Correlation between Blood Parameters and Symptomatic Vasospasm in Subarachnoid Hemorrhage Patients

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Abstract
Serial changes in platelet and white blood cell (WBC) counts and other blood parameters were analyzed in 103 patients with aneurysmal subarachnoid hemorrhage (SAH). The WBC counts during days 3-5, 6-8, 9-11, and 12-14 after the onset of SAH were significantly higher in patients with than in patients without symptomatic vasospasm. Platelet counts during days 0-2, 3-5, 6-8, 9-11, 12-14, 15-17, 18-21, and 22-28 after SAH were significantly higher in patients with than in patients without symptomatic vasospasm. Monitoring of platelet and WBC counts may provide an indicator of the occurrence of symptomatic vasospasm.

Key words: subarachnoid hemorrhage, symptomatic vasospasm, blood parameter

Introduction
Cerebral vasospasm is a significant cause of mortality and morbidity in patients who suffer subarachnoid hemorrhage (SAH) due to a ruptured intracranial aneurysm. Earlier prediction of the onset of symptomatic vasospasm might allow prophylactic therapy. However, the etiology and pathogenesis of the vasospasm after SAH are unclear.

Leukocyte-related inflammatory process and platelet-released substances such as serotonin, thromboxane, growth factor, and noradrenaline may induce vasospasm in the affected artery after SAH. This study investigated serial changes in blood parameters such as platelet and white blood cell (WBC) counts to assess whether monitoring of blood parameters is helpful for prediction of symptomatic vasospasm.

Subjects and Methods
This study reviewed the records of 103 patients, 39 males and 64 females aged 24 to 84 years (mean 55 ± 12 years), with ruptured intracranial aneurysm of the anterior circulation admitted to the Department of Neurosurgery of Prefectural Gifu Hospital between January 1992 and March 1996. Selection criteria were initial computed tomography grading of Fisher group 3 for the severity of SAH, treatment by aneurysmal clipping within 24 hours after the onset of SAH, and clinical status at admission of Hunt and Kosnik grade 1, 2, or 3. Thirty-five patients who showed signs and symptoms of vasospasm were included in the SV group, and 68 without signs or symptoms in the non-SV group.

Table 1 Clinical characteristics of patients with and without symptomatic vasospasm (SV)

<table>
<thead>
<tr>
<th>Hunt and Kosnik grade</th>
<th>SV group</th>
<th>Non-SV group</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>21</td>
<td>52</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>good</td>
<td>21</td>
<td>63</td>
</tr>
<tr>
<td>poor</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>died</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Normal pressure hydrocephalus</td>
<td>20</td>
<td>21</td>
</tr>
</tbody>
</table>
tion (Table 1).

Serial values of blood parameters including platelet count, WBC count, hematocrit, blood sugar, and serum albumin during the 3 weeks after the onset of SAH were measured. Comparison of the SV and non-SV groups used the values measured on the day closest to days 0 (0–2), 3 (3–5), 6 (6–8), 9 (9–11), 12 (12–14), 15 (15–17), and 18 (18–21). In addition, the platelet count during days 22 to 28 (closest day 22) after SAH was also studied. Mean value of blood parameters within 8 days was calculated from the data taken on days 0–2, 3–5, and 6–8, and that within 3 weeks on days 0–2, 3–5, 6–8, 9–11, 12–14, 15–17, and 18–21. Statistical analysis of the data used Student’s or Welch’s t-test, and significance was assessed as a p value less than 0.05.

Outcome was assessed at discharge according to the Glasgow Outcome Scale. One patient in the non-SV group died from postoperative acute renal failure and four patients had poor outcome because of intraoperative damage to the perianeurysmal perforating artery. Two patients in the SV group died of extensive cerebral infarction caused by vasospasm (Table 1).

### Results

Patients in the SV group had significantly higher platelet counts than those in the non-SV group at all sampling points (Table 2). Similarly, WBC counts were significantly higher between days 3–5, 6–8, 9–11, and 12–14 (Table 2). However, there was no significant difference in the other blood parameters examined (Table 3).

Patients in clinical grades 2 and 3 had very similar platelet counts, but patients in grade 3 tended to have higher WBC counts (Table 4).

### Discussion

The present study showed that WBC counts were significantly higher in patients with symptomatic vasospasm than in those without during days 3–5, 6–8, 9–11, and 12–14 after SAH. There was no significant difference in WBC counts during days 0–2, 15–17, and 18–21. WBC count was previously found to be correlated with the appearance of symptomatic vasospasm within 8 days after SAH, but not thereafter, which differs somewhat from our result. Although the reason for the difference in results is

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### Table 2  Comparison of platelet and white blood cell (WBC) counts in patients with and without symptomatic vasospasm (SV)

<table>
<thead>
<tr>
<th>Platelet count ($\times 10^3$/mm$^3$)</th>
<th>WBC count ($\times 10^3$/mm$^3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SV group</td>
<td>Non-SV group</td>
</tr>
<tr>
<td>Days 0–2</td>
<td>262 ± 66</td>
</tr>
<tr>
<td>Days 3–5</td>
<td>248 ± 59</td>
</tr>
<tr>
<td>Days 6–8</td>
<td>282 ± 61</td>
</tr>
<tr>
<td>Days 9–11</td>
<td>310 ± 102</td>
</tr>
<tr>
<td>Days 12–14</td>
<td>330 ± 118</td>
</tr>
<tr>
<td>Days 15–17</td>
<td>340 ± 119</td>
</tr>
<tr>
<td>Days 18–21</td>
<td>345 ± 126</td>
</tr>
<tr>
<td>Days 22–28</td>
<td>340 ± 118</td>
</tr>
</tbody>
</table>

Normal range

161–360

40–90

NE: not examined.

### Table 3  Comparison of blood parameters in patients with and without symptomatic vasospasm (SV)

<table>
<thead>
<tr>
<th>Within 8 days after SAH</th>
<th>Within 3 weeks after SAH</th>
</tr>
</thead>
<tbody>
<tr>
<td>SV group</td>
<td>Non-SV group</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>35 ± 4</td>
</tr>
<tr>
<td>Blood sugar (mg/dl)</td>
<td>156 ± 30</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.4 ± 0.4</td>
</tr>
</tbody>
</table>

NS: not significant, SAH: subarachnoid hemorrhage.
Table 4 Comparison of platelet and white blood cell (WBC) counts in patients in clinical grades 2 and 3 at admission

<table>
<thead>
<tr>
<th></th>
<th>Within 8 days after SAH</th>
<th>Within 3 weeks after SAH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Platelet count (× 10^9/mm³)</td>
<td>212 ± 64</td>
<td>214 ± 60</td>
</tr>
<tr>
<td>WBC count (× 10^9/mm³)</td>
<td>103 ± 31</td>
<td>118 ± 32</td>
</tr>
</tbody>
</table>

NS: not significant. SAH: subarachnoid hemorrhage.

difficult to explain, the trend of WBC counts in the previous report⁹) and the present study is similar. Higher WBC counts in the earlier period after SAH may have an influence on the occurrence of symptomatic vasospasm. In the present study, the WBC counts of both the SV and non-SV groups decreased in the later course, and no significant difference was found with the disappearance of the signs and symptoms of symptomatic vasospasm. A WBC count greater than 20,000, regardless of the clinical grade of admission, is associated with worse outcome in patients with SAH.¹²) Although leukocytosis is a non-specific index of infection, tissue necrosis, hemorrhage, or stress, patients with post-SAH vasospasm demonstrated a higher WBC counts.¹¹) Leukocytosis is reported to be an adverse prognostic factor for both mortality and the development of clinically significant vasospasm, suggesting that activated WBCs releasing oxygen free radicals may be the cause.¹⁰)

Our study demonstrated a decrease of platelet count in the early period after surgery, followed by an increase over approximately 2 weeks. Previously, platelet count was found to increase for 3 weeks after SAH.⁸) This difference in results may be attributable to differences in the selection of patients, such as inclusion of grade 4 and 5 patients, or patients with various timing of surgery. Symptomatic (clinical) vasospasm is the syndrome resulting from the ischemic consequences of cerebral arterial narrowing and is characterized by the insidious onset of confusion and decreased level of consciousness followed by focal motor and speech impairments.⁹) Patients in grades 4 and 5 often have consciousness disturbance and various degrees of neurological deficits, so the presence of symptomatic vasospasm may be difficult to detect. Our study excluded such patients to not overlook the occurrence of symptomatic vasospasm.

Our results demonstrated that platelet counts in the SV group were significantly higher than those in the non-SV group. Platelet count decreased after surgery followed by an increase over 2 weeks, and began to decrease on days 22-28 for the SV group and on days 18-21 for the non-SV group. The increase in platelet count was more pronounced in patients who developed ischemia than in those who did not.⁶) SAH patients demonstrated decreased platelet count in the early period, presumably because of the consumption of platelet for hemostasis after surgery.⁵)

Platelets aggregate on the damaged arterial endothelium of ruptured intracranial aneurysm,¹⁰) and adventitial blood from SAH causes intimal platelet accumulation in cerebral arteries.¹⁷) The histological findings of post-SAH vasospasm show intimal proliferation, adherence of platelets to the subendothelial structures, platelet aggregation, and thrombus formation in the affected arteries.¹⁰,¹⁶,¹⁷) Platelets contain various agents such as thromboxane, serotonin, and growth factor which can cause contraction of vascular smooth muscle, and these agents may be responsible for post-SAH vasospasm.¹,²,⁴,¹⁴,¹⁵) The release of various agents from the aggregation platelets promotes further platelet aggregation and vasoconstriction.¹⁰) Therefore, post-SAH vasospasm may result from contraction of cerebral arterial smooth muscle cells secondary to release of vasoactive substances such as thromboxane A₂ and serotonin, impairment of vasodilatory activity due to such factors as prostacyclin/thromboxane imbalance and oxyhemoglobin, proliferative vasculopathy owing to mitogenic substances in the platelets adhering to the arterial lumen, and inflammatory processes due to morphological changes in the arterial wall at which leukocytes within the vessel and adherent to the endothelial surface act.⁹)

Symptomatic vasospasm developed on day 8 on average, and platelet counts during days 0-2, 3-5, and 6-8 in these patients showed significantly higher values compared to those in patients without vasospasm. Therefore, higher platelet counts in the early period after SAH may have an adverse influence. Several factors such as the effects of stress hormones and consumption of platelets influence platelet function after SAH, and desensitization or activation of platelets may occur.⁹) Such disturbances in platelet function may influence the development of ischemic complications after the onset.
of SAH or after surgery. In the present study, symptoms and signs of symptomatic vasospasm persisted for 5 days on average, but platelet counts continued to increase or remain higher than on days 0–3 even after the disappearance of the signs and symptoms. This result suggested that a population of desensitized platelets might become dominant in the later stage after SAH.

Our present results demonstrated that in the early period after SAH clinical grade 3 patients had a significantly higher mean WBC counts than grade 2 patients. In contrast, there was no significant difference in platelet counts. The higher WBC count in grade 3 patients might reflect or cause the higher incidence of symptomatic vasospasm in grade 3 patients. Factors such as amount of subarachnoid blood and clinical grade influence the occurrence of vasospasm. Therefore, patients with Fisher group 3 SAH were selected for this study.

This study suggests that serial monitoring of platelet and WBC counts may provide an indicator of the occurrence of symptomatic vasospasm after the rupture of an aneurysm, which would be useful for the provision of prophylactic therapy.

References


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Commentary

This paper serves as a timely reminder that the complication of delayed vasospasm after SAH is not purely a local vascular phenomenon, but that systemic factors also may be important. As pointed out, although very significant increases in peripheral leukocyte and platelet counts were seen in the patients who developed symptomatic vasospasm, it cannot be said whether these were related to the causation of the spasm or were a consequence of it. It is interesting to speculate that high circulating levels of these cells, with the resultant higher availability of factors such as oxygen free radicals produced by leukocytes, or of
platelets to take part in intravascular adhesion or thrombosis, may be at least partly responsible for the changes of vasospasm. Further study on these changes, particularly from the point of view of timing, is obviously needed to try and clarify the cause and effect relationship with vasospasm.

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Cerebral vasospasm is a leading cause of mortality and morbidity in patients who have been attacked by subarachnoidal hemorrhage. Although energetic clinical and fundamental research work have been done, its pathogenesis has been remained to be elucidated. To detect the symptomatic vasospasm as early as possible, ultrasound arterial flow velocity has been advocated to be potent and useful. This paper reported the usefulness of monitoring of platelet and WBC counts to detect the occurrence of symptomatic vasospasm in early postsubarachnoidal hemorrhage period in grade III of Hunt and Kosnik grading scale. Although the pathogenesis of these phenomena is unclear now, this observation is another tool for early detection of symptomatic vasospasm patients. Early detection and treatment may ameliorate the prognosis of subarachnoidal hemorrhage patients. Further clinical study should be encouraged to perform by these authors to elucidate the pathogenesis of these phenomena.

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The authors have nicely described hematological parameters (thrombocytosis and leukocytosis) as predictors of SAH associated symptomatic vasospasm. A few observations need to be clarified by future study before wide clinical applicability of the results of the study.

1. The sample size of the SV group is small (i.e. 35 patients).

2. Leukocytosis is a non-specific indicator of inflammatory processes of any kind. In the present study, the difference between the SV and non-SV groups in leukocytosis is very great (2000/mm³) in the study. There is no suggestion of critical leukocyte count where we should suspect onset of vasospasm. In the SV group, leukocytosis does not reflect any trend over serial estimations. Increasing or decreasing trends would have been of more clinical applicability.

3. Thrombocytosis trends after SAH related vasospasm are important and need further study.

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Niikawa et al. attempted to analyze the relationship between serial changes in peripheral blood parameters and symptomatic vasospasm in patients with subarachnoidal hemorrhage. They reviewed the platelet and the white blood cell counts in 35 patients with symptomatic vasospasm and 68 patients without symptomatic vasospasm. They found that these counts were significantly higher, during a set period, in patients with symptomatic vasospasm. They suggested that serial monitoring of these peripheral blood parameters could be utilized as an indicator predicting the occurrence of symptomatic vasospasm after the rupture of an aneurysm. Although similar studies had been reported, this paper is a well-designed and valuable clinical research work.

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