Case Report

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A Case Report: Lenalidomide-Associated High-Grade Fever in a Multiple Myeloma Patient

Haozhen Sun*, Tong YinHui

Department of Pharmacy, The First Affiliated Hospital of College of Medicine, Zhejiang University, Hangzhou, Zhejiang, P.R. China

Abstract

Lenalidomide, a second-generation immunomodulatory agent and potent analogue of thalidomide, is primarily FDA-approved for treating multiple myeloma (MM) and transfusion-dependent anemia associated with low or intermediate-1-risk myelodysplastic syndromes (MDS) linked to 5q deletion, among other indications. By modulating the immune system, lenalidomide influences cytokine production, ultimately activating immune responses against tumors. However, this immune activation can result in collateral immune toxicities such as fever, angioedema, Stevens-Johnson syndrome, tumor flare, and others. We present a case of high-grade fever induced by lenalidomide in a patient with MM and provide a literature review on the underlying physiology of this reaction and strategies for managing this adverse event.

Keywords: Lenalidomide; Fever; Toxicity.

Corresponding author:
Haozhen Sun, Department of Pharmacy, The First Affiliated Hospital of College of Medicine, Zhejiang University, Hangzhou, Zhejiang, P.R. China. E-mail: sun_ha245@gmail.com

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Case Report

A 59-year-old woman, recently diagnosed with IgG kappa multiple myeloma (MM), presented to the emergency department with fever and generalized body aches one day after initiating her first cycle of therapy with lenalidomide, bortezomib, and dexamethasone. She denied respiratory symptoms, urinary issues, gastrointestinal complaints, or neurological symptoms. On examination, she exhibited fever (39°C) and tachycardia, with no other significant findings. Despite broad-spectrum antibiotics and extensive infectious workup, including blood and urine cultures, chest x-ray, and viral testing, all results were negative. Her blood count and differential remained within normal limits. The fever persisted for five days despite changes in antimicrobial therapy. After six days of hospitalization, antibiotics and lenalidomide were discontinued, resulting in rapid resolution of the fever. The patient was discharged in stable condition and subsequently treated with cyclophosphamide, bortezomib, and dexamethasone, followed by autologous hematopoietic cell transplant after achieving a very good partial remission [1]. However, she declined maintenance therapy post-transplant and experienced relapse two years later. Upon relapse, the patient received low-dose lenalidomide (10 mg daily), bortezomib, and dexamethasone, tolerating the regimen well. Later, the lenalidomide dose was escalated to the standard 25 mg daily [2].

Discussion

Lenalidomide, a 4-amino-glutamyl analogue of thalidomide, is a second-generation immunomodulatory agent primarily approved by the FDA for use in myelodysplastic syndromes with deletion of chromosome 5q and multiple myeloma, among other cancers. As an immunomodulatory drug, lenalidomide impacts both cellular (T and NK cells activation) and humoral components of the immune system, leading to changes in the tumor microenvironment through regulation of various cytokines and growth factors [3].

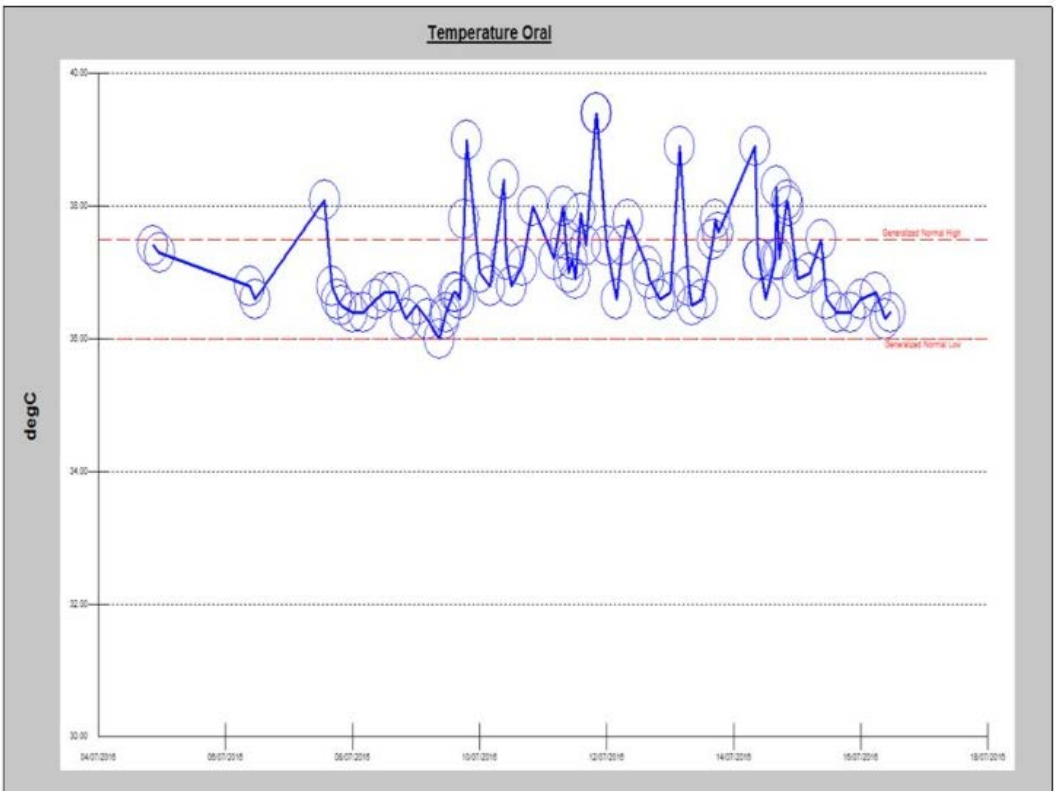

Figure 1: Pattern of temperature during lenalidomide uptake.

Fever is a common occurrence in patients with hematologic malignancies, and lenalidomide-induced fever is not uncommon but may be overlooked in clinical practice and literature. Drug fever, characterized by a febrile response coinciding with drug administration and resolving upon discontinuation, is often suspected when no other causes of fever are identified.

The exact mechanism of lenalidomide-induced fever remains unclear, but it is associated with increased production of pro-inflammatory cytokines such as IL-6 and TNF-α, leading to elevated CRP levels. Lenalidomide also enhances immunological synapse formation and upregulates CD80 on tumor cells, resulting in T cell activation and rapid cytokine release. Tumor flares have been reported in some cases, adding complexity to the understanding of lenalidomide-induced fever [4-6].

Management of lenalidomide-induced fever involves holding the medication until symptoms resolve, followed by rechallenge at a lower dose with dose escalation as tolerated. Despite its prevalence, further research is needed to fully elucidate the mechanisms underlying lenalidomide-induced fever and optimize management strategies.

Conclusion

In summary, fever associated with lenalidomide therapy appears to be common but often underreported in medical literature. Unlike thalidomide, the first-generation immunomodulatory agent, lenalidomide therapy has been linked to fever, with a reported incidence of 27% in the phase III registration trial for pomalidomide. This suggests that fever may be a class side effect related to the potency of different generations of immunomodulatory agents.

However, whether the incidence of fever correlates with the therapeutic activity of these agents remains uncertain. Studies have shown that neither the degree of T cell activation in vitro nor the severity of cytokine release syndrome correlates with the efficacy of lenalidomide in lymphomas.

In clinical practice, medical teams should consider holding lenalidomide therapy without immediately resorting to costly investigations or starting antibiotics, especially in the absence of infectious symptoms. Physicians should be mindful of this potential association given the increasing frequency of lenalidomide usage. Further research is warranted to elucidate the impact of fever on clinical outcomes and to better understand its underlying mechanisms.

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