

Case Report

Non-secreting multiple myeloma switches to IgD of lamda type: a case report and review of literature

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Abstract: We report a case of a woman, who initially presented with an non-secreting multiple myeloma, 11 months later, she was diagnosed as an IgD-secreting myeloma. In December, 2010, the patient's serum protein quantification and immunofixation electrophoresis (IFE) revealed polyclonal immunoglobulin with no evidence of monoclonal immunoglobulin. However, her bone marrow smears revealed an abnormal proliferation of atypical plasma cells (46.5%), so she was diagnosed as non-secreting multiple myeloma. After three cycles of administration of Velcade plus Dexamethasone (VD), she achieved a complete remission (CR). Unfortunately, on October 31, 2011, our patient was found to have a separate peak of monoclonal component on the γ -region of cellulose-acetate electrophoresis, and the serum immunofixation electrophoresis revealed the monoclonal component was IgD. Several months later, she presented with a large swelling of the left side of her neck. Microscopic examination of a biopsy specimen from the cervical mass showed a neoplastic plasma cell tumor and she died on January 28, 2013 from acute respiratory failure resulting from neoplastic plasma cells infiltration and infection. Here we report this rare case and review the literature for similar cases.

Keywords: Non-secreting multiple myeloma, IgD- λ , immunofixation electrophoresis, serum free light chain, relapse

Introduction

Multiple myeloma is a malignant disease characterized by the presence of clonal plasma cells in bone marrow, causing anemia, skeletal lesions, bone pain, hypercalcemia, renal insufficiency, and fractures [1]. It represents about 10% of all hematologic malignancies and 1% of all malignant disease [2]. The diagnosis of multiple myeloma is based on the major and minor criteria comprising tissue diagnosis, monoclonal gammopathy, bone marrow plasmacytosis, lytic bone lesions, and suppressed uninvolved immunoglobulin [3]. Non-secretory multiple myeloma (NSMM) was first described in 1958 by Serre [4]. It accounts for approximately 1% to 5% of all patients with multiple myeloma [5], and is characterized by the absence of detectable M-protein in serum and urine. While IgD myeloma was described for the first time in 1965 [6]. It accounts for less than 2% of the total of all MM cases [7], and companies with more aggressive clinical course (shorter survival time), resistance to multiple combination

chemotherapy, smaller size or absence of the monoclonal protein spike, predominance of lambda light chains, high incidence of renal failure, higher incidence of hypercalcemia and associated amyloidosis, presence of Bence-Jones proteinuria and poor prognosis [8, 9]. Several immunoglobulin isotypes switches were reported in patients undergoing myeloablative therapy, while cases associated with a shift from non-secreting to IgD- λ production have not been previously reported. Here, we report a rare case who developed a non-secreting multiple myeloma in December, 2010, and an IgD- λ myeloma 11 months later, review the literature for similar cases.

Case report

A 62-year-old woman presented with recurrent episodes of lumbago over 2 months requiring an emergency room visit and was admitted at our institution for further work-up. On admission, she was obviously ill and painful. Physical examination revealed a marked decrease in

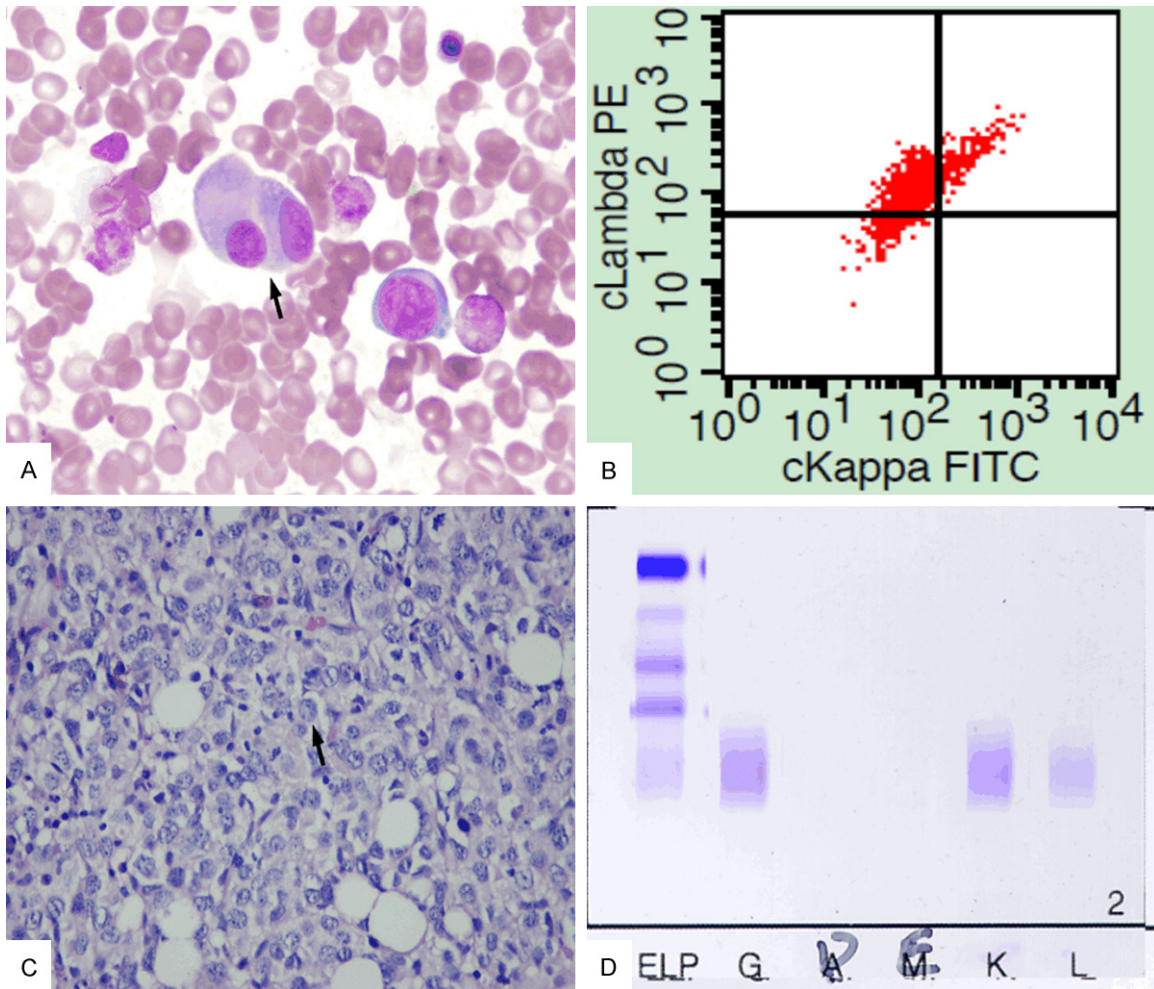


Figure 1. Bone Marrow Smear, Flow Cytometry, Bone Marrow Biopsy, Immunofixation Electrophoresis. A: Bone marrow smear (100×), showing abnormal proliferation of atypical plasma cells (46.5%) on diagnosis. B: Flow cytometry demonstrated an aberrant population of cLambda+, ckappa- neoplastic myeloid cells. C: Bone marrow biopsy (40×), revealing infiltration of atypical plasma cells. D: Immunofixation electrophoresis showed no evidence of monoclonal immunoglobulin.

lumbar mobility with intense pain in the lumbosacral joints upon palpation. Her laboratory studies revealed: peripheral white blood cell count, $3.42 \times 10^9/L$ (normal $4-10 \times 10^9/L$); hemoglobin, 96.4 g/L (normal 120-160 g/L); platelet count, $147 \times 10^9/L$ (normal $100-300 \times 10^9/L$); total serum protein, 57.6 g/L (normal 60-80 g/L); Serum albumin, 39.4 g/L (normal 35.0-52.0 g/L); Serum lactate dehydrogenase, 237 U/L (normal 6-42 U/L); calcium, 2.57 mmol/L (normal 2.15-2.55 mmol/L); Correction calcium, 2.72 mmol/L (normal 2.15-2.57 mmol/L); Serum Cr, 95.0 $\mu\text{mol/L}$ (normal 45-84 $\mu\text{mol/L}$); β -2microglobulin, 5.49 mg/L (normal 0.51-1.47 mg/L). Bone marrow smears (**Figure 1A**) revealed an abnormal proliferation of atypical

plasma cells (46.5%) and flow cytometry of the bone marrow aspirate demonstrated an aberrant population of CD138+, CD38+, CD9+, cLambda+ (**Figure 1B**); CD45-, CD56-, ckappa-, CD19-, CD117-, HLA-DR-, CD25-, CD13- neoplastic myeloid cells, immunophenotypically consistent with multiple myeloma, which comprised 17% of nucleated cell. A bone marrow biopsy showed an extensive plasma cell infiltration (**Figure 1C**). The serum protein quantification and immunofixation electrophoresis (IFE) revealed polyclonal immunoglobulin with no evidence of monoclonal immunoglobulin (**Figure 1D**). Computed tomography scan showed multiple lytic bone lesions in the ilium. Based on these findings, the patient was diag-

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nosed as non-secreting multiple myeloma stage III A according to the classification of Durie and Salmon [10].

In order to evaluate her prognosis, we sent a specimen of bone marrow aspirate for tyramine signal amplification and fluorescence in-situ hybridization (FICTION-TSA) test, the simultaneous application of interphase and metaphase fluorescence in situ hybridization (I-FISH) and immunofluorescent staining. Using FICTION-TSA technology, we found that the patient presented t (11;14) and del (17p). The IgH (14q32) translocation involving CCND1 (11q13) appears to be associated with a favorable outcome in most series and therefore, is regarded as neutral with regard to prognosis; however, the deletion of 17p confers a negative effect on survival and it is considered as the most important molecular cytogenetic factor for prognostication [11]. Therefore, our patient would have an adverse prognosis.

The patient administered bortezomib 1.3 mg/m² twice weekly plus dexamethasone 40 mg on the day of and the day after bortezomib for two weeks as a cycle (VD regimen). After three cycles of administration of VD, the proportion of plasma cells in patient's bone marrow had decreased to 2.5%; with non-detectable M component, normal serum light chain ratio, and no extramedullary myeloma, the patient achieved a complete remission (CR). She was maintained on this therapy until a peripheral neuropathie occurred. She ceased bortezomib due to the intolerable peripheral neuropathies and was followed-up for re-evaluation of her disease status every month. Five months later, she was admitted for re-evaluation of her disease status, and was found to have a relapse of her disease with evidence of 0.79% monoclonal malignant plasma cells in her bone marrow. Then she was treated with one cycle of reduced-intensity VD regimen in which bortezomib was attenuated to 1.0 mg/m² to minimize occurrence of peripheral neuropathies. After finishing this therapy, she was found to have a separate peak of monoclonal component on the γ -region of cellulose-acetate electrophoresis, and then serum immunofixation electrophoresis showed that the monoclonal component was IgD (**Figure 2A**), and the proportion of paraprotein was 4.3%. The bone marrow smears (**Figure 2B**), revealed 15% of naive plasma cells

and flow cytometry demonstrated 4.12% of monoclonal plasma cells and a higher percentage of the light chain-restricted (LCR) cells in the bone marrow (**Figure 2C**). The patient was therefore re-admitted in September 2011 and treated with another cycle of reduced-intensity VD regimen, however, the outcome turned out to be progressive disease (the proportion of paraprotein had raised up to 5.2%). As a consequence of progressive disease she was commenced on lenalidomide and dexamethasone (RD). After three cycles of administration of RD, she presented with a large swelling of the left side of her neck. The cervical mass was firm and immobile. Microscopic examination of a biopsy specimen from the cervical mass showed a neoplastic plasma cell tumor (**Figure 2D**), which demonstrated that the patient had an extramedullary myeloma. The patient was treated with radiotherapy and a series of chemotherapies, involving VP-16 plus ifosfamide, VRD (bortezomib, lenalidomide and dexamethasone), MPT (melphalan, prednisone and thalidomide), and DCEP (dichlorodiamine platinum, cytoxan, etoposide and dexamethasone). However, the patient still had a progressive disease of multiple myeloma with multiple bone pain and neoplastic plasma cells infiltrating her chest despite aggressive treatment including chemo- and radiation therapy, she died on January 28, 2013 from acute respiratory failure which was caused by neoplastic plasma cells infiltration and uncontrollable infection.

Discussion

Multiple myeloma is a malignancy of plasma cells within the bone marrow. It is characterized by clonal proliferation of plasma cells deriving from the B cell lineage. To measure circulating monoclonal immunoglobulin has been the standard measure for diagnosis, prognosis and management. However, in about 1% to 5% of multiple myeloma cases no monoclonal immunoglobulin can be detected and these patients are known as non-secretory myeloma (NSMM). NSMM is very difficult to diagnose due to its low incidence and scant analytical expression [12], whilst serum immunofixation electrophoresis (IFE) is a helpful assay to minimize occurrence of misdiagnosis. Our case presented with non-detectable M component and normal light chain ratio, IFE revealed no evidence of monoclonal immunoglobulin, while bone marrow rep-

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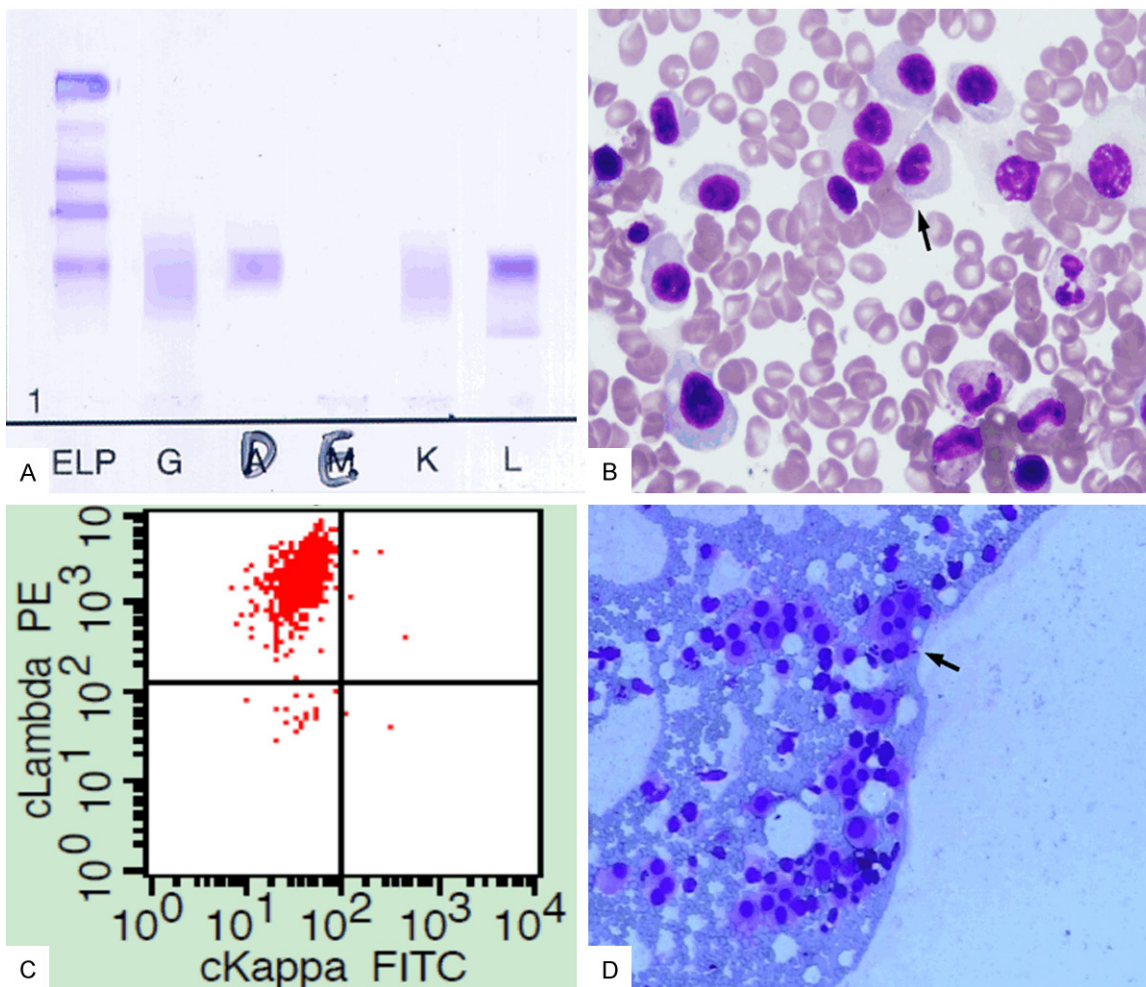


Figure 2. Immunofixation Electrophoresis, Bone Marrow Smear, Flow Cytometry, and Cervical Mass Biopsy. A: Immunofixation electrophoresis showed the existence of monoclonal immunoglobulin IgD. B: Bone marrow smear (100 \times), showing abnormal proliferation of atypical plasma cells (15%) at relapse. C: Flow cytometry demonstrated monoclonal aberrant population of cLambda⁺ myeloma cells. D: The cervical mass biopsy showed infiltration of neoplastic plasma cells.

resented 17% of malignant clonal plasma cells, complicated with progressive osteolysis lesion, consequently, she was diagnosed as non-secretory myeloma stage III A (with normal renal function) according to the classification of Durie and Salmon [10].

The lack of M-protein with NSMM patients may be explained by (1) reduced protein synthesis or increase in breakdown of abnormal immunoglobulin chains intracellular or extracellular, (2) capable to synthesize but incapable to secrete possibly due to reduced permeability or absence and alteration of intracellular transport of the light chains, or (3) intermittent excretion of immunoglobulin evading detection [13]. According to the finding of intracytoplas-

mic immunoglobulin, non-secretory myeloma were divided into two types-non-producer type (about 15%), in which the plasma cells are out of capability to produce immunoglobulin; and in the remaining 85% called producer type which is characterized by producing immunoglobulin but not secreting them out of the cell [14]. Intracytoplasmic immunoglobulin could be detected by immunohistochemical staining (IHC) or flow cytometry method. Our case was obviously belonged to the producer type due to the aberrant population of CD138⁺, CD38⁺, CD9⁺, cLambda⁺. In other words, our patient was able to synthesize immunoglobulin, but was unable to secrete them out of the cells due to paracrisis.

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Table 1. The clinical data of multiple myeloma patients involving Immunoglobulin class switch

Case No.	Gender	Age (yrs)	Class switch	Extramedullary infiltration	Chemotherapy regimens	CT	SDAC	Reference
1	Male	57	mainly IgG-λ to mainly IgD-λ	Kidney, spleen, retroperitoneal lymph nodes and choroid plexus.	VCMP×7, VBAP×9, MP×2	15	3	18
2	Male	67	Mainly IgG-λ to mainly IgA-λ	Inguinal lymph node	low doses of cyclophosphamide	10	20	19
3	Female	63	IgG-κ to mainly IgD-κ	None	CTX (200 mg/d, 5 d/month)×17, VAD×2	27	3	20
4	Female	77	IgA1-κ to IgG2-κ	None	Interferon α+MP	30	Unknown	21
5	Male	58	IgA-κ to κ chain	None	(Vincristine, cyclophosphamide, and prednisolone), (melphalan, prednisolone. Vincristine, and ACNU)×3 + interferon alpha, VAD	8	5	22
6	Male	63	IgA-κ to LEPP	Liver, Paraspinal, Perinephric, Presacral, retroperitoneum	CID×4 (T1), In-mel (T3)*, MP×3 (T4)* + Thalidomide (11 months) (T2)	16	5	23
7	Female	68	IgG-λ to LEPP	Pulmonary, Multiple subcutaneous, Right para-nephric, Pelvis	MP×12 (T1), VAD×2 (T2), Hi-DEX×3 (T3), CP (T4), Hi-Mel-SCT (T5) + Thalidomide (11 months) (T6) + Lenalinomide (8 months) (T7)*	19	10	23
8	Female	69	IgA-κ to LEPP	Epidural, Pleural, Multiple, subcutaneous, Left para-aortic	Hi-DEX×4 (T1), DCEP×1 (T3)* + Lenalinomide (2 months) (T2)	3	5	23
9	Female	62	Non-secreting to IgD-λ	Left neck soft tissue	VD×6, RD×3, VP16+IFO, VRD×1	10	8	Our case

CT: conversion time (months), from diagnosis to conversion; SDAC: survival duration after conversion (months); VCMP: vincristine, cyclophosphamide, melphalan and prednisone; VBAP: vincristine, BCNU, doxorubicin, and prednisone; MP: melphalan and prednisone; VAD: vincristine, doxorubicin and dexamethasone; CID: cyclophosphamide, idarubicin and dexamethasone; LEPP: light chain escape from plateau phase; *: therapy given after LEPP development; T(n): therapy number; Hi-Dex: pulsed high dose dexamethasone; CP: low dose cyclophosphamide and prednisolone; Hi-Mel: high dose melphalan 200 mg/m²; SCT: stem cell transplantation; DCEP: dexamethasone, cyclophosphamide, etoposide and cisplatin; VD: bortezomib and dexamethasone; RD: Lenalinomide and dexamethasone; VRD: bortezomib, Lenalinomide and dexamethasone.

The idea of class switch in immunoglobulin production was first brought up by Nossal et al. [15] in 1964, then Cooper et al. [16] developed the idea and established the concept of an intracloonal class switch, which was demonstrated by coexisting double monoclonal proteins derived from a common clone in MM patients [17]. These class switch MM cases were rare, so far, there were only 8 cases reported previously (**Table 1**). These cases could be divided into two groups: (1) case 1 to 4 [18-21], which were shifted from one intact monoclonal immunoglobulin to another, having the same isotype light chains, the mechanism beyond class switch from one heavy chain to another was supposed to be that the two heavy chains were derived from a common clonal immunoglobulin-producing cell lineage. (2) case 5 to 8 [22, 23], the transformation of multiple myeloma from a disease that produces both a heavy and a light chain to one that produces a light chain only, has been regarded as a signal of clonal evolution and traditionally identified with disease progression [24]. The mechanism beyond this phenomenon might be that genetic mutations during clonal evolution compromised the production of functional heavy chains. In addition, the lack of IgH mRNA transcription, instability or degradation of IgH mRNA or translation errors could underlie this loss of capacity [23].

Our patient exhibited the third type of class switch, a shift from non-secretory myeloma to IgD- λ myeloma, which had not been previously described. The hypothesis was that the patient was producer type NSMM, which made the patient have the ability to produce monoclonal heavy chain and light chain, while failed to secrete them out of cells; whereas bortezomib involved chemotherapy might induced an unusual C μ to C δ switch which was mediated by DNA recombination between JH-C μ intron and C μ -C δ intron and then allowed IgD to be secreted into serum [25]. In addition, besides case 2 and 5, all other patients were died from progressive disease or drug resistance within one year after class switch, demonstrating that class switch in MM patients predicted an adverse prognosis. Therapy of multiple myeloma has greatly improved over the last decade, many new drugs including proteasome inhibitors and immunomodulatory drugs are now available to patients. The era of new biological

therapies has changed the natural history of myeloma and this selective pressure has culminated in novel manifestations of relapsed disease.

Our case represents the first documented of this rare but clinically important mode of relapse. And through literatures reviewing, we found that most MM patients who underwent a class switch would have an adverse prognosis. We suggested that all patients with NSMM should accomplish IHC or flow cytometry measurement to distinguish producer types from the non-producer ones and then followed with IFE and serum free light chain (SFLC) measurement to detect the early relapse. Our case emphasized the changing natural history of multiple myeloma in the era of bortezomib involved chemotherapies and highlighted the role of IHC or flow cytometry in differentiating NSMM type and IFE plus SFLC in monitoring the early relapse of patients with NSMM.

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Disclosure of conflict of interest

None.

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