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【 CASE REPORT 】

Regression of Crizotinib-Associated Complex Cystic Lesions after Switching to Alectinib

Kageaki Taima, Hisashi Tanaka, Yoshihito Tanaka, Masamichi Itoga, Shingo Takanashi and Sadatomo Tasaka

Abstract:
Crizotinib, which is effective in patients with anaplastic lymphoma kinase (ALK) positive non-small cell lung cancer, is sometimes associated with the generation of complex renal cysts. A 56-year-old man with ALK positive adenocarcinoma received crizotinib. Ten months after the introduction of crizotinib, a cystic lesion developed from his right kidney to the iliopsoas muscle, accompanied by fever, anemia, and hypoproteinemia. After 17 months of treatment, crizotinib was switched to alectinib, followed by the recovery of hypoproteinemia and systemic inflammation. Switching to alectinib may be beneficial in patients demonstrating crizotinib-associated complex renal cysts with systemic inflammation and exhaustion.

Key words: crizotinib, alectinib, complex renal cysts, iliopsoas muscle, regression

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Introduction

Crizotinib is an inhibitor of several receptor tyrosine kinases, including anaplastic lymphoma kinase (ALK), hepatocyte growth factor receptor (c-Met), and the c-ros oncogene 1 (1). It has been approved for the treatment of advanced non-small cell lung cancer (NSCLC) with ALK gene rearrangement in many countries (1). The development of renal cysts (most of them complex) has been reported to be observed in 4% of the patients treated with crizotinib (2). Although the spontaneous regression of such renal cysts during continuous crizotinib treatment has been reported (3), the natural history and optimal management of crizotinib-associated cystic lesions remains to be determined. We herein describe the development of complex renal cysts with invasion into adjacent iliopsoas muscle and regression after switching to alectinib in a male patient with ALK-positive advanced NSCLC.

Case Report

A 56-year-old man who had a significant smoking history was initially diagnosed with locally advanced NSCLC and underwent right upper lobectomy in May 2013. Although he received adjuvant chemotherapy with cisplatin and vinorelbine, a recurrence of NSCLC was recognized in May 2014. The patient had normal urinalysis finding, but demonstrated mild anemia, hypoproteinemia and an elevated level of C-reactive protein (Table). Because his tumor was found to harbor an ALK gene rearrangement by fluorescence *in situ* hybridization and immunohistochemistry, he was treated with crizotinib and thus achieved a partial response. Serial body CT revealed the development of a complex cystic lesion extending from his right kidney to the iliopsoas muscle approximately 10 months after the initiation of crizotinib (Fig. 1). Although a tiny cyst had been previously observed in the right kidney, the complex cystic lesion emerged separately. Because of an increased uptake of fluorodeoxyglucose on a positron emission tomography scan (Fig. 2), the patient underwent an ultrasound-guided needle biopsy of the cystic lesion twice to rule out metastasis. Since the biopsy specimens revealed granulomatous inflammation with no evidence of malignancy, we therefore considered the complex cysts to be associated with crizotinib. As the cystic lesion gradually increased in size, the patient became febrile, lost weight, and developed anemia and hypoproteinemia (Fig. 3). His ECOG performance status, which had been 0

Department of Respiratory Medicine, Hirosaki University Graduate School of Medicine, Japan
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Correspondence to Dr. Sadatomo Tasaka, tasaka@hirosaki-u.ac.jp

Table. **Laboratory Test.**

	May 2014	Sep. 2015	Nov. 2015
Blood counts			
WBC (/mm^3)	3,960	3,550	4,890
Neutro. (%)	55.5	59.8	75.7
Lymph. (%)	29.3	22.5	17.2
Mono. (%)	13.4	13.8	5.3
Eosino. (%)	1.0	2.5	0.6
RBC (×10^6/mm^3)	4.26	356	374
Hb (g/dL)	11.8	8.9	10.0
Ht (%)	35.5	27.4	31.4
MCH (pg)	27.7	25.0	26.7
MCV (fL)	83	77	84
Plt (×10^3/mm^3)	426	485	309
Biochemistry			
TP (g/dL)	5.7	5.0	6.0
Alb. (g/dL)	2.9	1.9	3.1
BUN (mg/dL)	14	14	17
Cre (mg/dL)	1.05	0.98	0.91
Na (mEq/L)	139	139	142
K (mEq/L)	5.0	4.6	4.4
Cl (mEq/L)	102	103	102
AST (IU/L)	37	36	32
ALT (IU/L)	32	34	25
T-Bil (mg/dL)	0.4	0.3	0.8
Immunology			
CRP (mg/dL)	7.478	8.064	0.534
Tumor markers			
CEA (ng/mL)	6.4	8.3	5.9
Sialyl Lewis X (U/mL)	36.4		35.2
Urinalysis			
S.G.	1.018	1.023	1.009
Blood	-	-	-
Ketones	-	-	-
Glucose	-	-	-
Protein	-	-	-

at the introduction of crizotinib, increased to a score of 1. Because the ALK-targeted therapy was still considered to be effective, crizotinib was switched to alectinib in October 2015. After switching to alectinib, the complex cystic lesion rapidly regressed and the partial response was maintained for 6 months. The patient's blood counts showed a recovery of anemia (Table). The decreased serum protein and elevated C-reactive protein levels also returned to the normal ranges within two months (Table).

Discussion

In the present case, a regression of a crizotinib-associated complex cystic lesion was observed after switching to alectinib. The symptoms of coexisting systemic inflammation and emaciation also improved after switching the medication. To the best of our knowledge, this is the first report of the regression of a crizotinib-associated complex cystic lesion after switching to alectinib.

Crizotinib was the first clinically available tyrosine kinase inhibitor for the treatment of ALK-positive NSCLC, but it was initially designed as a MET inhibitor (1). In contrast, second-generation ALK inhibitors (i.e., alectinib and ceritinib) are selective inhibitors that are effective against second-site mutations of the ALK domain (4). In fact, there has been no report of the development of complex renal cysts during treatment with alectinib. c-MET activation is linked to cyst formation, suggesting that the inhibition of c-MET can be used for polycystic kidney disease treatment (3). The specific suppression of c-MET in the kidney has also been reported to be associated with an increase in apoptosis, inflammation and macrophage infiltration, leading to acute renal insufficiency (5). Considering these mechanisms, a MET inhibitor should therefore inhibit, rather than induce, cyst formation. However, the mechanisms by which crizotinib may increase the risk of developing renal cysts remain to be elucidated.

Schnell and colleagues reviewed a safety database of

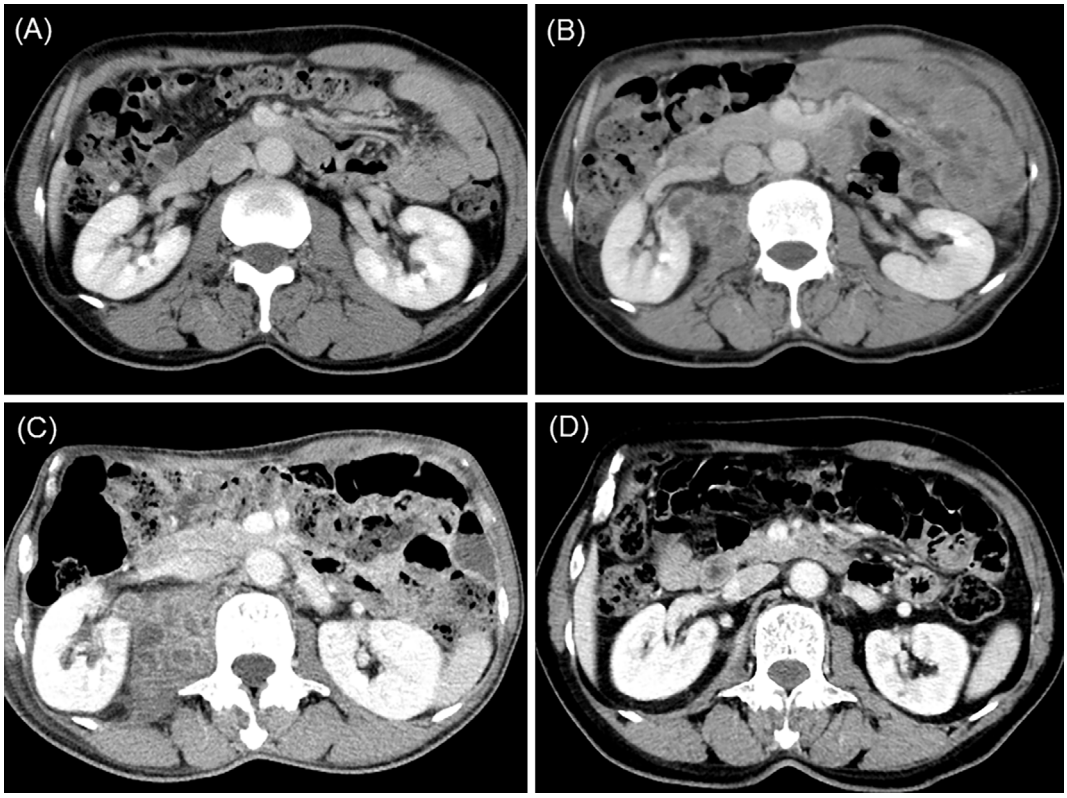

Figure 1. **Serial body CT revealed (A) no abnormal lesions before introduction of crizotinib, but (B) development of complex cystic lesion extending from the right kidney to the iliopsoas muscle was observed 10 months later. (C) Further growth of a complex cystic lesion was observed 17 months after the introduction of crizotinib. (D) The complex cystic lesion had regressed 2 months after switching to alectinib.**

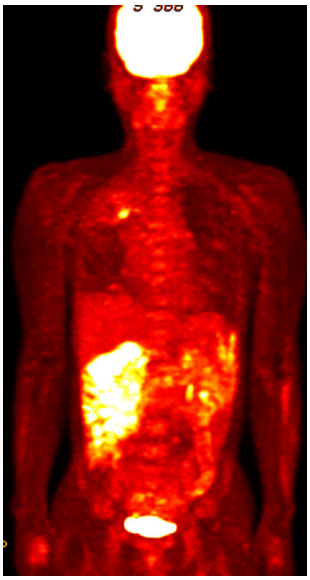

Figure 2. **Positron emission tomography taken 15 months after the introduction of crizotinib showed intense accumulation of fluorodeoxyglucose (FDG) around the complex cystic lesion (maximum standardized uptake value: 8.4).**

1,375 patients from four clinical trials of crizotinib and identified 17 patients (1.2%) with renal cysts which were reported as adverse events (6). Among them, evidence of invasion into adjacent structures was noted in seven patients, with no evidence of malignancy found (6). They also described that Asians appeared to have an increased risk of developing new cysts during such treatment (6). The median time to cyst diagnosis was 6.6 months (ranging from 1.2 to 15.2 months) after the initiation of crizotinib treatment, which is compatible with our case (6). Although two patients had chills and/or fever, it was not clear whether these symptoms were related to the existence of renal cysts. Whereas most patients were asymptomatic, inflammatory parameters, such as white blood cell counts and C-reactive protein levels, were elevated in some cases. In the present case, we observed a recovery of hypoproteinemia and systemic inflammation after switching to alectinib, indicating a causal relationship. Because the patient had no proteinuria or an elevated C-reactive protein level, the hypoproteinemia in this case could be associated with chronic inflammation. The present case suggests that switching to alectinib may be beneficial in patients demonstrating crizotinib-associated complex renal cysts with sustained systemic inflammation and exhaustion.

Written, informed consent was obtained from the patient for publication of this case report and any accompanying images.

The authors state that they have no Conflict of Interest (COI).

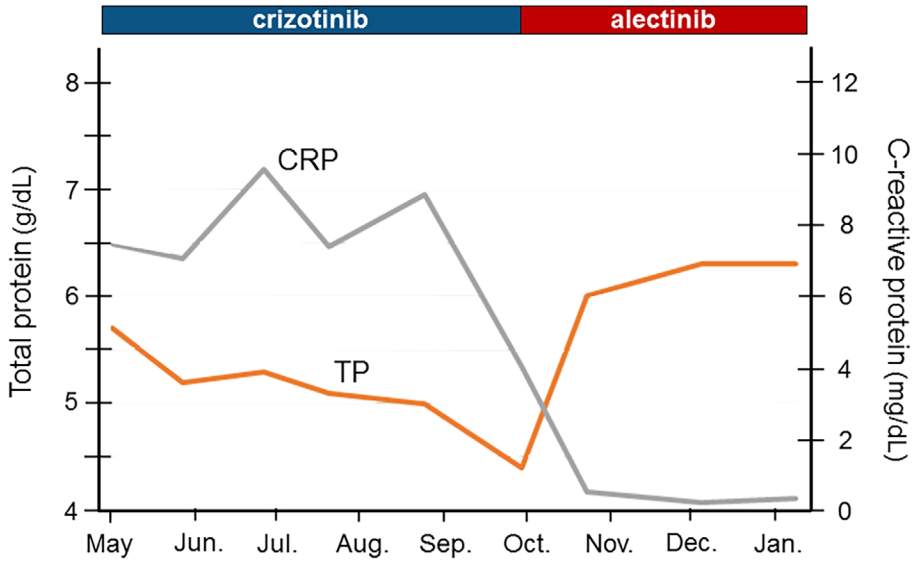

Figure 3. **The serum levels of total and C-reactive proteins. Decreased serum protein and elevated C-reactive protein levels returned to the normal ranges within two months after switching to alectinib. TP: total protein, CRP: C-reactive protein**

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