Cerebral Cavernous Malformations With Dynamic and Progressive Course

Correlation Study With Vascular Endothelial Growth Factor

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Background: Cerebral cavernous malformations (CCMs) are reported to exhibit a wide range of dynamic patterns including growth, regression, and de novo formation, which generally show slow and steady courses. Although the pathogenesis of CCMs is not well known, vascular endothelial growth factor (VEGF) has been suggested as a possible mediating factor.

Objectives: To report CCMs showing rapid progression over a short period and to investigate these biological characteristics.

Design: Experimental study.

Setting: Tertiary referral center, neurology department.

Patient: A 40-year-old man was admitted because of a left-sided numbness, vertigo, and ataxia, which were attributed to a pontine hemorrhage. He had experienced a left-sided weakness 6 months before admission, and thereafter had complained of intermittent headache. Serial brain magnetic resonance images showed multiple intracerebral microhemorrhages throughout the cerebral hemispheres. A biopsy of the lesion confirmed the diagnosis of CCM.

Main Outcome Measures: We investigated the expression of VEGF by immunohistochemistry of the biopsy specimen. Dynamic patterns of CCMs, obtained with spin-echo magnetic resonance images with gradientecho sequences, were compared with serial serum VEGF concentrations, determined by enzyme-linked immunosorbent assay.

Results: Immunohistochemistry of the specimen displayed increased VEGF expression. Serial magnetic resonance images during 7 months showed dynamic signal changes of the preexisting lesions and 15 de novo formations in many cortices. The VEGF level in serum increased during this dynamic period and became normal during the steady and resolving stages.

Conclusions: Cerebral cavernous malformations can be progressively deteriorating. The endothelial proliferation induced by VEGF is likely to be an important aspect of the pathogenetic mechanisms of CCMs.

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capillarylike vessels, without intervening parenchyma.¹ Although CCMs have been generally regarded as congenital lesions that arise as a result of disordered mesodermal differentiation during the early stages of embryogenesis,^{2,3} recent studies have documented the growth and de novo appearance of sporadic or familial CCMs.⁴⁻⁹

However, the molecular mechanisms underlying the genesis and maintenance of these abnormal vascular phenotypes are not well known. Several studies have supported the notion that 2 main systems of angiogenesis, vascular endothelial growth factors (VEGFs) and their endothelial cell– specific protein tyrosine kinase receptors (flk-1, flt-1), mediate various facets of blood vessel formation during vascular response to injury and disease.^{10,11}

We studied an unusual sporadic case of multiple CCMs that showed an aggressive behavior, and we investigated the biological activities of these CCMs to elucidate the mechanisms underlying their growth and de novo genesis.

REPORT OF A CASE

A 40-year-old man was admitted because of sudden vertigo, numbness, and leftsided ataxia. Six months before admission, he had suffered an intracerebral hemorrhage (ICH) with left-sided weakness. Magnetic resonance (MR) imaging of the brain at the time of this previous admis-

Figure 1. Representation of the dynamic signal changes of cerebral cavernous malformations (A-C, first event, initial magnetic resonance imaging; D-F, 6 months after the initial magnetic resonance imaging): Type III lesion (A) in the left anterior cerebellum changed to type I (D), and type I lesion (B) in the right frontal cortex changed to type III (E, arrow indicates the lesion studied by biopsy). Type II lesion (F) in the right pons had newly developed.

sion showed multiple intracerebral microhemorrhages throughout the cerebral hemispheres, suggestive of CCMs, although he had no relevant family history. He had also complained of a general weakness and intermittent headache during the preceding 6 months. He had no history of hypertension, dyslipidemia, trauma, seizure, or diabetes mellitus.

Brain MR images on the second admission showed dynamic signal changes and 12 de novo lesions, including a newly developed right pontine hemorrhage (**Figure 1** and **Figure 2**). On the 30th hospital day of the second admission, dysarthria, hoarseness, diplopia, and left-sided weakness developed, and follow-up MR images showed the enlarged pontine lesion and the presence of 3 de novo lesions. Investigations for coagulation abnormalities, systemic vasculitis, and cardioembolic sources showed no remarkable findings. The cerebral angiogram was also normal. The patient was treated with intravenous methylprednisolone acetate at 1 g/d for 5 days from the 30th hospital day, followed by oral prednisolone acetate (60 mg). His neurologic symptomsimproved steadily, and the oral prednisolone was slowly tapered over 4 weeks.

On the 50th hospital day, to clarify the cause of the highly dynamic, cerebral lesions, brain biopsy was performed stereotactically on the right frontal lesion. The patient was discharged in a much improved state on the 60th hospital day. One month after discharge, a follow-up brain MR image showed no signal changes or de novo formations. He remained free of recurrence of the disease during a 7-month follow-up period.

METHODS

MR IMAGING DATA ACQUISITION AND ANALYSIS

We performed MR imaging studies on a 1.5-T MR unit (Signa Horizon, Echospeed; General Electric Medical Systems, Waukesha, Wis) with echoplanar imaging, as described in previous studies from our group.^{12,13} The standardized MR imaging protocol consisted of fast spin-echo, T2-weighted images (repetition time/echo time, 4200/112 milliseconds; field of view, 21×21 cm; matrix, 256×192 ; and slice thickness, 5 mm with 1.5-mm gap) and T2*-weighted gradient-echo sequences (repetition time/ echo time, 200-500/15 milliseconds; flip angle, 20°; number of excitations, 2; slice thickness, 1.4 mm; and gap width, 0.7 mm).

The lesions were classified as previously described¹⁴: type I: a high-signal core on T1-weighted images and a high- or lowsignal core with a low-signal rim on T2-weighted images; type II: a reticular mixed-signal core on T1- and T2-weighted images and a low-signal rim on T2-weighted images; type III: homogeneously isointense or low-signal area on T1- and T2 weighted images; and type IV: seen poorly or not at all on spinecho images and focally with a decreased signal on gradientecho images. In the present study, we analyzed the dynamic changes of the different signal lesions and de novo CCM formation on serial brain MR images.

HISTOLOGIC PROCESSING OF THE BIOPSY TISSUE

Tissue specimens were fixed in 4% formalin and embedded in paraffin blocks. Sequential 6-µm sections cut from paraffin blocks were deparaffinized in xylene, rehydrated, and prepared for routine histologic examination (hematoxylin-eosin

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Figure 2. Representative de novo formations of cerebral cavernous malformations. A and D are images obtained at the time of the first event. Similar images were obtained 6 months (B and E) and 7 months (C and F) after the initial imaging.

staining), immunohistochemical studies for VEGF, and Congo red staining. After being rinsed in phosphate-buffered saline, the tissue on the slide was heated in 50mM L-glycine– hydrochloric acid buffer (pH 3.5) containing 0.01% wt/vol EDTA at 95°C for 5 minutes, as a pretreatment for VEGF. The specimen then was incubated with a 1:800 dilution of primary rabbit anti–VEGF polyclonal antibody (NeoMarkers; Lab Vision Corporation, Fremont, Calif) for 48 hours at 4°C. After washing with 0.5M Tris-buffered saline, the section was incubated with a 1:200 dilution of the secondary antibody, Cy3 conjugated goat anti–rabbit IgG (Jackson ImmunoResearch Laboratories, Inc, West Grove, Pa). Immunofluorescent labeling was analyzed with a laser confocal scanning microscope (Nikon PCM-2000; Nikon Inc, Melville, NY). Alternating sections were stained in a similar way but without primary antibody. Immunoreactivity to VEGF was not detected in these sections. Congo red staining was analyzed by means of a polarizing microscope.

ENZYME-LINKED IMMUNOSORBENT ASSAY

To determine VEGF concentrations in serum, we used a commercially available sandwich enzyme-linked immunosorbent assay kit, with elevated levels defined as greater than 55 pg/mg on the basis of normal population results (Quantikine Kit; R&D Systems Inc, Minneapolis, Minn). Among the isomers of VEGF,

 $VEGF₁₆₄$ was selected because it is the main isomer expressed in cerebrovascular disorders.15-18 Ratios of VEGF protein to total protein concentration were calculated and expressed as picograms per milligram of total protein. Intra-assay and interassay variations were within the range provided by the manufacturer. The VEGF concentration in serum was determined repeatedly during the clinical deterioration and regression, ie, at onset (current admission), during the deterioration period, at steady state, and during improvement. The VEGF levels were also compared with those of age-matched, healthy controls $(n=20)$ and subjects with hypertensive pontine ICH $(n=8, 3)$ days after onset).

RESULTS

MR IMAGING ANALYSIS

By MR imaging analysis, the initial MR images at the first admission showed 13 lesions of various types (1 lesion of type I, 7 of type III, and 5 of type IV). Six months after the first admission, these lesions had changed dramatically and the total number of lesions had increased to 25. These newly developed lesions were composed of 2 of type II, 4 of type III, and 6 lesions of type IV. Seven

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Figure 3. Timetable representing dynamic signal changes in serial follow-up magnetic resonance (MR) imaging (A) and changes in vascular endothelial growth factor (VEGF) concentration in serum (B) over 9 months (0 month, first event; 6 months, second event or current admission; 7 months, progression; 8 months, steady period; 9 months, improvement period).

Figure 4. A and B, A 1-cm lesion in the frontal lobe of a 40-year-old man, compatible with cerebral cavernous malformation, composed of thin-walled dilated vascular channels with fibrotic walls and with little or no intervening brain parenchyma (hematoxylin-eosin, original magnification ×40 [A]; ×200 [B]). C, Results of immunofluorescence labeling for vascular endothelial growth factor in the same section.

months after the initial MR imaging, with clinical deterioration, the lesion number increased to 28 and all the newly developed lesions were of type IV. After prednisolone treatment (9 months after the initial MR imaging), no new lesion was detected and further morphologic changes were not observed. The timetable for these events is illustrated in **Figure 3**.

PATHOLOGICAL STUDY

A biopsy was performed of the type III lesion in the right frontal area on the 50th hospital day (Figure 1E). On pathological examination, closely apposed dilated vascular channels with fibrotic walls were observed and little or no intervening brain parenchyma was seen. Some hemosiderin deposits were observed in the surrounding brain tissue (**Figure 4**A). The capillarylike vessel walls were lined by a single layer of endothelium and collagenous adventitia (Figure 4B). Routine pathological examination demonstrated the typical findings of CCMs. Immunohistochemical study showed significantly increased VEGF expression in the lesion (Figure 4C), in contrast to the rare expression in normal brain tissue (data not shown). There were no amorphous materials, which give apple-green birefringence on polarizing microscopy (data not shown).

MEASUREMENT OF SERUM VEGF LEVELS

The VEGF concentration in serum was increased from 228.6 pg/mg (at admission) to 419.4 pg/mg (at 4 weeks) during the dynamic period (healthy control group [n=20], 59.3 pg/mg; subjects with hypertensive pontine ICH, 3 days after onset $[n=8]$, 78.4 pg/mg). Despite this dramatic increase in the VEGF concentration, serum VEGF levels during the steady and improving phases became almost normal (8 weeks, 54.2 pg/mg; 12 weeks, 71.8 pg/mg). The timetable for these results is also illustrated in Figure 3.

COMMENT

Our patient had recurrent strokelike episodes and intermittent headaches without a relevant family history, and the diagnosis of CCMs in this patient was pathologically confirmed. Remarkably, serial examinations of brain MR images showed very dynamic changes in the signal intensities of multiple lesions, and 15 de novo lesions developed during 7 months. An immunohistochemical study showed significantly increased VEGF expression in the type III lesion studied by biopsy. The progression of CCMs on brain MR imaging correlated well with higher VEGF levels. Of note, elevated VEGF levels and disease pro-

gression were altered by the administration of prednisolone.

Clinical presentation of CCMs is characterized by ICH, seizures, and focal neurologic deficits, including nonspecific symptoms such as headache, vertigo, and tinnitus, but most of the lesions remain asymptomatic.^{19,20} The CCMs range in size from grossly invisible to the involvement of a large part of an entire hemisphere, and they may be single or multiple lesions and sporadic or familial.²¹ Traditionally, CCMs have been presumed to be congenital lesions that arise during the early embryonic stage, and that grow according to malformative mechanisms and blood-flow changes.²² More recently, however, dynamic activities including enlargement, regression, and de novo formation have been described in both the familial and sporadic forms of CCM (Table).^{1,14,23-31} The possibility that the number of lesions might increase with age has been also documented.^{20,32} Reportedly, the annual risk of hemorrhage in sporadic or familial CCMs has been estimated at 0.25% to 13% per patient-year, and de novo formations appear with an incidence of 0.2 to 0.4 lesion per year. Moreover, it might be expected that the rates of hemorrhage and of de novo formation of CCMs in the actual population lie between the lowest retrospective rates and the highest prospective rates. However, the CCMs in our patient showed dynamic features well beyond this type of estimation (Table).

The underlying mechanisms inherent to the genesis and maintenance of these abnormal vascular phenotypes are not well understood. Although the appearance of new lesions can represent initial hemorrhage into an already existent but undetected lesion, another possible explanation is that a second hit in an area of genetically predisposed vasculature gives rise to the development of hemorrhages and the typical appearance of CCMs.25 Radiotherapy and dural sinus obstruction were found to be the predisposing factors for new lesions.^{7,10} The hypothesis that a neoplasticlike process might be involved in the genesis of new lesions was also supported by some reports of new lesions occurring under hormonal influence during pregnancy⁷ and the apparent seeding of a lesion along a biopsy track.33 Recent studies have clarified that 2 main angiogenic factors, ie, VEGFs and their endothelial cell–specific protein tyrosine kinase receptors, mediate various facets of blood vessel forma-

tion during vasculogenesis.^{17,34} The VEGFs and their receptors are usually down-regulated after birth, except under some physiologic or pathologic conditions.¹¹ Some immunohistochemical studies have focused on the proliferation of cavernomas and the expression of angiogenic growth factors.³⁵⁻³⁷ The expression of proliferating cell nuclear antigen was detected in the endothelium of cavernomas, indicating growth potential in these lesions³⁵; the expression of VEGF was diffusely increased, and this correlated with the recurrence of cerebrovascular malformations.^{11,36}

In the present study, the expression of VEGF was much increased in type III lesions, without apparent recent hemorrhage, and serum VEGF level was higher than those of normal controls and subjects with hypertensive pontine ICH. Furthermore, VEGF level correlated well with the patterns of CCMs on brain MR images. Although it is not clear whether the expression of VEGF occurs as a result of a nonspecific pathologic response to intracranial hemorrhage or ischemia in various lesions, or whether it occurs in only truly proliferative lesions, our report demonstrates that CCMs can be progressive and highly dynamic because of the presence of as yet undetermined mediating factors, and VEGF may be one of these factors. Further research should assess serial serum VEGF levels in healthy control subjects, subjects with ICH of various causes, and subjects with ICH related to CCMs.

The clinical features, MR imaging patterns, and VEGF levels in our patient were stabilized by glucocorticoid treatment. Glucocorticoids have been found to have suppressive effects on the expression of VEGF or transforming growth factor. $37,38$ We assume that glucocorticoids might influence the behavior of CCMs through the down-regulation of VEGF. Surgical intervention is not practical in cases of familial CCMs with multiple lesions. Further research should lead to a greater understanding of the molecular mechanisms mediating abnormal vasculogenesis in CCMs, and such understanding might lead to novel strategies for the therapeutic alteration of CCMs.

Cerebral cavernous malformations can show a highly dynamic course, and their biological activities are likely to be correlated with VEGF. We speculate that endothelial proliferation induced by VEGF is an important element in the underlying developmental and pathogenetic mechanisms of CCMs.

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