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Rapid tumor growth with glial differentiation of central neurocytoma after stereotactic radiosurgery

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ABSTRACT

Although stereotactic radiosurgery (SRS) is effective for central neurocytoma (CN), the long-term outcome of SRS remains unclear. We present a case of recurrent CN that was diagnosed 10 years after surgical resection and consecutive stereotactic radiotherapy. The patient was treated with SRS for the recurrent tumor, but underwent two-staged surgery once again due to rapid tumor growth. Histological features of the recurrent tumor were consistent with the diagnosis of CN. However, an increased Ki-67 proliferation index (3.4%), aberrant angiogenesis and glial differentiation of the tumor cells were observed, which were not identified in the initial CN. In addition, vascular endothelial growth factor (VEGF) and VEGF receptor were highly expressed in the recurrent tumor cells, as well as in the vascular endothelial cells. Our case suggests that malignant transition with aberrant angiogenesis and glial differentiation may be attributable to SRS.

1. Introduction

Central neurocytomas (CN) are rare neuronal brain tumors that are typically found in young adults, and commonly arise from the wall of the lateral ventricle near the foramen of Monro [1]. Although the standard treatment for CN is total surgical resection, a secondary treatment that is effective for residual or recurrent tumors remains controversial. Since 2001, it has been reported that stereotactic radiosurgery (SRS) is effective for residual or recurrent CN [2,3]. However, little is known about the long-term outcome and pathological changes of CN following SRS. In this study, we observed rapidly-growing recurrent CN with marked angiogenesis and tumor glial differentiation after SRS treatment.

2. Case report

A 30-year-old woman with headaches underwent radiological examination and a brain MRI showed a mass with hemorrhage in the left lateral ventricle (Fig. 1a, b). Surgical resection was performed, and the tumor was subtotally resected. A year later, she was treated adjuvantly with stereotactic radiotherapy (SRT), 30 Gy in three fractions, and the overall time interval was 2 days. Five years after the SRT, the MRI showed no evidence of tumor recurrence. However, after another five years, the MRI showed tumor recurrence in the frontal horn of the left lateral ventricle and in the trigone of the right lateral ventricle (Fig. 1c, d). She was treated with SRS, 18 Gy per lesion in 1 day. However, the tumors rapidly enlarged, and a cyst in the posterior horn of the right lateral ventricle caused edema in the right occipital lobe (Fig. 1e, f). She developed a left homonymous hemianopia and a mild left hemiparesis. Thus, she underwent surgical resection of the tumors.

2.1. Pathological findings

The tumor cells obtained from the initial surgery revealed uniform oval to round nuclei with scant cytoplasm and a perinuclear halo, consistent with typical CN, grade 2, based on the World Health Organization (WHO) grading system (Fig. 2a). The diagnosis of the recurrent tumors was once again CN, WHO grade 2. However, the difference from the initial CN diagnosis was that conspicuous vascular proliferation and necrosis were seen in the recurrent CN, which was considered to be a response to SRS (Fig. 2b–d). On immunohistochemical analysis, the tumor cells were strongly

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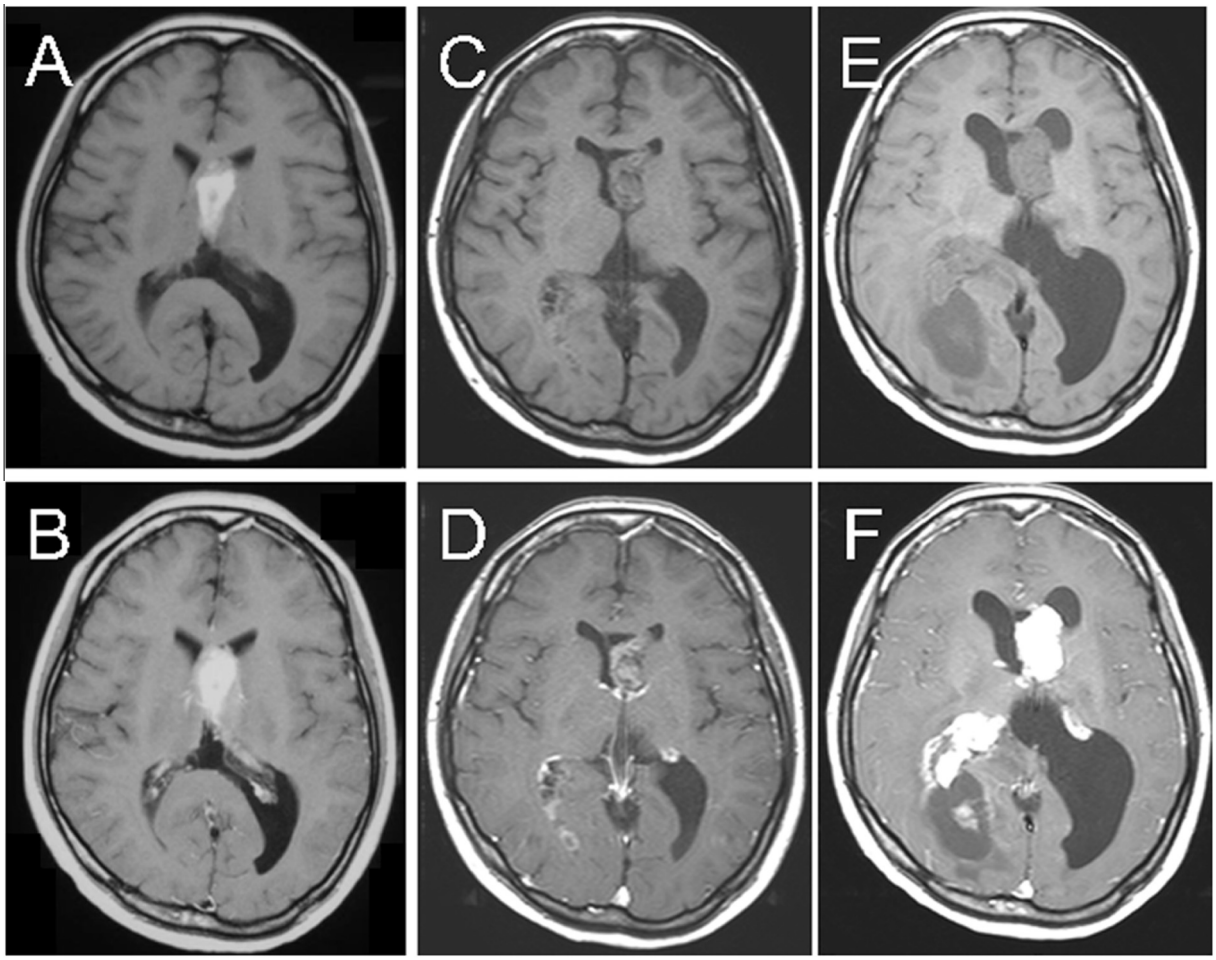

Fig. 1. (a, c, e) MRI T1-weighted images, (b, d, f) MRI gadolinium-enhanced T1-weighted images. (a, b) Initial MR axial images, showing a left intraventricular tumor with hemorrhage, (c, d) MR axial images after recurrence, showing tumors in the anterior horn of the left lateral ventricle and the trigone of the right lateral ventricle, (e, f) MR axial images after stereotactic radiosurgery, showing the enlarging bilateral intraventricular tumors with cyst formation in the trigone of the right lateral ventricle.

positive for synaptophysin in both the initial and recurrent CN (Fig. 2e). Interestingly, although the initial CN was negative for glial fibrillary acidic protein (GFAP) (data not shown), GFAP staining of the recurrent CN was strongly positive (Fig. 2f). The Ki-67 proliferation index (PI) was increased by up to 3.4% in the recurrent CN. In contrast, the initial CN had a low Ki-67 PI (<1%). Double-immunostaining examination revealed that many CN cells co-expressed GFAP and synaptophysin in the recurrent CN, suggesting astroglial differentiation (Fig. 3a).

To evaluate the microvascular density in the tumors, we performed immunohistochemistry against CD31 receptors (Fig. 3b). The immunoreactive area of the tumor was significantly increased in the recurrent CN (14.04%), compared with that in the initial tumor (3.81%) ($p < 0.001$, Student's t-test) (Fig. 3c). Vascular endothelial growth factor (VEGF) and VEGF receptor (VEGFR) expression was upregulated in the tumor cells, as well as in vascular endothelial cells (Fig. 3d). These findings indicated that aberrant angiogenesis and rapid tumor growth might be promoted by SRS via the VEGF–VEGFR pathway.

3. Discussion

Several studies have reported recurrence of CN during long-term follow-up. Bertalanffy et al. performed a literature search of recurrence using a large series, which reported a recurrence rate of 21% with a mean time-to-disease recurrence rate of 24 months [4]. Traditionally, conventional radiotherapy (cRT) has been used for the treatment of remnant or recurrent CN, but in recent decades, SRS has been adopted as an alternative to cRT. Rades et al. compared the tumor control rate between cRT and SRS after incomplete resection of CN and detected equal or higher local control rates for SRS [5].

Although the standard treatment for recurrent CN after SRS is not determined, there have been several reports on recurrent CN after SRS treated with repeat SRS [2,6]. In the present case, the tumor recurred 10 years after SRT, and a second round of treatment with SRS was performed and failed. A dose of 18 Gy may not be sufficient but may lead to malignant change rather than repressing tumor growth.

Little has been reported on the histological changes of CN after SRS. In our patient, the recurrent tumor had marked angiogenesis, intimal thickening of vessel walls, and necrosis, with a higher Ki-67 PI. The pathological significance of the increase in Ki-67 PI is unclear. Genc et al. reported no correlation between MIB-1 labeling and tumor response [7]. Because the necrosis was observed in a relatively broad area, it might reflect a coagulative change or radiation-induced necrosis after SRS. Aberrant angiogenesis might be due to the elevated expression of VEGF and VEGFR in tumor cells after SRS. Iwai et al. reviewed the histological changes of acoustic neuroma (AN) after SRS and have indicated that some