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Genetic and pathologic evolution of early secondary gliosarcoma

Kari-Elise T. Codispoti,

Department of Pathology, Johns Hopkins University, Baltimore, USA

Stacy Mosier,

Department of Pathology, Johns Hopkins University, Baltimore, USA

Robert Ramsey,

Department of Pathology, Banner Good Samaritan Medical Center, Phoenix, AZ, USA

Ming-Tseh Lin, and

Department of Pathology, Johns Hopkins University, Baltimore, USA

Fausto J. Rodriguez

Department of Pathology, Johns Hopkins University, Baltimore, USA

Division of Neuropathology, Johns Hopkins Hospital, Sheikh Zayed Tower, Room M2101, 1800 Orleans Street, Baltimore, MD 21231, USA

Fausto J. Rodriguez: frodrig4@jhmi.edu

Abstract

Gliosarcoma is a subset of glioblastoma with glial and mesenchymal components. True secondary gliosarcomas (i.e. progressing from lower-grade precursors) in the absence of radiation therapy are very rare. We report the unique case of a 61-year-old male who developed a fibrillary astrocytoma (WHO grade II). In the absence of adjuvant therapy the tumor recurred 3 years later as a gliosarcoma comprising an infiltrating glial component and a curious, early high-grade sarcomatous component surrounding intratumoral vessels. DNA was extracted from formalin fixed paraffin-embedded tissues from the precursor low-grade glioma and from the glioma and sarcomatous components at progression. Samples were hybridized separately to a 300 k Illumina SNP array. IDH1(R132H) mutant protein immunohistochemistry was positive in all tissue components. Alterations identified in all samples included dup(1)(q21q41), del(1)(q41qter), del(2)(q31.1), del(2)(q36.3qter), del(4)(q35.1qter), dup(7)(q22.2q36.3), del(7)(q36.3qter), del(9)(p21.3pter), dup(10)(p13pter), del(10)(q26.13q26.3), dup(17)(q12qter), and copy neutral LOH(20)(p11.23p11.21). The recurrent tumor had additional alterations, including del(3)(p21.31q13.31), del(18)(q21.2qter), and a homozygous del(9)(p21.3)(*CDKN2A* locus) and the sarcoma component had, in addition, del(4)(p14pter), del(6)(q12qter), del(11)(q24.3qter), and del(16)(p11.2pter). In conclusion, unique copy number alterations were identified during tumor

progression from a low-grade glioma to gliosarcoma. A subset of alterations developed specifically in the sarcomatous component.

Keywords

Gliosarcoma; IDH1; SNP array; Secondary glioblastoma; Brain

Introduction

Gliosarcoma (GS) is a biphasic tumor with malignant glial and mesenchymal elements, regarded as a variant of glioblastoma (GBM). The mesenchymal component can have a variety of histologic features [1]. Molecular genetic studies support a common origin for the morphologically distinct tissue types [2, 3]. Most GS are typically diagnosed at the time of initial surgery and are believed to develop de novo. A subset of GS is referred to as secondary, after intracranial radiation to treat high-grade gliomas. These secondary GS are distinct from radiation-induced GS which arise after cranial radiation in the absence of GBM [4]. True secondary GS in the absence of radiation therapy are very rare. In a large series of secondary GS, all but 2 of the 30 patients had received external beam radiation for treatment of their GBM [4]. This terminology varies from that of GBM in which secondary GBM develop via progression from a lower-grade precursor lesion and are not necessarily related to therapeutic intervention.

GS has been reported to have a similar genetic profile to GBM. Typical chromosomal imbalances seen in GS include gains in chromosomes 7, X, 9q, and 20q and losses from chromosomes 10, 9p, and 13q [2, 3]. In a small series of GS, examination of microdissected tissue from both the glial and sarcomatous components revealed *PTEN* mutations, *TP53* mutation, *p16* deletion, and amplification of *MDM2* and *CDK4* in both tissue components [5]. Because of the common origin of the tissue types, it is believed that any chromosomal imbalances restricted to either the glial or sarcomatous component of the tumor develop after it arises from a common precursor [2, 3]. High-density single-nucleotide polymorphism (SNP) arrays are a powerful means of identification of global chromosomal gains and losses with much higher resolution than traditional cytogenetic methods. Use of the technique with formalin-fixed paraffin-embedded tissues is also feasible. We report a case of true secondary GS arising in the absence of previous therapy in which we separately analyzed copy number alterations in the primary low-grade tumor and in the glial and sarcomatous components at the time of tumor progression. Identifying genomic alterations that occur during the natural progression of GS may reveal genetic pathways that are particularly important in the pathogenesis of malignant brain tumors.

Materials and methods

Clinical history

A 61-year-old male presented with recent-onset seizure. MRI revealed a non-enhancing 7.0 × 5.0 cm right frontotemporal mass. He did not receive any adjuvant therapy and the tumor subsequently recurred 3 years later at the age of 64 for which he underwent a second

resection. The study was conducted in accordance with Institutional Review Board guidelines.

Immunohistochemistry and SNP array analysis

Immunohistochemistry was performed using antibodies against glial fibrillary acidic protein (GFAP; prediluted, rabbit monoclonal; Ventana, Tucson, AZ, USA), p53 (clone BP53-11; Ventana; prediluted), Ki-67 (MIB1; Ventana; 1:1,000), and IDH1(R132H) (clone H09; Dianova; 1:50). Tissue macrodissection was performed on formalin-fixed paraffin embedded tissue, from the precursor low-grade glioma and from the glioma and sarcomatous components during progression. Samples were hybridized separately to a SNP array with 300,000 SNPs (Illumina, San Diego, CA, USA) as described elsewhere [6]. Genes localized to regions with copy number alterations unique to the recurrent tumor were searched using the UCSC genome browser [7].

Results

Pathology

The first resection measured $3.5 \times 3.1 \times 2.5$ cm in aggregate. Histologically, it was an infiltrating glioma with moderate pleomorphism lacking mitotic activity (Fig. 1a, b) and the ki67 labeling index was up to 1 % in the most proliferative areas (Fig. 1c, d). Diagnosis of diffuse astrocytoma (WHO grade II) was made, confirmed by three board-certified neuropathologists using current WHO criteria. The recurrent tumor had areas resembling the low-grade glioma precursor (Fig. 2a) but, in addition, a high-grade infiltrating glial component with focal microvascular proliferation, gemistocytic features, and areas of increased pleomorphism. There was also a curious, early high-grade spindle-cell component surrounding intratumoral vessels and the leptomeninges focally (Fig. 2b, c) with a pericellular pattern of reticulin staining, lacking GFAP immunoreactivity (Fig. 2d). This sarcomatous component accounted for less than 10 % of tumor cellularity. Mutant IDH1(R132H) protein was expressed in both tissue components (Fig. 2e). P53 nuclear labeling was stronger in the sarcomatous component (Fig. 2f). Synaptophysin was negative in both components. Proliferative activity, as reflected by the mitotic index, was higher in the sarcomatous component (up to 6 mitoses per 10 high-power fields) than in the glial component (1 mitosis per 10 high-power fields). This combination of findings supported bona-fide diagnosis of secondary GS arising in progression from a diffuse astrocytoma.

Molecular genetic studies

DNA copy number alterations identified in the precursor and different tissue components in the recurrent tumor are summarized in Table 1; selected alterations are illustrated in Fig. 3. All alterations present in the precursor were present in the glial and sarcomatous component of the recurrence, except for a $\text{del}(5)(\text{q}33.2\text{qter})$ that was unique to the low grade precursor. All alterations present in the glial component of the recurrent tumor were present in the sarcomatous component also, but the sarcomatous component contained additional unique alterations (Table 1). Select genes localized to the regions of genomic loss in both the glial and sarcomatous components of the recurrent tumor included *FOXP1*, *ROBO1*, *GNL3*, and *RASSF1* in Chr3(p21.31q13.31); *PHLPP1* in Chr18(q21.2qter); and *SMARCA2*, *CDKN2A*,

CDKN2B, and *MTAP* in Chr9(p21.3). Genes localized to areas of deletion unique to the sarcomatous component of the tumor at histologic progression included *BAI3*, *DDX43*, *SESN1*, *ROS1*, *WISP3*, and *MYCT1* in Chr6(q12qter) and *TSC2*, *RAB26*, *AXIN1*, *BAIAP3*, *LITAF*, and *MAZ* in Chr 16(p11.2pter).

Discussion

This unusual case of a diffuse astrocytoma progressing to GS in the absence of any therapeutic intervention provided a unique opportunity to investigate some of the molecular alterations that may occur early and during the course of tumor progression. *IDH1* and 2 mutations are early events in infiltrating gliomas [8], and supported the bona fide secondary GS nature of this case. The deletion at Chr 3(p21.31q13.31) is commonly found in solid tumors and is believed to harbor several known and putative tumor suppressors [9]. This deletion includes the gene Ras association family domain protein 1A (*RASSF1A*), which has tumor-suppressor functions and is involved in apoptotic pathways, microtubule stability, and cell cycle regulation [10, 11]. *RASSF1A* may be involved in the pathogenesis of gliomas, because it has been found to be down-regulated in gliomas by promoter methylation [12, 13]. Epigenetic silencing of *RASSF1A* by promoter methylation also correlates with tumor grade in gliomas [14]. Deregulation of *RASSF1A* is observed in other histologic types of central nervous system neoplasms, including primitive neuroectodermal tumors and medulloblastoma [15]. Although *RASSF1A* is typically silenced by promoter methylation in a variety of neoplasms, there are limited cases in which mutations have been identified [11]. Abnormalities of *FOXPI* expression have been identified in several solid organ tumors and cancer cell lines, although no specific relationship is seen for gliomas [16]. Interestingly, loss of *PHLPP1*(18q) has recently been found to act synergistically with loss of *PTEN* in glioblastoma [17].

Chromosome 9 is frequently altered in GBM, and the original tumor in our case had a heterozygous del(9p21.3), which was also seen at recurrence with an additional homozygous deletion at the location of the *CDKN2A* gene (*p16/INK4A*) (Fig. 3). Deletion of this gene is frequently seen with associated loss of *MTAP* in glioblastoma [18]. The p16/INK4A pathway is altered in both primary and secondary GBM via both deletions/mutations and promoter methylation [19]. In a study of GS by Reis et al., *p16* deletion was restricted to the sarcomatous region in a GS for which both glial and sarcoma portions were analyzed separately [5]. Although the authors raise the possibility that this may be because of dilution of the DNA in the glial portion from non-neoplastic neural tissue, it is also possible that this may indicate involvement of p16 loss in tumor progression. Loss of p16 leads to deregulation of the cell cycle, because p16 binds to CDK4, ultimately inhibiting transition to the S phase [20].

Copy number alterations unique to the sarcomatous component may be of particular interest in our case because they may reveal some of the factors associated with sequential progression. The deleted region of chromosome 16 harbors the tumor suppressor *AXIN1*. The encoded protein acts as a scaffold and binds to many components of the WNT pathway [21]. It acts as an inhibitor of WNT signaling and downregulates β -catenin [21, 22]. WNT signaling is linked to several types of cancer. However, the typical mutations found in β -

catenin are not seen in gliomas [23]. Loss of heterozygosity (LOH) of *AXIN1* has previously been identified in GBM but not in lower-grade gliomas [24].

Also located in this region of chromosome 16 is *TSC2*. Although the characteristic central nervous system lesions in tuberous sclerosis patients do not include high-grade gliomas, the product of the *TSC2* gene (tuberin) is involved in inhibition of the mTOR pathway, which is deregulated in many types of cancer. There are limited data indicating a relationship between *TSC2* alterations and high-grade gliomas. Reduced expression of *TSC2* mRNA and its protein product tuberin have been reported in sporadic astrocytomas, including high-grade astrocytomas [25]. In another study, LOH was examined for both *TSC1* and *TSC2* in several types of glial neoplasm. However, LOH for *TSC2* was observed for only 1 of 15 GBMs studied, and a second inactivating mutation was not identified [26].

Some of the alterations in early sarcomatous transformation in this unique glioma example may also provide important biological clues about mesenchymal induction in cancer. Recent studies have revealed a possible effect of the epithelial–mesenchymal transition in gliosarcoma [27, 28], an initial important biological step for invasion in epithelial cancer progression. Relevant to the case reported herein, *WISP3* loss leads to epithelial–mesenchymal transition in breast cancer [29]. Previous results have also shown that PDGF signaling induces the epithelial–mesenchymal transition by displacing AXIN from beta-catenin and enabling the latter to translocate to the nucleus [30]. As discussed above, both *WISP3* and *AXIN1* were included in the area of deletions.

A point of caution in interpreting this case is that the low-grade precursor was unusual in many respects. First, the patient was older than most patients with diffuse (grade II) gliomas. In addition, several molecular alterations, for example *CDKN2A* deletions are more typically seen in higher-grade neoplasms. IDH1(R132H) mutations occur in a small (7 %) subset of gliosarcomas [31], but the imaging features (lack of contrast enhancement) and pathologic characteristics, including lack of mitotic activity and very low ki67 labeling index, in a well sampled specimen are all supportive of the diagnosis despite the unusual age. Interestingly, recent studies have implicated homozygous deletions in *DMBT1* (at 10q26.13) in diffuse astrocytomas (WHO grade II) with worse prognosis [32], and a deletion in this region was present at first diagnosis in the present case. It is possible this neoplasm was “captured” at a time when it was starting to progress at the molecular level.

In conclusion, we report a rare case of secondary GS arising in the absence of previous radiotherapy for which we were able to identify unique copy number alterations seen during tumor progression from a low-grade glioma to GS. In addition, alterations that develop specifically in the sarcomatous components in the same tumor were observed. Notably, several tumor suppressors are present in these deletions, and these molecular pathways may be important for tumor progression from low to high-grade astrocytoma and maybe from glioma to sarcoma. Future studies including a larger number of cases may be required to validate these molecular findings, and clarify why a unique form of pathologic- molecular progression occurred in this patient.

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Fig. 1.

Pathologic features of the precursor at first resection. Histologic sections are indicative of a moderately cellular neoplasm with pleomorphism, but lacking mitotic activity (**a, b**). The low proliferation was confirmed by ki-67 staining, which was no higher than 1 % in any area of this well sampled neoplasm (**c, d**)

Fig. 2. Histologic and phenotypic properties of the secondary gliosarcoma. **a** Infiltrating astrocytic component resembling the tumor at first resection. **b, c.** Biphasic morphology, including glial/gemistocytic and focal perivascular sarcomatous components. **d** The sarcomatous component lacked GFAP expression (*right*). Mutant IDH1 protein was maintained in both tissue components (**e**) whereas strong p53 labeling was more conspicuous on the sarcomatous component (**f**)

Fig. 3.

Copy number alterations identified by SNP array analysis at first diagnosis and progression.

- a** Heterozygous del(9)(p21.3pter) in precursor lesion. **b** Homozygous del(9)(p21.3) seen at tumor progression. **c** del(3)(p21.31q13.31) seen in the glial component at tumor progression. **d** del (16)(p11.2pter) seen exclusively in the sarcomatous component

Table 1

Copy number alterations in original tumor and tissue components in recurrent/progressive tumor

Alterations present in the original and recurrent tumor	Alterations present in the glial and sarcomatous components of the recurrent tumor	Additional alterations present in the sarcomatous component only
dup(1)(q21q41)	del(3)(p21.31q13.31)	del(4)(p14pter)
del(1)(q41qter)	del(18)(q21.2qter)	del(6)(q12qter)
del(2)(q31.1)	Homozygous del(9)(p21.3)	del11(q24.3qter)
del(2)(q36.3qter)		del(16)(p11.2pter)
del(4)(q35.1qter)		
dup(7)(q22.2q36.3)		
del(7)(q36.3qter)		
del(9)(p21.3pter)		
dup(10)(p13pter)		
del(10)(q26.13q26.3)		
dup(17)(q12qter)		
Copy neutral LOH(20)(p11.23p11.21)		