Malignant Hypertension and Microangiopathic Hemolytic Anemia

Yoichi Otsuka, M.D., Keishi Abe, M.D., Yukiko Sato, M.D.,
Tetsuo Saito, M.D., Nobuo Irokawa, M.D.,
Masamichi Ohtaki, M.D., Masatsugu Mikami, M.D.,
Takao Saito, M.D., Takashi Furuyama, M.D.,
and Kaoru Yoshinaga, M.D.

Summary
The fourth case found in Japan manifesting the features of malignant hypertension and microangiopathic hemolytic anemia (MHA) was reported. In this case, bilateral nephrectomy brought down the blood pressure and relieved MHA. The patient has since been maintained alive and well on hemodialysis up to the time of this report.

Additional Indexing Words:
Red cell fragmentation  Malignant phase of hypertension  Bilateral nephrectomy  Hemodialysis

Since Brain et al (1962) has first described an association of MHA with malignant hypertension, increasing interest has been aroused in association of the 2 conditions. There have been many confirmatory reports in the literature from European countries and U.S.A., but only 3 such cases have hitherto been described in Japan.2),3)

Recently bilateral nephrectomy has been frequently performed on patients with malignant hypertension to save their lives.4)–6) It has been well established that nephrectomy is an effective means to treat patients with otherwise uncontrollable malignant hypertension.6)

This paper presents the fourth Japanese patient with malignant hypertension associated with MHA, who has been successfully treated by nephrectomy.

Case Report

The patient was a 17-year-old high school girl. She had been in good health until 1 year ago when she started to complain of headache. She noted severe
headache on January 18, 1974 and was admitted to her local hospital. Examination at this hospital revealed a blood pressure of 230/140 mmHg and reduced PSP test. The patient was transferred to Tohoku University Hospital on March 18, 1974 for further investigation and treatment of her hypertension.

At admission she complained of only headache. Her body weight was 52.5 Kg and body length 153.4 cm. Her blood pressure was 210/140 mmHg in the right arm and there was no difference in her blood pressure among 4 extremities. No abnormalities were noted on physical examination except high blood pressure.

Hematological values were as follows: red blood cell count, 4,080,000/mm³; hemoglobin, 78%; hematocrit, 38%; white blood cell count, 4,700/mm³. Serum electrolytes, proteins, and lipids were within normal limits and liver function tests were almost normal. But the urine gave + test for protein, and PSP test was 14.8% in 15 min. The creatinine clearance was 43.3 ml/min and the para- amino-hippuric acid clearance 219.0 ml/min.

Chest X-ray showed no increase in size of the heart, but the electrocardiogram showed grade III hypertrophy of the left ventricle. Hypertensive changes corresponding to Keith-Wagener III were observed in the ocular fundi.

Plasma renin activity (PRA) was measured by our modified method of Haber et al, using radioimmunoassay of angiotensin I (normal values ranged from 5.0 to 30 ng/ml). PRA in peripheral vein blood was 44 ng/ml at rest, and 72 ng/ml after stimulation of renin secretion by injection of furosemide and upright posture. Although PRA was elevated, intravenous pyelography, renography, renoscintigraphy, and renal angiography revealed no abnormalities.

Vanillyl mandelic acid in urine was 7.0 mg/day (normal range, 3.0 to 7.0 mg/day), and 17-OHCS in urine 4.3 mg/day (normal range, 2.0 to 4.9 mg/day). From

![Fig. 1. Clinical course showing blood pressure (mmHg), blood urea nitrogen (mg/100 ml), and hematologic values in reference to therapy with antihypertensive medication, dialysis, and bilateral nephrectomy. Abbreviation; LDH: lactic acid dehydrogenase](attachment:image.png)
these laboratory findings, she was diagnosed essential hypertension in an early malignant phase.

The hospital course is outlined in Fig. 1. Immediately after admission, methyl dopa, 1,500 mg daily, was begun and her blood pressure was reduced to 180/110 mmHg. Transfemoral abdominal aortography was performed with 40 ml of Conraxin (sodium and meglumine iodamide) in the second hospital week. Following the angiography, she complained of weakness, anorexia, and nausea; and vomited. Anemia appeared on the 3rd postangiographic day and rapidly increased. Red blood cell count reduced to 1,730,000/mm³ on the 10th day after the angiography.

Hematological examination revealed a prolonged bleeding time, thrombocytopenia, and reticulocytosis as shown in Table I. Serum LDH (lactic acid dehy-

Table I. Hematological Data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red blood cell count, 10,000/mm³</td>
<td>173–213</td>
</tr>
<tr>
<td>White blood cell count, /mm³</td>
<td>8,200–9,700</td>
</tr>
<tr>
<td>Hemoglobin, %</td>
<td>29–42</td>
</tr>
<tr>
<td>Platelets, 10,000/mm³</td>
<td>5.8–7.7</td>
</tr>
<tr>
<td>Reticulocytes, %</td>
<td>12.0–19.4</td>
</tr>
<tr>
<td>Red cell morphology (red cell fragment, %)</td>
<td>38</td>
</tr>
<tr>
<td>Bleeding time, min</td>
<td>6–10&gt;</td>
</tr>
<tr>
<td>Prothrombin time, % (normal 104.4±16.1)</td>
<td>80</td>
</tr>
<tr>
<td>Thrombo test, sec (normal 13.8±1.9)</td>
<td>23.0</td>
</tr>
<tr>
<td>Fibrinogen, mg /100 ml (normal 295.3±42.8)</td>
<td>271.9</td>
</tr>
<tr>
<td>Fibrin degradation products, µg/ml (normal 7.3±0.8)</td>
<td>80.0</td>
</tr>
<tr>
<td>Lactic acid dehydrogenase, unit (normal 100–350)</td>
<td>3,280</td>
</tr>
<tr>
<td>Coombs’ test</td>
<td></td>
</tr>
<tr>
<td>Direct</td>
<td>Negative</td>
</tr>
<tr>
<td>Indirect</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Fig. 2. Peripheral blood film demonstrating distortion of red cell morphology.
drenase) level was extremely elevated. Fibrin degradation products (FDP) in serum was also markedly elevated, but the fibrinogen level was normal. Moreover, the blood film showed considerable poikilocytosis and anisocytosis with large numbers of fragmented red blood cells (Fig. 2). These hematological findings clearly indicated that she was now suffering from MHA. Dipyridamole, 225 mg daily, was given in an attempt to prevent platelet aggregation, but her condition was not improved. The creatinine clearance was decreased to 4.5 ml/min, azotemia appeared and progressed. Peritoneal dialysis was instituted on the 23rd day after the angiography. Although serum urea nitrogen had been decreased after dialysis, it had no effect on MHA. The hypertension became severer and could not be controlled despite intensive treatments with such antihypertensive drugs, as methyl dopa, clonidine hydrochloride, bethanidine, guanethidine, and propranolol. The diastolic pressure remained at 140 mmHg or above. Furthermore, neurological symptoms, such as nausea, vomiting, flapping tremor, and numbness in the hands, appeared. She complained of poor vision. Bilateral retinal hemorrhages, exudates, and papilledema were noted in the ocular fundi. To save her life from impending death, bilateral nephrectomy was undertaken on May 11, 1974.

Excised kidneys were normal in size (right 130 Gm, left 140 Gm) with smooth surface. Histological examination showed severe hypertensive changes (Fig. 3). There were arteriolar sclerosis with luminal fibrinoid materials and occlusion. Moreover, areas of hyaline arteriolar sclerosis and necrosis were present. No perivascular inflammation or glomerular necrosis was found. In the majority of the glomeruli slight thickening of mesangium was observed. Atrophy of tubules and interstitial fibrosis were widely found. These findings were consistent with the diagnosis of malignant nephrosclerosis.

Blood pressure subsided after bilateral nephrectomy and returned to normal in 1 month after operation. She has since been kept normotensive on treatment with methyl dopa, 250 mg daily. The retinal abnormalities resolved. One month after operation, the platelet count rose to 206,000/mm³ and blood film showed no fragmentation of red blood cells. As is commonly observed after bilateral nephrectomy, the patient remained anemic with a red blood cell count in the range of 2,000,000/mm³ to 2,500,000/mm³. Otherwise, she is now well, receiving regular hemodialysis, and waiting renal transplantation.

Fig. 3. Histological examination on excised kidneys shows severe hypertensive vascular lesion. Azan and Mallory, × 400
DISCUSSION

It has been well known that the prognosis of malignant hypertension is poor even when it is treated intensively with antihypertensive drugs.\textsuperscript{9)} The prognosis is particularly worse in patients with elevated serum urea nitrogen.\textsuperscript{9)} Currently, hemodialysis is widely applied to the treatment of chronic renal failure. This trend has made it possible to treat malignant hypertension with more aggressive means than those tried in the past, nephrectomy. Thus, bilateral nephrectomy, as an attempt to save patient's life from rapidly deteriorating malignant hypertension, has been reported with increasing frequency in recent years.\textsuperscript{5,6,9,9)}

MHA is a disease with 2 main components: red cell fragmentation and intravascular coagulation.\textsuperscript{1)} Linton et al\textsuperscript{10)} have proposed criteria for the diagnosis of MHA as follows: at least grade 2 fragmentation\textsuperscript{1)} of red blood cells, hemoglobin level of 60\% or lower, and reticulocyte count of 5\% or more. All these criteria were satisfied in our patient. MHA is known to occur in thrombocytopenic purpura, hemolytic uremic syndrome, acute glomerulonephritis, acute renal failure, collagen disease, eclampsia, and carcinomatosis.\textsuperscript{10)} The syndrome also has been described in association with malignant hypertension. As far as we know, during the past 10 years from 1962 to 1972, 39 such cases have been reported in English literature.\textsuperscript{11,10-20)} In Japan, however, only 3 cases have been described.\textsuperscript{2,3)} Thus the present patient is the fourth case in Japan.

According to Brain et al,\textsuperscript{21)} fibrinoid degeneration of arterioles in malignant hypertension is a cause of MHA. In other words, they regarded MHA as a complication of malignant hypertension. Gavras et al\textsuperscript{19)} have proposed another hypothesis on the basis of their observations on patients and experimental animals: They regarded MHA as an initiating and aggravating factor rather than a consequence of malignant hypertension. It is likely that HMA starts usually as a complication of malignant hypertension, and, once started, it impedes the renal circulation further, resulting thus in a vicious circle to accelerate the terminal course of malignant hypertension. In some patients it may occur almost simultaneously with the development of malignant hypertension as observed by Gavras et al.\textsuperscript{19)}

In our patient, diagnosed on admission as malignant hypertension in its early stage, MHA developed after angiography. Following MHA her blood pressure became progressively more difficult to control. MHA made the malignant hypertension more malignant, manifesting clearly its aggravating nature.

Concerning a possibility of angiography to cause MHA, no report has
MALIGNANT HYPERTENSION WITH MHA

appeared in the literature. But it occurred in the present patient. Physicians have to keep this possibility in mind as a rare complication of angiography in hypertensive patients, especially in malignant hypertension.

ACKNOWLEDGEMENTS

The authors are deeply indebted to Dr. Y. Taguchi of the 2nd Department of Surgery for his skillful performance of bilateral nephrectomy and to Dr. K. Abe of Department of Clinical Laboratory for his skillful performance of hematological examination on our case.

REFERENCES

17. Eknoyan G, Siegel MB: Recovery from anuria due to malignant hypertension. JAMA 215:
1122, 1971


