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Association of Cavernous Malformation Within Vestibular Schwannoma: Immunohistochemical Analysis of Matrix Metalloproteinase-2 and -9

—Case Report—

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Abstract

A 65-year-old man presented with a rare case of cavernous malformation with hemorrhage located within vestibular schwannoma. He had suffered hearing impairment for 20 years, and was admitted to our hospital with vertigo and ataxic gait. Neurological examination revealed hearing loss, facial nerve paresis, and left cerebellar ataxia. Magnetic resonance imaging demonstrated a left vestibular schwannoma 35 mm in diameter, as well as a heterogeneous area associated with hypointense rim within the tumor, indicating intratumoral hemorrhage. Subtotal removal of the tumor together with the fibrously encapsulated hematoma was performed through a left retrosigmoid craniotomy. Histological examination of the surgical specimen revealed cavernous malformation within vestibular schwannoma. Immunohistochemistry for matrix metalloproteinase (MMP)-2 and -9, and tissue inhibitors of metalloproteinase-2 showed strong expression in the endothelial cells of the cavernous malformation, but not in the interstitial structures. His symptoms significantly improved after surgery and he underwent gamma-knife therapy for the residual tumor. Cavernous malformations may show dynamic characteristics such as repeated hemorrhage and de novo formation. MMP-2 and -9, which are implicated in angiogenesis and hemorrhage, may be upregulated in such tumors.

Key words: cavernous malformation, hemorrhage, matrix metalloproteinase, vestibular schwannoma

Introduction

Cavernous malformations are characterized by abnormally enlarged capillary cavities without intervening brain parenchyma,[2,6,12] and are generally considered to be congenital lesions with slow and static courses.[12] However, cavernous malformations may show dynamic characteristics such as de novo formation, recurrence after total removal, rapid growth, repeated hemorrhage, and occurrence within brain tumor.[1,3,4,10,11]

Matrix metalloproteinase (MMP)-2 and -9 are proteolytic enzymes that degrade all components of the extracellular matrix including the endothelial basal lamina, by digesting type IV collagen,[5,8] and are important in tissue remodeling including vascular reconstruction.[7] However, high levels of MMP-2 and -9 have been detected in various types of structurally unstable vasculature including cerebral aneurysms, atherosclerotic carotid arteries, and brain arteriovenous malformations.[9,15] Previously, we reported increased endothelial expression of MMP-2 and -9, and tissue inhibitors of metalloproteinase (TIMP)-2 in cerebral cavernous malformations with hemorrhage,[6] suggesting involvement in the pathophysiology of cavernous malformations.

Here we report a rare case of cavernous malformation with hemorrhage located within vestibular schwannoma, with the findings of immunohistochemical expression of MMP-2 and -9.

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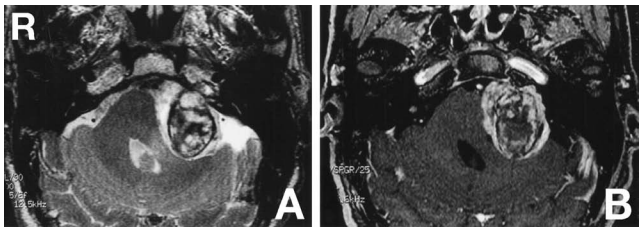

Fig. 1 **Preoperative T_2-weighted magnetic resonance image (A) demonstrating a mass 35 mm in diameter in the left cerebellopontine angle as a heterogeneous area associated with hypointense rim within the tumor, indicating intratumoral hemorrhage, and T_1-weighted image with contrast medium (B) showing strong enhancement of the circumference of the rim.**

Case Report

A 65-year-old man, who had suffered hearing impairment for 20 years, was admitted to our hospital with a 5-month history of vertigo and ataxic gait. On admission, he had no disturbance of consciousness. Pure-tone audiometry demonstrated profound left sensorineural hearing loss. Neurological examination revealed peripheral-type facial nerve paresis (House-Brackmann grade II) and left cerebellar ataxia. Magnetic resonance (MR) imaging demonstrated an extra-axial mass lesion 35 mm in diameter in the left cerebellopontine angle, which compressed the fourth ventricle and brainstem. T_1- and T_2-weighted MR imaging revealed a heterogeneous area associated with hypointense rim within the tumor, indicating intratumoral hemorrhage (Fig. 1A). The circumference of the hypointense rim was enhanced strongly with contrast material (Fig. 1B). These findings suggested left vestibular schwannoma in the cerebellopontine angle with hemorrhage.

Subtotal removal of the extra-axial tumor was performed through a left retrosigmoid craniotomy under intraoperative facial nerve monitoring. Organized old hematoma with fibrous capsule was identified within the soft tumor, which was totally removed together with the surrounding tumor except for the part located at the internal acoustic meatus and the surface of brainstem. The vestibular syndrome improved significantly after surgery, and facial nerve function was perfectly preserved. Postoperative MR imaging demonstrated that the tumor was subtotally removed. He underwent gamma-knife therapy for the residual tumor.

Histological examination revealed schwannoma consisting of spindle-shaped neoplastic Schwann cells with alternating areas of compact, elongated

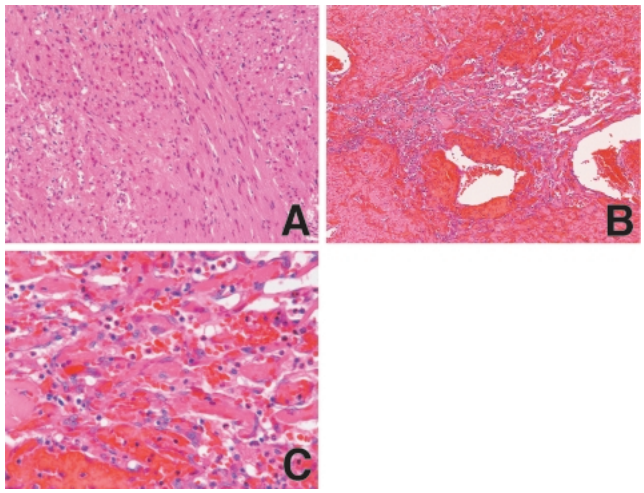

Fig. 2 **Photomicrographs of the surgical specimen showing the tumor consists of spindle-shaped cells with alternating areas of compact, elongated cells and less cellular, loosely textured tumor areas (A), with clusters of thin-walled vascular channels without intervening brain parenchyma containing blood at various stages of organization (B), and the vessel walls lack both smooth muscle and internal elastic lamina (C). Hematoxylin and eosin stains, original magnification A: ×200, B: ×100, C: ×400.**

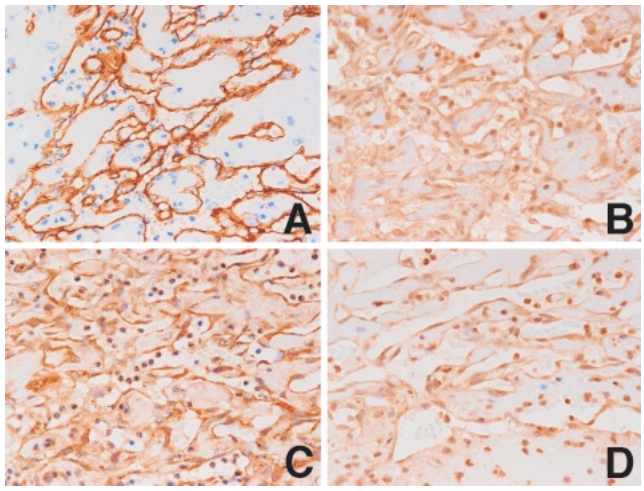

Fig. 3 **Photomicrographs showing strong immunochemical expression of CD34 (A), matrix metalloproteinase-2 (B) and -9 (C), and tissue inhibitors of metalloproteinase-2 (D) in the endothelial cells of the cavernous malformation, but not in the interstitial structures. A–D: ×400.**

cells (Antoni A) and less cellular, loosely textured tumor areas (Antoni B) (Fig. 2A). The tumor incorporated clusters of thin-walled vascular channels without intervening brain parenchyma containing blood at various stages of organization (Fig. 2B). The vessel walls lacked both smooth muscle and internal elastic lamina (Fig. 2C). Immunohistochemistry showed strong endothelial expression of CD34 (Fig. 3A). The histological diagnosis was cavernous malformation. Immunohistochemistry for MMP-2 and -9, and TIMP-2 showed strong expression in the endothelial cells of the cavernous malformation, but not in the interstitial structures (Fig. 3B–D).

Discussion

The clinical features of seven cases of cavernous malformation located within vestibular schwannoma including our present case are summarized in Table 1.[1,4,10] All patients but one had a history of hemorrhage from cavernous malformation, implying rather high incidence of hemorrhage in cavernous malformations within vestibular schwannomas.[1,4,10] In addition, fatal hemorrhage originated from the cavernous malformation in one patient. These findings indicate the relatively aggressive nature of cavernous malformation within vestibular schwannoma. In our case, preoperative MR imaging and intraoperative inspection found apparent hemorrhage from the cavernous malformation, although the patient had not experienced an apoplectic episode. Based on these findings, we recommend surgical removal if cavernous malformation within the tumor is suspected.

Table 1 Reported cases of cerebral cavernous malformation located within vestibular schwannoma

Author (Year)	Age (yrs)	Sex	Duration of symptoms (yrs)	Type of hemorrhage	Outcome
Bojsen-Moller and Spaun (1978)[1]	57	F	0.75	ITH	good
Kasantikul and Netsky (1979)[10]	47	M	26	ITH	NR
	64	M	7	SAH	death
	40	F	5	ITH	NR
	55	M	3	ITH	NR
Feiz-Erfan et al. (2006)[4]	76	M	1	none	good
Present case	65	M	20	ITH	good

ITH: intratumoral hemorrhage, NR: not reported, SAH: subarachnoid hemorrhage.

The underlying mechanism of the association of cavernous malformation within tumors and the dynamic behavior is totally unknown. Co-occurrence of cavernous malformation with nervous system tumors might be related to a common genetic pathway such as hyperactivation of the Ras oncogenes.[4] Cavernous malformation within tumors may occur as part of neoplastic growth which might be related to tumor angiogenic factors.[10] In fact, angiogenic growth factors, such as vascular endothelial growth factor (VEGF), may be involved in the development of cavernous malformation.[13,14] In the present case, we examined the expression of extracellular matrix proteins including MMP-2 and -9, and the endogenous inhibitor TIMP-2, and found increased endothelial expression of MMP-2 and -9, and TIMP-2 only in the cavernous malformation.

The marked increase in the endothelial expression of MMP-2 and -9, and TIMP-2 in our case may imply vascular instability in the cavernous malformation. Excessive degradation of the vascular matrix may contribute to the destabilization of vessels, leading to the weakness of the vessel wall, and vessel rupture. Furthermore, as MMPs may be involved in angiogenesis,[7] up-regulation of MMPs, which could be induced by tumor cytokines, may contribute to the formation of cavernous malformation within vestibular schwannoma. In our case, whether the cavernous malformation was newly formed remained undetermined, due to the lack of radiographic evaluation before the formation of the cavernous malformation. Further immunohistochemical study of angiogenic factors such as VEGF in cavernous malformations within brain tumor and sequential neuroimaging evaluation of patients with cavernous malformation within central nervous system tumors may clarify this important issue.

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