Case Reports in Oncology

Case Rep Oncol 2021;14:107–111
DOI: 10.1159/000512829
Received: October 18, 2020
Accepted: October 27, 2020
Published online: February 26, 2021



**Case Report**

# Liver and Pancreatic Injury in Response to ALK Inhibitors in a Patient with Primary Signet Ring Cell Carcinoma of the Lung: A Case Report

Ibrahim Yildiz

Department of Medical Oncology, Acibadem Mehmet Ali Aydinlar University Atakent Hospital, Istanbul, Turkey

**Keywords**
Anaplastic lymphoma kinase rearrangement · Lorlatinib · Pancreatitis · Adverse effects · Hypertriglyceridemia

**Abstract**
We report a patient with stage IV anaplastic lymphoma kinase (ALK)-rearranged non-small cell lung cancer (primary lung signet ring cell adenocarcinoma) who received serial crizotinib, chemotherapy, and lorlatinib over more than 4 years. The patient discontinued crizotinib after approximately 4 months due to crizotinib-associated hepatotoxicity. Twenty-five days later, when transaminases had normalized, crizotinib was resumed. However, the patient's liver enzymes rapidly increased again, and crizotinib was discontinued. After 6 cycles of platinum-based chemotherapy, lorlatinib was initiated. Hepatotoxicity did not recur with lorlatinib, a next-generation ALK inhibitor, but grade 4 hypertriglyceridemia and acute pancreatitis were induced by lorlatinib after 4 months. To our knowledge, this is the first case report of acute pancreatitis with lorlatinib. Additionally, stereotactic body radiation therapy (SBRT) was performed for residual small primary lesions in the lung without stopping lorlatinib. Given the rarity of radiation pneumonitis, especially with the relatively small fields treated by SBRT, we suspect that lorlatinib enhanced the pulmonary toxicity. Physicians should be aware that ALK inhibitors, such as lorlatinib and crizotinib, have potentially lethal side effects.



Ibrahim Yildiz
Department of Medical Oncology
School of Medicine, Acibadem Mehmet Ali Aydinlar University
Istanbul 21234 (Turkey)
dr_ibrahim2000@yahoo.com

Case Rep Oncol 2021;14:107–111
DOI: 10.1159/000512829




## Introduction

The majority of cases of signet ring cell adenocarcinoma (SRCA) of the lung originate from the gastrointestinal tract. Primary SRCA of the lung is an extremely rare subtype of lung adenocarcinoma with a poor prognosis [1]. The presence of a signet ring cell (SRC) component is considered to be a prominent clinicopathological characteristic of EML4-anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) [2].

ALK rearrangement is a therapeutically targetable oncogenic driver found in 3–7% of patients with NSCLC [3]. Crizotinib is the first tyrosine kinase inhibitor (TKI) targeting ALK, MET, and ROS1 and has shown marked antitumor activity compared to traditional chemotherapy in ALK-positive NSCLC patients. More recently, second-generation ALK TKIs (including ceritinib, alectinib, and brigatinib) and third-generation ALK TKIs (lorlatinib) have increased therapeutic options.

Given the rapid pace of drug discovery and development in this area, reporting the adverse effects of ALK inhibitors is crucial. Here, we report a case of a 36-year-old man diagnosed with metastatic ALK-rearranged NSCLC who received lorlatinib after crizotinib and platinum-doublet chemotherapy. The patient developed toxic hepatitis after 3 months of crizotinib and acute pancreatitis due to hypertriglyceridemia after 4 months of lorlatinib. To our knowledge, this is the first case report of lorlatinib-induced pancreatitis.

## Case Report

A 36-year-old man who was a nonsmoker was admitted to our hospital with a cough and back pain for 1 month. He had no comorbid diseases. Fluorodeoxyglucose (FDG)-positron emission tomography (PET) computed tomography (CT) scan was performed for staging in October 2016 and revealed a mass of approximately 4 cm in the right upper lobe of the lung, accompanied by multiple mediastinal, hilar, bilateral supraclavicular, left retroclavicular lymph node metastases and bone metastasis. Tru-Cut biopsy from the mass in the upper lobe of the right lung revealed SRC carcinoma. An inversion of the EML4-ALK gene was detected by immunohistochemistry and fluorescence in situ hybridization. Crizotinib, which is a first-generation ALK inhibitor, was initiated twice daily (250 mg) as the first-line treatment in November 2016. The size and metabolic activity of the primary lesion and lymph nodes remarkably decreased based on follow-up PET after 3 months. However, 4 months after treatment initiation, laboratory data revealed major hepatic cytolysis (ALT 1,719 IU/L [12–63] and AST 371 IU/L [10–37]). Other biochemical tests, including ALP and bilirubin, were within normal limits. Crizotinib was discontinued, and ursodeoxycholic acid, N-acetylcysteine, and vitamin E capsules were started by a gastroenterologist. Liver tests progressively improved, and there was no other cause of acute hepatitis identified in the patient (liver metastases, viral hepatitis, and concomitant medications). Liver biopsy findings were compatible with toxic hepatitis. This clinical manifestation was diagnosed as crizotinib-induced liver injury. Twenty-five days later, crizotinib was reintroduced at the same dose together with methylprednisolone (1 mg/kg), but after 1 week of treatment, liver enzymes rapidly increased again to more than 5 times the upper limit of normal. Crizotinib was therefore stopped, and liver tests returned to normal in 7 days.

Gemcitabine-cisplatin was initiated in April 2017. The patient achieved a stable response after 6 cycles of chemotherapy. No hepatotoxicity was observed. Then, since it was available with an early access programme, lorlatinib, which is a third-generation ALK inhibitor, was started in December 2017. The hemogram, routine biochemistry tests, and lipid profile (triglyceride 160 mg/dL, total cholesterol 262 mg/dL) were within normal limits at that time.

Case Rep Oncol 2021;14:107–111
DOI: 10.1159/000512829



After 3 months, the patient presented with fever, abdominal pain, and hyperglycemia to the emergency department. He was diagnosed with acute pancreatitis due to hyperlipidemia. Triglycerides were 4,107 mg/dL (250–150), total cholesterol was 512 mg/dL (82–200), amylase was 479 IU/L (25–115), lipase was 3,272 IU/L (73–393), AST was 69 IU/L (10–37), and other liver enzymes were normal. After being admitted to the intensive care unit, his treatment continued for 7 days in the gastroenterology department, and then he was discharged. Atorvastatin (10 mg), fenofibrate (250 mg), and metformin (2 g) daily were started. During lorlatinib treatment, mild side effects, such as weight gain, peripheral oedema, and carpal tunnel syndrome, were also observed.

After the symptoms and blood test abnormalities completely resolved, lorlatinib was re-initiated in March 2018. PET-CT was performed in May 2018 and showed a partial response of the primary lesion and complete response of the metastatic lesions. Additionally, stereotactic body radiation therapy (SBRT) was performed for primary residual lesions in the lung in May 2018.

In August 2018, he developed a mild nonproductive cough. The lesion in the right lung had worsened based on CT. There were no abnormalities in blood tests. Radiation pneumonia was considered because the lesion areas did not contain air bronchograms and did not have very active metabolism on PET-CT. We suspected that lorlatinib enhanced pulmonary toxicity when it was administered with SBRT. However, during this process, lorlatinib was never interrupted because the patient had no symptoms.

After 3 months, chest CT revealed a significant decrease in the size of the right upper lung mass with no evidence of disease progression. There were improvements in the previously noted interstitial and posttreatment changes throughout the lung fields.

Subsequently, there was no progression on chest CT, and PET-CT was performed every 3–4 months. Lorlatinib is still ongoing, with a near complete response for 2 years with no recurrence of pancreatitis or hepatitis with antihyperlipidemic therapy.

## Discussion

We reported this case because of its interesting and extremely rare features. This case involved primary SRCA, which is a rare histologic subtype, crizotinib-associated hepatotoxicity, hepatotoxicity relapse upon the reinduction of crizotinib despite supportive treatment, but not with lorlatinib (another TKI), and lorlatinib-related pancreatitis, which are very interesting. Additionally, we suspect that lorlatinib enhanced pulmonary toxicity when it was administered with SBRT.

Patients with primary lung SRCA have failed to respond to traditional chemotherapy. The significance of SRCA was not truly appreciated until the publication of recent study results, which linked SRC to EML4-ALK NSCLC [4]. In 1 case report, a patient with primary lung SRCA developed resistance to crizotinib treatment in a short time [5]. It remains unclear whether such resistance is specific to primary SRCA of the lung, which is a rare subtype, or whether crizotinib is responsible for generating extensive drug resistance [5]. However, our patient is still receiving lorlatinib and has maintained a near complete response for 2 years. Thus, we think newer TKIs may be superior in cases of primary lung SRCA.

Crizotinib is known to usually cause mild elevations in liver function tests, although the exact mechanism is still not well understood. The drug is metabolized in the liver by CYP3A4, and liver injury may be due to the accumulation of toxic metabolites or immune-related mechanisms. The symptoms of drug-induced hepatitis are generally nonspecific; thus, diagnosis is often delayed [6].

Case Rep Oncol 2021;14:107–111
DOI: 10.1159/000512829



Our patient presented with cytolytic hepatitis 117 days after the treatment initiation of crizotinib. Other potential causes of liver failure, such as viral hepatitis, hepatic metastasis, alcoholic liver disease, or other drug-induced liver injuries, were excluded. Relapse rapidly occurred after the re-initiation of crizotinib despite oral methylprednisolone treatment. However, hepatotoxicity of any grade did not develop with lorlatinib, which is another ALK TKI. Structural differences of the molecules may explain why there does not seem to be any cross-toxicity.

Lorlatinib is a potent, brain-penetrating, third-generation, macrocyclic ALK/ROS1 TKI with broad-spectrum potency against most known resistance mutations that develop during treatment with existing first- and second-generation ALK TKIs. Lorlatinib has a unique safety profile, which is distinct from other ALK TKIs, and is generally well tolerated with a low incidence of permanent discontinuations due to adverse reactions (2.0%). Hyperlipidemia is the most common adverse drug reaction associated with lorlatinib and is largely manageable with lipid-lowering therapy. Grade 3/4 hypercholesterolemia and hypertriglyceridemia both occurred at a frequency of 15% [7]. Our patient has also received atorvastatin and fenofibrate as lipid-lowering therapy.

SBRT delivers a very high dose of ionizing radiation to a relatively small region encompassing the tumor and spares a significant portion of the remaining lung from high radiation doses. However, predisposing factors, such as contralateral pneumonectomy, immunosuppression, the administration of concurrent chemotherapy, and interstitial lung disease, may cause an increased risk for radiation pneumonitis, and the higher doses delivered by this technique may lead to an increase in radiation pneumonitis [8]. ALK inhibitors may increase sensitivity to radiation and the risk of radiation necrosis [9]. Additionally, interstitial lung disease has also been reported in response to ALK inhibitors [10]. Although SBRT was performed in a small area in our patient, radiation pneumonitis developed. There were no risk factors for radiation pneumonitis. Thus, we think that lorlatinib may enhance pulmonary toxicity when administered with SBRT.

In conclusion, lorlatinib may be a viable alternative when crizotinib causes hepatitis, and it has an antitumor effect in ALK-positive primary SRCA of the lung. Despite having a favorable toxicity profile, lorlatinib can cause lethal side effects, such as acute pancreatitis. The proactive counseling of patients on how to manage adverse events, as well as preemptive monitoring and treatment, is an integral component of patient care when initiating lorlatinib or any new treatment regimen.

## Acknowledgement

I would like to thank Dr. Nigar Rustamova and Şeyma Bahşi for their help.

## Statement of Ethics

Written informed consent was obtained from the patient for the publication of this case report.

## Conflict of Interest Statement

The author has no conflicts of interest to declare.

## Funding Sources

No funding was received for this study.

## References

1 Iwasaki T, Ohta M, Lefor AT, Kawahara K. Signet-ring cell carcinoma component in primary lung adenocarcinoma: potential prognostic factor. Histopathology. 2008;52(5):639–40.
2 Shaw AT, Yeap BY, Mino-Kenudson M, Digumarthy SR, Costa DB, Heist RS, et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. J Clin Oncol. 2009;27(26):4247–53.
3 Soda M, Choi YL, Enomoto M, Takada S, Yamashita Y, Ishikawa S, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature. 2007;448(7153):561–6.
4 Ou SH, Ziogas A, Zell JA. Primary signet-ring carcinoma (SRC) of the lung: a population-based epidemiologic study of 262 cases with comparison to adenocarcinoma of the lung. J Thorac Oncol. 2010;5(4):420–7.
5 Hao YQ, Tang HP, Liu HY. Primary signet-ring cell carcinoma of the lung treated with crizotinib: A case report. Oncol Lett. 2015;9(5):2205–7.
6 van Geel RM, Hendrikx JJ, Vahl JE, van Leerdam ME, van den Broek D, Huitema AD, et al. Crizotinib-induced fatal fulminant liver failure. Lung Cancer. 2016;93:17–9.
7 Bauer TM, Felip E, Solomon BJ, Thurm H, Peltz G, Chioda MD, et al. Clinical management of adverse events associated with lorlatinib. Oncologist. 2019;24(8):1103–10.
8 Georgiou A, Farmer A. Severe and fatal multilobar nonclassic radiation pneumonitis following stereotactic body radiation therapy (SBRT) for treatment of inoperable non-small-cell lung cancer: A report of two cases and possible enhancement by concurrent amiodarone. Case Rep Pulmonol. 2019;2019:8754951.
9 Sun Y, Nowak KA, Zaorsky NG, Winchester CL, Dalal K, Giacalone NJ, et al. ALK inhibitor PF02341066 (crizotinib) increases sensitivity to radiation in non-small cell lung cancer expressing EML4-ALK. Mol Cancer Ther. 2013;12(5):696–704.
10 Hwang HJ, Kim MY, Choi CM, Lee JC. Anaplastic lymphoma kinase inhibitor related pneumonitis in patients with non-small cell lung cancer: Clinical and radiologic characteristics and risk factors. Medicine (Baltimore). 2019;98(48):e18131.