Case Report

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Interference of daratumumab with pretransfusion testing, mimicking a high-titer, low avidity like antibody

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Abstract:

Daratumumab is a monoclonal immunoglobulin against CD38 and has been approved for treating patients with refractory multiple myeloma. The presence of daratumumab in the sera can interfere with pretransfusion testing due to the weakly expression of CD38 on red cells. The reactivity could be mistaken as autoantibody (if autocontrol is positive) or alloantibody (if autocontrol is negative). We present a case that demonstrates daratumumab could mimic a high titer low avidity (HTLA) alloantibody. A 34-year-old male patient of refractory myeloma was recruited in phase three clinical trial involving daratumumab. Samples were sent to the blood bank for pretransfusion testing. Without knowledge of patient having used daratumumab, we mistook the reactivity in the patient's sera as an HTLA antibody due to the results of negative autocontrol and high titers of antibody activity. Antibody screen showed a panreactive pattern and the reactivity against screening cells was up to a titer of 1:1240. The reactivity was weaker against cord cells than adult cells, became weaker against ZZAP-treated cells and became negative against DDT-treated cells. A discussion with attending physician finally revealed the reactivity was due to the interference caused by daratumumab. The case demonstrates good communication is essential in performing pretransfusion testing for patients receiving daratumumab and other new biological regimens that can interfere with compatibility test.

Key words:

Antibody screen, daratumumab, pretransfusion testing

Introduction

Daratumumab is a humanized immunoglobulin against CD38 and has been approved by the USA Food and Drug Administration for the treatment of patients with refractory multiple myeloma.[1] Since red cells also express small amount of CD38 molecules, the infusion of daratumumab can interfere pretransfusion testing, mainly causing a positive antibody screen.[2-4] Handling samples from patients treated with daratumumab requires special strategy, and notification from and good communication with the clinicians and pharmacy department are essential. We reported our first laboratory experience with the patient using daratumumab. The patient was on a phase three clinical trial involving daratumumab. Without knowledge of patient's drug history, we mistook the reactivity of the sera as an HTLA antibody due to a negative autocontrol and high titers of antibody activity.

Case Report

A 34-year-old man was a victim of multiple myeloma which was diagnosed at another tertiary hospital in 2010. He was initially treated at that hospital with a standard myeloma regimen for patient eligible for autologous stem cell transplantation that included the combination of doxorubicin, dexamethasone, and bortezomib. In February 2011, he completed the autologous peripheral stem cell transplantation and

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achieved a complete remission. However, myeloma relapse occurred in January 2014, and he started to receive several courses of salvage therapy including a combination of bortezomib, thalidomide, and dexamethasone but could only obtain partial response.

In December 2014, his myeloma status was classified as Stage III by both the international staging system and Durie/Salmon staging system, and he had persistent mild anemia and required occasional red cell transfusions. At the time, our hospital was holding a Phase 3 randomized clinical trial that aimed to compare lenalidomide and dexamethasone (traditional group) versus lenalidomide, dexamethasone and the new monoclonal drug daratumumab for patients with refractory and relapsed myeloma. He agreed to participate in this clinical trial and was referred to this hospital.

After enrollment, he was randomly assigned to lenalidomide, dexamethasone, and daratumumab treatment group and admitted on March 11, 2015, to receive the first course of treatment. Before initiation of the clinical trial, a routine blood typing and antibody screen were tested. His blood type was O^+ and antibody screen was negative. One month later, he was readmitted for the second course of treatment, and a sample of pretransfusion testing was sent to the blood bank. This time, antibody screen showed positive against all three screening cells. A study of the positive antibody screen was initiated. The antibody identification result showed a pan-reactive pattern (column agglutination test, anti-human globulin card, Ortho diagnostics). Autocontrol and direct antiglobulin test (monospecific and polyspecific) were negative.

In light of the panreactive pattern and negative autocontrol result, an antibody against high-incidence antigen was suspected in the patient's sera and strategy for resolving antibodies against high-incidence antigen was employed.

Table 1: Characteristics of the immunological reactivity of patient's sera and comparison with those of high-titer low avidity antibody

	Effects on Ch/Rg antibodies	Effects on anti-Kn^a/-McC^a/-Yk^a	Effects on anti-JMH	Patient's sera
Papain-treated red cells	No	Weak	Sensitive	Weak
Inhibition by pooled plasma	Yes	No	No	No
Reactivity with cord cells compared with adults cells	Weaker	Weaker	Varied	Weaker
ZZAP-treated red cells	No	Sensitive	Sensitive	Weaker

At first, we determined the patient's phenotype and the result showed C+c+, E-e+, Fy(a+b−), Jk(a-b+), Le(a−b+), S−s+, K−k+, Mi^a(−), Di^a(−), excluding the possibility of null phenotypes such as JK_{null} phenotype. His red cells reacted positively with anti-H, excluding the possibility of para-Bombay subgroup. Second, we performed the titration study, and the sera reacted weakly positively against panel cells up to 1:1024 titration, suggesting the antibody could be one of a group of antibodies so-called HTLA.

To confirm or exclude if the antibody was one of the HTLA antibodies, we performed the following chemical treatments to characterize the antibodies: Patient's sera reacted more weakly against papain-treated red cells than against untreated cells. The reaction could not be neutralized with pooled plasma. The reactivity appeared weaker with cord blood cells than with adult cells. Patient's sera reacted weakly positively against ZZAP (W.A.R.M.™ Immucor Corp.)-treated red cells. These reaction patterns did not fit into any specific category of HTLA antibodies [Table 1].

We also obtained five rare cells to confirm or exclude the antibody specificity (the rare cells were one kind gift from reference laboratory of Mackay Hospital, Taipei, Taiwan): MC422 cell (negative for Cs^a, Wr^a and Yk^a), MC445 cell (negative for Wr^a, Chido, Kn^a, McC^a, McM^d, Sl^a), MC387 cell (negative for Wra, Kna, McC^a), MC520 cell (negative for Yk^a) and MC503 cell (negative for Kn^a). Patient's sera reacted positively against these cells.

Subsequently, we performed adsorption/elution study. It has been reported that antibodies of the HTLA group characteristically are not adsorbed well onto adsorbing cells due to their low antigen density, therefore, the eluate would not contain antibody.[5] However, the adsorption/elution study of the patient's sera showed that the eluate still reacted positively with panel cells.

Based on the above results, we could only tentatively classify the antibody as HTLA-like antibody with unknown specificity or against other unknown factor.

In May 2015, one of the authors (SC-LO) had a discussion with the attending physician of the patient and was informed that a new kind of monoclonal drug possessing the ability to interfere with blood bank routine testing was under clinical trial in this hospital, and it soon became clear that the patient was receiving this new drug daratumumab. Nearly at the same time, two papers regarding the interference from daratumumab were published.[6,7] Chapuy *et al*. reported that the dithiothreitol -treatment can remove the CD38 from red cells and distinguish daratumumab interference from reactivity of red cell alloantibodies.[6] We confirmed

the sera from our patient showed no reactivity against dithiothreitol-treated red cells and we adopted dithiothreitol treatment as part of compatibility test for this patient. He thereafter received several transfusions via this policy without clinically significant complications. Unfortunately, his myeloma remained refractory, and he passed away in May 2016.

Discussion

Several characteristics distinguish daratumumab from traditional drugs that induce alloantibody,[6-9] therefore presenting a new challenge to blood bank: (1) Daratumumab is a monoclonal antibody, not requiring preexposure for the development of antibody. (2) Direct antiglobulin test could be positive or negative. (3) If direct antiglobulin test is positive, the eluate from patient's red cells contains antibody activity.

The negative autocontrol of this patient led us to mistake the antibody as an alloantibody. In everyday pretransfusion testing, we often depend on the result of autocontrol to guide the investigational strategy of positive antibody screen: If the autocontrol is negative, one is likely dealing with an alloantibody, but if the autocontrol is positive and the patient has not transfused in recent 3 months, autoantibody is more likely (with or without alloantibody). After infusion of daratumumab, positive indirect antiglobulin test (antibody screen) is a consistent finding while direct antiglobulin test (and autocontrol) is varied. Chapuy *et al*.[6] reported that of four of their patients with available direct antiglobulin test results, three were positive and one negative. Only a small fraction of red cells are reported to express CD38 molecules, which is red cell age-independent. Moreover, the removal of daratumumab-coated red cell is unrelated to complement. Possible explanations for the negative autocontrol in our patient include that daratumumab-coated red cells may be removed more extensively in patients with advanced disease, or disease progression may alter the CD38 expression pattern on erythrocytes. Further study is needed to clarify this issue.

Two new methods are proposed to mitigate the interference from daratumumab:[4] Employment of anti-idiotype antibody and soluble CD38. Schmidt *et al*.[10] have proposed the use of cord blood reagent red blood cells as an alternative. In our experience, the sera from our patient reacted weakly against cord cells and the availability problem of cord cells, making a case against this alternative.

Lack of communication was the root cause of the mistakes we had made in dealing the pretransfusion testing of this patient. Blood bank staff obviously lacked adequate knowledge about this new kind of drug during the first laboratory encounter. The clinicians were unclear of the importance of the interference caused by daratumumab and failed to pass the information beforehand. The randomized practice of the trial rendered it difficult to assign personnel in advance to be responsible for the communicating with blood bank. Learning from our experience, we highly recommend that good communication is essential in performing pretransfusion testing for patients receiving daratumumab and other new biological regimens that can interfere with compatibility test. Designing special cards for the patients and help from information system with alert function are possible considerations.

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Conflicts of interest

There are no conflicts of interest.

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