A 71-Year-Old Woman with Multiple Myeloma Status after Stem Cell Transplantation

Leslie J. Donato,1 Steven R. Zeldenrust,2 David L. Murray,1 and Jerry A. Katzmann1,2*

CASE

A 71-year-old woman with a 9-year history of monoclonal gammopathy of undetermined significance presented with anemia [hemoglobin, 11.6 g/dL (116 g/L); reference interval (RI),3 12–15.5 g/dL (120–155 g/L)], an increased serum calcium concentration [10.2 mg/dL (2.55 mmol/L); RI, 8.9–10.1 mg/dL (2.22–2.52 mmol/L)], and a 4800-mg/dL (48-g/L) monoclonal protein band (M-spike) after serum protein electrophoresis (SPEP). Immunofixation electrophoresis (IFE) revealed a monoclonal IgAκ protein. Her IgA concentration was markedly increased to 4720 mg/dL [47.2 g/L; RI, 61–356 mg/dL (0.61–3.56 g/L)], and the serum immunoglobulin free light chain (FLC) κ/λ ratio was 7 (RI, 0.26–1.65). A bone marrow biopsy confirmed 40% involvement by monoclonal κ-restricted plasma cells with a plasma cell labeling index of 0.4% (intermediate). A bone survey revealed diffuse osteopenia, multiple small lytic lesions throughout the skeleton, and a lesion consistent with a plasmacytoma at T7. A diagnosis of multiple myeloma (MM) (Durie–Salmon stage IIIA, international stage 2) was confirmed. The patient was initially treated medically and then underwent successful autologous stem cell transplantation. The patient was asymptomatic, with negative results in serum and urine protein electrophoresis and IFE evaluations for 1.5 years.

A follow-up SPEP evaluation 2 years after the patient received her transplant revealed an M-spike of 3920 mg/dL (39.2 g/L) and an IgA concentration of 3810 mg/dL (38.1 g/L). A bone marrow biopsy showed 60%–70% involvement by monoclonal plasma cells. The results of a urine IFE test were negative. The patient was treated with a regimen of 25 mg Revlimid daily on days 1–21 and 20 mg dexamethasone weekly. The patient’s M-spike decreased to 1100 mg/dL (11 g/L) by 1 month after treatment, and her IgA concentration was reduced to 1260 mg/dL (12.6 g/L). Two months into treatment, the patient had detectable monoclonal protein but no measurable M-spike, and her IgA concentration was 402 mg/dL (4.02 g/L). The dexamethasone dosage was reduced to 10 mg weekly for the third month, and her serum IgA concentration decreased further, to 340 mg/dL (3.4 g/L), which is within the RI.

The patient was maintained on pamidronate monthly and with 25 mg Revlimid daily as a single agent. Bimonthly monitoring by SPEP and IFE testing and measurement of her IgA concentration were continued for 1 year. Follow-up SPEP and IFE results were normal (Fig. 1); however, the serum IgA concentration steadily increased above the upper reference limit, even in the presence of normal IFE results and normal serum FLC ratios (Table 1). Because of the patient’s history of IgA disease, her hematologist felt this increase in IgA might be a sign of relapsed disease.

DISCUSSION

BACKGROUND ON MM

MM is a hematologic malignancy characterized by expansion of a single clone of plasma cells in the bone marrow. The disease often produces skeletal lesions, osteopenia, and pathologic fractures, with nearly 60% of newly diagnosed MM cases presenting with bone pain (1). Other clinical features of MM include renal insufficiency, anemia, hypercalcemia, increased β2-microglobulin, and monoclonal protein present in the serum and/or urine (1, 2). With novel drugs, most pa-
Patients with newly diagnosed MM respond to treatment, but almost all MM patients who respond to initial treatment will relapse and require additional therapy. According to the International Myeloma Working Group, the criteria for ascertaining relapse from complete remission must include at least one of the following: (a) reappearance of serum or urine monoclonal protein by IFE or protein electrophoresis, (b) development of ≥5% plasma cells in the bone marrow, and (c) appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia) \( (3) \). Remission is usually monitored by periodic assessments for monoclonal protein in the serum or urine and by serum FLC quantification for an abnormal ratio caused by the involved FLC \( (4) \). An abnormality in one of these measurements raises the suspicion of disease relapse. Once identified, the treatment options for relapsed disease include stem cell transplantation, re-

![Fig. 1. SPEP and IFE analysis at various times throughout the course of disease.](image)

The patient’s broad M protein spike was typed as IgAκ at presentation. Monitoring of the second remission shows increased restriction in the A and K lanes in only the most recent examinations. SCT, stem cell transplantation.

**Table 1.** Laboratory results for IFE interpretation, immunoglobulin FLC ratio, IgA κ/λ HLC pair quantification ratio \( (\text{IgA } \kappa/\lambda) \), and IgA quantification at various times throughout the course of the disease.

<table>
<thead>
<tr>
<th>Date</th>
<th>IgA, mg/dL*</th>
<th>FLC κ/λ</th>
<th>IgA κ/λ</th>
<th>Clinical comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>RI</td>
<td>61–356</td>
<td>0.26–1.65</td>
<td>0.7–2.2</td>
<td></td>
</tr>
<tr>
<td>Jan 8, 2008</td>
<td>3810b</td>
<td>10.3b</td>
<td>463b</td>
<td>First relapse</td>
</tr>
<tr>
<td>Aug 13, 2008</td>
<td>328</td>
<td>1.9b</td>
<td>3.7b</td>
<td>After relapse, 25 mg Rev daily, 10 mg Dex weekly</td>
</tr>
<tr>
<td>Apr 22, 2009</td>
<td>434b</td>
<td>1.14</td>
<td>2.9b</td>
<td>Increased Dex to 20 mg weekly because of IgA</td>
</tr>
<tr>
<td>Nov 4, 2009</td>
<td>428b</td>
<td>1.06</td>
<td>2.8b</td>
<td>Dex removed owing to side effects</td>
</tr>
<tr>
<td>Jun 23, 2010</td>
<td>658b</td>
<td>1.21</td>
<td>4.1b</td>
<td>Single-agent Rev</td>
</tr>
<tr>
<td>Aug 25, 2010</td>
<td>767b</td>
<td>1.08</td>
<td>5.6b</td>
<td>Single-agent Rev</td>
</tr>
<tr>
<td>Oct 27, 2010</td>
<td>914b</td>
<td>1.36</td>
<td>5.6b</td>
<td>Add 10 mg Dex weekly</td>
</tr>
<tr>
<td>Dec 1, 2010</td>
<td>804b</td>
<td>1.38</td>
<td>8.2b</td>
<td>Bony disease progression, radiation to ilium</td>
</tr>
<tr>
<td>Dec 30, 2010</td>
<td>880b</td>
<td>2.07b</td>
<td>13b</td>
<td>Disease relapse, increase Dex to 20 mg weekly</td>
</tr>
<tr>
<td>Jan 20, 2011</td>
<td>1220b</td>
<td>4.75b</td>
<td>24.8b</td>
<td>Will switch to alternative regimen</td>
</tr>
</tbody>
</table>

* The factor for converting the IgA and M-spike concentrations in the traditional unit of measure (milligrams per deciliter) to SI units (grams per liter) is ×0.01.

b Abnormal result.

Rev, Revlimid; Dex, dexamethasone.
treatment with prior successful chemotherapies, or a trial of new agents.

After our patient’s relapse and subsequent second remission, monitoring of the monoclonal protein and serum FLC ratio for 1 year did not signal disease recurrence. Over the same period, however, the serum IgA concentration steadily increased. The hematologist was concerned, given the patient’s history of recurrence. The question that remained was whether this increase in IgA concentration was due to polyclonal expansion of IgA in response to a lung infection or whether it was an early indication of relapse of her monoclonal IgA disease. The monoclonal IgA protein had initially migrated as a broad band that was not easily demarcated from the polyclonal background on SPEP and IFE gels. In addition, the serum FLC concentration was abnormal but was not dramatically increased. To gain more insight into the clonality of the IgA, we performed immunoglobulin heavy/light chain (HLC) pair quantification (Hevylite™; The Binding Site) of both current and selected stored frozen serum samples. This immunoturbidimetric assay separately measures the concentrations of intact IgA κ and IgA λ chains (5). Table 1 shows that the IgA κ/λ ratios never normalized in this patient. In addition, IgA κ/λ ratios continued to be abnormal and to steadily increase during the period of increasing IgA concentrations, supporting the existence of an abnormal clone despite the apparently normal IFE results.

**IMMUNOGLOBULIN HLC PAIR ASSAY**

The HLC pair assay was performed to assess whether the increase in IgA was due to preferential synthesis of IgA κ. This nephelometric assay uses antibodies specific for the intersection of the heavy and light chain of each immunoglobulin and allows separate quantification of each immunoglobulin heavy chain and light chain combination (e.g., γκ, γλ, ακ, αλ, μκ, or μλ). Traditionally, a patient’s immunoglobulin is characterized by IFE. The monoclonal protein associated with our patient’s disease has always presented as a broadly restricted band after electrophoresis, and a recurrence of low concentrations of broadly migrating monoclonal proteins may be difficult to distinguish from the polyclonal background. Broadly migrating monoclonal IgA and IgM molecules often are a composite of closely migrating monomeric and multimeric molecules. Capillary electrophoresis and immune subtraction of κ or λ intact immunoglobulins may be useful in such patients. In our case, the ratio of the IgA κ and IgA λ HLC concentrations indicated preferential synthesis of IgA κ.

**CAN HLC PAIR QUANTIFICATION BE USED AS AN EARLY INDICATOR OF RELAPSE?**

In this case, a steadily increasing IgA concentration in the presence of normal protein electrophoresis results and IFE gels was concerning to the hematologist. Increases in immunoglobulin concentration, however, are not directly indicative of clonal increases and are insufficient to diagnose recurrence. Given that the patient’s FLC ratios were consistently normal, her SPEP and IFE results were normal, and she had experienced no significant cytopenias, hypercalcemia, or renal insufficiency, disease recurrence was not established. The patient’s bone pain, however, continued to progress during the latter period of increasing IgA and abnormal IgA HLC pair ratios. She developed severe right hip pain and progressive discomfort in the lateral aspect of her right leg and hip area. Recent MRI results showed the presence of a somewhat large destructive lesion in the right anterior ilium. There was no obvious displacement or fracture of the overlying cortical bone, but there was some spiculation and edema consistent with cortical destruction, suggesting involvement by her underlying MM, compared with previous images. When the patient’s IgA concentration was observed in October 2010 to have increased to 914 mg/dL (9.14 g/L), her dexamethasone therapy was increased. By the next appointment, the patient’s IgA concentration had decreased, causing her hematologist to conclude that her disease was responding to treatment. The results of the IgA HLC pair ratio test suggested, however, that although the patient’s total immunoglobulin concentration may have been decreasing, the polyclonal and monoclonal IgA responses had different kinetics of response.

The patient’s recent laboratory values clearly indicate disease progression (Fig. 1). The SPEP gel shows a small broad restriction in the polyclonal background in the same region where her original M-spike was detected, and the IFE results show multiple fuzzy bands in the α and κ lanes. In addition, the FLC ratio has now become abnormal. These indicators signal the relapse of the patient’s disease, which may have previously been heralded by the abnormal HLC pair ratio.

### POINTS TO REMEMBER

- Monitoring MM requires quantitative assessment of the serum M-spike, the urine M-spike, and/or the serum FLC.
- Normal serum and urine IFE results are required to indicate complete remission; conversely, detection of a monoclonal protein indicates relapse.
- Monoclonal proteins that migrate as broad bands can be difficult to distinguish, and quantitative assessment of immunoglobulin HLC pairs provides a measure of clonal synthesis.
Clinical Case Study

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Commentary

Arthur R. Bradwell*

Donato et al. draw attention to a new type of immunoglobulin measurement, i.e., immunoglobulin heavy chain/light chain (HLC) pairs. For decades, monoclonal immunoglobulins have been successfully monitored by serum protein electrophoresis (SPEP) and immunofixation electrophoresis (IFE), a practice that has led to the assumption that there is little need for improvement. Yet, these tests are not quantitative in the strictest sense; they require skilled interpretation and cannot assess immune suppression of polyclonal immunoglobulins of the same isotype as the monoclonal immunoglobulin. These features contrast with those of serum free light chain (FLC) assays, in which k/λ ratios are measured by immunoassays and polyclonal FLC suppression is an important part of their clinical utility. In a similar manner, HLC pairs provide benefits over SPEP and IFE. Thus, Donato et al. show that HLC ratios provide good sensitivity for monoclonality combined with numerical precision, allowing the patient to be monitored reliably. Importantly, the changing ratio was affected by varying immune suppression, suggesting that this feature may be an important aspect of tumor progression that is not normally considered.

From a clinical perspective, myeloma symptoms such as back pain, tiredness, weakness, and so forth are nonspecific, so reliable tests are necessary. In this patient, the authors demonstrated that the patient was unwell for many months, yet the conventional tests did not produce convincingly abnormal results. IgA disease is particularly challenging for SPEP analysis because broad bands often migrate with other serum proteins. HLC assays should have a useful role for such patients.

Remaining questions include whether isotype suppression is a constant feature of early relapse. If so, what is the trigger? A second question is whether HLC assays could replace IFE for identifying clonality and for monitoring, and whether the tests are useful for other monoclonal gammopathies. Early evidence in this and other reports (1, 2) suggests that HLC tests have an interesting clinical utility.

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Department of Immunology, University of Birmingham, The Medical School, Birmingham, UK.

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