

# A Challenging Case of IgD Kappa Multiple Myeloma Associated With Primary Amyloidosis: Importance of Serum Free Light Chains in Monitoring Treatment Response and Disease Relapse

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Rec date: Oct 10, 2014, Acc date: Oct 16, 2014; Pub date: Oct 24, 2014

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## Abstract

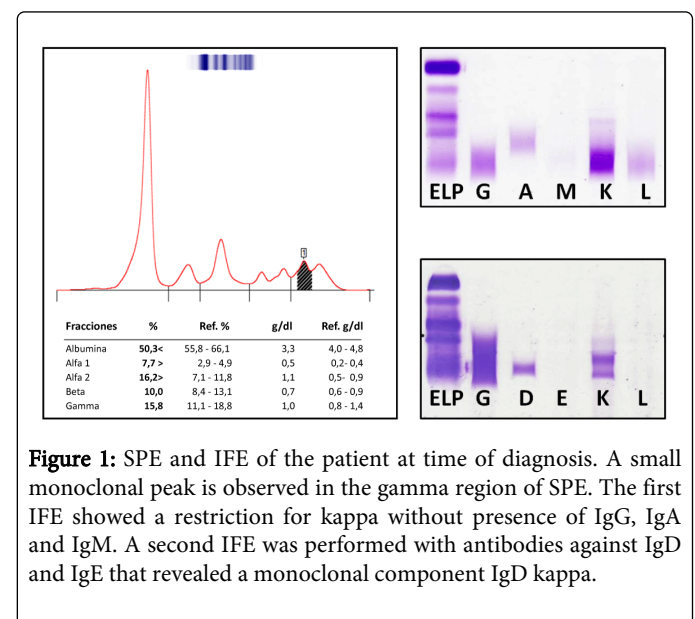
Multiple Myeloma (MM) is a malignancy of B cells characterized by an atypical proliferation of plasma cells. IgD MM has a very low incidence (2% of total MM cases) and it's characterized by an aggressive course and a worse prognosis than other subtypes. The serum free light chains (sFLC) are very important markers for monitoring patients with MM and other monoclonal gammopathies. When the sFLC are present in low concentrations, it is often difficult to detect them by conventional methods such as serum protein electrophoresis and serum immunofixation. This case is a good example of the utility of sFLC in the monitoring of treatment and relapse of patients with MM. The sFLC determinations detected when chemotherapy applied was not being completely effective and it predicted a relapse before new clinical findings were present. We report the rare case of a patient diagnosed of IgD MM with associated light chain kappa Primary (AL) Amyloidosis and characterized by clinical findings of very bad prognosis (high levels of sFLC kappa at diagnosis, high renal impairment and subsequent development of intracranial plasmacytoma), aggressive course and refractory to several lines of treatment.

**Keywords:** Serum free light chains; Amyloidosis; Multiple myeloma; Stringent complete response; Intracranial plasmacytoma

## Case Report

A 50 years old man was admitted to our Hospital in July 2011 due to asthenia and back pain of two months duration. The initial study identified an anemia of 10.9 g/dl of hemoglobin and renal failure (14 mg/dl of creatinine and 21.82 mg/l of beta-2 microglobulin). Further study of the renal failure by the Department of Nephrology identified a kappa light chain nephropathy by renal biopsy with kidney disease stage 5 (Glomerular filtration rate (sGFR)=4 mL/min/1.73 m<sup>2</sup> with MDRD-formule) requiring regular hemodialysis. Due to these findings the patient was remitted to the Department of Hematology to evaluate the presence of a possible monoclonal gammopathy. In the serum protein electrophoresis (SPE) a small monoclonal peak in the gamma region was observed (0.5 g/dl correspond to monoclonal component) with normal values of IgA (149 mg/dl) and IgM (31 mg/dl) and with decreased values of IgG (610 mg/dl). A Bence Jones positive kappa light chain was detected in urine (4.8 g/24 hours) and an abnormal sFLC ratio of 1570 with elevated levels of sFLC kappa (24769 mg/l) and normal levels of sFLC lambda (15.78 mg/l). Serum immunofixation (IFE) confirmed an IgD kappa monoclonal component (Figure 1). Bone marrow biopsy detected irregular plasma cells aggregates mostly immature with 4% of neoplastic plasma cell CD138+ positive for IgD and kappa light chains. The flow cytometry analysis identified a 2.5% of clonal kappa cells with pathological phenotype. Magnetic Resonance Imaging (MRI) scan and X-Rays examination of the skeletal system showed multiple osteolytic lesions in skull and pelvis with pathological vertebral fractures in D10, D11, D12 and L2 plus compressive myelopathy in D10. Furthermore, MRI

scan showed pathological diffuse infiltration of the bone marrow of the vertebral bodies. Biopsy of spine injury confirmed the diagnosis of MM. These findings led to a diagnosis of IgD kappa Multiple Myeloma ISS stage 3 with nephropathy due to kappa light chains deposition disease. Furthermore, the patient presented paresthesias in both hands. The study by Department of Neurology demonstrated the presence of a demyelinating affectionation in both lower limbs and a demyelinating neuropathy with discrete and axonal component of the bilateral median nerve.



**Figure 1:** SPE and IFE of the patient at time of diagnosis. A small monoclonal peak is observed in the gamma region of SPE. The first IFE showed a restriction for kappa without presence of IgG, IgA and IgM. A second IFE was performed with antibodies against IgD and IgE that revealed a monoclonal component IgD kappa.

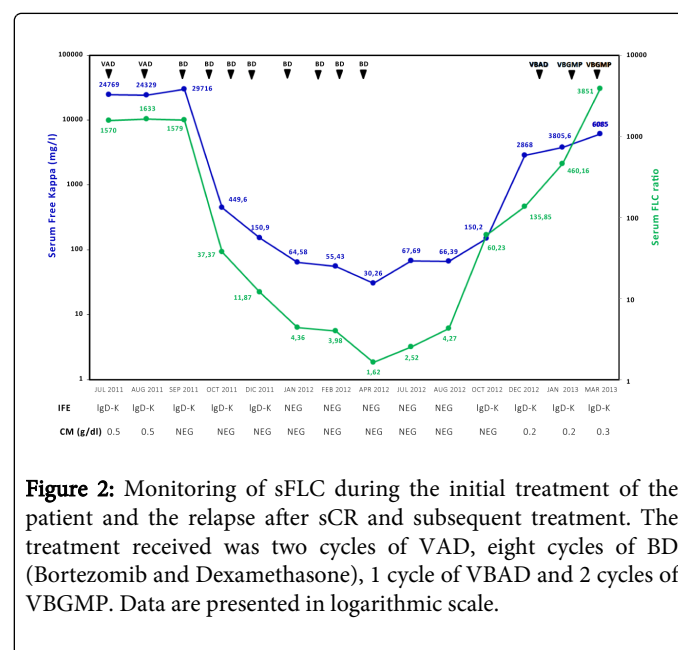
The patient began treatment with VAD (Vincristine, Doxorubicin and Dexamethasone) and hemodialysis in July 2011. Because the patient presented macroglossia during the first cycle of VAD, AL Amyloidosis was suspected. Subcutaneous fat biopsy revealed extensive deposition of kappa amyloid material positively stained by Congo red dye. No signs of structural cardiomyopathy observed in echocardiography. With these news findings, the diagnosis of the patient was reviewed as IgD kappa Multiple Myeloma ISS stage 3 with AL Amyloidosis associated. He received two cycles of VAD from July 2011 to September 2011 but the sFLC ratio remained abnormal during the treatment (from an initial value of 1570 in July to a value of 1579 at the beginning of September) with very high levels of sFLC kappa (24769 mg/l in July and 29716 mg/l in September). Uninvolved sFLC lambda remained normal (15.78 mg/l in July and 18.82 mg/l in September). The IFE was positive (IgD Kappa) during this treatment. Due to the minimum response to the treatment according to sFLC kappa levels and the progression of neuropathy, the therapy was changed to Bortezomib and Dexamethasone receiving eight cycles from September 2011 to April 2012 reaching a normalization of the sFLC ratio (value of 1.62) at the end of April 2012. At this point, the IFE was negative with absence of clonal plasma cells in bone marrow and the patient achieved stringent complete response (sCR) [1]. The response to this treatment resulted in the improvement of the neuropathy and reduction of sFLC kappa levels to 30.26 mg/l at the end of April 2012. Furthermore, the reduction in sFLC levels allowed the patient to leave the hemodialysis sessions in January 2012 where the sFLC kappa level was of 64.58 mg/l with a sFLC ratio of 4.36, creatinine of 3.08 mg/dl and a sGFR of 22.4 mL/min/1.73 m<sup>2</sup>. Three months after achieving sCR, the sFLC ratio becomes progressively more altered, predicting a relapse with values of 2.52 in July, 4.27 in August, 60.23 in October, and a maximum of 135.85 in December. The corresponding sFLC kappa levels were 67.69, 66.39, 150.2 and 2868 mg/l respectively whereas uninvolved sFLC lambda was in normal levels or decreased (26.9, 15.56, 2.49 and 21.11 respectively). An increase in sFLC difference (Kappa - Lambda) was observed predicting the relapse with values of 40.79, 50.83, 147.72 and 2847 mg/l, respectively. However, the IFE was normal from April to September 2012 remaining the patient in CR1. In October 2012, the bone marrow showed decreased cellularity with 1% of plasma cells, IFE was positive (IgD kappa) for the first time in the relapse and Bence Jones (BJ) protein was positive for kappa light chain (Figure 2). A MRI scan showed new pathological fractures at D3.

Later, in December 2012, the patient developed diplopia and palpebral ptosis. Computed tomography (CT) scan was performed and a mass was observed in both sides of frontal bone of the cranium that compresses the adjacent brain tissue (Figure 3a). This mass was described as intracranial plasmacytoma by Department of Pathology. The dimension of the extracranial component was 50 mm × 16 mm whereas intracranial side presented a dimension of 41 mm × 35 mm that compressed the brain tissue. The patient began treatment with VBAD (Vincristine, Carmustin, Doxorubicin and Dexamethasone) and received one cycle with increase of frontal mass size. The sFLC levels increased (sFLC kappa 3805.6 mg/l with sFLC ratio of 460.16 in January 2013) so the treatment was changed to VBGM (Vincristine, Carmustin, Melphalan, Ciclofosfamide and Prednisone) and received two cycles without decrease of frontal mass and significant increase of sFLC levels (sFLC kappa 6085 mg/l with sFLC ratio of 3851 in March 2013). One month later (April 2013) the patient was admitted to the Emergency Services of the Hospital with general malaise, hypotension, dyspnea and anemia. A CT scan revealed progression of intracranial

mass (Figures 3b and 3c). Unfortunately the patient became progressively worse with increased dyspnea, sudden blindness and neurological impairment with coma and dying after three days.

## Discussion

IgD MM was described for first time in 1965 by Rowe and Fahey [2]. This is a rare entity with very low incidence that accounts for less than 2% of total MM cases and it is characterized to have poor prognosis; the median survival time is 12 months following diagnosis [3] or at most, two years [4]. In the clinical characteristic of IgD MM patients, Kim et al. found a younger age at time of presentation with advanced stage and a more aggressive clinical course [5]. In a cases series of 53 patients with IgD MM described by Blade et al., they reported the main presenting features were bone pain (72%), fatigue (36%), renal function impairment (33%), weight loss (32%), hypercalcemia (22%), extramedullary plasmacytomas (19%) and associated amyloidosis (19%) [6]. In other series of 16 patients was found that IgD MM had aggressive clinical features, male predominance, a high frequency of renal function impairment, high incidence of M-protein undetected by serum protein electrophoresis, a predilection for lambda-light chains and a short period of survival. Our patient is in agreement with these studies and his clinical features reported, underline the worse characteristics of IgD MM: younger age at disease presentation (50 years), aggressive clinical course (ISS stage 3) with short survival of 22 months, bone pain with multiple bone lesions, neuropathy, AL amyloidosis, intracranial plasmacytoma and renal impairment due to free light chains nephropathy. Knudsen et al. in a study about occurrence of renal failure in newly diagnosed cases of MM, observed that myeloma nephropathy was present in all patients with IgD MM. This finding highlights the frequency of light chains proteinuria in these patients [7] being our patient a good example of this finding. Nevertheless, our case is a rare exception presenting a kappa light chain expression against the characteristic bias for lambda light chain with a reversed light chain ratio observed in IgD MM [8]. The presence of lambda light chain expression was reported by Jancelewicz et al. in 90% of a series of 133 patients with IgD MM [9].



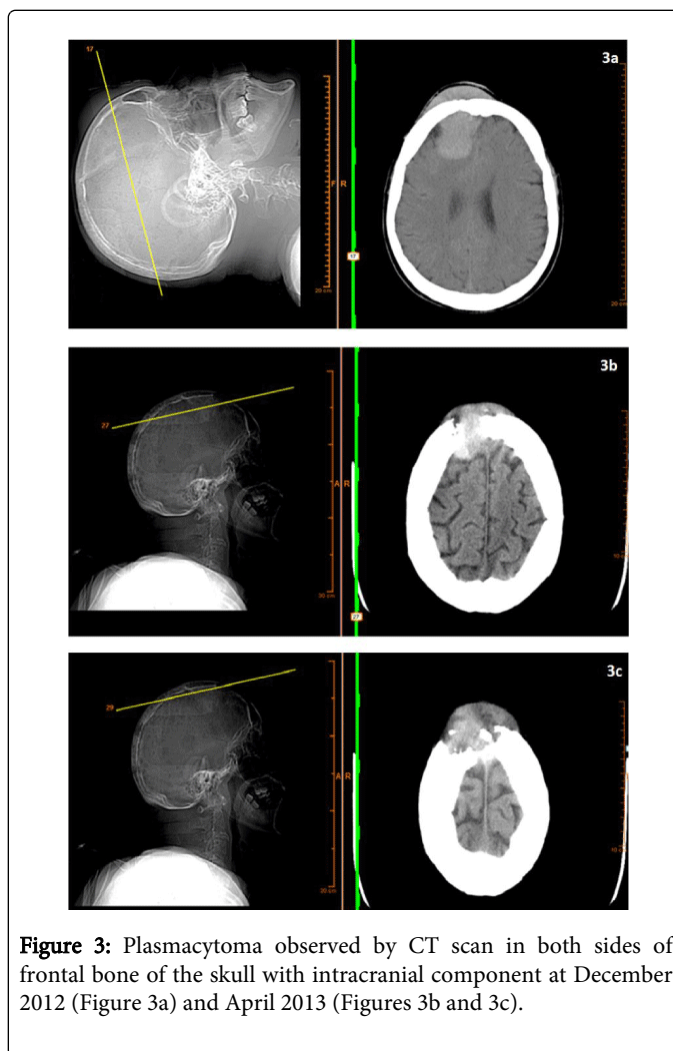
**Figure 2:** Monitoring of sFLC during the initial treatment of the patient and the relapse after sCR and subsequent treatment. The treatment received was two cycles of VAD, eight cycles of BD (Bortezomib and Dexamethasone), 1 cycle of VBAD and 2 cycles of VBGM. Data are presented in logarithmic scale.

Gertz et al. described that IgD amyloidosis is a distinct entity, predominantly of lambda light chain type that causes the typical amyloidosis syndromes of cardiomyopathy, nephrotic-range proteinuria, hepatomegaly and peripheral neuropathy. They suggest that amyloidosis must be kept in the differential diagnosis when a patient with IgD monoclonal protein is recognized [10]. As in this study, our patient presents three clinical findings associated with AL amyloidosis at diagnosis: neuropathy, nephrotic-range proteinuria and macroglossia. After this last finding and completing the study, the patient was diagnosed with AL amyloidosis associated to IgD MM.

Patients with IgD myeloma usually present a small or non-visible monoclonal spike on SPE and light chain proteinuria, thus resembling Bence Jones myeloma [6]. So, the recognition of IgD monoclonal component can be sometimes difficult to detect and requires expertise. During the last decade, a new assay based on polyclonal antibodies for the quantification of sFLC (Freelite™, The Binding Site Ltd., Birmingham, UK) has become a key biomarker in the study of monoclonal gammopathies like troponin in myocardial infarction and procalcitonin in sepsis. Its use has been recommended by the International Myeloma Working Group (IMWG) in their guidelines [11]. The use of sFLC in combination with SPE in the initial screening of monoclonal gammopathies provides a high diagnostic sensitivity [12]. The application of this initial screening protocol to our patient revealed a small peak in SPE and high levels of sFLC kappa by Freelite immunoassay. These findings, in addition to the clinical parameters, a positive IgD-kappa IFE and Bence Jones proteinuria led to the final diagnosis of MM. During the first line of treatment based on VAD (from July 2012 to September 2012); sFLC kappa levels remain almost unchanged with worsening of the neuropathy. These were the criteria used by the hematologist to change the treatment to Bortezomib and Dexametasona. Therefore, the quantification of sFLC levels helped to evaluate whether the treatment was being effective for this patient. During the second line of treatment, the progressive decrease of sFLC levels reflects the efficacy of the new treatment and, most importantly, correlates with an improvement of the clinical status of the patient. In fact, the patient became hemodialysis independent, ameliorated the neuropathy and reached a sCR in April 2012 after normalization of the sFLC ratio and absence of monoclonal cells in the bone marrow. Achieving sCR in patients with MM is essential because it represents a deeper response state compared with conventional CR [13]. However, this level of response was not sustained and three months later the sFLC ratio became abnormal with increasing sFLC levels, despite the fact that the IFE was still negative for three additional months. Recently, Kapoor and coworkers showed that improved long-term outcome is seen in patients with sustained sCR after post-ASCT (autologous stem-cell transplantation) compared with patients reaching a lesser degree of response [14]. The high sensitivity of sFLC indicated a relapse of the patients three months earlier than IFE and urine BJ proteinuria and 5 months before the development of new clinical symptoms. Interestingly, in October 2012, when IFE was already positive and the sFLC levels had increased to 150.2 mg/l, well above the definition of measurable disease, the bone marrow study showed only 1% of plasma cells. This apparent inconsistency is probably explained by the appearance of an intracranial plasmacytoma which could be the source of the increase in monoclonal free light chains in the relapse.

Currently, there are two ways of analyzing free light chains; by detecting monoclonal free light chains directly in the serum, or by confirming the presence of BJ protein in urine. In our case, it was difficult to obtain urine samples to study BJ protein due to the high

grade of renal impairment of the patient. The patient presented oliguria making quantification of light chains in urine difficult for monitoring treatment with chemotherapy and during hemodialysis. Additional problems with urine testing derive from incorrect collection, sample not representative or non 24-hours urine, whereas sFLC samples were easy and rapid to obtain and their quantification helped us to follow this patient during the various phases of treatment and relapse. Therefore, we found sFLC determinations to be a better option than BJ protein for monitoring patients with monoclonal gammopathies. As we have seen in this clinical case, the short half-life (2-6 hours) of sFLC allow us to evaluate the efficient elimination of sFLC during dialysis; analyze the efficiency of chemotherapy during treatment, with the option of adjusting the treatment regimen as needed; determine the moment in which the patient has recovered renal function, starting to metabolize the sFLC again; and detect early relapse of the disease [15].



Finally, the most common neurologic complications of MM are spinal cord compression due to epidural plasmacytomas or vertebral fractures and peripheral polyneuropathy due to the presence of antibodies directed against myelin structures or due to amyloid deposits. Conversely, neurologic symptoms due to plasmacytomas located either in the base of the skull or at intracranial locations are extremely rare [16]. This was the case of our patient which, on relapse,

presented an intracranial plasmacytoma affecting the VI cranial nerve with neurological symptoms of diplopia and palpebral ptosis.

## Conclusion

IgD MM presents clinical and laboratory findings that defines a distinct entity. In patients newly diagnosed with IgD MM, the coexistence of AL amyloidosis has to be included in the differential diagnosis to avoid a delay in the diagnosis and the choice of adequate therapy. The existence of new clinical test of high sensitivity and specificity such as the sFLC immunoassay, help us to improve the management of patients with MM, especially those where the monoclonal components are in low concentrations or difficult to identify by conventional methods as SPE and IFE. This case is an example of the great utility of sFLC determinations in the diagnosis, monitoring and relapse of a patient with a challenging case of MM, and it was the only technique able to provide accurate values of the monoclonal component secreted by the tumor cells. Without this information, the change in the initial ineffective treatment would have been delayed.

## Acknowledgments

The authors would like to thank Luisa Campos and Tiago Pais from The Binding Site Group (Birmingham, UK) for helpful comments in the writing of the manuscript.

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