Case Report

Light Chain Escape in 3 Cases: Evidence of Intraclonal Heterogeneity in Multiple Myeloma from a Single Institution in Poland

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1. Introduction

Multiple myeloma (MM) is characterised by the production of a monoclonal protein which could be an intact immunoglobulin, free light chain (FLC), both, or neither. MM is almost always preceded by a premalignant disease called monoclonal gammopathy of undetermined significance (MGUS), an incidental laboratory finding also characterised by the production of a monoclonal protein [1, 2]. MGUS may evolve to MM or other B cell lymphoproliferative diseases and this evolution is thought to be due to the acquisition of genetic mutations by the tumour cell clones and associated changes in the bone marrow microenvironment [3, 4]. Originally this transformation from MGUS to MM was considered to occur in a linear fashion; however emerging evidence suggests that disease evolution follows a Darwinian-like branching process giving rise to multiple clones present at MM diagnosis [5, 6]. A study by Ayliffe et al. identified the presence of dual populations in the bone marrow of a proportion of MM patients, where bone marrow plasma cells (BMPCs) produced either monoclonal FLCs or intact immunoglobulins, indicating the presence of separate clones [7]. The discovery of this intraclonal heterogeneity in MM suggests that serological analysis could act as a surrogate marker for bone marrow tumour cell populations [7, 8].

Intraclonal heterogeneity may impact response to treatment, including disease progression and relapse, as the independent clones may have different response kinetics to treatment resulting in changes in clonal dominance [9]. Such clonal change was first described by Hobbs in 1971 during the first MRC myeloma trial. He reported that 5% of intact immunoglobulin MM patients relapsed with only Bence Jones proteinuria. It was termed Bence Jones escape and is now more commonly referred to as light chain escape (LCE) [10–12], defined as an increase in monoclonal FLCs without a corresponding increase in monoclonal intact immunoglobulins. In the most recent MRC myeloma trial, the incidence of LCE was 6.5% for IgG and 19.9% for IgA [10].
Here we report three cases of LCE observed at a single institution in Poland: 2 MM patients and a rare biclonal MGUS. These cases serve to highlight the importance of utilising sensitive monitoring tools capable of detecting clonal change at an early stage in order to allow therapeutic intervention aimed at preventing irreversible end-organ damage.

2. Case Presentation

2.1. Case 1. A 71-year-old woman was hospitalised with a diagnosis of hypertension and coronary artery disease; routine haematological investigations identified an IgG monoclonal protein (SPE: 3.9 g/L) and monoclonal λ sFLC (λ sFLC concentration 316 mg/L; κ/λ sFLC ratio 0.07). Retrospective HLC analysis identified an abnormal HLC ratio (IgGκ/ IgGλ HLC ratio; 4.75). A bone marrow biopsy revealed a 3% monoclonal plasma cell infiltration; a bone survey was negative for osteolysis and haemoglobin, calcium and creatinine levels were all normal. The patient was diagnosed with a biclonal MGUS (low/moderate risk) and was followed up annually by SPE, in accordance with IMWG guidelines (Figure 1(a) and Table 1). A year following diagnosis, the IgGκ monoclonal protein concentration was stable but, by contrast, the dFLC (involved FLC-uninvolved FLC) concentration had increased to 452.9 mg/L. Five months later, the patient was diagnosed with temporal artery inflammation and polymyalgia rheumatica (PMR) and treated with oral methylprednisolone for 11 months. The steroid treatment resolved the PMR and, coincidently, caused a reduction in the IgGκ concentration (trace quantities detectable by IFE) and normalisation of the κ/λ sFLC ratio (0.55) and IgGκ/ IgGλ HLC ratio (1.34). A year after steroidal treatment, whilst the IgGκ monoclonal protein concentration remained stable (trace by IFE, normal IgGκ/ IgGλ HLC ratio) and the patient remained asymptomatic, the dFLC levels increased to 1052 mg/L (κ/λ sFLC ratio: 0.008), indicating the reemergence of a λ FLC clone. Four months later, the patient progressed to symptomatic disease with severe renal impairment (creatinine 16.9 mg/dL; eGFR 703 mL/min/1.73 m²), anaemia (Hb 9.0 g/dL), and 70% clonal bone marrow plasma cells and the dFLC concentration had further increased to 9726 mg/L. However, the IgGκ monoclonal protein was no longer detectable by IFE and the IgGκ/ IgGλ HLC ratio remained within the normal range, indicating that the biclonal MGUS had progressed to a λ light chain multiple myeloma.

2.2. Case 2. A 62-year-old woman presented with anaemia (haemoglobin; 9.2 g/dL) in March 2011 and was diagnosed with stage I oligosectomy IgGκ MM (SPE: 16 g/L; κ sFLCs: 3440 mg/L; κ/λ sFLC ratio 558) with 17% clonal bone marrow plasma cells. The patient’s characteristics are described in Table 1. The patient was serially monitored with SPE, IFE, total IgA (due to the β-region migration of the monoclonal protein), and sFLC. Retrospective HLC analysis revealed an abnormal IgGκ/ IgGλ HLC ratio at diagnosis (24.2) and this remained abnormal throughout the patient’s disease course (Figure 1(c)). The patient was treated initially with vincristine, doxorubicin, and dexamethasone (VAD; 6 cycles) and achieved a PR. In March 2011, the patient was treated with 5 cycles of CTD and achieved a VGPR (SPE negative, IFE positive, normal total IgA concentration, dFLC 24 mg/L; κ/λ sFLC ratio 3.5). Due to the cardiac side effects of thalidomide, the patient was subsequently only treated with CD. Between March 2012 and July 2012, the patient was monitored by SPE only and during this time the IgGκ monoclonal protein remained stable (data not shown). In September 2012, progression of osteolysis was noted and whilst both SPE and total IgA measurements were uninformative, the dFLC levels increased from 24.5 mg/L to 821 mg/L (κ/λ sFLC ratio 103.5). The osteolytic lesions were irradiated with 2000 cGy/t, resulting in stable disease. However, in March 2013, the dFLC levels increased again (dFLC 938 mg/L; κ/λ sFLC ratio 157.9) indicating progressive disease and 1 month later, whilst the IgGκ monoclonal protein remained stable, progression of bone disease was identified. Treatment with 4 cycles of bortezomib, cyclophosphamide, and dexamethasone (VCD) was initiated and the patient achieved a VGPR (IgGκ trace by IFE, normal total IgA concentration and >90% reduction in dFLC). Treatment with VCD was interrupted due to severe neuropathy and Herpes viral infection. He then remained without treatment until clinical relapse in January 2014, characterised by renal impairment and hypercalcaemia. At this time, the IgGκ
Figure 1: Disease course of patients with (a) biclonal MGUS progressing to LCMM (case 1), (b) oligosecretory IgGκ MM (case 2), and (c) IgAκ IIMM (case 3). MGUS: monoclonal gammopathy of undetermined significance, LCMM: light chain multiple myeloma, MM: multiple myeloma, IIMM: intact immunoglobulin multiple myeloma, SPE: serum protein electrophoresis, dFLC: difference in concentration between involved and uninvolved free light chain measurement (Freelite), dHLC: difference in concentration between involved and uninvolved heavy/light chain measurement (Hevylite), MPS: methylprednisolone, CTD: cyclophosphamide, thalidomide, and dexamethasone, PAD: bortezomib, doxorubicin, and dexamethasone, VAD: vincristine, doxorubicin, and dexamethasone, CD: cyclophosphamide and dexamethasone, IR: ionising radiation, VCD: bortezomib, cyclophosphamide, and dexamethasone, and ASCT: autologous stem cell transplant; blue open circle indicates a normalised sFLC ratio, red open circle indicates a normalised HLC ratio, and green open circle indicates normalised sFLC and HLC ratio.

A monoclonal protein remained stable (trace quantities by IFE, normal Total IgA concentration) but the dFLC had increased to 5404 mg/L, indicating relapse by the κ FLC producing clone.

3. Discussion

Disease progression from MGUS to MM is now thought to be the result of Darwinian-like evolution which leads to multiple clones being present at MM diagnosis, possibly producing different monoclonal proteins. The cases presented here indicate that disease progression and relapse may be associated with selective outgrowth of a FLC producing clone. The MGUS patient (case 1) had two separate clones present at diagnosis, one producing monoclonal IgGκ and another monoclonal λ FLC. Over time, the combined selective pressure applied by the bone marrow microenvironment and steroid treatment for PMR resulted in the λ FLC producing clone becoming dominant, leading to the development of LCMM. Similarly, the two MM cases highlight that the selective pressure of treatment (alongside the pressure applied by the microenvironment) resulted in the outgrowth of a more aggressive FLC producing clone.
<table>
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<tr>
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<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>71</td>
<td>62</td>
<td>70</td>
</tr>
<tr>
<td>Gender</td>
<td>F</td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td>MGUS/MM type</td>
<td>IgGκ + λ FLC</td>
<td>IgGκ</td>
<td>IgAκ</td>
</tr>
<tr>
<td>M-protein by SPE at diagnosis (g/L)</td>
<td>3.9</td>
<td>7.4</td>
<td>16</td>
</tr>
<tr>
<td>HLC ratio at diagnosis</td>
<td>4.8</td>
<td>6.9</td>
<td>24.2</td>
</tr>
<tr>
<td>iFLC [κ/λ ratio] at diagnosis (mg/L)</td>
<td>316 [0.07]</td>
<td>47.3 [5.9]</td>
<td>3440 [558]</td>
</tr>
<tr>
<td>uBJP at diagnosis</td>
<td>+</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>ISS stage</td>
<td>N/A</td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>Symptoms at relapse</td>
<td>Renal impairment</td>
<td>Renal impairment</td>
<td>Renal impairment</td>
</tr>
<tr>
<td>dFLC concentration at relapse (mg/L)</td>
<td>9726</td>
<td>2665</td>
<td>5404</td>
</tr>
<tr>
<td>Time prior to clinical relapse that increases in FLC detected (days)</td>
<td>114</td>
<td>187</td>
<td>0</td>
</tr>
<tr>
<td>Maximum response</td>
<td>N/A</td>
<td>PR</td>
<td>VGPR</td>
</tr>
<tr>
<td>Treatment</td>
<td>Methylprednisolone</td>
<td>CTD, PAD, and ASCT</td>
<td>VAD, CTD, CD, IR, and VCD</td>
</tr>
<tr>
<td>Follow-up (days)</td>
<td>1310</td>
<td>1019</td>
<td>1570</td>
</tr>
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In this study, all 3 cases relapsed with renal impairment. This result is in agreement with a previous study which reported renal impairment in 50% of patients with LCE escape [12]. As renal impairment is known to be associated with significant morbidity and mortality, it is important to identify LCE early. Interestingly, in this study we found that two of the three cases had an increase in their sFLC concentrations prior to clinical relapse (114 and 187 days), highlighting the clinical benefit of serially monitoring not only MM patients but also MGUS patients with sFLC to ensure early identification of disease relapse/progression and help prevent the development of irreversible end-organ damage. Supporting this, the study of Brioli et al. reported that patients relapsing with sFLC involvement (either LCE or alongside an increase in the intact immunoglobulin) had a significantly shorter overall survival compared to those patients relapsing without a sFLC component [10].

It is noteworthy that, in case 1 presented here, one year after steroidal treatment for PMR, the patient’s sFLC ratio was highly abnormal (0.008; involved/uninvolved ratio = 125) although they remained asymptomatic. The recently updated IMWG criteria for the definition of multiple myeloma no longer require a patient to display symptoms of end-organ damage in the presence of one or more biomarkers of malignancy (plus at least 10% clonal bone marrow plasma cells/biopsy proven bony or extramedullary plasmacytoma), one of which being a sFLC involved/uninvolved ratio of 100 [13]. Therefore, had these updated criteria for myeloma been in effect at the time the patient described in case 1 was monitored, upon observation that the sFLC involved/uninvolved ratio had increased to 125, it is tempting to speculate that this may well have prompted further investigation to look for evidence of progression to myeloma. Importantly, this was some 4 months before the patient developed symptomatic disease, and if progression to asymptomatic myeloma had been confirmed at this time, this may have allowed earlier therapeutic intervention to help prevent the severe renal impairment that the patient ultimately acquired.

The IMWG guidelines recommend that, for patients with oligosecretory MM (<10 g/L or <200 mg/24 h M-protein), response should be assessed by sFLC, if the involved FLC (iFLC) is ≥100 mg/L [14]. In case 2 (SPE 7.4 g/L M-protein, uBJP negative), the iFLC concentration was 47.3 mg/L and therefore the IMWG guidelines recommend monitoring such patients with BMPCs. However, this case highlights that sFLC analysis is still a valuable monitoring tool even if the iFLC is below 100 mg/L as the increase in the dFLC identified disease progression 6 months prior to development of renal impairment. In addition, this case highlights that HLC analysis could be used alongside sFLC to monitor the M-lg producing clone in oligosecretory disease. This is supported by a number of other studies which have shown that HLC assays can be used to accurately monitor oligosecretory patients [15–17], especially those with an iFLC < 100 mg/L [17].

IgA monoclonal proteins that migrate within the β region by SPE can be difficult to identify and/or accurately quantify due to comigration with other serum proteins (such as transferrin and complement proteins). Although the use of nephelometric/turbidimetric immunoglobulin quantification alongside electrophoresis is recommended by the IMWG...
guidelines, when total IgA measurements fall within the normal range, it is not clear if a monoclonal protein is still present [18]. This is illustrated by case 3 presented here, as the total IgA measurements were borderline normal throughout the patient’s disease course and therefore uninformative. However, the HLC ratio remained abnormal throughout the patient’s disease course indicating the presence of a monoclonal IgAx producing clone that remained stable and was not responsive to any of the therapies. The HLC ratio has been shown previously to be an accurate measurement of clonality and useful in the monitoring of MM patients [16, 19]. Furthermore, a recent study from Katzmann and colleagues concluded that IgA HLC immunoassays can be used instead of SPE, IFE, and total IgA quantification for monitoring β-region migrating IgA monoclonal proteins, as was the situation in case 3 presented here [20].

In conclusion, the cases presented here highlight the importance of being able to monitor clonal evolution over the course of the disease in multiple myeloma, particularly as disease progression in the form of LCE can result in rapid and irreversible end-organ damage that may be preventable if the disease progression can be detected early. To this end, the combined use of more sensitive monitoring tools, such as using sFLC and HLC assays together, may fulfill this requirement and permit closer monitoring of multiple myeloma patients.

Conflict of Interests

Dr. K. Endean is an employee of The Binding Site Group Ltd. All other authors declare that there is no conflict of interests regarding the publication of this paper.

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References


