Research Article

Malignant Hypertension in Lupus Nephritis

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Abstract

Hypertension with rapid worsening of renal function is a rare presentation of lupus nephritis. The aim of this work is to ascertain the prevalence and prognostic importance of malignant hypertension at the onset of LN. We also searched for a correlation between malignant hypertension and LN histological class. We have retrospectively assessed 15 cases of malignant hypertension and SLE with LN. Eleven were males (73.3%). Mean age was 36 years. Mean interval between diagnosis of SLE and the appearance of renal complications was 110 months. Clinical presentation consisted of malignant hypertension (DBP > 115 mm Hg with hypertensive retinopathy grades III-IV). At presentation, 12/15 (80%) showed renal insufficiency (mean creatinine was 3.8 mg/dl). Mean proteinuria level was 4.2 g/24h and microhematuria was observed in 73.3% of cases. Immunologic studies showed decreased C3 (66.6%) and circulating cryoglobulins in 13.3%. Renal biopsies showed class IV (10/15, 66.7%), III (1/15, 6.6%) and V GN (4/15, 26.7%). Of the 15 patients, crescentic transformation occurred in 7 (46.6%) and TMA occurred in one patient (6.6%) on top of class IV-S. After a mean follow up of 24 months, 5 patients (33%) had recovered normal renal function, and 6 (40%) had started chronic dialysis.

Conclusion: Malignant hypertension associated with LN was a high risk clinical presentation with rapid worsening of renal function.

ABBREVIATIONS

LN: Lupus Nephritis; SLE: Systemic Lupus Erythematosus; C3: Complement 3; C4: Complement 4; TMA: Thrombotic Microangiopathy

INTRODUCTION

SLE is characterized by a wide spectrum of clinical manifestations, including renal, pulmonary, cardiovascular, and neuropsychiatric abnormalities [1]. Numerous studies report a high prevalence of hypertension in women with SLE, reaching as high as 74% in some cohorts [2-6]. Development of hypertension, in patients with SLE, is more common in patients with advanced lupus-related renal pathology or impairment of renal function. In addition to advanced renal disease as a cause of hypertension, anti-rheumatic drugs including corticosteroids and cyclosporin might be associated with either the onset or aggravation of hypertension [7].

Malignant hypertension has been reported in association with autoimmune rheumatic diseases and in patients with the antiphospholipid antibody syndrome (APS) alone or with SLE and is relatively well described in the medical literature [8]. However, there are few reports on the clinical presentation of malignant hypertension in patients with SLE in the medical literature.

Here, our objective is to ascertain the prevalence and prognostic importance of malignant hypertension at the onset of clinical LN. We also searched for a correlation between malignant hypertension and histological class of LN.

MATERIALS AND METHODS

In the period 1999-2010, all patients with SLE who presented to Nephrology and/or Rheumatology departments of Kasr al-Aini School of Medicine and had undergone renal biopsies were retrospectively assessed. Patients who had no evidence of LN according to the WHO classification were excluded, as were patients who were on corticosteroid therapy just prior to the renal biopsy.

A total of 63 patients (42 females) satisfied these criteria and were selected for the study. Patients were regarded as being hypertensive’s if they had a sitting blood pressure equal to or greater than 140/95 mmHg on at least two different occasions. The recorded blood pressure was the mean diastolic pressure of the two determinations. None of the patients was...
receiving antihypertensive medication before being admitted. Hypertension was classified as being mild (diastolic 95-99 mmHg), moderate (100-114 mmHg) or severe (> 115 mmHg). Clinical presentation of malignant hypertension was the presence of diastolic BP> 115 mmHg with hypertensive retinopathy grades III-IV.

The histological classification was obtained from the pathologist’s reports which utilize the standard WHO classification of glomerular involvement in SLE. All histology was subsequently re-evaluated by a single senior pathologist who searched specifically for hypertensive renal vascular lesions. Informed consent was obtained from each patient for blood sampling and renal biopsy. The research was in compliance with the Declaration of Helsinki.

RESULTS

Table 1 shows characteristics of all LN patients. Of the 15 patients with LN and malignant hypertension, eleven were males (73.3%). Their mean age was 36 years (26-51). Nine out of 15 (60%) had associated lower limb skin rash and the number of positive antineutrophil cytoplasm antibodies (p-ANCA) at presentation was seen in 5 out of 15 (33.3%). Two out of 15 (13.3%) were co-infected by hepatitis C virus and 1/15 (6.6%) by hepatitis B. Mean interval between diagnosis of SLE and the appearance of renal complications was 110 months (4-206). Clinical presentation consisted of malignant hypertension (diastolic BP> 115 mmHg with hypertensive retinopathy grades III-IV). At presentation, 12/15 (80%) showed renal insufficiency (mean serum creatinine was 3.8 mg/dl). Mean level of proteinuria was 4.2 g/24h and micro hematuria was observed in 73.3% of cases. Immunologic studies showed decreased C3 (66.6%) and circulating cryoglobulins in 13.3%

Table 2 shows the WHO histological classification of renal biopsies for malignant and non-malignant hypertensives compared to normotensives. For the 15 patients with LN and malignant hypertension, renal biopsies showed diffuse (IV) proliferative glomerulonephritis (10/15, 66.7%), focal (III) proliferative glomerulonephritis (1/15, 6.6%) and membranous (V) GN (4/15, 26.7%). In addition, crescentic transformation occurred in 7 of them (46.6%) and TMA occurred in one patient (6.6%) on top of class IV-S.

DISCUSSION

In our study, we found that patients with malignant hypertension were predominantly males (73%). This is consistent with what was reported by Kaplan [9] that men are affected 2 times more often than women by malignant hypertension. However, Tao et al. [10], who retrospectively studied 19 patients with LN complicated by malignant hypertension, found that 3 only were men (16%).

In addition, of the 15 patients with malignant hypertension, 12 (80%) presented with renal insufficiency with a mean serum creatinine of 3.8 mg % compared to 1.9 mg % in the non-malignant hypertensive and normotensive groups (P-value = 0.001). Similar results were found by Tao et al. [10], who reported that impaired renal function was noticed in 17 of the 19 patients (89%) with an average serum creatinine of 2.08 mg%. This could be explained by 2 factors; first, most of our patients with malignant hypertension had proliferative LN which is known to be associated with renal insufficiency and hypertension. Second, with severe elevations of BP, endothelial injury and fibrinoid necrosis of the arterioles ensue [11]. This process results in ischemia and the release of additional vasoactive mediators generating a vicious cycle of on-going injury. The renin–angiotensin system is often activated leading to further vasoconstriction and the production of proinflammatory cytokines such as interleukin-6 (IL-6) [12,13]. Furthermore, NADPH oxidase activity increases and generates reactive oxygen species [14]. The volume depletion that results from pressure natriuresis further simulates the release of vasoconstrictor substances from the kidney. These collective mechanisms can culminate in end-organ hypoperfusion, ischemia and dysfunction that manifests as a hypertensive emergency [15].

Moreover, of the 15 patients with malignant hypertension, 9 (60%) were found to have skin rash on the lower limbs compared to 7 patients only (14.6 %) in the non-malignant hypertensive and normotensive groups (P-value = 0.0001). However, we did not find a more detailed description of this rash in the medical records.

It is known that skin and/or mucous membranes are involved at some point in over 80 % of patients with SLE [16]. Skin lesions from vascular involvement in lupus in dede periungual erythema, live do reticularis, telangiectasia, Raynaud phenomenon, and
Table 1: Clinical and laboratory parameters of patients with SLE.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Malignant hypertension N=15</th>
<th>No malignant hypertension N=48</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, males (%)</td>
<td>11 (73.3)</td>
<td>10 (20.1)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Mean age (range)</td>
<td>36 (26-51)</td>
<td>32 (19-47)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean interval to renal complications in months (range)</td>
<td>110 (4-206)</td>
<td>102 (1-197)</td>
<td>NS</td>
</tr>
<tr>
<td>Renal insufficiency at presentation (serum creatinine &gt;1.35 mg/dl), number (%)</td>
<td>12 (80)</td>
<td>28 (58.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Skin rash on lower limbs, number, %</td>
<td>9 (60)</td>
<td>7 (14.6)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Serum creatinine at presentation, mean ±SD</td>
<td>3.8 ±3.4</td>
<td>1.9 ± 1.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Proteinuria in gm/24 hour at presentation, mean ± SD</td>
<td>4.2±3.1</td>
<td>3.0 ± 2.5</td>
<td>NS</td>
</tr>
<tr>
<td>Microhematuria at presentation, number (%)</td>
<td>11 (73.3)</td>
<td>29 (60.4)</td>
<td>NS</td>
</tr>
<tr>
<td>ANCA at presentation, number (%)</td>
<td>5 (33.3)</td>
<td>3 (6.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>HCV co-infection, number (%)</td>
<td>2 (15.3)</td>
<td>1 (6.6)</td>
<td>NS</td>
</tr>
<tr>
<td>HBV co-infection, number (%)</td>
<td>1 (6.6)</td>
<td>7 (14.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Decreased serum C3, number (%)</td>
<td>10 (66.6)</td>
<td>25 (52.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Circulating cryoglobulins, number (%)</td>
<td>2 (13.3)</td>
<td>9 (18.8)</td>
<td>NS</td>
</tr>
</tbody>
</table>

ANCA: Anti-Neutrophil Cytoplasmic Antibody; HCV: Hepatitis C Virus p HBV: Hepatitis B Virus p C3: Complement 3

Table 2: WHO histological classification of malignant and non-malignant hypertensive’s compared to normotensives. Percentages are given in parentheses.

<table>
<thead>
<tr>
<th>WHO class</th>
<th>Malignant hypertensives N= 15</th>
<th>Mild and moderate hypertensives N= 19</th>
<th>Normotensives N= 29</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>II</td>
<td>-</td>
<td>3 (15.8)</td>
<td>17 (58.7)</td>
</tr>
<tr>
<td>III</td>
<td>1 (6.6)</td>
<td>1 (5.2)</td>
<td>4 (13.8)</td>
</tr>
<tr>
<td>IV</td>
<td>10 (66.7)</td>
<td>5 (26.3)</td>
<td>1 (3.5)</td>
</tr>
<tr>
<td>V</td>
<td>4 (26.7)</td>
<td>8 (42.2)</td>
<td>7 (24.0)</td>
</tr>
<tr>
<td>VI</td>
<td>-</td>
<td>2 (10.5)</td>
<td>-</td>
</tr>
</tbody>
</table>

NB: Among the 15 patients with LN and malignant hypertension, crescentic transformation occurred in 7 of them (3 with class IV, 3 with class V and the one with class III) and thrombotic microangiopathy occurred in one patient on top of class IV-S.

Various forms of vasculitis; they occur in approximately 50% of patients [17].

In our study and in relation to ANCA prevalence in SLE patients, of the 15 patients with malignant hypertension, 5 (33.3%) were found to have positive p-ANCA compared to 3 patients only (6.3%) in the non-malignant hypertensive and normotensive groups (P-value = 0.001).

Approximately 20% of patients with SLE have ANCA positivity by indirect IF (IIF), mainly with a perinuclear pattern (p-ANCA). ANCA seropositivity by ELISA is less frequent and the target antigens are most commonly lactoferrin, cathepsin G, and MPO [18].

There are conflicting reports on the significance of ANCA positivity in patients with SLE [18]. Pauzner et al. [19], reported that Antineutrophil cytoplasmic antibodies may be seen in some patients with SLE but do not correlate with disease activity or the presence or severity of vasculitis and are rarely if ever directed against either the protease-3 or myeloperoxidase antigen. Others reported that SLE and LN may promote neutrophil degranulation and facilitate ANCA autoantibody formation [20].

Nasr et al. [20], reported 10 cases of LN with ANCA-associated glomerulonephritis, the evolution of these patients after the treatment by corticosteroids and cyclophosphamide was marked by lethal infectious complications in three patients, complete remission in six patients with a relapse in one case and resistance to treatment in one patient.

Nasr et al. [20], evoked the probability of an overlap between lupus nephropathy and ANCA extracapillary glomerulonephritis and suggested to search systematically the positivity of ANCA by ELISA test in a lupus patient whenever renal histology shows extensive necrotizing lesions with a non-significant endocapillary proliferation and rare sub-endothelial deposits.

Regarding the renal pathology of our patients, class IV LN was found to be the most predominant class among patients with malignant hypertension (66.7%), while classes II and V were the most frequently encountered ones among the normotensives and those having non-malignant hypertension respectively. In addition, of the 15 patients with malignant hypertension, crescentic transformation occurred in 7 of them (46.6%) and TMA occurred in one patient (6.6%) on top of class IV-S.

It is known that SLE involves the kidney in up to 60% of patients.
Although with more intensive immunosuppressive therapy, patients with TMA had a poorer renal outcome than those without renal TMA. Renal TMA was found as an independent risk factor for renal outcome in LN [32].

In this study, we showed that ESRD remains highly prevalent among lupus patients who were previously admitted with malignant hypertension, with 40% started regular hemodialysis, 27% had CKD and 33% recovered normal renal function after a mean follow-up of 24 months. In comparison, most of the patients with non-malignant hypertension recovered normal renal function (47%), while 16% only started regular hemodialysis after a mean follow-up of 21 months.

Although the prognosis of malignant hypertension has improved considerably over the past decades, renal dysfunction remains an important cause of morbidity and mortality [35]. Yet some patients have a remarkable recovery of kidney function after adequate control of blood pressure is achieved [36].

There are few data regarding the outcomes of a hypertensive crisis. In a study of 315 patients with malignant hypertension, 40% were alive after 33 months. The most common causes of death were renal failure (39.7%), stroke (23.8%), MI (11.1%), and heart failure (10.3%) [25].

Furthermore, studies of patients presenting to the emergency room with a hypertensive crisis have demonstrated that most do not receive the appropriate evaluation, medical regimen, and discharge instructions proposed by the current guidelines. Two studies of patients presenting to the emergency room with a hypertensive crisis found that serum chemistry was only obtained in 70% to 73% of patients, electrocardiogram in 53% to 70% of patients, chest x-ray in 24% to 46% of patients, and urinalysis in 43% to 44% of patients. Two-thirds of the total number of patients evaluated did not have a funduscopic examination in the emergency room, and only 19% discharged had modification of their antihypertensive regimen. Overall, only 6% obtained the tests recommended by the guidelines, and 10% had no tests performed [37,38].

The known duration of hypertension and procuring the serum urea level at presentation has been found to be the main predictors of survival in hypertensive crisis, with poorer outcomes for black patients [39].

The 1-year mortality rate is 79% for patients with untreated hypertensive emergencies [40], and 5-year survival rate among all patients who present with hypertensive crisis is 74% [25].

This study has both strengths and limitations. Strengths include the contribution of clinically relevant and previously unavailable data on long-term renal outcome of an unselected and well described cohort of patients with LN and malignant hypertension. Limitations include its retrospective nature and consequently the possibility of coding errors. In addition, unavailability of antiphospholipid antibodies for many patients was another limitation.

CONCLUSION

In conclusion, malignant hypertension associated with LN was a high risk clinical presentation with rapid worsening of renal function. Inhibition of renin-angiotensin system in addition to immunosuppressive drugs might induce a recovery of normal renal function.
REFERENCES


