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Cytomegalovirus Reactivation in a Patient With Extensively Pretreated Multiple Myeloma During Daratumumab Treatment

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Clinical Practice Points

- We report a case of symptomatic cytomegalovirus (CMV) reactivation upon initiation of daratumumab monotherapy treatment in a heavily pretreated patient with multiple myeloma (MM).
- In patients with MM, the risk of CMV reactivation is increased following autologous stem cell transplantation.
- Limited data is available on the incidence of CMV reactivation in patients with MM who did not receive a stem cell transplantation.
- To our knowledge, this is the first report of a symptomatic CMV reactivation during daratumumab monotherapy treatment.
- Although routine monitoring for CMV is not recommended, the possibility of a CMV reactivation should be considered in patients with MM treated with daratumumab and infectious symptoms that cannot otherwise be explained.

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Case Report

We present the case of a 57-year-old woman with a symptomatic cytomegalovirus (CMV) infection during daratumumab monotherapy treatment for relapsed/refractory multiple myeloma (MM).

The patient was diagnosed with monoclonal gammopathy of unknown significance in 2001, which progressed to smoldering MM in 2005, and to symptomatic MM requiring systemic treatment in 2010. In August 2017, the disease relapsed again, being refractory to immunomodulatory agents (thalidomide, lenalidomide, and pomalidomide), bortezomib, and alkylators (melphalan, cyclophosphamide), as well as the SLAMF7-targeting antibody elotuzumab at that time. Daratumumab monotherapy (16 mg/kg) was initiated as seventh line of treatment. After 2 infusions, she presented with fever. History and physical examination revealed no signs of infection. Blood, urine, and sputum cultures were negative for microorganisms. Chest x-ray showed no pulmonary infiltrates. She was treated empirically with broad-spectrum antibiotics, amoxicillin/clavulanate, for 1 week, and the peripherally inserted central venous catheter was removed. No pathogens were cultured on the tip.

Because of persisting fever, additional diagnostic tests were performed. Repeated laboratory examinations showed no abnormalities, and there was no evidence for mycobacterial disease or respiratory viruses (influenza virus A/B, metapneumovirus, respiratory syncytial virus, parainfluenza virus [types 1-4], rhinovirus, and coronavirus). A computed tomography scan of the chest and abdomen, as part of the diagnostic workup of fever of unknown origin, revealed no explanation for her symptoms. Meanwhile, her clinical condition deteriorated with the development of night sweats, anorexia, weight loss (5 kg), and fatigue. At this time, her platelet count (131 to 53 $\times$ 10^9/L) and hemoglobin level (8.0 to 6.3 mmol/L) decreased in the absence of neutropenia. Upon the development of chills, 3 weeks after she first reported fever, she was admitted to the hospital. Repeated cultures of blood, urine, and sputum remained negative for microorganisms. Given the persistence of fever, her immunocompromised status, and, at this point, inconclusive workup, we analyzed the potential reactivation of viral infections. Epstein-Barr virus DNA was not present in blood samples. However, high levels of CMV-DNA were detected in blood by quantitative polymerase chain reaction assay (> 100.000 copies/mL) indicating a symptomatic CMV infection. There was no CMV end-organ disease such as pneumonitis or hepatitis. She reported abdominal discomfort and diarrhea coinciding with the onset

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of fever, suggesting a possible CMV-colitis. However, because she refused endoscopic evaluation, this diagnosis could not be confirmed. Importantly, serologic antibody tests in 2010 already showed positivity for CMV-specific IgG, indicating CMV reactivation and not primary infection in the current situation.[1] Treatment with intravenous ganciclovir 5 mg/kg twice daily was initiated, resulting in normalization of her temperature within 24 hours. After 48 hours, the CMV-DNA load decreased to 58.000 copies/mL. She was discharged with continuation of valganciclovir orally 900 mg twice daily, and 2 months after diagnosis, the CMV-DNA load was repeatedly below the detection limit (< 500 copies/mL) and eventually became negative. Her symptoms did not recur, while at the same time, platelet counts and hemoglobin levels returned to baseline values and her diarrhea resolved.

When this symptomatic CMV reactivation occurred, the patient had already achieved a partial response to daratumumab treatment. Owing to her extensive MM treatment history, alternative treatment options were limited, and would all induce additional immunosuppression. This, in combination with the rapid response to ganciclovir treatment, led to the decision to continue daratumumab according to the recommended schedule with regular monitoring of CMV-DNA load. At the same time, dexamethasone, which was given as infusion-related reaction prophylaxis, was tapered. She achieved a very good partial response with a duration of 7 months, during which her CMV DNA-load remained negative.

Discussion

Here, we describe a patient who suffered from a symptomatic CMV infection upon initiation of daratumumab monotherapy treatment.

The risk of recurrent CMV infection is increased in immunocompromised patients, such as patients with primary immunodeficiencies or HIV infection, solid organ transplant recipients, and patients on hemodialysis.[2] In patients with hematologic disorders, the risk of CMV infection is markedly increased following allogeneic stem cell transplantation or autologous stem cell transplantation (ASCT) with $CD34^+$-selected cells, as well as following treatment with high-dose corticosteroids, alemtuzumab, cladribine, or fludarabine, as a result of lower levels and dysfunction of natural killer (NK) cells, $CD8^+$ T-cells, and $CD4^+$ T-cells.[2-4]

Patients with MM have increased susceptibility to infections as a result of myeloma-induced immune dysfunction, including impaired T- and NK-cell activity, and decreased polyclonal immunoglobulin production, as well as cumulative immunosuppression of anti-MM treatment regimens.[5] The incidence of CMV DNAemia, defined as presence of CMV-DNA without CMV-related symptoms,[1] and CMV disease in patients with MM are best studied following ASCT. In prospective studies, the incidence of CMV-DNAemia without CMV-related symptoms post-ASCT ranges from 14.7% to 42.3%. Given the low rate of patients with CMV-DNAemia that develop a symptomatic CMV infection, prospective monitoring of CMV titers in these patients is not recommended.[3] When CMV-DNA quantification was performed on clinical indication, the rate of symptomatic CMV infection post-ASCT ranges from 0.7% to 30.7%.[3] Bortezomib-containing induction regimens are associated with a higher incidence of CMV reactivation post-ASCT.[3,6,7]

Daratumumab is a monoclonal IgG kappa antibody targeting CD38, which is highly and ubiquitously expressed on MM cells. Daratumumab induces killing of tumor cells via classical Fc-dependent immune effector mechanisms.[8] Furthermore, daratumumab depletes regulatory T-cells, regulatory B-cells, and myeloid-derived suppressor cells, leading to increased T-cell numbers and clonal T-cell expansion, which may result in an improved host–anti-tumor immune response.[9] Daratumumab has high single-agent efficacy in heavily pretreated patients with MM who have relapsed from and/or are refractory to immunomodulatory agents and proteasome inhibitors,[10,11] and combines well with several standards of care.[12,13]

During daratumumab monotherapy, infection-related serious adverse events occurred in 10% of patients treated in the GEN501 trial.[11] In a similar trial, 2 patients out of 106 discontinued treatment owing to H1N1 infections.[10] When daratumumab is combined with bortezomib-dexamethasone, the incidence of grade ≥ 3 infections is slightly higher compared with daratumumab monotherapy, but similar to the bortezomib-dexamethasone control group (21.4% compared with 19.0%), whereas in patients treated with daratumumab and lenalidomide-dexamethasone, this risk was higher compared with lenalidomide-dexamethasone alone (28.3% vs. 22.8%). In these studies, the incidence of pneumonia did not differ between patients treated with a daratumumab-based combination and those treated with lenalidomide-dexamethasone or bortezomib-dexamethasone alone.[12,13] Until now, no CMV infections have been reported during daratumumab monotherapy treatment.

The CMV reactivation in this patient is thought to be the result of the cumulative immunosuppressive effects of prior MM treatment in combination with daratumumab-mediated effects. Indeed, additional investigations performed directly after the diagnosis of CMV reactivation, showed very low $CD4^+$ T-cell (50×10^3/mL; reference value, 404-1612 $\times 10^3$/mL) and B-cell counts (0.21×10^3/mL; reference value, 114-436 $\times 10^3$/mL), probably as a result of treatment with pomalidomide plus low-dose cyclophosphamide and dexamethasone prior to daratumumab therapy (Table 1). In addition, daratumumab has been shown to rapidly decrease NK cell counts, which occurred in all patients and is already evident after the

Table 1 Peripheral Blood Immunophenotyping at Time of CMV Infection

	Measured Value	Reference Value
Absolute leukocyte count	3.0 $\times 10^6$/mL	3.0-10.0 $\times 10^6$/mL
Absolute lymphocyte count	0.3 $\times 10^6$/mL	0.6-2.9 $\times 10^6$/mL
Lymphocyte subsets		
T-cells	297 $\times 10^3$/mL	700-2100 $\times 10^3$/mL
$CD4^+$ T-cells	50 $\times 10^3$/mL	404-1612 $\times 10^3$/mL
$CD8^+$ T-cells	216 $\times 10^3$/mL	216-499 $\times 10^3$/mL
B-cells	0.21 $\times 10^3$/mL	114-436 $\times 10^3$/mL
NK cells	1.2 $\times 10^3$/mL	100-400 $\times 10^3$/mL
CD4/CD8 ratio	0.2	1.0-3.6

Abbreviations: CMV = cytomegalovirus; NK = natural killer.

first infusion.[14,15] Indeed, our patient had a low number of circulating NK cells in peripheral blood (1.2×10^3/mL; reference value, 100-400 $\times$ 10^3/mL) (Table 1).

To further characterize potential CMV reactivation during daratumumab treatment, we performed a quantitative CMV-DNA polymerase chain reaction in a cross-sectional manner in 19 patients with relapsed/refractory MM (median of 4 prior lines of treatment; range, 2-11) treated with daratumumab as a single agent. There was no CMV-DNAemia in these patients. Altogether, routine screening of CMV does not seem beneficial in patients treated with daratumumab. However, the possibility of a CMV reactivation should be taken into consideration in case of unexplained fever or bone marrow suppression, such as occurred in our patient, or signs suggestive of CMV end-organ disease.

Conclusion

In conclusion, to the best of our knowledge, we report for the first time a patient who developed fever, diarrhea, anemia, and thrombocytopenia owing to CMV reactivation during daratumumab monotherapy treatment, which was associated with low T-cell and NK cell counts. We currently do not recommend routine screening for CMV in patients with MM during daratumumab treatment. However, CMV reactivation should always be considered in patients with MM treated with daratumumab or other novel agents with immunosuppressive effects, who develop fever or other complaints that cannot be otherwise explained.

Disclosure

S. Zweegman serves in advisory boards for Celgene, Janssen Pharmaceuticals, Takeda, Amgen, and Sanofi; and received research funding from Celgene, Janssen Pharmaceuticals and Takeda. NWCJ van de Donk serves in advisory boards for Janssen Pharmaceuticals, Celgene, Amgen, Novartis, Bayer, and Servier; and received research support from Janssen Pharmaceuticals, Celgene, Amgen, and BMS. All other authors state that they have no conflicts of interest.

References

1. Ljungman P, Boeckh M, Hirsch HH, et al. Definitions of cytomegalovirus infection and disease in transplant patients for use in clinical trials. *Clin Infect Dis* 2017; 64:87-91.
2. Styczynski J. Who is the patient at risk of CMV recurrence: a review of the current scientific evidence with a focus on hematopoietic cell transplantation. *Infect Dis Ther* 2018; 7:1-16.
3. Marchesi F, Pimpinelli F, Ensoli F, Mengarelli A. Cytomegalovirus infection in hematologic malignancy settings other than the allogeneic transplant. *Hematol Oncol* 2018; 36:381-91.
4. Drylewicz J, Schellens IM, Gaiser R, et al. Rapid reconstitution of CD4 T cells and NK cells protects against CMV-reactivation after allogeneic stem cell transplantation. *J Transl Med* 2016; 14:230.
5. Schutt P, Brandhorst D, Stellberg W, et al. Immune parameters in multiple myeloma patients: influence of treatment and correlation with opportunistic infections. *Leuk Lymphoma* 2006; 47:1570-82.
6. Hasegawa T, Aisa Y, Shimazaki K, Ito C, Nakazato T. Cytomegalovirus reactivation in patients with multiple myeloma. *Eur J Haematol* 2016; 96: 78-82.
7. Marchesi F, Mengarelli A, Giannotti F, et al. High incidence of post-transplant cytomegalovirus reactivations in myeloma patients undergoing autologous stem cell transplantation after treatment with bortezomib-based regimens: a survey from the Rome transplant network. *Transpl Infect Dis* 2014; 16:158-64.
8. van de Donk NWCJ, Richardson PG, Malavasi F. CD38 antibodies in multiple myeloma: back to the future. *Blood* 2018; 131:13-29.
9. Krejcik J, Casneuf T, Nijhof IS, et al. Daratumumab depletes CD38+ immune regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma. *Blood* 2016; 128:384-94.
10. Lonial S, Weiss BM, Usmani SZ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. *Lancet* 2016; 387:1551-60.
11. Lokhorst HM, Plesner T, Laubach JP, et al. Targeting CD38 with daratumumab monotherapy in multiple myeloma. *N Engl J Med* 2015; 373:1207-19.
12. Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med* 2016; 375:1319-31.
13. Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. *N Engl J Med* 2016; 375:754-66.
14. Krejcik J, Frerichs KA, Nijhof IS, et al. Monocytes and granulocytes reduce CD38 expression levels on myeloma cells in patients treated with daratumumab. *Clin Cancer Res* 2017; 23:7498-511.
15. Casneuf T, Xu XS, Adams H 3rd, et al. Effects of daratumumab on natural killer cells and impact on clinical outcomes in relapsed or refractory multiple myeloma. *Blood Adv* 2017; 1:2105-14.