Case Report

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Remission with quadruplet therapy in rare immunoglobulin D lambda myeloma lacking CRAB features, with 13q deletion and monosomy 12

Suresh Prajapati[1], Charmi Jyotishi[1], Dharmesh Vaghasiya[2], Reeshu Gupta[1,3]

Abstract:

Immunoglobulin D (IgD) multiple myeloma (MM) is a rare and aggressive subtype of plasma cell neoplasm, comprising <2% of cases. It often presents with atypical clinical features and may be misdiagnosed due to low levels of detectable M-protein. A 55-year-old male presented with progressive fatigue and mild pallor. He had no bone pain, hypercalcemia, renal impairment, or lymphadenopathy. Laboratory evaluation revealed normocytic anemia (hemoglobin: 12 g/dL), hypoalbuminemia (3 g/dL), and normal creatinine and calcium levels. Serum protein electrophoresis showed a monoclonal spike (1.5 g/dL), and immunofixation confirmed monoclonal IgD lambda. Bone marrow aspirate revealed 44% of plasma cells with lambda light chain restriction. Free lambda chains were markedly elevated (2734 mg/L), with a kappa/lambda ratio of 0.005. Biopsy of a buccal mass confirmed extramedullary plasmacytoma. Fluorescence *in situ* hybridization studies showed the deletion of 13q and monosomy 12. Based on bone marrow findings, laboratory data, and cytogenetics, the patient was diagnosed with IgD lambda MM, Revised International Staging System Stage IIIB. He was started on bortezomib, dexamethasone, lenalidomide, and liposomal doxorubicin. After two cycles, the patient showed significant clinical improvement and a reduction in serum free light chains, M-protein, and Bence–Jones proteinuria. This case underscores the importance of early recognition of IgD myeloma and the role of cytogenetics in guiding therapy, especially in cases lacking full partial hypercalcemia, renal dysfunction, anemia, bone lesions (CRAB) profile features.

Keywords:

CRAB, monosomy 12, multiple myeloma, quadruplet therapy

[1]*Department of Applied Sciences, Parul Institute of Applied Sciences, Parul University, Parul Institute of Applied Sciences, Parul University,* [3]*Department of Research, Research and Development Cell, Parul University Vadodara,* [2]*Department of Hematology, Blood and Cancer Institure, Surat, Gujarat, India*

Address for correspondence:
Dr. Reeshu Gupta, Department of Research, Research and Development Cell, Parul University, Vadodara, India.
E-mail: greshu12@gmail.com

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Introduction

Multiple myeloma (MM) is a clonal plasma cell neoplasm with significant clinical and genetic heterogeneity. MM can be of various types, involving different isotypes of immunoglobulin (Ig) heavy and light chains. While IgG and IgA subtypes are common comprising 52% and 21%, respectively, IgD myeloma represents <2% of all cases and is frequently associated with an aggressive course, absence of monoclonal protein on serum protein electrophoresis, low survival of 13–21 months, hypercalcemia, bone lesions, amyloidosis, and extramedullary infiltration.[1] IgD is classified into two types, kappa and lambda. The type lambda is rare while kappa is common. Compared to other types of MM, IgD is common in younger males with a higher incidence of kidney failure. The patients usually have high creatinine, lactate dehydrogenase, beta-2 macroglobulin, and C-reactive protein than other MM subtypes. The M spike in electrophoresis is not obvious due to low levels of IgD.[2] However, lambda light chains are observed in serum

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or urine immunofixation electrophoresis. Serum immunoelectrophoresis (SIE) do not measure IgD, and therefore, such cases are misinterpreted as light chain MM.[3] Cytogenetic abnormalities play a critical role in prognosis and therapeutic decision-making. Here, we present a case of IgD lambda MM with a rare cytogenetic profile involving the deletion of chromosome 13q and monosomy 12.

Case Report

A 55-year-old male was referred to the Haematology Department at Parul Sevashram Hospital with a primary complaint of exertional fatigue persisting over several months. He denied weight loss, fever, or bone pain. There was no history of recurrent infections or bleeding tendencies. Physical examination was unremarkable except for mild pallor. His past medical and family histories were unremarkable, and he was not on any long-term medications. On physical examination, the patient appeared clinically stable with normal vital signs. Mild pallor was noted; however, there was no lymphadenopathy, hepatosplenomegaly, or bone tenderness.

Initial laboratory evaluation revealed a hemoglobin level of 12 g/dL (normal range: 13–17 g/dL) with a mean corpuscular volume of 86.6 fL, indicating normocytic normochromic anemia. The absolute leukocyte count was 1.3 × 10^3/μL (normal range: 4–12 × 10^3/μL), and the platelet count was within the normal range at 211 × 10^9/μL (150–450 × 10^9/μL). Renal function tests showed a creatinine level of 0.79 mg/dL (0.6–1.3), and serum calcium was 8.42 mg/dL (normal range: 8.5–10.5 mg/dL), both within normal limits. However, hypoalbuminemia was noted, with a serum albumin level of 3 g/dL (normal range: 3–5 g/dL).

Given the mild anemia and persistent fatigue, serum protein electrophoresis was performed and revealed a monoclonal spike (M-protein) measuring 1.5 g/dL. Subsequent immunofixation electrophoresis confirmed the presence of a monoclonal IgD lambda paraprotein. Bone marrow aspiration was undertaken to further characterize the monoclonal process. The aspirate showed increased cellularity with plasma cells comprising 44% of the nucleated cell population. Several binucleated and atypical plasma cells were noted. Immunophenotyping revealed lambda light chain restriction, consistent with a clonal plasma cell disorder. Extended serum studies were significant for markedly elevated free lambda light chains at 2734 mg/L (reference range: 5.71–26.3 mg/L) and normal kappa chains at 12.9 mg/L (reference: 3.3–19.4 mg/L), resulting in a profoundly decreased kappa/lambda ratio of 0.005 (normal: 0.26–1.65). Serum beta-2 microglobulin was elevated at 4.78 mg/L (normal range: 1.5–3 mg/L). Quantitative Ig testing demonstrated markedly elevated IgG levels at 44.36 g/L (reference range: 7–16 g/L), with concurrently reduced IgA at 0.27 g/L (reference range: 0.7–4 g/L) and IgM at 0.28 g/L (reference range: 0.4–2.5 g/L). Urine protein electrophoresis confirmed the presence of Bence–Jones proteinuria. To assess disease burden and confirm extramedullary involvement, a biopsy of a buccal mass was performed. Histology with immunohistochemistry showed strong positivity for plasma cell markers CD38 and CD138, along with lambda light chain restriction, establishing the diagnosis of an extramedullary plasmacytoma of clonal origin. This finding distinguished the lesion from other lymphoid or epithelial malignancies and carried important prognostic and therapeutic implications, guiding the decision to pursue intensified therapy. Conventional imaging revealed no lytic bone lesions. Although advanced modalities such as positron emission tomography–computed tomography (PET-CT) or magnetic resonance imaging provide higher sensitivity, resource limitations precluded their use. The absence of bone involvement was, therefore, inferred from clinical evaluation, laboratory findings, and available imaging, though PET-CT would have been valuable for comprehensive staging.

Cytogenetic analysis

Cytogenetic analysis by conventional karyotyping revealed a normal diploid chromosomal complement [Figure 1]. However, fluorescence *in situ* hybridization (FISH) studies identified deletion of chromosome 13q and monosomy 12 [Figure 2]. The latter is a rare and possibly novel abnormality in the context of MM and may carry prognostic significance.

Based on clinical features, laboratory findings, bone marrow morphology, and cytogenetic abnormalities, a final diagnosis of IgD lambda MM, Revised International Staging System (R-ISS) Stage IIIB, was made. The patient was subsequently referred for comprehensive staging and initiation of systemic therapy.

Treatment and response

Following confirmation of the diagnosis of IgD lambda MM, R-ISS stage IIIB, the patient was initiated on an

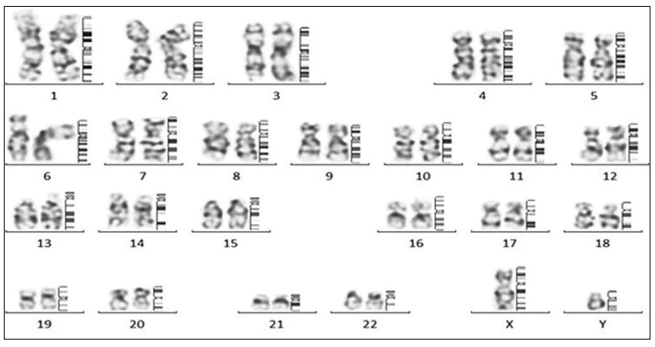

Figure 1: The karyotype of the patient

CHROMOSOME 12/13	ORANGE 13q14.2	GREEN CEN 12	Blue /Aqua 13q34	NO. OF CELLS SHOWING Monosomy 12	NO. OF CELLS SHOWING Deletion 13q14.2/13q34	INTERPRETATION
SIGNALS PER CELL	1	1	1	70	70	70% Positive
SIGNALS PER CELL	2	2	2	00	30	30% Normal
RESULT: nuc ish (D13S319,13q34,CEN 12)×1[70/100]/ nuc ish (D13S319,13q34,CEN 12)×2 [30/100]						
INTERPRETAION						
Positive						

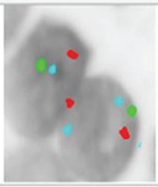

Figure 2: Fluorescence *in situ* hybridization showing monosomy 12 and deletion 13 q

induction regimen comprising of bortezomib 2 mg, dexamethasone 8 mg for 5 days, lenalidomide 25 mg for 20 days, and liposomal doxorubicin 4 mg (VRD-Dox), given in 21-day cycles. This combination was selected in view of the patient's high-risk cytogenetic profile and extramedullary disease, both of which are associated with a more aggressive clinical course and poorer prognosis. Bortezomib, a proteasome inhibitor, was included for its efficacy in high-risk disease and renal safety profile. Liposomal doxorubicin was incorporated to enhance the depth of response, particularly given the high tumor burden and extramedullary involvement.

The regimen was well tolerated, with no significant hematologic or nonhematologic toxicities noted during the initial treatment cycles. Response was evaluated using clinical improvement, reduction in serum free lambda chains, decline in M-protein concentration on electrophoresis, and decreased Bence–Jones proteinuria. The patient reported significant clinical improvement after the first cycle, with marked reduction in fatigue and enhanced exercise tolerance. Follow-up serum studies showed a substantial reduction in free lambda light chain levels (before therapy: 434 g/dL; after therapy 395 g/dL) and a progressive decline in the M-protein concentration on serum protein electrophoresis (M-protein concentration after therapy: 1.67 g/dL; before therapy 2.08 g/dL). Repeat urine protein electrophoresis demonstrated reduced Bence–Jones protein excretion. These findings were consistent with a favorable hematological response to therapy. The patient continued to receive regular follow-up and monitoring for treatment response and potential adverse effects, with plans for consolidation and further disease reassessment upon completion of the initial induction phase.

Discussion

This case highlights a rare presentation of IgD lambda MM with extramedullary involvement and uncommon cytogenetic abnormalities. Unlike classical myeloma presentations with overt anemia, hypercalcemia, renal impairment, and lytic bone lesions, this patient's initial manifestations were nonspecific, with exertional fatigue and normocytic normochromic anemia being the only apparent findings. IgD myeloma is often underrecognized because of its subtle biochemical profile and low serum IgD levels. In this instance, the anemia most likely reflected marrow infiltration by plasma cells rather than the usual CRAB-related end-organ damage, underscoring the importance of advanced diagnostic evaluation in patients with unexplained anemia and otherwise nonspecific clinical features. Although the patient did not exhibit the classical CRAB features typically associated with symptomatic MM, the presence of significant bone marrow infiltration (44% of plasma cells), markedly elevated free lambda light chains with an abnormal kappa/lambda ratio, extramedullary involvement, elevated β2-microglobulin, and high-risk cytogenetic abnormalities collectively indicate a biologically aggressive form of the disease. This underscores the need for high clinical suspicion in cases with subtle or isolated abnormalities, particularly when standard electrophoresis may miss low-concentration IgD monoclonal proteins.

Deletion of 13q is a well-established adverse prognostic factor in MM. However, monosomy 12 has not been previously well described in the literature and may represent a novel aberration associated with disease biology or drug resistance. Such abnormalities call for further genomic characterization in future studies. In this case, the patient experienced noticeable clinical improvement after two cycles of bortezomib-based combination regimen, reflecting an encouraging initial response to proteasome inhibitor-based therapy. This treatment plan is consistent with established protocols for managing high-risk MM.[4] However, IgD myeloma is known for early relapse following initial therapy[5]

or autologous transplantation.[6] Therefore, long-term monitoring of the disease and proactive planning for consolidation strategies are needed.

This case shows how difficult it can be to diagnose IgD lambda myeloma, especially when the usual CRAB signs are missing. The patient only had tiredness and mild anemia, so the disease could have been missed without careful testing. Since IgD levels are often too low to pick up on routine electrophoresis, tests like immunofixation and FISH are very important. The finding of uncommon genetic changes such as monosomy 12 also points to the need for full cytogenetic workup. In this patient, a four-drug treatment gave good remission even though the disease was aggressive with plasmacytoma outside the bone marrow. After such induction, the best plan is to move to stem cell transplant, if possible, then continue with maintenance drugs like lenalidomide or bortezomib, and keep the patient under close watch. Because IgD myeloma tends to relapse early, planning ahead for transplant and maintenance is necessary to keep remission for longer.

Limitations

The main limitations of this report are as follows: (i) there is no long-term follow-up, so we cannot comment on how durable the remission will be; (ii) next-generation sequencing was not done, which could have given more genetic details; and (iii) this is a single patient report, so the findings cannot be generalized.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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