



Case report

A case of IgD myeloma representing a missed biclonal paraproteinemia or isotype switch in a patient previously diagnosed with IgA-lambda myeloma



Julie Chepovetsky*, Ajai Chari, Sundar Jagannath, Lakshmi Ramanathan

Mount Sinai Hospital, Dept of Pathology, Gustave L Levy Place, Box 1194, New York, NY 10128, USA

ARTICLE INFO

Article history:

Received 28 June 2013

Received in revised form 30 July 2013

Accepted 2 August 2013

Available online 13 August 2013

Keywords:

Multiple myeloma

IgD

Biclonal myeloma

Isotype switch

Immunofixation

ABSTRACT

Background: Multiple myeloma is a clonal plasma cell neoplasm that is identified in the laboratory by a presence of a monoclonal immunoglobulin or increased plasma light chain levels.

Methods: The most commonly identified and tested immunoglobulins are IgA, IgG and IgM.

Results: Rare cases of multiple myeloma present with monoclonal IgD and IgE paraproteins.

Conclusion: We present a case of IgD myeloma diagnosed in a patient who had achieved partial remission from a previously diagnosed IgA myeloma, possibly representing a missed biclonal paraproteinemia or isotype switch after treatment.

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1. Introduction

Multiple myeloma (MM) is characterized by an expansion of a clonal plasma cell population. Diagnostic criteria include a monoclonal plasma cell population that comprises $\geq 10\%$ of cellularity on a bone marrow biopsy, presence of a serum or a urine monoclonal immunoglobulin (M-protein) and evidence of end-organ damage attributed to one of the underlying neoplastic disorders, such as hypercalcemia, renal insufficiency, anemia, and lytic bone lesions. Exceptions to these criteria include patients with true non-secretory multiple myeloma [1]. Laboratory diagnosis of MM includes serum and urine protein electrophoresis (SPEP and UPEP respectively), nephelometric or turbidometric quantitative measurement of immunoglobulins IgG, IgA and IgM, measurement of free serum light chains (K and λ) and immunofixation electrophoresis (IFE) using antisera for IgG, IgM and IgA.

The majority of myeloma cases present with an SPEP positive for a single M-protein composed of an intact immunoglobulin (heavy and light chains) as well as abnormal serum free light chain concentrations. The frequencies of the various immunoglobulin paraproteins are: IgG – 52%, IgA – 21%, light-chain only – 16%, non-secretory – 6%, IgD – 2%, and IgM – 0.5% [2]. We present a case of a patient who was diagnosed with and treated for an IgA- λ MM. The patient did not achieve complete remission and was later found to have a monoclonal IgD paraprotein

representing either a missed case of biclonal MM or a clonal isotype switching.

2. Case report

A 41-y-old male initially presented to an outside hospital with low back pain and was found to have diffuse lytic lesions of the lumbar spine and pelvis and a paravertebral soft tissue mass. Serum protein electrophoresis (SPEP) identified a monoclonal protein in the late beta region totaling 0.96 mg/dl. This was classified on immunofixation electrophoresis (IFE) to be a monoclonal intact immunoglobulin (IgA λ) with free λ light chains (λ). Bone marrow biopsy showed diffuse infiltration by atypical plasma cells. The diagnosis at that time was multiple myeloma, Durie–Salmon Stage IIIA with undefined ISS staging.

The patient was treated with lenalidomide, dexamethasone and monthly zometa and eventually achieved partial remission. The patient then underwent an autologous stem cell transplant with good engraftment. He continued to be monitored with standard laboratory follow-up care (including SPEP, immunoglobulin quantification, free light chain quantification and IFE) but never achieved complete remission.

Approximately 2 y after initial diagnosis the patient transferred his care to our institution. At that time there was no longer an identifiable monoclonal protein (M-protein) on SPEP, excess free λ but his free κ /free λ ratio never achieved normal levels. His IgG and IgM levels were continuously suppressed and his IFE results using antisera for IgG, IgA and IgM did not show a monoclonal heavy chain component. Because these values were discordant with his previous findings, the lab was

* Corresponding author.

E-mail address: juliechepovetsky@gmail.com (J. Chepovetsky).

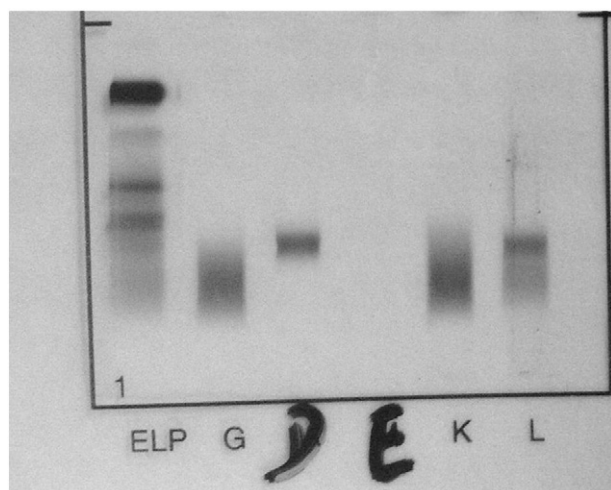


Fig. 1. Immunofixation electrophoresis with anti-sera for IgD and IgE. A monoclonal band can be seen with application of IgD heavy chain and lambda light chain antisera. Polyclonal production of IgG and kappa is also seen. ELP = control, G = anti-IgG, D = anti-IgD, E = anti-IgE, K = anti-kappa, L = anti-lambda.

asked to perform additional IFE with anti-IgD and anti-IgE and a monoclonal IgD band was discovered with monoclonal λ (see Fig. 1).

On follow-up testing an IgD band, without a corresponding light chain, was identified. The original finding of monoclonal IgA was not confirmed, although free λ light chain levels continued to be elevated and the patient continued a chemotherapy regiment. A new diagnosis of IgD myeloma with free λ light chains was established. The laboratory data for this case are summarized in Table 1.

3. Discussion

IgD myeloma was first described in 1965 by Rowe and Fahey [3]. It is typically associated with younger presenting age, increased clonal serum free light chains (most commonly λ chains), Bence-Jones proteinuria, high incidence of renal failure and short survival time after diagnosis. Clinically, these patients are more likely to develop extramedullary lesions as well as amyloidosis [4]. As a fairly rare entity (comprising only 2% of all myeloma cases), IgD myeloma has become a diagnostic pitfall in clinical laboratory testing. Of all immunoglobulins IgD is present in the lowest concentration in serum, has a significantly lower synthetic rate and the highest catabolic rate, making it the most difficult immunoglobulin to identify by standard laboratory methods [5]. Because a significantly larger tumor load would be required to produce a recognizable M-protein on SPEP, IgD myeloma is frequently missed or identified only late in its course. Since the standard laboratory protocol for myeloma work-up does not call for IFE testing with anti-IgD and since an M-protein is frequently not readily identifiable on SPEP, the presence of a monoclonal light chain component may easily be misdiagnosed as the more common light-chain only myeloma.

Approximately 1.5% of myeloma cases present with a biclonal paraproteinemia. The pathologic mechanism is undetermined and possibilities include a single genetically distinct clone producing 2 immunoglobulin types and the presence of 2 separate clonal neoplasms. A large percentage of cases of biclonal myeloma include IgG as one of the component immunoglobulins. The presence of IgD in biclonal myelomas is also comparatively rare and has only been sparingly described [6].

Our case represents a particularly rare situation of a patient with a standing diagnosis of IgA λ myeloma in partial remission being diagnosed with IgD λ myeloma after treatment with chemotherapy and autologous stem cell transplant. Because the original laboratory work-

Table 1

Laboratory values in myeloma follow-up panel.

Test	8/20/10	10/18/10	12/22/10	06/21/11	04/04/12
IgA (mg/dl)	93	90	136	114	189
Lambda (λ) (mg/l)	564.38	179.52	557.54	87.58	95.04
Kappa (κ) (mg/l)	6	5.63	6.54	11.18	12.44
κ/λ ratio ^a	0.011	0.031	0.012	0.128	0.131
B2 microglobulin (g/dl)	1.47		1.66		
Creatinine (mg/dl)	0.8	0.8	0.9	0.95	0.88

^a Normal κ/λ ratio is 0.26–1.65 in a healthy individual.

up of this patient did not include IFE studies with IgD antisera, it is impossible to determine whether the patient originally presented with a missed biclonal paraproteinemia or if an isotype shift had occurred after treatment. As the patient never met the established criteria for complete remission and continued to produce high levels of serum free light chains with no recognizable M-protein component (commonly associated with IgD myeloma) it is not unlikely that the IgD immunoglobulin was originally present. However, because an IgA component was not identified in later testing, the possibility of an isotype switch event cannot be ruled out.

Current literature reports cases of myeloma in partial or complete remission that undergo recurrence with marked rise in serum free light chain levels with low or undetectable M-protein bands, corresponding to a low production of a monoclonal heavy chain component. This is called the light chain escape phenomenon. The majority of these patients have been treated with biological therapy or stem cell transplants. Incidents of light-chain escape have not been reported to be associated with a new class of monoclonal heavy-chain immunoglobulin [7].

Several cases of immunoglobulin isotype shift have been reported in a myeloma with biclonal paraproteinemia (IgG λ and IgD λ). One case exhibited a shift from primarily IgG (with a minor IgD component) to predominantly IgD immunoglobulin production after chemotherapeutic treatment. The findings in this report suggested that the neoplastic plasma cells originated from a single B-cell clone [8]. Another case described a shift from a single paraprotein (IgG K) to a biclonal paraprotein (IgG K and IgD K) [9]. Similar to our case, the clinical history did not indicate the clonal nature of the disease.

Complete isotype switching is a rarely reported phenomenon in the multiple myeloma population and is usually associated with post-stem-cell transplant recovery. It is not uncommon to see oligoclonal or biclonal bands on IFE in this patient population and these findings are not associated with adverse prognosis. Most cases of isotype switch are also associated with eventual development of oligoclonal banding and are considered transient phenomena as opposed to a neoplastic recurrence [10].

Because of the constellation of established diagnostic difficulties for IgD myeloma: lack of an M-protein component, production of high levels of monoclonal free light chains, and the association with more aggressive clinical course (high incidence of renal impairment, increased tumor burden at the time of diagnosis), it is important to diagnose this entity in order to properly stratify patients and monitor treatment response. A most cost-effective approach would be to perform IFE with less common antisera (anti-IgD and anti-IgE) in cases where a monoclonal light chain is identified in the absence of a heavy-chain component. This would be particularly useful in avoiding misdiagnosing a light-chain only myeloma and provide more accurate information about prognosis and treatment. Further research should be aimed at the clinical utility of including this testing into the initial myeloma work-up in order to identify a potential biclonal myeloma.

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