RESEARCH PAPER

Daratumumab - Induced Serologic Interference in Pre - Transfusion Testing: A Case Report

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ABSTRACT

Introduction: Pretransfusion testing is an essential prerequisite before releasing blood components for transfusion. Daratumumab, an anti-CD38 monoclonal antibody used in the treatment of Multiple Myeloma, is known to interfere with immunohematological testing by causing panagglutination in Antibody screening using 3 cell panel testing due to binding with CD38 expressed on reagent red blood cells. This interference may lead to positive antibody screening and incompatible crossmatches, thereby complicating timely transfusion support.

Case Report: A 70-year-old male with Multiple Myeloma on daratumumab-based chemotherapy presented with symptomatic severe anemia (Hb 7.1 g/dL) associated with generalized weakness, exertional dyspnea, and dizziness. Pretransfusion testing revealed blood group A Rh-positive, weakly positive direct antiglobulin test (1+), auto-control of 0.5+, and panreactivity on antibody screening using 3 cell panel and further Antibody identification using 11 cell panel demonstrated panagglutination with weak to moderate against reagent red cells. Crossmatching with 13 donor packed red blood cell (PRBC) units demonstrated varying degrees of incompatibility, with one unit showing least incompatibility (0.5+). In view of urgent transfusion requirement and recent daratumumab administration, the serological findings were interpreted as daratumumab-associated interference. The least incompatible A Rh-positive PRBC unit was transfused safely under close monitoring without any adverse transfusion reaction. Post-transfusion hemoglobin improved from 7.1 g/dL to 8.1 g/dL with significant clinical improvement.

Discussion: Daratumumab-associated serologic interference represents a major challenge in transfusion medicine practice. Binding of the drug to CD38 on reagent red cells can result in persistent panreactivity in antibody screening, antibody identification, and antiglobulin crossmatching despite absence of clinically significant alloantibodies. Similar findings have been reported in previous studies, emphasizing the importance of awareness among clinicians and transfusion medicine specialists. Although mitigation strategies such as dithiothreitol-treated reagent cells and extended phenotyping are recommended, these techniques may not always be available in urgent settings. In such situations, transfusion of least incompatible blood after careful clinical and serologic correlation may be safely performed.

Conclusion: This case highlights the significant immunohematological challenges posed by daratumumab therapy during pretransfusion testing in patients with Multiple Myeloma. Recognition of characteristic serologic interference patterns, detailed drug history, and effective communication between clinicians and transfusion services are essential to avoid delays in transfusion support. In urgent clinical scenarios, transfusion of least incompatible PRBC units can be safely administered with appropriate monitoring when clinically significant alloantibodies are excluded.

Keywords: *Daratumumab; Multiple Myeloma; Pretransfusion testing; Panagglutination; Anti-CD38 monoclonal antibody; Crossmatch incompatibility; Indirect antiglobulin test; Packed red blood cell transfusion; Immunohematology; Transfusion medicine.*

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INTRODUCTION

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Pretransfusion testing is an essential prerequisite before releasing blood components for transfusion (1). Patients receiving Daratumumab, an anti-CD38 monoclonal antibody, often face clinically significant interference in pretransfusion testing (2). By binding to CD38 on reagent red blood cells, the drug causes panagglutination in indirect antiglobulin tests, producing positive antibody screens and seemingly incompatible crossmatches without evidence of underlying alloantibodies (3).

Various mitigation strategies have been described, such as dithiothreitol-treated reagent cells, Fab-fragment blocking, or neutralization with soluble CD38, but they are not always available or may prolong turnaround time (4),(5). Recognition of this phenomenon is therefore crucial for transfusion services to avoid unnecessary work-ups and to safely issue the least incompatible blood components in urgent settings.

CASE REPORT

A 70-year-old male, a known case of Multiple Myeloma, presented to the hematology department with complaints of generalized weakness, easy fatigability, exertional dyspnea, and dizziness for one week. He had been diagnosed with multiple myeloma 8 months earlier and was on chemotherapy consisting of Daratumumab 1800 mg subcutaneous injection once monthly, Lenalidomide 10 mg orally once daily for 21 days in a 28-day cycle, and injection Dexamethasone 20 mg weekly. The patient had completed six cycles of therapy, with the last dose of daratumumab administered 3 days prior.

On examination, the patient appeared pale and lethargic. Vital signs were stable. Laboratory investigations revealed hemoglobin of 7.1 g/dL, hematocrit 21%, total leukocyte count 5.8 × 10^9/L, and platelet count 1.8 × 10^5/µL. Renal and liver function tests were within acceptable limits. Peripheral smear showed normocytic normochromic anemia.

In view of symptomatic severe anemia with hemoglobin of 7.1 g/dL associated with fatigue, dyspnea on exertion, and underlying hematological malignancy on active chemotherapy, transfusion of one unit of packed red blood cells (PRBC) was requested to improve oxygen-carrying capacity, relieve symptoms, and prevent further cardiovascular compromise.

Pre-transfusion immunohematological evaluation was performed in the transfusion medicine laboratory. The patient's blood group was identified as A, Rh-positive using Column Agglutination technique. The direct antiglobulin test (DAT/DCT) was demonstrated 1+ using polyspecific Coombs gel card by Column agglutination technique showed in figure 1, while the auto-control showed 0.5. Antibody screening using Coombs gel card with the commercial three-cell panel revealed the following reactions: Panel I – 1+, Panel II – 0.5, and Panel III – 1+ showed in figure 2. Further antibody identification using an 11-cell panel using the demonstrated panagglutination with weak to moderate reactivity against all reagent red cells, suggestive of widespread serologic interference.

Major crossmatching was subsequently carried out with 13 donor PRBC units using antiglobulin phase with a Coombs gel card . Among the tested units, 8 units showed 2+ incompatibility, 4 units demonstrated 1+ incompatibility, and 1 unit exhibited only weak incompatibility of 0.5+ reaction strength showed in figure 3. In the context of recent daratumumab administration, panreactivity on antibody screening and identification panels, auto-control 0.5+, the serologic findings were considered consistent with daratumumab-associated interference in pre-transfusion testing.

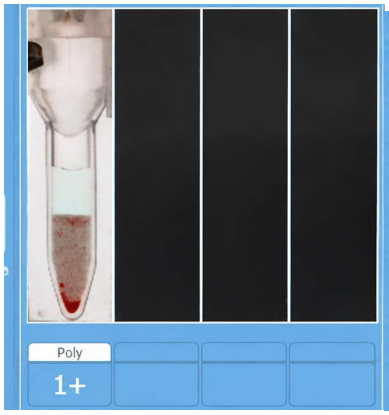

Figure 1.

Figure 2

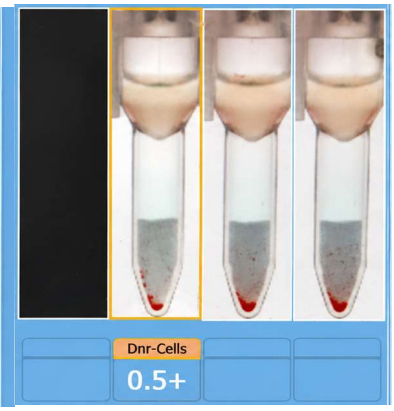

Figure 3

Figure 1. Direct Coomb test by column agglutination technique demonstrated 1+ grading. **Figure 2.** Antibody Screening using 3 cell panel in column agglutination technique showed Panel I- 1+, Panel II-0.5+ & Panel III-1+. **Figure 3.** Cross match testing of one A Rh(D) positive pack red cell using column agglutination technique showed 0.5+ (Least Incompatible)

As the patient required urgent transfusion support for symptomatic anemia, the least incompatible A Rh-positive PRBC unit was selected after discussion with the treating clinician and transfusion medicine specialist. The transfusion was administered under close monitoring for any adverse transfusion reactions. One unit of least incompatible PRBC was transfused uneventfully without any evidence of hemolytic, allergic, or febrile transfusion reactions. The patient showed clinical improvement following transfusion, and repeat hemoglobin estimation demonstrated an increase from 7.1 g/dL to 8.1 g/dL. The patient remained hemodynamically stable throughout the transfusion period.

DISCUSSION

Daratumumab (DARA) is a monoclonal antibody used in the treatment of refractory multiple myeloma that targets CD38. DARA targets the CD38 protein because it is overexpressed on myeloma cells (6). Additionally, CD38 is minimally expressed on red blood cells, which complicates antibody screening, antibody identification procedures, and compatibility testing prior to transfusion. It has been reported that this interference may persist for up to two to six months after infusion. However, daratumumab does not affect standard ABO blood grouping (7).

The present case highlights the diagnostic and transfusion-related challenges associated with daratumumab therapy in patients with Multiple Myeloma. Our patient demonstrated characteristic serological findings including weakly positive DAT, panreactivity on antibody screening and identification panels, and incompatible crossmatches in coomb's phase with multiple donor units following recent daratumumab administration. Similar observations have been increasingly reported in recent literature, emphasizing the growing importance of awareness among transfusion medicine specialists (8).

The serologic interference observed in our case is comparable to findings reported by Nedumcheril MT et al., who described persistent panagglutination in Antibody screening using 3 cell panel due to daratumumab binding to CD38 expressed on reagent red cells. Their review highlighted that such interference may persist for several months after therapy and can result in significant delays in issuing compatible blood units. Similar to our patient, widespread reactivity in antibody screening and crossmatching was attributed to drug-induced interference rather than underlying alloantibodies (8).

A comparable case was described by Rajput S et al. in 2024, where a patient receiving daratumumab for multiple myeloma exhibited panreactivity during pretransfusion testing with incompatible crossmatches. In that report, DTT-treated reagent cells were used to negate interference and compatible blood was successfully transfused. In contrast, our center relied on selection of the least incompatible PRBC unit because advanced mitigation techniques such as DTT treatment were not immediately available in the urgent setting. Despite this difference, both cases demonstrated safe transfusion without adverse reactions (9).

Similarly, Gupta Abhaykumar Malind et al. reported daratumumab-associated interference in a non-myeloma patient requiring granulocyte transfusion support. Their patient showed persistent incompatibility in immunohematological testing despite absence of clinically significant alloantibodies. Comparable to our findings, transfusion support was eventually provided safely after correlation with clinical history and laboratory interpretation. However, unlike our patient with symptomatic anemia requiring PRBC transfusion, their report involved granulocyte support in a neutropenic setting (10).

Our findings also resemble the observations reported by Kokoris SI et al., who described panagglutination in indirect antiglobulin testing as a major immunohematological challenge in patients receiving anti-CD38 therapy. The authors emphasized that weak to moderate panreactivity across reagent cells can mimic underlying alloantibodies and complicate transfusion decisions. Similar weak to moderate reactions ranging from 0.5+ to 2+ were observed in our patient across donor crossmatches and antibody panels (11).

A contrasting feature in our case compared with the report by Ho Chak-Sum et al. was the clinical setting and type of serological interference. Their case demonstrated false-positive allogeneic flow cytometry crossmatches in a renal transplant candidate receiving daratumumab, leading to repeated donor incompatibility and transplant delay. While both reports illustrate the broad immunohematologic impact of daratumumab, our case specifically involved RBC serologic testing and urgent transfusion support rather than transplant immunology assessment (12).

Another notable difference from previously published reports is that our patient demonstrated a weakly positive DAT and auto-control, whereas many reported cases describe negative DAT despite marked indirect antiglobulin panreactivity. This variation may be related to differential expression of CD38 on patient erythrocytes, recent transfusion exposure, or ongoing chemotherapy-related immune modulation (13).

The successful transfusion outcome in our patient supports previous evidence suggesting that transfusion of least incompatible or phenotype-matched blood can be safely performed when daratumumab interference is recognized appropriately. The absence of hemolytic or febrile transfusion reactions and the post-transfusion hemoglobin increment from 7.1 g/dL to 8.1 g/dL further support the safety of this approach in urgent clinical situations (9,13).

Overall, this case reinforces the importance of obtaining a detailed drug history before immunohematological workup, particularly in patients receiving anti-CD38

monoclonal antibodies. Early communication between clinicians and transfusion services is essential to prevent unnecessary delays in blood availability. Adoption of mitigation strategies such as DTT-treated reagent cells, extended phenotyping/genotyping, or use of anti-idiotype neutralization methods may further improve transfusion support in these patients (8,13).

CONCLUSION

This case highlights the significant immunohematological challenges posed by Daratumumab therapy in patients with Multiple Myeloma undergoing pre-transfusion testing. Daratumumab-associated interference can result in panreactivity on antibody screening, antibody identification, and antiglobulin crossmatching, thereby complicating the timely provision of compatible blood units. Recognition of this characteristic serologic pattern, along with careful clinical correlation and detailed drug history, is essential to avoid unnecessary delays and misinterpretation of alloantibody presence.

In urgent clinical situations, transfusion of the least incompatible PRBC unit may be safely undertaken with close monitoring when clinically significant alloantibodies are excluded. This case further emphasizes the importance of effective communication between clinicians and transfusion medicine specialists, as well as the need for implementation of mitigation strategies such as DTT-treated reagent cells, extended phenotyping/genotyping, and awareness of anti-CD38 monoclonal antibody interference in routine transfusion practice.

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