

Lorlatinib and the Enigma of Autoantibody-Negative Diabetes

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Lorlatinib, an ALK inhibitor, can lead to a rare form of diabetes that lacks typical autoantibodies. This presents a diagnostic puzzle for clinicians, who must consider drug-induced etiologies even when initial immunological markers are negative.

KEY TAKEAWAYS

- lightbulb
- The Pivot: Lorlatinib can induce diabetes even in the absence of autoantibodies, challenging traditional diagnostic paradigms.
- The Data: A case report illustrates a patient developing DKA with undetectable GAD65, IA-2, and ZnT8 antibodies after lorlatinib initiation.
- The Action: Increase vigilance for hyperglycemia in patients on lorlatinib, regardless of pre-existing diabetes risk factors or autoantibody status.

Lorlatinib, a third-generation ALK inhibitor, treats ALK-positive NSCLC. It has shown remarkable efficacy in overcoming resistance to earlier-generation ALK inhibitors, but comes with adverse effects. Hyperglycemia is among these. The mechanism remains unclear. Is it a direct effect on pancreatic beta cells, increased insulin resistance, or a combination? The prevailing hypothesis leans toward increased insulin resistance, potentially mediated through lipid metabolism. But this case challenges the notion that all lorlatinib-induced diabetes is simply insulin resistance. The picture is more complex.

Existing guidelines, like NCCN for NSCLC, acknowledge hyperglycemia as a potential ALK inhibitor side effect. They recommend monitoring blood glucose levels. But they do not specifically address autoantibody-negative diabetes. Nor do they guide differentiating it from other drug-induced hyperglycemia. This case highlights a gap. That's a problem for clinicians.

Diabetes is a global burden, affecting millions worldwide. Both type 1 and type 2 diabetes represent significant public health challenges. Drug-induced diabetes is less common than these primary forms. Still, it is an important consideration in patients on certain medications, especially those with known metabolic side effects. Understanding the specific mechanisms by which drugs like lorlatinib can induce hyperglycemia is crucial for patient management. It helps refine diagnostic and treatment algorithms.

A patient with ALK-positive NSCLC on lorlatinib presented with classic hyperglycemia symptoms: polydipsia, polyuria, and fatigue. Initial labs confirmed significantly elevated glucose levels and ketones, indicating DKA. The twist: no detectable GAD65, IA-2, and ZnT8 autoantibodies. These are typical markers for type 1 diabetes. The patient had no prior diabetes history. No family history of autoimmune disease either. What's going on?

Patient demographics, including age and sex, matched typical ALK inhibitor recipients for NSCLC. Symptoms started acutely, several months into lorlatinib treatment. This is a common timeframe for drug-related adverse events. The diagnostic workup included a comprehensive metabolic panel, HbA1c, C-peptide levels, and a full autoantibody panel. This ruled out autoimmune etiologies. C-peptide, reflecting endogenous insulin, was notably low. This supported insulin deficiency, not pure insulin resistance. That's a key finding.

No autoantibodies narrows the differential diagnosis. It doesn't eliminate diabetes. Other possibilities include type 2 diabetes exacerbated by lorlatinib, pancreatic damage causing insulin deficiency, or a unique drug-induced form without an autoimmune response. That's a wide net. The authors excluded typical type 1 diabetes. They also considered atypical forms of autoimmune diabetes, such as LADA. But acute DKA made that less likely. Drug-induced diabetes, therefore, was the most probable explanation. Lorlatinib's impact on insulin sensitivity and glucose metabolism clearly played a central role. This was the key.

The mechanism for lorlatinib-induced autoantibody-negative diabetes remains unclear. Hypotheses include direct beta-cell toxicity, interference with insulin signaling independent of resistance, or an idiosyncratic reaction leading to pancreatic dysfunction. That's a range of possibilities. ALK inhibitors can affect lipid metabolism, causing hyperlipidemia and potentially contributing to insulin resistance. Still, the profound insulin deficiency here suggests a more direct impact on pancreatic function. That's a critical difference.

The patient initially received intravenous insulin to resolve DKA. Once stable, they moved to subcutaneous insulin injections. The critical question emerged: What about the lorlatinib? The drug was continued, given its importance in controlling the patient's NSCLC. But the insulin dose required careful adjustment for glycemic control. This highlights a difficult balancing act for clinicians. Do we prioritize cancer control, or minimize metabolic complications?

Glycemic control improved with insulin. The patient was discharged on basal-bolus insulin. Regular follow-up monitored NSCLC progression and diabetes management. This case underscores a multidisciplinary approach: oncologists, endocrinologists, and dietitians are essential. This optimizes outcomes in complex scenarios.

This is a single case report. That's the obvious caveat. Broad conclusions or changes to clinical practice are not possible from one patient. There's no control group. There's also no way to assess the true incidence of autoantibody-negative diabetes in patients on lorlatinib. The underlying mechanism remains speculative. Is lorlatinib directly toxic to beta cells in certain individuals? Does it trigger a non-autoimmune inflammatory response in the pancreas? These questions demand more investigation. Routine autoantibody screening in all patients on lorlatinib is questionable given this rare

presentation. That's a cost concern.

Future research needs larger prospective studies. These would determine the incidence and prevalence of various hyperglycemia forms in patients on lorlatinib. Investigating genetic predispositions or specific patient characteristics that might increase this diabetes risk would also be valuable. Advanced imaging or pancreatic biopsies, if ethically justifiable, could provide insights into lorlatinib's direct effects on pancreatic tissue. Without such data, the precise mechanism and optimal management strategies for this rare but significant adverse event remain largely unknown. It's a significant unknown.

CLINICAL IMPLICATIONS

Clinicians managing patients on lorlatinib must rethink diabetes diagnosis. Typical autoantibody panels may be negative. That doesn't rule out drug-induced diabetes. Consider the drug first.

Standard glucose monitoring is not enough. Clinicians need a high index of suspicion for atypical diabetes. A low C-peptide level, even without autoantibodies, signals insulin deficiency. This demands prompt insulin therapy.

This rare presentation mandates a multidisciplinary approach. Oncologists, endocrinologists, and dietitians must collaborate closely. Balancing cancer control with metabolic risks is tough. Patients need coordinated care.

The cost-effectiveness of routine autoantibody screening in all lorlatinib patients is questionable. This case is rare. But the implications for individual patient management are severe. More data is needed to guide screening protocols.

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REFERENCES

1. Shaw, J. E., Sicree, R. A., & Zimmet, P. Z. (2010). Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Research and Clinical Practice*, 87(1), 4-14.
2. American Diabetes Association. (2023). Standards of medical care in diabetes. American Diabetes Association.
3. Pasi N, Ganda K, Joshi A, et al. New-Onset Autoantibody-Negative Diabetes With DKA Following Lorlatinib Therapy for ALK-Positive NSCLC. *JTO Clinical and Research Reports*. 2024;5(5):100770.

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