

Recurrence of Tumor Flare Reaction in a Chronic Lymphocytic Leukemia Patient During Chlorambucil-Rituximab Treatment 6 Years After Lenalidomide

Neno Živković¹, Koraljka Gjadrov², Klara Dubravčić³, Sandra Bašić-Kinda⁴ and Igor Aurer^{1,4*}

¹Medical School, University of Zagreb, Croatia

²Department of Pathology and Cytology, University Hospital Centre Zagreb, Croatia

³Department of Laboratory Diagnostics, University Hospital Centre Zagreb, Croatia

⁴Division of Hematology, Department of Internal Medicine, University Hospital Centre Zagreb, Croatia

ABSTRACT

In chronic lymphocytic leukemia, tumor flare reactions, characterized by sudden increase in tumor lesions caused by host immune effector cell infiltration, have been described exclusively after treatment with immunomodulators, most frequently lenalidomide. Here we describe a patient who had recurrence of tumor flare 6 years after the initial event, during treatment with rituximab and chemotherapy. This case report suggests that lenalidomide causes a long-lasting effect on lymph node microenvironment and host T cells.

KEYWORDS: Tumor flare reaction; Chronic lymphocytic leukemia; Rituximab; Lenalidomide

ABBREVIATIONS: CLL: Chronic Lymphocytic Leukemia; TRF: Tumor Flare Reaction

INTRODUCTION

Tumor flare reaction (TRF) is an increase in tumor lesion size, caused by sudden and massive infiltration of tumor by host effector cells, easily mistaken for disease progression [1]. In hematological diseases it has been most frequently described during treatment with immunomodulatory drugs lenalidomide and thalidomide [2-4]. Pathophysiology of TRF is still poorly understood. It is hypothesized that immunomodulatory drugs activate the host immune system's T-cell mediated immune response. Treatment of TRF is symptomatic with non-steroidal anti-inflammatory drugs and corticosteroids. Due to similarities with tumor progression, careful evaluation is needed, but once tumor progression is excluded, same anti-tumor therapy may be continued. In chronic lymphocytic leukemia (CLL)

TRF presents with enlarged painful tender lymph nodes with rash and low-grade fever usually occurring in lymph nodes primary enlarged due to tumor infiltration. We present a case report of a patient with CLL who developed two tumor flare reactions in the same lymph node 6 years apart, the first after lenalidomide and the second after rituximab treatment.

CASE PRESENTATION

A 73-year-old Caucasian female with progressive CLL was started on lenalidomide 2.5 mg daily. After 2 days, fever and painful massive swelling of cervical lymph nodes and pharyngeal Waldeyer's ring lymphatic tissue occurred. Fine needle aspirate of

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Address for correspondence: Igor Aurer, Division of Hematology, Department of Internal Medicine, University Hospital Centre Zagreb, Croatia

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affected lymph nodes confirmed a tumor flare reaction. Ibuprofen did not sufficiently alleviate the symptoms, the patient received steroids, lenalidomide was stopped and treatment with rituximab and chlorambucil initiated, resulting in remission. After 5.5 years progressive lymphadenopathy and splenomegaly occurred. Evaluation confirmed CLL progression. Due to long first remission, a decision to repeat treatment with chlorambucil and rituximab was made. She received her first dose of rituximab 70 months after the initial tumor flare reaction. Three weeks later, while on prophylactic acyclovir, she developed fever, painful swelling of lymph nodes in cervical regions 1 and 2, edema of pharyngeal mucosa and aftous stomatitis, consistent with a tumor flare reaction. At that time her neutrophil count was $2,7 \times 10^9/l$, and her lymphocyte count dropped from pretreatment 14.3 to $0.5 \times 10^9/l$, with less than 1% being B-cells. No pathogenic bacteria nor fungi were isolated from swabs. Antimicrobial treatment was ineffective, but the patient promptly responded to steroids. Treatment with rituximab and chlorambucil was continued and a 2nd remission achieved uneventfully.

DISCUSSION

We performed a search of PubMed and found that all reported tumor flare reactions in CLL patients occurred during treatment with lenalidomide. No reports were related to rituximab and chlorambucil treatment. We hypothesize that this tumor flare reaction is related to previous exposure to lenalidomide. The study of Strati et al shows that clinical effects of lenalidomide persist long after its discontinuation [5], possibly due to interactions between CLL cells and the immune microenvironment. Lenalidomide activates the host immune system by activating CD8+ cytotoxic T lymphocytes and downregulating regulatory T-cell suppressor function [6,7]. It also enhances antitumor immune responses mediated by NK and CD4+ T cells [8]. Lenalidomide promotes CD154 expression on CLL cells and enhances production of antibodies by normal B cells through a PI3-kinase-dependent pathway [9]. These effects on the host immune system are long-lasting. Our patient developed her second tumor flare reaction in the same lymphatic region 71 months after the first one, consistent with a possible long lasting lenalidomide effect on lymph node microenvironment and host T cells triggered by tumor cell destruction caused by immunochemotherapy.

CONCLUSION

In conclusion, this case report suggests that the immune effects of lenalidomide causing TFR might be permanent and be

triggered by local tumor cell destruction by other agents besides immunomodulators.

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CONFLICT OF INTEREST

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REFERENCES

1. Taleb AB (2019) Tumour flare reaction in cancer treatments: a comprehensive literature review. *Anti-Cancer Drugs* 30: 954-958.
2. Chanan-Khan A, Miller KC, Takeshita K, Koryzna A, Donohue K, et al. (2005) Results of a phase 1 clinical trial of thalidomide in combination with fludarabine as initial therapy for patients with treatment-requiring chronic lymphocytic leukemia (CLL). *Blood* 106: 3348-3352.
3. Chanan-Khan AA, Chitta K, Ersing N, Paulus A, Masood A, et al. (2011) Biological effects and clinical significance of lenalidomide-induced tumour flare reaction in patients with chronic lymphocytic leukaemia: in vivo evidence of immune activation and antitumour response. *Br J Haematol* 155: 457-467.
4. Andritsos LA, Johnson AJ, Lozanski G, Blum W, Kefauver C, et al. (2008) Higher doses of lenalidomide are associated with unacceptable toxicity including life-threatening tumor flare in patients with chronic lymphocytic leukemia. *J Clin Oncol* 26: 2519-2525.
5. Strati P, Ferrajoli A, Wierda WG, Jain N, Thompson PA, et al. (2018) Sustained long-lasting responses after lenalidomide discontinuation in patients with chronic lymphocytic leukemia. *Leukemia* 32: 2278-2281.
6. Ramsay AG, Johnson AJ, Lee AM, Gorgun G, Le Dieu R, et al. (2008) Chronic lymphocytic leukemia T cells show impaired immunological synapse formation that can be reversed with an immunomodulating drug. *J Clin Invest* 118: 2427-2437.
7. Ramsay AG, Evans R, Kiaii S, Svensson L, Hogg N, et al. (2013) Chronic lymphocytic leukemia cells induce defective LFA-1-directed T-cell motility by altering Rho GTPase signaling that is reversible with lenalidomide. *Blood* 121: 2704-2714.
8. Acebes-Huerta A, Huergo-Zapico L, Gonzalez-Rodriguez AP, Fernandez-Guizan A, Payer AR, et al. (2014) Lenalidomide induces immunomodulation in chronic lymphocytic leukemia and enhances antitumor immune responses mediated by NK and CD4 T cells. *Biomed Res Int* 2014: 265840.
9. Lapalombella R, Andritsos L, Liu Q, May SE, Browning R, et al. (2010) Lenalidomide treatment promotes CD154 expression on CLL cells and enhances production of antibodies by normal B cells through a PI3-kinase-dependent pathway. *Blood* 115: 2619-2629.