

Glioblastoma with concomitant moyamoya vasculopathy in neurofibromatosis type 1: illustrative case

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BACKGROUND In a case of concurrent glioblastoma and moyamoya vasculopathy, it is arduous to safely perform surgery because the brain is highly vulnerable and collaterals are sometimes well developed. In addition, radiotherapy carries a risk of aggravating moyamoya vasculopathy, and chemotherapeutic agents also have a risk of interfering with collateral development.

OBSERVATIONS A 48-year-old woman with neurofibromatosis type 1 was admitted because of left hemiparesis and hemispatial neglect. Brain imaging studies revealed a large mass with peripheral enhancement in the right frontal lobe and occlusion of the bilateral middle cerebral arteries with an abnormal vascular network at the base of the brain. Total tumor resection was performed, and the pathological diagnosis was isocitrate dehydrogenase–mutant glioblastoma. Radiotherapy with a total dose of 60 Gy was delivered with concurrent temozolomide, and thereafter six cycles of adjuvant temozolomide were given. Progression of moyamoya vasculopathy without symptoms was observed after the completion of each of radiotherapy and adjuvant temozolomide.

LESSONS The authors present the first adult case of glioblastoma with moyamoya vasculopathy. Careful consideration and attention should be given throughout treatment to avoiding moyamoya vasculopathy–related ischemic and hemorrhagic events. Although the patient did not exhibit neurological deterioration, progression of moyamoya vasculopathy occurred early after radiotherapy and continued thereafter.

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KEYWORDS glioblastoma; moyamoya vasculopathy; neurofibromatosis type 1

Moyamoya vasculopathy is characterized by stenosis or occlusion of the distal intracranial internal carotid artery or the proximal anterior and/or middle cerebral artery and abnormal collateral network at the base of the brain.^{1–3} Patients with known associated conditions such as neurofibromatosis type 1, sickle cell disease, and Down syndrome are classified as having moyamoya syndrome, whereas those without are said to have moyamoya disease.^{2,3} Moyamoya vasculopathy rarely coexists with brain tumors: Only 13 cases have been reported so far, whereas only 1 case of a child with moyamoya vasculopathy and glioblastoma has been described.^{4–16} In moyamoya vasculopathy, the brain is highly vulnerable due to reduced blood flow, so that special attention should be given to anesthetic management and surgical procedures

when performing surgery. Moreover, postoperative radiotherapy and chemotherapy can exacerbate moyamoya vasculopathy, for which careful consideration is also required.^{17–22} Here, we present the first adult patient with glioblastoma with concomitant moyamoya vasculopathy in neurofibromatosis type 1 who underwent gross total resection of the tumor and postoperative chemoradiotherapy, and we discuss treatment strategies for such a challenging case.

Illustrative Case

A 48-year-old woman with familial neurofibromatosis type 1 was admitted to our hospital because of progressive gait disturbance. On admission, the patient exhibited mild left hemiparesis and

ABBREVIATIONS 5-ALA = 5-aminolevulinic acid; ET_{CO}₂ = end-tidal carbon dioxide; MRI = magnetic resonance imaging; SpO₂ = peripheral oxygen saturation; TTFields = tumor-treating fields; VEGF = vascular endothelial growth factor.

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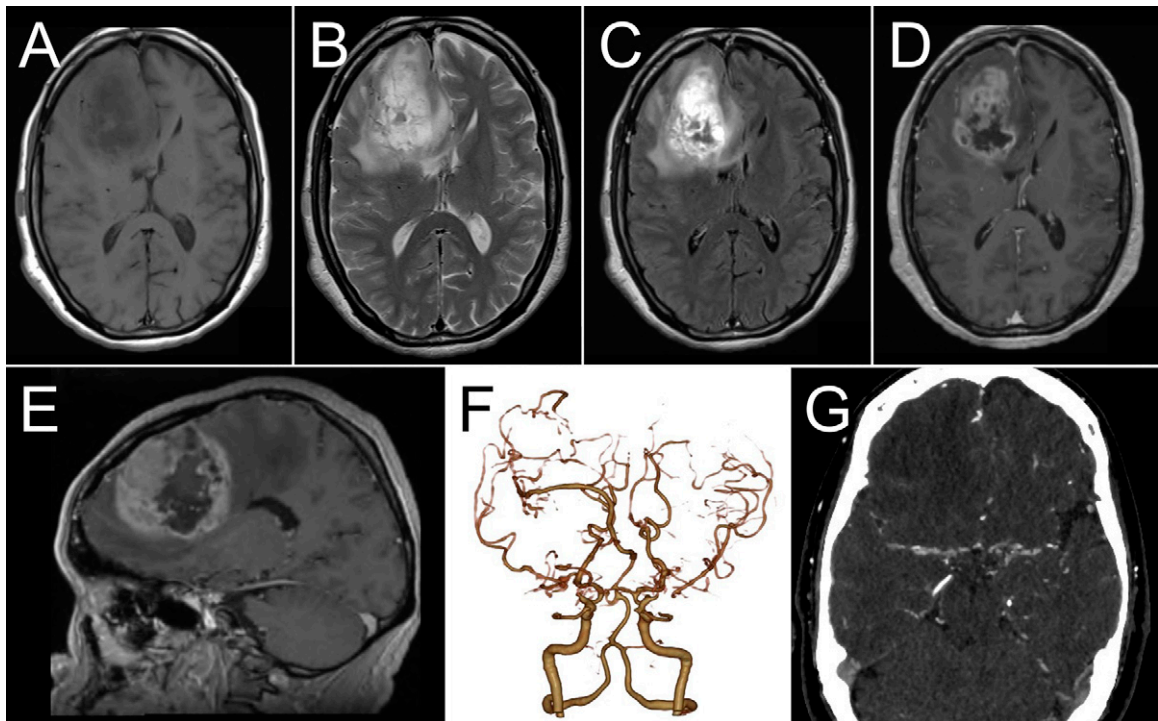


FIG. 1. T1-weighted (A), T2-weighted (B), fluid-attenuated inversion recovery (C), and contrast-enhanced T1-weighted (D and E) magnetic resonance images on admission show a large mass in the right frontal lobe with peripheral enhancement and surrounding edema. Contrast-enhanced computed tomography shows occlusion of the proximal portions of the bilateral middle cerebral arteries (F) and abnormal vasculature at the base of the brain (G).

hemispatial neglect. Magnetic resonance imaging (MRI) and computed tomography disclosed a large mass in the right frontal lobe with peripheral enhancement and surrounding edema (Fig. 1A–E) and occlusion of the proximal portions of the bilateral middle cerebral arteries with an abnormal vascular network at the base of the brain (Fig. 1F and G), which were suggestive of a brain tumor with concomitant moyamoya vasculopathy. In order to evaluate the vasculature at the base of the brain and around the tumor and collaterals from the ophthalmic and external carotid arteries, digital subtraction angiography was performed. The bilateral middle cerebral arteries were occluded proximally, and the abnormal networks with puff-of-smoke appearance were found (Supplementary Figs. 1A, 1B, and 2). The tumor was supplied by the cortical branches of the anterior and middle cerebral arteries through

abnormal, degenerated vessels with a faint tumor blush (Supplementary Fig. 1A–D). An ophthalmic artery collateral via the anterior ethmoidal and anterior falcine arteries to the frontal lobe anterior to the tumor was identified (Supplementary Fig. 1B and D). Minor transdural supply to the tumor via the occipital and middle meningeal arteries was also observed (Supplementary Fig. 1E). On the basis of angiographic findings and underlying neurofibromatosis, we made the diagnosis of moyamoya syndrome. Single-photon emission computed tomography with *N*-isopropyl-*p*-[¹²³I]-iodoamphetamine revealed reduced blood flow in the tumor and its surrounding edema (Fig. 2). Echocardiography and chest radiography findings were within normal limits.

The patient underwent total tumor resection with the aid of neuronavigation and 5-aminolevulinic acid (5-ALA) fluorescence. 5-ALA

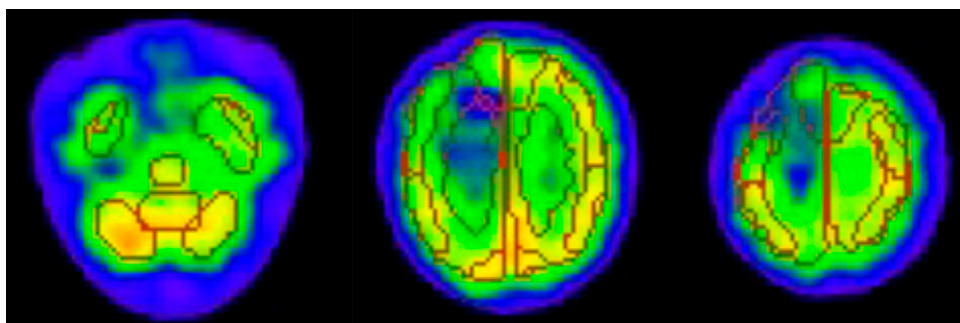


FIG. 2. Single-photon emission computed tomography with *N*-isopropyl-*p*-[¹²³I]-iodoamphetamine shows reduced blood flow in the tumor and its surrounding edema in the right frontal lobe, with the ratio of blood flow in the territory of the right middle cerebral artery to that in the ipsilateral cerebellum being 0.71.

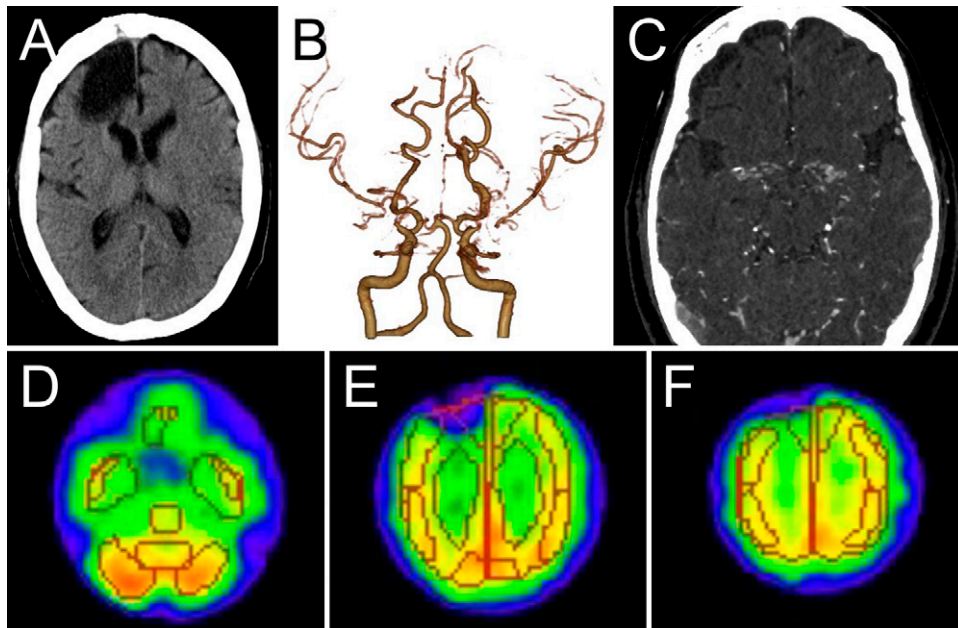


FIG. 3. **A:** Computed tomography (CT) shows the tumor resection cavity with no surrounding edema in the right frontal lobe. **B and C:** Contrast-enhanced CT before radiotherapy shows no significant change in the intracranial arteries or abnormal vasculature at the base of the brain compared with that before surgery (Fig. 1F and G), except for the disappearance of the right anterior cerebral artery sacrificed during surgery. **D–F:** Single-photon emission computed tomography with *N*-isopropyl-*p*-[¹²³I]-iodoamphetamine shows improved blood flow in the right frontal lobe (Fig. 2), with the ratio of blood flow in the territory of the right middle cerebral artery to that in the ipsilateral cerebellum being 0.78.

at a dose of 20 mg/kg was administered orally 2 hours before induction of general anesthesia. The dura mater was incised at the anterior edge of the tumor under neuronavigation so as not to disrupt the dural collateral from the anterior falcine artery. The largest branch of the anterior cerebral artery supplying the tumor was sacrificed (Supplementary Fig. 1B and D). Only slight fluorescence was observed in some areas of the tumor. Bleeding from the tumor was mild and readily controlled; total blood loss was approximately 200 mL. The pathological diagnosis was isocitrate dehydrogenase-mutant glioblastoma (Supplementary Fig. 3). During surgery, although normotension, normovolemia, and normocapnia were consciously maintained, the patient experienced several temporary decreases in peripheral oxygen saturation (SpO₂) and end-tidal carbon dioxide (ETCO₂). Pulmonary embolism was suspected, but deep vein thrombosis was not detected by in situ ultrasonography. Repeated endotracheal tube suctioning ameliorated SpO₂ and ETCO₂.

A postoperative chest radiograph obtained in the operating room disclosed development of pulmonary edema (Supplementary Fig. 4), so ventilation was continued in the intensive care unit. Laboratory analysis revealed a serum albumin level of 1.9 g/dL (3.3 g/dL preoperatively) and a hemoglobin level of 12.1 g/dL (12.4 g/dL preoperatively). Because hypoalbuminemia seemed to contribute to exacerbation of the patient's respiratory condition, human serum albumin was administered. The patient's respiratory condition gradually improved, and, 1 day after surgery, extubation was performed. There was no neurological deterioration, and MRI showed gross total resection with no residual contrast enhancement (Supplementary Fig. 5). Over the ensuing 4 weeks, left hemiparesis and hemispatial neglect resolved; brain edema was significantly reduced, and cerebral blood flow was also improved

(Fig. 3). Then, according to the Stupp protocol, radiotherapy (total dose of 60 Gy in 2-Gy fractions) with concurrent temozolomide was started, and the internal carotid arteries was included in the radiation field; temozolomide was withdrawn for the last 2 weeks because of neutropenia. At the end of radiotherapy, the patient exhibited no manifest neurological deficit, but mild progression of moyamoya vasculopathy was observed (Fig. 4). After a 4-week break, six cycles of adjuvant temozolomide were undertaken, and, at the end, no neurological deficit was found, but further mild progression of moyamoya vasculopathy was observed (Fig. 5).

Discussion

Observations

In a case of concurrent brain tumor and moyamoya vasculopathy, it is arduous to formulate and safely implement treatment strategies. There are caveats for each of the surgical procedures, perioperative management, radiotherapy, and chemotherapy. In the present case, careful consideration and attention were given to all of those, and no noticeable neurological deterioration was observed at the end of chemotherapy. However, progression of moyamoya vasculopathy occurred in the early stage after radiotherapy and continued thereafter.

When planning surgery of patients with moyamoya vasculopathy, information regarding collaterals from ophthalmic superficial temporal, occipital, and middle meningeal arteries is essential.^{3,23} If the collaterals supply a brain tumor, sufficient attention should be paid to collateral vessel injury and bleeding during skin incision and dural manipulation. Moreover, if the collaterals supply brain regions

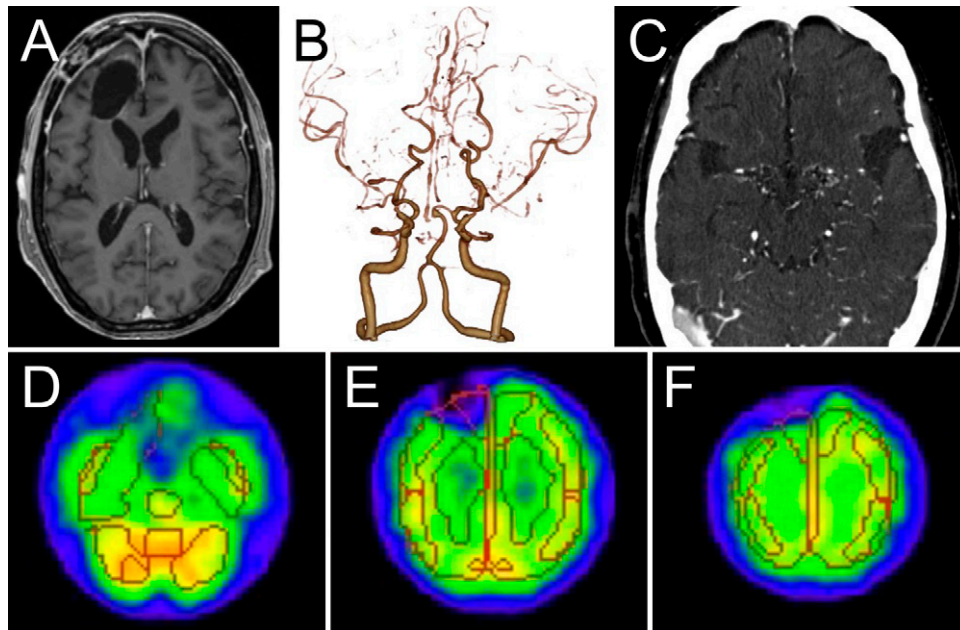


FIG. 4. A: Contrast-enhanced T1-weighted magnetic resonance imaging shows no recurrence of the tumor, with small high-intensity regions around the tumor resection cavity indicating the postoperative degeneration. **B and C:** Contrast-enhanced computed tomography 1 day after the completion of radiotherapy shows attenuation of the middle cerebral arteries and abnormal vasculature at the base of the brain compared with that before surgery (Fig. 1F and G) or that before radiotherapy (Fig. 3B and C). **D–F:** Single-photon emission computed tomography with *N*-isopropyl-*p*-[¹²³I]-iodoamphetamine shows reduced cerebral blood flow (Fig. 3D–F), with the ratio of blood flow in the territory of the right middle cerebral artery to that in the ipsilateral cerebellum being 0.70.

other than the tumor, their disruption may cause cerebral infarction. In the present case, transdural collateral supply to the brain region anterior to the tumor existed, which could be safely preserved by incising the dura mater at the anterior edge of the tumor with the use of neuronavigation.

In general, during surgery of patients with moyamoya vasculopathy, it is imperative to maintain adequate fluid balance and normocapnia and to avoid hypotension.^{2,3} Although these were appropriately managed throughout surgery, and although preoperative echocardiography and chest radiography showed no abnormalities, the patient developed pulmonary edema with hypoalbuminemia. The underlying mechanism of pulmonary edema may be neurogenic;²⁴ there have been no reports so far regarding neurogenic pulmonary edema that developed during surgery for glioblastoma or moyamoya vasculopathy. The etiology of neurogenic pulmonary edema is suspected to be a surge of catecholamine resulting from the stimulation of the hypothalamus or the medulla, though not well elucidated.²⁴ In the present case, major surgical manipulation of the vulnerable brain due to reduced blood flow may have triggered the catecholamine surge through some pathway, which led to a direct injury to the pulmonary endothelium or physical opening of the tight junctions in the endothelium, allowing albumin leakage.^{24–26} Mercifully, the patient's respiratory condition improved early, but a case of fatal neurogenic pulmonary edema after brain tumor surgery has also been reported.²⁵

Nine cases of radiotherapy for brain tumors with concomitant moyamoya vasculopathy have been reported.^{4,5,7–10,13,15,16} The median age was 9 years (range, 3–66 years); the most common

tumor type was craniopharyngioma, followed by meningioma; the median radiation dose was 48 Gy (range, 46–60 Gy); the median follow-up period was 7 months (range, 0–60 months); and only one case experienced a progressive decrease in cerebral blood flow during the 18-month follow-up period. However, on the one hand, because the number of cases and the follow-up period are limited, and because the radiation dose and location differ between cases, it is difficult to fully understand the effect of radiotherapy on moyamoya vasculopathy from past reports. On the other hand, there are several reports of radiation-induced moyamoya vasculopathy. Most were young patients; vasculopathy developed at a median of 5 years after radiotherapy with doses exceeding 50 Gy; and the incidence was highest in optic pathway glioma because of its proximity to the circle of Willis.^{17,19,20} In the present case, radiotherapy with a total dose of 60 Gy was planned and delivered after the improvement of cerebral edema and blood flow, where it was impossible to avoid irradiation of the internal carotid arteries. As a result, mild aggravation of moyamoya vasculopathy was observed early after radiotherapy, and thereafter its further aggravation was observed. Although fortunately the patient exhibited no noticeable neurological deficit, we need to bear in mind that progression of moyamoya vasculopathy can occur even in the early stage after delivery of radiation. Careful long-term follow-up is necessary.

Special consideration is also required in chemotherapy for patients with moyamoya vasculopathy. The addition of bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor, to radiotherapy with concurrent temozolomide may improve progression-free survival,

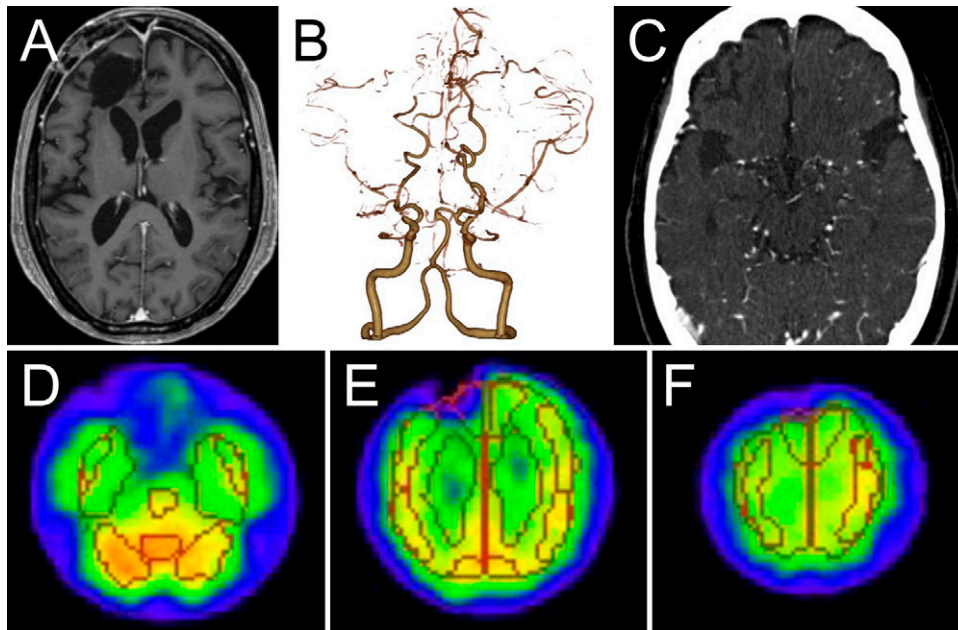


FIG. 5. A: Contrast-enhanced T1-weighted magnetic resonance imaging shows no recurrence of the tumor. **B and C:** Contrast-enhanced computed tomography after the completion of six cycles of adjuvant temozolomide shows further attenuation of the middle cerebral arteries and abnormal vasculature at the base of the brain compared with that 1 day after the completion of radiotherapy (Fig. 4B and C). **D–F:** Single-photon emission computed tomography with *N*-isopropyl-*p*-[¹²³I]-iodoamphetamine shows that the ratio of cerebral blood flow in the territory of the right middle cerebral artery to that in the ipsilateral cerebellum was 0.71.

whereas higher plasma concentration of VEGF and increased VEGF expression in the dura mater leading to collateral formation were observed in patients with moyamoya vasculopathy,^{27–29} bevacizumab administration has a risk of interfering with collateral development and causing ischemic events.³⁰ Therefore, bevacizumab was not used in the present case.

This is a single case report with limited follow-up data. Therefore, a case series with longer-term follow-up is required to further support our findings. In addition, tumor-treating fields (TTFields) therapy has been reported to improve progression-free survival and overall survival of patients with glioblastoma. Although TTFields therapy was not performed in this case, it might have altered the postoperative course.³¹

Lessons

We present the first adult case of glioblastoma with concomitant moyamoya vasculopathy. Careful consideration and attention should be given to each of surgical procedures, perioperative management, radiotherapy, and chemotherapy to avoid moyamoya vasculopathy-related ischemic and hemorrhagic events. Although the patient did not exhibit neurological deterioration, progression of moyamoya vasculopathy occurred in the early stage after delivery of radiation and continued.

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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: Tanioka, Tanaka, Suzuki. Acquisition of data: Tanioka, Fujiwara, Yago, Tanaka. Analysis and interpretation of data: Tanioka, Fujiwara, Yago, Suzuki. Drafting the article: Tanioka, Ishida. Critically revising the article: Tanioka, Tanaka, Suzuki. Reviewed submitted version of manuscript: Tanioka, Fujiwara, Yago, Ishida, Suzuki. Approved the final version of the manuscript on behalf of all authors: Tanioka.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article. *Supplementary Figs. 1–5.* <http://thejns.org/doi/suppl/10.3171/CASE21708>.

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