Subarachnoid Hemorrhage and Granulomatous Angiitis of the Basilar Artery: Demonstration of the Varicella-Zoster-Virus in the Basilar Artery Lesions

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SUMMARY A 70-year-old man, with regional herpes zoster (C2) of 10 weeks duration, died following subarachnoid hemorrhage caused by the rupture of an aneurysm in the basilar artery. Granulomatous angiitis, with multinucleated giant cells, was found at autopsy in the wall of the aneurysm. Electron microscopy of the basilar artery disclosed intracytoplasmic viral particles with an envelope which measured 150–220 nm in diameter. Immunohistochemistry studies revealed varicella-zoster-virus-related antigen in the cytoplasm and/or in the nucleus of histiocytes in the vessel wall. These findings suggest that varicella-zoster virus may be linked to the development of granulomatous angiitis.

Case Report
In May 1983, a 70-year-old Japanese man consulted a dermatologist because of pain and cutaneous lesions in the occipital region following symptoms of a common cold. He was admitted to Shin-Nittetsu Hospital and was treated with analgesics, vitamins, anti-inflammatory drugs, gamma-globulin and occasional stellate ganglion blocks. He also received antiviral therapy. Fever and pain persisted. About 70 days after the onset of this illness, he fainted and cardiac arrest occurred. He was soon resuscitated and transferred to the intensive care unit in Kyushu University Hospital. Massive inoperable subarachnoid hemorrhage was diagnosed following brain computer assisted tomography. The patient died several hours later.

Laboratory Data
Blood pressure, complete blood count, chest X-ray, blood-glucose, serum-enzymes and -electrolytes were within normal limits for the full period of this episode. Mild proteinuria was present, but renal dysfunction and inflammation were mild. Left axis deviation, left ventricular hypertrophy and coronary ischemic changes were detected on the electrocardiograms. Serum antibody titers to varicella-zoster virus were 32X, 32X, and 16X (normal; below 4X), 40, 50 and 60 days after the onset of the common cold-like symptoms, respectively.

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GRANULOMATOUS ANGIITIS BY V-Z VIRUS/Fukumoto et al

Pathologic Observations

Autopsy revealed pulmonary emphysema, cardiomegaly (430 gram), splenomegaly (130 gram), chronic cystitis and benign prostatic nodular hyperplasia. Vasculitis was present only in the central nervous system.

Neuropathologic Findings

The subarachnoid space was filled with blood caused by rupture of an aneurysm in the basilar artery (fig. 1) and bilateral uncinate and cerebellar herniations were present. Microscopic examination of the walls of the above aneurysm (fig. 2) revealed a granulomatous angiitis infiltrated with multinucleated giant cells, lymphocytes and histiocytes (fig. 3). Destruction of internal elastic lamina was also evident (fig. 4). Gram staining and Periodic Acid Schiff reaction for microorganisms were negative. Neuropathological examination of cortex, white matter, pia and dura showed neither evidence of encephalitis nor meningitis.

Immunohistochemical Findings

Formalin-fixed materials were embedded in paraffin, cut into 4 μm thick sections, and studied using an enzyme-labeled antibody technique (Avidin Biotin Peroxidase Complex method). Anti-Varicella-zoster virus human antiserum was obtained from Fukuoka Anaesthetic Center. The antiserum used here was taken from patients affected with herpes zoster, whose serum antibody titer was sufficiently high for usage on immunohistochemical study as written in the text. The deparaffinized sections were immersed in methanol for 30 minutes, in 0.03% (v/v) hydrogen peroxide in 0.01 M PBS (Phosphate buffered saline, pH 7.4) for 30 minutes at room temperature and then in 1:30 (v/v) diluted goat serum in 0.01 M PBS for 30 minutes, at room temperature. Varicella-zoster virus human antiserum (titer; 128X) were applied to the sections at 1:1600 dilution and preparations incubated at room temperature in a moist chamber for about 18 hours. The diluted biotinylated anti human IgG goat serum and avidin-biotinylated peroxidase were each incubat-
ed for one hour at room temperature. Visualization of the peroxidase was achieved by the diaminobenzidine method. The sections were then stained with Methyl Green and examined under light microscope. Non-immune human sera (anti-varicella-zoster virus titer; beneath 4X) and anti herpes-simplex virus sera were used for the negative control. Antigen related to varicella-zoster-virus was present in the nuclei and cytoplasm of histiocytes in the granulomatous angiitis of basilar artery (fig. 5) but antigen related to herpes-simplex-virus (either type I or II) was not found in this lesion.

**Ultrastructural Findings**

Several parts of the granulomatous lesion of the aneurysm in the formalin-fixed basilar artery were postfixed in 1% oxmium tetroxide and embedded in Epon 812. Various cellular elements could be identified and histiocytes showed intracytoplasmic virus particles. Most of these virus particles measuring 150–220 nm in diameter were surrounded by envelopes (fig. 6) but there was no evidence of aggregation.

**Discussion**

This is probably the first report of a subarachnoid hemorrhage apparently caused by a rupture of varicella-zoster-virus-induced granulomatous angiitis. The clinicopathologic entity of granulomatous angiitis in the central nervous system was described originally by Cravioto and Feigin and later by other authors (table 1). Their reports of this granulomatous angiitis in the central nervous system showed characteristic features of the inflammatory cells — predominantly histiocytes, lymphocytes, mononuclear cells and multinucleated giant cells, but no eosinophils — occurring in the wall of the small arteries, veins, arterioles and venules. The histologic appearance of the vascular lesions in this case resembles that of the giant cell arteritis described by Kolody and Nurick but the location of the arteritis and the absence of cerebral changes and vascular abnormalities usually noticed in giant cell arteritis help separate the entities from each other.
### TABLE 1 Documented Cases of Granulomatous Angiitis of the Central Nervous System

<table>
<thead>
<tr>
<th>Authors (published year)</th>
<th>Age (yr)/sex</th>
<th>Herpes-zoster infection</th>
<th>Principally affected blood vessels</th>
<th>Infiltrated inflammatory cells</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cravioto &amp; Feigin (1959)</td>
<td>56/F (-)</td>
<td>Arteries and veins of varying caliber, from the middle cerebral artery to the intraparenchymal vessels</td>
<td>Lymphocytes, large mononuclear cells and a few multinucleated giant cells</td>
<td></td>
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<tr>
<td></td>
<td>18/M (-)</td>
<td>Middle cerebral artery and leptomeningeal vessels</td>
<td>Lymphocytes, large mononuclear cells and multinucleated giant cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Budzilovich et al (1963)</td>
<td>46/M (-)</td>
<td>Small blood vessels</td>
<td>Lymphocytes, large mononuclear cells, phagocytes, a few plasma cells and multinucleated cells, but no eosinophils</td>
<td></td>
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<tr>
<td></td>
<td>63/M (-)</td>
<td>Arteries and veins of the leptomeninges, and small blood vessels</td>
<td>Lymphocytes, large mononuclear cells, occasional plasma cells, occasional neutrophils and multinucleated giant cells, but no eosinophils</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hughes &amp; Brownell (1966)</td>
<td>66/M (-)</td>
<td>Small arteries</td>
<td>Lymphocytes and multinucleated giant cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kolodny et al (1968)</td>
<td>54/M (-)</td>
<td>Small arteries, arterioles and venules</td>
<td>Lymphocytes, histiocytes and multinucleated giant cells</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>64/M (-)</td>
<td>Small arteries, arterioles, venules and capillaries</td>
<td>Lymphocytes, pleomorphic histiocytes and multinucleated giant cells</td>
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<td></td>
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<tr>
<td></td>
<td>21/M (-)</td>
<td>Small arteries, arterioles and venules</td>
<td>Lymphocytes, large histiocytes and multinucleated giant cells</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>96/F (-)</td>
<td>Small arteries, small and medium-sized veins and major tributaries of the basilar and carotid arteries</td>
<td>Lymphocytes, histiocytes and multinucleated giant cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosenblum &amp; Handfield (1972)</td>
<td>32/F (+)</td>
<td>Small arteries</td>
<td>Mononuclear cells, histiocytes and multinucleated giant cells</td>
<td>Hodgkin’s disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>64/M (+)</td>
<td>Small arteries and arterioles</td>
<td>Lymphocytes, mononuclear cells and multinucleated giant cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reyes et al (1976)</td>
<td>67/F (+)</td>
<td>Small blood vessels</td>
<td>Lymphocytes, histiocytes, eosinophils, occasional plasma cells and multinucleated giant cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20/M (+)</td>
<td>Small basilar arteries</td>
<td>Mononuclear cells, histiocytes and multinucleated giant cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present case</td>
<td>70/M (+)</td>
<td>Basilar artery (single)</td>
<td>Lymphocytes, histiocytes and a few multinucleated giant cells</td>
<td></td>
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</tr>
</tbody>
</table>

The etiology of granulomatous angiitis is considered to be related to immune complexes, mechanical factors, mycoplasma infection and varicella-zoster infection. Rosenblum and Hadfield first reported granulomatous angiitis in the central nervous system in a patient with herpes zoster and speculated that granulomatous angiitis might have been the result of viral infection. Varicella-zoster virus may cause granulomatous angiitis only in the central nervous system, possibly because of a high affinity that may exist between the varicella-zoster virus and the vessel wall of the central nervous system. An additional factor may be thrombosis.

Our study revealed enveloped virions 150–220 nm in diameter scattered in the cytoplasm of histiocytes in the granulomatous arteritis; these particles resemble those of varicella-zoster virus. Histochemical examination also revealed that the varicella-zoster antigen was present in the cytoplasm or nuclei of histiocytes, but herpes-simplex antigen was absent from these le-
sions. These histological, immunohistochemical and electronmicroscopical studies suggest that varicella-zoster-virus may be the cause of granulomatous angiitis in the central nervous system. The mechanism of aneurysm formation and rupture is not clear, but necrosis of the vascular wall with giant cell reaction does play an important role in this course. Thus, clinicians should be aware of the granulomatous angiitis in the central nervous system in patients with herpes zoster.

References

Progressive Lacunar Infarction With Demonstrated Patency of the Middle Cerebral Artery

JAMES H. HALSEY, M.D.

SUMMARY Two cases of progressive hemiplegia were closely followed by daily clinical examination. In both, the CT scan and CSF were normal on admission. In both, objective aggravation occurred in three or more steps over four days, progressing from minor finger clumsiness to total paralysis of the arm. In both cases a second CT scan a day after appearance of hemiplegia demonstrated a lacune in the corona radiata just above the internal capsule. In one case an intravenous digital subtraction angiogram demonstrated patent patency of the middle cerebral artery during the course of the progression. In the other case, serial study with transcranial Doppler ultrasound documented the continued patency of the middle cerebral artery. These two cases demonstrate that it is not necessary to postulate transient occlusion of the middle cerebral artery as an essential mechanism for progressive lacunar infarction.

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THE TERM LACUNE refers to a small infarction of the basal ganglia, internal capsule, or brain stem. Characteristic clinical syndromes which are highly predictive of the anatomical lesion have been described by Fisher. The subject has recently been definitively reviewed by Mohr. The lesion is usually attributed to occlusion of a penetrating end arterial branch of one of the major vessels of the circle of Willis or basilar artery. The evidence for this is usually an inference from the appearance of the lesion on CT scan or at autopsy, though the occluded vessel itself has been recovered by very careful painstaking examination of serial sections in some cases. Mohr, in his article, emphasized the frequency of a progressive evolution in many cases, sometimes with a time course of up to 48 hours or more. The underlying lesion in these has often remained speculative since arteriography performed later, or subsequent autopsy, could not take account of the possibility of transient occlusion of a large parent artery with subsequent spontaneous clot lysis.

As a contribution to this issue we wish to present two similar cases in whom serial neurologic examination documented progressive evolution from minor hemiparesis to total hemiplegia, while intravenous digital subtraction angiography in one, and ultrasound in the other clearly documented that the horizontal portion of the middle cerebral artery was patent during
Subarachnoid hemorrhage and granulomatous angiitis of the basilar artery: demonstration of the varicella-zoster-virus in the basilar artery lesions.
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