A clinicopathologic evaluation of renal artery stenosis with abdominal aortic aneurysm

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Aims: Renal artery stenosis (RAS) and aortic aneurysm are becoming more common growing because of the increased mean age of the population and the greater prevalence of hypertensive and diabetic patients. Here we report on the clinical course of abdominal aortic aneurysm (AAA) associated with RAS, and analyze the laboratory data and pathological findings.

Patients and Methods: Thirty-eight operated patients and two treated conservatively were divided into two groups, i.e., 10 patients with RAS and 30 without RAS. Then we observed the prognosis of five young patients with renal artery fibromuscular dysplasia without AAA to clarify that of systemic atherosclerotic patients.

Results: Renal function had already declined before admission and rapidly decreased further after surgery in 7 of the 10 patients with RAS and their prognosis was very poor, particularly in the case of 3 patients with cholesterol crystal embolism. Two RAS patients suffered rupture of aneurysm while waiting for surgery on hemodialysis. Advanced ischemic changes were observed in the kidneys of RAS patients. Two patients with unilateral renal artery stenosis showed severe histologic changes of both kidneys.

Conclusion: The pathogenesis and symptoms of RAS with AAA are complex, and it is important to select adequate treatment for each patient, considering the systemic status carefully.

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Introduction
The incidence and prevalence of end-stage renal disease, especially in the elderly population, have continued to increase. It is reported that 10% to 20% of elderly patients with end-stage renal disease have potentially treatable renovascular disease, renal artery stenosis (RAS), and renovascular hypertension. The presence of RAS accelerated cardiovascular disease independent of atherosclerosis and causes poor prognosis⁷. Moreover chronic

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inflammation may be an important player to the pathogenesis of RAS\textsuperscript{2,3}. So workers in this field have begun to pursue the diagnosis of renovascular disease more aggressively in elderly patients with progressive renal failure. Over several years, the techniques for surgery and percutaneous revascularization of the renal vessels have undergone various modifications, but whether revascularization can slow the rate of progression of renal failure remains uncertain\textsuperscript{4}, although several researchers have suggested an improvement. Here we report the clinical course of patients who had abdominal aortic aneurysm with or without RAS, and analyze their laboratory data and pathological findings to clarify the clinical features of RAS.

Patients and methods

1) Patients (Table 1)

Forty patients with AAA were divided into two groups; group A was 10 patients with RAS (7 men and 3 women with an average age of 63.4 $\pm$ 9.4 years) and group B was 30 patients without RAS (25 men and 5 women with an average age of 70.0 $\pm$ 9.5 years). Two patients of group A were put on hemodialysis while waiting for surgical treatment, considering their poor general condition. Moreover we observed the prognosis of five young patients with renal artery fibromuscular dysplasia without AAA (group C: 3 males and 2 females with an average age of 28.6 $\pm$ 10.7 years) to clarify that of systemic atherosclerotic patients. All patients gave signed informed consent before inclusion, and the study was approved by the Japan Self Defense Forces Central Hospital ethics committee taking into account the principles of the Declaration of Helsinki.

2) Methods

We examined the differences of clinical, laboratory and pathological findings in the three groups. Data were assessed by 1-way ANOVA for comparisons within groups followed by post hoc Dunnett’s test. Three cases in group A, four cases in group B, and two cases in group C underwent histological examination (groups A and B at autopsy and group C by biopsy).

Results

1) Clinical course

There was no significant difference of age between the groups A and B. Uncontrolled hypertension was recognized in groups A and C, with a hypertensive crisis being observed in one patient from group B and two from group C. Diabetes was not so common (Table 1).

2) Complications and prognosis

The prognosis was very poor in group A. Including three patients with cholesterol crystal embolism (CCE), six patients were

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<td>Δ UI/ Cr-year</td>
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Abbreviations: ARF: acute renal failure, CCE: cholesterol crystal embolism, MOF: multiple organ failure syndrome, GFR: glomerular filtration rate, UI: creatinine, PRA: plasma renin activity

* $p<0.03$

\textsuperscript{Fig.1} Angiographic study and pathological findings of the kidney at necropsy in a 72-year-old Japanese woman

The right main renal artery shows severe stenosis (>60%) in the angiogram. Her kidneys tissues showed severe tubulointerstitial changes and ischemic glomerular damage not only on the right side but also on the left. The pathological changes of left side kidney are displayed here (X200; PAM). Bar scale is 100 nm.
placed on hemodialysis in the postoperative period and five died of multiple organ failure syndrome. Two patients in group A suffered rupture of aneurysm while waiting for surgery on hemodialysis. One patient suffered from CCE in group B, but she recovered from renal failure, requiring hemodialysis. Multiple organ failure was recognized in about 20% of group B patients. In group C, two patients were treated with conservative therapy, one with percutaneous transluminal renal angioplasty (PTRA), and two with graft replacement. While re-stenosis occurred once after PTRA, all five patients are now doing well (Table 1).

3)Laboratory findings
The glomerular filtration rate was significantly lower on admission and deteriorated quickly in group A compared with group B after follow-up for 2.03 years on average. Plasma renin activity was very high in groups A and C, but showed no statistical difference from that in group B (Table 1).

4)Angiographic and pathological studies
Advanced ischemic changes were observed in the kidneys of groups A and C. Angiography of two patients in group A revealed unilateral stenosis, but their kidneys showed severe ischemic changes on both sides, including collapse and hyalinization of the glomeruli, interstitial cell infiltration, and tubular damage (Fig.1 and Table 2). Pathological features of CCE were observed around the small sized arteries in 2 autopsy cases. In group B, the kidneys only showed mild glomerular mesangial proliferation, interstitial cell infiltration, and ischemic changes.

Discussion
End-stage renal disease has shown an increase recently and RAS has been observed at a relatively high frequency along with manifestations of atherosclerosis such as coronary artery disease, especially in elderly patients. Establishing a diagnosis of RAS in patients with chronic renal failure presents a challenge and none of the available methods has 100% specificity. Surgery is still the treatment choice in patients with ischemic nephropathy of atherosclerotic origin. Almost all patients in this study had an abdominal aortic aneurysm that was treated with surgery. The patients with RAS already showed chronic renal failure when they were admitted to our hospital; complications of surgery were common and the prognosis was very poor. Dajani et al. reported that a high complication rate of revascularization for RAS, including a decline of renal function, eosinophilia, significant atheroembolic complications, and renal artery dissection.
Several authors have stated that coronary artery disease and peripheral vascular disease are predictors of RAS, and it may always be associated with systemic vascular changes in atherosclerotic patients. Whether surgical or catheter intervention is associated with a better outcome than conservative treatment remains unclear for RAS patients.

We also examined the renal pathology in several patients. In RAS patients, the kidneys revealed severe ischemic changes such as collapse of the glomeruli and tubulo-interstitial damage. The renal function of a control patient with fibromuscular dysplasia became stable for over ten years without any intervention, although her renal pathological changes were also very severe. It is clear that progression of renal artery stenosis is the main pathogenesis of ischemic nephropathy, so the vascular changes of fibromuscular dysplasia may advance slowly. All patients in this study received angiography and computed tomography. In two patients, their selective renal angiography showed unilateral renal artery stenosis, but revealed severe histological changes of both kidneys. As a result of the experiments by Goldblatt et al., arterial hypertension due to unilateral renal artery stenosis is known to be a cause of bilateral kidney damage. Farmer et al. found that some kidneys with normal renal arteries in patients who had atherosclerotic unilateral renal artery stenosis showed a significant reduction of function. They suggested that there was a process causing renal dysfunction in patients with atherosclerotic disease that existed independently of renal artery narrowing. Textor proposed a sequence of events for chronic
ischemic renal injury wherein repetitive episodes of renal hypoperfusion might produce irreversible parenchymal damage beyond a stenotic main renal artery lesion\textsuperscript{[12]}. Meyrier et al suggested that an increase of intrarenal angiotensin II levels played a crucial role in sustaining the development of parenchymal damage\textsuperscript{[15]}. Some reports described that chemokines and cytokines are very important to the pathogenesis of ischemic kidney damages and that the possibility of remedy, targeting these factors\textsuperscript{[14,15]}. Even reperfusion of RAS causes transient elevation of several inflammatory mediators\textsuperscript{[16,17]}. We speculate that similar process caused ischemic nephropathy in our two patients with unilateral stenosis. We also suggest that ischemic glomerulopathy progresses quickly, even on the non-ischemic side, in the early stage of the disease, because we observed many severe hyalinized glomeruli in the kidneys of these patients, via humoral mediators such as renin-angiotensin system and inflammatory factors.

Cholesterol crystal embolism (CCE) is a systemic disease that features cholesterol embolization to multiple organs, including the kidneys. Cholesterol crystals from vascular plaques cause embolization of blood vessels around 100-200 \( \mu \)m in diameter after catheter procedures or surgical treatment. It is considered that the immune system is also involved in the pathogenesis of CCE, because laboratory tests often show eosinophilia, hypocomplementemia, and high level of immunoglobulin E. All four cases with CCE in this study developed acute renal failure and required therapy with corticosteroids, plasma exchange, and hemodialysis. CCE may be important to provide chronic and systemic inflammation in RAS patients.

In summary, the present study suggests that although RAS is often observed in patients with aortic aneurysm and renal insufficiency, the decision to intervene is complex and difficult. Complications of surgical treatment are severe, and it is unclear whether conservative treatments are effective or not, including hemodialysis.

References


