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# IgD Myeloma with Mott Cells, Adverse Prognosis Cytogenetics and Persistent Minute IgD M-Protein Following Treatment

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## Abstract

Immunoglobulin D-secreting Multiple Myeloma (IgD MM) is a rare form of the disease, accounting for 1% to 2% of cases. Patients present frequently at a younger age and with more advanced disease than in the more common myeloma isotypes, contributing to shorter Overall Survival (OS) and Progression Free Survival (PFS). Autologous Stem Cell Transplant (ASCT) and greater access to novel agents are key to reducing this gap. As with other myeloma isotypes, there is a small group of long-term survivors. Interphase Fluorescence *in situ* Hybridization (iFISH) detects abnormalities in the majority of cases. 1q21 amplification, associated with late myeloma, and t(11;14), are more common than in other myeloma isotypes. No clear difference in del(17p) frequency has been shown. We present a case report of an IgD MM patient in our care which, whilst not entirely typical of the genre, illustrates the diagnostic and management challenges when caring for these patients.

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## Case Presentation

A 73-year-old man presented in October 2016 with a 4-month history of left upper quadrant pain exacerbated by movement. He had a history of myocardial infarction in 2007 and paroxysmal atrial fibrillation but, apart from his upper quadrant pain, was generally quite well and active. Capillary electrophoresis demonstrated the presence of panhypogammaglobulinemia. Discretionary reflex Immunofixation Electrophoresis (IFE) confirmed the presence of a minute IgDL M-protein. Freelite® assay quantified lambda 937 mg/l, kappa 11 mg/l, ratio 0.01, and 0.3 g BJP/24 h was identified in his urine. Bone Marrow (BM) trephine biopsy showed a heavy infiltrate of plasma cells, with 50% CD138 positive, IgD positive, lambda restricted cells. Mott cells with Russell bodies were observed in the BM aspirate (Figure 1a). Flow cytometry showed a large population of plasma cells (CD38+ CD138+) (Figure 1b, green), almost all of which showed aberrant CD19- CD56+ phenotype, with variable CD45 expression identifying two subclones (purple and yellow). Interphase FISH showed gain of 1q21 (*CKS1B*) (Figure 1c, top) and *TP53* deletion in over 90% of cells (Figure 1c, bottom). Another subclone was present, consisting of larger cells showing additional aberrations, namely gain of 1p32.3 (*CDKN2C*) and a further gain of 1q21 (Figure 1c, top). Whole body MRI was performed. Coronal T1 turbo spin echo, coronal T2 short tau inversion recovery and multiple axial diffusion-weighted imaging with multiplanar maximum intensity projection reformats were obtained. The findings reported no convincing focal STIR hyperintensity within the visualized skeleton to suggest focal myeloma deposits. The background marrow signal appeared within normal limits on the T1-weighted imaging. There was a large hiatus hernia present. No significant pericardial or pleural effusion or renal tract obstruction was seen. The imaging report concluded there were no convincing skeletal lesions identified. Our patient was diagnosed with R-ISS Stage II MM. He was initially treated with Bortezomib, Thalidomide and Dexamethasone (VTD), with thalidomide replaced by cyclophosphamide following an adverse reaction. He was deemed not a suitable candidate for ASCT on assessment following initial response to therapy. Although he achieved a partial response, the M-protein persisted throughout and the lambda Free Light Chains (FLC) only achieved a nadir of 116 mg/l and then rose (309 mg/l). He was then commenced on lenalidomide and dexamethasone

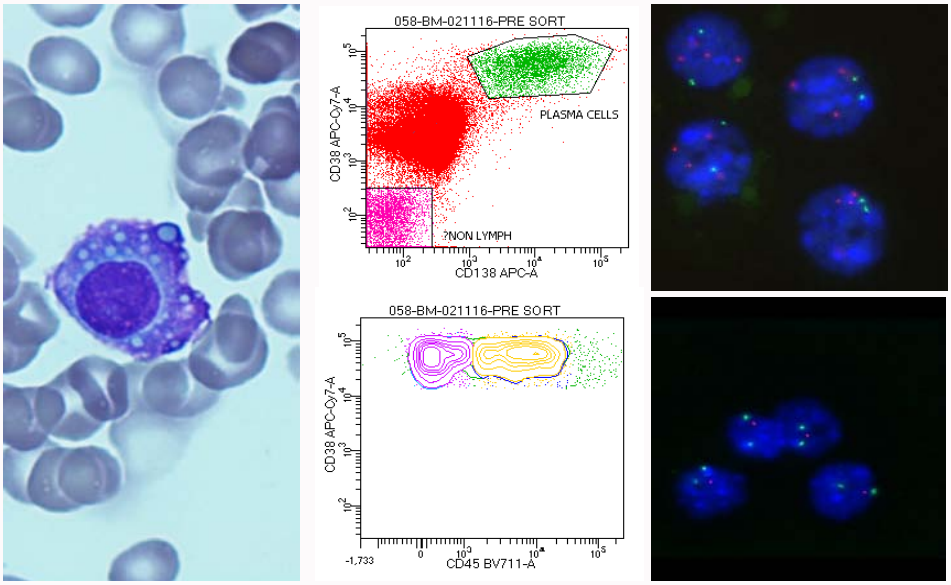


**Figure 1**: Laboratory investigations of IgD myeloma. a) Romanowsky stain shows Mott cell with Russell Bodies; b) Clonal plasma cell populations detected and characterized using flow cytometry, showing two clones, one CD45 positive and the other CD45 negative; c) Interphase FISH carried out on CD138 selected plasma cells. Top: Gain of 1q21 (*CKS1B*) detected (3 red) with normal 1p32.3 (*CDKN2C*) (2 green). A sub-population (~10%) of large plasma cells has 3 copies of 1p32.3 (*CDKN2C*) with 4 copies of 1q21 (*CKS1B*). Bottom: 93% of plasma cells have a *TP53* gene deletion (1 red, 2 green).

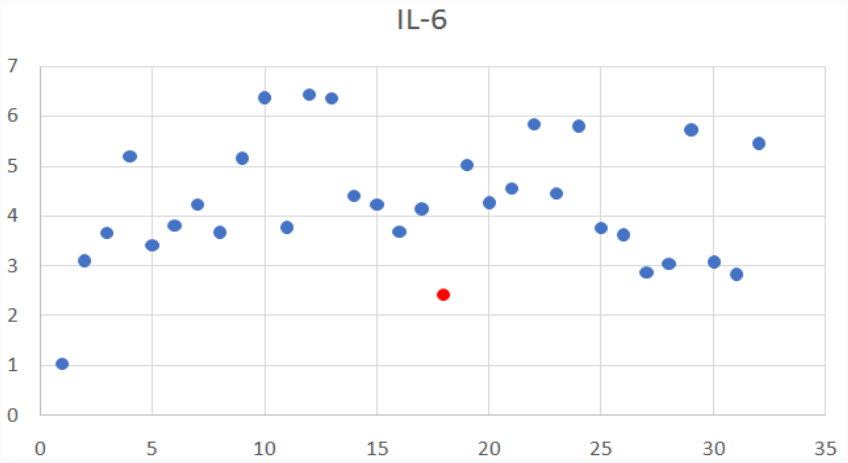


**Figure 2:** Plasma IL-6 values in newly diagnosed multiple myeloma patients. X axis denotes patient identification number; Y axis denotes Normalized Protein Expression (NPX) value. Red dot represents the IgD patient; blue dots denote common Ig isotype patients. The only lower value was observed in a relapsed refractory terminally ill patient.

with a modest initial response. Cyclophosphamide was added to the regimen (Cycle 10), and after 37 cycles in total (~3 years) he achieved normalization of his quantitative FLC, and with a normal LC ratio. The IgD M-protein was only detectable by IFE and quantifiable by immunoturbidimetry. The patient's clinical course was monitored as an outpatient at monthly intervals. Although he had several comorbidities and was physically frail, his maintenance regimen of Cyclophosphamide, Lenalidomide, and Dexamethasone (CRD) kept his immunoprotein parameters at a stable level. However, in late December 2020, during his 41st cycle of CRD therapy, he suffered a basilar artery thrombosis leading to a posterior circulation stroke attributed to a basilar aneurysm. Intervention was not considered on the basis of risk versus benefit. Unfortunately, his clinical condition deteriorated, and he passed away peacefully. Intriguingly, in a preliminary proteomics study of plasma cell dyscrasias we have found that this patient had a particularly low IL-6 level at presentation, in contrast to all but one of the remaining MM patients studied (IgG, IgA, IgM or LCMM) (Figure 2). Several other proteins, important in key functions and pathways, were abnormally expressed when compared to common (IgG, IgA, LC) Newly Diagnosed MM (NDMM). Although we have no further IL-6 data currently on our more recently diagnosed IgD MM patients, all have presented with low normal C-Reactive Protein (CRP) values, which would be in keeping with low IL-6 expression. We are continuing to investigate this in our ongoing MM study.

## Conclusion and Discussion

Despite an IgD M-protein isotype and adverse prognosis cytogenetic aberrations, the patient, whilst physically frail, continued in a stable condition as determined by the persistence of the M protein, evident only by IFE, and including FLC analyses, maintained on CRD [1-5]. Whilst not succumbing directly to his MM, his OS of

50 months was typical of that recorded for IgD MM [6]. However, although associated with poor outcomes in many patients, this account illustrates the importance of recording the cause of death when quoting survival data as, in this IgD MM patient with high risk acquired cytogenetic aberrations; his MM was not the cause of death [7-10]. Finally, we hypothesize that the above ongoing extensive proteomics analysis on all patients recruited to our current plasma cell dyscrasia study may enhance our understanding of factors contributing to the generally poor outcomes in IgD MM.

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