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Case Report

Lorlatinib-Induced Acute Pancreatitis Secondary to Severe Hypertriglyceridemia and Hyperglycemia: A Case Report

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Abstract

Background: *Lorlatinib, a third-generation ALK tyrosine kinase inhibitor, is widely used in ALK-positive non–small cell lung cancer (NSCLC). While dyslipidemia and hyperglycemia are recognized adverse effects, acute pancreatitis secondary to these metabolic disturbances is rarely reported.*

Case Presentation: *We describe the case of a 39-year-old male with stage IIIB ALK-positive lung adenocarcinoma who was initiated on lorlatinib therapy. Two months into treatment, he presented with acute abdominal pain and recurrent bilious vomiting. Laboratory investigations revealed severe hypertriglyceridemia (>9000 mg/dL), hyperglycemia (RBS 411 mg/dL), metabolic acidosis, and markedly elevated pancreatic enzymes. Imaging confirmed acute interstitial edematous pancreatitis with a CT severity index of 6. The patient was admitted to intensive care and managed with insulin infusion, fibrate therapy, heparin, bowel rest, and broad-spectrum antibiotics. Gradual improvement was observed, with triglycerides reduced to ~1100 mg/dL and resolution of abdominal pain and ileus. Lorlatinib was withheld at discharge for reassessment.*

Discussion: *This case highlights the rare but significant risk of lorlatinib-induced acute pancreatitis secondary to severe hypertriglyceridemia and hyperglycemia. Although dyslipidemia is a well-recognized toxicity, progression to life-threatening pancreatitis remains uncommon. Routine monitoring of lipid and glucose profiles during therapy, particularly in the initial months, is critical to early detection and prevention.*

Conclusion: *Prompt recognition of lorlatinib-induced metabolic derangements and a multidisciplinary management approach can lead to full recovery. Clinicians should maintain a high index of suspicion and ensure close metabolic monitoring in patients receiving lorlatinib.*

Keywords: *Lorlatinib, ALK-positive lung cancer, pancreatitis, hypertriglyceridemia, hyperglycemia, targeted therapy, toxicity Introduction*

Background

Lung cancer remains the leading cause of cancer-related mortality worldwide, accounting for nearly 1.8 million deaths annually[1]. Non–small cell lung cancer (NSCLC) constitutes about 80–85% of all lung cancers, and among these, anaplastic lymphoma kinase (ALK) rearrangements are present in approximately 3–7% of cases, typically in younger, non-smoker patients with adenocarcinoma histology[2]. The introduction of ALK tyrosine kinase inhibitors (TKIs) has dramatically improved outcomes compared to conventional chemotherapy, offering higher response rates and prolonged survival[3].

Lorlatinib, a potent third-generation ALK TKI, was specifically designed to overcome resistance to earlier TKIs (crizotinib, ceritinib, alectinib) and to penetrate the central nervous system effectively[4]. It has demonstrated durable responses in both treatment-naïve and previously treated patients. However, lorlatinib therapy is frequently complicated by metabolic toxicities, particularly hypercholesterolemia, hypertriglyceridemia, and hyperglycemia. In pivotal trials, dyslipidemia was reported in up to 80% of patients, with grade ≥3 hypertriglyceridemia observed in nearly 20%[5].

While dyslipidemia is a recognized adverse effect, acute pancreatitis secondary to severe hypertriglyceridemia during lorlatinib therapy is rarely documented in the literature[6]. Hypertriglyceridemia-induced pancreatitis typically develops when triglyceride levels exceed 1000 mg/dL, with the risk increasing substantially above 2000 mg/dL[7]. Moreover, the synergistic metabolic disturbances of lorlatinib-induced dyslipidemia and hyperglycemia may predispose susceptible patients to this life-threatening complication[8].

Here, we report the case of a 39-year-old male with ALK-positive lung adenocarcinoma who developed acute pancreatitis due to lorlatinib-induced severe hypertriglyceridemia and hyperglycemia. This case emphasizes the need for routine metabolic monitoring, early recognition, and multidisciplinary management to prevent and treat such serious toxicities.

Case Presentation

A 39-year-old man, a non-smoker with no significant past medical or family history of metabolic disease, was diagnosed in July 2024 with ALK-positive lung adenocarcinoma after presenting with progressive breathlessness and a massive right-sided pleural effusion. Pleuroscopy and biopsy confirmed poorly differentiated adenocarcinoma that was TTF-1 positive, and next-generation sequencing demonstrated an EML4-ALK fusion. Baseline PET-CT revealed a right lung mass with mediastinal, hilar, and supraclavicular nodal involvement, without evidence of distant metastasis, consistent with stage IIIB disease. He initially received two cycles of pemetrexed plus carboplatin chemotherapy and was subsequently started on lorlatinib 100 mg once daily as targeted therapy.

The patient tolerated treatment for the first two months without major issues. However, in early August 2025 he presented to the emergency department with sudden onset severe epigastric pain, radiating to the back, associated with multiple episodes of bilious vomiting and inability to tolerate oral intake. He denied fever, alcohol intake, or prior history of pancreatitis. On admission, he was tachycardic, mildly hypotensive, and in obvious distress from abdominal pain. Laboratory evaluation revealed severe hypertriglyceridemia (9112 mg/dL), marked hyperglycemia (random blood sugar 411 mg/dL), metabolic acidosis, and elevated pancreatic enzymes (amylase 774 U/L and lipase 1710 U/L). Urine ketones were positive. Serum creatinine was elevated at 3.2 mg/dL, reflecting acute kidney injury.

Imaging with abdominal ultrasound and contrast-enhanced CT confirmed acute interstitial edematous pancreatitis with a CT severity index score of 6, along with mild ascites, splenomegaly, bilateral pleural effusions, and a small pericardial effusion. A small ground-glass opacity in the left upper lobe was also noted, thought to be infective in nature. Given the temporal relationship with therapy and the absence of other identifiable risk factors, a diagnosis of lorlatinib-induced acute pancreatitis secondary to severe hypertriglyceridemia and hyperglycemia was established.

The patient was managed in the medical intensive care unit with intravenous fluids, electrolyte replacement, and insulin infusion to address both hyperglycemia and triglyceride reduction. Fenofibrate and heparin infusion were initiated for lipid lowering, while bowel rest and nasogastric aspiration were provided for gastrointestinal decompression. He was also started on broad-spectrum antibiotics and subcutaneous basal insulin for glycemic stabilization. A multidisciplinary team comprising gastroenterology, endocrinology, and nephrology specialists was involved in his care. Over the next several days, his abdominal pain resolved, ileus improved, and his triglyceride levels decreased significantly to ~1100 mg/dL. His renal function stabilized and he was gradually advanced to soft oral feeds. Lorlatinib was withheld during admission.

At discharge one week later, he was hemodynamically stable, conscious, oriented, tolerating oral diet, and maintaining oxygen saturation on room air. He was continued on fibrate and statin therapy along with subcutaneous insulin, and was scheduled for follow-up in oncology, endocrinology, and gastroenterology clinics. Plans for reevaluating the possibility of lorlatinib rechallenge versus alternative therapy were deferred until full metabolic recovery. Discussion

The advent of targeted therapy has transformed the treatment landscape of ALK-positive NSCLC, offering substantial survival benefits compared with conventional chemotherapy regimens[1–3]. Among the newer agents, lorlatinib has emerged as a powerful third-generation ALK tyrosine kinase inhibitor (TKI), designed to overcome resistance mutations and achieve better central nervous system penetration[4]. Despite its efficacy, lorlatinib has a distinct toxicity profile characterized predominantly by metabolic derangements. Clinical trials and post-marketing studies have consistently reported high rates of hypercholesterolemia and

hypertriglyceridemia, with grade 3–4 dyslipidemia observed in up to 20% of patients[5].

Although dyslipidemia is a recognized and expected side effect of lorlatinib, progression to acute pancreatitis remains rare and only sparsely documented[6]. Hypertriglyceridemia-induced pancreatitis accounts for 1–4% of all acute pancreatitis cases in the general population, typically occurring when triglyceride levels exceed 1000 mg/dL, with markedly increased risk above 2000 mg/dL[7]. In our patient, serum triglycerides were found to be >9000 mg/dL, reflecting an unusually severe manifestation. In addition, lorlatinib has been linked to hyperglycemia and insulin resistance, both of which may exacerbate lipid abnormalities and further predispose to pancreatitis[8]. The simultaneous occurrence of extreme hypertriglyceridemia, hyperglycemia, and metabolic acidosis in our case highlights the potential for lorlatinib to trigger life-threatening metabolic crises.

The exact mechanism underlying lorlatinib-induced dyslipidemia is not fully understood, but proposed pathways include off-target effects on lipid metabolism, alterations in hepatic cholesterol synthesis, and disruption of glucose-lipid regulatory networks[5]. The synergistic metabolic burden may overwhelm pancreatic physiology, precipitating acute inflammation and injury. Notably, our patient had no prior history of diabetes, alcohol use, or pancreatitis, strengthening the causal association with lorlatinib.

Management strategies in hypertriglyceridemia-induced pancreatitis focus on rapid reduction of triglyceride levels and stabilization of systemic complications. In our patient, a combination of insulin infusion, fibrates, heparin, and supportive measures led to a dramatic improvement, with triglyceride levels falling from >9000 mg/dL to ~1100 mg/dL within days. Importantly, withholding lorlatinib during the acute episode was essential, as continued exposure may have worsened metabolic toxicity. Similar reports describe recovery following drug cessation and intensive lipid-lowering therapy[6].

This case has several important clinical implications. First, it reinforces the need for baseline and serial monitoring of lipid and glucose profiles in all patients receiving lorlatinib, particularly during the initial months of therapy when toxicities are most likely to emerge. Second, patients with pre-existing metabolic risk factors may warrant closer surveillance or prophylactic lipid-lowering therapy. Third, a multidisciplinary approach involving oncologists, endocrinologists, and gastroenterologists is crucial for prompt recognition and effective management of these rare but severe toxicities.

Conclusion

In conclusion, our case adds to the limited body of evidence linking lorlatinib with severe hypertriglyceridemia complicated by acute pancreatitis. With the increasing use of lorlatinib in routine practice, clinicians must maintain a high index of suspicion for metabolic complications, ensure early detection through vigilant monitoring, and act promptly to prevent life-threatening outcomes. Conclusion

This case highlights a rare but clinically significant adverse effect of lorlatinib therapy—the development of

acute pancreatitis secondary to severe hypertriglyceridemia and hyperglycemia. While dyslipidemia is a well-documented toxicity of lorlatinib, its progression to life-threatening metabolic crises such as pancreatitis is unusual and underreported. In our patient, the absence of conventional risk factors for pancreatitis, combined with the extreme derangements in lipid and glucose metabolism shortly after initiating lorlatinib, strongly supports a causal association.

The favorable outcome observed underscores the importance of early recognition, prompt metabolic control, and multidisciplinary collaboration in managing such toxicities. Intensive measures including insulin infusion, fibrates, heparin therapy, electrolyte correction, and supportive care not only led to stabilization but also allowed recovery without long-term sequelae. Temporarily withholding lorlatinib was essential to prevent further exacerbation of metabolic stress.

This case emphasizes several important clinical lessons. First, routine and vigilant monitoring of serum lipids and glucose is critical in all patients receiving lorlatinib, especially in the first few months of therapy. Second, a proactive approach to managing even moderate metabolic abnormalities may prevent progression to severe complications. Finally, oncologists should be aware of these rare but serious toxicities, and patients should be counseled about early warning symptoms such as abdominal pain, nausea, or vomiting.

As the use of lorlatinib continues to expand in both frontline and relapsed ALK-positive NSCLC, awareness of its unique toxicity profile will be vital. With careful monitoring and timely intervention, the benefits of this highly effective therapy can be maximized while minimizing the risk of serious harm.

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