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Identification and Impact of Daratumumab Interference in Protein Electrophoresis: A Case Series of Relapsed Multiple Myeloma Patients

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ABSTRACT

Background: Therapeutic anti-CD38 monoclonal antibodies, notably daratumumab, have transformed the therapeutic landscape for Multiple Myeloma (MM). However, circulating therapeutic monoclonal antibodies present a significant diagnostic challenge by interfering with routine Serum Protein Electrophoresis (SPE) and Immunofixation Electrophoresis (IFE) assays [1]. Daratumumab migrates as an IgG-kappa band in the slow gamma region, mimicking or masking an endogenous monoclonal protein (M-protein) [1,2]. This interference complicates response evaluation under International Myeloma Working Group (IMWG) criteria, potentially preventing accurate assignment of Complete Response (CR) [3].

Case Presentation: We present two clinical cases of relapsed multiple myeloma evaluated at Tata Memorial Centre ACTREC. Case 1 involves a 68-year-old male with an endogenous IgG-kappa clone who displayed a persistent abnormal monoclonal band (100 mg/dL) on SPE with cross-reactivity on IFE following daratumumab therapy. Case 2 involves a 64-year-old female presenting with a biclonal pattern 400 mg/dL and 200mg/dL exhibiting cross-reactivity across IgG-Lambda and IgG-kappa

Conclusion: This case studies demonstrates that Daratumumab, a humanized IgG1-kappa monoclonal antibody, frequently appears as a distinct band in the cathodal gamma-region during electrophoresis. As evidenced by the clinical data, this "drug band" can be misinterpreted as a persistent disease-related M-protein.

Ultimately, distinguishing therapeutic antibodies from endogenous M-proteins is not merely a technical laboratory requirement but a clinical necessity to ensure the accurate assessment of treatment response.

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Introduction

Multiple Myeloma (MM) is a hematologic malignancy characterized by the neoplastic proliferation of clonal plasma cells within the bone marrow. These rogue plasma cells overproduce a single monoclonal immunoglobulin or light chain, clinically recognized as the Monoclonal (M) protein [3]. The quantitative tracking of serum M-protein concentration serves as a direct biomarker for tumor burden and therapeutic response assessment. End-organ damage caused by myeloma is classically described by the CRAB criteria: Calcium elevation, Renal insufficiency, Anemia, and Bone lesions [3].

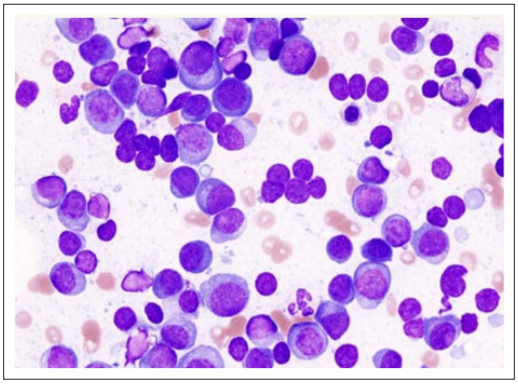

Figure 1: Microscopy Showing Plasma Cell in Peripheral Blood Smear

Table 1: Standard Monitoring tool Kit

Test Method	Clinical Purpose	What it Detects
SIEP	Quantification	Detects and measures the size of the "M-Spike" (g/dl).
IFE	Identification	Determines the antibody type (e.g., lgG Kappa, lgA Lambda).
sFLCAssay	Sensitive Screening	Measures Free Kappa and Lambda light chains in serum
24h UPEP	Renal Assessment	Identifies Bence-Jones proteins in the urine

In routine clinical laboratory workflows, serum protein electrophoresis (SPE) separates proteins into albumin, alpha_1, alpha_2, beta, and gamma fractions according to charge and molecular mass. Immunoglobulins predominantly reside in the gamma-region. Immunofixation electrophoresis (IFE) subsequently characterizes the heavy chain ({IgG}, {IgA}, {IgM}) and light chain (kappa, lambda) isotypes.

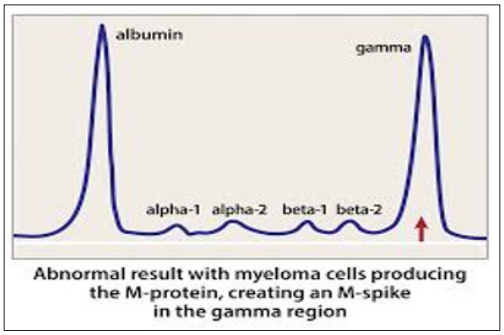

Figure 2: Serum Protein Electrophoresis

The therapeutic landscape of relapsed/refractory MM has been revolutionized by monoclonal antibodies (mAbs) [1]. Daratumumab is a first-in-class humanized {IgG1-}kappa monoclonal antibody that targets CD38, a transmembrane glycoprotein highly expressed on myeloma cells.

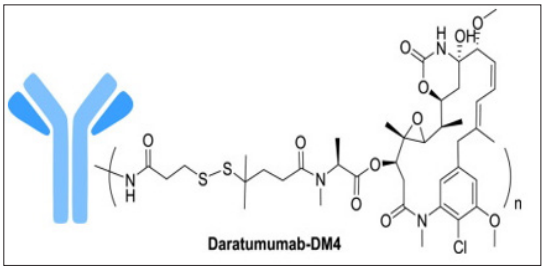

Figure 3: Daratumumab Antibody Structure

Its antitumor activity operates through multiple mechanisms.

Complement-Dependent Cytotoxicity (CDC)
Initiating the complement cascade to induce plasma cell lysis.

Antibody-Dependent Cellular Cytotoxicity (ADCC)
Recruiting natural killer (NK) cells to eliminate target cells.

Antibody-Dependent Cellular Phagocytosis (ADCP)
Promoting macrophage-mediated phagocytosis.

Because Daratumumab is an engineered intact IgG1 kappa antibody, its structural and electrophoretic properties are identical to endogenous human {IgG-}kappa M-proteins. At standard therapeutic dosing schedule (16 mg/kg), serum trough concentrations of Daratumumab frequently range from 0.05 to 0.20 g/dL (50- 200mg/dL), appearing as a distinct, restricted band in the cathodal gamma-region on capillary or gel electrophoresis. When a patient's endogenous clone is also IgG-kappa, or when co-migrating with IgA or IgM bands, this therapeutic "drug band" creates false-positive M-protein results [1]. Under International Myeloma Working Group (IMWG) criteria, achieving Complete Response (CR) strictly mandates total disappearance of the M-protein on serum and urine IFE [3]. Consequently, unmasked therapeutic antibody interference risks underestimating response rates and leads to inappropriate treatment prolongation [1].

Materials and Methods

Study Design & Setting
This retrospective case series was conducted at Tata Memorial Centre ACTREC, Navi Mumbai, India. De-identified clinical and laboratory data were retrieved from the institutional Laboratory Information System (LIS).

Ethical Considerations
The study involved retrospective review of leftover serum samples drawn during routine disease monitoring, entailing no additional blood draws or procedures. The study protocol received expedited institutional ethical review approval.

Analytical Instrumentation Suite
Serum Protein Electrophoresis (SPE)
Performed using capillary electrophoresis on the Sebia MiniCap automated platform to screen and quantify abnormal monoclonal or biclonal bands.

Immunofixation Electrophoresis (IFE)
Performed on the Sebia Hydrasys gel electrophoresis platform using standard antisera IgG, IgA, IgM, free and bound kappa, and lambda to identify heavy and light chain isotypes.

Quantitative Immunoglobulins
Total serum IgG, IgA, and IgM levels were measured by nephelometry on the Beckman Coulter IMMAGE-800 system.

Serum Free Light Chain (sFLC) Assay
Quantitative measurement of free kappa and free lambda light chains was conducted via turbidimetry on the Binding Site Optilite analyzer.

Case Presentations
Case 1
A 68-year-old male with relapsed Multiple Myeloma was receiving maintenance treatment with Inj. Daratumumab (400 mg). Routine monitoring laboratory results are summarized in Table - 2

Case 2
A 64-year-old female patient with known IgG-Lambda relapsed Multiple Myeloma undergoing Daratumumab therapy was evaluated during routine follow-up Table 2.

Table 2: Summary of Case 1 &2 Laboratory Parameters

Parameter	Case 1 (68 yrs / Male)	Case 2 (64 yrs / Female)
Clinical Diagnosis	Relapsed Multiple Myeloma	Relapsed Multiple Myeloma
SPE Pattern	Monoclonal Band 500mg/dL	Biclonal Banding 600mg/dL& 100mg/dL
IFE Pattern	IgG-kappa band present	IgA-kappa and IgG-kappa bands present
Total Immunoglobulins	IgG: 981mg/dL IgA: 63.2mg/dL IgM: 26.0mg/dL	IgG: 1537 mg/dL IgA: 170mg/dL IgM: 42 mg/dL
Total Light Chains	kappa: 681mg/dL lambda: 395mg/dL	kappa: 1520mg/dL lambda: 605mg/dL
SFLC Measurements	Free kappa: 29.72 mg/L Free lambda: 17.74mg/L	Free kappa: 75.77 mg/L Free lambda: 31.50mg/L
SFLC Ratio (kappa/\lambda)	1.68	2.42

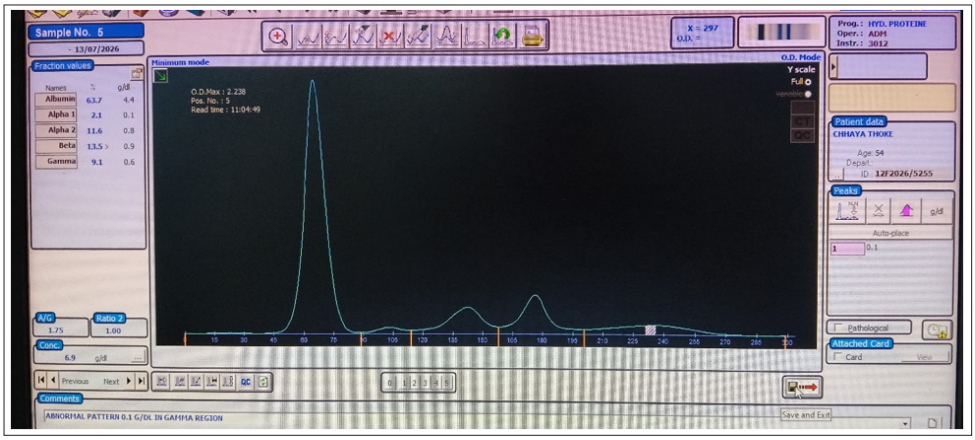

Figure 3: Case no-1 Serum Protein Immuno Electrophoresis

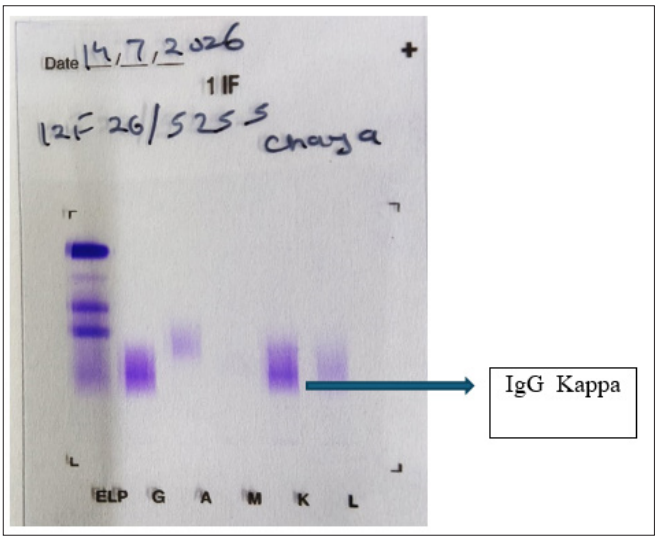

Figure 4: Case no 1 Immunofixation

Immunofixation (Qualitative): Cross reactivity seen with IgG kappa

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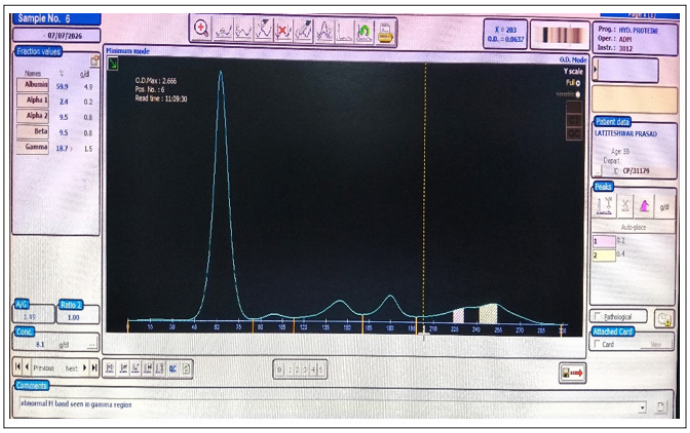

Figure 5: Case no 2 Serum Protein Immuno Electrophoresis

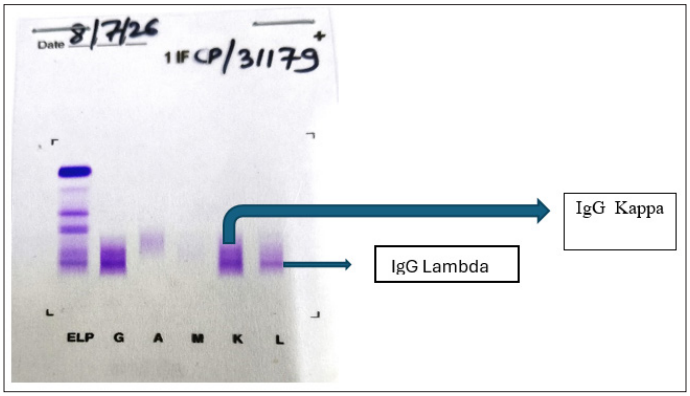

Figure 6: Case no 2 Immunofixation (Qualitative): Cross Reactivity Seen with IgG Lambda and IgG Kappa only

Discussion

Diagnostic Hurdle & Mechanics of Interference

Daratumumab circulates at concentrations that are readily observable on routine electrophoretic media 0.05--0.20 g/dL. Because it is a humanized IgG1-kappa immunoglobulin, it migrates predictably into the cathodal region of the gamma-globulin zone [1].

In patients with non-IgG-kappa myeloma (such as IgA-kappa disease), the drug band produces a pseudo-biclonal pattern. While visually distinct, this can cause clinical confusion regarding secondary oligoclonal responses or clonal evolution. In patients with IgG- kappa disease, Daratumumab directly co-migrates with residual endogenous M-protein. This co-migration prevents the laboratory from confirming total disappearance of the disease band, leaving the patient falsely classified as Very Good Partial Response (VGPR) rather than Complete Response (CR) under IMWG definitions [1-3]. Differentiating therapeutic monoclonal antibodies from true disease-derived M-protein is essential for preventing response misclassification and unnecessary treatment extension [4,5].

Standardized Solutions to Resolve Interference

Hydrashift 2/4 Daratumumab Immunofixation Reflex Assay (DIRA)

To abrogate this interference, specialized reflex assays have been developed [1,4]. The Hydrashift 2/4 Daratumumab Assay (Sebia) utilizes a specific anti-Daratumumab antibody added to patient serum prior to gel electrophoresis.

When the anti-Daratumumab antibody binds to circulating Daratumumab, it alters the overall size and charge of the drug molecule, shifting its electrophoretic migration point away from the cathodal gamma-region toward the anodal alpha_2 position. If the cathodal band disappears entirely after addition of the reagent, the band was purely therapeutic Daratumumab (DIRA negative for disease). If a band remains in the original position, endogenous disease M-protein is still present (DIRA positive). Studies at major cancer centres have demonstrated 100% specificity for the Hydrashift assay in unmasking true disease status.

Mass Spectrometry (MALDI-TOF MS)

Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF MS) offers an ultra-sensitive molecular mass-based alternative [6]. Because mass spectrometry measures the exact mass-to-charge ratio (m/z) of immunoglobulin light and heavy chains, it easily distinguishes the fixed mass signature of Daratumumab (147.5 kDa) from unique patient-specific monoclonal proteins, eliminating electrophoretic co-migration errors [6].

Clinical Decision Matrix & Laboratory SOP

To eliminate diagnostic errors without incurring excessive reagent costs, clinical laboratories should establish standardized decision algorithms integrated with the hospital Laboratory Information System (LIS) [2].

M-Spike Cutoff (> 0.25 g/dL)

Because circulating daratumumab contributes a maximum peak magnitude of approx 0.20 g/dL on SPE, any distinct M-spike measuring > 0.25 g/dL represents true residual disease M-protein, making reflex testing unnecessary [2].

Low-Level M-Spikes (0.25 g/dL)

When an IgG-kappa band measures 0.25g/dL, reflex Hydrashift DIRA or MALDI-TOF MS testing is mandatory to evaluate true response status [2-4].

Non-IgG-kappa Baseline Clones

For patients with known IgA, IgM, or λ disease presenting with a secondary minor IgG-kappa band, an LIS auto-comment should be appended to clarify that the secondary band reflects therapeutic antibody interference [2].

Expected Clinical & Economic Impact

Prevention of Overtreatment

Correctly identifying drug-induced bands enables clinicians to document true Complete Response (CR). This prevents unnecessary dose escalation or toxic chemotherapy, sparing patients from adverse effects.

Improved Accuracy of Prognostic Indicators

Integrating Serum Free Light Chain (SFLC) ratios alongside electrophoretic patterns provides a robust dual-check system to assess underlying light-chain activity when heavy-chain bands are confounded.

Implementation of Standardized Laboratory SOPs

Laboratories should establish automated LIS-driven reflex protocols. When a patient record indicates active anti-CD38 therapy, any detected IgG-kappa band should trigger DIRA testing or automatically include a standardized warning comment for the attending oncologist.

Economic Benefit

High-cost monoclonal antibody regimens can be optimized. Timely transition of patients in true CR to observation or less intensive maintenance phases reduces financial burden on both healthcare systems and patients [7].

Conclusion

Daratumumab frequently manifests as a distinct monoclonal or co-migrating band in the cathodal gamma-region on routine serum protein electrophoresis and immunofixation. As demonstrated by clinical observations at Tata Memorial Centre ACTREC, failing to recognize therapeutic antibody interference can lead to misinterpretation of persistent disease. Adopting reflex assays such as Hydrashift 2/4 DIRA or mass spectrometry into standard laboratory workflows is a clinical necessity to ensure precise response assessment, prevent overtreatment, and uphold IMWG diagnostic standards.

Declarations

Ethical Approval

The study was approved by the Institutional Ethics Committee. Leftover routine clinical serum samples were used under expedited approval.

Conflict of Interest

The author declares that this study was conducted independently without external funding or support from the manufacturers of Daratumumab.

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None.

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