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Case Report

CASE REPORT

Progressive renal insufficiency related to ALK inhibitor, alectinib

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Abstract

Alectinib is a second generation anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor and is generally effective and tolerated in patients who have demonstrated disease progression or adverse effects while on the first generation inhibitor, crizotinib. ALK inhibitors can cause a reversible chronic increase of serum creatinine concentration; however, they rarely induce progressive renal insufficiency. We herein report a case of a 68-year-old woman diagnosed with ALK-positive advanced non-small cell lung cancer and who received ALK inhibitors. Due to dysgeusia and transaminitis, her medication was switched from crizotinib to alectinib. Rapid progressive glomerulonephritis developed 1 year after the initiation of alectinib treatment. A renal biopsy revealed unique kidney lesions in both tubules and glomeruli. Glucocorticoid therapy partially reversed kidney impairment. However, re-administration of alectinib caused kidney dysfunction, which was improved by the cessation of alectinib. Our case suggests that much attention should be paid to kidney function when using ALK inhibitors.

INTRODUCTION

Alectinib is a tyrosine kinase inhibitor of anaplastic lymphoma kinase (ALK), applicable in patients with advanced non-small cell lung cancer with ALK rearrangements [1]. Common adverse effects reported in alectinib trials include constipation, dysgeusia, vomiting, neutropenia and transaminitis [2]. ALK inhibitors can cause a chronic increase of serum creatinine concentration, which usually occurs within 2 weeks of drug initiation and then levels out [3, 4]. However, ALK inhibitors rarely induce progressive renal insufficiency. We herein describe a case of rapid progressive glomerulonephritis occurring in a patient who had taken alectinib for 1 year. A renal biopsy revealed unique kidney damage in both tubules and glomeruli related to alectinib.

CASE REPORT

A 68-year-old woman was diagnosed with ALK-positive advanced non-small cell lung cancer in the left lower lobe and left iliac bone metastasis (cT2N0M1b, Stage IV). Disease progression was observed after four cycles of pemetrexed and carboplatin combination chemotherapy. Five hundred milligram

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per day of crizotinib was administered for 2 months and worked well to reduce tumor size. The patient's serum creatinine concentration increased from 0.68 to 0.75 mg/dl (estimated glomerular filtration rate (eGFR) 65.7 to 59.0 mL/min/1.73 m^2) over 2 months. However, due to dysgeusia and transaminitis, crizotinib was substituted for 600 mg/day of alectinib. Prior to alectinib treatment, the patient's creatinine was 0.72 mg/dl (eGFR 61.4 ml/min/1.73 m^2). Alectinib was effective and well tolerated in the patient. After 1 year of treatment with alectinib, the patient reported bubbling urine and low extremity edema. Urinalysis revealed proteinuria of 3.42 g/g creatinine and gross hematuria. Urine *N*-acetyl-beta-D-glucosaminidase (NAG) and β_2-microglobulin (β_2-MG) were also elevated to 61.9 U/l (reference range <11.2 U/l) and 13 841 μg/l (<360 μg/l), respectively. Serum creatinine concentration increased from 0.90 to 3.66 mg/dl (eGFR 47.9 to 10.3 ml/min/1.73 m^2) during the prior 3 months. All of the drugs including alectinib, pregabalin and codein phosphate were terminated and a renal biopsy was performed. A light microscopy examination revealed interstitial nephritis with tubular vacuolization and tubulitis. Fibrocellular crescent formations were also seen in several glomeruli (Fig. 1A and B). An immunofluorescent study was negative. An electron microscopic study showed diffuse foot process effacement (Fig. 1C). Gallium-67 scintigraphy showed an increased uptake in kidneys, indicating the existence of diffuse interstitial nephritis (Fig. 1D) [5]. These findings suggest that alectinib caused a unique combination of tubulointerstitial nephritis and diffuse podocyte damages. The clinical course is shown in Fig. 2. We started 500 mg of methylprednizolone for three consecutive days, followed by 40 mg/day of oral predonizolone. Glucocorticoid administration was effective in suppressing proteinuria and hematuria. However, 5 days after the initiation of glucocorticoid treatment, the patient began suffering from pancreatitis. We discontinued glucocorticoid use temporarily and treated her with gabexate mesilate. After the pancreatitis was relieved, we started 20 mg/day of oral predonisolone and camostat mesilate concurrently. One month later, the patient's serum creatinine concentration decreased to 2.63 mg/dl (eGFR 14.8 ml/min/1.73 m^2). Proteinuria and hematuria disappeared and the values of urine NAG and β_2-MG normalized. Thus, 600 mg/day of alectinib was restarted and the glucocorticoid dose was tapered. Serum creatinine concentration gradually increased and reached a peak level of 3.91 mg/dl (eGFR 9.6 ml/min/1.73 m^2) without developing proteinuria, hematuria, urine NAG and β_2-MG elevation for 6 months after alectinib re-administration. Due to patient preference, alectinib was discontinued again, resulting in the sudden decrease of serum creatinine concentration to 2.33 mg/dl (eGFR 16.9 ml/min/1.73 m^2) without changing the dose of predonizolone. The serum creatinine concentration was maintained at approximately 2.3 mg/dl by use of 5 mg/day of predonizolone.

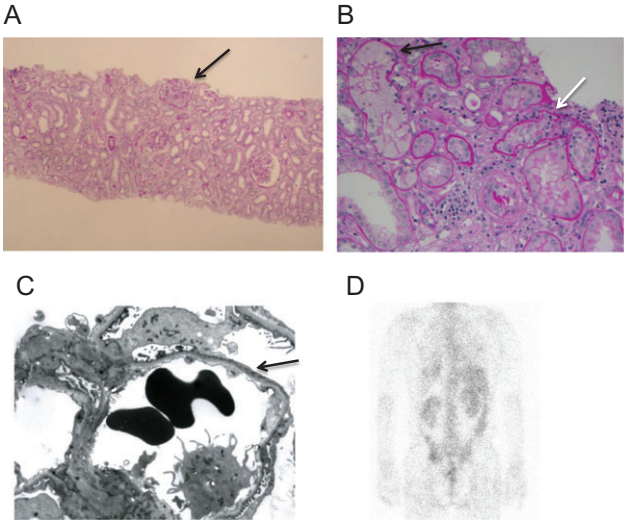

Figure 1: Representative pictures obtained from the renal biopsy and gallium-67 scintigraphy. (**A**) Overview of renal biopsy. Diffuse interstitial nephritis was seen. Black arrow shows crescent formation in glomeruli. Periodic acid–Schiff (PAS) stain at 40× magnification. (**B**) Tubular vacuolization (brack arrow) and tubulitis (white arrow) were prominent. PAS stain at 200× magnification. (**C**) Electron microscopy revealed diffuse effacement (black arrow) at 2000× magnification. (**D**) Increased uptake of gallium-67 was seen in kidneys

DISCUSSION

ALK inhibitors can cause a reversible increase of serum creatinine concentration. In fact, crizotinib rapidly produces a mean 23.9 % drop in eGFR. Upon cessation of crizotinib treatment, eGFR recovered to 84 % or more of baseline values [3, 4]. Despite this, ALK inhibitors rarely cause progressive renal insufficiency. To our knowledge, this is the first case report of alectinib-related rapid progressive glomerulonephritis.

We think that kidney impairment in this case was due to administration of alectinib. Alectinib administration has been related to progressive renal insufficiency twice in this patient. We cannot exclude some possibility of nephrotoxicity induced by pregabalin and/or codein phosphate as contributory to the first event. However, nephrotoxicities due to these agents rarely occur [6, 7]. Moreover, the second episode of kidney impairment was dramatically improved by the cessation of alectinib alone. Next, the findings from a renal biopsy enhanced the probability of alectinib-induced progressive renal insufficiency. Generally speaking, kidney disease primarily causes either glomerular or tubulointerstitial damage. However, in this case, the combination of diffuse interstitial nephritis and glomerular podocyte damage was observed. The immunofluorescent study was negative, suggesting the kidney impairment was not related to immune complex kidney disease. Of note, the serological kidney injury-related markers such as angiotensinogen converting enzyme, antidouble-stranded DNA, Sm, SS-A, SS-B, MPO-ANCA, PR3-ANCA and glomerular basement membrane antibodies were negative (data not shown). Therefore, we diagnosed this case as alectinib-induced progressive renal insufficiency.

Our case was unique because the manifestations of the first and second kidney impairment were somewhat different. Initially, proteinuria, hematuria and elevations of representative tubular injury markers in urine such as NAG and β_2-MG were prominent. Cessation of alectinib was able to decrease NAG and β_2-MG in the urine, but not enough to reverse kidney dysfunction. In contrast, serum creatinine concentration increased without having abnormal proteinuria, hematuria, NAG or β_2-MG excretion during the second event. At that time, cessation of alectinib provided a dramatic improvement of kidney function. The difference may be due to glucocorticoid treatment, which could inhibit the development of urine abnormalities.

Of note, clinical and pathological manifestations were uncommon compared with other drug-induced renal insufficiency, especially at the first event. Drug-induced renal insufficiency is most commonly caused by acute interstitial nephritis [8]. Drug-induced interstitial nephritis rarely shows heavy proteinuria and hematuria. However, drugs can also damage glomerular cells directly and drug-induced glomerular disease manifests

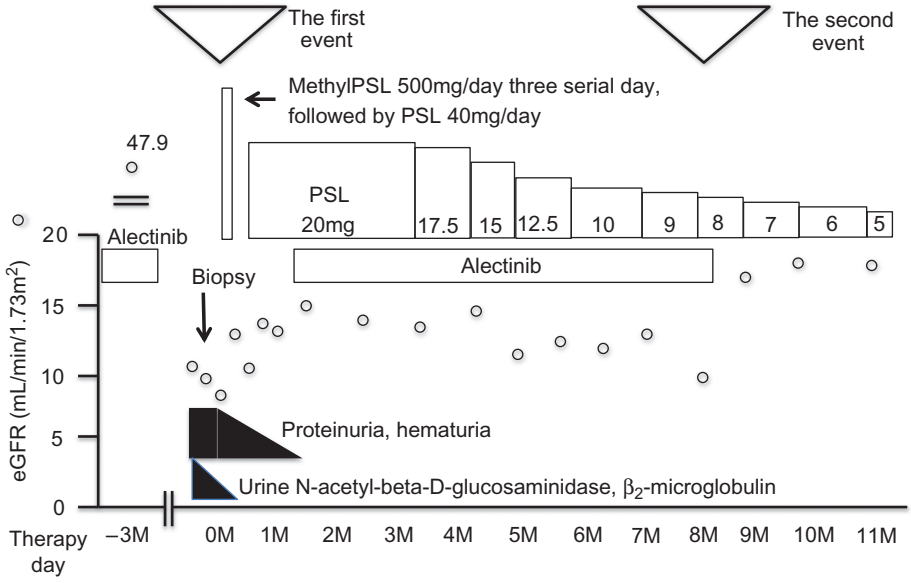

Figure 2: Clinical course of this case. MethylPSL, methylpredonizolone; PSL, predonizolone; eGFR, estimated glomerular filtration rate; M, month

with proteinuria and hematuria [9]. For example, non-steroidal anti-inflammatory drugs are associated with minimal change disease (podocyte injury) in addition to ischemic acute tubular injury. However, in our case, alectinib affected podocytes and tubules, resulting in foot process effacement, crescent formation and tubulointerstitial nephritis accompanied with massive proteinuria, gross hematuria and renal insufficiency. It is rare to have such a variety of pathological changes and clinical features simultaneously in drug-induced nephropathies [8]. Conversely, the mechanism of creatinine increase at the second event is unknown due to a lack of pathological examination. However, this can be partly explained by an interference with the tubular secretion of creatinine, because another ALK inhibitor, crizotinib is thought to be a competitive inhibitor at the creatinine transporter [3, 4]. As described in 'CASE REPORT', serum creatinine slightly increased with 2 months of crizotinib treatment, though a limited number of blood tests were performed (once a month) for this period. One year of alectinib therapy before the first event also increased serum creatinine chronically.

Alectinib demonstrated promising efficacy and was well tolerated in patients with ALK-positive disease who have disease progression or adverse effects on crizotinib [1, 10]. Crizotinib rarely causes progressive renal insufficiency, except in one case with acute tubular necrosis [11]. In this case, a small amount of proteinuria and macroscopic hematuria were detected. Pathological examination revealed acute tubular necrosis with focal mesangiolysis. Clinical manifestations and kidney pathological changes in our case were different from the crizotinib-induced progressive renal insufficiency. These findings suggest that we should recognize crizotinib and alectinib as different drugs with regard to effects and toxicity.

In conclusion, we experienced an unusual progressive renal insufficiency case related to alectinib. We must monitor kidney function when we use alectinib, even if crizotinib did not cause kidney injury in the same patient.

CONFLICT OF INTEREST STATEMENT

None declared.

FUNDING

None.

ETHICAL APPROVAL

Our institution does not require ethical approval for case reports.

CONSENT

A written consent was obtained from the patient.

GUARANTOR

K.N. is the guarantor of this article.

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