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LETTER TO EDITOR

Double CD38⁻/CD138⁻ negative multiple myeloma

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Abstract
The standard diagnosis of multiple myeloma by flow cytometry is based on selection of population of CD38⁺/CD138⁺ positives cells. As the result treatment with proteasome inhibitors, CD138 may be underexpressed on atypical plasma cells. Thus, in order to improve this strategy, recently new CD138-independent method, based on CD38 positivity of plasma cells was developed. We present an unusual case of CD138⁻ negative multiple myeloma which had become double CD138⁻/CD38⁻ negative after treatment with daratumumab by which we would like to illustrate potential pitfalls of both strategies.

Introduction

The standard diagnosis of multiple myeloma by flow cytometry is based on selection of population of CD38⁺/CD138⁺ cells [1–3]. However, as a result of treatment with bortezomib, one of the most widely used therapeutic agents, CD138 might be negative or underexpressed, which makes this marker unsuitable for detection of residual plasma cells. To improve minimal residual disease (MRD) detection, a new CD138-independent strategy, based on CD38 positivity of plasma cells, was recently published by Muz et al. [4] Using this method, plasma cells are selected from the population of CD38⁺ cells by exclusion of all nonplasma cells with CD38 positivity, using lineage specific markers such as CD3, CD14, CD16, CD19, and CD123. This strategy, in our opinion, might have a potential pitfall in patients treated with daratumumab (human IgG1 kappa monoclonal anti-CD38 directed antibody); the use of which is increasing and the efficacy of daratumumab in first-line treatment is currently being evaluated in multiple trials [5,6]. As an illustration of this phenomenon we present an unusual case of CD138⁻ multiple myeloma that has become double CD138⁻/CD38⁻ after treatment with daratumumab.

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Case report

A 57-year-old man presented with a chest wall mass and 25.4 g/L IgA lambda paraprotein. Initial bone marrow aspirate was hypocellular, and diagnostic biopsy of the mass revealed involvement of atypical plasma cells with lambda light chain restriction, which were positive for CD79a, MUM1, epithelial membrane antigen, and CD45, and negative for CD138, paired box protein 5, cyclin D1, and CD56.

The patient was primary refractory to bortezomib-based therapy, and was retreated with dexamethasone, lenalidomide plus PACE (cisplatin, doxorubicin, cyclophosphamide, and etoposide). After two cycles of treatment he achieved complete response according to International Myeloma Working Group criteria and the response was consolidated with autologous stem cell transplantation. He was started on maintenance with lenalidomide, but relapsed 14 months after transplantation. His bone marrow aspirate showed 70% atypical plasma cells at the time of relapse. Flow cytometry detected a population of $CD45^{+}$, $CD38^{+}$, $CD71^{+}$(weak), $CD138^{-}$, $CD56^{-}$, and $CD19^{-}$ plasma cells, with intermediate side scatter (SSC) and lambda light chain restriction.

The patient was commenced on daratumumab monotherapy, but 9 weeks after treatment new extramedulary infiltration was detected, and his paraprotein rose to 76.4 g/L. Another bone marrow study, performed 9 days after the last dose of daratumumab, demonstrated heavy infiltration by plasma cells (Fig. 1), and flow cytometry showed an abnormal population with the same characteristics of SSC and CD45 as before treatment with daratumumab, with lambda light chain restriction, but CD38 had become negative. Therefore, at that stage, we were dealing with $CD138^{-}$, $CD38^{-}$ multiple myeloma (Fig. 2).

The patient was resistant to bortezomib and lenalidomide, but responded to standard combination chemotherapy like PACE and VCMP/VBAP (vincristine, melphalan, cyclophosphamide, and prednisolone/vincristine, carmustine, doxorubicin, and prednisolone); two cycles of which he received after daratumumab, achieving short remission. Unfortunately, the patient still has active disease and is undergoing further therapy with bendamustine and dexamethasone with a view to allogenic stem cell transplantation.

Discussion

Following treatment with daratumumab, low expression of CD38 by plasma cells in vitro, without reduction or loss of the CD38 expression in vivo, was reported by Alici et al.[7] In contrast to that observation, in our case we observed reduced expression of CD38 in vivo. Minor partial recovery of CD38 positivity was observed in the plasma cell population in the bone marrow aspirate 20 days after the final dose of daratumumab. Thus, we do not think that CD38 negativity is due to selection of a new $CD138^{-}$, $CD38^{-}$ clone, and likely is related to a direct effect of daratumumab on the transmembrane glycoprotein CD38.

We report an unusual case of $CD138^{-}$ multiple myeloma, with which we would like to highlight pitfalls in the standard flow cytometry strategy in multiple myeloma patients, as well as in the CD138-independent strategy reported by Muz et al. [4] in patients treated with daratumumab. Also, we report decreased CD38 positivity in the plasma cells in vivo, after treatment with daratumumab, which differs from the results reported by Alici et al. [7] We cannot conclude whether CD138 negativity of the plasma cells is related to resistance to bortezomib and lenalidomide.

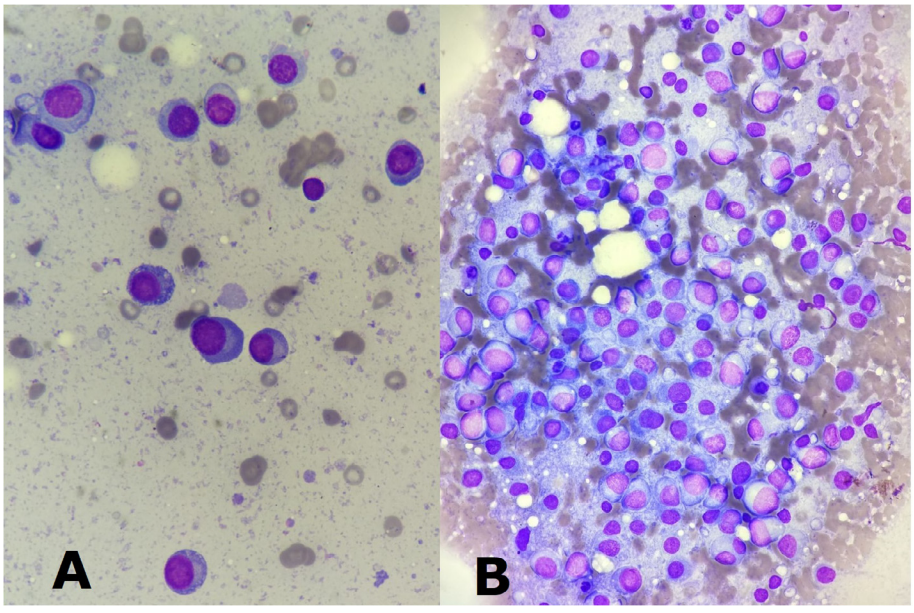

Fig. 1 Bone marrow aspirate showing infiltration by a typical plasma cells A. 100-fold magnification, B. 60-fold magnification.

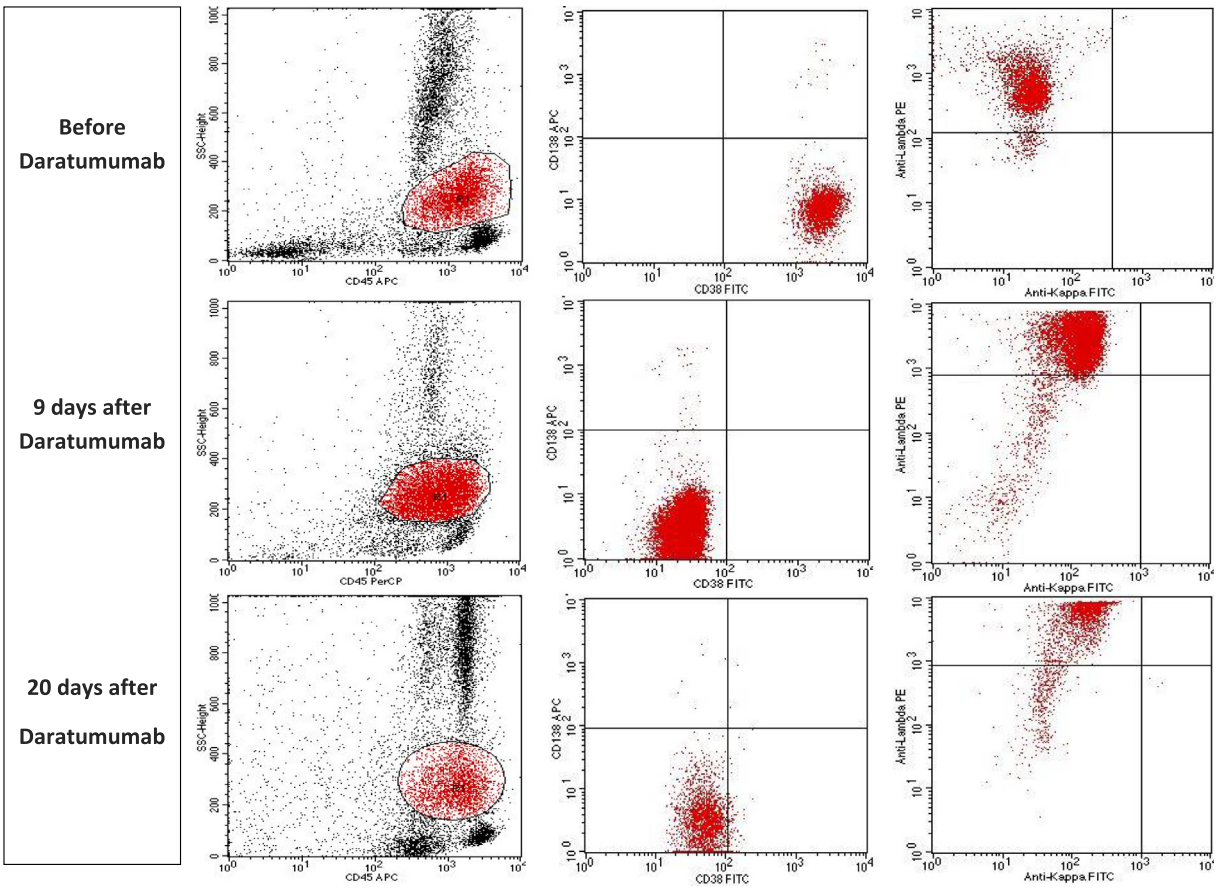

Fig. 2 Flow cytometry of the bone marrow. Top to bottom: Population of malignant plasma cells before, at day 9 and at day 20 of treatment with daratumumab. Left to right: malignant plasma cells gating on SSC/CD45-PerCP, expression of CD138-PE/CD38-FITC, expression of Lambda-PE/Kappa-FITC.

Conflicts of interest statement

The authors have no conflicts of interest to declare.

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