CASE STUDY

IgD-kappa multiple myeloma. Case report and brief review of the literature

Omayma Saad Eldeen Bakheet[1], Leong Chooi Fun[1], Azlin Ithnin[1] and Siti Fadilah Abdul Wahid[2]

[1]Department of Pathology and [2]Cell Therapy Center, Department of Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Center, Kuala Lumpur

ABSTRACT

Immunoglobulin D multiple myeloma is considered a rare subtype of myeloma, accounting for less than 2% of all myelomas. It is associated with an increased frequency of undetectable or small monoclonal protein levels in electrophoresis. It also accompanied with an aggressive course, resistance to chemotherapy and poor outcome. We report a 71-year-old man with a background history of chronic kidney disease. He presented with history of low back pain for two months and noted during follow-up worsening of his renal function and decreasing trend of haemoglobin levels. Subsequent workup for multiple myeloma showed presence of a small monoclonal protein band between the beta and gamma region in serum protein electrophoresis. Urine protein electrophoresis showed presence of Bence-Jones proteinuria. However, the routine immunofixation electrophoresis of the serum and urine samples showed kappa light chains but was negative for anti IgG, A and M. Further immunofixation with IgD and IgE antisera identified IgD-kappa paraproteinaemia and kappa light chain in the urine. Bone marrow examination showed infiltration by plasma cells, which was further confirmed by immunohistochemistry staining and in situ hybridization. Furthermore, fluorescence in situ hybridization analysis showed deletion of 13q14.3. He was given various chemotherapy regimes, which he was refractory to. This case is reported to highlight the necessity of performing immunofixation for IgD routinely for all patients with suspected multiple myeloma as many cases are misdiagnosed as light chain disease.

Keywords: immunoglobulin D, multiple myeloma, renal failure, velcade, 13q14.3 deletion.

N Z J Med Lab Sci 2016; 70: 08-11

INTRODUCTION

Multiple myeloma is a malignant disorder characterized by the proliferation of a single clone of plasma cells that produce monoclonal protein and are derived from B cells in the bone marrow (1). This proliferation results in extensive skeletal involvement, with osteolytic lesions, anaemia, hypercalcaemia and/or soft tissue plasmacytomas (2). In addition, the excessive production of nephrotoxic monoclonal immunoglobulin can result in renal failure and the lack of functional immunoglobulins may lead to potentially life-threatening infections (2). Multiple myeloma comprises about 10-15% of haematopoietic neoplasms and leads to 20% of deaths from haematologic malignancies (3). The incidence of multiple myeloma is twice as high in blacks as in whites and is lower in Asian populations. Multiple myeloma is slightly more frequent in men than in women and the median age at diagnosis is 65–70 years (2).

Multiple myeloma of the IgD isotype is a rare entity, accounting of 1- 2% of all reported myeloma cases in the literature (4). Given their rarity, the characteristic features of this disorder have mostly been collected from case reports or larger case series (5). This condition is more common in men than in women; often accompanied by hepatomegaly, lymphadenopathy, extraosseous lesions, renal failure, and amyloidosis; and has a poorer prognosis than other multiple myeloma isotypes with a median survival time of 13–21 months (4).

We report here one of the rare variants of multiple myeloma, namely IgD-kappa multiple myeloma. Its clinical course, response to therapy and outcome is highlighted.

CASE REPORT

A 71-year-old man, with a background history of diabetes mellitus, hypertension and chronic kidney disease, was referred to our center for multiple myeloma work-up as the patient had history of low back pain for two- months and was noted to have deteriorating renal function and decreasing trend of haemoglobin levels. Physical examination was unremarkable apart from pallor. There was no lymphadenopathy or hepatosplenomegaly.

His full blood count report revealed anaemia (haemoglobin 8.1 g/dL) with normal white blood cell and platelets counts. Peripheral blood smear showed no Rouleaux formation, circulating plasma cells, or leukoerythroblastosis. Blood chemistries showed elevated levels of urea (9.1 mmol/L) and creatinine (200 umol/L). The liver function tests yielded normal results. His serum total protein, albumin and albumin adjusted calcium levels were normal; 72 g/L, 46 g/L, and 2.47 mmol/L respectively. His ESR (9 mm/hr) and LDH level were also normal (233 U/L). The patient's biochemistry results are summarized in Table 1. A spinolumbar radiograph demonstrated osteolytic lesions in both T11 pedicles. The serum protein electrophoresis (agarose gel) showed the presence of a monoclonal band in between beta and gamma regions and urine protein electrophoresis showed presence of Bence-Jones protein. The immunofixation electrophoresis of the serum and urine reported as IgD-kappa paraproteinaemia (Figure 1).

At diagnosis, the SPE showed small M-band in between beta and gamma regions with a quantitation of 2.8g/L, whereas the UPE showed Bence-Jones protein of 1.1 g/L. The immunofixation electrophoresis of the serum and urine samples showed kappa light chains but was negative for anti IgG, A and M. The sample then was sent to a referral pathology laboratory, for possible presence of IgD and IgE, and reported as IgD-kappa paraproteinaemia. Quantification of the serum immunoglobulins was as follows: IgG; 666 mg/dL (reference range, 751-1560) and IgM; 10 mg/ dL (reference range, 46-304). Furthermore, the serum free light chain assay showed high level of free kappa (3890.0 mg/L) and normal level of free lambda (15.0 mg/L) with serum free K/λ ratio of 59.33 (reference range, 0.26-1.65). In contrast to the common isotype of MM where the serum M-protein is usually >30g/L of IgG and >20g/L of IgA (3), our patient serum M-protein quantification was of 2.8g/L in keeping with the literature review (5, 7). Furthermore, his serum immunoglobulins quantification's were reduced, these findings were consistent with previous reports by Shimamoto et al and Blade et al (19, 20).

The bone marrow aspirate showed presence of 20% plasma cells. The plasma cells were heterogenous in size with moderate amount of basophilic cytoplasm and displayed eccentric nuclei and clumped chromatin pattern with perinuclear halo. Numerous mott cells and occasional plasmablasts were also noted (Figure 2). These findings were consistent with multiple myeloma. Furthermore, the trephine biopsy sections showed interstitial infiltration of the bone marrow by sheets and clusters of plasma cells (Figure 3). Additionally, these plasma cells showed kappa light chain restriction by *in situ hybridization*. The cytogenetics showed no chromosomal abnormalities. However, FISH analysis showed deletion of 13q14.3 in 5% of the analysed cells.

Whole body fluorodeoxyglucose- positron emission tomography/computed tomography scan for disease assessment demonstrated solitary skeletal involvement (T11 vertebra) with no evidence of extramedullary involvement. As a part of the staging procedure, β2-microglobulin level was done which revealed a high level (8.83 ug/L; (reference range: 1.1 - 2.6). He was staged as IIIB according to the international staging system and was started on melphalan/thalidomide/ prednisolone (MPT) chemotherapy along with bisphosphonate and radiotherapy conducted for T10-T12 region.

Three months later after completion of the 3rd course of chemotherapy, he was admitted complaining of bilateral lower limb weakness to the point where he was unable to walk unaided with associated numbness for three days. For this, an urgent MRI of the spine was performed to rule out acute spinal cord compression. This showed diffuse vertebral metastases and worsening T11 compression fracture with spinal cord compression and significant T11 exiting nerve root compression bilaterally. Spinal cord decompression together with posterior instrumentation and fusion was done. Histopathological examination of the thoracic spinal bone fragments was consistent with osseous plasmacytoma.

The patient received a total of seven courses of MPT chemotherapy. However, in view of the suboptimal response to the treatment, the chemotherapy regimen was changed to velcade/dexamethasone/thalidomide (VDT). He did well initially after starting this bortezomib-containing regimen, his routine serum protein electrophoresis showing undetectable M-protein band but persistent Bence-Jones proteinuria in the urine protein electrophoresis. Unfortunately, subsequent serum protein electrophoresis revealed the presence of a M-protein band with a paraprotein quantitation of 15.7g/L and urine protein electrophoresis showed the presence of urine Bence-Jones protein with a quantitation of 4.4 g/L. Half way through this chemotherapy regime, he developed peripheral neuropathy secondary to thalidomide, thus this drug was stopped but velcade/dexamethasone was continued.

Later, he developed acute renal failure secondary to dehydration and hypercalcaemia. His condition took a downfall when he developed *Pseudomonas* septicemia and metabolic acidosis. Following this he declined further treatment and was placed on palliative care. Eventually, he developed multiorgan failure and succumbed to his condition.

Table 1. Patient's relevant biochemistry results.

Blood test	Result	Reference range
Urea mmol/L	9.1	3.2 – 7.4
Creatinine umol/L	200	63.6 – 110.5
Total Protein g/L	72	64 – 83
Albumin g/L	46	34 – 48
Albumin-adjusted calcium mmol/L	2.47	2.14 – 2.58
LDH U/L	233	125 – 220
ESR mm/hr	9	1 - 20

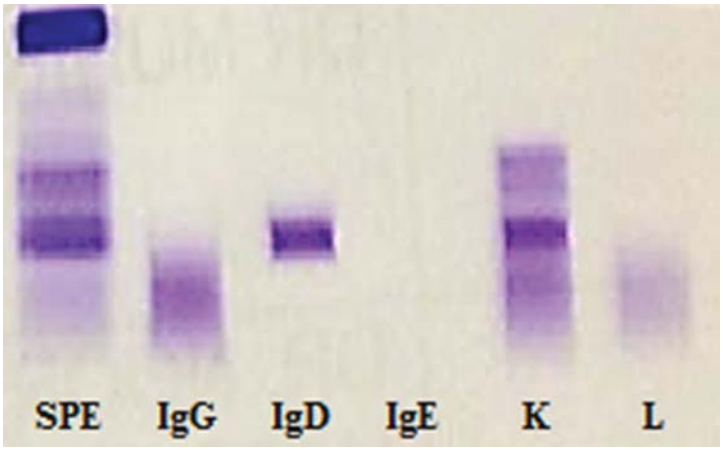

Figure 1. Immunofixation electrophoresis of the serum sample showing IgD-kappa paraproteinaemia.

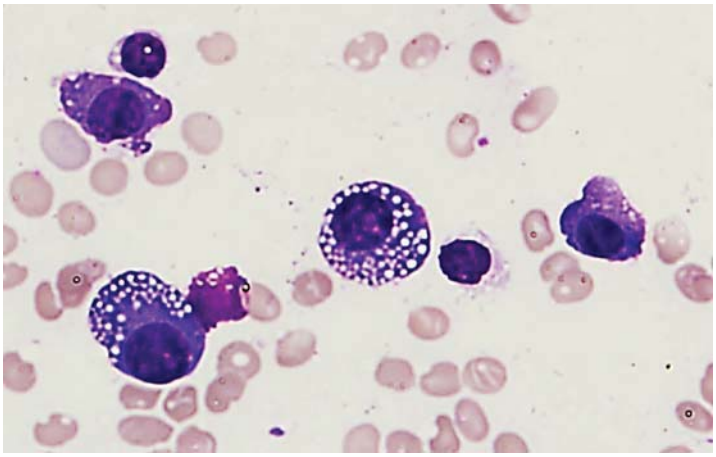

Figure 2. Bone marrow aspirate showing plasma cells and mott cells. MGG x600.

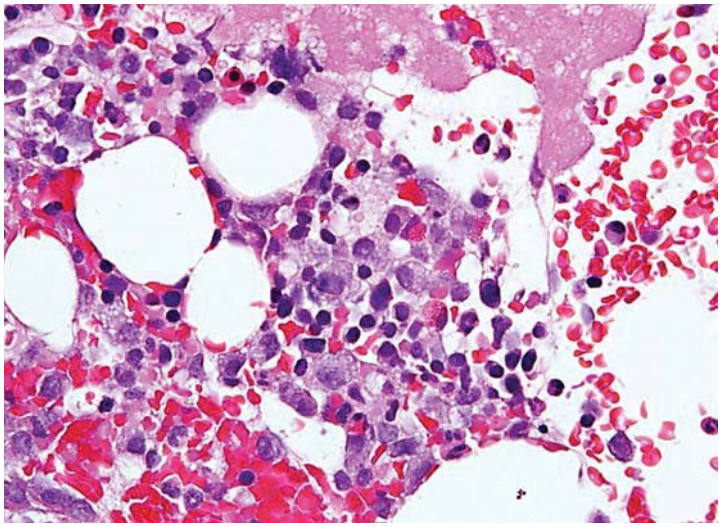

Figure 3. Bone marrow trephine biopsy section showing bone marrow infiltration by clusters of plasma cells and some plasma cells with multiple cytoplasmic vacuolation (mott cells). H&E x600.

DISCUSSION

Immunoglobulin D multiple myeloma (IgD MM) was first recognized by Rowe and Fahey in 1965 (6). It affects less than 2% of all patients with MM and is known to have a more aggressive clinical behavior than other subtypes of MM (6).

CLINICAL FEATURES

A review of the literature showed that the clinical features of IgD multiple myeloma are similar to those of IgG multiple myeloma, IgA multiple myeloma, and light chain myeloma. However, patients with IgD multiple myeloma were younger at time of presentation, had a male predominance; and higher rate of bone lesions, anaemia, hypercalcaemia and renal failure (4,6,7). Spinal cord compression is the most common neurological complication of all MM subtypes and reported in 11 -24% of patients (8). Most cord-compression lesions occur due to a pathological fracture of the involved vertebral body or extension of a vertebral body myeloma lesion (8). Lolin et al reported that extra-osseous spread and soft tissue tumors were common in IgD multiple myeloma and more than 50% of the patients had lymphadenopathy, splenomegaly and hepatomegaly (9). Furthermore, plasma cell leukaemia and amyloidosis were reported more frequently in IgD multiple myeloma than the other types of multiple myeloma (10). IgD multiple myeloma is characterized by a small or absent M-protein band in electrophoresis, a Lambda (λ) light chain bias, and Bence-Jones proteinuria, which occurred in at least 90% of patients (7). Morris et al found that albumin, β2 micrglobulin and serum creatinine levels were higher and haemoglobin concentrations were significantly lower in IgD multiple myeloma compared with more common myelomas (11). Additionally, IgD multiple myeloma was reported more likely to present at an advanced stage, have a more aggressive clinical course, and a poorer prognosis with a shorter period of survival (4, 12). Nevertheless, the underlying tumor biology responsible for the differences between IgD multiple myeloma and other myeloma isotypes have yet to be determined (4, 13).

IMMUNOGLOBULIN ANALYSIS

Laboratory analysis of IgD multiple myeloma cases by serum protein electrophoresis typically demonstrated a minimally detectable M-protein spike, often in the beta, gamma, or beta-gamma region (5). A large percentage of cases may show hypogammaglobulinaemia or a normal serum electrophoretic pattern making detection of the paraprotein difficult (5). However, Bence Jones proteinuria appears in almost all patients (5). Since immunofixation for IgD is not routinely performed many cases are misdiagnosed as light chain disease (5). Because of the issue of frequent small or undetectable M-protein on standard serum protein electrophoresis, Stulik et al analysed the serum from four IgD MM patients using two-dimensional (2D) gel electrophoresis.

In this study they detected heavy chains of IgD M-protein using high resolution 2D-gel electrophoresis, with demonstration of both size and charge differences between the various monoclonal immunoglobulins examined. Based on these results, the authors considered 2D-gel electrophoresis has higher sensitivity and resolution of the IgD paraproteins than the conventional gel electrophoresis (14). Furthermore, Lolin et al (1994) suggested that immunofix with IgD and IgE antisera should routinely be performed for all patients with a suspected Bence-Jones proteinuria myeloma, irrespective of whether a suspicious band was detected on serum protein electrophoresis or after immunofixation with light chains (9). In addition, Amy et al found that some features can suggest the presence of IgD such as: (a) higher concentration of free light chains than usual in the serum, (b) urine free light chains that migrate on electrophoresis to a point different from that seen with the serum (15). Two studies have mentioned that patients with renal failure of unknown cause, bone pain, small serum M-protein bands, or undefined Ig isotype should be suspected of having IgD multiple myeloma (4,13).

Lambda (λ) -type light chains were found in 60-95% of IgD M-components (12). The rarity of IgD Kappa (κ) secretion was explained by a block in the assembly, glycosylation, and secretion of this immunoglobulin or rapid intracellular catabolism of IgD κ destined for secretion (16).

CYTOGENETICS

More than 50% of patients with IgD multiple myeloma have chromosomal abnormalities (4). Monosomy or deletion of chromosome 13 (13q14) is found in nearly half of multiple myeloma cases by FISH (3) and it associated with an inferior outcome (17). Lu et al found that there were no significant differences in terms of cytogenetic abnormalities between IgD and IgG multiple myeloma types using conventional karyotyping and FISH analysis (12). Juge-Morineau et al analysed the immunoglobulin heavy chain V-region (Ig HV) genes of three IgD, one IgM, and one biclonal (IgG and IgM) multiple myeloma for the presence of somatic mutations based on molecular analysis of the Ig HV. That study illustrated that IgD and IgM were rare variants derived from a preswitched memory B cell that had passed through a stage of positive antigenic selection and was no longer exposed to the somatic mutation process or able to undergo further isotype switching in vivo (18).

STAGING

The clinical staging systems proposed by Durie and Salmon or by the British Medical Research Council have shown to be important in predicting the prognosis. However, these staging systems did not include IgD multiple myeloma because its rarity made analysis difficult. Thus, no data are available concerning the staging of IgD multiple myeloma (19). Some studies suggested that IgD multiple myeloma should be considered as a rare subgroup of multiple myeloma with aggressive features rather than a single parameter of poor prognosis (4,13).

Shimamoto et al, based on multivariate analysis of 165 cases with IgD multiple myeloma, found that λ light chains and a white blood cell count of more than 7×10^9/L were adverse prognostic markers. In light of these findings, they proposed a new staging system specifically for IgD myeloma using these two prognostic factors; the light chain subtype and leukocyte count.

Accordingly, patients were divided into three risk groups; low, intermediate and high risk. The overall survival rate was 66% in low risk patients, 23% in intermediate risk patients and 0% in high risk patients (19). Whereas, Kim et al found that the prognostic factors for reduced overall survival rate in patients with IgD multiple myeloma were advanced age, the presence of cytogenetic abnormalities such as del(13) or hypodiploidy, extramedullary plasmacytoma, and high serum β2 microglobulin. Additionally, in the same study they found that 89% of IgD multiple myeloma patients had λ light chain and that these patients had poorer outcomes than those with κ light chains (4). On the other hand, Blade et al reported that the median survival of patients with κ vs λ light chains were 20 months and 29 months respectively (20).

IgD multiple myeloma is reported to have a poor prognosis and worst survival compared to other multiple myeloma isotypes (12). Morris et al reported a progression-free survival of 27 months vs 24 months in non-IgD vs IgD multiple myeloma respectively, while median overall survival rate was 62 months vs 43 months (P =.0001). Interestingly, response to therapy both before and after autologous stem cell transplantation reported by the aforementioned study was better in patients with IgD multiple myeloma compared with other isotypes; however, this did not translate into increased survival. Similarly a greater proportion of IgD myeloma patients achieved complete remission after transplantation (11). As a result of the discovery of new drugs such as bortezomib and thalidomide, the complete remission rate and long-term survival rate of patients with multiple myeloma have improved worldwide over the past 10 years (12). Little is known regarding the effectiveness of autologous stem cell transplantation or the effects of the new drugs in patients with IgD multiple myeloma. Most studies were small case series, lacking complete data on individual patients and yielding contradictory results (4). However, some studies have suggested that new drugs such as bortezomib, thalidomide, and lenalidomide, as well as autologous stem cell transplantation, may improve the outcomes of patients with IgD multiple myeloma (4,13).

CONCLUSIONS

We described a rare case of IgD-kappa multiple myeloma in a 71-year-old man, staged as IIIB and associated with unfavourable cytogenetics. Although his initial serum and urine protein electrophoresis revealed a small M-protein band and Bence-Jones proteinuria; however, the routine serum and urine immunofixation showed kappa light chains but was negative for the common MM isotypes. The diagnosis of IgD- kappa multiple myeloma was established only after further immunofixation with IgD and IgE antisera. During the clinical course, he suffered from spinal cord compression caused by osseous plasmacytoma, and progressive deterioration of his renal function. He was started on MPT; however, due to partial response to the treatment chemotherapy regimen was changed to a bortezomib-containing regimen. Ultimately, he developed multiorgan failure and succumbed to his condition. The case is reported to address the necessity of routine immunofixation with IgD and IgE antisera, irrespective of whether a suspicious band is detected on serum protein electrophoresis, to avoid a false diagnosis of non-secretory or light chain myeloma.

AUTHOR INFORMATION

Dr. Omayma Saad Eldeen Bakheet, MBBS, DPath (UKM), Haematopathologist[1]
A/Prof. Leong Chooi Fun, MD, MPath, FRCPA (Aust.), FRCP (Edin.), FAMM, Consultant Haematologist & Head of Blood Bank Unit[1]
Dr. Azlin Ithnin, MBBchBAO (Ire), MPath (UKM), Haematopathologist[1]
Prof. Dr. Siti Fadilah Abdul Wahid, MD, MMED, PhD, FRCPE, Senior Consultant Haematologist & Head of Cell therapy Center[2]
[1]Department of Pathology, Universiti Kebangsaan Malaysia Medical Center, Kuala Lumpur, Malaysia
[2]Department of Medicine, Universiti Kebangsaan Malaysia Medical Center, Kuala Lumpur Malaysia
Author for correspondence: Dr. OSE Bakheet. Email: ombakheet@gmail.com.

REFERENCES

1. Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. *Leukemia* 2009; 23: 3-9. Erratum in: *Leukemia* 2014; 28: 980.
2. Hoffbrand AV, Catovsky D, Tuddenham EG, Green AR. Postgraduate Haematology. 6th Edition. John Wiley & Sons Ltd, UK. 2011.
3. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. WHO Classification of Tumors of the Hematopoietic and Lymphoid Tissue. 4th Edition. IARC, Lyon, France. 2008.
4. Kim MK, Suh C, Lee DH, Min CK, Kim SJ, Kim K, et al. Immunoglobulin D multiple myeloma: response to therapy, survival, and prognostic factors in 75 patients. *Ann Oncol* 2011; 22: 411-416.
5. Multiple Myeloma of the IgD Isotype http://path.upmc.edu/cases/case193/dx.html.
6. Chong YP, Kim S, Ko OB, Koo JE, Lee D, Park SH, et al. Poor outcomes for IgD multiple myeloma patients following high-dose melphalan and autologous stem cell transplantation: a single center experience. *J Korean Med Sci* 2008; 23: 819-824.
7. Pandey S, Kyle RA. Unusual myelomas: a review of IgD and IgE variants. *Oncology* 2013; 27: 798-803.
8. Ha KY, Kim YH, Kim HW. Multiple myeloma and epidural spinal cord compression: case presentation and a spine surgeon's perspective. *J Korean Neurosurg Soc* 2013; 54: 151-154.
9. Lolin YI, Lam CW, Lo WH, Au KL, Masarei JR. IgD multiple myeloma with thoracic spine compression due to epidural extra-osseous tumour spread. *J Clin Pathol* 1994; 47: 669-671.
10. Bahat G, Erten N, Saka B, Uzun S, Onur I, Kalayoglu-Besisik S, et al. Immunoglobulin D lambda multiple myeloma and amyloidosis with predominant soft tissue involvement. *Amyloid* 2007; 14: 305-308.
11. Morris C, Drake M, Apperley J, Iacobelli S, van Biezen A, Bjorkstrand B, et al. Efficacy and outcome of autologous transplantation in rare myelomas. *Haematologica* 2010; 95: 2126-2133.
12. Lu J, Lu J, Chen W, Huo Y, Huang X, Hou J. Clinical features and treatment outcome in newly diagnosed Chinese patients with multiple myeloma: results of a multicenter analysis. *Blood Cancer J* 2014; 4: e239.
13. Pisani F, Petrucci MT, Giannarelli D, Bongarzoni V, Montanaro M, De Stefano V, et al. IgD multiple myeloma a descriptive report of 17 cases: survival and response to therapy. *J Exp Clin Cancer Res* 2012; 31: 17.
14. Stulík J, Tichý M, Kovárová H. Two-dimensional gel electrophoresis of four serum samples from patients with IgD myeloma. *Clinica Chimica Acta* 1993; 218: 149-158.
15. Tharp AM, Woodruff RD, Shihabi ZK. IgD-kappa myeloma. An unusual case. *Ann Clin Lab Sci* 2003; 33:97-100.
16. Kanoh T, Niwa Y. Nonsecretory IgD (kappa) multiple myeloma. Report of a case and review of the literature. *Am J Clin Pathol* 1987; 88: 516–519.
17. Zhan F, Sawyer J, Tricot G. The role of cytogenetics in myeloma. *Leukemia*. 2006; 20: 1484-1486.
18. Juge-Morineau N, Heirman C, Bakkus M, Van Camp B, Malfait R, Harousseau JL, et al. Immunoglobulins D and M multiple myeloma variants are heavily mutated. *Clin Cancer Res* 1997; 3: 2501-2506.
19. Shimamoto Y, Anami Y, Yamaguchi M. A new risk grouping for IgD myeloma based on analysis of 165 Japanese patients. *Eur J Haematol* 1991; 47: 262-267.
20. Bladé J, Lust JA, Kyle RA. Immunoglobulin D multiple myeloma: presenting features, response to therapy, and survival in a series of 53 cases. *J Clin Oncol* 1994; 12: 2398-2404.