An *IDH1*-mutated primary gliosarcoma: case report

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The authors present the case of a primary gliosarcoma with an isocitrate dehydrogenase-1 (*IDH1*) mutation. A 75-year-old man presented with a 3-day history of multiple focal seizures and was found on MRI to have a 2.2-cm left parietal enhancing mass lesion. Brain MRI for tremor performed 8 years prior to this presentation was normal. En bloc resection revealed a high-grade glioma with sarcomatous components that was immunoreactive for the R132H variant of *IDH1* by antibody. Gliosarcoma is a rare variant of glioblastoma that arises most frequently as a primary tumor, and has equal or worse survival and an increased propensity for extracranial metastases compared with other Grade 4 gliomas. In contrast, isocitrate dehydrogenase-1 and -2 mutations are associated with low-grade gliomas with increased survival and less commonly with glioblastoma. To the authors' knowledge, there has been only 1 other published report of a primary gliosarcoma carrying an isocitrate dehydrogenase mutation. This rare genetic-histological combination highlights potential differences between glioblastoma and gliosarcoma and may warrant additional study.

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ISOCITRATE dehydrogenase-1 (*IDH1*) mutations were first identified in glioblastoma by Parsons and colleagues in 2008,³⁰ and were discovered to be particularly prevalent in younger patients and secondary glioblastomas. Notably, patients with *IDH1* mutation-positive gliomas demonstrated strikingly increased overall survival compared with those with *IDH1* wild-type tumors, a finding corroborated in 2 seminal studies^{35,41} among many others. Subsequent work has demonstrated that *IDH1* mutations occur early in tumorigenesis, preceding further genetic alterations including *TP53* loss and 1p/19q codeletion.¹⁸ *IDH1* mutations have since come to differentiate secondary glioblastoma from primary glioblastoma, the latter characterized by *IDH1* wild-type status and early phosphatase and tensin homolog loss and epidermal growth factor receptor (EGFR) amplification.¹⁴ *IDH1* mutation-positive tumors diagnosed as primary glioblastoma have been proposed to be glioblastomas that progressed rapidly from a previously undiagnosed lower-grade glioma.^{27,29}

Gliosarcoma is a relatively uncommon pathological variant of glioblastoma characterized by mixed glial and mesenchymal components. It comprises approximately 2.2% of glioblastomas,^{11,17,24} arising most often as a pri-

mary tumor.²¹ Compared with glioblastoma, gliosarcoma is found more frequently in the temporal lobes^{16,26} and may have an increased predilection for local invasion and extracranial metastasis.^{3,9,10,22,23,25,28,31,32} It often presents surgically as a firm, superficial lesion adherent to the meninges that may be mistaken intraoperatively for a meningioma.^{3,26}

Although most gliosarcomas are diagnosed at the time of surgery and are believed to arise de novo (primary gliosarcoma),⁶ a small fraction of gliosarcomas develop after cranial irradiation for glioblastoma or other cranial lesions, and an even smaller fraction develop from lower-grade precursors in the absence of radiation or other intervention.^{6,13,38} For instance, in 1 series by Perry and colleagues³⁰ of 32 gliosarcomas, 25 were considered primary tumors whereas the remaining 7 cases occurred after irradiation, and in a series of 30 secondary gliosarcomas by Han and colleagues,¹² only 1 case developed from a primary glioblastoma after resection in the absence of adjuvant external beam radiation or Gamma Knife radiosurgery.

To date, there exists only 1 report of a putatively primary gliosarcoma with *IDH1* mutation positivity,¹⁹ whereas secondary gliosarcoma in the absence of radiation treatment is exceedingly rare. In this paper we present the case of an

ABBREVIATIONS EGFR = epidermal growth factor receptor; GFAP = glial fibrillary acidic protein; *IDH1* = isocitrate dehydrogenase-1.

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elderly gentleman with no history of previous intracranial mass lesions who presented to the hospital with new-onset seizures and was found to have an *IDH1* mutation-positive gliosarcoma.

Case Report

History and Presentation

A 75-year-old man presented to an outside hospital with a 3-day history of multiple focal seizures manifesting as episodes of right hand and arm numbness, weakness, and pain. Of note, approximately 8 years before this presentation he had experienced a transient episode of right arm tremor and underwent brain MRI, which revealed no abnormal mass lesions. His past medical, surgical, family, and social histories were otherwise noncontributory. He underwent a CT scan that revealed a left parietal lesion, and was transferred to our institution (University Hospitals-Case Medical Center and the Seidman Cancer Center) under the care of the neurosurgical service.

On admission, the patient endorsed right arm pain and numbness as well as word finding difficulties. On physical examination he was grossly intact aside from mild hypoesthesia in the right upper extremity, mild global hyperreflexia, and altered extraocular pursuit movements likely secondary to medication. The patient underwent volumetric MRI that confirmed the presence of a rounded 2.2×2.2 -cm left parietal mass with surrounding hazy hyperintensity on FLAIR and T2-weighted images, potentially representing either vasogenic edema or nonenhancing infiltrating tumor. Postcontrast images revealed irregular enhancement within the mass and probable necrosis. A CT PET scan demonstrated peripheral intensely hypermetabolic activity within the lesion with relatively decreased activity centrally, but otherwise found no evidence of extracranial lesions.

Operation and Postoperative Course

Left occipitoparietal craniotomy with stereotactic computer-aided navigation and electrophysiological motor mapping was performed. After electrophysiological determination that the motor cortex lay at least 1 gyrus anterior to the anterior margin of the tumor, a sulcal plane was opened under the microscope and a biopsy of the tumor was taken, which revealed a high-grade glioma. The sulci around the tumor were opened and the tumor was grossly removed in 1 piece. The patient recovered without complication and was discharged from the hospital on postoperative Day 2.

Postoperative MRI showed gross-total resection. At the 1-month follow-up, the patient had recovered well from surgery, with mild persistent sensory changes in his right arm and grossly normal speech with occasional word-finding difficulty. The final pathology revealed a high-grade astrocytic tumor; glial fibrillary acidic protein (GFAP) and reticulin stains confirmed sarcomatous differentiation within the tumor, and it was immunoreactive for IDH1-R132H (Fig. 1).

The patient received adjuvant temozolomide therapy and 6000 cGy external beam radiation therapy to the surgical bed in 30 fractions. At his most recent follow-up

evaluation approximately 7 months after surgery, the patient continued to do well with some mild sequelae in the form of steroid myopathy and an isolated seizure. Brain MRI at that time revealed increased irregular enhancement, without increased mass effect, around the resection cavity that could represent progression or pseudoprogression of his disease.

Discussion

This unusual case highlights our evolving understanding of the molecular genetics of glioblastoma and its rare variant, gliosarcoma. Although gliosarcoma resembles glioblastoma with regards to clinical presentation and is often managed under similar or identical protocols, gliosarcoma may be a unique clinicopathological entity.^{7,39} For instance, gliosarcoma may have an increased propensity for local and systemic invasive metastasis, and while data suggest that patients derive benefit from resection and aggressive treatment under existing glioblastoma-directed temozolomide- and radiotherapy-based protocols,^{32,39} survival for primary gliosarcoma may be worse than for primary glioblastoma.^{7,17,21}

Sequencing and comparative genomic hybridization studies of microdissected gliosarcoma have revealed that tumor cells from its glial and mesenchymal components contain identical alterations in specific genes, suggesting that both tumor compartments arise from the same precursor.^{4,5} However, despite having a common clonal cell of origin, the 2 compartments may differ substantially in their genetic alterations. In 1 study by Actor and colleagues, only 57% of chromosomal imbalances were shared by both glial and mesenchymal subpopulations.¹ Compared with primary glioblastoma, gliosarcomas in this study had a smaller number of chromosomes involved in imbalances, and though not significant, more gliosarcomas exhibited a loss on chromosomes 9p and fewer on chromosome 10 and 22 than glioblastoma.¹ The majority of gliosarcomas had a gain on chromosome 7 (15/20 analyzed), possibly highlighting a role of chromosome 7 in the evolution of gliosarcoma.

Another study by Reis and colleagues of 19 gliosarcomas also found an increased frequency of gains on chromosome 7, as well as a complete absence of EGFR amplification.³³ It is not known at what stage in tumorigenesis the glial and mesenchymal components of gliosarcoma diverge; however, the genetic and clinical differences between gliosarcoma and glioblastoma raise the possibility that gliosarcoma may warrant consideration as an independent clinical entity.

As mentioned earlier, *IDH1* mutations play an important role in the evolution of gliomas. The majority (approximately 90%) of *IDH1* mutations involve the substitution of histidine for arginine at position 132 (R132H). Rarely, *IDH2* mutations occur instead, affecting the arginine residue at codon 172, representing the structural analog of the R132 position in *IDH1*.^{2,42} *IDH1/2*-mutated subunits form heterodimers with their wild-type counterparts to catalyze the conversion of the citric acid cycle metabolite, alpha-ketoglutarate, into D-2-hydroxyglutarate in an nicotinamide adenine dinucleotide diphosphate-depen-

FIG. 1. Photomicrographs. **A:** H & E stain showing nests of astrocytic cells within a dense collagenous stroma. **B:** Reticulin stain disclosing a dense pericellular reticulin network throughout the tumor. **C:** GFAP stain highlighting the astrocytic elements embedded within the collagenous matrix. **D:** Positive immunoreactivity for mutant IDH-1 R132H. Bar = 100 μ m. Figure is available in color online only.

dent manner.⁸ Accumulation of D-2-hydroxglutarate leads to inhibition of the functionally diverse family of 2-oxoglutarate oxygenases, resulting in downstream oncogenic consequences, including maintenance of a hypermethylator phenotype, perturbation of collagen maturation and basement membrane function, induction of the HIF-1 α pathway, and increased oxidative damage.^{36,37,40,41,43}

Whether IDH mutations play a role in the evolution of gliosarcoma is unknown. In a few case reports of secondary gliosarcoma arising from oligodendroglioma (“oligo-

sarcoma”), IDH mutations were identified.^{15,38} *IDH1* and *TP53* mutation analysis were used in 1 case report of a secondary gliosarcoma to demonstrate that it likely arose from a previous anaplastic astrocytoma.³³ To date, we have found only 1 report of a primary gliosarcoma with *IDH1* positivity in a series of 25 gliosarcomas; interestingly, this tumor also contained a focal oligodendroglial component.¹⁹ A review of studies investigating IDH mutations in gliosarcomas is presented in Table 1.

Secondary gliosarcoma is exceptionally rare, and among

TABLE 1. Previous reports investigating IDH status in gliosarcomas*

Authors & Year	Study Design	No. of Gliosarcomas†	Detection Method	<i>IDH1</i> Mutant Gliosarcomas
Balss et al., 2008	Retrospective 685-case series	5	Sequencing of <i>IDH1</i> (codon 132)	None detected
Lusis et al., 2010	Retrospective 3-case series	2	Immunohistochemistry	None detected
Romeike et al., 2011	Case report	1	Immunohistochemistry & sequencing of <i>IDH1</i>	1 secondary tumor (after treatment)
Vajtai et al., 2012	Case report	1	Immunohistochemistry	1 secondary tumor (after treatment)
Lee et al., 2012	Retrospective 26-case series	26	Sequencing of <i>IDH1</i> (codon 132) & <i>IDH2</i> (codon 172)	1 primary tumor, 1 secondary tumor (after treatment)
Hiniker et al., 2013	Case report	1	Immunohistochemistry	1 secondary tumor (after treatment)
Joseph et al., 2013	Retrospective 167-case series	45	Immunohistochemistry	3/23 secondary tumors; 0/22 primary tumors
Codispoti et al., 2014	Case report	1	Immunohistochemistry	1 secondary tumor (no adjuvant treatment)

* Studies include those specifically investigating gliosarcoma and studies of other brain tumors that also reported the presence of gliosarcoma.

† Number assessed for IDH status in each study.

secondary gliosarcomas, the vast majority arise from glioblastoma or other intracranial lesions in the context of irradiation. As such, *IDH1* mutation positivity in gliosarcomas may reflect the early time course of *IDH1* mutations in gliomagenesis. It is unknown whether primary gliosarcoma may harbor IDH mutations, in contrast to primary glioblastoma. Our patient presented to the hospital, in the context of previous negative head imaging, with a new mass lesion that was clinically diagnosed as a primary tumor. Whether his lesion was a rare primary gliosarcoma with IDH positivity, or a gliosarcoma that arose from a lower-grade precursor in the absence of irradiation, is unclear. Although gliosarcoma shares many features with glioblastoma, its unique genetic and clinical aspects may offer opportunities for alternative treatment and consideration beyond that offered for glioblastoma.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Sloan, Hsieh, Manjila. Acquisition of data: Hsieh, Manjila, Cohen. Analysis and interpretation of data: Hsieh. Drafting the article: Sloan, Hsieh, Hong. Critically revising the article: all authors. Reviewed submitted version of manuscript: Hsieh, Hong, Manjila, Cohen, Lo, Rogers. Approved the final version of the manuscript on behalf of all authors: Sloan. Study supervision: Sloan.

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