

## Symptomatic Developmental Venous Anomaly with an Increased $\beta$ 2-microglobulin Level in Cerebrospinal Fluid: A Case Report

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### ABSTRACT

**Background:** Gadolinium-enhanced magnetic resonance imaging (MRI) can be used to observe the progression of cerebral infarction, which sometimes mimics malignant brain tumors. While the  $\beta$ 2-microglobulin ( $\beta$ 2MG) level in blood plasma or cerebrospinal fluid (CSF) is useful for the diagnosis of malignant tumors or degenerative diseases, these results may create confusion regarding a definitive diagnosis, because it is not a specific marker. We present a rare case of symptomatic developmental venous anomaly (DVA), accompanied by transient, irregular, enhanced cerebral lesions and elevated  $\beta$ 2MG in the CSF.

**Case Description:** A 56-year-old woman developed dysarthria and underwent MRI, which revealed a right frontal hyperintense area around a previous lesion on diffusion-weighted imaging (DWI). She was treated based on the tentative diagnosis of an ischemic cerebrovascular event, and symptoms subsided in 3 days. MRI on day 7 revealed an enlargement of the hyperintense area on DWI. Post-gadolinium MRI showed multiple, enhanced patchy areas in the right frontal lobe and an abnormally large vein connected to dilated medullary venules, indicating DVA. Magnetic resonance angiography showed no stenosis or arterial occlusion. The  $\beta$ 2MG level in the CSF was elevated at 2,061  $\mu$ g/l, and a differential diagnosis from malignant tumor was required. However, MRI on day 23 revealed total disappearance of the enhanced lesions and a decrease in the high intensity area on DWI. Considering the clinical course, the DVA was symptomatic because of the perfusion disturbance.

**Conclusion:** Careful evaluation is necessary when considering the associated pathologies and potential complications of DVA if detected near a gadolinium-enhanced lesion.

**Key words:** developmental venous anomaly, venous infarction,  $\beta$ 2-microglobulin

### INTRODUCTION

Developmental venous anomaly (DVA) refers to converging, dilated medullary veins that drain centripetally and radially into a transcerebral collector that opens into either superficial subcortical veins or deep pial veins<sup>9</sup>. DVA is a congenital venous drainage malformation that occurs sporadically as a result of intrauterine ischemia, leading to the aberrant development of the venous architecture. The incidence of this condition has been reported to be as high as 2.5%, as indicated by post-mortem autopsies<sup>16</sup>. DVA accounts for nearly 50% of all cerebral vascular malformations that are discovered in magnetic resonance imaging (MRI) studies<sup>5</sup>. Most of these lesions are benign neurovascular malformations

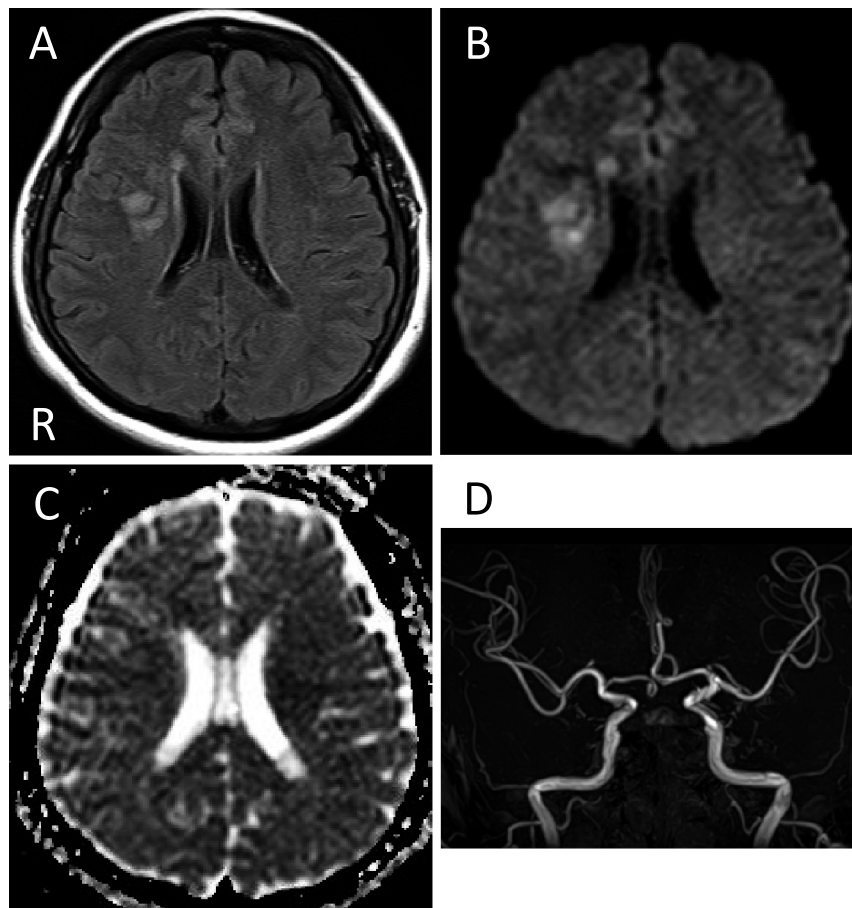
without accompanying symptoms. When DVA becomes symptomatic, mechanical, flow-related, or idiopathic mechanisms can underlie the condition, and flow-related causes account for approximately 70% of symptomatic cases<sup>14</sup>. Hemorrhages and infarctions are common morphological changes induced by DVA.

The MRI findings differ slightly depending on the time course and etiology of DVA. Diffusion-weighted imaging (DWI) and an apparent diffusion coefficient (ADC) assessment in MRI facilitate the diagnosis of the acute phase of cerebral infarction<sup>22</sup>; whereas, ischemic lesions can often be enhanced by gadolinium, as has been found with brain tumors, if the blood-brain barrier (BBB) is impaired<sup>15</sup>. In such situations, the diagnosis of DVA becomes complicated if other laboratory findings suggest the presence of a brain tumor. We present a rare case of

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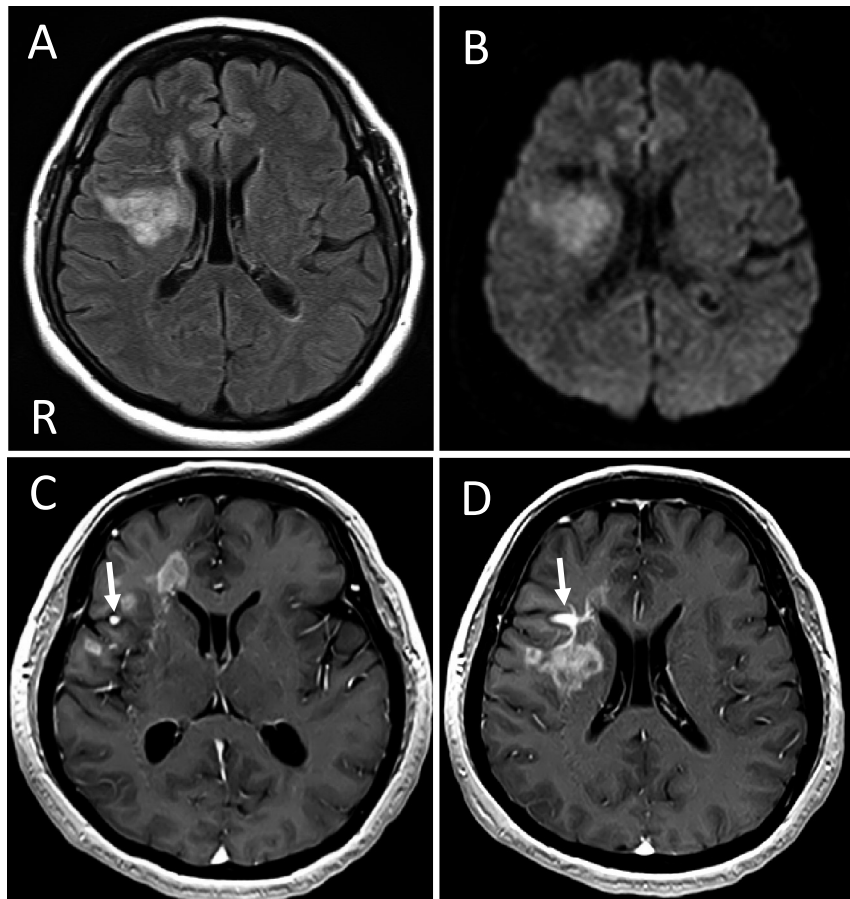
**Figure 1** Magnetic resonance imaging on day 1. A hyperintense area in the white matter of the right frontal lobe was detected by fluid-attenuated inversion recovery (A) and diffusion-weighted imaging (B). The lesion was normointense on an apparent diffusion coefficient map (C). Magnetic resonance angiography of the arterial phase did not show obvious stenosis (D).

symptomatic DVA, accompanied by transient, enhanced lesions in the cerebrum and increased  $\beta$ 2-microglobulin ( $\beta$ 2MG) in the cerebrospinal fluid (CSF).

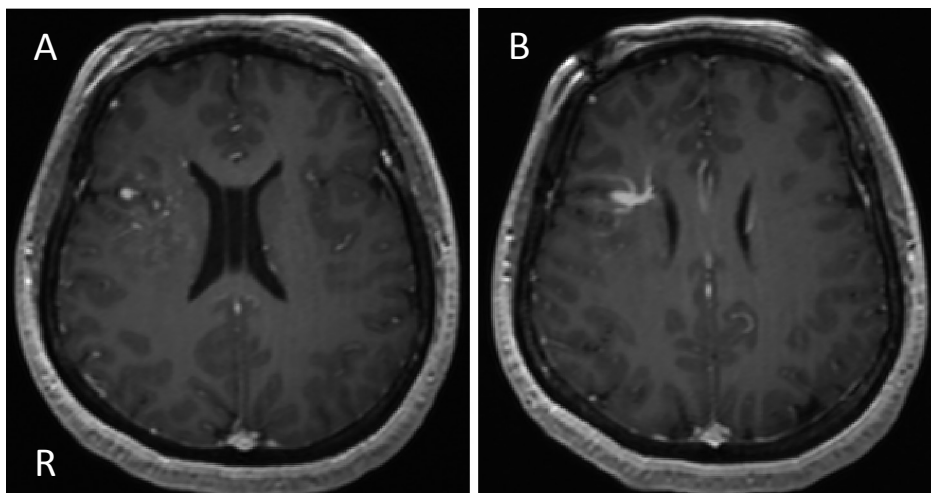
### CASE PRESENTATION

A 56-year-old woman had been taking 100 mg/day of aspirin for the last 6 years, because of a right frontal white matter lesion in the right frontal lobe that had been found during a voluntary brain MRI check-up. On the day of onset, the patient was aware of mild dysarthria and visited a primary care hospital. She had mild dysarthria during the consultation, and the MRI showed a hyperintense lesion in the right frontal lobe near an old lesion on DWI and in the fluid-attenuated inversion recovery (FLAIR) images (Figure 1). On the other hands, the ADC was not changed in the lesion. Magnetic resonance imaging (MR) angiography did not reveal stenosis or the occlusion of any arteries, and T2-weighted imaging showed an abnormal large vein, which indicated DVA. The results of the blood studies, which consisted of blood cell counts, and the results of both the biochemistry and coagulation studies were within the normal limits. The patient's symptom was diagnosed as a brain infarction, and infusion therapy was initiated with oza-grel sodium and edaravone. With the treatment, the dysarthria subsided in 3 days, and she had no other

neurological deficits. However, a follow-up MRI on day 7 revealed that the hyperintense lesion had increased on DWI, and the post-gadolinium MRI on day 8 revealed an inhomogeneous enhanced lesion. Post-gadolinium MRI also detected DVA with the appearance of classical caput medusae in the right frontal lobe, which drained to the superior sagittal sinus through the cortical veins (Figure 2). The  $\beta$ 2MG level increased to 2,061  $\mu$ g/l in the CSF study, which ruled out a malignant or degenerative disease. The patient was moved to the university hospital for a differential diagnosis. After the patient was moved to the hospital, the post-gadolinium MRI on day 23 demonstrated the complete disappearance of the enhanced lesions (Figure 3). MRI on day 30 did not show any changes with DWI, but the ADC of the lesion showed an increase. No obvious stenosis of the DVA was observed (Figure 4). From the CSF study on day 29, the  $\beta$ 2MG level was 1,600  $\mu$ g/l, and the myelin basic protein and oligoclonal bands were not detected. In addition, a computerized tomography scan of the body did not detect any obvious abnormalities. She was diagnosed with venous congestion from the course of the disease. She has been followed for more than 5 years; she has not been taking medication, and she has been living without any neurological events.



**Figure 2** Magnetic resonance imaging on days 7 and 8. The hyperintense area increased in size, and new lesions appeared around the previous lesion, as detected by fluid-attenuated inversion recovery (A) and diffusion-weighted imaging (B). The lesions were enhanced heterogeneously, and small vessels were shown to collect and drain the dilated medullary vein (arrows) with post-gadolinium T1-weighted imaging (C, D).

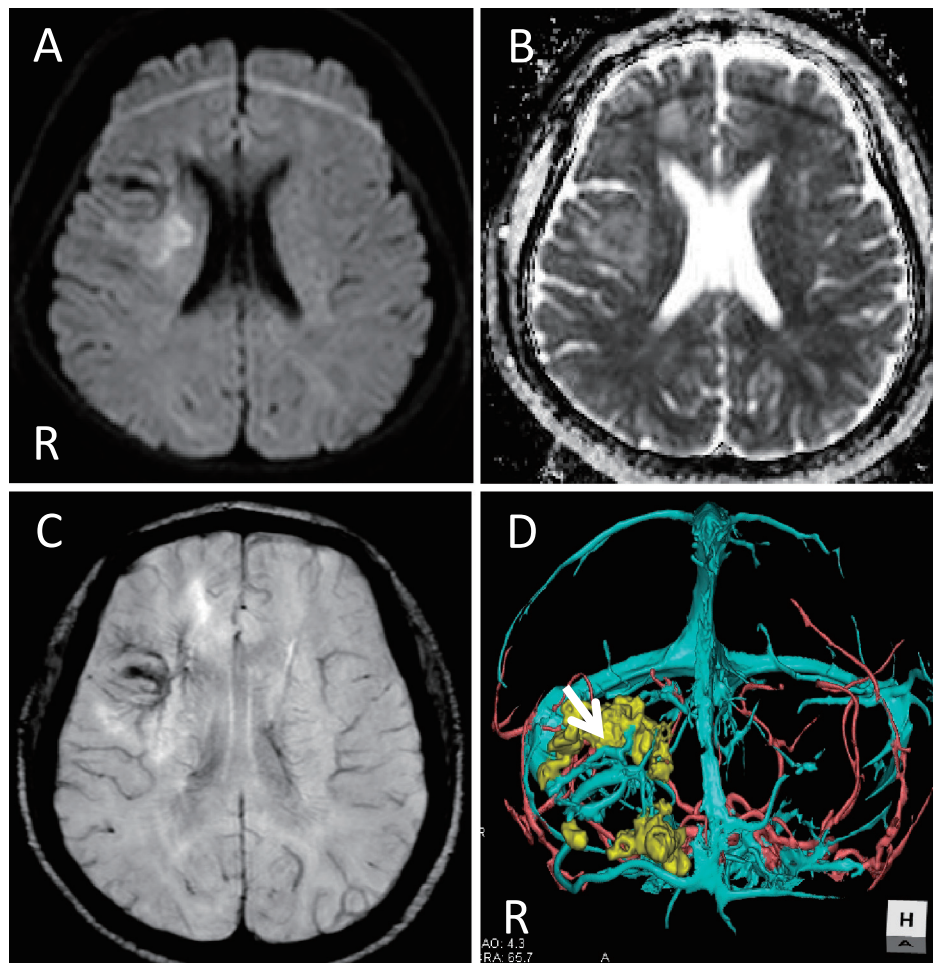


**Figure 3** Magnetic resonance imaging on day 23. The previously enhanced lesions almost disappeared. The veins had no remarkable changes with post-gadolinium T1-weighted imaging (A, B).

## DISCUSSION

DVAs occur most frequently in the frontal lobe (36–56%), followed by the parietal (12–24%), occipital (4%), and temporal (2–19%) lobes; cerebellum (14–29%); basal ganglia (6%); thalamus and ventricles (11%); and brainstem (< 5%)<sup>9,21</sup>. DVAs are often difficult to identify

with routine MRI scans, because they consist mainly of small vessels with decreased blood flow. Susceptibility-weighted imaging is ideal for detecting small vascular structures that are not visible via conventional images without the use of a contrast medium<sup>12</sup>. Although it was not performed for this patient, angiography can provide additional information regarding the hemodynamics of DVAs, potentially ruptured points, venous stenosis, and



**Figure 4** Magnetic resonance imaging on day 30. The hyperintense area in the white matter of the right frontal lobe decreased in size on diffusion-weighted imaging (A) but could be detected using an apparent diffusion coefficient map (B). Susceptibility-weighted imaging revealed small vessels that had collected and drained into the dilated medullary vein (C). Magnetic resonance venography revealed a venous anomaly (arrow) without obvious stenosis (D).

other associated pathologies, such as dural arteriovenous shunts or arteriovenous malformations (AVMs)<sup>14</sup>.

Flow-related complications, which result from either an increase in the inflow or a decrease in the outflow, are estimated to account for approximately 70% of symptomatic DVAs<sup>14</sup>. Increased inflow is caused by microshunts into DVAs or AVMs that drain into DVAs; whereas, decreased outflow occurs due to anatomical obstruction of the venous collector or draining sinus or due to a functionally distant high-flow shunt. Our patient experienced neurological deficits without signs of an obvious AVM, arterial venous shunt, or venous/sinus obstruction on MRI. These findings suggest that the etiology of her condition is attributed to the increased inflow of a microshunt into the DVA. On the other hand, it may be possible that our patient had a transient obstruction or stenosis of the draining vein and that the condition improved following the initial treatment, because deep cerebral venous thrombosis can lead to extensive venous congestion and vasogenic edema without early infarction<sup>6</sup>. The MRI lesion with high signal intensity on the T2-weighted image and the post-gadolinium MRI findings indicated the presence of vasogenic edema, due to destruction of the BBB. Twelve percent of venous ischemia have been reported to be

associated with this finding<sup>8</sup>. ADC, calculated based on the DWI, can facilitate the differential diagnosis of a malignant tumor, because the ADC decreases with a malignant tumor and increases with vasogenic edema which usually occurs in the early phase of brain infarction<sup>23</sup>. However, an increased DWI intensity in brain infarction may correspond to both an increase and a decrease in the ADC, indicating the coexistence of vasogenic and cytotoxic edemas<sup>10</sup>. The interpretation of the ADC results in patients with venous infarction requires caution; Lövblad et al. reported 6 cases of this, 4 of which had superficial venous thrombosis and areas of decreased ADC, while 2 of which had deep venous thrombosis and areas of increased ADC<sup>10</sup>.

The increases in the  $\beta$ 2MG levels in the CSF are believed to be local changes in the central nervous system<sup>1</sup>. The increase in  $\beta$ 2MG in the blood plasma or CSF may be indicative of many different disease conditions, such as multiple sclerosis, Neuro-Behçet's disease, sarcoidosis, acquired immunodeficiency syndrome-dementia complex, meningeal metastasis of malignant tumors, and especially, the meningeal dissemination of acute leukemia and malignant lymphoma<sup>1</sup>.  $\beta$ 2MG is not specific for the diagnosis of such diseases, but elevation of the  $\beta$ 2MG level, accompanied by the intracranial

gadolinium-enhanced lesion, served as a great marker for the diagnosis of central nervous system lymphoma<sup>18</sup>. Alternatively, Terent et al. reported that patients with infarction had increased  $\beta$ 2MG levels. In these patients, the levels of  $\beta$ 2MG gradually increased and peaked on day 4 or 5 after the infarct, and then, they remained elevated even 2 weeks after the onset of symptoms, as was observed with our patient<sup>19</sup>. Considering the existence of such cases, we had to consider the early indication of <sup>18</sup>F fluorodeoxyglucose or <sup>11</sup>C methionine positron emission tomography for the differential diagnosis of a malignant tumor<sup>4</sup>. A cerebral perfusion assessment with MR perfusion imaging may also help to differentiate cerebral infarction and malignant lymphoma, because the regional cerebral blood volume is moderately increased in malignant lymphoma<sup>3</sup>.

The therapies used to treat a thrombosis related to symptomatic DVA vary widely from serial observations to anticoagulation therapy<sup>13</sup>. Patel et al. reported 31 cases of spontaneous thrombosis related to DVA; in these cases, the average age of the patient was 27.9, and there appeared to be no predilection for sex. Several instances of DVA-related thrombosis have been reported in patients with conditions or habits, including the Factor V Leiden mutation, smoking, and oral contraceptive use, that make them susceptible to hypercoagulabilities<sup>17,20</sup>. Therefore, a laboratory workup is required for the examination of procoagulation factors or prothrombotic conditions<sup>7</sup>. When DVA is thrombosed, congestive edema with the breakdown of the BBB is a potential consequence that can lead to a hemorrhage or a true ischemic transformation<sup>14</sup>, though early recanalization of the venous collector will most likely prevent this complication<sup>23</sup>. Thus, anticoagulation has been suggested as the first-line treatment in patients with symptomatic DVA, regardless of the presence of a hemorrhage<sup>2,11</sup>. The prognosis appears to generally be good, with 73% of the cases having a good or complete recovery and 83% experiencing some form of improvement<sup>13</sup>.

## CONCLUSION

The elevation of  $\beta$ 2MG in CSF, accompanied by gadolinium-enhanced lesions in MRI, often indicates the presence of a malignant tumor. However, careful evaluation is required when considering the associated pathologies and the potential complications of DVA, if it is detected near a gadolinium-enhanced lesion.

## Conflicts of Interest Disclosure

The authors have no competing interests to disclose.

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