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Case Report

An uncommon triad of toxicity: sinus bradycardia, cytopenia and gastrointestinal symptoms induced by thalidomide

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ABSTRACT

Thalidomide, an immunomodulatory and antiangiogenic agent, is widely used in oncology but rarely causes cardiac conduction abnormalities such as sinus bradycardia. Chemotherapy with temozolomide may also result in cytopenia. Early recognition of these adverse effects is critical for patient safety. We report a 50-year-old female with malignant melanoma undergoing chemotherapy with thalidomide (400 mg/day) and temozolomide (150 mg/day) who presented with persistent nausea, recurrent vomiting, generalized weakness, and bradycardia. On admission, vital signs revealed sinus bradycardia (heart rate 40 beats/min) with prolonged QTc, and laboratory findings demonstrated mild anemia, leukopenia, neutropenia, thrombocytopenia, hyponatremia, and borderline hyperkalemia. Imaging and echocardiography were largely unremarkable except for mild tricuspid regurgitation and pulmonary hypertension. A diagnosis of thalidomide-induced bradycardia with chemotherapy-associated cytopenia was established. Thalidomide was discontinued, and the patient received supportive care including intravenous fluids, electrolyte correction, antiemetics, corticosteroids, thyroid hormone replacement, and cardiac monitoring. Atropine was administered for bradycardia as needed. Over 48 hours, the patient's symptoms and laboratory abnormalities improved, with stabilization of heart rate and resolution of vomiting. This case highlights a rare but significant manifestation of thalidomide-induced sinus bradycardia with cytopenia and gastrointestinal symptoms in a patient receiving chemotherapy for malignant melanoma. Early recognition, prompt drug withdrawal, and comprehensive supportive care were crucial for recovery. Clinicians should remain vigilant for uncommon cardiac and hematologic adverse effects of thalidomide and coordinate multidisciplinary management to optimize patient outcomes.

Keywords: Thalidomide-induced bradycardia, Malignant melanoma, Chemotherapy-induced cytopenia, Drug-induced cardiotoxicity, Anti-angiogenic therapy, Immunomodulatory effects

INTRODUCTION

Thalidomide was first introduced in 1953 by the Swiss pharmaceutical firm CIBA and later brought to market in 1956 by the German and under the brand name Contergan. It was promoted as a non-barbiturate sedative that could induce restful sleep without causing hangovers or leading to dependence.¹ During the late 1950s and early 1960s, thalidomide was widely prescribed to pregnant women as

an antiemetic to relieve nausea and vomiting.² Originally regarded as safe because it showed no immediate toxic effects in adults, thalidomide was extensively prescribed throughout Europe, Canada, Australia and other parts of the world. However, in 1961, serious concerns arose when reports linked the drug to babies being born with phocomelia a rare condition characterized by severely shortened or absent limbs as well as other birth defects involving the ears, eyes, heart, and internal organs.³ The possible value of thalidomide in treating cancer was first

proposed in the 1960s, soon after its teratogenic effects were identified. Researchers suggested that the same mechanisms causing birth defects might also be useful in combating cancer. However, for several reasons, the initial clinical trials investigating thalidomide as an anticancer agent.¹ In the 1990s, the drug found new medical use when the FDA approved it for treating conditions like erythema nodosum leprosum. This renewed interest prompted further investigation into how it works, leading to the discovery of its anti-inflammatory, immunomodulatory, and anti-angiogenic effects. These properties later supported its approval for treating multiple myeloma.⁴

Thalidomide is a synthetic glutamic acid derivative with a two-ring structure and one chiral center. It exists as rapidly interconverting R and S forms and is used as a racemic mixture. Its four amide bonds are easily hydrolyzed, especially above pH 6.⁵ Thalidomide is absorbed gradually, reaching peak plasma levels about 2–5 hours after oral administration. At physiological pH, it undergoes spontaneous hydrolysis, resulting in over 90% being eliminated via the kidneys, with less than 5% excreted unchanged. Its elimination half-life ranges from 5 to 7 hours.⁴ The long-term clinical outcomes of the initial 169 patients enrolled in UARK 98-003 protocol, which involved administering thalidomide using a dose-escalation strategy.

Treatment began at 200 mg per day, with the dose increased by 200 mg every two weeks as tolerated, up to a maximum of 800 mg per day. Among the 53 patients who received second line treatments the median time to the next therapy was three months, with 29% undergoing additional high-dose melphalan regimens and only 7% receiving bortezomib. Of the 140 patients with detailed dosing data after 90 days in the trial, 58% reached the planned target dose of 800 mg, 68% achieved 600 mg, and 87% reached 400 mg, while 13% did not advance beyond the initial 200 mg dose.⁶ Recent randomized clinical studies have shown that regimens containing thalidomide achieve higher response rates and longer event-free survival compared to standard therapies.⁷

Researchers have found that thalidomide therapy can prolong survival in myeloma patients, though it may not be appropriate for all individuals with the disease. A study conducted at The Institute of Cancer Research, London revealed that patients classified as low-risk for myeloma recurrence experienced improved survival when treated with thalidomide, while high-risk patients showed reduced survival rates. In this study, thalidomide was administered as a maintenance therapy, meaning it was given after initial treatment to lower the likelihood of the cancer returning.⁸ Although the use of thalidomide was controversial and its distribution was not officially encouraged, most Indian physicians likely preferred prescribing more readily available medications.

Additionally, they generally avoided prescribing thalidomide to women of childbearing age due to its

known risk.⁹ Thalidomide has demonstrated significant therapeutic potential in the treatment of immune-mediated gastrointestinal disorders, including inflammatory bowel disease (IBD), intestinal Behçet's disease, and Immunoglobulin G4 (IgG4)-related disease. In addition, it has been found to be effective in managing non-immune-mediated gastrointestinal conditions, such as gastrointestinal bleeding and malignancies of the digestive tract.¹⁰

CASE REPORT

A 50-year-old woman (height: 162 cm; weight: 53 kg; BMI: 20.16 kg/m²) presented to the emergency department with complaints of persistent nausea, multiple episodes of vomiting, and worsening generalized weakness over the preceding four days. She had a known history of malignant melanoma and was receiving chemotherapy with Thalidomide (400 mg orally once daily; an immunomodulatory and antiangiogenic agent) The patient had been taking thalidomide as per a previously prescribed regimen for a known duration and Temozolomide (150 mg orally once daily; an oral alkylating chemotherapeutic agent) for one-week post-cycle. Upon admission, she was alert but fatigued, with vital signs showing bradycardia (heart rate 40 beats/min), blood pressure 110/60 mmHg, temperature 98.6 °F, and respiratory rate 22 breaths/min. ECG demonstrated sinus bradycardia with prolonged QTc interval, while cardiovascular and neurological examinations were otherwise unremarkable.

Laboratory evaluation revealed mild anemia (Hb 11.8 g/dL), leukopenia (TLC $1.27 \times 10^3/\mu\text{l}$), neutropenia (ANC 970 cells/ μl), and thrombocytopenia (PLT $70 \times 10^3/\mu\text{l}$). Electrolytes demonstrated hyponatremia (Na^+ 126 mmol/l), borderline hyperkalemia (K^+ 5.1 mmol/l), and hypochloremia (Cl^- 93 mmol/l). Renal function was normal, with serum creatinine 0.66 mg/dL and urea 15 mg/dL. Inflammatory markers were mildly elevated (CRP 9.74 mg/l) with normal procalcitonin (<0.15 ng/ml). Cardiac biomarkers showed troponin I of 2.4 ng/ml.

Abdominal ultrasonography revealed a normal-sized liver with preserved echotexture and a 2.9×1.1 cm hypoechoic lesion in the left lobe consistent with a hemangioma. Both kidneys were normal in size, with the right kidney showing increased cortical echogenicity and a lower pole cortical cyst. Pelvic imaging confirmed post-surgical status of the uterus and ovaries.

Echocardiography demonstrated normal left ventricular systolic function, mild tricuspid regurgitation, and mild pulmonary arterial hypertension. A diagnosis of thalidomide-induced nausea, vomiting, and bradycardia with cytopenia was established. Thalidomide was withheld, and supportive management was initiated. Intravenous fluids (Dextrose Normal Saline 1000 ml over 4 hours, followed by 0.9% normal saline 60 ml/hr; isotonic crystalloid solutions) were administered for hydration and correction of electrolyte imbalances. Ondansetron (8 mg

IV twice daily; a 5-HT₃ receptor antagonist) was used to control chemotherapy-induced nausea and vomiting. Pantoprazole (40 mg IV once daily; a proton pump inhibitor) was given to prevent stress-related gastric mucosal injury. Deriphylline (150 mg orally twice daily; a methylxanthine bronchodilator) supported respiratory function. Thyronorm (levothyroxine 137.5 µg orally once daily; synthetic thyroid hormone) was administered for correction of thyroid hormone deficiency. She had been previously maintained on levothyroxine 112 µg once daily. Hydrocortisone (25 mg IV stat; a corticosteroid) provided anti-inflammatory support and adjunctive management of nausea. For bradycardia, Atropine (1 ml IV as needed; an anticholinergic agent) was used with close cardiac monitoring. Furosemide (Lasix 40 mg IV stat; loop diuretic) was given when indicated to manage fluid overload.

Over the subsequent 48 hours, the patient demonstrated marked clinical improvement, with reduced vomiting, correction of electrolyte abnormalities, maintenance of adequate urine output, and stabilization of heart rate. Serial monitoring of blood counts and cardiac rhythm showed no further hemodynamic compromise, and the patient remained afebrile. This multidisciplinary approach, combining drug withdrawal, targeted pharmacologic therapy, and supportive care, facilitated rapid recovery while minimizing potential complications associated with chemotherapy and drug-induced adverse effects.

DISCUSSION

This case highlights an uncommon but clinically significant occurrence of thalidomide-related sinus bradycardia with QTc prolongation during combination chemotherapy for malignant melanoma. The patient developed a marked reduction in heart rate to 40 beats/min without evidence of significant structural cardiac abnormalities. The subsequent improvement in cardiac rhythm following discontinuation of thalidomide strengthens the likelihood of a drug-associated adverse effect. Previous reports have also documented reversible sinus bradycardia during thalidomide therapy, including cases involving doses up to 400 mg/day, comparable to the dosage administered in the present case.¹¹

A previous clinical study found that bradycardia occurred in approximately 15% of patients receiving thalidomide, with some patients developing heart rates as low as 32 beats/min. These findings indicate that clinically significant bradycardia can occur even with relatively lower thalidomide doses.¹² The exact mechanism underlying thalidomide-associated bradycardia has not yet been clearly established; however, alterations in autonomic control and cardiac electrophysiological activity have been suggested as possible contributing factors.^{11,12}

Thalidomide-induced bradycardia may show a relationship with treatment dose and appears to be reversible in many cases. Previous clinical evidence has demonstrated a

decline in heart rate with increasing thalidomide exposure, followed by recovery after dose reduction, supporting a possible dose-dependent association with the cardiac adverse effect observed in the present case.¹³ Persistent nausea and vomiting may have resulted in fluid depletion and electrolyte imbalance, potentially worsening the cardiac abnormalities. The patient's rapid clinical recovery after discontinuation of thalidomide, supportive therapy, and correction of metabolic disturbances suggests that the adverse effects were reversible. This case highlights the importance of promptly recognizing uncommon cardiovascular complications associated with thalidomide therapy. Regular monitoring of ECG findings, electrolyte levels and hematological parameters may help identify treatment-related toxicity early and facilitate appropriate management.

CONCLUSION

This case highlights a rare manifestation of thalidomide-induced sinus bradycardia accompanied by nausea, vomiting, and cytopenia in a patient undergoing chemotherapy for malignant melanoma. Early recognition and prompt withdrawal of the offending agent, alongside comprehensive supportive care, were critical to the patient's recovery. Clinicians should maintain a high index of suspicion for rare cardiac and hematologic adverse effects in patients receiving thalidomide and other chemotherapeutic agents. Vigilant monitoring, interdisciplinary collaboration, and timely interventions are essential to minimize morbidity and optimize patient outcomes.

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