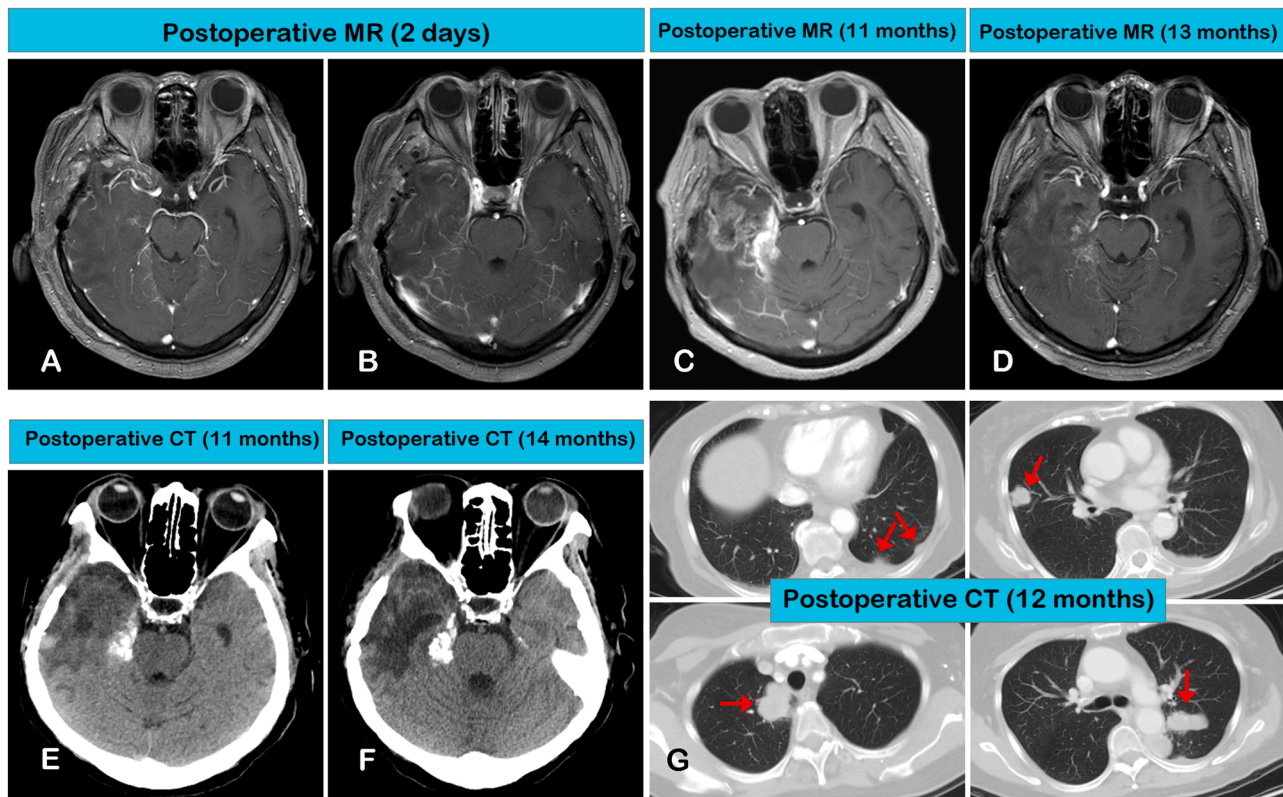


Fig. 2. Postoperative radiological images. (A, B) Enhanced T1-weighted MR images revealed that the tumor was grossly resected 2 days after the craniotomy; (C) Enhanced T1-weighted imaging showed a recurrent tumor occupying the tumor-resected cavity 11 months after the craniotomy; (D) MR imaging indicated the recurrent tumor was significantly regressed 2 months after the novel adjuvant therapy; (E) CT scanning revealed calcified lesion mixed in intracranial recurrent tumor 11 months after the surgery; (F) Reviewed CT image indicated that calcified lesion from recurrent tumor showed poor response to novel adjuvant therapy; (G) Chest CT scanning revealed multi-lesions scattered in the pleura and lung of bilateral sides (Red arrows). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

therapy regimens, following CT scanning indicated a gradually enlarged volume of recurrent calcification (Fig. 2F). However, the patient faced a new challenge, simultaneously. The chest CT scanning revealed multiple lesions scattered in the lung of bilateral sides with regular morphology, which is consistent with the radiology characteristics of metastases (Fig. 2G).

The tumor tissues were subjected to histo- and molecular pathological examination. Histopathological examination of the bulk of tumor tissue revealed a biphasic histologic pattern, which displayed both gliomatous and fibro-sarcomatous components (Fig. 3A). Immunohistochemical analysis indicated specific expression of GFAP in gliomatous component (Fig. 3B), high expression of mesenchymal cells marker Vimentin in fibro-sarcomatous component (Fig. 3C), and approximately 40% of Ki-67 positive rate in whole tumor tissue (Fig. 3D). However, histopathological analysis of the calcific lesions scattered inside the bulk of the tumor observed osteoid structure (Fig. 3E). Immunohistochemical analysis of this component presented reactivity with Vimentin and Special AT-rich sequence-binding protein 2 (SATB2, a marker of osteosarcoma) (Figure F, G), and GFAP expression was excluded. Additionally, P53 was expressed positively in this region (Fig. 3H). Molecular pathological analysis verified IDH1/2 wild-type in both gliomatous/fibro-sarcomatous and osteosarcomatous components of the tumor, and MGMT promoter island methylated (Method: Methylation-Specific PCR, MSP) (Fig. 4A). However, further comparative analysis of the TES (Method: 638 genes panel) (Platform: Illumina Novaseq 6000) data from gliomatous/fibro-sarcomatous and osteosarcomatous components of fresh tumor tissue was summarized in Table 1. We found that somatic mutations of the gliomatous/fibro-sarcomatous component occurred in TERT promoter (c.-146 C>T), RB1, TP53, and NF1. While TERT

promoter (c.-146 C>T), RB1, and TP53 somatic mutations were also observed in the osteosarcomatous component, except for NF1. Copy number variation (CNV) analysis of the gliomatous/fibro-sarcomatous component implied that gain on chromosome 7, losses on chromosomes 11q, 12, 13 (RB1), and 22 (NF2), and copy neutral loss of heterozygosity (LOH) on chromosomes 10q and 17. However, CNVs were more frequent in the osteosarcomatous component, involving gains on chromosomes 3q and 7, losses on chromosomes 10 (PTEN), 11, 12, 13 (RB1), and 17 (NF1 and TP53), and copy neutral LOH on chromosomes 2q, 8, 9, 15, 16, 18, 19 and 22. (Fig. 4B). Nevertheless, EGFR gene amplification was not observed, while gain on chromosome 7 occurred in both gliomatous/fibro-sarcomatous and osteosarcomatous components (Fig. 4C). Comprehensive analysis of tumor mutation burden (TMB) showed a relatively low level (1.28 mutants/Mb in gliomatous/fibro-sarcomatous component, 0.64 mutants/Mb in osteosarcomatous component).

1.2. Literature review

A retrieved result from Web of Science, PubMed, and Medline databases since 1950, with the terms gliosarcoma and osteosarcomatous/osteoid, only articles published in English with essential information of the cases were included. We collected 13 cases of GS with osteosarcomatous differentiation [1,12–19,21–23]. As exhibited in Table 2, patient information, clinical features, calcific lesions, treatments, overall survival times, and extracranial metastatic information of the cases were included.

Twelve articles and 13 cases of GS with osteosarcomatous features were included for this retrospective study. Sex distribution (Male vs.

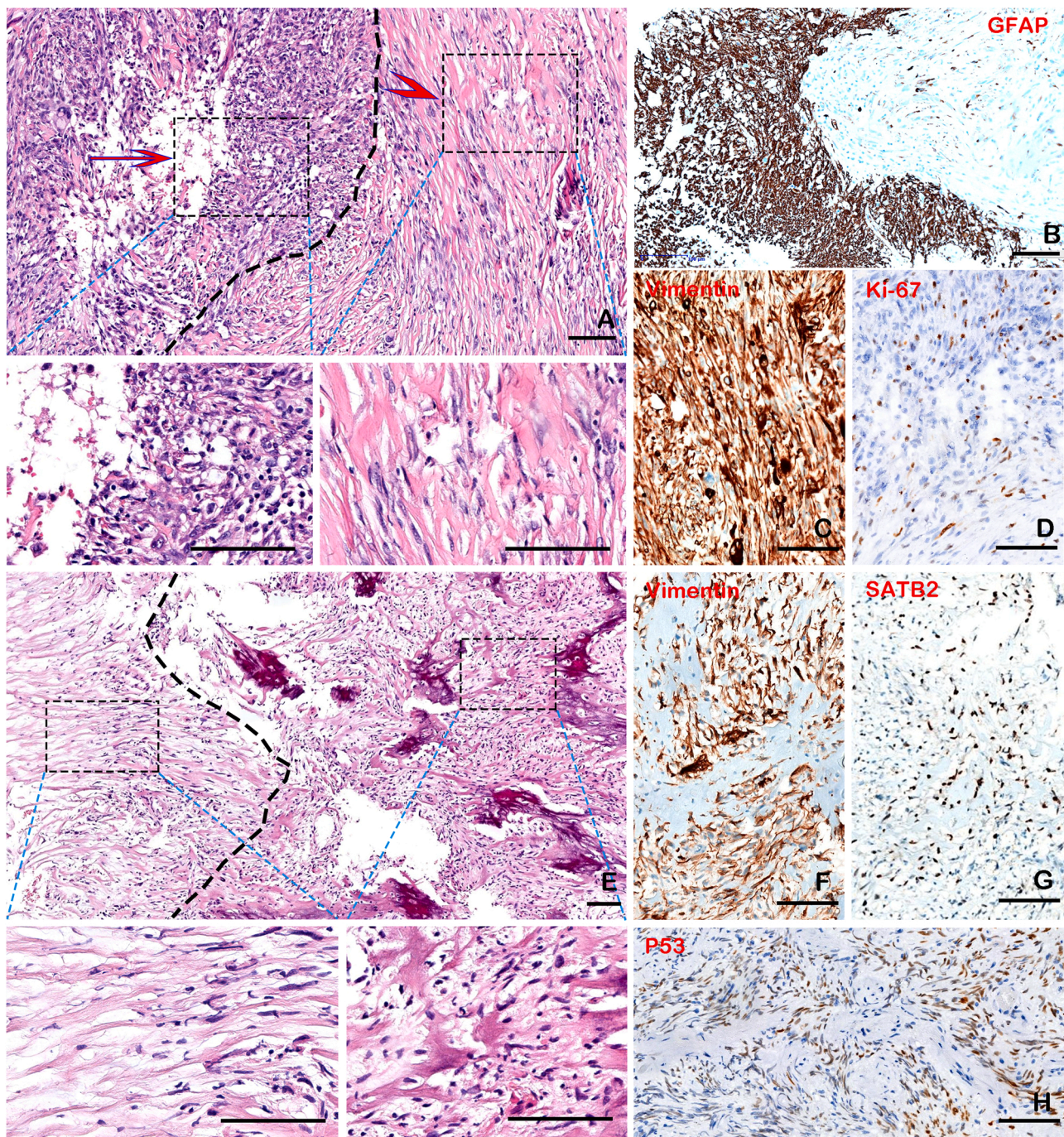


Fig. 3. Histopathological analysis of the brain tumor specimen revealed multi-components intra-tumor. (A) The black dotted line divides the H&E staining of the tumor slice into gliomatous (Red arrow) and fibro-sarcomatous (Red arrowhead) components. The lower panel is the high-resolution images of the black frames (the upper panel). (B) Immunohistochemical staining of GFAP shows specific expression in the gliomatous component. (C) Immunohistochemistry for Vimentin highlighting the fibro-sarcomatous component. (D) Ki-67 labeling index approximately 40%. (E) H&E staining of the calcified lesion shows fibro-sarcomatous and osteosarcomatous components with black dotted-line distinguished. The lower panel is the high-resolution images of the black frames (the upper panel). H&E staining of sarcomatous component showed typical neoplastic osteogenesis, with atypical spindle-shaped or irregular nuclei. (F) Vimentin staining displays mesenchymal components in calcified tumor tissue. (G) STAB2 staining shows osteosarcomatous differentiation in the calcified tumor specimen. (H) P53 staining shows positivity expression in the mesenchymal component of tumor tissue. Scale bar = 100 μ m. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Female; 8:5). The age ranged from 33 to 69 years old, with the mean age 51.85 ± 9.17 . The most common clinical presentations were headache, epilepsy, and focal neurological dysfunction, with no specific clinical manifestations. Among them, 9 pGS cases and 4 sGS cases, all 4 sGS cases arose from various intracranial malignant neoplasm and shared history of radiation therapy. Calcifications can be observed in almost all

cases of preoperative CT scans, with varying ranges. Nevertheless, histopathological analysis discovered osteosarcomatous component remains the golden criteria for diagnosing this specific type of GS. In this series of cases, only one case completed molecular pathology analysis, which demonstrated IDH1/2 wild-type and TERT promoter mutant phenotype. No extracranial metastasis of this specific type of GS was

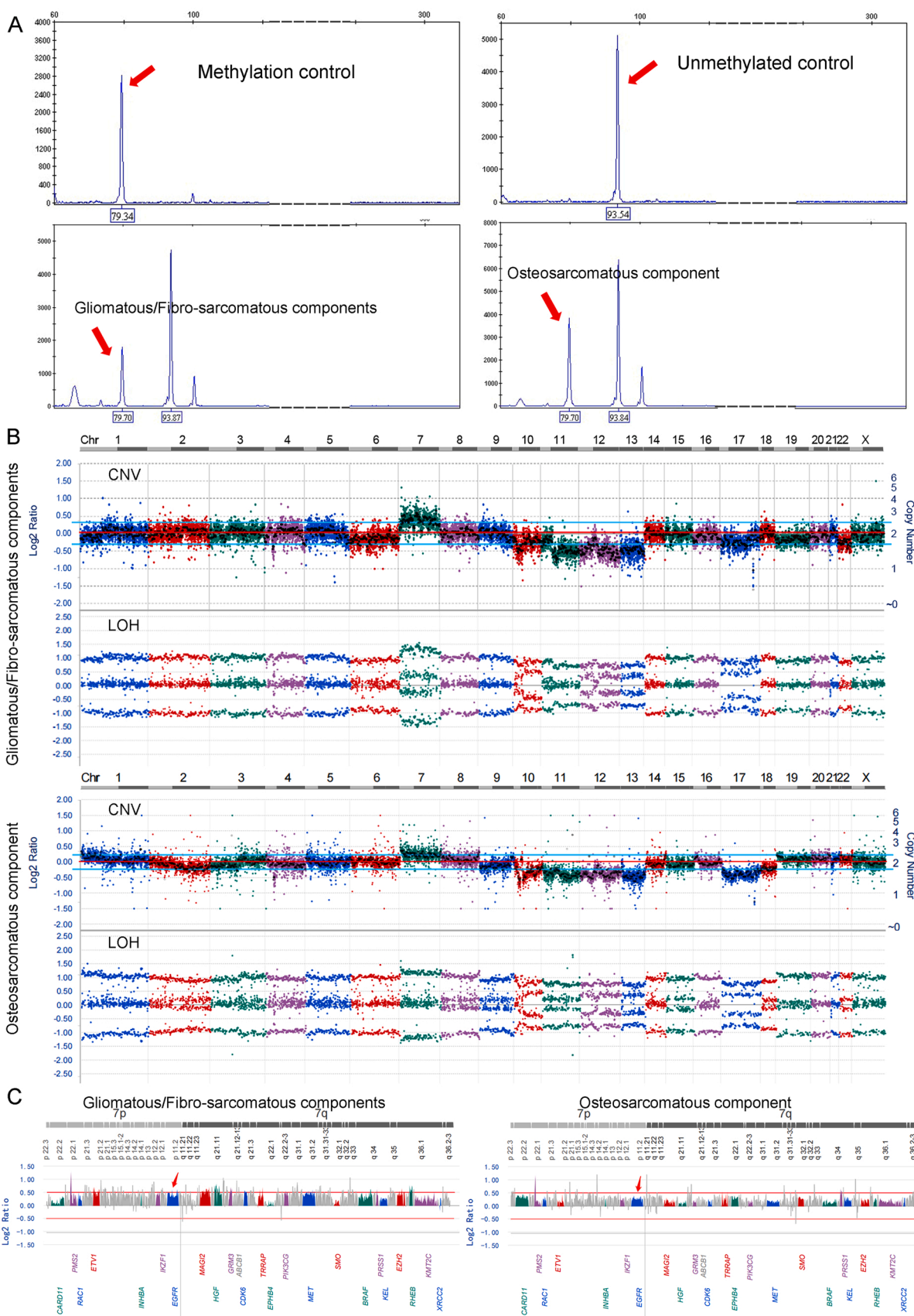


Fig. 4. Molecular pathology and genomic alteration analysis. (A) MGMT promoter island methylation was detected both in gliomatous/fibro-sarcomatous and osteosarcomatous components; (B) CNV analysis of gliomatous/fibro-sarcomatous and osteosarcomatous components, respectively; (C) EGFR (Red arrow) amplification was undetected in chromosome 7. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
Summary of the somatic alterations.

Variation	Gliomatous/fibro-sarcomatous components	Osteosarcomatous component
Mutations	TERTp, c.-146 C>T, 31%RB1, c.1049 + 1 G>A, 37.0%TP53, c.0.730 G>A, p.G244S, 53.9% NF1, c.0.3708 G>A, p.W1236X, 51.0%	TERTp, c.-146 C>T, 26.9% RB1, c.1049 + 1 G>A, 44.8% TP53, c.0.730 G>A, p.G244S, 43.0%
CNVs	Gain: chr 7Loss: chr 11q, 12, 13, 22CN-LOH: 10q, 17	Gain: chr 3q, 7Loss: chr 10, 11, 12, 13, 17CN-LOH: 2q, 8, 9, 15, 16, 18, 19, 22
TMB (muts/Mb)	1.28	0.64

Abbreviations: CNV. Copy number variation; TMB. Tumor mutation burden; muts. Mutations; Mb. Megabase; TERTp. TERT Promoter; c. Coding sequence; p. Protein; chr. Chromosome; CN-LOH. Copy neutral-Loss of heterozygosity.

reported. One case suffered extradural tumor progression with cutaneous permeation.

2. Discussion

Osteosarcomatous differentiation rarely occurs in sarcomatous component of GS. As mentioned above, only quite a few case reports can be retrieved. To date, the etiology of this specific type of GS remains unknown. Radiological calcifications of pre-operative CT scans and post-operative pathological features are helpful for diagnosing this unusual type of differentiation in GS. The GS with osteosarcomatous feature may arise from supratentorial cerebral hemispheres of various parts, usually locates in the cerebral cortex, abutting dura mater and resembling meningiomas [24,25].

Although there is no obvious difference between GS and GBM in clinical presentations, radiological features, treatment strategy, and survival outcomes. GS shares a much higher tendency of extracranial metastases than GBM [26]. The approximate occurrence of GS extracranial metastasis is 11% [27]. GS extracranial metastases are mostly located in the lungs and liver, and dissemination within neuraxis is uncommon even have been reported [25]. Although the mechanism of GS extracranial metastasis remains controversial, one assumption is that the history of craniotomy causes meningeal, skull and parenchymal blood vessel defects, which provide an opportunity for cancer cell

dissemination [26]. One vital clue is that almost all extracranial metastases of GS occurred several months after craniotomy. In this article, we present an even rarely reported GS case with osteosarcomatous feature, which also occurred distance dissemination, verifying the metastatic potential of GSs.

Apart from specific histopathological characteristics of GS, GS also inhibits numerous molecular pathological and genomic alterations. Molecular pathological classification of the case was referred to as IDH1/2 wild-type and MGMT promoter methylated. The previous report suggested that specific genomic alterations of GS might be associated with epithelial to mesenchymal transition (EMT) [28]. However, the molecular pathological characteristics of GS with osteosarcomatous differentiation were even rarely reported [13]. A cohort comparative study has noted a lower frequency of EGFR copy number amplification in GS (8%) than in GBM (up to 50%) [29]. In our presented case, we didn't observe EGFR copy number amplification in both gliomatous/fibro-sarcomatous and osteosarcomatous components by analyzing TES data, which was consistent with the molecular characteristic of GS. Moreover, TERT promoter mutation (c.-146 C>T) was observed in both gliomatous/fibro-sarcomatous and osteosarcomatous components. Oh et al. also reported that TERT promoter mutations were detected in 83% GS, and that TERT promoter mutations were detected in 19/20 glial and mesenchymal components of GS, respectively [30]. However, NF1 mutation was exclusively observed in gliomatous/fibro-sarcomatous components. NF1 is a negative regulator of the Ras signal transduction pathway and a characteristic of the Mesenchymal subtype of GBM. Dysfunction of NF1 has been shown to facilitate EMT [31]. The above-mentioned molecular pathological and genomic alterations of our presented case were consistent with the characteristics of GS, high incidence of TP53 mutation and, rarely, EGFR and IDH1/2 mutations [32]. Though TP53 mutations are widely observed in various types of malignant tumors, TP53 and RB1 gene mutations are more common in osteosarcoma [33]. Additionally, osteosarcoma is a propensity to accumulate more CNVs [34]. In this case, both TP53 and RB1 gene mutations were observed in the osteosarcomatous component, and the osteosarcomatous component suffered more CNVs than the gliomatous/fibro-sarcomatous component. All these genomic alterations are consistent with the phenotype of osteosarcoma, although none of these genomic alterations are specific.

When we discuss the origin of multi-components in GS, whether monoclonal or polyclonal origin model? Which model is predominant in the GS formation? It remains controversial. Feigin [4] hypothetically

Table 2
Literature summary of GS with osteosarcomatous component cases since 1950.

Authors (dates)	Patient information		Clinical features			Calcific lesions		Treatments	OS (months)	Mol. pathology	EM
	Age (years)	Gender	Clinical presentations	Primary GS	Location	Radiology	Macroscopy				
[12]	49	Female	Headache	Yes	Lt. Frontal	Yes	Yes	NA	NA	NA	No
[19]	56	Male	NA	Yes	Rt. Temporal	Yes	NA	NA	NA	NA	No
[23]	39	Female	NA	No	Temporal-Parietal	Yes	Yes	RT+CT	11	NA	No
[1]	55	Male	Headache/Memory disturbance	Yes	Lt. Frontal	Yes	Yes	RT+CT	12	NA	No
[14]	46	Male	Blackouts	Yes	Lt. Frontal	Yes	Yes	RT	4	NA	No
[18]	49	Male	Headache	No	Rt. Frontal	Yes	Yes	RT	24	NA	No
[17]	53	Female	Seizures	No	Lt. Parietal	Yes	Yes	RT+CT	24	NA	No
[16]	65	Female	Headache/Cognitive decline	Yes	Lt. Temporal-Occipital	NA	Yes	NA	NA	NA	No
[15]	52	Male	Headache	No	Rt. Parietal	NA	Yes	RT+CT	10	NA	No
[15]	69	Male	Gait imbalance	Yes	Rt. Frontal	NA	Yes	NA	3	NA	No
[22]	33	Female	Headache/Blurring of vision	Yes	Lt. Parietal	Yes	Yes	No	9	NA	Yes
[21]	57	Male	Dizziness/Seizures	Yes	Lt. Temporal	NA	Yes	CT	NA	NA	No
[13]	51	Male	Malaise	Yes	Rt. Frontal	NA	Yes	RT+CT	> 20	IDH1/2-WTTERT-Mut	No

Abbreviations: RT. Radiotherapy; CT. Chemotherapy; EM. Extracranial metastasis; OS. Overall survival; GS. Gliosarcoma; Mol. Molecular; NA. No available; Lt. Light; Rt. Right; WT. Wildtype; Mut. Promoter Mutant

suggested that sarcomatous component of GS might be derived from the malignant transformation of vascular proliferation, which actually represented a kind of polyclonal origin hypothesis. However, recent transcriptional and genomic studies preferred to support the monoclonal formation of GS, in which gliomatous and sarcomatous components arise from a common precursor cell clone, differentiating divergently toward gliomatous and sarcomatous subclones [13,30,35]. In our study, the TES data from gliomatous/fibro-sarcomatous and osteosarcomatous components showed high similarities in genomic alteration, which implied that gliomatous and mesenchymal components may arise from a common precursor. All the above-mentioned evidence validates the hypothesis of the monoclonal origin of GS, which may also apply to this specific type of GS with osteosarcomatous differentiation.

3. Conclusions

In conclusion, we exhibit a rare case of GS with osteosarcomatous differentiation, which includes comprehensive histopathology, molecular pathology, and genomic alteration analysis. Together with reviewed literature, our study of the unusual differentiation of GS into osteosarcoma provides novel insight into the natural history of GS and indirectly about the natural history of glioblastoma.

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of The Second Affiliated Hospital of Soochow University.

Consent for publication

Written informed consent for publication of the clinical details and clinical images was obtained from the relative of patient.

Competing interests

All authors declared no conflict of interest.

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Authors' contributions

Yanming Chen and Jun Dong designed this study. Sujuan Zhou, Xiaoxiao Dai, Ping Chen, Shengbin Zhao, Changjun Shi and Sheng Xiao were responsible for pathological diagnosis and immunohistochemical experiments. Xuelan Zhou and Liping Wang supported clinical data. Jun Dong and Ping Chen guided this work. All authors approved the final version of the submitted manuscript.

Data Availability

Not applicable.

Acknowledgements

Not applicable.

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