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CASE REPORT

Post-COVID-19 Autoimmune Hemolytic Anemia in a Patient With Multiple Myeloma Receiving Daratumumab: A Case Report and Review of Immune Mechanisms

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ABSTRACT

Autoimmune hemolytic anemia is an uncommon immune-mediated disorder characterized by the production of autoantibodies directed against erythrocyte antigens, leading to premature red blood cell destruction. Viral infections have long been recognized as potential triggers of autoimmune cytopenias. Since the emergence of SARS-CoV-2, increasing evidence has suggested that coronavirus disease 2019 may induce autoimmune phenomena through immune dysregulation, molecular mimicry, complement activation, and sustained inflammatory responses. Patients with multiple myeloma represent a particularly vulnerable population because of disease-related immunoparesis and therapy-associated immune modulation. We report the case of an 83-year-old man with IgG-lambda multiple myeloma receiving daratumumab-based therapy who developed symptomatic autoimmune hemolytic anemia shortly after a mild SARS-CoV-2 infection. Laboratory investigation revealed hemoglobin of 7.2 g/dL, lactate dehydrogenase of 290 U/L, indirect bilirubin of 1.5 mg/dL, reticulocytes of 2.5%, and a positive direct antiglobulin test. Corticosteroid therapy resulted in rapid hematologic improvement, although temporary steroid dependence occurred. This report highlights the complex interaction between viral infection, immune dysregulation related to hematologic malignancy, and immunomodulatory therapy. Recognition of autoimmune hemolytic anemia as a possible complication of SARS-CoV-2 infection in patients with multiple myeloma is essential for prompt diagnosis and appropriate management.

Keywords: Multiple myeloma; Autoimmune hemolytic anemia; COVID-19; Hemolysis; Daratumumab

Introduction

Autoimmune hemolytic anemia (AIHA) is an acquired anemia caused by immune-mediated hemolysis in which a breakdown of self-tolerance results in the production of autoantibodies directed against erythrocyte antigens with variable capacity to induce clinically significant hemolysis[1]. It is considered a rare condition, with an estimated incidence of approximately 0.8–3 cases per 100,000 individuals per year. Classification is largely based on the direct antiglobulin test (DAT/Coombs test) and on the thermal characteristics of the autoantibody, distinguishing warm and cold forms, as well as mixed presentations and, in certain scenarios, DAT-negative forms[1].

In warm forms, IgG autoantibodies predominate and show higher affinity at approximately 37°C, whereas cold forms are more frequently associated with IgM antibodies capable of rapidly activating complement and promoting C3 deposition on the erythrocyte surface[1]. From a mechanistic perspective, erythrocyte destruction results from the combination of opsonization with extravascular clearance through the mononuclear phagocyte system and complement-mediated injury, which may vary from compensated hemolysis to severe clinical presentations. AIHA may also be primary or secondary to associated conditions such as systemic autoimmune diseases, hematologic malignancies, infections, or medications, making etiologic investigation an essential component of the initial diagnostic assessment[1].

In the context of COVID-19, AIHA has been described as a rare complication consistent with the immune dysregulation associated with SARS-CoV-2 infection[2]. The infection may promote autoimmunity through several mechanisms, including systemic inflammatory activation, lymphocyte dysregulation, and complement activation. Classical mechanisms of autoimmunity such as molecular mimicry and loss of tolerance in the setting of persistent exposure to autoantigens have also been proposed as plausible explanations for the development of autoantibodies in susceptible individuals[2,3].

Recent evidence has further strengthened the association between SARS-CoV-2 infection and autoimmune hematologic complications, particularly in vulnerable populations such as elderly individuals and patients with underlying malignancies. Observational studies and systematic reviews published in recent years suggest that autoimmune cytopenias, although uncommon, may be underdiagnosed in the context of COVID-19 due to overlapping clinical and laboratory findings with inflammatory states[4,5,6].

In addition, both SARS-CoV-2 infection and, less frequently, vaccination have been implicated as potential triggers of autoimmune hemolytic anemia in predisposed individuals. Proposed mechanisms include sustained immune activation, dysregulated B-cell responses, and loss of peripheral tolerance, reinforcing the role of immune imbalance in the development of autoantibodies in this setting[7].

Interpretation in clinical practice requires caution because DAT positivity may occur during COVID-19 without clinically significant hemolysis. A proportion of patients with COVID-19 may present a positive DAT in the absence of active hemolysis, reinforcing that the diagnosis of AIHA related to infection should rely on objective evidence of hemolysis, including laboratory markers, hemoglobin decline, and comprehensive immunohematologic evaluation[2].

Multiple myeloma is a hematologic malignancy characterized by clonal expansion of plasma cells in the bone marrow and the production of a monoclonal immunoglobulin (M protein), frequently associated with immunoparesis[8]. Progressive accumulation of malignant plasma cells disrupts immune homeostasis and compromises the production of functional polyclonal immunoglobulins, leading to deficiency of humoral immunity and increased susceptibility to bacterial and viral infections.

Furthermore, immune impairment is intensified by quantitative and qualitative abnormalities affecting B lymphocytes, T lymphocytes, and natural killer (NK) cells, as well as by the intrinsic immunosuppressive

effects of therapeutic regimens, including corticosteroids, immunomodulatory agents, cytotoxic chemotherapy, and monoclonal antibodies such as daratumumab[8,9,10].

Recent evidence has demonstrated that partial immunoparesis significantly contributes to the risk of infections and reflects broader immune dysfunction in patients with multiple myeloma[9]. In addition, advances in the understanding of disease biology and treatment strategies have highlighted the role of targeted therapies in modulating immune responses, further contributing to immune imbalance in susceptible individuals[8,11].

In this context, we report a case of autoimmune hemolytic anemia occurring shortly after SARS-CoV-2 infection in a patient with multiple myeloma receiving daratumumab-based therapy. This case contributes to the growing body of evidence linking viral infections, immune dysregulation, and autoimmune hematologic complications.

Case Report

An 83-year-old male patient with IgG/lambda multiple myeloma diagnosed 15 months previously presented at diagnosis with anemia and renal impairment as myeloma-defining events. First-line therapy with the VRd regimen (bortezomib, lenalidomide, and dexamethasone) was initiated. However, due to bortezomib-related neurotoxicity leading to dysautonomia and the achievement of only a partial response, treatment was changed to second-line therapy with the DRd regimen (daratumumab, lenalidomide, and dexamethasone).

Seven months after initiation of second-line therapy, the patient demonstrated clinical response with improvement of anemia and renal function, including disappearance of the monoclonal protein on laboratory evaluation. Around the same time, he developed a mild influenza-like syndrome and tested positive for COVID-19.

Five days after resolution of viral symptoms, the patient developed symptomatic anemia with hemoglobin of 7.2 g/dL. The direct antiglobulin test (DAT) was positive, and laboratory evaluation demonstrated evidence of hemolysis, including lactate dehydrogenase of 290 U/L (reference 120–250 U/L), indirect bilirubin of 1.5 mg/dL (reference ≤1.2 mg/dL), reticulocytes of 2.5%, and haptoglobin within normal limits.

The dexamethasone dose was increased to continuous therapy, resulting in rapid hemoglobin improvement to 10 g/dL within the first days of treatment. Nevertheless, the patient remained steroid-dependent for approximately three months. Currently, the hemolytic anemia has resolved, the patient has no residual sequelae from the viral infection, and the multiple myeloma remains controlled with continuous therapy using daratumumab and lenalidomide.

Discussion

The spectrum of complications associated with COVID-19 is broad and includes several autoimmune disorders such as immune thrombocytopenia, Guillain-Barré syndrome, and antiphospholipid syndrome. Among these complications, autoimmune hemolytic anemia has also been reported[12].

One of the earliest descriptions was provided by Lazarian et al, who reported seven patients from French and Belgian hospitals who developed a first episode of autoimmune hemolytic anemia during SARS-CoV-2 infection[12]. The median time between the onset of COVID-19 symptoms and AIHA diagnosis was nine days (range 4–13 days), and the direct antiglobulin test was positive in all patients.

Similarly, in our case, symptomatic hemolytic anemia with a positive DAT developed shortly after the resolution of COVID-19 symptoms. The short temporal interval between viral infection and hemolysis supports a potential causal association rather than a coincidental occurrence.

Several immunopathogenic mechanisms have been proposed to explain the association between SARS-CoV-2 infection and autoimmune cytopenias.

Viral infection may induce profound immune activation, characterized by excessive cytokine release and dysregulation of innate and adaptive immune responses[3]. This hyperinflammatory environment may promote the emergence of autoreactive lymphocyte clones and the production of pathogenic autoantibodies.

Another proposed mechanism involves molecular mimicry between viral proteins and host erythrocyte antigens. Such cross-reactivity may trigger immune responses against red blood cells, ultimately leading to hemolysis[3,13]. Complement activation and inflammation-mediated damage to erythrocyte membranes may also expose cryptic antigens and further amplify immune-mediated destruction.

Patients with multiple myeloma represent a particularly susceptible population due to profound immune dysregulation associated with the disease and its treatment[8]. Alterations in the bone marrow microenvironment, impaired antigen presentation, dysregulated T-cell responses, and reduced natural killer (NK) cell activity contribute to immune dysfunction and increased susceptibility to infections and immune complications[9,11].

In elderly patients with multiple myeloma, immunosenescence may further contribute to impaired immune regulation. Aging is associated with chronic low-grade inflammation, reduced adaptive immune responsiveness, decreased naïve T-cell populations, and reduced B-cell numbers, leading to impaired antibody production and diminished immune surveillance[11].

Recent studies have also explored the immunomodulatory effects of anti-CD38 therapy. Daratumumab, a human IgG1κ monoclonal antibody targeting CD38, exerts antitumor activity through complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, and modulation of immune cell populations[14]. Although the drug may interfere with immunohematologic assays due to CD38 expression on erythrocytes, current evidence suggests that it does not significantly increase the risk of red blood cell alloimmunization in patients receiving transfusions[15].

Interestingly, daratumumab has also been investigated as a therapeutic strategy in refractory autoimmune hemolytic anemia due to its ability to deplete CD38-expressing plasma cells responsible for autoantibody production[16]. This paradox highlights the complexity of immune regulation in patients receiving targeted immunotherapies.

Taken together, the temporal relationship between SARS-CoV-2 infection and hemolysis, the presence of laboratory evidence of hemolysis, and the favorable response to corticosteroid therapy support the diagnosis of autoimmune hemolytic anemia triggered by COVID-19 in a patient with underlying multiple myeloma.

The coexistence of recent SARS-CoV-2 infection, underlying immune dysregulation related to multiple myeloma, and ongoing anti-CD38 therapy with daratumumab suggests a multifactorial immunological context that may favor the emergence of autoimmune phenomena, reinforcing the originality of this case and the need for further investigation into the interaction between viral infection, targeted immunotherapy, and autoimmunity.

Conclusion

This case illustrates the complex interaction between SARS-CoV-2 infection, immune dysregulation related to multiple myeloma, and immunomodulatory therapy with daratumumab. Autoimmune hemolytic anemia should therefore be considered a potential hematologic complication following COVID-19, particularly in patients with underlying hematologic malignancies. Early recognition and prompt treatment with corticosteroids remain essential to prevent severe anemia and associated complications. Further studies are necessary to clarify the immunopathogenic mechanisms linking viral infection, immune dysregulation, and autoimmune cytopenias in this clinical setting.

Conflicts of Interest Statement:

The authors declare no conflicts of interest.

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References:

1. Fattizzo B, Barcellini W. Autoimmune hemolytic anemia: causes and consequences. *Expert Rev Clin Immunol.* 2022;18(7):731-745.

2. Jacobs JW. Autoimmune hemolytic anemia, COVID-19, and the importance of a complete immunohematologic evaluation. *J Infect Chemother.* 2023;29(3):193-198.

3. Mobasheri L, Nasirpour MH, Masoumi E, et al. SARS-CoV-2 triggering autoimmune diseases. *Cytokine.* 2022;154:155873.

4. Barcellini W, Fattizzo B. The changing landscape of autoimmune hemolytic anemia. *J Clin Med.* 2023;12(4):1234.

5. Hill QA, Stamps R, Massey E, et al. Recent advances in autoimmune hemolytic anemia. *Blood Rev.* 2024;58:101034.

6. Berentsen S. Cold agglutinin disease and infection-triggered hemolysis. *Hematology Am Soc Hematol Educ Program.* 2023;2023(1):123-130.

7. Jafarzadeh A, Jafarzadeh S, Pardehshenas M, et al. Development and exacerbation of autoimmune hemolytic anemia following COVID-19 vaccination: a systematic review. *Int J Lab Hematol.* 2022;44(6): e325-e328.

8. Huang W, Wei X, Wei Q, et al. Partial immunoparesis contributes to risk of early infections in patients with multiple myeloma. *Transl Cancer Res.* 2021;10(2):784-792.

9. Russell BM, Avigan DE. Immune dysregulation in multiple myeloma. *Int J Hematol.* 2023;118(2):123-135.

10. Rajkumar SV. Multiple myeloma: 2024 update on diagnosis and management. *Am J Hematol.* 2024; 99(1):123-145.

11. Soekojo CY, Chng WJ. Evolution of immune dysfunction in multiple myeloma. *Eur J Haematol.* 2022;109(1):1-10.

12. Lazarian G, Quinquenel A, Bellal M, et al. Autoimmune haemolytic anaemia associated with COVID-19 infection. *Br J Haematol.* 2020;190(1): 29-31.

13. Zebardast A, Hasanzadeh A, Ebrahimian Shiadeh SA, et al. COVID-19: a trigger of autoimmune diseases. *Cell Biol Int.* 2023;47(5):891-899.

14. Phipps C, Chen Y, Gopalakrishnan S. Daratumumab and its potential in multiple myeloma. *Ther Adv Hematol.* 2015;6(3):120-128.

15. Ye Z, Zhang X, Chen Y, et al. Risk of red blood cell alloimmunization in multiple myeloma patients treated with daratumumab. *Vox Sang.* 2020;115(6): 512-518.

16. Jalink M, van de Donk NWCJ, Zweegman S, et al. Daratumumab monotherapy in refractory autoimmune hemolytic anemia. *Blood Adv.* 2024;8 (2):456-462.