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Changes in Protein Level in the Cerebrospinal Fluid of a Patient with Cerebral Radiation Necrosis Treated with Bevacizumab

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ABSTRACT: A 32-year-old woman underwent surgeries and radiation therapy for astrocytoma. She developed symptomatic radiation necrosis in the lesion, which caused hydrocephalus. She initially underwent ventricular drainage, because the protein level in the cerebrospinal fluid (CSF) was 787 mg/dL, which was too high for shunt surgery. Because she also had breast cancer, which was pathologically diagnosed as an invasive ductal carcinoma, standard bevacizumab therapy in combination with paclitaxel every 2 weeks was selected. Interestingly, after 2 days, the agents had dramatically reduced the CSF protein level. However, it returned to approximately the initial level within 2 weeks. After two courses of this regimen, a ventriculoperitoneal shunt was placed. After 10 courses of this regimen, the CSF protein level decreased to 338 mg/dL, which is less than half of the initial level. Long-term administration of bevacizumab might decrease leakage of protein from the vessels around the ventriculus.

KEYWORDS: bevacizumab, radiation necrosis, cerebrospinal fluid protein, glioma, radiosurgery, tomotherapy

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Introduction

Bevacizumab, an anti-vascular endothelial growth factor (VEGF) agent, is often used to treat radiation necrosis (RN) induced by stereotactic radiosurgery of brain tumors. However, the pharmacodynamic effect of bevacizumab on cerebrospinal fluid (CSF) has never been reported. We report the first observed change in total protein level in the CSF of a patient with RN treated using bevacizumab. We discuss the significance of this agent in the treatment of RN in terms of the CSF protein level.

Case Presentation

A 32-year-old woman presented with a left frontal brain mass, which was revealed using computed tomography (CT) and magnetic resonance imaging (MRI) (Fig. 1A). She underwent partial removal of the tumor, which was diagnosed as a fibrillary astrocytoma (Fig. 1B). Two years after the operation, the residual tumor re-grew (Fig. 1C), and she underwent a second surgery. The recurrent tumor was diagnosed as an anaplastic astrocytoma (Fig. 1D).

Postoperatively, she received intensity-modulated radiation therapy using tomotherapy with temozolomide at a marginal dose of 56 Gy (Fig. 2A). Eighteen months after the radiation therapy, her daily activities gradually deteriorated. Enhanced MRI revealed a small lesion with extensive edema in the left frontal lobe (Fig. 2B). The positron emission tomography (PET) scan showed no uptake of fluorodeoxyglucose and low uptake of

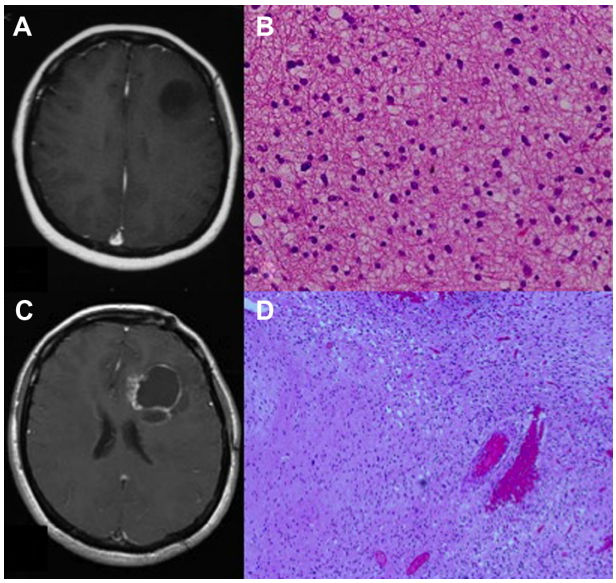

Figure 1. Gadolinium enhanced magnetic resonance imaging (MRI) scans and hematoxylin and eosin (HE)-stained sections before the first and second surgeries. (**A**) A pretreatment gadolinium-enhanced MRI scan showing a non-enhanced round tumor in the left frontal lobe. (**B**) Photomicrographs of HE-stained sections showing a fibrillary astrocytoma. (**C**) A gadolinium-enhanced MRI scan at 18 months after tomotherapy showing the cystic lesion with a well-enhanced cyst wall. (**D**) Photomicrograph of an HE-stained section of the specimen obtained at the second surgery showing the malignant transformation to an anaplastic astrocytoma.

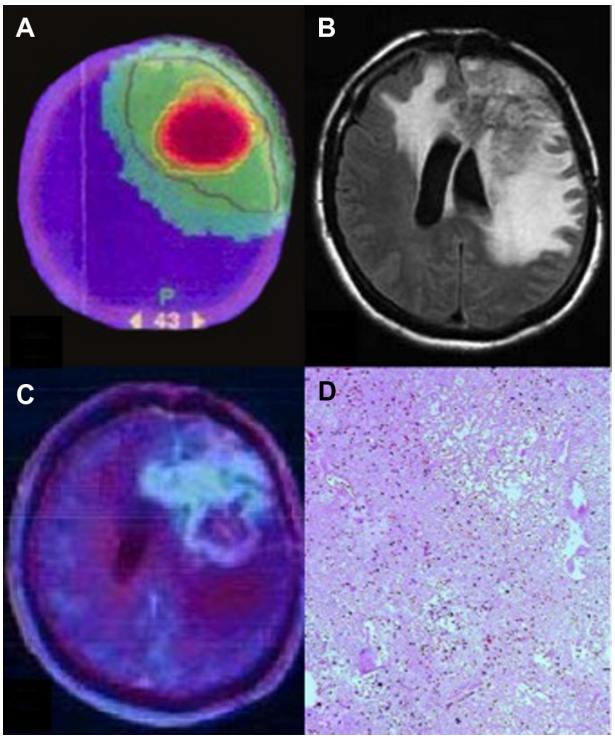

Figure 2. (**A**) Tomotherapy planning and findings confirming radiation necrosis. The yellow circle indicates the 56 Gy dosage. (**B**) An axial fluid attenuated inversion recovery image showing the left frontal lesion with broad brain edema extending to the contralateral hemisphere. (**C**) A methionine positron emission tomography scan showing only a small uptake of methionine. (**D**) A photomicrograph of the hematoxylin and eosin-stained section of the specimen obtained at the third surgery shows radiation necrosis.

methionine (Fig. 2C). She underwent a third surgery to remove the lesion, which was pathologically confirmed as RN (Fig. 2D).

Up to this point, the patient had led an independent life in her own home for several years. At 40 years of age, she detected a lump in her right breast. A biopsy of the tumor was performed and an invasive ductal carcinoma was confirmed. Because the tumor was aggressive and refractory to endocrine therapy, she was advised to undergo chemotherapy immediately. However, her activities had become slow, and she presented with urinary incontinence. A CT scan showed ventricular dilatation that indicated normal pressure hydrocephalus caused by the RN. Her symptoms gradually subsided after drainage of the CSF; however, the CSF protein level was 787 mg/dL, which is approximately 20 times higher than the normal level. Accordingly, we hesitated to insert a ventriculoperitoneal (V-P) shunt immediately after the drainage because we were concerned that she was at high risk for obstruction of the shunt. We then utilized an Ommaya reservoir for ventricular drainage before placing the V-P shunt. We observed her neurological conditions during the external ventricular drainage by using an Acti-valve system (medium pressure) (Kaneka Medix Corporation, Osaka, Japan). Despite systemic hydration, a high CSF protein level persisted. We selected bevacizumab to treat the breast cancer (BC) and the RN. Furthermore, we anticipated that the therapy would reduce the CSF protein level by means of reconstructing the vessels that had sustained endothelial damage from the radiation therapy. According to the standard therapy for BC, we intended to administer bevacizumab at a dose of 10 mg/kg of the body weight for 2 weeks in combination with paclitaxel (93 mg/kg of the body weight); however, after the first round of treatment, we could not continue this course because of the general fatigue (grade 2) and the leukopenia (grade 2) as an adverse effect. Consequently, she received only bevacizumab during the second course. Before and after administration of bevacizumab, we measured the changes in the protein level in the CSF obtained from the drainage system (Fig. 3). During the first course, the protein level decreased from the initial level of 787 mg/dL to 582 mg/dL 2 days after administration. However, the level increased to 677 mg/dL on day 10, and the second course (only bevacizumab) was initiated on day 15. The protein level again decreased to 557 mg/dL on day 17; however, it then increased to 723 mg/dL on day 26. Therefore, we observed that the agents dramatically reduced the CSF protein level by >150 mg/dL after 1–2 days of bevacizumab administration. However, the value returned to its initial level within 2 weeks after the first dose. The

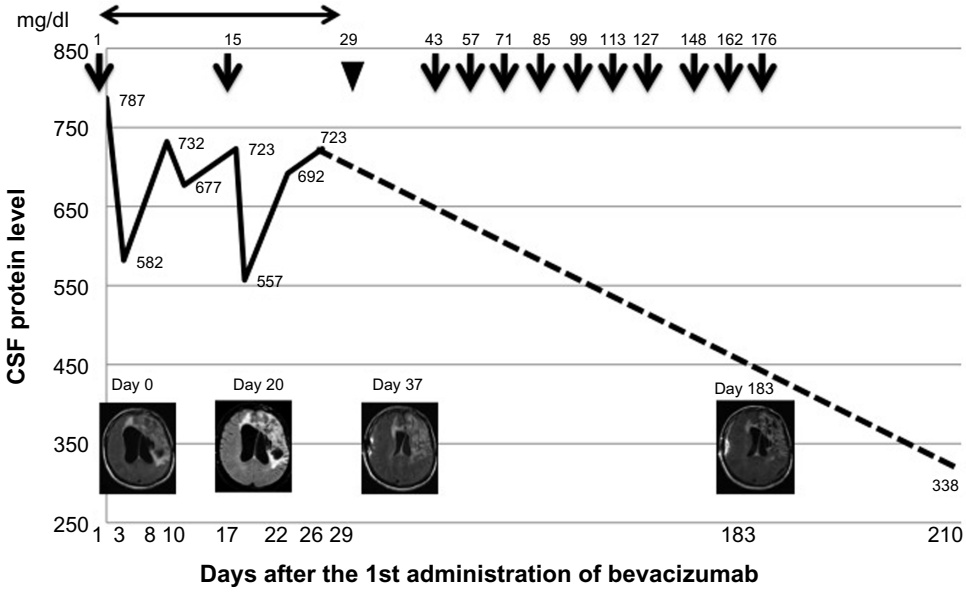

Figure 3. Changes in the cerebrospinal fluid protein level during bevacizumab therapy. The graph shows the changes in protein level in the cerebrospinal fluid during chemotherapy. Arrows show the timing of administration of the agents (bevacizumab and paclitaxel). In the second course, only bevacizumab was administered. Arrowhead shows the day of ventriculoperitoneal shunt. The figures on the arrows show the day, of which Day 1 shows the first day of administration. Bidirectional arrow indicates the period of ventricular drainage. The magnetic resonance imaging scans show the axial fluid attenuated inversion recovery images at days 0, 20, 37, and 183.

patient was able to walk smoothly and speak clearly during ventricular drainage that was never occluded, despite the high CSF protein level. Two weeks after the second administration of bevacizumab, we performed a procedure to place a V-P shunt and removed the ventricular drainage system on day 29. At this point, she was barely capable of living independently. Because bevacizumab-related adverse effects had improved, she continued to receive therapy using bevacizumab (10 mg/kg) and paclitaxel (75 mg/kg body weight) for BC after the placement of the V-P shunt. At day 210 (after 10 courses of treatment), the CSF protein level was 338 mg/dL (Fig. 3). She showed no critical adverse effects (more than grade 3) related to bevacizumab therapy after the second course.

Discussion

Intensity-modulated radiation therapy with tomotherapy is often used to treat patients with malignant glioma following surgery.[1] However, such radiation therapy applies relatively high doses to lesions and surrounding local tissue, and therefore, unfortunately may increase the incidence of RN. The incidence rates of symptomatic RN following stereotactic radiosurgery are reported as 1–5%.[2] Methionine PET is considered the most reliable diagnostic tool for RN.[3,4] The etiology of RN is not well known; however, endothelial cell dysfunction is thought to contribute to the pathogenesis that increases capillary permeability and extracellular edema.[5] It has been reported that resected RN lesions overexpress VEGF, which potentiates capillary permeability, contributing to RN pathogenesis.[6,7] von Baumgarten studied the bevacizumab effect on the morphologic and functional vascular changes using U87 mouse model. As a result, morphologic features of vascular normalization and reduced permeability were observed in a dose-dependent manner.[8] Accordingly, a VEGF-blocking agent, such as bevacizumab, is considered useful for treating RN.[4] Retrospective evidence in a few studies suggests that the agent is effective for the treatment of steroid-refractory RN[9–11] via decreased vessel permeability and resultant edema.[12] These studies reported mean reduction rates of 48–80% of the contrast enhanced lesion on MRI following the bevacizumab treatments.[4,12–14] These results mean the improvement of vascular permeability in the RN. Concerning the association between VEGF and hydrocephalus, elevated VEGF levels have been observed in the CSF of very young children with hydrocephalus.[15–17] VEGF infusion experiments have reportedly led to ventriculomegaly, ependymal changes, loss of adhesion molecules[18] and cilia,[19] and ependymal denudation.[20] It is thought that these pathological changes might lead to increased CSF protein levels. Accordingly, anti-VEGF agents have been considered potentially useful in the treatment of hydrocephalus.

In the present case, in addition to needing treatment for RN, our patient required chemotherapy for BC, and bevacizumab was chosen because it is among the standard chemotherapy agents for treating human epidermal growth factor receptor 2 negative BC.[21] Moreover, we intended to observe whether the CSF protein level of the patient would decrease during the administration of bevacizumab. Furthermore, we anticipated improvement in the conditions caused by the RN, such as brain edema and hydrocephalus, through the above-mentioned

mechanisms. To the best of our knowledge, there have been no reports about the changes in the CSF protein level following administration of bevacizumab, because usually there is no opportunity to examine the CSF in patients treated with bevacizumab. In this patient, we needed to determine the CSF protein level in order to perform insertion of the V-P shunt, and we were able to collect the CSF easily and safely from the ventricular drainage system.

We observed that the CSF protein level decreased immediately within 2 days after administration of bevacizumab in each of the two courses of this regimen, without any improvement in the hydrocephalus or brain edema. It is admittedly possible that paclitaxel also contributed to the reduction of CSF protein level. In the second course, only bevacizumab was administered; however, the CSF protein level decreased in the same fashion as observed in the first course, in which paclitaxel was concomitantly used. Accordingly, it was considered that bevacizumab played an important role in decreasing the CSF protein level. Unfortunately, the CSF protein level returned to its initial level within 2 weeks each time. The terminal half-life of bevacizumab is reported to be approximately 20 days.[22,23] Consequently, the working time of the agent is 2–3 weeks. However, hydrocephalus had not improved after bevacizumab therapy in this case. It is likely that either VEGF was not the only factor contributing to the hydrocephalus and increased CSF protein level or that the working time of bevacizumab was too short to improve the hydrocephalus. Accordingly, we removed the ventricular drainage system and replaced it with a V-P shunt because the external drainage system had never been occluded despite the high CSF protein levels. After the V-P shunt was inserted, hydrocephalus and brain edema improved in due course. The patient continued to undergo 10 more courses of the combination therapy at 2-week intervals. Finally, at the end of therapy with bevacizumab, the CSF protein level had decreased to 338 mg/dL, which was less than half the level it was before the therapy was initiated. Possible mechanisms explaining the decrease in CSF protein level include the gradual reduction of capillary permeability in the ependyma due to improvements in the ventricular size after V-P shunt placement and the long-term usage of bevacizumab, which may also have exerted an effect in reducing leakage of protein through the functional normalization of the intracranial vascular endothelium.

Conclusion

Bevacizumab had a dramatic effect on the reduction of the CSF protein level of a patient with RN that resulted from tomotherapy used to treat an anaplastic astrocytoma. The long-term administration of bevacizumab could serve to reduce the leakage of protein from the vessels around the ventriculus without any critical side effects. This is the first report concerning a change in the CSF protein level of a patient with RN treated using bevacizumab. Further studies are needed to confirm the effect itself and to analyze the association between the frequency of bevacizumab administration and the duration of its effect.

Author Contributions

Conceived and designed the study: HY, TI. Performed medical operations: HY, NN, TI. Pathology: HY, NO. Performed the radiosurgery: KMi, JS. Performed chemothrerapy and follow-up care: KMo, MF. Contributed to the writing of the manuscript: HY, JS, TI. Agree with manuscript results and conclusions: HY, NN, KMo, MF, NO, MiK, JS, TI. Made critical revisions and approved final version: HY. All authors reviewed and approved of the final manuscript.

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