frontiers | Frontiers in Hematology

TYPE Case Report
PUBLISHED 20 October 2022
DOI 10.3389/frhem.2022.1035281

OPEN ACCESS

EDITED BY
Alessandro Gozzetti,
University of Siena, Italy

REVIEWED BY
Daniele Derudas,
Ospedale Oncologico Armando Businco, Italy
Srinivas Devarakonda,
The Ohio State University, United States

*CORRESPONDENCE
Elisabetta Antonioli
elisabettaantonioli@libero.it

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Blood Cancer, a section of the journal Frontiers in Hematology

RECEIVED 02 September 2022
ACCEPTED 03 October 2022
PUBLISHED 20 October 2022

CITATION
Palazzo M, Ciolli G, Pilerci S, Attucci I, Pengue L, Vannucchi AM and Antonioli E (2022) Case report: Unexpected parvovirus B19 infection in a myeloma patient treated with daratumumab.
Front. Hematol. 1:1035281.
doi: 10.3389/frhem.2022.1035281

Case report: Unexpected parvovirus B19 infection in a myeloma patient treated with daratumumab

Marianna Palazzo[1†], Gaia Ciolli[1†], Sofia Pilerci[1], Irene Attucci[1], Ludovica Pengue[1], Alessandro Maria Vannucchi[1,2] and Elisabetta Antonioli[2*]

[1]Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy, [2]Haematology Department, Careggi Hospital, Florence, Italy

Multiple myeloma patients have an increased risk of infections due to both the inherent nature of the disease and ongoing treatment. We describe the case of a patient who was treated with daratumumab-lenalidomide-dexamethasone regimen for two years and developed a parvovirus B19 infection. The clinical picture, characterized by trilinear cytopenia, was initially attributed to anti-neoplastic treatment. Later on, when the patient's condition worsened, an extensive diagnostic workup was applied and parvovirus B19 infection was detected by PCR. Due to the lack of effective antiviral drugs, the patient received IV immunoglobulins and it took 10 days to achieve a decrease in viral copies. Physicians should be aware that recent changes in the therapeutic scenario of multiple myeloma would make patients more susceptible to atypical infections in this patient setting.

KEYWORDS

multiple myeloma, daratumumab, immunotherapy, parvovirus B19 (B19), infection

Introduction

Infections are a significant cause of morbidity and a leading cause of death in multiple myeloma (MM) patients (1). The increased risk of infectious complications is associated with both inherent disease-related immunodeficiency –involving B-cell dysfunction, such as hypogammaglobulinemia, as well as T-cell, dendritic cell, and NK-cell abnormalities (2)– and therapy-related alterations in the immune status. In addition, a changing spectrum of infections has been recently described, probably due to novel treatment approaches for MM (3). Daratumumab is a human anti-CD38 monoclonal antibody (mAb) initially approved in patients with Relapsed/Refractory MM (RRMM) as monotherapy (4) and subsequently in combination with proteasome inhibitors (PIs, Dara-Vd) (5) or with immunomodulatory

drugs (IMiDs, Dara-Rd) (6); currently, it is also employed for the treatment of newly diagnosed patients with MM (7, 8). The association between daratumumab-containing regimens and the development of infections has been repeatedly investigated (9). Recently, two retrospective real-world studies have focused on infectious complications after daratumumab administration in patients with MM, reporting approximately 40% bacterial, 60% viral and 3% fungal and parasitic infections (10, 11). Exogenous viruses such as Respiratory Syncytial Virus or Metapneumovirus, and Herpes Virus reactivations (Cytomegalovirus, VZV and HSV) were the most frequently among viral infections (9). This figure data has been recently confirmed by the data from Food and Drug Administration's Adverse Events Reporting System (FAERS), a pharmacovigilance monitoring database that reported Herpes Zoster as the most common infectious event during daratumumab therapy (25,1%), followed by CMV reactivation (22.0%) (12).

Herein we present the case of a 50-year-old man with an unexpected Parvovirus B19 infection during Dara-Rd treatment for RRMM.

Case description

The patient was diagnosed in 2016 with IgG lambda MM complicated by Light Chain (AL) Amyloidosis with renal and cardiac involvement. The disease was defined as R-ISS stage III due to b2-microglobulin level of 18 mg/L and the presence of translocation t(4;14) detected by fluorescent *in situ* hybridization (FISH) analysis. The patient was treated with bortezomib-based regimen with subsequent single autologous stem cell transplantation, obtaining a stringent complete response (sCR). Despite the cytogenetic risk of the disease, considering the cardiovascular risk and the renal function impairment due to AL Amyloidosis, the patient did not proceed to a second transplant procedure.

In November 2019, the disease relapsed, and a treatment with daratumumab-lenalidomide-dexamethasone (Dara-Rd) was started with rapid achievement of a sCR. In September 2021, after two years of Dara-Rd treatment, the patient developed pancytopenia characterized by G3 neutropenia, mild anemia (Hb 10.1 gr/dl) and G1 thrombocytopenia. The pathogenesis of pancytopenia was initially attributed to the toxicity of lenalidomide; on this basis, the treatment was withdrawn, and a slow recovery of blood values was observed. In November 2021, Dara-Rd treatment was reintroduced, again with a rapid worsening of all blood count parameters. Moreover, the patient presented with fever, cough, vomiting and diarrhea. SARS-CoV2 PCR test was negative. Physical examination was normal. Blood and urine cultures were negative. Chest x-ray showed no pulmonary infiltrates. A transient amelioration was obtained with broad-spectrum antibiotics, again followed Performance Status deterioration, accompanied by pallor and asthenia. In February 2022 blood tests revealed anemia (Hb 7.6 g/dL), severe neutropenia (ANC 0.17x10 (9)/L) and thrombocytopenia (PLT 67x109/L). The patient required RBC transfusions and G-CSF stimulation. A diagnostic workup for acute pancytopenia was initiated. Peripheral blood smear did not show morphological abnormalities. Haemolytic markers were negative, and a low reticulocyte count was revealed without any vitamin deficiency. Viral infections were investigated by quantitative polymerase chain reaction (PCR) assay. EBV, CMV and HHV6 tested negative, whereas high levels of Parvovirus-B19 DNA (1,559,000 copies/ml) were detected. Anti-Parvovirus B19 IgM and IgG were both positive. Low absolute lymphocyte count (0.4x10 (9)/L) and low IgG level (2.7 g/L) were revealed. A decrease in the CD4/CD8 ratio, as the result of the reduction of CD4+ lymphocytes, and a depression of B-lymphocytes and NK-cells, with a relative increase in activated T lymphocytes, were documented by flow cytometry. The patient was treated with intravenous immunoglobulin (IVIG) 0.4 gr/kg for 5 days obtaining only a slight reduction in copies of Parvovirus-B19 (1,151,000 copies/ml). The treatment with IVIG was thus repeated for another 5 days, obtaining a slow reduction in viral copies (600,000 copies/ml). The patient's performance status rapidly improved, as did the laboratory tests (Table 1). Parvovirus-B19 viral load was monitored monthly, with progressive decrease to 43,000 copies/ml (after one month) and 714 copies/ml the following. Based on clinical and haematological recovery, in May 2022 Dara-Rd was resumed in association with monthly subcutaneous IG anti-infective prophylaxis. Finally in June 2022 only a few copies of the viral load were found. Treatment with Dara-Rd is still ongoing and the patient is on continuous sCR Figure 1.

TABLE 1 Blood values during ParvovirusB19 infection.

Lab. parameters	Dec 2021	Feb 2022	Mar 2022	Apr2022	May 2022	Jun 2022	Jul 2022
HB (GR/DL)	12.1	7.6	10.8*	11.5	13.1	13.1	13.4
Reticulocytes (%)	1,5	0,1	0,7	1,2	2,2	2,2	2,4
Neutrophils (x10^9)	2,25	0,17	1,27	1,99	2,17	1,95	2,09
Lymphocytes (x10^9)	0,52	0,4	0,7	1,37	1,14	1,24	1,25
Platelets (x10^9)	135	67	72	75	91	85	90
IgG (g/L)	4,03	2,53	7,53	13,4	9,37	7,67	6,8

10.3389/frhem.2022.1035281

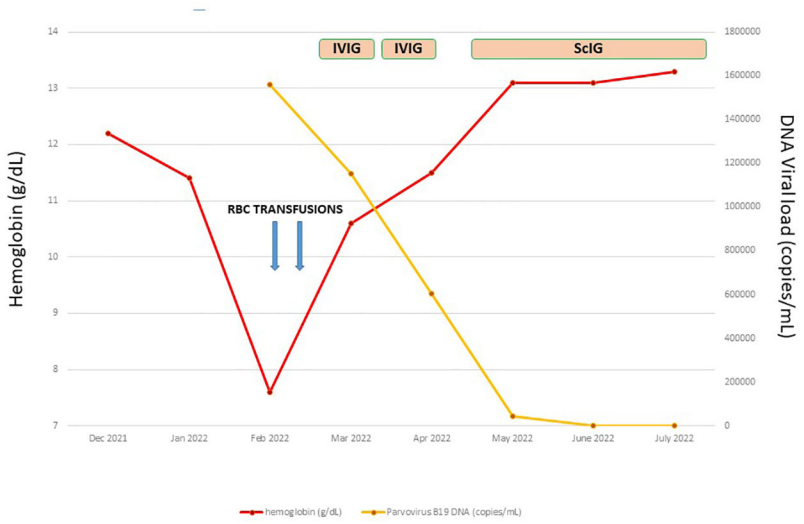

FIGURE 1
The progressive changes in hemoglobin [Hb] (on the left y-axis) and ParvovirusB19 viral load (on the right y-axis) in samples collected at different times during infection. Clinically relevant events are marked on the top of the figure.

Results and discussion

The most common Parvovirus B19 clinical manifestation in the immunocompromised host is pure red-cell aplasia (PRCA), characterized by chronic or recurrent hypo-regenerative anemia. However, bone marrow involvement can also extend to neutropenia and thrombocytopenia, as it did in our patient, until neutralizing antibodies are produced by the host or passively administered. The standard diagnostics of Parvovirus B19 infection relies on serology with detection of specific IgM and IgG antibodies. However, immunocompromised patients may fail to develop antibodies, thus making detection of parvovirus B19 DNA by PCR of paramount importance in these patients. To date, no specific antiviral treatment is available and IVIGs represent the standard of care. The optimal dose and duration of IVIGs have not been established, and a regimen of 0.4 g/kg/day for five to ten days has been suggested (13). After treatment, patients should be closely monitored and monthly maintenance with IG may be indicated in selected cases as PRCA may recur once passive antibodies disappear. To date, cases of Parvovirus B19 infection in MM patients have been described exclusively in the setting of bone marrow transplantation. In particular, few episodes of chronic PRCA have been documented after allogeneic-SCT (14, 15) and five cases of Parvovirus B19-induced pancytopenia after autologous-SCT have been reported (16).

As mentioned before, treatment with daratumumab has been shown in both clinical trials and real-life setting to be associated with an increased risk of infections, mainly due to frequent neutropenia and lymphopenia during treatment but also direct depletion of NK cells and other CD38-expressing immune cells involved in the control of pathogens (17). Patients are highly susceptible to bacterial and viral infections, especially upper respiratory tract infections and pneumonia. Anecdotal cases of atypical infections such as HVZ, CMV or EBV reactivation, pneumocystis jirovecii pneumonia (PJP), progressive multifocal leukoencephalopathy (PML), bronchopulmonary aspergillosis, fungal meningitis, listeriosis and disseminated cryptococcosis have been described (18, 19). As expected, infections occur more frequently in patients with higher-grade neutropenia, lymphopenia and hypogammaglobulinemia, particularly in patients heavily pretreated and treated with combination regimens. Another important infectious consideration is the reactivation potential of hepatitis B virus (HBV) related to drug-associated natural killer (NK) cell depletion and suppression of humoral immunity (20).

Consistently, our patient developed lymphopenia and hypogammaglobulinemia on chronic treatment with daratumumab. Initially, the infection was missed, as cytopenia in the absence of other symptoms was considered secondary to drug toxicity. Only later, the worsening of the patient's general condition, the transfusion need and the appearance of new systemic symptoms prompted further investigations. We were unable to classify the event as a primary infection or reactivation as the previous serological status for Parvovirus-B19 was unknown. Depression of B-lymphocytes and NK cells, with an increase in activated T lymphocytes, represented an immunological state consistent with prolonged exposure to daratumumab, as previously described (10). Our case report suggests the importance of performing an accurate diagnostic

workup for acute pancytopenia in patients with MM undergoing treatment with monoclonal antibodies. Once the toxic effects of known drugs have been excluded, it is suggested to consider hemolytic causes and vitamin or iron deficiency. A peripheral blood smear may also be useful to evaluate any morphological changes in erythrocytes and rule out the presence of immature cells. At this point it is of fundamental importance to investigate the infectious causes by performing blood tests including C-reactive protein, erythrocyte sedimentation rate, ferritin, fibrinogen and blood cultures even in the absence of fever. A chest x-ray and abdominal ultrasound can be helpful in setting up the diagnosis. The search for viral infections by quantitative assay of the polymerase chain reaction (PCR) is therefore recommended, mainly for CMV, EBV, HBV, HCV but also more atypical infections such as HHV6, Adenovirus and Parvovirus-B19. As a last step, it may be necessary to perform a bone-marrow biopsy to rule out the presence of immature cells or haemophagocytosis. The current therapeutic scenario in multiple myeloma is constantly evolving with multi-agent composite therapeutic strategies. The introduction of new drugs is dramatically changing. the epidemiology of infections in MM patients and mandates for an accurate estimation of relative risks as well as the adoption of adequate protocols for monitoring, prophylaxis and treatment, even more considering the impact of new drugs on the homeostasis of the immune system.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

EA were responsible of the study design, collected the clinical data and wrote the report. GC and MP collected the clinical data and wrote the report. IA, LP, SP and AV contributed to the critical review and finalised the report. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Kyle RA, Rajkumar SV. Multiple myeloma. *N. Engl. J. Med.* (2004) 351:1860–73. doi: 10.1056/NEJMra041875

2. Pratt G, Goodyear O, Moss P. Immunodeficiency and immunotherapy in multiple myeloma. *Br. J. Haematol.* (2007) 138:563–79. doi: 10.1111/j.1365-2141.2007.06705.x

3. Blimark C, Holmberg E, Mellqvist UH, Landgren O, Björkholm M, Hultcrantz M, et al. Multiple myeloma and infections: a population-based study on 9253 multiple myeloma patients. *Haematologica* (2015) 100(1):107–13. doi: 10.3324/haematol.2014.107714

4. Lonial S, Weiss BM, Usmani SZ, Singhal S, Chari A, Bahlis NJ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): An open-label, randomised, phase 2 trial. *Lancet* (2016) 387 (10027):1551–60. doi: 10.1016/S0140-6736(15)01120-4

5. Palumbo A, Chanan-Khan A, Weisel K, Nooka AK, Masszi T, Beksac M, et al. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. *N. Engl. J. Med.* (2016) 375(8):754–66. doi: 10.1056/NEJMoa1606038

6. Dimopoulos MA, Oriol A, Nahi H, San-Miguel J, Bahlis NJ, Usmani SZ, et al. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. *N. Engl. J. Med.* (2016) 375(14):1319–31. doi: 10.1056/NEJMoa1607751

7. Facon T, Kumar S, Plesner T, Orlowski RZ, Moreau P, Bahlis N, et al. Daratumumab plus lenalidomide and dexamethasone for untreated myeloma. *N. Engl. J. Med.* (2019) 380(22):2104–15. doi: 10.1056/NEJMoa1817249

8. Mateos M-V, Dimopoulos MA, Cavo M, Suzuki K, Jakubowiak A, Knop S, et al. Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma. *N. Engl. J. Med.* (2018) 378(6):518–28. doi: 10.1056/NEJMoa1714678

9. Girmenia C, Cavo M, Corso A, Di Raimondo F, Musto P, Offidani M, et al. Management of infectious risk of daratumumab therapy in multiple myeloma: A consensus-based position paper from an. *ad hoc Ital. Expert panel Crit. Rev. Oncol. Hematol.* (2022) 172:103623. doi: 10.1016/j.critrevonc.2022.103623

10. Nahi H, Chrobok M, Gran C, Lund J, Gruber A, Gahrton G, et al. Infectious complications and NK cell depletion following daratumumab treatment of multiple myeloma. *PloS One* (2019) 14:e0211927. doi: 10.1371/journal.pone.0211927

11. Johnsrud AJ, Johnsrud JJ, Susanibar SA, Kamimoto JJ, Kothari A, Burgess M, et al. Infectious and immunological sequelae of daratumumab in multiple myeloma. *Br. J. Haematol.* (2019) 185(1):187–9. doi: 10.1111/bjh.15433

12. Burns EA, Ensor JE, Anand K, Gentille C, Guerrero C, Kieser RB, et al. Opportunistic infections in patients receiving daratumumab regimens for multiple myeloma (MM). *Blood* (2021) 138(1):4740–0. doi: 10.1182/blood-2021-152068

13. Crabol Y, Terrier B, Rozenberg F, Pestre V, Legendre C, Hermine O, et al. Intravenous immunoglobulin therapy for pure red cell aplasia related to human parvovirus B19 infection: A retrospective study of 10 patients and review of the literature. *Clin Infect Dis* (2012) 56(7):968–77. doi: 10.1093/cid/cis1046

14. Koda Y, Mori T, Kato J, Kohashi S, Kikuchi T, Mitsuhashi T, et al. Persistent parvovirus B19 infection resulting in red cell aplasia after allogeneic hematopoietic

stem cell transplantation. *Transpl Infect Dis* (2013) 15(6):E239-42. doi: 10.1111/tid.12155

15. Karrasch M, Schmidt V, Hammer A, Hochhaus A, Rosée P, Petersen I, et al. Chronic persistent parvovirus B19 bone marrow infection resulting in transfusion-dependent pure red cell aplasia in multiple myeloma after allogeneic haematopoietic stem cell transplantation and severe graft versus host disease. *Hematology* (2016) 22(2):93–8. doi: 10.1080/10245332.2016.1183288

16. Katragadda L, Shahid Z, Restrepo A, Muzaffar J, Alapat D, Anaissie E, et al. Preemptive intravenous immunoglobulin allows safe and timely administration of antineoplastic therapies in patients with multiple myeloma and parvovirus B19 disease. *Transpl Infect Dis* (2013) 15(4):354–60. doi: 10.1111/tid.12067

17. Glaría E, Valledor AF. Cells roles of CD38 in the immune response to infection. (2020) 9(1):228. doi: 10.3390/cells9010228

18. Steinbach M, Julian K, McClune B, Sborov DW. Toxicity management strategies for next-generation novel therapeutics in multiple myeloma. *Ther. Adv. Hematol.* (2022) 13:1-22. doi: 10.1177/20406207221100659

19. Sato S, Kambe E, Tamai Y. Disseminated cryptococcosis in a patient with multiple myeloma treated with daratumumab, lenalidomide, and dexamethasone. *Intern. Med.* (2019) 58:843–7. doi: 10.2169/internalmedicine.1726-18

20. Mustafayev K, Torres H. Hepatitis b virus and hepatitis c virus reactivation in cancer patients receiving novel anticancer therapies. *Clin. Microbiol. Infect.* (2022) 28(10):1321–7. doi: 10.1016/J.CMI.2022.02.042