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

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

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**Running title:** Daratumumab in autologous stem cell preparations

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**Manuscript**

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.

Multiple myeloma 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 chains immunoglobulins, also known as M-protein or paraprotein. According to WHO 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 (MoAb), 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 over-expressed 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 diagnostic although the patient had not received Daratumumab in the previous seven months and several immunohematological tests performed in the meantime were 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.

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

However, auto controls (AC) of patients receiving anti-CD38 MoAb therapy usually remain non-reactive as CD38 is down-regulated on autologous RBCs.[5]

Due to the long half-life of IgG-antibodies, this effect usually persists for up to six months after the last administration of Daratumumab. To reverse this interference, specific, genetically engineered Fab-fragments of anti-CD38 are available for pretreatment of RBCs 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 RBCs. 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 of 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 was, however, more than seven months ago (day -221, table 1) and the IAT had been negative several times in the meantime (most recently three days before index day, table 1). According to

clinical data, no Daratumumab had been administered since the last unremarkable blood sample (day -3, table 1). But 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 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 three 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 (table1).

Therefore, we analyzed both the archived plasma samples obtained on the day of stem cell collection (day -200, table 1) as well as the stem cell product itself.

The samples from stem cell collection day showed presence of Daratumumab in the patient's plasma: Antibody screening in IAT was negative after pretreatment of test RBCs 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 RBCs, all reactions after DaraEx-pretreatment were negative.

Additionally, we confirmed these findings using a semi-quantitative ELISA (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 approx. 50.5 ml plasma).

Beyond its implications for immunohematology, the presence of anti-CD38 MoAbs 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] have shown 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 cause interferences in immunohematological diagnostics.

In patients with no history of anti-CD38 MoAb administration like Daratumumab in recent months but with pan-reactive pre-transfusion testing for RBC antibodies, the possibility of other sources of anti-CD38 MoAb 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 be easily neutralized using DaraEx. Physicians should be aware of the importance to inform the laboratory about current and recent (up to 6 months) anti-CD38 MoAb therapy, considering the long half-life of anti-CD38 MoAbs. 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 MoAb 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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**Table 1: Results of immunohematological diagnostics - overview**

| Day | Information | AC | IAT | DaraEx |
|---|---|---|---|---|
| -435 | | negative | negative | N/A |
| -425 | | negative | negative | N/A |
| -361 | Begin 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 | N/A |
| -6 | | negative | negative | N/A |
| -3 | sample taken prior to autologous stem cell transplantation | negative | negative | N/A |
| -3 | Autologous stem cell transplantation | | | |
| 0 | Index day with first unexpected results | negative | pan-reactive | negative |
| 2 | Photographs: see Fig 1a | negative | pan-reactive | negative |
| 4 | | negative | pan-reactive | negative |
| 7 | | negative | pan-reactive | negative |
| 9 | | negative | negative | negative |
| 11 | | negative | negative | N/A |

**Tab 1:**

Pan-reactive IAT with subsequent negative results when using DaraEx indicates presence of anti-CD38 MoAb Daratumumab in the patient's plasma. (Day 0 = index day, when unexpected results in immunohematological testing were obtained for the first time)
AC = auto control, IAT = indirect antiglobulin test, DaraEx = IAT after pretreatment with anti-CD38 Fab-fragment DaraEx, N/A = not applicable (test was not performed due to negative results in IAT)

**Figure 1: Photographs of immunohematological diagnostics**

Fig 1a: patient sample day 2 (= 2 days after index day with first unexpected results in immunohematological testing and 5 days after ASCT, respectively)

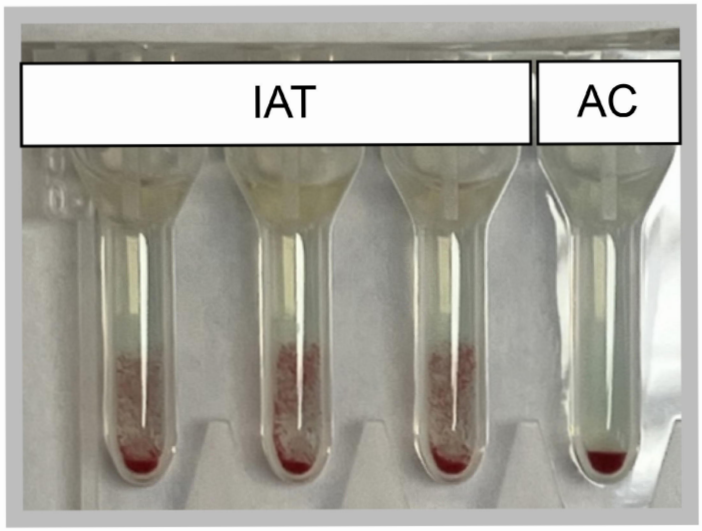
Fig 1b: sample of stem cell preparation itself (stem cell supernatant)

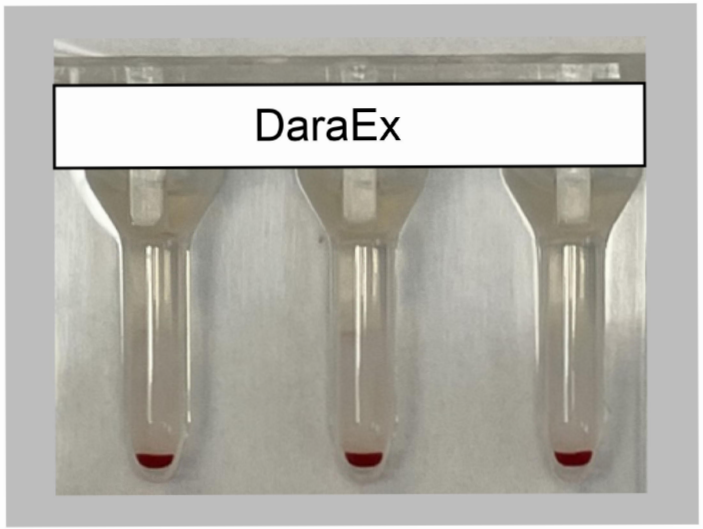
Pan-reactive results in IAT (AC is negative) in combination with negative results in IAT with DaraEx indicate the presence of anti-CD 38 MoAb Daratumumab

ASCT = autologous stem cell transplantation, IAT = indirect antiglobulin test, AC = auto control, DaraEx = IAT after pretreatment with anti-CD38 Fab-fragment DaraEx

A

Patient day 2 (= 5 days after ASCT)




B

Stem cell preparation