Clinical Case Report

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Severe acute interstitial nephritis induced by valsartan

A case report

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Abstract

Rationale: Angiotensin receptor blocker (ARB) can increase serum creatinine or potassium levels in patients with renal insufficiency, renal artery stenosis, heart failure or hypovolemia, but hardly cause severe kidney injury in patients without any risk factors. A case of severe acute interstitial nephritis (AIN) induced by valsartan was reported here.

Patient concerns: A 62-year-old female with nausea for 1 month and acute deterioration of kidney function for 2 weeks was admitted. She had a history of hypertension for 5 months and had taken valsartan 40 mg daily for 4 months. Although the valsartan had been stopped for 2 weeks, the serum creatinine continuously increased after admission. Kidney biopsy demonstrated the eosinophils infiltration in interstitium.

Diagnoses: AIN induced by valsartan.

Interventions: The patient was treated with glucocorticoid.

Outcomes: The serum creatinine decreased gradually and got back to normal level 5 months later. Then therapy of glucocorticoid was stopped. Renal artery stenosis was excluded by computed tomography angiography (CTA).

Lessons: Although valsartan-induced allergy has been reported previously, AIN was firstly recognized as a severe complication of this drug. We suggest when there is a ARB-associated continuous deterioration of kidney function for patients without renal insufficiency, renal artery stenosis, heart failure or hypovolemia, AIN should be thought of and therapy with glucocorticoid should be considered if necessary.

Abbreviations: AIN = acute interstitial nephritis, ARB = angiotensin receptor blocker, CTA = computed tomography angiography.

Keywords: acute interstitial nephritis, case report, kidney biopsy, valsartan

1. Introduction

Angiotensin receptor blocker (ARB) is one of renin angiotensin system (RAS) blockers and is commonly used as an antihypertensive drug. It can also reduce urinary protein and protect heart function. The ARB has some potential side effects of increasing serum creatinine and potassium due to its effect of reducing renal hemoperfusion.[1,2] According to the previous studies, these side effects mainly occur in patients with pre-existing kidney disfunction, renal artery stenosis, heart failure or hypovolemia. Therefore, ARB are generally safe for patients who do not have these risk factors.[3,4] However, like angiotensin-converting enzyme inhibitors (ACEI) which is an another RAS blocker,[5] ARB also cause allergic reactions in some patients.[6] Although ACEI such as captopril has been demonstrated to induce acute interstitial nephritis (AIN),[7] ARB-induced AIN has not been reported before. We reported a case of severe acute kidney injury after valsartan treatment. All risk factors were excluded by careful examination. Percutaneous kidney biopsy confirmed the renal failure was caused by AIN. Renal function returned to normal after treatment with corticosteroid. This case reminds us that we should closely monitor the renal function for all patients receiving ARB therapy.

1.1. Ethics approval and consent to participate

The Ethics Committee of Tianjin Medical University General Hospital gave approval for the publication of this case report (IRB2018-002-01), and patient has provided informed consent for publication of the case.

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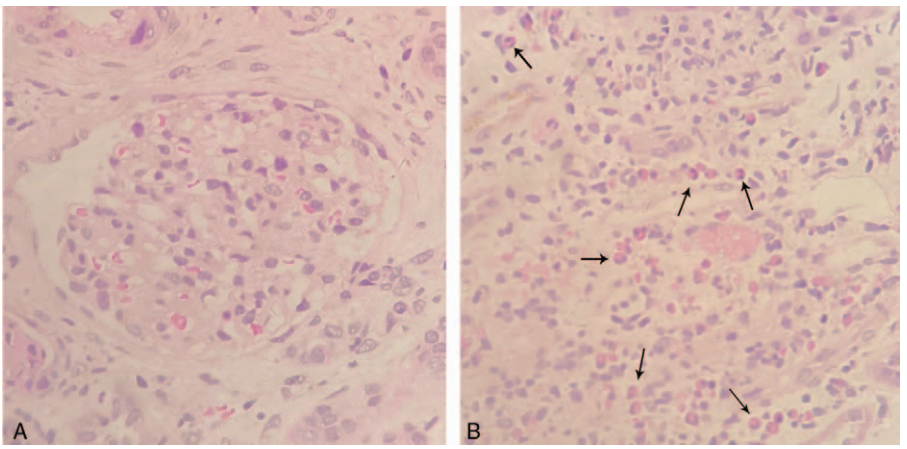

Figure 1. Manifestations of kidney biopsy. (A) No obvious injury of glomerulus was found. (B)There were lymphocytes and eosinophils infiltration (arrows). There were also slight tubular atrophy and fibrosis in interstitium (H&E stain ×400).

1.2. Case report

A 62-year-old female with nausea for 1 month and increased serum creatinine for 2 weeks was admitted. She did not have a history of chronic kidney disease and the serum creatinine was 1.01 mg/dL when she did routine physical examination 13 months ago. She had a history of hypertension for 5 months and had taken valsartan dispersible tablets (Lunan pharmaceutical group, Shandong, China) 40 mg daily for 4 months. Two weeks before admission, she stopped the valsartan since serum creatinine showed as high as 4.29 mg/dL. Pertinent physical examination findings were normal except a hypertension of 160/100 mm Hg. Abdominal ultrasonography showed no obvious abnormality of 2 kidneys. Echocardiogram showed slight left ventricular hypertrophy with a normal ejection fraction 61%. Blood routine showed a mild anemia with hemoglobin 101 g/L, Total white blood cells counts and eosinophils counts were normal. Serum creatinine increased to 5.60 mg/dL. Urinalysis revealed glucosuria 2+ (Fasting blood glucose was 5.8 mmol/L), leukocyturia 1+ and proteinuria 1+. The 24 h urine protein excretion revealed 0.2596 grams (normal range was below 0.15 grams). Urine N-acetyl-beta-D-glucosamidase was increased (21.2 U/g creatinine, normal range was 1.1–12.0 U/g creatinine). Immunologic examinations were normal except a slight rise of C-reactive protein (0.89 mg/dL, normal range was below 0.8 mg/dL).

Serum creatinine was reviewed 2 days later and the result showed as high as 5.75 mg/dL. Then kidney biopsy was performed immediately. Light microscopy showed no obvious abnormality of glomeruli (Fig. 1**A**), while there were obvious inflammatory changes in the interstitium with increased eosinophils infiltration. There were also mild interstitial fibrosis and tubular injury (Fig. 1**B**). Immunofluorescence showed no immune complex deposition. The AIN was diagnosed and the patient was given intravenous methylprednisolone 40 mg daily. One week later the serum creatinine decreased to be 5.67 mg/dL, then the patient was discharged with oral methylprednisolone 20 mg daily. Levamlodipine besylate 5 mg daily was given in order to control hypertension.

During follow-up for 5 months, the serum creatinine decreased gradually and the glucocorticoid was tapered (Fig. 2). Her serum creatinine had recovered to normal before the follow-up on August 4th 2018. To exclude renal artery stenosis, computed tomography angiography (CTA) was done. The results showed no abnormality for bilateral renal arteries (Fig. 3).

2. Discussion

Until now, the pathogenic mechanism of anaphylaxis caused by ARB has remained unclear. Losartan, which is the 1st marketed ARB, has been reported to cause lymphoid hyperplasia,[8] vasculitis,[9] and angioneurotic edema[10] in literature. Valsartan-associated allergy is similar to losartan including drug eruption,[11–14] angioedema[15–20] and mucocutaneous bullous pemphigoid[21] (Table 1). Drug eruption of valsartan is relatively common in clinic and usually start after weeks to 1 month of therapy. To our knowledge, this is the 1st case of AIN caused by valsartan (The Naranjo score is 5). The AIN mainly injure the tubules and interstitium and causes acute to subacute deterioration of kidney function. The pathophysiology of AIN is induced by a hypersensitive allergic reaction to an offending agent with the activation of eosinophils causing inflammatory infiltrates in the interstitium of kidney. Most AIN is due to non-steroidal anti-inflammatory drugs and antibiotics. A kidney biopsy is required to confirm the diagnosis of AIN. Supportive findings including eosinophils in urine or blood in laboratory testing can help to diagnose. None of the preceding clinical findings is sensitive or specific to AIN. In the present study, when the patient was admitted, the possibility of AIN was considered because the serum creatinine increased rapidly and valsartan was the only drug used before admission. However, the diagnose of AIN could not be confirmed for our patient until the kidney biopsy demonstrated the infiltration of eosinophils in the interstitium.

Since ARB could cause severe increase of serum creatinine in patients with pre-existing kidney disfunction, renal artery stenosis, heart failure or hypovolemia, all these risk factors were carefully checked for our patient. After reviewing the history and doing echocardiogram examination, the pre-existing kidney disfunction, heart failure and hypovolemia were easily excluded. However, the exclusion of the renal artery stenosis was difficult because the patient had a new-onset hypertension and the high level of serum creatinine did not allow doing imaging examination which needed contrast. Fortunately, the patient got complete recovery of kidney function 5 months later and a CTA excluded the renal artery stenosis at last.

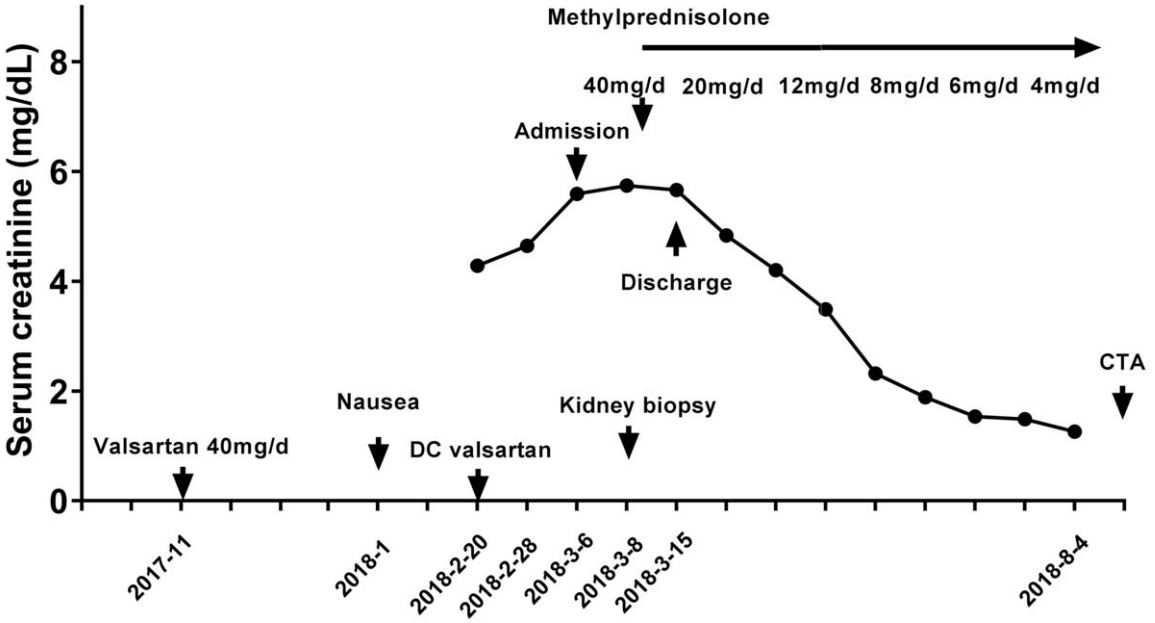

Figure 2. The clinical course of the patient. Since the kidney function recovered, CTA was done to excluded renal artery stenosis. The glucocorticoid was stopped before the examination of CTA. CTA = computed tomography angiography.

The AIN is a dose-independent allergic reaction. The time from exposure to appearance of symptoms is widely variable and can be from a few days to years.[22,23] In the current study, the patient only took valsartan 40 mg daily. We thought the low dose of drug postponed the occurrence of AIN. The patient felt nausea after 2 months of valsartan therapy, but she did not test kidney function at that time. Generally speaking, mild increase of serum creatinine does not cause nausea. So we speculated the

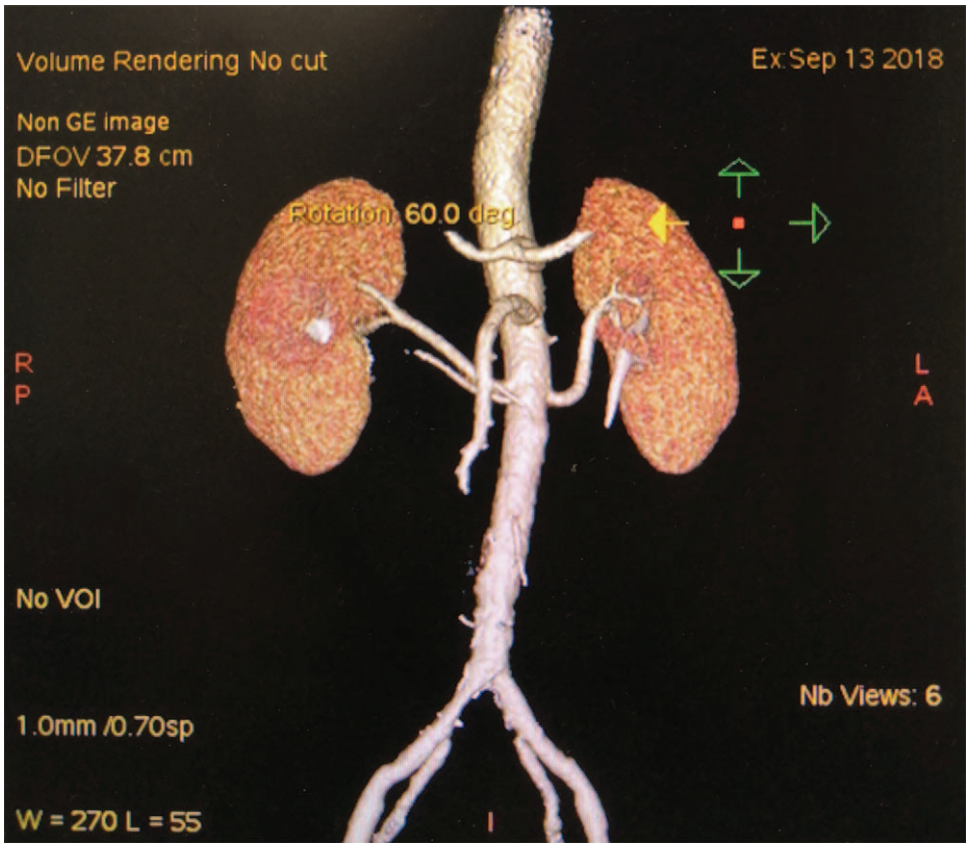

Figure 3. The CTA examination for renal artery. Iohexol was used as contrast. No stenosis was found for bilateral renal arteries. CTA = computed tomography angiography.

Table 1

Anaphylaxis induced by valsartan in reported cases.

Side effects	Year	Area	Reference
Lymphomatoid drug eruption	2003	USA	Mustasim DF[11]
Linear lichenoid drug eruption	2009	Turkey	Gencoglan G[12]
Drug eruption followed by CD30+ pseudolymphomatous eruption	2010	Japan	Sawada Y[13]
Exanthematous drug eruption	2012	Turkey	Ozturk G[14]
Angioedema and photosensitive rash	1998	USA	Frye CB[15]
Angioedema and urticarial reaction	2000	Spain	de la Serna Higuera C[16]
Angioedema	2003	Spain	Martínez Alonso JC[17]
Angioedema	2003	USA	Irons BK[18]
Angioedema in the oral floor and epiglottis	2011	Japan	Shino M[19]
Angioedema	2012	USA	Kalra A[20]
Mucocutaneous bullous pemphigoid	2003	Italy	Femiano F[21]

CD30 = cluster of differentiation 30.

appearance of AIN should be earlier than the appearance of nausea.

Controversy exists about whether corticosteroid therapy is necessary in the treatment of drug-induced AIN. Some studies have reported corticosteroid induced a more rapid and complete recovery of kidney function, while the others have failed to confirm the results.[24–27] In a recent research, Quinto LR et al made a systemic review of 8 retrospective studies comparing the effects of corticosteroid therapy versus non-corticosteroid therapy in the treatment of drug induced AIN.[28] Four studies showed no difference in serum creatinine between corticosteroid and non-corticosteroid therapy, while 4 studies found a benefit of corticosteroid therapy. Regretfully, a meta-analysis was not performed due to considerable heterogeneity. The authors proposed larger well-designed trials are needed to draw a conclusion. In the present study, the deterioration of kidney function did not cease although valsartan had been discontinued for 2 weeks. In order to accelerate the recovery of kidney function, glucocorticoid was administrated after kidney biopsy. Although the serum creatinine decreased slowly, the patient got complete kidney recovery after treatment for 5 months.

3. Conclusion

This is the 1st case of valsartan-induced AIN. We suggest when there is a ARB-associated continuous deterioration of kidney function for patients without renal insufficiency, renal artery stenosis, heart failure or hypovolemia, AIN should be considered and kidney biopsy should be done when necessary. Besides, close monitoring of the renal function for all patients receiving ARB therapy is recommended.

Author contributions

Conceptualization: Peng-cheng Xu.
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