Unexpected impact on immunohematological diagnostics from transplantation of autologous stem cell preparations containing daratumumab

An unexpected interference in immunohematological diagnostics led to the retrospective identification of daratumumab in the autologous stem cell preparation administered to a patient with multiple myeloma (MM) shortly before. In addition to its implication for immunohematology, the presence of anti-CD38 antibodies in the stem cell product may also have biological relevance for the transplant itself, since CD38 is also expressed on hematopoietic stem cells.

MM is one of the most common hematologic neoplasms. It is a malignancy of terminally differentiated B cells (plasma cells) and is characterized by the clonal proliferation of monoclonal plasma cells in the bone marrow, often accompanied by the secretion of monoclonal intact or light chain immunoglobulins, also known as M-protein or paraprotein. According to the World Health Organization classification MM is classified as a plasma cell neoplasm and represents a separate entity within the spectrum of B-cell malignancies.

In most cases, MM therapy is not curative and primarily aims to reduce disease progression in order to prolong overall survival, while preventing or treating associated complications (e.g., bone disease, anemia, renal impairment, infections and hypercalcemia).

Standard first-line treatment typically includes combination induction therapy (often triplet or quadruplet regimens), which may be followed by high-dose chemotherapy with melphalan and autologous hematopoietic stem cell transplantation (ASCT) in transplant-eligible patients.[1]

Combination therapies often include monoclonal, human IgG1 antibodies, e.g., daratumumab or the later-approved isatuximab, which induce an apoptotic pathway through various mechanisms by binding to the CD38 antigen, a transmembrane glycoprotein overexpressed with high density on MM plasma cells.[2,3]

Patients with MM often require red blood cell (RBC) and platelet transfusions, particularly during intensive treatment phases, either because of suppressed hematopoiesis caused by the myeloma cells infiltrating the bone marrow or because of the myelosuppressive effects of chemotherapy.[2]

Here we report a case of serological interference caused by daratumumab in the context of pre-transfusion diagnostics although the patient had not received daratumumab in the preceding 7 months and several immunohematological tests performed in the meantime had been unremarkable. The research complied with the International Conference on Harmonization Good Clinical Practice Guideline and the Declaration of Helsinki. The patient provided written informed consent.

Before providing RBC concentrates to patients an indirect antiglobulin test (IAT) is routinely performed in order to screen for irregular erythrocyte antibodies which may cause hemolytic transfusion reactions.

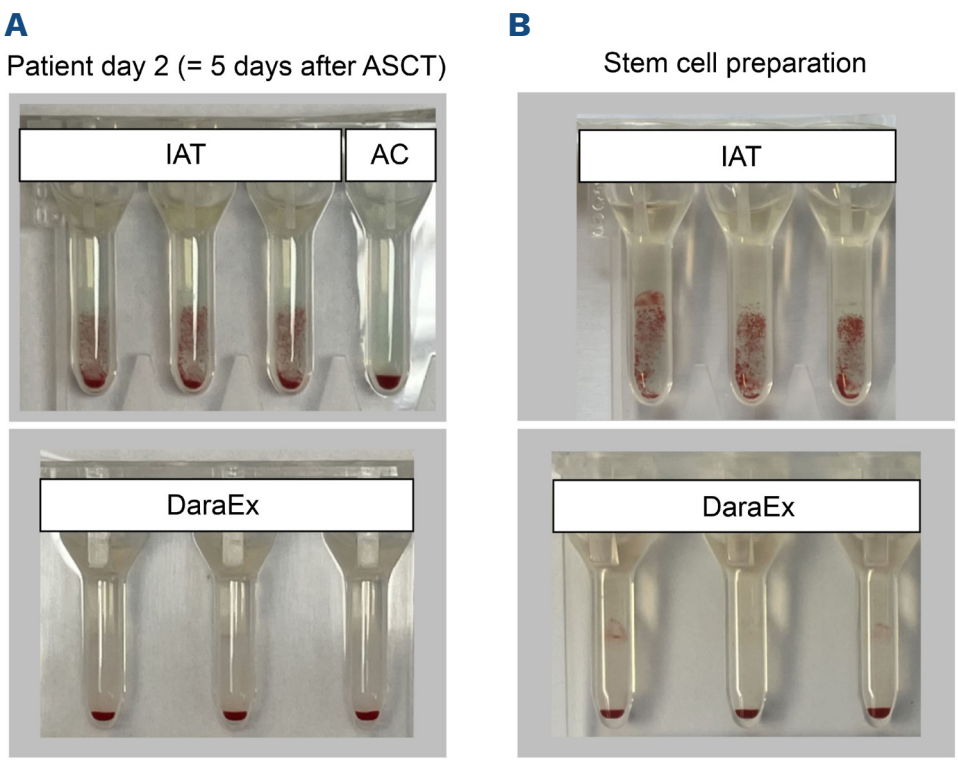

Figure 1. Photographs of immunohematological diagnostics. (A) The patient's sample on day 2 (i.e., 2 days after the index day with the first unexpected results in immunohematological testing and 5 days after autologous stem cell transplantation). (B) A sample of the stem cell preparation itself (stem cell supernatant). Pan-reactive results in the indirect antiglobulin test (autocontrol negative) in combination with negative results in the indirect antiglobulin test with DaraEx indicate the presence of the anti-CD38 monoclonal antibody, daratumumab. ASCT: autologous stem cell transplantation; IAT: indirect antiglobulin test; AC: autocontrol; DaraEx: IAT after pretreatment with the anti-CD38 Fab fragment, DaraEx.

CD38 is not only expressed on MM plasma cells but is also expressed on the surface of RBC, albeit to a lesser extent.[2] Thus, monoclonal antibodies, such as daratumumab, circulating in the plasma interfere with pre-transfusion immunohematological diagnostics by causing pan-reactivity with RBC used for antibody screening and differentiation in the IAT. Such pan-reactivity is known to mask any irregular RBC antibodies present.[4]

However, autocontrols of patients receiving anti-CD38 monoclonal antibody therapy usually remain non-reactive as CD38 is downregulated on autologous RBC.[5]

Due to the long half-life of IgG antibodies, this effect usually persists for up to 6 months after the last administration of daratumumab. To reverse this interference, specific, genetically engineered Fab fragments of anti-CD38 are available for pretreatment of RBC used for diagnostic purposes. These Fab fragments prevent daratumumab contained in the patient's plasma from binding to the CD38 docking sites on the test RBC. Due to the absence of the Fc fragment, which normally serves as the target of the secondary antibody used in the IAT, this pretreatment prevents false-positive agglutinations.[6]

In the presented case the following unexpected constellation was found: In pre-transfusion testing antibody screening and antibody differentiation a 53-year-old female patient showed the typical reaction pattern of patients who had received daratumumab (day 0 = index day) (Table 1).

The last documented administration of daratumumab had, however, been more than 7 months previously (day -221) (Table 1) and the IAT had been negative several times in the meantime (most recently 3 days before the index day) (Table 1). According to clinical data, no daratumumab had been administered since the last unremarkable blood sample (day -3) (Table 1). However, after pretreatment with anti-CD38 Fab fragment (DaraEx plus, Imusyn, Hannover, Germany) the IAT was negative (index day) (Table 1). The same reaction pattern was observed on several occasions

Table 1. An overview of the results of immunohematological diagnostics.

Day	Information	Autocontrol	IAT	DaraEx
-435	-	Negative	Negative	NA
-425	-	Negative	Negative	NA
-361	**Beginning of daratumumab therapy**			
-269	Sample taken during first attempt of stem cell collection	Negative	Pan-reactive	Negative
-262	-	Negative	Pan-reactive	Negative
-221	**End of daratumumab therapy**			
-213	-	Negative	Pan-reactive	Negative
-200	Sample taken during stem cell collection	Negative	Pan-reactive	Negative
-164	-	Negative	Pan-reactive	Negative
-7	-	Negative	Negative	NA
-6	-	Negative	Negative	NA
-3	Sample taken prior to autologous stem cell transplantation	Negative	Negative	NA
-3	**Autologous stem cell transplantation**			
0	Index day with first unexpected results	Negative	Pan-reactive	Negative
2	Photographs: see Figure 1A	Negative	Pan-reactive	Negative
4	-	Negative	Pan-reactive	Negative
7	-	Negative	Pan-reactive	Negative
9	-	Negative	Negative	Negative
11	-	Negative	Negative	NA

A pan-reactive indirect antiglobulin test with subsequent negative results when using DaraEx indicates the presence of the anti-CD38 monoclonal antibody daratumumab in the patient's plasma. (Day 0 = index day, when unexpected results in immunohematological testing were obtained for the first time). IAT: indirect antiglobulin test; DaraEx: IAT after pretreatment with the anti-CD38 Fab fragment, DaraEx; NA: not applicable (the test was not performed because of negative results in the IAT)

in the following days (Table 1, Figure 1A).
Further inquiries revealed that the patient had undergone ASCT between the last unremarkable blood sample (day -3) (Table 1) and the unexpected pan-reactivity in IAT during pre-transfusion testing (day 0) (Table 1). The autologous stem cells had been collected 3 weeks after the last daratumumab administration (stem cell collection day = day -200) (Table 1) and had been stored for several months prior to reinfusion at ASCT (Table 1). We, therefore, analyzed both the archived plasma samples obtained on the day of stem cell collection (day -200) as well as the stem cell product itself.
The samples from stem cell collection day showed the presence of daratumumab in the patient's plasma. Antibody screening in the IAT was negative after pretreatment of test RBC with anti-CD38 Fab fragments (DaraEx) whereas without DaraEx-pretreatment antibody screening in IAT was pan-reactive (Table 1).
Moreover, for the first time we showed that the stem cell product itself also contained daratumumab (Figure 1B). While the normal antibody screening in IAT with the supernatant of the stem cell product showed a pan-reactive pattern with the test RBC, all reactions after DaraEx-pretreatment were negative.
Additionally, we confirmed these findings using a semi-quantitative enzyme-linked immunosorbent assay performed with a Daratumumab (Human) ELISA Kit (Abcam, Cambridge, UK), which detected daratumumab in both samples: in the archived plasma sample taken during the stem cell collection (day -200, stem cell collection day) (Table 1) and in the stem cell product supernatant itself. These findings strongly suggest that daratumumab was reinfused into the patient with the ASCT via the 101 mL residual plasma contained in the supernatant of the two administered stem cell units (each unit contained approximately 50.5 mL plasma).
Beyond its implications for immunohematology, the presence of anti-CD38 monoclonal antibodies in the stem cell product may also have biological relevance for the transplant itself since CD38 is also expressed on hematopoietic stem cells. Initial studies[7,8] showed that administration of daratumumab prior to stem cell apheresis impedes stem cell mobilization, whereas another study found no clinically significant differences.[9] To date, only one study has shown that patients pretreated with daratumumab require slightly more RBC and platelet concentrates after ASCT than patients who are not pretreated with daratumumab.[10]
It is largely unknown whether daratumumab contained in the stem cell preparation and reinfused with ASCT influences the engraftment of the stem cells. This issue is currently being further investigated.
In conclusion, to the best of our knowledge, this is the first case demonstrating that daratumumab contained in the supernatant of a stem cell preparation and re-infused via ASCT can interfere with immunohematological diagnostics. In patients with no history of anti-CD38 monoclonal antibody administration, e.g., daratumumab, in recent months but with pan-reactive pre-transfusion testing for RBC antibodies, the possibility of other sources of anti-CD38 monoclonal antibody such as plasma supernatants of stem cell products should be kept in mind. In such cases, close communication between the immunohematology laboratory and the treating physicians is required, since this interference can easily be neutralized using DaraEx. Physicians should be aware of the importance of informing the laboratory about current and recent (up to 6 months) anti-CD38 monoclonal antibody therapy, considering the long half-life of anti-CD38 monoclonal antibodies. This ensures that immunohematological diagnostics and, consequently, the provision of blood products are not unnecessarily delayed.
In addition to immunohematological interference, the presence of an anti-CD38 monoclonal antibody such as daratumumab in the stem cell preparation itself might affect the stem cells and thus impair the engraftment of the autologous stem cell transplant, a potential side effect that has not yet been considered and should be investigated.

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Contributions
KL designed the study, performed experiments, analyzed data and wrote the manuscript. FW designed the study and reviewed the manuscript. PG performed experiments and reviewed the

manuscript. SG designed the study and reviewed the manuscript. DJ designed the study and wrote the manuscript.

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Data-sharing statement

Qualified researchers can request access to data and related study documents by contacting the corresponding author.

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