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CASE REPORT

Resolving Therapeutic Monoclonal Antibody Interference in an Immunoglobulin M Kappa Multiple Myeloma Patient Using a Mass Spectrometry Assay

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ABSTRACT

Background: **Therapeutic monoclonal antibodies can interfere with immunofixation electrophoresis (IFE) during multiple myeloma monitoring.**
Case Presentation: **Serum samples from an immunoglobulin M kappa (IgMκ) myeloma patient on daratumumab therapy were analyzed by serum protein electrophoresis (SPEP)/IFE and a mass spectrometry assay. A new immunoglobulin G kappa (IgGκ) band appeared on IFE during active treatment. Mass spectrometry identified a monoclonal peak at *m/z* 23,386, matching daratumumab. The band disappeared at trough concentration.**
Conclusions: **Mass spectrometry rapidly identified daratumumab interference, serving as a reagent-independent confirmatory tool to avoid misinterpreting therapeutic antibodies as clonal evolution.**
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KEYWORDS

multiple myeloma, immunofixation electrophoresis, mass spectrometry assay, therapeutic antibody interference

INTRODUCTION

Multiple myeloma is a plasma cell neoplasm characterized by the production of monoclonal immunoglobulin (M-protein) [1]. While multiple myeloma remains incurable, patient survival rates are steadily improving [2]. Laboratory monitoring, primarily through serum protein electrophoresis (SPEP) and immunofixation electrophoresis (IFE), is essential for assessing treatment response. According to the International Myeloma Working Group (IMWG) criteria, the absence of a detectable M-protein by both SPEP and IFE immunofixation is required for a Complete Response [3].
Daratumumab, a human IgGκ monoclonal antibody targeting CD38, improves outcomes in multiple myeloma when combined with lenalidomide and dexamethasone. The phase III MAIA study demonstrated that the DRd regimen significantly prolonged progression-free sur-

vival and overall survival compared with Rd alone in patients with newly diagnosed multiple myeloma ineligible for autologous stem cell transplantation [4]. However, as an IgGκ protein detectable by SPEP/IFE, daratumumab produces an electrophoretic band indistinguishable from an M-protein, thereby complicating response assessment.

Methods exist to distinguish therapeutic antibodies from disease-related M-proteins, such as the daratumumab IFE reflex assay (DIRA). However, these approaches are inherently limited by their dependence on drug-specific anti-idiotypic antibodies and remain applicable only to the targeted agent [5]. In contrast, the iMS-IP assay enables precise determination of M-protein light chain *m/z* values by mass spectrometry. This case report demonstrates the utility of the iMS-IP assay in rapidly identifying daratumumab interference in a patient with IgMκ multiple myeloma.

CASE PRESENTATION

A 65-year-old woman was diagnosed with IgMκ multiple myeloma on December 12, 2024. Pre-treatment serum protein electrophoresis (SPEP) revealed a dense, monoclonal band in the γ region, and immunofixation electrophoresis (IFE) confirmed this band as an IgMκ M-protein (Figure 1a).

The physician initiated combination therapy with daratumumab, lenalidomide, and dexamethasone (the DRd regimen) on December 17, 2024. Daratumumab was administered at the standard dosage of 16 mg/kg intravenously, following the recommended schedule: weekly for the first 8 weeks, biweekly until week 24, and then monthly for maintenance therapy.

The key clinical timepoints were: diagnosis on December 12, 2024; initiation of the DRd regimen on December 17, 2024; appearance of a new IgGκ band on April 14, 2025 (during active biweekly dosing); and disappearance of the IgGκ band at trough concentration on July 21, 2025 (during maintenance therapy).

On April 14, 2025, while on a biweekly dosing regimen, SPEP revealed a new, distinct band in the mid-γ region adjacent to the original IgMκ band (Figure 1b, arrow). IFE identified this new band as IgGκ. We suspected this represented daratumumab interference.

For confirmation, analysis was performed using the iMS-IP assay. The iMS-IP assay is an immunoenrichment-coupled MALDI-TOF mass spectrometry method operated in linear positive ion mode over an *m/z* range of 2,000 - 20,000, with an internal control for signal normalization and a turnaround time of approximately 4 hours. The results revealed three monoclonal light chain peaks (Figure 2): one in the IgG fraction at *m/z* 23,386, and another in the IgM fraction at *m/z* 23,413, corresponding to the patient's original IgMκ M-protein. Previous studies have demonstrated that spiking normal human serum with daratumumab to a concentration of 1 g/L, as well as analyzing the pure drug itself at 1 g/L, yields monoclonal peaks by mass spectrometry at approximately *m/z* 23,387 and 23,385 [6]. The monoclonal peak observed at *m/z* 23,386 in our case closely matches these reference values and can therefore be attributed to the therapeutic daratumumab.

On July 21, 2025, after transitioning to monthly maintenance therapy, a serum sample drawn just before the next infusion (trough concentration) was analyzed. SPEP showed only a faint residual band in the mid-gamma region (Figure 1c). Crucially, IFE showed the IgGκ component was no longer detectable, with only the patient's faint IgMκ band present. This temporal correlation - appearance during active treatment and disappearance at trough - strongly supported the origin of the IgGκ band as daratumumab.

Clinical response and follow-up: At the trough timepoint (July 21, 2025), the patient achieved a very good partial response (VGPR) according to IMWG criteria, with > 90% reduction in serum M-protein from baseline and normalization of the serum free light chain ratio. No adverse events were observed during the entire DRd treatment period. The ongoing monitoring plan includes SPEP/IFE every 3 months, serum free light chain assay, and routine safety assessments at each cycle. As of the last follow-up (December 2025), the patient remains on monthly daratumumab maintenance with sustained M-protein negativity and no evidence of disease progression.

DISCUSSION

In this case, we demonstrate that daratumumab interferes with M-protein detection by both SPEP and IFE. This interference was rapidly identified using an iMS-IP assay-a MALDI-TOF mass spectrometry-based method that requires no antibody enrichment and is simple to perform.

The diagnostic challenge arises primarily from daratumumab's pharmacological properties. As an anti-CD38 IgGκ monoclonal antibody, daratumumab requires therapeutic serum concentrations of 0.5 - 2 g/L during treatment, with an average peak of approximately 0.9 g/L [7]. However, the detection limit of SPEP for M-proteins is approximately 0.4 g/L, while IFE has a limit of approximately 0.2 g/L [8]. Thus, daratumumab remains detectable by both methods during active treatment, creating a potential source of misinterpretation. During maintenance therapy, trough concentrations - sampled immediately before the next infusion - may fall below the IFE detection limit given the drug's 21-day half-life, at which point the therapeutic band may no longer be visible.

This challenge is not unique to daratumumab. Other anti-CD38 monoclonal antibodies present similar interpretive difficulties. Belimumab appears as an IgGλ band in the gamma region, and pemivibart demonstrates an anodally-migrating IgGλ band [9,10]. Distinguishing these therapeutic antibodies from endogenous M-proteins on

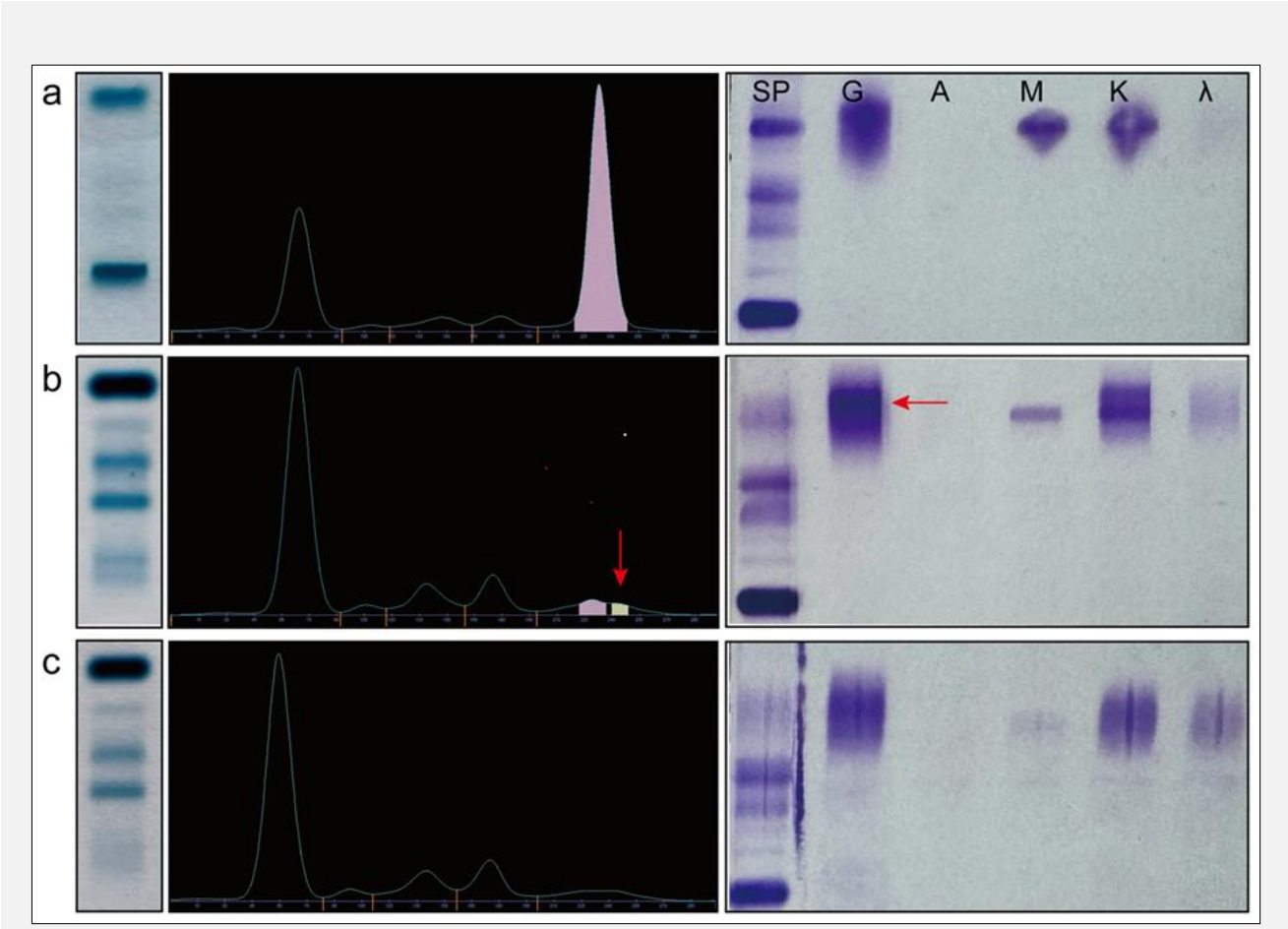

Figure 1. SPEP and IFE results for the patient during three treatment phases.

Figure 1a: SPEP and IFE results before daratumumab treatment (December 12, 2024), showing a dense monoclonal band in the γ region confirmed as IgMκ M-protein.
Figure 1b: SPEP and IFE results during active daratumumab treatment (April 14, 2025). Following biweekly dosing, a new, distinct band appeared in the mid-γ region adjacent to the original IgMκ band, identified as IgGκ by IFE. Red arrow: new IgGκ band attributable to daratumumab.
Figure 1c: SPEP and IFE results during daratumumab maintenance therapy (July 21, 2025). A serum sample drawn at trough concentration showed only a faint residual band in the mid-γ region by SPEP, and the IgGκ component was no longer detectable by IFE.

IFE is therefore critical to avoid misclassification of disease response.

Several strategies exist to mitigate this interference. The daratumumab-specific IFE reflex assay (DIRA) uses an anti-daratumumab antibody to shift the drug's electrophoretic migration, allowing differentiation from endogenous M-proteins [11]. However, this approach is specific to daratumumab and does not address interference from other therapeutic antibodies [6]. Moreover, developing new anti-idiotypic antibodies for each novel therapeutic agent is costly and time-consuming.

Here, we used an iMS-IP assay to rapidly resolve daratumumab interference. This mass spectrometry-based approach offers a more universal, reagent-independent solution. Recent validation studies demonstrate that the iMS-IP assay achieves a high detection rate of 86.5% (32/37) of identifying daratumumab interference in treated patients, significantly outperforming conventional IFE [12].

Based on these considerations, we propose an integrated, tiered laboratory diagnostic pathway: use cost-effective SPEP/IFE as first-line screening; when therapeutic antibody interference is suspected, utilize mass spectrometry as the primary confirmatory tool due to its broad-spectrum detection capability; if mass spectrometry is unavailable or further confirmation is needed, specific assays such as DIRA can be employed as a supplementary approach. This pathway balances diagnostic

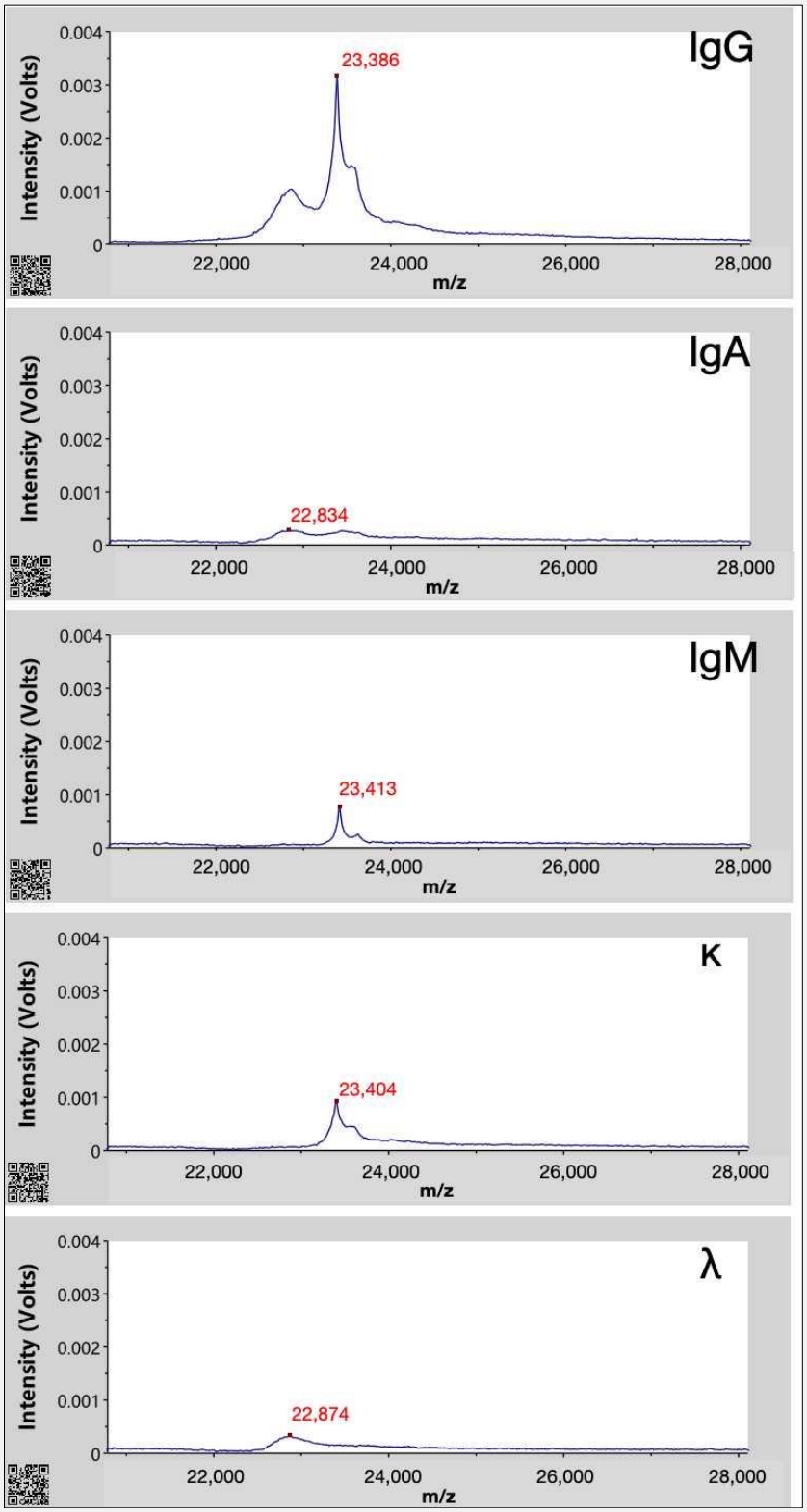

Figure 2. Results of the iMS-IP analysis performed on April 14, following a regimen of twice-weekly drug treatments.

Red numerals: detected *m/z* values of the most intense monoclonal peaks.

efficiency, cost, and precision.

Finally, we emphasize the importance of interdisciplinary communication. When a new IgGκ band is detected in a myeloma patient, clinicians should review the medication history for potential therapeutic antibody interference, and laboratory professionals should proactively communicate with clinical teams when such interference is suspected. This collaboration is essential for accurate disease monitoring and informed clinical decision-making.

Several limitations should be acknowledged. This is a single case report, limiting generalizability. Co-existing therapeutic antibody interference could be missed if the *m/z* value overlaps with that of the endogenous M-protein. Additionally, mass spectrometry is not widely available in routine laboratories and incurs higher costs than conventional electrophoresis.

In conclusion, this case demonstrates that the iMS-IP mass spectrometry assay can rapidly and accurately resolve daratumumab interference in IFE monitoring of multiple myeloma patients, serving as a reagent-independent confirmatory tool to avoid misinterpreting therapeutic antibodies as clonal evolution. When therapeutic antibody interference is suspected, mass spectrometry should be considered as the primary confirmatory method.

Ethics Approval and Consent to Participate:

This work was approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang University School of Medicine (reference number: IIT20260511A). Due to the retrospective nature of the study and the anonymization of all patient data, the committee granted a waiver of informed consent. Written informed consent for publication of de-identified case data and images was obtained from the patient's legal representative. A patient perspective statement could not be obtained due to the retrospective study design and the inability to contact the patient directly at the time of manuscript preparation.

Declaration of Generative AI in Scientific Writing:

The author used DeepSeek R1 for grammar polishing only. The author takes full responsibility for the manuscript content.

Declaration of Interest:

All authors declare no conflict of interest.

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