CEREBRAL VASCULAR CHANGES IN SYSTEMIC LUPUS ERYTHEMATOSUS

BY
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ABSTRACT

Cerebral vascular lesions of 26 cases in systemic lupus erythematosus during a period from 1963 to 1978 were examined histologically and the following conclusions were made:

1. The prominent vascular changes of the brain were thrombosis, fibrinoid degeneration, endothelial swelling and proliferation, arteriolsclerosis, and perivascular infiltration of inflammatory cells.

2. From clinico-pathological viewpoints, thrombosis seemed to play an important role in the development of neurological signs. In five cases, characteristic granular or homogeneous thrombi were observed in the small blood vessels including venule. Infarct without proved vascular obstruction but probably due to thrombosis was seen in four cases. The true character of the granular thrombi was not determined, either electronmicroscopically or immunohistochemically. These suggested the presence of a tendency for in situ formation of thrombus.

3. Fibrinoid degeneration seen in four cases mainly affected arteriole of less than 50 µm in diameter in the cerebral cortex, basal ganglia, and brain stem. This change of arteriole did not play a significant role in neurological signs.

4. Endothelial swelling and proliferation of the small blood vessels were prominent in the cases with thrombosis and fibrinoid degeneration.

5. Perivascular infiltration of the inflammatory cells was observed in about one-half of the cases but its significance was not clear.

INTRODUCTION

Since Kaposi23) described disturbed cerebral function associated with systemic lupus erythematosus (SLE), neuropsychiatric abnormalities in this disease have been thought to be one of the important clinical pictures, and a symptom of psychosis and/or convulsions has been included in criteria for SLE by American Rheumatism Association.14)

Although many histological investigations of the central nervous system in SLE have described changes of cerebral blood vessels and their related conditions, e.g., encephalomalacia and hemorrhages,6,16,18,22,32,55) there are only a few studies dealing with unselected and a large number of cases of SLE in Japan.18,35) However, vascular alterations cited in above publications were not always sufficient to account for neuropsychiatric signs, especially mental disturbance,18,38,46) and some researchers mentioned pathological factors in blood and serum,29) including antibody reactive with neurons.45)

On the other hand, Shibata47) stressed the significant role of angitis in the clinical pictures of SLE.

In the present study, changes of the cerebral blood vessels were examined histologically in relatively unselected 26 cases of SLE

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and their role in the neurological symptom was discussed.

Materials and Methods

Thirty-six cases of SLE were examined. Twenty-six of 36 cases were available for investigation of the central nervous system. These 26 autopsies were performed during a period from 1963 to 1978 (Table 1). Samples fixed in 10% formaldehyde solution were used. Six micrometer sections were cut and stained with Hematoxylin-Eosin (HE), Kluver-Barrera (KB), periodic acid-Schiff (PAS), Elasticavon Gieson (EVG), Azan-Mallory (AM), and, in case of necessity, phosphotungstic acid-Hematoxylin (PTAH) were applied. Case No. 13 was selected for serial sections in order to observe the vascular changes stereoscopically.

For the immunohistological study of vascular thrombi, the above paraffin-embedded blocks of case Nos. 9, 14, and 17 were used. Sections were cut at 4 μm and deparaffinized in usual manner. The sections were post-fixed in Bouin's solution for 20 min and then washed in water for 30 min. Thereafter, the sections were rinsed in 0.15 M phosphate-buffered saline (PBS) (pH 7.2) and then in PBS containing 2% bovine serum albumin for 2 hr. Indirect immunofluorescent method was applied. Sections were stained with rabbit anti-human fibrinogen antisera, fibrinogen split product D and E antisera (Boehringer), and subsequently with FITC-labeled goat anti-rabbit γ-globulin antisera (Boehringer). For immunostaining of blood platelets, sections were treated with human serum containing anti-platelet antibody obtained from the patients who had repeated platelet transfusion (by courtesy of Dr. T. Juji) and subsequently with FITC-labeled rabbit anti-human IgG antisera (Boehringer).

For the electron microscopic observation of the thrombotic lesion, the 6-μm thick paraffin sections of the heart in case No. 14 was processed according to the method of Hiraokoh and Miyamoto. The ultrathin sections were doubly stained with uranyl acetate and lead citrate.

Results

I. Clinical data (Table 1).

There were 6 cases before 1970 and 20 cases after 1970. Twenty-three were females (88%) and 3 were males.

At the time of death, 3 patients were in teens, 10 in twenties, 6 in thirties, 6 in forties, and 1 in fifties.

Duration of illness ranged from 3 months to 10 years (Patient No. 17 had suffered from thrombophlebitis of the thigh for 22 years, but died 3 years after the onset of symptoms suggestive of SLE).

At the terminal stage of the disease, most patients showed moderately and severely renal dysfunction and 12 died of uremia, which was the main cause of death before 1970. Four were thought to have died with central nervous system injury (cerebral infarct or softening in three and subarachnoid hemorrhage in one) and all were the cases after 1970. The immediate cause of death became varied since 1970, e.g., interstitial pneumonia, mycosis, and so on.

Neurological signs developed mostly during the terminal stage but in case No. 15, impairment of visual acuity, reeling gait, numbness of hand, dysarthria, and loss of light reflex waxed and waned during the illness and she died of respiratory paralysis and bronchopneumonia. The clinical diagnosis was SLE with multiple sclerosis.

II. Macroscopic findings of the brain (Table 2).

Macroscopically, up to soybean sized softening foci could be identified in four cases. In case No. 14, there was extensive
### Table 1.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Year</th>
<th>Autopsy No.</th>
<th>Age</th>
<th>Sex</th>
<th>Duration of Illness</th>
<th>Cause of death</th>
<th>Neuropsychiatric signs &amp; Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1963</td>
<td>SN–2717</td>
<td>22</td>
<td>F</td>
<td>1 y. 4 m.</td>
<td>Uremia</td>
<td>Not described.</td>
</tr>
<tr>
<td>2</td>
<td>1964</td>
<td>KA–24</td>
<td>34</td>
<td>F</td>
<td>3 y.</td>
<td>Uremia</td>
<td>Unknown.</td>
</tr>
<tr>
<td>3</td>
<td>1965</td>
<td>SN–3049</td>
<td>23</td>
<td>F</td>
<td>3 y. 9 m.</td>
<td>Uremia</td>
<td>Not described.</td>
</tr>
<tr>
<td>4</td>
<td>1966</td>
<td>SN–3433</td>
<td>14</td>
<td>F</td>
<td>4 y. 8 m.</td>
<td>Uremia</td>
<td>Impairment of visual acuity and agitation 1 hr. prior to death.</td>
</tr>
<tr>
<td>6</td>
<td>1968</td>
<td>SN–3818</td>
<td>31</td>
<td>F</td>
<td>2 y. 4 m.</td>
<td>Uremia, Pneumonia.</td>
<td>Excitement at night. 4 d.</td>
</tr>
<tr>
<td>7</td>
<td>1970</td>
<td>AN–2</td>
<td>28</td>
<td>F</td>
<td>5 y. 7 m.</td>
<td>Uremia</td>
<td>Not described.</td>
</tr>
<tr>
<td>8</td>
<td>1970</td>
<td>SN–4206</td>
<td>43</td>
<td>F</td>
<td>6 y. 4 m.</td>
<td>Uremia</td>
<td>Sensory disturbance, 4 m. prior to death.</td>
</tr>
<tr>
<td>10</td>
<td>1972</td>
<td>SN–243</td>
<td>11</td>
<td>M</td>
<td>2 y. 8 m.</td>
<td>Cerebral infarct</td>
<td>Epilepsy since age of 6 y. Hemiparesis. 4 d.</td>
</tr>
<tr>
<td>11</td>
<td>1972</td>
<td>SN–4455</td>
<td>26</td>
<td>M</td>
<td>2 y. 3 m.</td>
<td>Cryptococcosis</td>
<td>Epilepsy since age of 10 m. Convulsion and unconscious, 18 d.</td>
</tr>
<tr>
<td>12</td>
<td>1972</td>
<td>SN–562</td>
<td>23</td>
<td>F</td>
<td>1 y. 10 m.</td>
<td>Aspergilosis</td>
<td>Difficulty in walking. 2 d.</td>
</tr>
<tr>
<td>13</td>
<td>1973</td>
<td>SN–667</td>
<td>43</td>
<td>F</td>
<td>4 y. 10 m.</td>
<td>Uremia</td>
<td>Depressive during the illness.</td>
</tr>
<tr>
<td>14</td>
<td>1973</td>
<td>SN–344</td>
<td>26</td>
<td>F</td>
<td>3 y. 10 m.</td>
<td>Cerebral infarct, Pneumonitis</td>
<td>Hemiparesis. 22 d.</td>
</tr>
<tr>
<td>15</td>
<td>1975</td>
<td>SN–4877</td>
<td>31</td>
<td>F</td>
<td>2 y. 3 m.</td>
<td>Pneumonia, Cerebral softening</td>
<td>Impairment of visual acuity, reeling gait, dysarthria. 1 y. 10 m.</td>
</tr>
<tr>
<td>16</td>
<td>1975</td>
<td>SN–4878</td>
<td>35</td>
<td>F</td>
<td>1 y. 7 m.</td>
<td>Miliary Tb, Drug eruption (Lyell),</td>
<td>Delirium, 17 d. prior to death.</td>
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<tr>
<td>17</td>
<td>1975</td>
<td>SN–4913</td>
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<td>F</td>
<td>2 y. 10 m.</td>
<td>Systemic thrombosis?</td>
<td>Disorientation. 1 d.</td>
</tr>
<tr>
<td>18</td>
<td>1975</td>
<td>SN–4943</td>
<td>36</td>
<td>F</td>
<td>8 y. 3 m.</td>
<td>Uremia</td>
<td>Not described.</td>
</tr>
<tr>
<td>19</td>
<td>1975</td>
<td>SN–4950</td>
<td>45</td>
<td>F</td>
<td>7 y. 7 m.</td>
<td>Purulent pleuritis, pericarditis</td>
<td>Not described.</td>
</tr>
<tr>
<td>20</td>
<td>1976</td>
<td>SN–4965</td>
<td>27</td>
<td>M</td>
<td>9 y. 6 m.</td>
<td>Uremia, Pneumonia</td>
<td>Convulsion, 2 d. prior to death.</td>
</tr>
<tr>
<td>22</td>
<td>1976</td>
<td>SN–5087</td>
<td>29</td>
<td>F</td>
<td>10 y.</td>
<td>Subarachnoidal hemorrhage</td>
<td>Headach, nausea, coma. 7 d.</td>
</tr>
<tr>
<td>24</td>
<td>1978</td>
<td>RSN–2637</td>
<td>41</td>
<td>F</td>
<td>2 y. 4 m.</td>
<td>Pneumonitis</td>
<td>Not described.</td>
</tr>
<tr>
<td>26</td>
<td>1978</td>
<td>SN–5222</td>
<td>56</td>
<td>F</td>
<td>4 y. 5 m.</td>
<td>Heart failure?</td>
<td>Not described.</td>
</tr>
</tbody>
</table>
### Table 2.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Macroscopic findings</th>
<th>Granular thrombosis</th>
<th>Fibrinoid necrosis</th>
<th>Endothelial Proliferation</th>
<th>Arteiolo-sclerosis</th>
<th>Perivascular cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SAH(^3), mild</td>
<td>$-$</td>
<td>$-$</td>
<td>$\pm$</td>
<td>$\pm$</td>
<td>$\pm$</td>
</tr>
<tr>
<td>2</td>
<td>Hemorrhagic infarct, a few.</td>
<td>$-$</td>
<td>$-$</td>
<td>$+$</td>
<td>$+$</td>
<td>$#$</td>
</tr>
<tr>
<td>3</td>
<td>Edema, slight</td>
<td>$-$</td>
<td>$+$</td>
<td>$-$</td>
<td>$+$</td>
<td>$\pm$</td>
</tr>
<tr>
<td>4</td>
<td>Non remarkable</td>
<td>$-$</td>
<td>$-$</td>
<td>$+$</td>
<td>$-$</td>
<td>$\pm$</td>
</tr>
<tr>
<td>5</td>
<td>Non remarkable</td>
<td>$-$</td>
<td>$-$</td>
<td>$\pm$</td>
<td>$+$</td>
<td>$-$</td>
</tr>
<tr>
<td>6</td>
<td>Edema</td>
<td>$-$</td>
<td>$\pm$</td>
<td>$#$</td>
<td>$+$</td>
<td>$+$</td>
</tr>
<tr>
<td>7</td>
<td>SAH, slight</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
</tr>
<tr>
<td>8</td>
<td>Unknown</td>
<td>$-$</td>
<td>$-$</td>
<td>$\pm$</td>
<td>$\pm$</td>
<td>$-$</td>
</tr>
<tr>
<td>9</td>
<td>Small softening in pons, thalamus &amp; parietal lobe</td>
<td>$+$</td>
<td>$-$</td>
<td>$#$</td>
<td>$+$</td>
<td>$+$</td>
</tr>
<tr>
<td>10</td>
<td>Hemorrhagic infarct, several</td>
<td>$-$</td>
<td>$-$</td>
<td>$+$</td>
<td>$-$</td>
<td>$#$</td>
</tr>
<tr>
<td>11</td>
<td>Scattered cyst (Cryptococcosis)</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$\pm$</td>
</tr>
<tr>
<td>12</td>
<td>Small softening in basal ganglia</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$#$</td>
</tr>
<tr>
<td>13</td>
<td>Edema, slight</td>
<td>$-$</td>
<td>$#$</td>
<td>$+$</td>
<td>$+$</td>
<td>$\pm$</td>
</tr>
<tr>
<td>14</td>
<td>Extensive softening of the right cerebral hemisphere</td>
<td>$#$</td>
<td>$-$</td>
<td>$#$</td>
<td>$+$</td>
<td>$+$</td>
</tr>
<tr>
<td>15</td>
<td>Small softening in pons, midbrain &amp; thalamus</td>
<td>$-$</td>
<td>$-$</td>
<td>$\pm$</td>
<td>$-$</td>
<td>$-$</td>
</tr>
<tr>
<td>16</td>
<td>SAH, slight</td>
<td>$+$</td>
<td>$-$</td>
<td>$\pm$</td>
<td>$-$</td>
<td>$\pm$</td>
</tr>
<tr>
<td>17</td>
<td>Edema, slight</td>
<td>$#$</td>
<td>$-$</td>
<td>$#$</td>
<td>$+$</td>
<td>$#$</td>
</tr>
<tr>
<td>18</td>
<td>Edema</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
</tr>
<tr>
<td>19</td>
<td>Opaque meninx, slight</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$\pm$</td>
</tr>
<tr>
<td>20</td>
<td>Opaque meninx</td>
<td>$-$</td>
<td>$+$</td>
<td>$\pm$</td>
<td>$#$</td>
<td>$+$</td>
</tr>
<tr>
<td>21</td>
<td>Non remarkable</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$+$</td>
</tr>
<tr>
<td>22</td>
<td>SAH, Extensive</td>
<td>$-$</td>
<td>$-$</td>
<td>$+$</td>
<td>$#$</td>
<td>$+$</td>
</tr>
<tr>
<td>23</td>
<td>Non remarkable</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$\pm$</td>
</tr>
<tr>
<td>24</td>
<td>Petechiae in white matter</td>
<td>$-$</td>
<td>$-$</td>
<td>$\pm$</td>
<td>$-$</td>
<td>$-$</td>
</tr>
<tr>
<td>25</td>
<td>Small softening in basal ganglia</td>
<td>$+$</td>
<td>$+$</td>
<td>$+$</td>
<td>$+$</td>
<td>$\pm$</td>
</tr>
<tr>
<td>26</td>
<td>Non remarkable</td>
<td>$-$</td>
<td>$\pm$</td>
<td>$#$</td>
<td>$+$</td>
<td>$+$</td>
</tr>
</tbody>
</table>

\(^3\) Subarachnoid hemorrhage

Recent anemic infarct of the right frontoparietal hemisphere of the brain, and thrombus was found in the right middle cerebral artery. Hemorrhagic infarct was noted in two cases. Subarachnoid hemorrhage occurred in four cases but it was the immediate cause of death in only case No. 22.

III. Microscopic findings of the brain (Table 2).

Histological examination revealed encephalomalacia, hemorrhages, degeneration and loss of neuron, and axonal swelling. These changes were related to the vascular changes.

Prominent vascular lesions were (A)
<table>
<thead>
<tr>
<th>Case No.</th>
<th>Glomerular lesion(^1)</th>
<th>Wire loop lesion</th>
<th>Endocarditis</th>
<th>Onion skin lesion</th>
<th>Thrombosis</th>
<th>Fibrinoid angionecrosis(^2)</th>
<th>Necrotizing angitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Diffuse GN</td>
<td>-</td>
<td>-</td>
<td>±</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>Diffuse GN</td>
<td>-</td>
<td>+</td>
<td>±</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>Diffuse GN</td>
<td>±</td>
<td>-</td>
<td>+</td>
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<td>Diffuse GN</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>#</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Diffuse GN</td>
<td>-</td>
<td>-</td>
<td>±</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Diffuse GN</td>
<td>±</td>
<td>-</td>
<td>+</td>
<td>-</td>
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</tr>
<tr>
<td>8</td>
<td>Membranous GN</td>
<td>-</td>
<td>-</td>
<td>+</td>
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</tr>
<tr>
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<td>Diffuse GN</td>
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</tr>
<tr>
<td>10</td>
<td>Diffuse GN</td>
<td>+</td>
<td>-</td>
<td>±</td>
<td>-</td>
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</tr>
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</tr>
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<td>Diffuse GN</td>
<td>+</td>
<td>-</td>
<td>±</td>
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</tr>
<tr>
<td></td>
<td>(mural thrombi)</td>
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</tr>
<tr>
<td>15</td>
<td>Membranous GN</td>
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<td>(healed?)</td>
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</tr>
<tr>
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<td>Membranous GN</td>
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<td>±</td>
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</tr>
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<td>+</td>
<td>±</td>
<td>+</td>
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</tr>
<tr>
<td>19</td>
<td>Minimal involvement</td>
<td>-</td>
<td>±</td>
<td>(healed?)</td>
<td>±</td>
<td>-</td>
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</tr>
<tr>
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<td>+</td>
<td>-</td>
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</tr>
<tr>
<td>26</td>
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\(^1\) classification of Pollak\(^4\)
\(^2\) Excluding the kidney.

Thrombosis, (B) fibrinoid degeneration, (C) endothelial swelling and proliferation, (D) arteriosclerosis, and (E) perivascular inflammatory cell infiltratoin.

(A) Thrombosis

Thrombi were found histologically in case Nos. 3, 9, 12, 14, 16, 17, 20, 24, and 25. In case Nos. 3, 13, and 20, a few fibrin thrombi were present associated with fibrinoid degeneration of arteriole, and in case No. 12, proliferation of Aspergillus with fibrin was seen in blood vessels. In case No. 24, fibrin microthrombi were observed in systemic organs due to dissemi-
nated intravascular coagulation.

In other five cases (19%) (Nos. 9, 14, 16, 17, and 25), granular and homogeneous thrombi were revealed in many organs. Four cases (Nos. 9, 16, 17, and 25) were associated with atypical verrucous endocarditis and in case No. 14, microscopic mural thrombi without endocarditis of the right ventricle (Table 3). Most of these five cases showed some neurological abnormalities. All were cases after 1970.

Case No. 9, a 22-year-old female, developed Jacksonian seizures seven days before death and nystagmus 2 days later. Macroscopic examination of the brain revealed several, up to soybean sized softenings in pons, thalamus, and cortex of the parietal lobe.

Histologically, in addition to organized thrombi with recanalization of the small blood vessels in the meninx and parenchyma (Fig. 1), fresh thrombi were seen in the arteriole, capillary, and occasionally in venule (Fig. 2). These fresh thrombi were granular or homogeneous, and stained eosinophilic by HE, red purple by PAS, and purplish blue by AM methods. By PTAH staining, these thrombi were focally blue (Fig. 3a). Occasionally, endothelium proliferated and covered these thrombi. Several vascular walls underwent necrosis with petechial hemorrhage, hemosiderosis, and infiltration of microglia around the vessels. Thrombosis, endothelial swelling and proliferation, and intimal fibrosis were prominent in the cerebral cortex and meninx. Perivascular fibrosis and lymphocytic infiltration were also noted. In the cortex, there were scattered softenings and loss of neurons. Microinfarct was also present in the white matter, but less marked. Occasional axonal swelling was observed.

These granular or homogeneous thrombi were seen throughout many organs (Fig. 3b). There were small, grayish white to grayish yellow vegetations on mitral and tricuspid leaflets (Fig. 4), and small myocardial scars and degeneration related to organized and fresh thrombi in the small blood vessels were found. In this case, necrotizing angitis similar to polyarteritis nodosa (PN) was present in the esophagus, small intestine, gallbladder, and pancreas but none in the brain (Fig. 5 and Table 3).

In case No. 17, small blood vessel of the brain and other organs showed the same changes as in case No. 9. In the brain, these lesions were prominent in the cerebral cortex, subcortical white matter, and meninx. There were vegetations on mitral leaflet. The lung presented many organized emboli in the medium-sized and small pulmonary arteries, which were thought to result from thrombophlebitis of the thigh and she had suffered from pulmonary hypertension during the course.

In case Nos. 16 and 25, a few homogeneous thrombi in the arteriole were seen predominantly in cerebral cortex, subcortical white matter, and meninx. Atypical verrucous endocarditis was associated in both cases.

In case No. 14, predominantly in the meninx and cerebral cortex, numerous organized thrombi were seen in the small but larger artery and arteriole than those of the afore-mentioned cases but no destruction of the vascular wall was found (Fig. 6). Fresh granular thrombi were seen in the arteriole, capillary, and occasionally in venule throughout the brain, with endothelial proliferation. Intimal thickening was prominent and in some places obstructed the lumen. There was also a mild perivascular fibrosis. Cerebral infarct of the right cerebral hemisphere was extensive and marked stenosis of right intracranial carotid artery and thrombosis in the right middle cerebral artery were found, but unfortunate-
ly, histological examination could not be made. Organized and granular thrombi were also systemically observed with splenic infarction. The heart presented minute mural thrombi of granular appearance on the right ventricle, but none in the left ventricle, as far as examined.

In addition to these thrombotic cases, there were four cases of cerebral infarct (case Nos. 4 and 15 showed anemic infarct and case Nos. 2 and 10 showed hemorrhagic one) where no vascular obstruction could be proved in the brain and other organs.

In case No. 4, a few small glial scars around the arterioles were noticed predominantly in the cerebral cortex (Fig. 7), but no significant vascular lesions could be found. Several organs other than the brain showed PN-like necrotizing angitis and the heart presented atypical verrucous endocarditis (Table 3).

In case No. 15, clinical diagnosis was SLE with multiple sclerosis. At autopsy, up to soybean-sized old softenings with fat granule cells were seen in pons, midbrain, and thalamus. No significant vascular changes could be found except for slight perivascular lymphocytic infiltration in the parenchyma and slight intimal thickening of a few meningeal arterioles. Mitral valve showed hyaline thickening (Table 3).

In case No. 2, the brain presented several hemorrhagic infarction in the cerebellar cortex and the base of the fourth ventricle. Occasional microglial infiltration around the arteriole was noticed. Necrotizing angitis was seen in a few organs other than the brain, and the heart showed atypical verrucous endocarditis (Table 3).

In case No. 10, hemorrhagic infarction was present in cerebral and cerebellar cortices. Purkinje cell and granular layer of the cerebellum were relatively preserved in hemorrhagic infarction, and it was suggested that there might be thrombi in the vein. The left ventricle of the heart showed mural endocarditis with fibrinoid degeneration and inflammatory cell infiltration (Table 3).

(A) Fibrinoid degeneration

Fibrinoid degeneration of arteriole was found in four cases No. 3, 13, 20 and 25.

In case No. 3, several arterioles in the sub-pialmatral regions of medulla and pons showed fibrinoid degeneration. Vascular wall was eosinophilic and homogeneous with fibrin thrombus in the lumen and microglial infiltration around the vessel (Fig. 8). In some place, there was fibrin exudation into the surrounding tissue and perivascular microglia arranged in a ring (Fig. 9). Axonal swelling was prominent near the diseased vessel. Fibrinoid degeneration of arteriole was also found in the kidney, bronchus, adrenal, and pancreas (Table 3).

In case No. 13, numerous arterioles of the brain showed fibrinoid degeneration and fibrin impregnation of surrounding tissue was marked. Adventitial cells were swollen and proliferated. Frequently, globules of fibrin were found in the perivascular space around the degenerated vessels (Fig. 10). There was also proteinic exudation with a little fibrin in the perivascular space of the small artery. The lesion was predominant in the cerebral cortex, basal ganglia, and brain stem, but hardly visible in the cerebral white matter. Frequently, fibrin was observed in the perivascular space around the intact arteriole but when serial sectioning was done, fibrinoid necrosis of that vessel could be seen nearby on occasion. Some arterioles showed fibrin infiltration into subendothelium (Fig. 11). There was slight perivascular edema and microglial infiltration. Cerebral parenchyma showed loss of neurons, edema, and axonal swelling, but its damage was slight compared to extensive...
vascular change.

In this case, prominent interstitial mucinous edema of the heart was characteristic. This exudation was partly PTAH positive (Fig. 12-a). Fibrin infiltration within the intima of small coronary vein and perivascular fat tissue was also evident (Fig. 12-b).

In case Nos. 20 and 25, fibrinoid degeneration of arteriole was located in the cerebral cortex and basal ganglia, but was few in number.

In all the four cases, arteriole showing fibrinoid degeneration had a diameter less than 50 μm, mostly 20 to 30 μm.

(C) Endothelial swelling and proliferation

There were nine cases where endothelial swelling and proliferation was relatively prominent (>± in Table 2). This change was especially marked in the cases with thrombosis and fibrinoid degeneration. In thrombotic case, swollen endothelium covering thrombus showed polypoid proliferation (Fig. 13-a) and obliterated the lumen (Fig. 13-b).

(D) Arteriolosclerosis

There were 12 cases that showed hyaline arteriolosclerosis (>± in Table 2). This change was especially marked in the cases with renal dysfunction following a prolonged course.

In addition to hyalinosis, the entire medial smooth muscles of smaller arterioles became poorly stained with HE, PAS, and AM methods, giving an appearance of hyaline (Fig. 14).

(E) Perivascular inflammatory cell infiltration

There were 11 cases where perivascular inflammatory cell infiltration was relatively prominent (>± in Table 2) (Fig. 15). These included three cases of thrombosis, three cases of uremia and severe infection, two cases of uremia and hemorrhagic infarct, one case of uremia and subarachnoidal hemorrhage, one case of heart failure and one case of pulmonary hypertension and heart failure. The inflammatory cell was mostly composed of lymphocytes, but in the area of infarction and near subarachnoidal hemorrhage, perivascular neutrophils were prominent as in the case of systemic aspergillosis.

the case of systemic aspergillosis.

IV. Ultrastructural and immunohistological observation of thrombosis

Electron microscopically, granular thrombus of case No. 14 was composed of aggregated spherical materials, but the fine structures could not be discerned due to marked postmortem and artificial modification (Fig. 16).

Immunohistologically, granular and homogeneous thrombi of case Nos. 9, 14, and 17 were positive for fibrinogen, fibrinogen split products D and E (Fig. 17). However, all the three cases were immunohistologically negative for platelet in this study.

Discussion

It has been frequently mentioned that the patients suffering from SLE show signs of the central nervous system involvement. In 1872, Kaposi(23) reported the cases of delirium. In 1900, Oster(43) described the cases of recurrent delirium and hemiplegia among the “visceral lesions of the erythema group”. Dubois(33) reported that central nervous system damage (hemiparesis, etc.) occurred in 25.5% of 520 cases, psychosis in 12.1%, and convulsion due to lupus in 13.8%. In Japan, Nou and Igata(37) by reviewing the literature, reported that neurological abnormalities were seen in 70% of 343 cases and psychosis in 57%. The incidence of neuropsychiatric signs is varied among the investigators(20,22,38) but all are consistent that clinical picture of the central nervous system involvement is important in SLE, and
Dubois\textsuperscript{15}) stressed central nervous system damage as major cause of death.

Neuropsychiatric signs include schizophrenic reaction, convulsion, paralysis, dysarthria, and so on\textsuperscript{13,22,37}) but, as to pathogenesis for these signs, although many investigators mentioned the vascular changes and their related parenchymal damages,\textsuperscript{6,16,18,22,32,35}) these changes are not always sufficient to account for neuropsychiatric abnormalities, especially for psychosis,\textsuperscript{18,22,38}) and there are some claims that place a great emphasis on blood and serum factors,\textsuperscript{20}) including antibody reactive with neurons.\textsuperscript{45})

In this study, many cases presented encephalomalacia and hemorrhagic infarct which were thought to be of vascular origin and they were especially prominent in the patients developing neurological signs.

Lowman and Slocumb\textsuperscript{31)} studied the peripheral vascular lesions in skeletal muscle and nerve, and subdivided them into four main groups: arteritis, phlebitis, fibrinoid degeneration, and endothelial proliferation.

Baehr et al.\textsuperscript{43}) described vascular changes as simple dilatation of capillary beds with blood and serous extravasation, proliferative lesions of the lining endothelium of capillaries, arterioles, and venules, associated with thrombi, and degenerative and necrotizing lesions in the wall of such vessels associated with thrombosis and sometimes with hemorrhages into the adjacent tissue. They considered these three types as different stages of the same underlying morbid process.

Cerebral vascular changes that have been described are the same as those of other organs. The following are the most frequently mentioned.

1. Endothelial swelling and proliferation of small blood vessels with occasional thrombus formation.\textsuperscript{6,10,12,18,22,26})

2. Fibrinoid degeneration.\textsuperscript{3,6,16,22,32,35})

3. Inflammatory cells around the vessel\textsuperscript{3,16,22,32,46}) and in the wall.\textsuperscript{42})

Harada\textsuperscript{18}) described homogeneous substance between endothelium and adventitia of arteriole (homogenization) with endothelial proliferation, which, he thought, was neither hyalinosis nor fibrinoid degeneration, but Kondo et al.\textsuperscript{27}) considered the same change as intimal hyalinosis.

In the present study, histological changes of cerebral blood vessels are almost the same as have been described, and (A) thrombosis, (B) fibrinoid degeneration, (C) endothelial proliferation, (D) arteriolosclerosis, and (E) perivascular inflammatory cell infiltration are the most remarkable findings.

The group which had a cerebral blood vessel damage also showed severe renal dysfunction and this differed from the observation of Kashiwazaki et al.\textsuperscript{24}) that, in the patients with minimal renal injury, significant symptom of the central nervous system developed.

(A) Thrombosis and infarction

There were two groups in cases of infarction, i.e., (1) cases with proved thrombosis and (2) those without proved thrombosis.

(1) Cerebral infarction with proved thrombosis: There were five cases where systemic thrombosis was found. Four of five cases had atypical verrucous endocarditis and one had mural thrombosis of the right ventricle without endocarditis. Libman and Sacks\textsuperscript{30}) mentioned the possibility that neurological signs might be due to embolism in verrucous endocarditis. Adams et al.\textsuperscript{31}) stated that most striking brain lesions in SLE were embolic and secondary to verrucous endocarditis. Alvertini and Alib\textsuperscript{25}) reported the case where emboli could be found in the brain and other organs in a patients with verrucous endocarditis. On the other hand, Johnson and Richardson\textsuperscript{22})
insisted that there was no relationship between endocarditis and cerebral lesions, and verrucae rarely cause embolism.\(^5\)

It is reasonable to consider these granular or homogeneous plugging as thrombi formed \textit{in situ}, because these were also found in venules in case Nos. 9, 14, and 17.

In case No. 14, right intracranial carotid artery showed marked stenosis, and thrombus occluded the right middle cerebral artery with numerous recanalized ones in relatively large artery in the meninx. Honda\(^20\) reported a similar case to this, which showed thrombus of internal carotid artery but no significant changes of the vascular wall. Silverstein\(^38\) also described two cases that showed obstruction of anterior and middle cerebral artery in one and internal carotid artery in the other by angiography. He mentioned that healed arteritis was demonstrated on autopsy in the former case and arteritis of SLE might involve vessel large enough to allow for the angiographic abnormalities. Generally, small vessels are preferably involved in SLE, and so far as the literature was examined there were no published cases that demonstrated the presence of arteritis of intracranial main artery except for that of Silverstein. Therefore, it cannot completely exclude the possibility of thrombosis in Silverstein's case. Mori\(^23\) mentioned that in recent years SLE cases are increasing that die of thrombosis of large artery and vein, and/or with systemic thrombosis in small vessels. He concluded that this increased frequency of thrombosis does not result from the therapy for SLE or uremia but there must be a factor for thrombosis characteristic of SLE. Sugie and Oguri\(^29\) stated that the abnormalities of fibrinolysis-coagulation mechanism common to collagen disease bring about increase of fibrinogen, acceleration of coagulability, and decrease of plasminogen and proactivator. These suggest that there might be some tendency for thrombosis in SLE.

In addition to thrombosis in relatively large artery seen in case No. 14, there were five cases (19\%) that showed diffuse granular or homogeneous thrombi in arterioles, capillaries, and occasionally in venules, with varying degree in each case. These thrombi were PAS positive and focally PTAH positive, and immunologically, positive for fibrinogen, fibrinogen split product D and E (case Nos. 9, 14, and 17). Anti-human platelet alloantiserum could not stain the thrombi, but there were some problems in respect to preservation of antigenicity of Formalin-paraffin section and titer of antibody.

Ultramicroscopically, the granular thrombus in case No. 14 was composed of aggregated spherical profiles, but fine structures could not be recognized. These pictures might suggest that granular or homogeneous materials are composed of a mixture of platelets and fibrin, and probably platelets are predominant, although definite evidence is lacking.

Do these five cases have any relation to thrombotic thrombocytopenic purpura (TTP) which was first described by Moschcowitz\(^24\) and studied in details by Baehr \textit{et al.}\(^5\)? There are arguments for\(^7,29,32\) and against\(^1,5,11,22\) the relationship between the two. Moreover, a variety of causes are proposed and some insist that these thrombi are mainly composed of platelets\(^5,7,36\) and others report that these are fibrin without platelets.\(^9\) Although Dekker\(^11\) mentioned that hyalin thrombi could be rarely found in the autopsy case of SLE without clinical signs of TTP, these thrombi could be seen in 19\% of the present cases, and it is suggested that this thrombosis might be responsible for the neurological signs on occasion. In organs other than the brain in
SLE, Gross\textsuperscript{7} described “granular plugged vessel” and organized “channeled vessels” in the arteriole and venule of the heart and extensive granular plugs caused minute myocardial infarcts. His observation of the heart might correspond to granular thrombosis seen in the brain of the present series, although he did not mention thrombotic lesion of other organs.

Compared with histological findings of TTP that followed acute course,\textsuperscript{1} granular thrombi were few in number and vascular changes were more subtle in case Nos. 16 and 25. In case Nos. 9, 14, and 17, there were relatively prominent endothelial proliferation, granular thrombi, and vessel necrosis, but vascular changes were also seen in the small arachnoidal artery, and parenchymal damage was more prominent. Furthermore, the vascular and parenchymal changes were in various stages of healing. These observations suggest that these cases are not identical with the cases described by Moschowitz\textsuperscript{84} and Baehr \textit{et al.}\textsuperscript{5} that followed acute and fatal course. On the other hand, Umlas and Kaiser\textsuperscript{52} insisted that TTP is not a disease entity but a syndrome and it may be caused by diverse etiology including primary vascular disease, glomerulonephritis, and intravascular coagulation.\textsuperscript{52} Platelet aggregation might be another important factor.\textsuperscript{86} Levine and Shearn\textsuperscript{29} mentioned that the duration of illness was longer in TTP+SLE group than in TTP. At present, when there are many varied opinions for TTP, these five cases in the present series could be regarded as SLE with TTP-like lesion.

Atypical verrucous endocarditis was seen in 27\% of this series and the figure rose to 35\% when possibly “healed valvulitis” was included (Table 3). All the thrombotic cases had verrucous endocarditis or mural thrombi and there might be some relationship between the two lesions.\textsuperscript{29}

It seems necessary to examine systematically the state of blood coagulation system in the cases with neurological signs, as not only “lupus vasculitis” but also thrombotic lesion could involve the central nervous system.

(2) Hemorrhagic infarction and multiple softenings without proved thrombosis: Except for case No. 12 where softenings occurred due to proliferation of \textit{Aspergillus} in the cerebral blood vessels, there were two cases of hemorrhagic infarct and two cases of multiple softenings without proved thrombosis. Neither vasculitis nor significant vascular changes were seen in the brain, while thrombo-embolism might be responsible in these cases.

In case No. 15 showing neurological signs suggesting multiple sclerosis, brain presented several, up to soybean sized softenings, without related vascular lesions but, in a similar reported case, cerebral softenings and vascular changes were found.\textsuperscript{28}

Gliarial scars in case No. 4 seems to correspond to “granuloma-like nodule” described by Harada\textsuperscript{18} but he assumed that some unknown process other than vascular obstruction might work on its pathogenesis.

It was remarkable that most of the cases with softening or hemorrhagic infarction had active or healed endocarditis. This is against the observation of Johnson and Richardson\textsuperscript{22} that no constant relationship between cerebral lesion and endocarditis was present. Thrombosis had no relationship to duration of illness or therapy.

(B) Fibrinoid degeneration

Fibrinoid degeneration of arteriole was predominant in the cerebral cortex, basal ganglia, and brain stem. Fibrinoid degeneration of blood vessel in organs other than the kidney seems to have decreased since 1970, as shown in Table 3, but in brain its
frequency is invariable. Fibrinoid degeneration of small blood vessel has been frequently described. Johnson and Richardson\(^{22}\) found that this change occurred in five of 24 cases and was a predominant finding in three who died with acute central nervous system signs but mentioned that in one of them the necrosis might have been the result of hypertensive vascular disease. Mozai\(^{25}\) also found fibrinoid degeneration predominantly in the patients who had recurrent terminal convulsions, which was similar to the finding of Johnson and Richardson.

Most investigators regard fibrinoid degeneration of the small blood vessel as intrinsic character of SLE, but Berry and Hodges\(^{6}\) stated that acute fibrinous vascular disease associated with hypertension and uremia was present. In this study, all the four cases with fibrinoid degeneration of arteriole had severe renal dysfunction and typical wire-loop lesion, and were thought to be in a significant autoimmune disorder. At the terminal stage, they showed uremic signs, and peritoneal dialysis (case No. 25) or hemodialysis (case No. 20) was performed. In pathogenesis of fibrinoid degeneration of arteriole, hypertension and uremia must be considered as one of the causes. Ooneda\(^{51}\) stressed the important role of hypertension in angioneurosis of the vessel with a diameter more than 50 \(\mu\)m but claimed that necrosis of arteriole with a diameter less than 50 \(\mu\)m seen in cerebral hemorrhage was secondary to hemorrhage. According to Suwa,\(^{51}\) the estimated blood pressure of the artery with a radius of 100 \(\mu\)m is highest in cerebral ganglia as well as in the kidney and pancreas, and drops down in the cerebral cortex. Ogata\(^{80}\) stated that, as the artery on cerebral surface runs a long and meandering course with branching, blood pressure gradually lowers and, therefore, hemorrhage and angioneurosis are rarely seen in the cortex. Therefore, fibrinoid necrosis in SLE which occurs in arterioles of less than 50 \(\mu\)m, mostly 20 to 30 \(\mu\)m, in diameter cannot be brought about by hypertension. In the study on uremia, Olsen\(^{40}\) found arteriosclerosis and hyalin thickening of the arteriole but there was no description about fibrinoid degeneration. In malignant nephrosclerosis, Kimura and Matsuoka\(^{25}\) described fibrinoid swelling of small vessel with narrowing and obliteration of lumen, and radiated fibrin exudation around the small vessel in pons, thalamus, and cerebral white matter. These histological findings are similar to those observed in SLE but cerebral white matter was not the favorite site in SLE. Therefore, most of fibrinoid necrosis of arteriole in the brain must be an inherent character of SLE.

Concerning the primary site of fibrinoid degeneration, Glaser\(^{46}\) described irregular patches of eosinophilic material ("fibrinoid"), extending from the adventitia through the media to intima, but Malamud and Saver\(^{22}\) found eosinophilic fibrinoid deposits in the subendothelium which tended to extend into the rest of the wall of the blood vessel. In the present investigation, some arterioles showed fibrinoid deposits in the subendothelium, and this finding is consistent with that of Malamud and Saver.

Andreucci\(^{51}\) observed two types of vascular alterations, i.e., plasma exudation around the intact vessel and fibrinoid necrosis of the vessel, which, he thought, resulted from the same pathological process, and different histological figures were related to the severity of "noxe". In case Nos. 13 and 20, fibrin was also found around the intact arteriole, but on serial sectioning in case No. 13, it was confirmed that fibrin exudation around the vessel concerned was derived from adjacent fibrinoid-degenerative vessel.
It is possible that fibrinoid necrosis of arteriole produces the ischemic brain damage and neurological signs but, in the present series, there was only one case that showed neurological signs terminally. Case No. 20 presented tonic convulsion but this could have been secondary to uremia. Case Nos. 13 and 15 suddenly developed cardiac arrest without acute central nervous system signs. Therefore, the present observation differs from those of Johnson and Richardson\(^\text{22}\) and of Mozi\(^\text{15}\) who found prominent fibrinoid degeneration in the group with terminal convulsion.

(C) Endothelial swelling and proliferation

Since Daly\(^\text{10}\) described proliferative endarteritis of the cerebral blood vessels of under 100 \(\mu\)m in diameter, there have been many investigators who described endothelial swelling and proliferation, which produce ischemic changes of the cerebral parenchyma in the pronounced case.\(^\text{10,18,22}\) However, Adams \textit{et al.}\(^\text{3}\) did not observe hyperplasia of endothelial cell in SLE. Harada\(^\text{18}\) considered this proliferative change as nonspecific “Endoarteritis der kleinen Hirnnindengefäße” which could be seen in cases such as cerebral syphilis, typhoid fever, malaria, erysipelas, toxemia of pregnancy, and rheumatic fever. In the present series, endothelial swelling and proliferation of the small blood vessel were seen to some extent in most cases, especially at the cerebral cortex, and were more prominent in the group with thrombosis and fibrinoid degeneration. Probably, proliferative vascular change might be a reactive phenomenon to thrombosis and some “noxe.”

(D) Arteriolosclerosis

Arteriolosclerosis was relatively prominent in 12 cases which had significant renal dysfunction and a prolonged course. This is compatible with the view that frequency and severity of cerebral arteriolosclerosis increase with age and long-standing hypertension.\(^\text{49}\)

The change that media of smaller arteriolar wall became hyalinous seems to correspond to homogenization of the arteriolar wall mentioned by Harada.\(^\text{18}\) In his study the vascular alteration was accompanied by endothelial swelling, intimal proliferation, and thickening of the wall, but in the present study, there was no such constant endothelial and intimal changes. This type of the change was thought to come from swelling of smooth muscle cells due to hypertension, and the view of Kondo \textit{et al.}\(^\text{27}\) that homogenization described by Harada was hyalinous intimal fibrosis could not be supported.

(E) Perivascular inflammatory cell infiltration

It has been generally admitted that necrotizing angiitis similar to PN develops in SLE.\(^\text{21,47}\) In the present series, there were five cases which showed PN like angiitis in the organs other than the brain but none in the brain, though such angiitis in the brain was reported.\(^\text{21}\) On the other hand, perivascular infiltration of inflammatory cells was found in about one-half of the cases. Perivascular inflammatory cell infiltration has been frequently noted but Harada\(^\text{18}\) did not observe this. In the present study, perivascular infiltration was relatively prominent in 11 cases. These include three cases with thrombosis and softening, three cases with uremia and severe infection, two cases with uremia and hemorrhagic infarction, one with uremia and subarachnoidal hemorrhage, one with heart failure and moderate renal dysfunction, and one with pulmonary hypertension and heart failure. In the last case of pulmonary hypertension, tremor of the right side developed 20 days before death, and autopsy examination re-
vealed mild lymphocytic infiltration, mostly around the vessel and few in the wall, but these findings could not be regarded as arteritis and were presented throughout the brain. Therefore, no definite relationship between neurological signs and perivascular inflammatory cell infiltration could be deduced. Olsen\(^{40}\) stated that infiltration of cells around small vessel is quite nonspecific and can be observed in connection with a number of irritants of a toxic or infectious nature and, in his study, 14\% of uremic patients, excluding the case with softenings and hemorrhage, showed perivascular infiltration to a considerable extent and in his opinion, this change could be explained mainly by the coexistence of a severe infection in the patients. Taking into consideration that primary cause of death in SLE was uremia and infection, and perivascular infiltration could be seen secondary to hemorrhage and infarction, it was not clear to what extent inflammatory cell around the vessel had a significance in vascular pathology of SLE. There was no case that showed infiltration of the cell similar to LE cell described in the case of Orthner and Rossner.\(^{42}\)

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**References**


EXPLANATION OF FIGURES

Plate 1.

Fig. 1. Recanalized arteriole with endothelial proliferation covering thrombus in the cerebral cortex (case No. 9). (Hematoxylin-Eosin, ×300)

Fig. 2. Granular thrombus in venule of the cerebral cortex (case No. 9). (Azan-Mallory, ×500)

Fig. 3-a. Granular thrombus showing partly PTAH positive fibrin in the cerebral cortex (case No. 9). (Phosphotungstic acid-hematoxylin, ×500)

Fig. 3-b. Granular thrombus in arteriole of myocardium (case No. 9). (Phosphotungstic acid-hematoxylin, ×300)

Fig. 4. Small vegetation on mitral leaflet with vulvitis (case No. 9). (Hematoxylin-Eosin, ×30)

Plate 2.

Fig. 5. Necrotizing angitis similar to polyarteritis nodosa in the muscle layer of esophagus (case No. 9). (Hematoxylin-Eosin, ×120)

Fig. 6. Recanalized small artery of the cerebral meninx. Internal elastic lamina is preserved. Note extensive cerebral infarct due to thrombosis in right middle cerebral artery (case No. 14). (Elastica Azan-Mallory, ×30)

Fig. 7. Glial scars around arteriole in the cerebral cortex (case No. 4). (Hematoxylin-Eosin, ×120)

Fig. 8. Fibrinoid degeneration of arteriole and microglial infiltration in medulla (case No. 3). (Hematoxylin-Eosin, ×300).

Plate 3.

Fig. 9. Fibrin impregnation into the surrounding tissue and arrangement of infiltrating microglia in ring in medulla (case No. 5). (Hematoxylin-Eosin, ×300)

Fig. 10. Marked fibrinoid necrosis of arteriole in the cerebral cortex (case No. 13). Fibrinous exudation into the surrounding tissue. Several fibrin globules around the vessels. (Phosphotungstic acid-hematoxylin, ×300)

Fig. 11. Fibrinoid infiltration into the subendothelium of arteriole in midbrain (case No. 13). (Hematoxylin-Eosin, ×600)

Fig. 12-a. Mucinous edema with fibrinous exudation in the myocardium (case No. 13). (Phosphotungstic acid-hematoxylin, ×300)

Fig. 12-b. Focal fibrinoid infiltration into the subendothelium of the coronary vein and fibrinous exudation around the wall (case No. 13). (Phosphotungstic acid-hematoxylin, ×120)

Plate 4.

Fig. 13-a. Thrombosis with marked endothelial swelling and polypoid proliferation covering thrombus in the arteriole of cerebral meninx (case No. 9). (Azan Mallory, ×120).

Fig. 13-b. Occlusion of arteriole by thrombus and endothelial proliferation in the cerebral cortex (case No. 17). (Hematoxylin-Eosin, ×300)

Fig. 14. Homogenization of arteriolar wall (case No. 13). Media becomes poorly stained. (Hematoxylin-Eosin, ×600)

Fig. 15. Mild perivascular lymphocytic infiltration in midbrain (case No. 21). (Hematoxylin-Eosin, ×120)

Fig. 16. Granular thrombus is composed of aggregated spherical materials, but the fine structures cannot be discerned (case No. 14). (×13,200)

Plate 5.

Fig. 17. Thrombus was stained with antifibrinogen antiserum (case No. 9). (Indirect immunofluorescent method)
CEREBRAL VASCULAR CHANGES IN SLE
N. FUNATA

Plate 5

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