Clin. Lab. 2026;72:XXX-XXX

CASE REPORT

Interference of Daratumumab Treatment in the Biological Monitoring of Multiple Myeloma

O. Skalante [1], Y. Eddair [1], Z. Elidrissi [2], C. Echiguer [1], R. Bella-Tedga [1], A. Biaz [1], S. Bouhsain [1], H. Elmaaroufi [2], A. Dami [1], S. El-Machtani-Idrissi [1]

[1] *Biochemistry-Toxicology Department, Mohammed V Military Hospital, Rabat, Morocco*
[2] *Department of Clinical Haematology at The Mohammed V Military Hospital, Rabat, Morocco*

SUMMARY

Background: **Multiple myeloma is a plasma cell malignancy characterized by monoclonal immunoglobulin production. Daratumumab has improved therapeutic outcomes but can interfere with laboratory assessments.**
Methods: **A 73-year-old woman with IgG kappa multiple myeloma achieved remission after initial treatment, then relapsed and received DRD. A monoclonal IgG kappa spike was observed on follow-up SPEP and IFE.**
Results: **Daratumumab, due to its IgG1 kappa structure, may mimic disease-related monoclonal proteins, potentially leading to false detection of residual disease and misclassification of complete response as very good partial response.**
Conclusions: **Recognizing such interference and ensuring strong clinician-biologist collaboration is essential for accurate response interpretation.**
(Clin. Lab. 2026;72:xx-xx. DOI: 10.7754/Clin.Lab.2025.250510)

Correspondence:
Oumaima Skalante
Biochemistry-Toxicology Department
Mohammed V Military Hospital
FAR Avenue
Hay Riad, Rabat
Morocco
Phone: +212 631497873
Email: Skalanteouma@gmail.com

KEYWORDS

multiple myeloma, Daratumumab, IgG kappa, interference, SPEP

LIST OF ABBREVIATIONS

CR - complete response
VGPR - very good partial response
SPEP - serum protein electrophoresis
IFE - serum immunofixation electrophoresis
FLC - free light chains
IMWG - International Myeloma Working Group
DIRA - Daratumumab-specific Immunofixation electrophoresis Reflex Assay

INTRODUCTION

Multiple myeloma is a common hematologic malignancy characterized by bone marrow invasion by malignantly proliferating plasma cells, producing monoclonal immunoglobulin and leading to renal impairment, bone

Case Report accepted May 24, 2025

lysis, and bone marrow failure. The introduction of new targeted therapies has significantly improved the prognosis of this disease [1,2].

Among these new targeted agents, Daratumumab (Darzalex®), a monoclonal IgG kappa antibody, has gained a prominent role in the treatment of heavily pretreated and relapsed multiple myeloma patients [2]. Its efficacy and safety have been demonstrated in several clinical studies [3].

However, the use of Daratumumab can lead to misinterpretation of treatment response in patients with IgG kappa multiple myeloma. Specifically, it interferes with serum protein electrophoresis and immunofixation, two key assays used for disease monitoring and therapeutic response assessment, as defined by the International Myeloma Working Group (IMWG) criteria [4].

CASE REPORT

We report the case of Mrs. M. K., a 73-year-old patient with a medical history of surgically treated colonic adenocarcinoma and cervical squamous cell carcinoma. She has been followed for the past three years for IgG kappa multiple myeloma.

Initially, the patient was treated with chemotherapy consisting of VTD cycles (Bortezomib [Velcade], Thalidomide, and Dexamethasone), which resulted in clinical and biological improvement, leading to disease remission.

The patient subsequently developed severe lower back pain that significantly limited her mobility, prompting rehospitalization. Upon further investigation, a loss of hematological response and both biochemical and skeletal relapse were diagnosed. This was evidenced by a progressive increase in free kappa light chains and the appearance of a monoclonal spike on serum protein electrophoresis (SPEP), migrating in the gamma region and measured at 14.6 g/L (Figure 1). Serum immunofixation electrophoresis (IFE) identified this monoclonal spike as an IgG kappa, corresponding to the patient's known monoclonal component of multiple myeloma (Figure 1).

In light of the relapse, the decision was made to initiate targeted therapy, and the patient was started on a DRD regimen (Daratumumab, Lenalidomide, and Dexamethasone).

Following initiation of this treatment, and during routine disease monitoring, the patient's new SPEP revealed a decrease in the gamma globulin region, accompanied with a discrete monoclonal peak migrating into this zone (Figure 2). Serum immunosubtraction and IFE were then performed: the discrete monoclonal peak corresponded to a monoclonal immunoglobulin of IgG kappa isotype (Figures 2 and 3).

After discussion with the clinician, it became clear that the patient was progressing well clinically and that this IgG kappa did not correspond to residual Ig but certainly to the Daratumumab.

DISCUSSION

Daratumumab (Darzalex®) is the first anti-CD38 monoclonal antibody approved for the treatment of patients with multiple myeloma. It received marketing authorization in 2016. Its mechanism of action involves direct targeting of myeloma cells expressing the CD38 surface antigen. In addition to its direct cytotoxic effect, Daratumumab also exerts antitumor activity through immune-mediated mechanisms and possesses immuno-modulatory properties [2].

This antineoplastic agent is indicated as monotherapy in adult patients with relapsed and refractory multiple myeloma whose previous treatments included a proteasome inhibitor and an immunomodulatory agent and in combination with Lenalidomide and Dexamethasone or with Bortezomib and Dexamethasone, in adult patients with multiple myeloma who have received at least one line of treatment [2]. In 2022, the French Authority for Health (Haute Autorite de Sante, HAS) recommended its use for all patients for first-line therapy, regardless of eligibility for autologous peripheral stem cell transplantation [5].

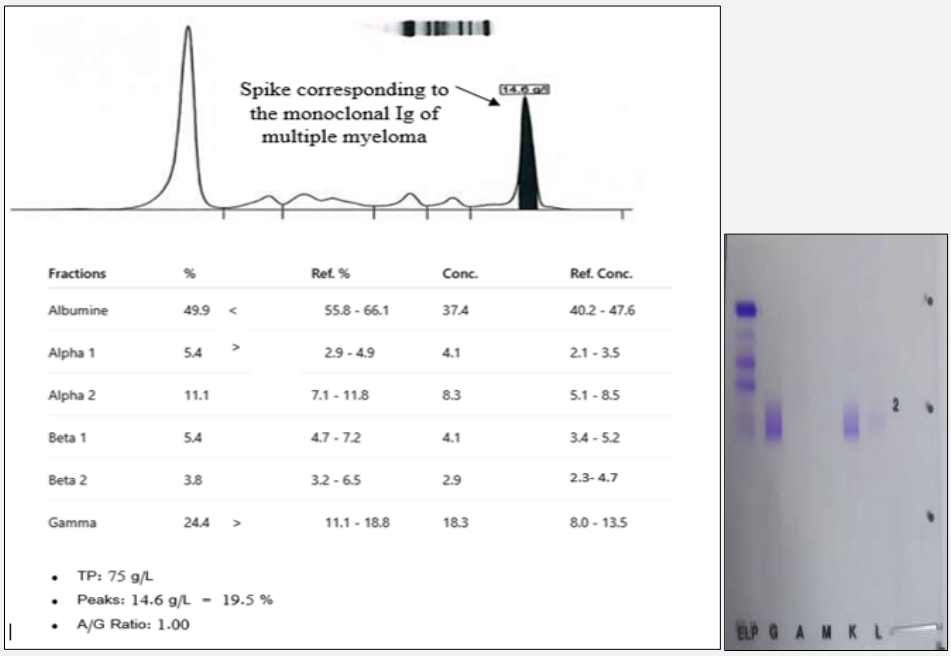
According to several studies, its use has produced impressive results with complete responses (CR) and improved patient survival rates [6-8].

However, Daratumumab can be mistaken for the monoclonal Ig of multiple myeloma, as it closely migrates with or co-migrates in the gamma region on SPEP and may even cause restriction in gamma region heterogeneity [4,9]. Due to its IgG1-κ structure, Daratumumab may be detected as a monoclonal immunoglobulin on both SPEP and IFE, the key assays used to monitor monoclonal gammopathies, resulting in false-positive findings that may interfere with accurate assessment of treatment response. This interference may lead to underestimation or misclassification of a CR as a very good partial response (VGPR), which can have serious clinical and therapeutic implications [4,10].

According to the 2012 IMWG criteria, CR is defined by negative serum and urine immunofixation for the patient's endogenous IgG kappa, normal free light chain ratio, and ≤ 5% bone marrow plasma cells. In contrast, VGPR is defined as a ≥ 90% reduction in serum monoclonal protein and urine M-protein < 100 mg/24 hours, but without complete disappearance [4,11,12].

When interpreting SPEP results, Daratumumab is generally easy to identify when it migrates in a position distinct from that of the endogenous monoclonal immunoglobulin. However, co-migration with the patient's myeloma-related monoclonal IgG kappa can introduce bias in the quantification of this endogenous component, potentially masking its clearance on SPEP, a critical requirement for documenting CR. According to pharmacokinetic studies, the concentration of the monoclonal spike attributable to Daratumumab on SPEP can reach approximately 1 g/L on average [4,9].

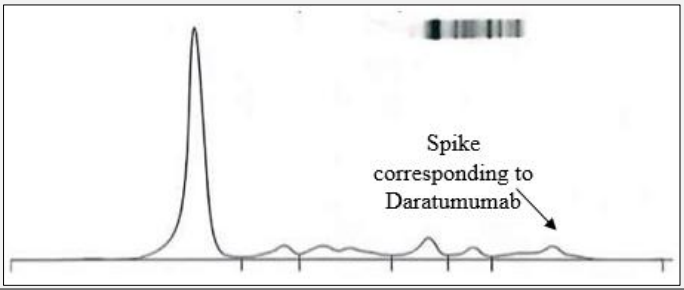
In contrast, Daratumumab does not appear on urine protein electrophoresis or immunofixation, as it is not re-



Fractions	%		Ref. %	Conc.	Ref. Conc.
Albumine	49.9	<	55.8 - 66.1	37.4	40.2 - 47.6
Alpha 1	5.4	>	2.9 - 4.9	4.1	2.1 - 3.5
Alpha 2	11.1		7.1 - 11.8	8.3	5.1 - 8.5
Beta 1	5.4		4.7 - 7.2	4.1	3.4 - 5.2
Beta 2	3.8		3.2 - 6.5	2.9	2.3- 4.7
Gamma	24.4	>	11.1 - 18.8	18.3	8.0 - 13.5

- TP: 75 g/L
- Peaks: 14.6 g/L = 19.5 %
- A/G Ratio: 1.00

Figure 1. Serum protein electrophoresis and serum protein immunofixation before initiation of Daratumumab therapy.



Fractions	%	Ref. %	Conc.	Ref. Conc.
Albumine	65.5	55.8 - 66.1	34.1	40.2 - 47.6
Alpha 1	5.4	2.9 - 4.9	2.8	2.1 - 3.5
Alpha 2	10.5	7.1 - 11.8	5.5	5.1 - 8.5
Beta 1	7.2	4.7 - 7.2	3.7	3.4 - 5.2
Beta 2	3.8	3.2 - 6.5	2.0	2.3 - 4.7
Gamma	7.6	11.1 - 18.8	4.0	8.0 - 13.5

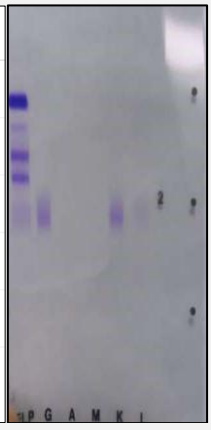


Figure 2. Serum protein electrophoresis and serum protein immunofixation after initiation of Daratumumab therapy.

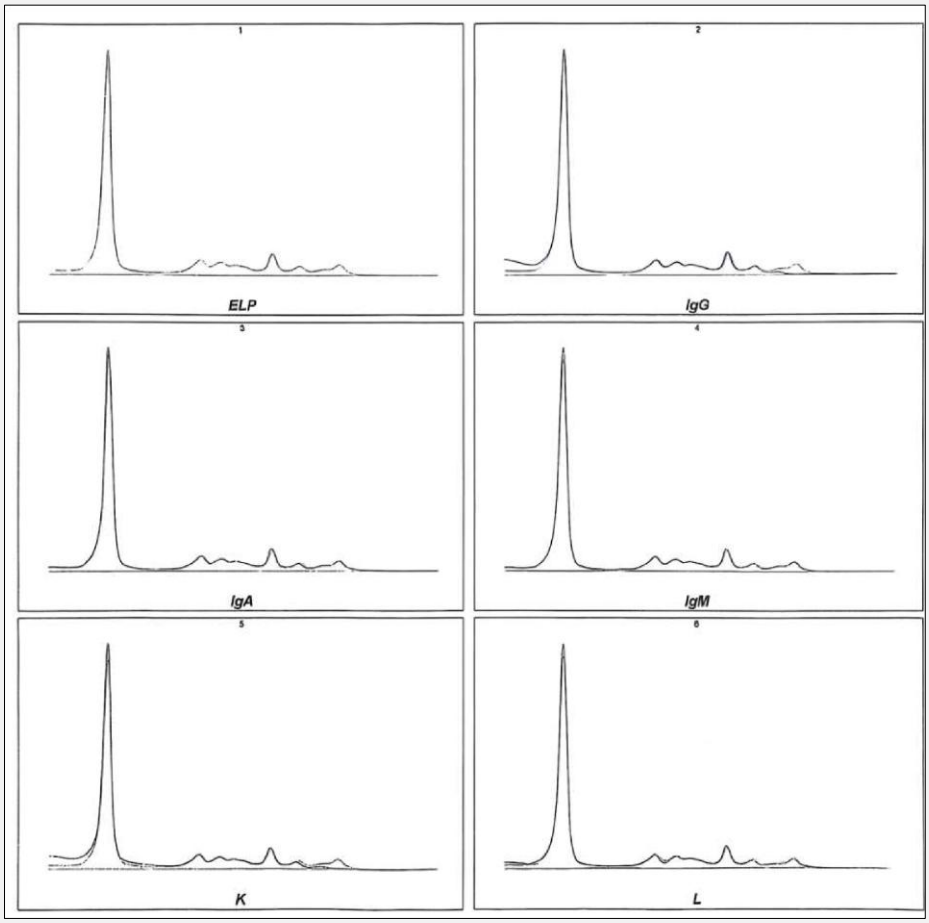


Figure 3. Serum immunosubtraction.

The faint monoclonal spike corresponds to an IgG kappa.

nally excreted. Additionally, it does not interfere with the measurement of serum free light chains (sFLCs), since it is a complete monoclonal immunoglobulin [13].
To overcome the interference caused by Daratumumab, the company Sebia developed the DIRA test (Daratumumab-specific Immunofixation electrophoresis Reflex Assay), marketed under the name Hydrashift 2/4 Daratumumab®. This assay involves the addition of a murine anti-idiotype monoclonal antibody to the patient's serum, which specifically targets the variable region of Daratumumab, resulting in the formation of an immune complex.
During protein electrophoresis, the anti-Daratumumab-Daratumumab complex migrates outside the γ-globulin region, typically into the α- or β-globulin regions, allowing it to be distinguished from the patient's endogenous monoclonal Ig. As a result, the γ-globulin zone is cleared of Daratumumab interference, enabling accurate interpretation of the immunofixation results.
In a positive DIRA test, Daratumumab is shifted, and the pathological IgG kappa monoclonal protein remains visible. A negative DIRA test is characterized by the absence of the monoclonal band after Daratumumab is shifted, indicating a favorable therapeutic response.
The DIRA test is automatable, easy to implement, and is noted for its high specificity, sensitivity, and reproducibility. However, it remains relatively costly [11,10].
The issue of interference between Daratumumab and the monoclonal immunoglobulins of multiple myeloma has thus been resolved by the development of the DIRA test, which is specific to Daratumumab. However, for other monoclonal antibodies, the development of additional specific antisera would be required [10].
Indeed, Daratumumab is not the only therapeutic antibody that can cause this interference. Many other monoclonal antibodies are prescribed by clinicians for the treatment of neoplastic or autoimmune diseases and may similarly cause interference with SPEP and IFE

[10]. A case of a patient with multiple myeloma with IgD kappa, treated with Siltuximab, was reported, where follow-up by SPEP revealed the association of IgG kappa with IgD kappa, which is rare. A study was then conducted on other patients receiving the same treatment for multiple myeloma, where SPEP revealed the presence of this IgG kappa, which corresponded to the interference caused by Siltuximab [14]. Other monoclonal antibodies were tested in the same study: Rituximab, Trastuzumab, Bevacizumab, Infliximab, Cetuximab, and Adalimumab. They were detected by SPEP and IFE as monoclonal IgG kappa proteins [14]. In another study, patients treated with Ofatumumab (IgG kappa) for Waldenstrom's disease (monoclonal gammopathy with IgM) showed a faint IgG kappa band on SPEP/IFE in addition to the endogenous IgM during treatment. These IgG Kappa bands corresponded to Ofatumumab and disappeared after treatment ended [15].

Furthermore, mass spectrometry represents a promising alternative approach that enables the identification of any therapeutic monoclonal antibody based on its molecular mass, allowing for easy detection and discrimination between therapeutic monoclonal antibodies and monoclonal Igs from myeloma. It provides a conclusive analysis with detection thresholds lower than those of electrophoretic techniques. However, this technology is not yet available for routine use in all laboratories [10].

CONCLUSION

The interference of therapeutic monoclonal antibodies, including Daratumumab, with monoclonal Ig of multiple myeloma in SPEP and IFE is possible during treatment.

It is therefore essential to emphasize the importance of clinicobiological discussions, which allow the biologist to properly interpret the results of SPEP and IFE, and enable the clinician to reliably assess the therapeutic response in multiple myeloma patients treated with monoclonal antibodies.

Source of Funds:
We gratefully acknowledge the financial support provided by Masterlab.

Declaration of Interest:
None.

References:

1. Berenson J. Multiple myeloma - Hematology and oncology. MSD Manuals August 2024. https://www.msdmanuals.com/professional/hematology-and-oncology/plasma-cell-disorders/multiple-myeloma
2. Croizier C, Bailly S. Daratumumab for multiple myeloma. Bulletin du Cancer 2018;105:985-91. https://www.sciencedirect.com/science/article/abs/pii/S0007455118302790
3. Wang Y, Li Y, Chai Y. Efficacy and safety of daratumumab in the treatment of multiple myeloma: a systematic review and meta-analysis. J Int Med Res 2021 Aug;49(8):30006052110381 35. (PMID: 34433331)
4. van de Donk NW, Otten HG, El Haddad O, et al, Interference of daratumumab in monitoring multiple myeloma patients using serum immunofixation electrophoresis can be abrogated using the daratumumab IFE reflex assay (DIRA). Clin Chem Lab Med 2016 Jun 1;54(6):1105-9. (PMID: 26812873)
5. Haute Autorite de Sante. DARZALEX (daratumumab). https://www.has-sante.fr/upload/docs/application/pdf/2023-04/darzalex_071222_summary_ct19668.pdf
6. Usmani SZ, Nahi H, Plesner T, et al. Daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma: final results from the phase 2 GEN501 and SIRIUS trials. Lancet Haematol 2020 Jun;7(6):e447-e455. (PMID: 32470437)
7. Lokhorst HM, Plesner T, Laubach JP, et al. Targeting CD38 with Daratumumab Monotherapy in Multiple Myeloma. N Engl J Med 2015 Sep 24;373(13):1207-19. (PMID: 26308596)
8. Plesner T, Arkenau HT, Gimsing P, et al. Phase 1/2 study of daratumumab, lenalidomide, and dexamethasone for relapsed multiple myeloma. Blood 2016;128(14):1821-8. https://ashpublications.org/blood/article/128/14/1821/35650/Phase-1-2-study-of-daratumumab-lenalidomide-and
9. N. W. C. J. van de Donk, Philippe Moreau, Torben Plesner, et al , Clinical efficacy and management of monoclonal antibodies targeting CD38 and SLAMF7 in multiple myeloma , Blood 2016; 127(6):681-95. https://ashpublications.org/blood/article/127/6/681/34986/Clinical-efficacy-and-management-of-monoclonal
10. F. Lussac-Sorton, Multiple myeloma treatment with Daratumumab : interference in biological response assessment and interest of Sebia Hydrashift for serum immunofixation electrophoresis interpretation. Sciences du Vivant [q-bio] 2019. dumas-02361129. https://dumas.ccsd.cnrs.fr/dumas-02361129v1/document
11. McCudden C, Axel AE, Slaets D, et al. Monitoring multiple myeloma patients treated with daratumumab: teasing out monoclonal antibody interference. Clin Chem Lab Med 2016 Jun 1;54(6): 1095-104. (PMID: 27028734)
12. Modglin L. Multiple Myeloma Treatment Response Levels: CR, VGPR, PR and More. Patient Power Mar 11, 2025. https://www.patientpower.info/multiple-myeloma/vgpr-multiple-myeloma
13. Rosenberg AS, Bainbridge S, Pahwa R, Jialal I. Investigation into the interference of the monoclonal antibody daratumumab on the free light chain assay. Clin Biochem 2016 Oct;49(15):1202-4. (PMID: 27475249)
14. McCudden CR, Voorhees PM, Hainsworth SA, et al. Interference of Monoclonal Antibody Therapies with Serum Protein Electrophoresis Tests. Clin Chem 2010 Dec;56(12):1897-9. (PMID: 20940329)
15. Genzen JR, Kawaguchi KR, Furman RR. Detection of a monoclonal antibody therapy (ofatumumab) by serum protein and immunofixation electrophoresis. Br J Haematol 2011 Oct;155(1): 123-5. (PMID: 21521182)