Microangiopathic Hemolysis and Renal Failure in Malignant Hypertension

Bert Jan H. van den Born, Uwkje P.F. Honnebier, Richard P. Koopmans, Gert A. van Montfrans

Abstract—Renal dysfunction is an important cause of morbidity and mortality in patients with malignant hypertension. Microangiopathic hemolysis (MAHA) related to malignant hypertension may cause renal insufficiency by obstruction of interlobular arteries. We hypothesized that the presence of MAHA is an important indicator of renal dysfunction and recovery in malignant hypertension. We retrospectively analyzed 97 patients admitted between April 1994 and April 2004 with malignant hypertension. MAHA was defined as a low platelet count (<150×10^9/L) with either an elevated lactic dehydrogenase (>220 U/L) or presence of schistocytes. MAHA was present in 26 of 97 patients (27%). Serum creatinine levels at admission were significantly higher in those with than in those without MAHA: median serum creatinine 690 μmol/L (interquartile range [IQR] 394 to 1105) and 120 μmol/L (IQR 82 to 211), respectively (P<0.01). Patients with MAHA were more often black (73%; P<0.01) and had higher systolic blood pressure (mean 242 mm Hg versus 225 mm Hg; P<0.01). Dialysis was needed in 15 patients with MAHA (58%) versus 2 patients (3%) without MAHA. In 6 patients with MAHA, dialysis could be stopped. Cox regression analysis showed that MAHA and systolic blood pressure were the most important indicators of renal improvement during follow-up, with a hazard ratio of 0.24 (95% confidence interval [CI], 0.08 to 0.75; P=0.01) and 1.02 per mm Hg increase in systolic blood pressure (95% CI, 1.01 to 1.05; P=0.01). In conclusion, MAHA is an important indicator of renal insufficiency and recovery in patients with malignant hypertension. (Hypertension. 2005;45:246-251.)

Key Words: hypertension, malignant ▪ kidney ▪ blacks

Microangiopathic hemolysis (MAHA) is a well-known complication of malignant hypertension. However, little is known about its epidemiology and relationship with renal dysfunction. Although the prognosis of malignant hypertension has improved considerably over the past decades, renal dysfunction remains an important cause of morbidity and mortality.1–4 Yet some patients have a remarkable recovery of kidney function after adequate control of blood pressure is achieved.5–8 It has been suggested that in patients with malignant hypertension and kidney dysfunction, the presence of MAHA may be an indicator of renal recovery.9,10 In most renal biopsy specimens from patients with renal failure related to malignant hypertension, an obliterative vasculopathy is observed with fibriboin necrosis and sometimes frank thrombosis of interlobular arteries.9,10 These fibrinoid depositions are caused by continued seepage of fibrin en serum proteins through a necrotic vessel wall into surrounding viable tissue.11 The presence of MAHA, as evidence of profound endothelial damage, may point toward such an obliterative vasculopathy with subsequent renal dysfunction. Resolution of MAHA by blood pressure treatment may, in turn, result in reperfusion and improvement of kidney function.

We hypothesized that the presence of MAHA may be an important predictor of renal dysfunction and recovery in malignant hypertension. Therefore, we performed a retrospective analysis of patients admitted with malignant hypertension to assess whether the presence of MAHA was related to renal dysfunction at admission and with improvement of renal dysfunction during follow-up.

Patients and Methods

We retrospectively analyzed charts of consecutive patients admitted with malignant hypertension at 2 large teaching hospitals (the Academic Medical Centre and Onze Lieve Vrouwe Gasthuis), catering for a large multiethnic community in Amsterdam, the Netherlands, between April 1994 and April 2004. Both hospitals use the same database in which the diagnosis at discharge is recorded according to the International Classification of Diseases (ICD) codes.

The following ICD codes were reviewed: essential malignant hypertension (ICD 401.0), hypertensive encephalopathy (ICD 437.2), secondary malignant hypertension (ICD 405.09), hypertension with cardiac disease/malignant (ICD 402.0), and hypertension with kidney disease/malignant (ICD 403.0). To identify the presence of registration errors, computer data of all patients discharged with the diagnosis essential hypertension (ICD 401.9) were also analyzed.

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Correspondence to B.J.H. van den Born, Department of Internal Medicine, Academic Medical Centre, Meibergdreef 9, Room F4-222, PO Box 22660, 1100 DD, Amsterdam, the Netherlands. E-mail b.j.vandenborn@amc.uva.nl
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In all patients, the diagnosis malignant hypertension was verified according to the World Health Organization (WHO) criteria of 1978: high blood pressure together with bilateral linear or flame-shaped hemorrhages or “cotton-wool” exudates with or without papilledema during fundoscopic examination (grade III and IV hypertensive retinopathy, respectively, according to the Keith–Wagener and Barker classification).

We defined MAHA related to malignant hypertension as: (1) the presence of a low platelet count (<150×10^9/L) together with either an elevated lactic dehydrogenase (LDH) level (>220 U/L) or presence of schistocytes, or both; and (2) normalization of platelets and LDH or schistocytes after adequate blood pressure control was achieved.

Excluded from analysis were patients <18 years of age, pregnant women, patients with papilledema and an intracranial mass (hemorrhage), patients already on dialysis before admission, and patients in whom MAHA could not be assessed or who had an alternative explanation for a low platelet count. Macroalbuminuria was defined as urinary protein excretion >300 mg/L, or 2+ for dipstick proteinuria. Left ventricular hypertrophy was defined according to the Sokolow–Lyon criteria. Significant renal artery stenosis was defined if narrowing of the renal artery lumen exceeded 50% during computed tomography, MRI, or conventional angiography. Schistocytes were considered present if “several” red cell fragments could be detected on a peripheral blood film.

End points were: (1) serum creatinine levels and urinary protein excretion at admission; and (2) improvement of renal function on follow-up, defined as a 50% reduction in serum creatinine compared with baseline.

Statistics
Baseline variables were described using mean and SD, median and range, or interquartile range for variables with a skewed distribution. Differences between groups were calculated using Yates correction or a t test for parametric and Mann–Whitney U test for nonparametric distributions where appropriate. Linear regression analysis was used to assess the contribution of platelet count on serum creatinine, with serum creatinine expressed on a logarithmic scale. R² was used to give an estimate of the variations in serum creatinine explained by platelet count at admission. The confidence interval (CI) of this estimate was calculated using the Fisher z transformation. Univariate ANOVA was performed to test the association between serum creatinine and MAHA, adjusted for race, blood pressure at admission, and established secondary causes of malignant hypertension. To analyze indicators of improvement of renal function during follow-up, Cox regression was used. First, single variables were used to test an association with improvement of renal function. Single variables that showed a significant association or could have a possible pathophysiological relationship with improvement of renal function were retained and used for the model. Then, a backward elimination method was used in which the variable with the smallest partial correlation with the dependent variable was removed first. For all tested variables in this model, the hazard ratio (HR) with its 95% CI was calculated. Variables that had a significant association with renal improvement were used to test an association with improvement of renal function. For statistical analysis, the SPSS software package for Windows version 12.0 was used.

Results
A total of 110 patients fulfilled the WHO criteria for malignant hypertension. Thirteen patients were excluded because: (1) they had an alternative explanation for the presence of papilledema attributable to an intracranial mass,4 (2) the platelet count at admission was unknown,5 or (3) they had an alternative explanation for the thrombocytopenia4 (Figure 1). For the remaining 97 patients, imaging studies of the renal arteries were conducted in 79 (81%), ≥1 endocrine tests for pheochromocytoma, Cushing’s disease or Conn’s syndrome in 44 (45%), and renal biopsies in 18 (19%) patients. In 19 of 26 patients with thrombocytopenia, schistocytes were present; in 3, schistocytes were absent, and in 4, this test was not performed. The number of patients with primary and secondary malignant hypertension is listed in Table 1. The clinical characteristics according to the presence or absence of MAHA are summarized in Table 2.

The main outcome measures, serum creatinine level and urinary protein excretion at admission, were significantly higher in the group with MAHA (Figure 2). After correction for blood pressure, ethnicity, and secondary causes, differences in serum creatinine levels between patients with and without MAHA remained statistically significant (P<0.01). Linear regression analysis of serum creatinine and platelet count is shown in Figure 3.

Dialysis was needed in 15 of 26 (58%) patients with MAHA during admission and in 2 patients (3%) without MAHA. In 6 patients with MAHA, dialysis could be stopped:

### Table 1. Secondary Causes of Malignant Hypertension According to the Presence or Absence of MAHA

<table>
<thead>
<tr>
<th>Causes of Malignant Hypertension</th>
<th>MAHA Present</th>
<th>MAHA Absent</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cause identifiable (essential malignant hypertension)</td>
<td>17 (65%)</td>
<td>48 (68%)</td>
<td>0.84</td>
</tr>
<tr>
<td>Renal parenchymal disease</td>
<td>6 (23%)</td>
<td>8 (11%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Renal artery stenosis</td>
<td>2 (8%)</td>
<td>6 (8%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Other (endocrine, drug-induced)</td>
<td>1 (4%)</td>
<td>9 (13%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Total</td>
<td>26 (100%)</td>
<td>71 (100%)</td>
<td></td>
</tr>
</tbody>
</table>
4 within 2 months, and in 2 others, after 8 months and 2 years, respectively. Follow-up was complete for 87 of 97 patients (90%). Ten patients either moved or did not show up at the outpatient department. The total number of patients who died or were lost to follow-up were equally distributed in both groups. Nine patients died: 3 from cardiovascular complications, 2 from cerebral hemorrhage, and 1 from myocardial infarction. Characteristics for those at follow-up are listed in Table 3.

Improvement of renal function, defined as a reduction of serum creatinine ≥50% compared with baseline, was noted in 17 patients during follow-up. Cox regression analysis showed that MAHA and systolic blood pressure at admission were the
most powerful indicators of renal improvement with an HR of 0.24 (95% CI, 0.08 to 0.75) and 1.02 per mm Hg increase in systolic blood pressure (95% CI, 1.01 to 1.05; Table 4). The interaction between systolic blood pressure and MAHA was not significant ($P_{110050.28}$). Improvement of kidney function over time in patients with and without MAHA is shown in Figure 4.

**Discussion**

We found a marked difference between serum creatinine levels and proteinuria in patients with and without MAHA in the sense that renal dysfunction was more severe in patients with MAHA. Also after adjusting for ethnicity, blood pressure, and secondary causes of malignant hypertension, the association between kidney dysfunction and MAHA remained significant. There was a negative log-linear relationship between serum creatinine and platelet count, indicating that a decline in platelet count, as evidence of MAHA, was related to a decline in renal function. Furthermore, platelet count could explain 37% of the variations in serum creatinine at admission. The predominance of black patients with MAHA in our study is consistent with previous reports in which a high prevalence of MAHA in blacks with malignant hypertension was found.\textsuperscript{4,7,11} There was no difference in severity of retinopathy or left ventricular hypertrophy between the groups with and without MAHA, which supports the theory from previous studies in which clinical characteristics and survival are not different for patients with grades III or IV hypertensive retinopathy.\textsuperscript{12,13}

Although recovery from renal failure has been reported previously in patients with malignant hypertension,\textsuperscript{14–17} few have noted a possible association with MAHA.\textsuperscript{5,6,18} However, in several case reports and case series, a possible link between MAHA and recovery from renal failure has been suggested.\textsuperscript{5–7} In the largest series on renal failure related to malignant hypertension, 12 patients who recovered from dialysis were compared with 42 patients who did not.\textsuperscript{7} The presence of MAHA was found as a possible predictor of renal recovery, although this finding was not significant, possibly because of small group size. In our study, patients with MAHA had a 4\times higher chance of renal improvement than patients without MAHA. Furthermore, dialysis could be stopped in 6 of 15 (40%) patients with MAHA who needed kidney replacement therapy during admission.

The reason MAHA develops in malignant hypertension has not been fully clarified. Most evidence regarding MAHA pathogenesis comes from animal studies: rats double transgenic for the human renin and angiotensinogen genes develop severe hypertension and profound endothelial damage similar to MAHA seen in humans with malignant hypertension.\textsuperscript{19} Furthermore, animal studies have shown that high levels of angiotensin II have a direct cytotoxic effect on the vessel wall.\textsuperscript{20,21} Finally, rats with a unilateral renal artery stenosis develop malignant hypertension when refrained from water and saline, suggesting that pressure natriuresis further enhances renin-angiotensin-aldosterone system (RAAS) activation through induction of kidney ischemia.\textsuperscript{22}

**TABLE 3. Patient Characteristics on Follow-Up**

<table>
<thead>
<tr>
<th>Patient Characteristics at Follow-Up</th>
<th>MAHA Present</th>
<th>MAHA Absent</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lost to follow-up, No. (%)</td>
<td>3 (11%)</td>
<td>7 (10%)</td>
<td></td>
</tr>
<tr>
<td>Follow-up time, months (mean±SD)</td>
<td>52±33</td>
<td>40±33</td>
<td>0.09</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg (median, IQR)</td>
<td>140 (128–152)</td>
<td>140 (122–150)</td>
<td>0.87</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg (median, IQR)</td>
<td>90 (80–100)</td>
<td>89 (79–99)</td>
<td>0.58</td>
</tr>
<tr>
<td>Antihypertensive drugs, No.</td>
<td>3.3</td>
<td>3.6</td>
<td>0.66</td>
</tr>
<tr>
<td>Increase in serum creatinine more than one-third of baseline, No. (%)*</td>
<td>3 (21%)</td>
<td>14 (23%)</td>
<td>0.90</td>
</tr>
<tr>
<td>Died, No. (%)</td>
<td>2 (8%)</td>
<td>7 (10%)</td>
<td></td>
</tr>
</tbody>
</table>

*Calculated for those not in need of permanent kidney replacement therapy.

IQR indicates interquartile range.

**TABLE 4. Cox Regression Analysis Using a Backward Elimination Method to Predict Indicators for Improvement of Renal Dysfunction**

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Rank*</th>
<th>$P$</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>3</td>
<td>0.58</td>
<td>0.98</td>
<td>0.93–1.04</td>
</tr>
<tr>
<td>Male</td>
<td>2</td>
<td>0.72</td>
<td>0.83</td>
<td>0.29–2.35</td>
</tr>
<tr>
<td>Black</td>
<td>5</td>
<td>0.14</td>
<td>2.36</td>
<td>0.75–7.45</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>...</td>
<td>0.01</td>
<td>1.02</td>
<td>1.01–1.05</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>4</td>
<td>0.57</td>
<td>0.99</td>
<td>0.94–1.03</td>
</tr>
<tr>
<td>Log creatinine</td>
<td>1</td>
<td>0.77</td>
<td>0.76</td>
<td>0.12–4.8</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td>6</td>
<td>0.11</td>
<td>0.28</td>
<td>0.06–1.35</td>
</tr>
<tr>
<td>MAHA</td>
<td>...</td>
<td>0.01</td>
<td>0.24</td>
<td>0.08–0.75</td>
</tr>
</tbody>
</table>

HR, 95% CI, and $P$ value were determined just before elimination.

*Indicates the rank of elimination in stepwise backward Cox regression.
The evidence for the importance of RAAS activation in development of malignant hypertension and MAHA seems in contrast with the high prevalence of MAHA in black hypertensive patients because they tend to have lower plasma renin and angiotensin levels. In our population, all blacks were immigrants from western Africa and Dutch Surinam and, in most cases, had never visited a doctor. Delay in presentation could explain a more severe presentation of malignant hypertension with coexisting MAHA and renal dysfunction. However, another explanation is also possible: recent reports have suggested a more active role of the intrarenal renin-angiotensin system in blacks. In accordance with this finding is a reduced renal plasma flow attributable to renal vasoconstriction in these patients, which is reversible after administration of an angiotensin-converting enzyme (ACE) inhibitor. This vasoconstriction could make blacks more prone to development of renal ischemia, with subsequent activation of the RAAS, and to development of MAHA, through high levels of angiotensin II. Pre-existent renal arteriolar or glomerular disease, caused by hypertension or otherwise, may contribute to development of MAHA by enhancing renal ischemia. In turn, MAHA may cause further renal damage by narrowing and thrombosis of renal arteries. In kidney biopsy specimens, this may be reflected by the presence of fibrinoid necrosis and thrombosis of interlobular arteries with subsequent ischemic glomerular and tubular changes. However, because kidney biopsies were not routinely taken in this and previous reports, further histological evidence for this association is needed.

To differentiate MAHA related to malignant hypertension from other causes of microangiopathic hemolysis, particularly thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, can be difficult. Therefore, we included normalization of platelet count and LDH or disappearance of schistocytes after blood pressure control in our definition, making alternative explanations for the thrombocytopenia unlikely. In 3 patients, the presence of a low platelet count together with an elevated LDH was not accompanied by the presence of schistocytes. However, in our experience, the prevalence of schistocytes in a peripheral blood smear is low in malignant hypertension, probably making it a less-sensitive criterion for establishing MAHA. Using an increased LDH level as an exclusive marker may overestimate the prevalence of MAHA because it can also be elevated in several other conditions.

Selection bias in this retrospective study may have been introduced by the way patients were referred. Because both hospitals contain a dialysis unit, patients with malignant hypertension and renal insufficiency would be more likely to be included. However, in all patients, renal insufficiency was established only after presentation to the emergency department; no patients were referred from elsewhere for dialysis treatment. Second, although patients with possible malignant hypertension are routinely examined by an ophthalmologist in both hospitals, some patients without symptoms and severe elevation of blood pressure could have been missed. Third, patients with renal parenchymal or renovascular disease were not excluded because MAHA may also be related to renal dysfunction in patients with pre-existent renal parenchymal disease. When patients without evidence of renal parenchymal or renovascular disease were analyzed separately, no difference in outcome was observed. Because kidney biopsies were not taken routinely, some patients with renal parenchymal disease could have been missed. However, macroalbuminuria disappeared in all patients said to have essential malignant hypertension after adequate blood pressure control was achieved during follow-up, suggesting hypertensive kidney disease instead of renal parenchymal disease. Furthermore, ultrasonography of kidneys and imaging studies of renal arteries performed in these patients showed no evidence of postrenal obstruction, cystic disease, or renal artery stenosis.

**Perspectives**

We have shown that MAHA is an important predictor of renal insufficiency and recovery in malignant hypertension. Analysis of platelets, LDH, and schistocytes in patients with malignant hypertension may serve as an important marker for those who are at risk of renal failure. The predominance of black patients with MAHA may suggest that a more active intrarenal renin-angiotensin system is primarily involved in the onset of MAHA, as is shown recently. Furthermore, MAHA as evidence of profound endothelial damage may further limit renal blood flow by narrowing and obstruction of renal arterioles. It would be of interest to examine whether early ACE inhibition, besides standard therapy with sodium nitroprusside or labetalol, in patients with malignant hypertension and MAHA could result in a more rapid reduction of microangiopathy and relative preservation of renal function.

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References


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