

Neoplasm

Glioblastomatous recurrence of oligodendroglioma remote from the original site: a case report

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Abstract

Background: As in all diffuse gliomas, recurrence is an inherent feature of oligodendrogliomas, either as the same or higher grade neoplasm at the primary site. The rate of remote recurrence after surgery for the primary tumor cannot be estimated from the scarce literature, but delayed treatment of the primary tumor and genetic alterations may be associated with this phenomenon.

Case Description: A 40-year-old man presented with generalized seizures. A magnetic resonance imaging scan disclosed a right frontal mass lesion showing features of a low-grade glioma for which he refused any treatment. Seven months after diagnosis upon uncontrollable seizures, he underwent a stereotactic biopsy, which was followed by a right frontal craniotomy, both of which confirmed the lesion as a grade 2 oligodendroglioma. Six months after surgery, the patient presented with a left frontal lobe GBM without evidence of recurrence at the primary site. The genetic analysis of the primary and recurrent tumors showed trisomy 7, monosomy 10, but not 1p or 19q deletions, which have been proposed as markers for favorable prognosis.

Conclusion: Recurrence of a frontal lobe oligodendroglioma remote from the primary site as a GBM is a rare occurrence. Single-cell invasion across the corpus callosum with subsequent or simultaneous malignant degeneration into a secondary GBM is the likely mechanism. As the genetic analysis suggests, conversion of oligodendroglioma to GBM may be associated with gain of chromosome 7, loss of chromosome 10, and other genetic markers that may represent late events in the oncogenesis of oligodendroglial tumors.

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Keywords:

Oligodendroglioma; Recurrence; Glioblastoma multiforme; Genetic analysis

1. Introduction

Diffuse infiltrative gliomas are composed of a heterogeneous collection of histologic subtypes, including astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas. Although these tumors are often grouped together, differences in their clinical behavior and response to therapy

warrant segregation into different subtypes. Astrocytomas contain nonrandom chromosomal abnormalities that correlate with shortened patient survival. In addition, these tumors are characterized by trisomy 7 and monosomy 10 [17,19]. Allelic deletions spanning the entire or partial chromosome 10q play a role in GBM formation [5,6,11]. According to conventional histologic classification, oligodendroglial tumors account for between 5% and 33% of all gliomas [4]. It is known that oligodendrogliomas with combined loss of chromosome 1p and 19q are associated with chemotherapeutic responsiveness and prolonged recurrence-free survival postchemotherapy [11,12,16,18]. Other genetic alterations such as p16/CDKN2A deletion, loss of chromosome 10, and EGFR amplification, which is located

Abbreviations: DAPI, 4',6-diamidino-2-phenyl-indole; EGFR, epidermal growth factor receptor; FISH, Fluorescence in situ hybridization; GBM, glioblastoma multiforme; MRI, magnetic resonance imaging.

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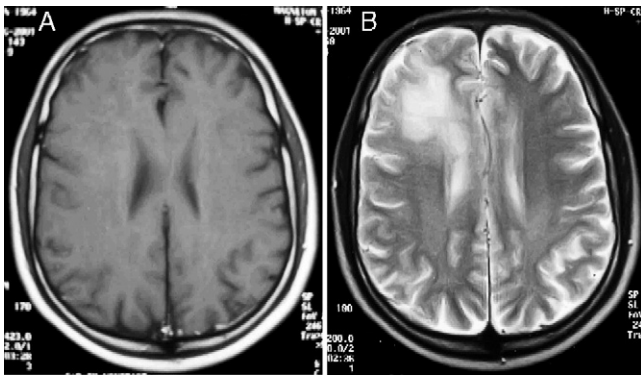


Fig. 1. Axial cranial MRI scan shows a $3 \times 3\text{-cm}^2$ nonenhancing lesion in the right superior frontal region which was iso- and hyperintense on T1- (A) and T2-weighted images (B), respectively.

on chromosome 7, also have been reported to be correlated with tumor progression [10,15].

We present here a patient with a right frontal lobe oligodendroglioma who had developed a glioblastomatous recurrence remote from the original site after total removal. The primary and recurrent tumor tissues were investigated using centromere-specific chromosome 7 and 10 probes, and telomere-specific chromosomal arm 1p and 19q probes to define potential molecular markers that may be responsible for the conversion of oligodendroglioma to GBM.

2. Case report

This 40-year-old otherwise healthy man presented with generalized seizures 13 months before hospitalization. His general physical examination and neurologic examination were otherwise normal. A cranial MRI revealed a $3 \times 3\text{-cm}^2$ nonenhancing lesion in the right superior frontal region which was iso- and hyperintense on T1- and T2-weighted images, respectively (Fig. 1). A stereotaxic biopsy was planned for histopathologic diagnosis, but the patient refused any medical intervention. Seven months after admission, when his seizures became more frequent despite antiepileptic medication, he agreed to a stereotaxic biopsy,

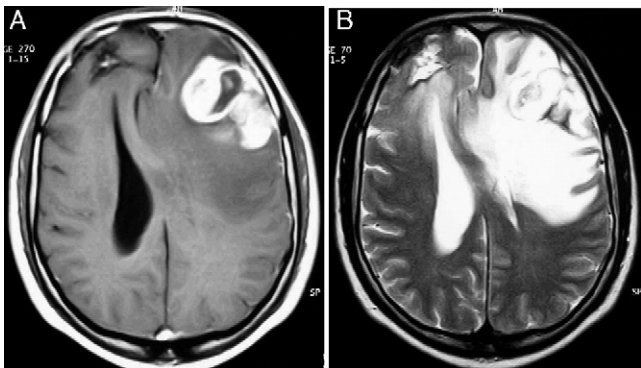


Fig. 2. Axial cranial MRI scan demonstrates a $5 \times 5\text{-cm}^2$ mass lesion with shift of midline structures, which is heterogeneous on both T1- (A) and T2-weighted images (B).

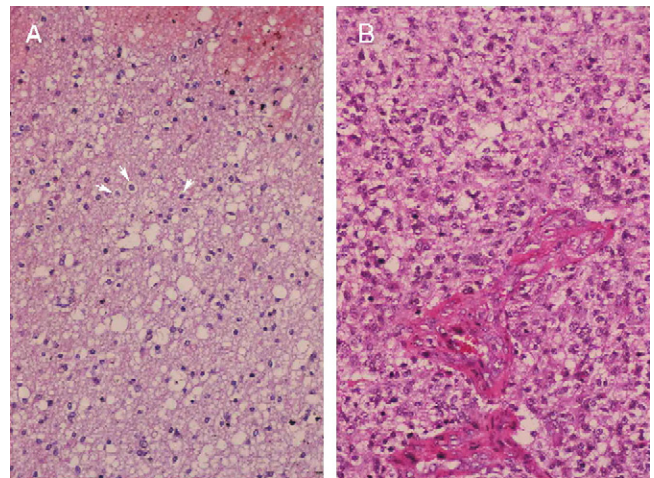


Fig. 3. A: Photomicrograph of the tumor tissue (grade 2 oligodendroglioma) obtained at craniotomy showing diffuse round cells with regular round nuclei and perinuclear halo artifact forming perinuclear satellitosis (hematoxylin and eosin, original magnification $\times 400$). B: Photomicrograph of recurrent tumor tissue (GBM) showing cells with nuclear pleomorphism, atypical endothelial hyperplasia, necrosis, and mitosis (hematoxylin and eosin, original magnification $\times 400$).

which revealed a grade 2 oligodendroglioma. The patient then underwent a right frontal craniotomy for removal of the lesion which displayed identical histologic features (Fig. 3). As the genetic analysis of the resected tissue did not reveal deletion of 1p and 19q, the patient did not receive chemotherapy.

Six months after surgery, the patient presented with headache and difficulty in speaking. His neurologic examination revealed dysphasia, bilateral papilledema, and a right hemiparesis. A cranial MRI disclosed a $5 \times 5\text{-cm}^2$ heterogeneous lesion in the left frontal region which caused a shift of the midline structures (Fig. 2A). The patient underwent an emergency left frontal craniotomy, which revealed a highly vascular and firm lesion with areas of old

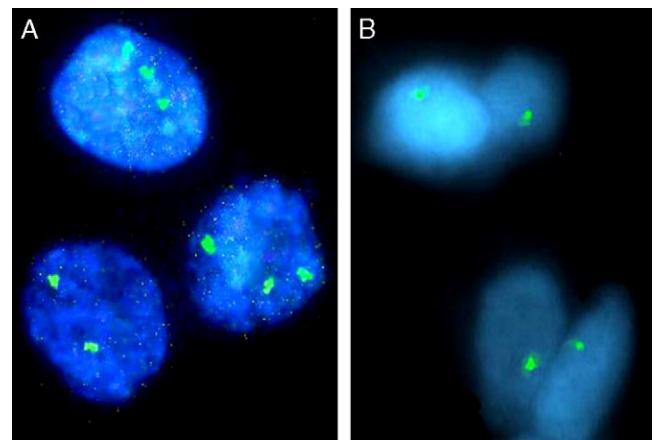


Fig. 4. A: Green signals show centromere region of chromosome 7: FISH images of the recurrent tumor shows trisomy 7. B: Green signals show centromere region of chromosome 10: FISH images of the recurrent tumor shows monosomy 10.

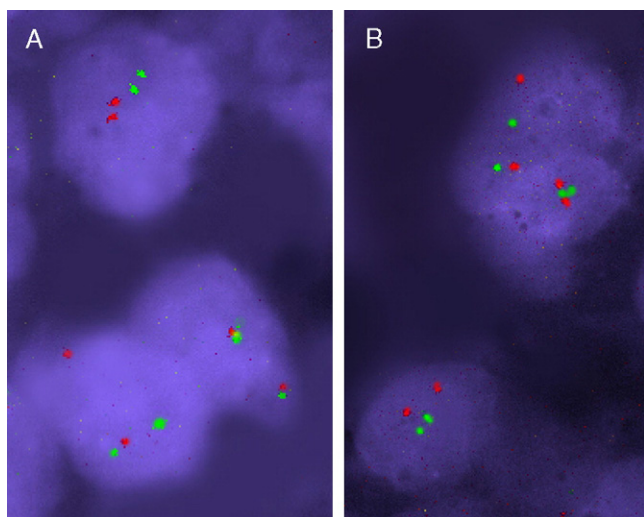


Fig. 5. A: Green signals show chromosome 1p telomeric region; red signals show chromosome 1q telomeric region. B: Green signals show chromosome 19p telomeric region; red signals show chromosome 19q telomeric region: FISH images of the primer tumor show lack of chromosome 1p and 19q deletions.

hemorrhage. As the lesion was a GBM (Fig. 3), the patient was scheduled for radiotherapy.

3. Materials and methods

Fluorescence in situ hybridization technique was performed for both the primary and recurrent resected tumor tissues using 2 types of probes, including directly labeled probes for chromosome 1p/1q (spectrum—green/orange) and 19p/19q (spectrum—green/orange) telomere regions, and directly labeled probes for chromosome 7 (spectrum—green/orange) and 10 (spectrum—green/orange) centromere regions obtained from Vysis (Downers Grove, IL, USA). The probes were denatured, and the sections were incubated with 40 μ L pepsin (100 mg/mL) in 100 mL HCl (0.01N) solution at 37°C for 10 minutes. Hybridization was allowed to take place overnight at 37°C, a posthybridization wash was performed twice in 50% formamide at 47°C for 3 minutes and then twice in 2 \times SSC at room temperature for 3 minutes. Slides were counterstained with DAPI and examined on a Quips Imaging System (Applied Biosystem, Cambridge, UK) equipped with Nikon E 600 (Kanagawa, Japan) standard conventional epifluorescence microscope and a filter set (triple: DAPI/red/green; dual color: red/green, single red and single green; Vysis). System filters showed orange signals as red color. Hybridization signals were counted within 200 interphase nuclei per specimen. The results of genetic analysis of the primary and recurrent tumors showed trisomy 7 and monosomy 10 (Fig. 4), but not 1p and 19q deletions (Fig. 5), which have been proposed as a marker for favorable prognosis.

4. Discussion

Oligodendrogliomas are one of the 3 major histologic types of diffuse infiltrative brain tumors [2,3]. They most

commonly occur in the frontal lobes extending into the perisylvian region. Oligodendrogliomas characteristically infiltrate the cortex and may extend into the leptomeninges. Rarely, they may present as gliomatosis cerebri. Multifocal presentation is also rare, and drop metastasis via the cerebrospinal fluid has been reported [2]. Complete resection of tumors in accessible regions has been advocated to improve survival of patients with pure oligodendrogliomas and oligoastrocytomas [2,4]. Because of the difficulty of the diagnosis, it is difficult to extract a definite rate of recurrence from the literature at the primary site, either as the same grade or as a higher grade neoplasm [3].

Invasiveness is an inherent character of all gliomas, and invading glioma cells do so by following the path of blood vessels or myelinated axons. This type of single-cell invasion is associated with minimal destruction of the preexisting neural structures which may occur along the optic radiation, across the corpus callosum or the anterior commissure [7]. Our review of the literature did not reveal any case of an oligodendroglioma that recurred remote from the primary site as a secondary GBM. Although not visualized radiologically, the most likely explanation for this phenomenon is with single tumor cell invasion across the corpus callosum with subsequent or simultaneous malignant degeneration into a secondary GBM. Histopathologic delineation of GBMs with or without oligodendroglial differentiation and high-grade oligodendrogliomas is difficult [12,14]. Of the central nervous system intrinsic tumors, the responsible cell type is usually the astrocyte, and the resulting tumors typically progress through stages of increasing malignancy with time [5,13]. Studies on molecular pathways have demonstrated that genetic alterations involving the p53 gene and overexpression of platelet-derived growth factor A and its receptor, platelet-derived growth factor receptor α , are involved in the progression of astrocytomas to secondary GBM [9]. In contrast, there are limited data regarding the molecular profiles of oligodendroglioma progression [10]. It is known that oligodendrogliomas with combined loss of chromosome 1p and 19q are associated with chemotherapeutic responsiveness and prolonged recurrence-free survival postchemotherapy [11,12,16,18]. Other genetic alterations such as p16/CDKN2A deletion, 10q loss, and EGFR amplification, which is located on chromosome 7, have been shown to be associated with unfavorable prognosis [10,15].

Overrepresentation of chromosome 7 was seen in both the primary astrocytoma and in the high grade recurrence of oligodendroglioma [1,8,16]. Primary and recurrent tumors of the present case exhibited trisomy of chromosome 7 and monosomy of chromosome 10. Chromosome 7 harbors the EGFR gene, which has been shown to play a role in GBM pathogenesis. Deletion of chromosome 10q has also been reported to occur in GBMs. MMCA1 (PTEN), a tumor suppressor gene that resides on chromosome 10q23, encodes a dual specificity protein phosphatase that is lost with GBM but not with oligodendroglioma [5,6]. Considering these

findings, it may be suggested that delay in surgical intervention and genetic alterations such as trisomy 7, monosomy 10, and absence of loss of 1p and 19q may represent possible factors associated with the conversion of grade 2 oligodendroglioma to a secondary GBM in our case.

In conclusion, this case emphasizes the importance of surgical removal of oligodendrogliomas at the time of diagnosis, keeping in mind the possibility of single-cell dissemination. Also, a gain of chromosome 7, loss of chromosome 10, and absence of 1p and 19q losses in both tumor tissues may be late events in the oncogenesis of oligodendroglial tumors. Identification of this genetic subtype and other genetic markers in these tumors may represent an important clue for prognosis.

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Commentary

The authors report the unusual occurrence of a low-grade oligodendroglioma that subsequently recurred in the contralateral hemisphere as a glioblastoma 6 months later. They support their diagnosis with histopathologic and genetic data, showing that the 2 tumors have a common clonal origin. Both the primary low-grade oligodendroglioma and the recurrent GBM contained trisomy of chromosome 7 and monosomy of chromosome 10, but not 1p or 19q deletions. The authors postulate that the GBM may have developed from tumor cell invasion of the primary low-grade glioma across the corpus callosum with subsequent malignant degeneration. This theory is probably correct; however, it would be important to at least discuss the other possibilities in more detail. For instance, there may have been some “mosaic effect” in the bifrontal lobes, given that there may be a genetic predisposition to neoplastic change in the glia of this patient. On the MRI scans, there appear to be some vague T2 abnormalities along the corpus callosum even at initial diagnosis, suggesting that the “leading edge” of the tumor (presumably the most malignant part) may have already been crossing the corpus callosum but was not sampled during the initial resection of the right frontal lobe lesion.

Although probably not as rare as the authors purport, this case report does have implications for our understanding of the pathogenesis of unusual multifocal gliomas. The