


Linezolid Associated Asymptomatic Hypoglycemia in a Patient with Advanced Gynecologic Cancer: A Case Report and Literature Review

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Abstract: Hypoglycemia is a rare but documented adverse effect of linezolid. We report a 72-year-old patient with late-stage gynecologic cancer and abdominal MRSA peritonitis, who developed persistent asymptomatic hypoglycemia after starting linezolid. The patient had type 2 diabetes on metformin-glibenclamide. Fasting blood glucose dropped to 2.08 mmol/L (reference: 3.9–6.1 mmol/L) 1 day post-linezolid initiation; hypoglycemia persisted despite stopping oral hypoglycemics and administering dextrose, but normalized within 24 hours after linezolid discontinuation (replaced with tigecycline). Naranjo ADR Scale scoring (7 points) confirmed a “probable” causal link. We present dynamic glucose trends (reinforcing causality) and review linezolid-associated hypoglycemia literature. This case highlights the need for glucose monitoring in linezolid-treated patients, especially at high risks, even without diabetes or symptoms.

Keywords: therapeutic drug monitoring, drug safety, cancer, antibiotics, adverse drug reactions

Introduction

Peritoneal fluid accumulation (ascites) is a significant clinical challenge in end-stage malignant patients. Percutaneous catheter drainage is a common palliative treatment; however, prolonged use of indwelling peritoneal catheters increases the risk of catheter-associated infections (CAIs), which are often challenging to predict and manage.¹ *Staphylococci* are the most frequent pathogens causing drain-related infections.²

We present a case of a 72-year-old woman with poorly differentiated uterine carcinoma managed with catheter drainage, who developed multidrug-resistant peritonitis. Methicillin-resistant *Staphylococcus aureus* (MRSA) was identified on microbiological analysis. Asymptomatic hypoglycemia occurred following the initiation of linezolid therapy.

Linezolid, an oxazolidinone antibiotic, is effective against multidrug-resistant Gram-positive pathogens, including MRSA and vancomycin-resistant *Enterococcus* (VRE).³ Although hypoglycemia is a rare complication of linezolid,⁴ it has been documented in case reports.^{5,6} Our case provides dynamic blood glucose (BG) evidence supporting this association, highlighting the need for vigilance, particularly in high-risk populations. BG monitoring is recommended to mitigate the risk of asymptomatic hypoglycemia.

Case Presentation

A 72-year-old woman diagnosed with poorly differentiated clear cell carcinoma (FIGO, International Federation of Gynecology and Obstetrics; grade G3) was admitted to the hospital for supportive treatment due to ascites. Catheter drainage was performed to manage the ascites; however, the catheter became dislodged due to inadequate home care. Without professional medical supervision, the patient's family attempted to reinsert the drainage catheter and utilized non-sterile techniques—this improper manipulation directly led to secondary bacterial peritonitis. The drained ascitic



Table 1 Laboratory Data

Items	Main Results
Complete Blood Count	WBC $16.45 \times 10^9/L$, L $0.51 \times 10^9/L$, N $15.22 \times 10^9/L$, RBC $3.75 \times 10^{12}/L$, Hb 94.00g/L, PLT $378.00 \times 10^9/L$
Liver Function Tests	TBIL 19.58 μ mol/L, ALT 110.54U/L, AST 390.10U/L, ALB 29.39g/L
Kidney Function Tests	Cre 151.76 μ mol/L, Urea 16.26mmol/L, UA 590.65 μ mol/L
Coagulation Function	PT 25.60s, INR 2.32, APTT 62.30s, FIB 5.37g/L, TT 16.60s, D-Dimer 5.41mg/L
Blood Glucose	FBG 10mmol/L, HbA1c 8.00%
Inflammation	CRP 162.66mg/L, IL-6 200.89pg/mL

Abbreviations: WBC, White Blood Cell Count; L, Lymphocyte Count; N, Neutrophil Count; RBC, Red Blood Cell Count; Hb, Hemoglobin; PLT, Platelet Count; TBIL, Total Bilirubin; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; ALB, Albumin; Cre, Creatinine; UA, Uric Acid; PT, Prothrombin Time; INR, International Normalized Ratio; APTT, Activated Partial Thromboplastin Time; FIB, Fibrinogen; TT, Thrombin Time; FBG, Fasting Blood Glucose; HbA1c, Glycated Hemoglobin; CRP, C-reactive Protein; IL-6, Interleukin-6.

fluid appeared purulent, and subsequent analysis confirmed a MRSA infection; the isolated MRSA strain showed marked susceptibility to vancomycin, linezolid, and tigecycline.

Her comorbidities included long-standing T2DM (Type 2 Diabetes Mellitus; switched from insulin to metformin-glibenclamide 250/1.25mg TID post-cancer due to better glucose control); hypertension (amlodipine 5mg OD); DVT (Deep Vein Thrombosis; rivaroxaban 10mg BD); hydronephrosis.

Pre-treatment laboratory findings (Table 1): high inflammatory burden, renal insufficiency, and hepatic impairment (Child-Pugh class C, 10 points).

Clinical Findings, Treatment and Diagnostic Assessment

Changes in BG Levels (FIGURE 1) and Corresponding Therapeutic Interventions

Pre-Linezolid Baseline (Admission Day 1)

BG Status: Immediate fingertip BG upon hospital admission was 10mmol/L without signs of hypoglycemia.

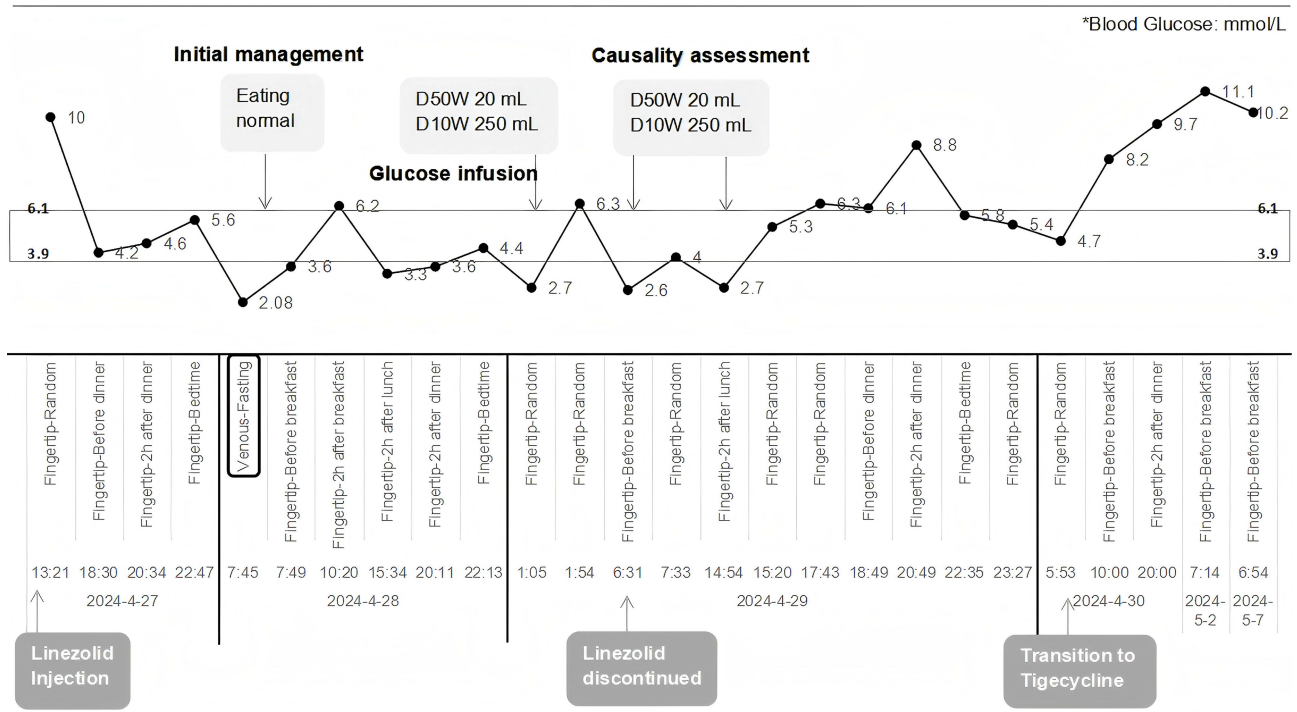


Figure 1 Changes in BG levels. The patient developed recurrent hypoglycemia following linezolid administration, which persisted despite high-carbohydrate diet and IV glucose supplementation. Hypoglycemia resolved after linezolid was discontinued and tigecycline was initiated, suggesting a causal association with linezolid. *Blood glucose levels are expressed in millimoles per liter (mmol/L).

Abbreviations: D50W, dextrose 50% in water; D10W, dextrose 10% in water.

Medication: (1) Magnesium Isoglycyrrhizinate (*Zhengda Tianqing Pharmaceutical Group Co., Ltd, Tianli, Jiangsu, China*) 150mg QD Intravenous; (2) Linezolid (*Zhengda Tianqing Pharmaceutical Group Co., Ltd, Tianli, Jiangsu, China*) at a dose of 0.6g in glucose injection, administered intravenously every 12 hours; (3) Oral intake: metformin-glibenclamide 250/1.25mg TID, and amlodipine 5mg OD. Rivaroxaban discontinued due to the patient's severe hepatic dysfunction.

Post-Linezolid Hypoglycemia Onset (Hospital Day 2)

BG Abnormality: Venous testing revealed profound asymptomatic hypoglycemia (2.08 mmol/L), notable for: 1) rapid onset (<24h post-dose), 2) absence of symptoms despite critical values, and 3) discordance with prior normal fingertip readings (>3.9 mmol/L).

Therapeutic Interventions: Initiation of a high-carbohydrate diet and Cessation of oral metformin-glibenclamide.

Persistent Refractory Hypoglycemia (Hospital Day 3)

BG Deterioration: Routine nocturnal BG surveillance at 01:05 revealed a BG dropped again to 2.7 mmol/L, indicating persistent hypoglycemia. Within the subsequent 14 hours, refractory hypoglycemia recurred twice, with BG levels of 2.6 mmol/L and 2.7 mmol/L, respectively.

Therapeutic Interventions: (1) Emergency glucose correction: Immediate intravenous bolus of 20 mL 50% dextrose (D50W), which rapidly normalized BG; (2) Preventive glucose supplementation: Initiation of continuous intravenous infusion of 250 mL 10% dextrose (D10W) to maintain stable BG, but this failed to prevent recurrent hypoglycemia; (3) Antibiotic replacement: Discontinuation of linezolid on Hospital Day 3; plans were made to switch to tigecycline for anti-infection treatment the next day.

Hypoglycemia Resolution Phase (Hospital Day 4–Day 10)

After linezolid discontinuation, BG gradually rebounded and stabilized at approximately 10 mmol/L (consistent with the admission baseline). On Hospital Day 4, the patient started receiving tigecycline injection (*Wyeth Pharmaceuticals Co., Ltd, Tygacil, Jiangsu, China*) at an initial loading dose (doubled) followed by 50 mg every 12 hours. During the 7-day tigecycline treatment course, no recurrent hypoglycemia was observed.

Differential Diagnosis

- a. Hunger-induced hypoglycemia – Likely precipitated by prolonged fasting prior to morning blood tests (*typical for transient hypoglycemia, but recurrent episodes suggest additional factors*).
- b. Paraneoplastic hypoglycemia – Secondary to advanced malignancy (*given disease progression*).
- c. Hepatogenic hypoglycemia – Caused by severe liver disease (eg, cirrhosis, acute liver failure, hepatocellular carcinoma).
- d. Drug-induced hypoglycemia
 - Glibenclamide (*sulfonylurea*): Known insulin secretagogue.
 - Linezolid: Label-reported hypoglycemia risk.

Causality Assessment

Our team conducted interviews with the patient and her family, who confirmed no history of hypoglycemic episodes in the days prior to linezolid initiation—effectively ruling out pre-existing hypoglycemia.

First, diagnosis a was excluded: it typically manifests as transient post-fasting glucose decline resolving with carbohydrate intake, yet the patient's hypoglycemia persisted despite both such dietary intervention and the administration of intravenous glucose infusions—further confirming that hunger-induced factors were not the cause.

Second, diagnosis b was ruled out: if hypoglycemia were paraneoplastic, it would have persisted or worsened with tumor progression, rather than resolving with antibiotic substitution. This temporal disconnect confirms paraneoplastic hypoglycemia is not the cause.

Third, diagnosis c was excluded based on the patient's lack of a prior liver disease history (eg, cirrhosis, hepatocellular carcinoma/metastasis), dynamic liver function monitoring (Child-Pugh class C, 11 points, re-examination 8 days

Table 2 ADR Probability Scale to Assess the Adverse Drug Reaction, Please Answer the Following Questionnaire and Give the Pertinent Score

Question	Yes	No	Do Not Know	Score
1.Are there previous conclusive reports on this reaction?	+1	0	0	1
2.Did the adverse event appear after the suspected drug was administered?	+2	-1	0	2
3.Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	1
4.Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	0
5.Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	2
6.Did the reaction reappear when a placebo was given?	-1	+1	0	0
7.Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8.Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	0
9.Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10.Was the adverse event confirmed by any objective evidence?	+1	0	0	1
			Total score	7

Notes: Result interpretation: Definite ≥ 9 ; probable 5 to 8; possible 1 to 4; doubtful ≤ 0 . Bold values indicate the score result. The bolded values shown in the table correspond to the case summarized in this article.

after tigecycline administration), and details of subsequent interventions (regular diet, no recurrent hypoglycemia, and no additional glucose supplementation).

Given that hypoglycemia persisted despite the discontinuation of metformin-glibenclamide, ruling out this sulfonylurea agent as the primary cause, linezolid was suspected to be the culprit. This temporal association supports a probable causal relationship between hypoglycemia and linezolid. We assessed causality using the Naranjo Adverse Drug Reaction (ADR) Probability Scale, which yielded an 7-point score—classifying the relationship as “probable” (see Table 2).

Follow-Up

After switching to tigecycline (post-linezolid cessation), the patient had no recurrent hypoglycemia, but her intra-abdominal MRSA infection persisted. Given her advanced gynecologic cancer, the family chose discharge for home-based care. Nine days later, she was readmitted due to abdominal pain; venous blood glucose was 9.74 mmol/L. She was transferred to hospice for symptom management and expired 2 days later.

Discussion

In female cancer patients, ascites is most commonly seen in advanced gynecological tumors.⁷ Women with advanced gynecological cancers often require repeated drainage of ascites.⁸ For cancer patients requiring repeated drainage of ascites, permanent tunnelled catheters may be a better option for home care and reduced hospitalization.^{9,10} The overall infection rate of ascites drainage is 4%, which is the main risk event for the use of permanent catheters.¹¹ Infection outcomes include peritonitis, drain-site cellulitis and infected ascitic fluid without clinical features of peritonitis.¹ *Staphylococci*, particularly *Staphylococcus aureus*, are common pathogens responsible for drain-related infections and are a leading cause of nosocomial infections, often exhibiting antibiotic resistance.^{2,12}

In our case, the patient was a 72-year-old female admitted with advanced gynecologic cancer, concurrent intra-abdominal MRSA infection, renal insufficiency, and severe liver dysfunction (Child-Pugh class C, 10 points). Linezolid, the first clinically approved oxazolidinone,¹³ belongs to a class of synthetic antimicrobials that exhibit potent activity against multidrug-resistant Gram-positive pathogens, including MRSA and VRE.³ It was selected for our patient with intra-abdominal MRSA infection—a choice aligned with the 2021 UK guidelines, which recommend vancomycin, linezolid, and tigecycline for MRSA infections.¹⁴ Linezolid is the preferred alternative to vancomycin in cases of contraindication or resistance, particularly for intraperitoneal MRSA infections, due to its lower renal toxicity and acceptable adverse effects.^{15,16} Moreover, given the patient’s severe liver dysfunction, drug selection must prioritize hepatotoxicity risks. Vancomycin carries a risk of supratherapeutic exposure in liver impairment,¹⁷ while tigecycline requires dose adjustments¹⁸ and may impair coagulation (reducing fibrinogen and prolonging aPTT/PT).^{19,20} In contrast, linezolid exhibits minimal hepatotoxicity without necessitating dosage modifications, though thrombocytopenia risk^{4,21}

and therapeutic monitoring should be considered,²² making it the safest choice for the patient. Common ADRs to linezolid include diarrhea, nausea, vomiting, bone marrow suppression, peripheral neuropathy, and headache.^{4,21} None of these ADRs were observed in our patient.

Nevertheless, during the administration of linezolid in our patient, asymptomatic hypoglycemia occurred. We documented the dynamic changes in the patient's blood glucose throughout the periods of linezolid administration, therapeutic interventions for hypoglycemia, and linezolid discontinuation. While tigecycline has also been reported to be associated with hypoglycemia,²³ no hypoglycemic episodes occurred in this patient during the 7-day tigecycline treatment course. This temporal correlation suggests a potential causal link between linezolid and the development of hypoglycemia in our patient. According to Prabha Viswanathan's evaluation criteria,²⁴ our case is judged as highly probable. Using Naranjo's method,²⁵ the ADR probability scale self-test is 7 points which means probable (See Table 2). Issues 4, 6, 7, 8, and 9 in the scale cannot be implemented and confirmed.

Literature Summary of Linezolid-Associated Hypoglycemia

Linezolid-Associated Hypoglycemia in Clinical Context

Hypoglycemia is recognized as a rare adverse reaction of linezolid in clinical practice, with existing evidence based on published case reports. In 2014, Prabha Viswanathan²⁴ conducted a search of the FDA Adverse Event Reporting System (FAERS), identifying 41 cases of hypoglycemia associated with linezolid use reported between April 2000 and March 2012. Of the 41 unique reports, only 15 cases were identified as linezolid associated hypoglycemia. Ten years later in 2024, Fan Zou⁴ conducted a real-world pharmacovigilance study using the FAERS database, covering the period from 2004 to 2023, and reported a hypoglycemia incidence rate of 0.44% (n=135/30,431).

We systematically searched PubMed and Elsevier databases for case reports on linezolid-associated hypoglycemia, ultimately selecting 10 eligible reports that included a total of 12 specific cases (see Table 3 and Table 4). Among the 12 reported cases (median age: 70.5 years), 10 patients (83.3%) were male. Seven patients (58.3%) had diabetes, including one with type 1 diabetes. Hypoglycemia was isolated in 6 cases (50.0%); others had varying combinations of lactic acidosis (5 cases), pancreatitis (3), thrombocytopenia (3), anemia (2), and hyponatremia (1). Hypoglycemia (range: 1.06–3.4 mmol/L; median: 2.5) developed within 1 day to 6 weeks. Glucose fluctuations were described in 5 cases. After discontinuing linezolid, hypoglycemia resolved in 10 patients (83.3%); one case showed no improvement and resulted in death, and one case had missing outcome data. Five cases (41.7%) had chronic kidney disease, and 2 cases (16.7%) were treated with sulfonylureas. Only case 5 and case 8 achieved the re-challenge of linezolid.^{26,27}

Mechanisms of Linezolid-Associated Hypoglycemia

Investigators have proposed several plausible mechanisms: (1) Mitochondrial toxicity. By inhibiting bacterial (and potentially mitochondrial) protein synthesis, linezolid disrupts oxidative phosphorylation, reducing ATP production.^{28,29} This may impair hepatic gluconeogenesis, lowering glucose levels while promoting lactic acidosis—a phenomenon observed clinically.²⁹ (2) Monoamine Oxidase(MAO) Inhibition and Neurotransmitter Effects. Linezolid inhibits the metabolism of dopamine, norepinephrine, and serotonin,^{5,30} which may influence insulin secretion and increase insulin sensitivity through neuroendocrine mechanisms,³¹ particularly in patients using insulin or sulfonylureas.³² (3) Pancreatic injury, though reported (eg, dysfunction of beta cells or direct toxicity),²⁹ still requires further explanation.

Risk Factors for Linezolid-Associated Hypoglycemia

Patients with: (1) Comorbidities: Renal insufficiency, hepatic dysfunction, or critical illness;²² (2) Demographics: Advanced age (≥ 65 years),^{33,34} (3) Concomitant Medications: Sulfonylureas, meglitinides or other antibiotics³⁵ linked to hypoglycemia (eg, fluoroquinolones, tigecycline).

Limitations

First, the exact mechanism of linezolid-associated hypoglycemia remains unclear, particularly the roles of mitochondrial dysfunction versus neuroendocrine modulation, and whether pancreatic injury is population-specific. While confounding

Table 3 Baseline Characteristics and Medication Information of 12 Cases from 10 Case Reports

Case ID, *[RN]	Age/Sex	Diabetes Status	Diabetes Intervention	Comorbidities	Linezolid Route	**Concomitant Antibiotics
1[5]	52y/F	No	No	Hypertension, ulcerative colitis, osteoarthritis, and diverticulitis complicated by abscess	lv→po	Meropenem; Ertapenem
2[6]	59y/F	Type II	Not mentioned	Coronary artery disease, hypertension, multiple venous thromboembolism, chronic renal insufficiency, and asthma.	lv	Single
3[36]	34y/M	No	No	Sickle cell disease (SCD), end-stage renal disease, secondary hemochromatosis, strokes, seizures, deep vein thromboses	lv	Amphotericin B, micafungin, piperacillin/tazobactam
4[37]	70y/M	Type I	Insulin	Micro- and macrovascular complications	lv→po	Single
5[27]	71y/M	Type II	No	Coronary heart disease	lv	Biapenem; Single
6[27]	82y/M	No	No	None	lv	Biapenem
7[27]	84y/M	No	No	None	lv	Cefoperazone/ sulbactam
8[26]	93y/M	Type II	Insulin	Hypertension, chronic kidney disease, chronic lung inflammation, etc	Po/iv	Isoniazid, levofloxacin; Imipenem
9[38]	64y/M	Type II	Insulin, glibenclamide, metformin	Coronary artery disease, atrial fibrillation, hypertension, dyslipidemia, hypothyroidism, and gout	Po	Single
10[39]	77y/M	Type II	Insulin, glimepiride	Congestive heart failure with biventricular implanted cardioverter defibrillator, atrial fibrillation, hypertension, chronic kidney disease stage II, and hypothyroidism	Po	Single
11[40]	68y/M	Type II	Not mentioned	Hypertension, chronic kidney disease	Po	Cefepime
12[41]	82y/M	No	No	None	Po	Single

Notes: A review of PubMed and Elsevier databases identified 10 case reports encompassing a total of 12 individual cases. *[RN], an abbreviation for reference number.**Concomitant Antibiotics: "single" indicates that the patient was treated with linezolid alone; A semicolon (";") in this column denotes different combinations of antibiotics used concomitantly with linezolid.

Table 4 Hypoglycemic Reactions and Clinical Outcomes of 12 Cases from 10 Case Reports

Case ID. *[RN]	Complications (Other Than Hypoglycemia)	Lowest BG (mmol/L)	Time to Hypoglycemia After Linezolid Initiation	BG Trend Documentation	Hypoglycemia Resolution
1[5]	Lactic acidosis,pancreatitis	2.22	6w	–	Yes
2[6]	Lactic acidosis, thrombocytopenia	3.0	Days	Chart	Yes
3[36]	Lactic acidosis, pancreatitis	1.06	12days	Line graph	Yes
4[37]	No	2.89	19days	Line graph	Yes
5[27]	No	2.8	3days	–	Yes
6[27]	No	2.6	1day	–	Yes
7[27]	No	1.9	2days	–	–
8[26]	Anaemia	2.6	6days	Line graph	Yes
		2.5	4days		
9[38]	No	1.67	In 7days	–	Yes
10[39]	No	1.67	9.5days	Line graph	Yes
11[40]	Pancreatitis, lactic acidosis, thrombocytopenia	3.4	<1Month	–	Yes
12[41]	Lactic idosis,anemia, thrombocytopenia, hyponatremia	2.0	10days	–	No

Note: A review of PubMed and Elsevier databases identified 10 case reports encompassing a total of 12 individual cases. *[RN], an abbreviation for reference number.

factors were addressed, causality assessment is complicated by linezolid's dual effects (potentiating hypoglycemic drugs²⁴ and inducing independent hypoglycemia), alongside possible antibiotic interactions.

Second, the Naranjo ADR Probability Scale has inherent limitations in this case. Key questions (4, 6, 7, 8) were unanswerable: linezolid re-challenge was ethically prohibited (risk of life-threatening hypoglycemia), placebo use violated infection management standards, linezolid therapeutic drug monitoring was not performed (with no defined “toxic concentrations” for hypoglycemia), and dose adjustment was unfeasible (would compromise MRSA efficacy). These gaps reduce the scale's ability to capture clinical complexity in vulnerable patients.

Finally, the single-case design limits generalizability. Although supported by literature review, small sample sizes and publication bias preclude robust conclusions. Larger prospective studies are needed to validate linezolid's association with asymptomatic hypoglycemia, especially in patients with liver/renal dysfunction or advanced malignancy.

Conclusion

This case addresses key literature gaps: it highlights the real-world diagnostic challenge of differentiating linezolid-induced hypoglycemia from other causes in complex comorbid patients, documents asymptomatic persistence in an understudied population (advanced gynecologic cancer with hepatic dysfunction), and reinforces the need for proactive monitoring. These insights refine risk assessment and clinical decision-making, ultimately improving patient safety in the management of multidrug-resistant Gram-positive infections.

Abbreviation

BG, Blood glucose; MSRA, Methicillin-resistant *Staphylococcus aureus*; ADRs, Adverse Drug Reaction; FAERS, FDA Adverse Event Reporting System.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article. Additional information related to this work is available from the corresponding author upon reasonable request.

Ethics Approval Statement

Medical Ethics Committee of Puyang Traditional Chinese Medicine Hospital approved the research. Ethical approval No.202412. In accordance with the ethical policies of Puyang Traditional Chinese Medicine Hospital, institutional approval for the publication of de-identified case details is not required as a separate step, provided that the original study (which generated the case data) has already obtained ethical approval and the case information has been fully anonymized to protect patient privacy. Thus, the publication of the case details in this manuscript complies with the institutional ethical requirements.

Written Informed Consent

Written informed consent was obtained from the patient's family to publish this report in accordance with the journal's patient consent policy.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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