Pathomorphological Examination of Patients with the Simultaneous Rupture of Dissecting Intracranial Vertebral and Intraperitoneal Arteries: Involvement of Segmental Arterial Mediolysis in Intracranial Artery Dissection

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Objective: To examine the involvement of segmental arterial mediolysis (SAM) in intracranial artery dissection.

Methods: In four autopsy cases of subarachnoid hemorrhage related to the rupture of the intracranial vertebral artery (IVA) with intraperitoneal hemorrhage, we calculated the extent of arterial dissection using elastica van Gieson staining from the tissue sections of the left/right IVAs and intraperitoneal arteries (IPAs), and examined the properties of the vascular smooth muscle and responses of mesenchymal cells using immunostaining with anti-α smooth muscle antibody (SMA) and anti-S100A4 antibodies.

Results: The length of the adventitia at the site of IVA rupture was ≤2.4 mm, and that of disruptions of the internal elastic lamina was 5.4–11 mm. The IVA/IPA rupture sites showed acute arterial dissection. In the blood vessels at the sites of dissection, defect/necrosis of the vascular smooth muscle, which are characteristic of SAM, were noted. In three cases, the topical infiltration of mesenchymal cells was observed in the adventitia at the dissected site of the ruptured IVA. In all cases, dissection of unruptured intracranial or -peritoneal arteries was also present. Its pathological properties vary from acute to old dissection.

Conclusion: Autopsy revealed SAM-related systemic multiple arterial dissection in all cases, suggesting the involvement of SAM in the development of intracranial artery dissection.

Keywords ▶ segmental arterial mediolysis, subarachnoid hemorrhage, vertebral artery dissection, autopsy

Introduction

The etiology of intracranial artery dissection remains to be clarified. We previously investigated histopathological findings in 50 autopsy cases of the rupture of the dissecting intracranial vertebral artery (IVA), and reported that segmental arterial mediolysis (SAM) associated with extensive necrosis of the vascular media was observed at the site of IVA dissection.1) SAM is an idiopathic arterial disease proposed by Slavin et al. in 1976.2) It is histopathologically characterized by segmental medial defect/necrosis of muscular arteries as a result of mediolysis. If prior lesions, such as inflammation and arteriosclerosis, are absent as an etiological factor, a diagnosis of this disease can be made. The progression of SAM-related medial lesion induces acute arterial dissection through a disruption of the internal elastic lamina. If acute dissection is repaired by organization in the absence of adventitial rupture, its history can be histologically confirmed as old arterial dissection.

SAM occurred at intracranial arteries is rare. Before 2012, 15 patients were reported.3) In only nine of these,
pathologically verified as SAM simultaneously occurring both intracranial and -peritoneal vascular lesions.3)

In this study, we examined the pathogenesis of intracranial artery dissection based on histopathological findings in four autopsy cases of IVA-rupture-related subarachnoid hemorrhage complicated by intraperitoneal hemorrhage.

## Subjects

We investigated four autopsy cases in which administrative autopsy confirmed that mortality was related to IVA-rupture-related subarachnoid hemorrhage, and intraperitoneal hemorrhage was simultaneously observed (Cases 1–4). All patients were male, and their ages ranged from 30 to 59 years. There was no medical history, and no patient had any arterial lesion during his lifetime. In Case 1, the patient consulted a hospital twice with headache and abdominal pain the day before death, and underwent blood and urine examinations, but a diagnosis was not made. In Case 2, the patient had complained of a bad condition for a few days before death. In Cases 1–3, deaths were detected at home. In Case 4, the patient suddenly snored and died.

## Methods

After examining the distribution and volume of intracranial and -peritoneal hematomas, the left/right IVAs and intraperitoneal blood vessel at the hemorrhagic site were fixed in formalin, and embedded with paraffin.

For IVA investigation, the serial cross sections of the left and right entire areas were prepared at 0.2-mm intervals, and vascular lesions were confirmed using hematoxylin & eosin (HE) staining and elastica van Gieson (EVG) staining. The length of a dissected lesion was calculated from the number of slides with the appearance of histologic findings. In addition, immunostaining of specimens prepared at 2-mm intervals was conducted using anti-α smooth muscle antibody (SMA; DAKO; Agilent, Santa Clara, CA, USA) and anti-S100A4 (Abcam plc, Cambridge, UK) antibodies as primary antibodies.

To investigate intraperitoneal arteries (IPAs), tissue sections at approximately 30 points per patient were prepared from the cross sections of the blood vessel at the hemorrhagic site, which were prepared at 3-mm intervals. After examining the vascular histology of the entire area using HE-/EVG-stained sections, immunostaining of vascular sections at the site of dissection and its periphery with anti-αSMA and anti-S100A4 antibodies was performed.

In Cases 1 and 2, an intraperitoneal muscular artery at the non-hemorrhagic site, which is the common site of SAM, was similarly investigated. In Case 4, other sites of the cerebral arterial circle were also investigated in addition to the IVA.

## Results

### Autopsy findings

The characteristic macroscopic and histologic findings in the four cases are shown in Figs. 1–4. In all cases, thick-layer subarachnoid hemorrhage was observed at the base of the brain involving the ruptured IVA. In Case 1, intraperitoneal hemorrhage (volume: 1100 mL) was noted. In Cases 2, 3, and 4, slight localized intraperitoneal hemorrhage was observed around the greater omentum or mesentery (Figs. 2d and 4g).

### Distribution of new/old IVA dissection

In all cases, the site of rupture showed acute arterial dissection. A medial hematoma related to a longitudinal disruption of the internal elastic membrane was present, and adventitial rupture was noted at the center of the hematoma-extended site of the adventitia (Figs. 1a and 3b). The length of adventitial rupture, which was calculated on EVG staining, was ≤2.4 mm, and that of the disruption of internal elastic lamina at the rupture was 5.4–11 mm (Table 1). In Cases 1–3, multiple disruptions of the internal elastic lamina, which contributed to arterial dissection at the site of rupture, were present at several points (Figs. 1a and 2b).

In Case 1, acute dissection of the ruptured-side IVA was observed apart from the site of rupture (Fig. 1c). In Cases 2 and 3, new dissection of the non-ruptured-side IVA was present. In Cases 3 and 4, old arterial dissection with organization was noted (Figs. 3b and 4b). In Case 3, a false lumen was formed (Fig. 3b).

### Vascular properties of the IVA

Anti-αSMA antibody and EVG staining showed topical deciduation of the vascular smooth muscle in all cases. The state of deciduation varied: partial rarefaction of the arterial wall (Fig. 3c) to segmental deciduation (Figs. 1a–1d and 4b). There was no prior lesion or inflammatory change at the site of deciduation.

In Cases 1, 2, and 4, the anti-S100A4-antibody-positive mesenchymal cells were topically present at adventitia, involving the sites of intimal tears which contributed to dissecting artery rupture (Figs. 1b, 2c, and 4c). In Cases 3
Other cerebrovascular and intraperitoneal vascular lesions (Table 2)

In Case 4, in which the cerebral arterial circle was investigated, segmental decidualization of the anterior cerebral artery smooth muscle (Fig. 4e) and old dissection of this artery were observed. In addition, old dissection of the internal carotid artery (Fig. 4f) was noted.

In Case 1, several hemorrhagic sites were macroscopically present (Fig. 1e), and new dissection of the bilateral gastric arteries, bilateral gastroepiploic arteries, inferior...
pancreaticoduodenal artery, and right renal artery was observed. Old dissection of the middle colic artery, nearby the main source of hemorrhage, was noted (Fig. 1f).

In Case 2, there was no dissecting lesion in any IPA at the non-hemorrhagic site in the extent of investigation.

**Discussion**

The incidence of SAM of intracranial arteries is the second highest, following that of IPAs. It accounts for 18% of all SAM lesions. Its frequent sites are the internal carotid and vertebral arteries. SAM affects multiple arteries. We previously reported a patient who died of SAM-related subarachnoid hemorrhage, with new/old multiple intracranial artery dissection, and a patient who died of SAM-related intraperitoneal hemorrhage, with old IVA dissection. However, there has been only one case report in which the SAM-related rupture of both intracranial and -peritoneal arteries led to subarachnoid and intraperitoneal hemorrhage. Yonas et al. reported a patient who died of sudden intraperitoneal hemorrhage (the source of hemorrhage was unclear, and the rupture of an intraperitoneal arteriole was estimated), but not of subarachnoid hemorrhage, suggesting the involvement of SAM. Since their report, IVA dissection has been clinically focused on.

In our cases, the etiology of subarachnoid/intraperitoneal hemorrhage was the rupture of acute arterial dissection. Furthermore, deciduation of the vascular smooth muscle, with no prior lesion or inflammatory change in the dissecting blood vessel, was present, and it may have resulted from SAM-related medial defect/necrosis. Segmental deciduation characteristic of SAM was also observed. In addition, medial defect/necrosis or new/old non-ruptured artery dissection was noted not only in the blood vessel at the site of rupture, but also at the non-hemorrhagic site of the contralateral IVA or intracranial/peritoneal arteries. These findings suggested multiple arterial dissection related to SAM, as a systemic vascular lesion, in all cases.
If SAM is a systemic disease, it may affect any muscular artery. However, previous reports of SAM were mostly located at intracranial/-peritoneal arteries. The peripheral stroma of both arteries is relatively rough, and may cause hemorrhage at the time of rupture; therefore, this disease can be diagnosed based on the appearance of symptoms. In particular, SAM of the IVA often induces serious subarachnoid hemorrhage, and it may be clinically confirmed with a high possibility.

On the other hand, only a small number of patients with the simultaneous onset of intracranial/-peritoneal SAM have been reported; a low detection rate may be related to this. If SAM is a systemic disease, it may affect any muscular artery. However, previous reports of SAM were mostly located at intracranial/-peritoneal arteries. The peripheral stroma of both arteries is relatively rough, and may cause hemorrhage at the time of rupture; therefore, this disease can be diagnosed based on the appearance of symptoms. In particular, SAM of the IVA often induces serious subarachnoid hemorrhage, and it may be clinically confirmed with a high possibility.

Concerning the state of dissecting IVA rupture in our cases, disruptions of the internal elastic lamina measuring approximately 0.5 to 1 cm were present around the site of adventitial rupture measuring approximately 2.5 mm.

Fig. 3 Outline of Case 3. (a) Macroscopic findings of the IVA. The diameter of the right IVA was dilated due to old arterial dissection (arrow). A hematoma of the left IVA was observed around the site of rupture (arrow head). (b) Histology of the IVA (EVG staining). The true lumen of the right IVA showed narrowing (arrow head) due to old arterial dissection, with a false lumen (*). A portion of the false lumen was organized, but blood cell components remained. The left IVA was dissected, and adventitial rupture was noted (arrow). (c) Histology at the non-hemorrhagic site of the left IVA (EVG staining). Deciduation of the vascular smooth muscle (arrow) was observed. (d) Histology of the gastro-epiploic artery (EVG staining). Acute arterial dissection led to rupture (arrow). EVG: elastica van Gieson; IVA: intracranial vertebral artery; VA: vertebral artery
Table 1  Extent of intracranial vertebral artery dissection

<table>
<thead>
<tr>
<th></th>
<th>Ruptured IVA</th>
<th>Apart from the adventitial rupture</th>
<th>Contralateral IVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adventitia</td>
<td>IEL disruption</td>
<td>Adventitia</td>
</tr>
<tr>
<td>Length of rupture (mm)</td>
<td>Without</td>
<td>With</td>
<td>Without</td>
</tr>
<tr>
<td>Case 1</td>
<td>1.8</td>
<td>3 (11.0)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Case 2</td>
<td>0.4</td>
<td>3 (8.6)</td>
<td>0</td>
</tr>
<tr>
<td>Case 3</td>
<td>2.4</td>
<td>3 (5.4)</td>
<td>0</td>
</tr>
<tr>
<td>Case 4</td>
<td>0.6</td>
<td>1 (5.4)</td>
<td>0</td>
</tr>
</tbody>
</table>

*described as “number (maximum length [mm]).” IEL: internal elastic lamina; IVA: intracranial vertebral artery

Fig. 4  Outline of Case 4. (a) Vertebobasilar artery. The diameter of the right IVA around the site of rupture was dilated (arrow head). (b) Histology of the IVA (EVG staining). Segmental deciduation of the vascular smooth muscle (arrow) was observed at the non-hemorrhagic site of the right IVA. The left IVA showed repair of old arterial dissection (arrow head). (c) Histology of the IVA around the site of rupture (anti-S100A4-antibody [DAKO; Agilent, Santa Clara, CA, USA] staining). The marked infiltration of mesenchymal cells in the adventitia at the site of dissection was observed. (d) Histology of old dissection of the non-ruptured-side IVA (anti-S100A4-antibody staining). Intimal thickening (*) was present around the site of internal elastic laminal disruption (arrow head). Mesenchymal cells were partially observed. (e) Histology of the anterior cerebral artery (EVG staining). Segmental deciduation of the vascular smooth muscle (arrow) was observed. (f) Histology of the intracranial internal carotid artery (EVG staining). Old arterial dissection (arrow head) was noted. (g) Intraperitoneal cavity. Omental hemorrhage was observed at two points (arrows). (h) Histology of the left gastroepiploic artery (anti-S100A4-antibody staining). The appearance of mesenchymal cells in the blood vessel at the site of dissection (arrow) was only slight. EVG: elastica van Gieson; IVA: intracranial vertebral artery
This was similar to the results of our previous study. Adventitial rupture due to excessive extension by hematoma from arterial dissection may have led to fatal subarachnoid hemorrhage in a short period. In addition, we confirmed the repair response to the blood vessel at the site of rupture using anti-S100A4-antibody staining. In three cases, the topical responses of mesenchymal cells were observed in the adventitia at the sites of the disruptions of internal elastic lamina, which contributed to dissecting artery rupture. This may have resulted from the appearance of the mesenchymal cells in the adventitia may act as a repair response to adventitial extension related to a gradual increase in the medial hematoma size, from the development of arterial dissection until rupture.

In Case 1, the patient complained of headache the day before death, suggesting the presence of a dissecting lesion during the same period. On the other hand, in Case 3, there was no appearance of mesenchymal cells in the adventitia at the site of IVA dissection. This may have been because there was no repair response due to a relatively short interval from adventitial extension related to arterial dissection until rupture. Intracranial artery dissection may cause fatal subarachnoid hemorrhage in a short period if adventitial rupture occurs. However, the interval from hematoma invasion into the false lumen related to a disruption of the internal elastic lamina resulting from deciduation of the medial smooth muscle until adventitial extension may vary among cases. The morphology of mesenchymal-cell appearance differed among our cases, reflecting such a course of SAM; therefore, observation by anti-S100A4-antibody staining is useful for evaluating the pathogenesis in each case.

On the other hand, there was no response of mesenchymal cells in the adventitia at the site of dissecting IPA rupture in any case. This may have been because dissecting IPA rupture occurred following vertebral artery dissection in our cases, shortening the interval from rupture until death and resulting in the absence of a repair response. Additional study of patients with IPA dissection is required.

SAM affects systemic blood vessels, recurring or newly developing in another blood vessel after a specific period. In three of the four cases, we confirmed old arterial dissection that had developed prior to the present rupture. When SAM is clinically confirmed, blood flow at the lesion site is blocked to prevent hemorrhage in many cases. However, changes in hemodynamics resulting from this strategy may influence adjacent blood vessels. In our previous study, old arterial dissection was confirmed in 43% of 58 patients who died of subarachnoid hemorrhage related to acute IVA dissection, and contralateral IVA dissection was detected in 68% of these. In this study, ipsilateral or contralateral IVA dissection, differing from that at the site of rupture, was present in all cases. In Case 3, arterial dissection with adventitial extension did not lead to rupture through an organization response, but the subsequent development of acute contralateral IVA dissection resulted in rupture. If SAM is clinically confirmed, peripheral blood vessels may be fragile due to latent-SAM-related medial defect/necrosis or non-ruptured artery dissection. It is necessary to predict/prevent recurrent IVA dissection.

In addition, SAM may cause IPA dissection following head and neck artery dissection or its reverse. Kalva et al. reported the development of new extracranial internal carotid artery dissection during follow-up in 3 of 14 patients with IPA dissection. Furthermore, Shinoda et al. presented a case in which dissecting middle colic artery rupture-related intraperitoneal hemorrhage occurred 8 days after endoscopic hemostasis for subarachnoid hemorrhage related to IVA dissection. In patients with IVA dissection, the presence of systemic SAM and new onset of dissection must be considered in addition to intracranial artery dissection.

In this study, we indicated the involvement of SAM in the development of intracranial artery dissection. However, the mechanism of medial defect/necrosis in the presence of SAM remains to be clarified. An animal experiment

### Table 2: Systemic dissecting lesions

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Contralateral IVA</th>
<th>New dissection</th>
<th>Old dissection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Contralateral IVA</td>
<td>Other intracranial artery</td>
<td>Intra-abdominal artery</td>
</tr>
<tr>
<td>Case 1</td>
<td>–</td>
<td>N.E</td>
<td>+*</td>
</tr>
<tr>
<td>Case 2</td>
<td>+</td>
<td>N.E</td>
<td>–</td>
</tr>
<tr>
<td>Case 3</td>
<td>+</td>
<td>N.E</td>
<td>N.E</td>
</tr>
<tr>
<td>Case 4</td>
<td>–</td>
<td>–</td>
<td>N.E</td>
</tr>
</tbody>
</table>

**Note:**
- +*: Right and left gastric artery, right and left gastroepiploic artery, Inferior pancreaticoduodenal artery. Right renal artery; +**: Middle colic artery; +***: Anterior cerebral artery, Internal carotid artery; IVA: intracranial vertebral artery; N.E.: not examined
showed that ractopamine administration induced SAM. 15) Furthermore, a short-acting dopamine D1 receptor agonist, fenoldopam, caused experimental IPA dissection. 16) These findings suggest that angiopathy related to a rapid increase in the blood pressure in vivo is involved in the development of SAM.

We previously reported the presence of medial defect/necrosis prior to IVA dissection. 11) In addition, in this study, in autopsy cases of the simultaneous onset of IVA dissection and intraperitoneal muscular artery dissection, we confirmed medial defect/necrosis of both arteries, suggesting the involvement of SAM in the pathogenesis of intracranial artery dissection. To clarify the pathogenesis, further detailed examination of intraperitoneal vascular lesions must be conducted in patients with intracranial artery dissection. This issue should be investigated in a larger number of patients and autopsy cases.

## Conclusion

We reviewed patients with multiple dissecting intracranial and -peritoneal artery rupture, and indicated systemic multiple arterial dissection involving SAM as a background factor. The results suggested the involvement of SAM in the development of intracranial artery dissection. In patients with intracranial artery dissection, the presence or absence of concomitant dissection of other systemic arteries or post-treatment recurrence must be carefully checked, considering SAM.

## Acknowledgment

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## Disclosure Statement

There is no conflict of interest for the main author and coauthors.

## References