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Case Report

Severe Hyperglycemia Due to Protein Kinase Inhibitor Therapy in a Patient With Poorly Controlled Diabetes Mellitus

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Abstract

The efficacy and safety of zanubrutinib, a highly selective next-generation Bruton's tyrosine kinase (BTK) inhibitor, in chronic lymphocytic leukemia and lymphoplasmocytoides immunocytoma seems favorable. Adverse events comprise neutropenia, thrombocytopenia, infection, anemia, and atrial fibrillation. This report describes a 75-year-old man suffering from polydipsia, polyuria, and blurred vision for 10 days. He was diagnosed with lymphoplasmocytoides immunocytoma in 2003. After various therapies, he was started on zanubrutinib in October 2022. A diagnosis of diabetes mellitus had never been established before. On arrival in the emergency department, his plasma glucose was 37.2 mmol/L (671 mg/dL) and glycated hemoglobin (HbA1c) was 14.2%. Circulating antibodies showed positivity for glutamic acid decarboxylase (GAD-65), and his C-peptide level was 1.3 nmol/L (normal range, 0.37-1.47 nmol/L), equivalent to 3.9 ng/mL (normal range 1.1-5.0 ng/mL). From the patient's medical history, it became obvious that the metabolic situation had been problematic for many years, and that diabetes could have been taken into account at least in the summer of 2020 when HbA1c was 6.7%. In patients on tyrosine kinase inhibitors, careful assessment of glycemic control (monitoring HbA1c and blood glucose levels periodically even for nondiabetic patients) is recommended to prevent a major diabetic emergency.

Key Words: hyperglycemia, protein kinase inhibitor therapy, lymphoplasmocytoides immunocytoma

Abbreviations: BTK, Bruton's tyrosine kinase; GAD, glutamic acid decarboxylase; HbA1c, glycated hemoglobin; LADA, latent autoimmune diabetes in adults; TKI, tyrosine kinase inhibitor.

Introduction

Protein kinases regulate cellular signaling cascades that control cell functions such as proliferation and metabolism [1]. They can be subclassified into transmembrane receptors and non-receptor intracellular signaling tyrosine kinases [2]. Protein kinase activity dysregulation plays an important role in the pathogenesis of a number of chronic inflammatory, vascular, and autoimmune diseases as well as a variety of cancers [3]. A widespread use of small molecule kinase inhibitors has been successfully implemented into the therapy of cancerous malignancies, and many small molecule kinase inhibitors are being investigated in nonmalignant conditions, including type 1 and type 2 diabetes [4].

One of these kinases is Bruton's tyrosine kinase (BTK); its inhibitors have demonstrated remarkable anticancer effects in terms of efficacy and safety. BTK is expressed not only in B- lymphocytes but also in other types of immune cells, such as mast cells and macrophages. Therefore, BTKs show a wide range of signaling pathways [5]. Currently, a handful of BTK inhibitors have been approved by different national drug administrations: ibrutinib, acalabrutinib, zanubrutinib, tirabrutinib, and orelabrutinib. All of these are capable of irreversibly inhibiting BTK. Additional BTK inhibitors are under clinical or preclinical investigation.

It is well known that kinase inhibitors alter metabolism, blood glucose, and insulin. Many clinical reports have outlined a decreased need for exogenous insulin or diabetic medications in diabetic cancer patients receiving tyrosine kinase inhibitor (TKI) therapy. The exact route by which TKIs alter blood glucose or insulin is not completely understood. While oncologists are aware of the cardiovascular, dermatological, neurological, and renal adverse reactions of TKI therapy, metabolic dysfunctions can often go unnoticed.

The main objective of this case report is to describe a rare presentation of severe hyperglycemia in a patient with immunocytoma under zanubrutinib, a highly selective, irreversible second-generation BTK inhibitor. We discuss the management of severe hyperglycemia in order to continue BTK inhibitor therapy and point out the need to closely monitor patients' diabetes under zanubrutinib therapy.

Case Presentation

A 75-year-old man was admitted to the emergency department suffering from polydipsia, polyuria, and blurred vision

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for 10 days. He had been diagnosed with lymphoplasmocytic immunocytoma in 2003. Rituximab, an antibody therapy directed against CD20, and bendamustine, an alkylating agent with properties of a purine analog, were given in first-line and relapse settings. Specific metabolic side effects are not known [6]. Glucocorticoids had never been administered either prior to the present situation or concurrently.

After another relapse, the patient was started on zanubrutinib in October 2022. A few months later (March 2023), new onset of atrial fibrillation was diagnosed, a common side effect of TKI therapy. Since there are well known drug interactions between zanubrutinib and medications commonly used to manage atrial fibrillation, the patient was only shortly put on oral anticoagulants and referred to the cardiologist for left atrial appendage occlusion (LAAO).

Diagnostic Assessment

Initial vital signs on arrival in the emergency department (July 2023) were blood pressure 150/95 mmHg, heart rate 104 beats/min, respiratory rate 21 breaths/min, and body temperature 36.7 °C. His plasma glucose was 37.2 mmol/L (671 mg/dL) and glycated hemoglobin (HbA1c) was 14.2%. Arterial blood gas analysis on room air demonstrated normal values. Circulating antibodies showed positivity for glutamic acid decarboxylase (GAD-65), the C-peptide level was 1.3 nmol/L [normal range 0.37-1.47 nmol/L] equivalent to 3.9 ng/mL [normal range 1.1-5.0 ng/mL]. Based on laboratory results, he was diagnosed with acute hyperglycemia due to a new onset, insulin-dependent diabetes mellitus.

Treatment

Treatment was immediately provided with intravenous fluid and regular insulin via infusion pump. Hyperglycemia was improved, and on admission, the patient showed an optimal adjustment of his diabetes (normoglycemia). Thus, it was decided to continue the BTK inhibitor therapy under intensified conventional insulin therapy.

After a thorough review of the patient's medical history, it became clear that the metabolic situation had been problematic for many years (Fig. 1). Diabetes could have been taken into account at least in the summer of 2020 when his HbA1c was 6.7%. When zanubrutinib was started, a documented random blood glucose of >11.1 mmoL (>200 mg/dL) was ignored. During the patient's stay in the Department of Cardiology an HbA1c level of 8.6% was documented without further evaluation.

Outcome and Follow-Up

Three months after admission, the patient attended the outpatient oncological clinic symptom-free for a routine control examination. Upon continued intensified conventional insulin therapy, GAD antibodies and HbA1c (6.2%) were only marginally increased, and his random serum glucose was 6.4 mmol/L (114 mg/dL).

Discussion

Zanubrutinib is an orally available, irreversible second-generation BTK inhibitor. Compared to first-generation inhibitors it shows increased specificity. Documented side effects are atrial fibrillation, hypertension, and hemorrhage [7]. A recent phase 2 study at 20 centers in the United States reported atrial fibrillation in 4% of patients, and single events concerning anemia, bronchitis, COVID-19, febrile neutropenia, salmonella gastroenteritis, trigeminal nerve disorder, and urinary tract infection [8].

Historically, patients with significant cardiovascular issues have generally been considered poor candidates for BTK inhibitor therapy; however, with the availability of second-generation zanubrutinib, more of these patients may be able to take advantage of treatment with BTK inhibition [9]. Overall, a multidisciplinary approach is most important to assess the eligibility of chronic lymphocytic leukemia (CLL) patients for BTK inhibitor therapy. Particularly relevant aspects to consider include a history of valvular heart disease or other disorders that may increase the risk of atrial fibrillation, as well as a history of ventricular arrhythmias, clinical heart failure or left ventricular dysfunction, and reduced cardiac ejection fraction. Regular monitoring for heart failure during chemotherapy is recommended and helps with early detection of cardiotoxicity either leading to the continuation of cardioprotective measures or permanently discontinuing chemotherapy [10].

Since tumor cells potentiate proliferation by enhancing cellular glucose metabolism, both elevated and decreased blood glucose levels have been attributed to TKIs. The mechanism by which TKIs alter blood glucose levels is not known [11]. Regression of pancreatic islets, modulation of insulin-like growth factor 1 (IGF-1) signaling, and decreased glucose uptake are the proposed hypotheses [12]. As a matter of fact, some agents even show opposing behavior [13].

The safety profile of zanubrutinib is generally favorable [14]. A recently published meta-analysis does not report on hyperglycemic adverse events at all [15]. Contrary to this, an earlier phase 2 study reported metabolic adverse events associated with zanubrutinib therapy in about 20% of patients [16]. Awareness of hyperglycemia as an adverse event must be improved until monitoring fasting plasma glucose (FPG) or HbA1c in patients on TKI can be promoted by scientific societies. There can be no doubt that risk assessment and screening practices for patients during TKI therapy have to be established in order to control for metabolic side effects so that adequate therapy can be continued. The management of cardiovascular toxicities of BTK inhibitors has been addressed in an international consensus statement [17]. As long as equivalent guidelines in regard to hyperglycemic risks are missing, oncologists should take metabolic side effects into account and initiate an accompanying endocrinologic treatment at an early stage (eg, HbA1c > 6.1%). This strategy may substantially prevent discontinuation of TKI therapy [18].

Since multiple mechanisms may be responsible, the glycemic effects of TKI inhibitors on blood glucose and insulin are complex [19]. Whether the positivity of pancreatic beta cell antibodies is “the chicken” or “the egg” in this case remains undetermined, since we could not find former GAD results in the patient's medical history. Thus, it remains unclear whether the patient had initially emerged as having latent autoimmune diabetes in adults (LADA) or whether zanubrutinib triggered β-cell destruction. To the best of our knowledge, there has only been one case report on a male patient with LADA diagnosed about 10 years before a BTK inhibitor therapy (ibrutinib) was started due to newly diagnosed CLL. Within 9 weeks of initiation of ibrutinib, his GAD antibodies decreased without clinical signs, or changes in insulin requirement [20]. Since hyperglycemia seems to be a serious but

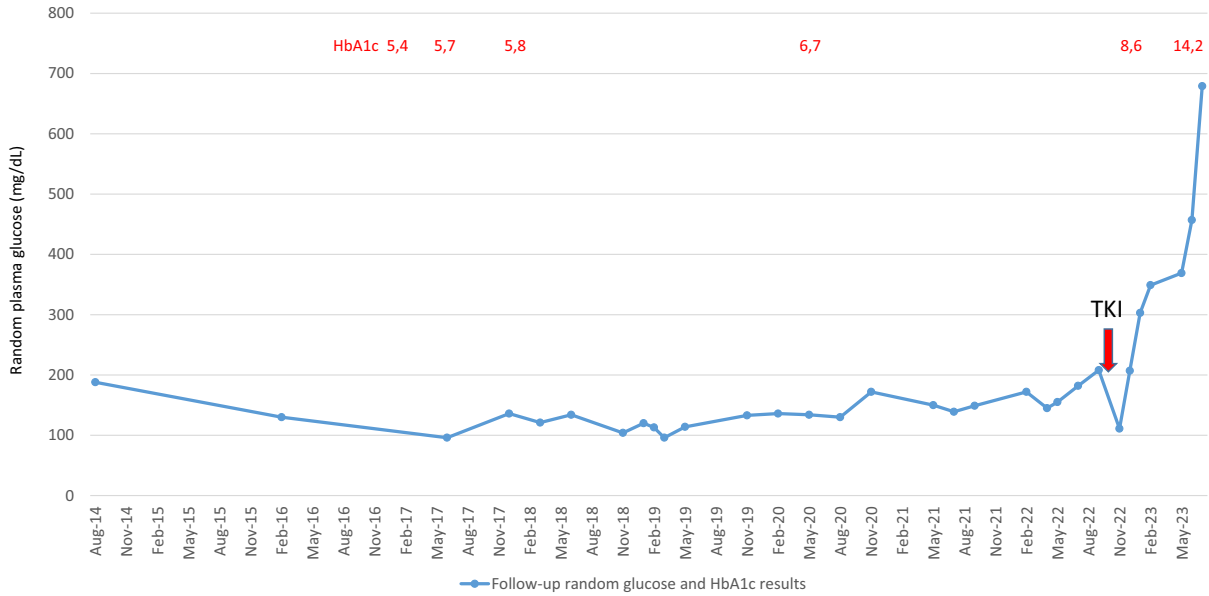

Figure 1. Development of random plasma glucose and HbA1c before and during zanubrutinib therapy. Abbreviations: TKI, tyrosine kinase inhibitor.

rather rare event in kinase inhibitor therapy, we consider the financial expense for antibody testing before and during therapy on a regular basis not to be justified.

Learning Points

- There is accumulating evidence about the metabolic actions of TKIs.
- Clinicians should be familiar with the careful assessment of glycemic control in patients on TKIs.
- Monitoring HbA1c and blood glucose levels periodically, even for nondiabetic patients, is recommended.
- Advising patients to report symptoms like polydipsia, polyuria, or blurred vision is reasonable to prevent a major diabetic emergency.

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Contributors

All authors made individual contributions to authorship. I.S. was responsible for diagnosis and management of this patient, and for critical revision of important literature; L.B. was responsible for the patient's insulin therapy and editing the figure; H.E.A. was responsible for drafting the text and manuscript submission. All authors reviewed and approved the final draft.

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Disclosures

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Informed Patient Consent for Publication

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Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed.

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