Case Report

Report of 6 Cases of Large Granular Lymphocytic Leukemia and Plasma Cell Dyscrasia

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Clinical Practice Points

- Both large granular lymphocytic leukemia (LGLL) and multiple myeloma (MM) are rare diseases. This report describes 6 cases of concurrent LGLL and MM from a database of 858 patients with LGLL.
- The present results suggest that the association of the 2 disorders is not a mere coincidence. This report also explores the effects of one disease treatment on the other.

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Introduction

Large granular lymphocytic leukemia (LGLL) is a rare lymphocytic malignancy that was discovered in 1985.1,2 There are 2 types of LGLL: the type with T-cell large granular lymphocytes (LGLs), called T-LGLL (85%), and the type with natural killer—cell LGLs, called NK-LGLL (15%). Clinical features of LGLL include cytopenias and rheumatoid arthritis. The majority of patients have an indolent clinical course.

Chronic B-cell dyscrasia is an important clinical feature of LGLL, including monoclonal gammopathy of undetermined significance (MGUS), chronic lymphocytic leukemia, and B-cell lymphoma.3 One study reported 15 patients with LGLL and coexisting hairy cell leukemia.4 In a French registry, 12 of 229 patients with LGLL had associated B-cell lymphoid neoplasms.5 Moreover, monoclonal B-cell lymphocytosis has been found to be frequently associated with LGLL.6

This report describes 6 patients with coexistent LGLL and multiple myeloma (MM). The concomitant presence of the 2 disorders presented the opportunity to retrospectively observe the effect of bortezomib and lenalidomide, 2 novel agents used for the treatment of MM, on the LGLL clone.

Patients and Methods

The authors screened a clinical database of 629 patients with LGLL followed up at Penn State Hershey Cancer Institute and 229 patients with LGLL at the French LGL Registry between January 2007 and December 2011. This search identified 6 patients with concomitant LGLL and MM, 5 from the Penn State Hershey Cancer Institute Registry (cases 1 to 5) and 1 from the French LGL Registry (case 6). The study was approved by the institutional review boards of both institutes. The authors retrospectively reviewed all available medical records.

Results

The basic clinical characteristics of the 6 patients are summarized in Table 1. The median follow-up of the 6 patients with LGLL and MM was 76 months (range, 30-121). A brief history of each case is given in subsequent sections.

Case 1

A 56-year-old African American man was diagnosed with LGLL after a 5-year history of asymptomatic neutropenia. Marrow biopsy found low-level infiltration by T-cell LGLL. Eleven years later, he developed MGUS, with progression to smoldering MM 1 year later. He remains on close observation, without specific treatment. His LGLL has remained stable.

Case 2

A 71-year-old white woman was diagnosed with MM and LGLL during workup for anemia. Bone marrow biopsy found low-level infiltration by T-cell LGLL. Eleven years later, he developed MGUS, with progression to smoldering MM 1 year later. He remains on close observation, without specific treatment. His LGLL has remained stable.
<table>
<thead>
<tr>
<th>Case No.</th>
<th>Plasma Cell Dyscrasia</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Serum M Component</th>
<th>Serum Immunofixation</th>
<th>Bone Marrow Biopsy</th>
<th>CRAB Symptomsa</th>
<th>LGLL Phenotype</th>
<th>TCR Gene Clone</th>
<th>Follow-Up (mo)b</th>
<th>Treatment</th>
<th>Outcome of Plasma Cell Dyscrasia</th>
<th>Outcome of LGLL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, JC-908</td>
<td>Smoldering multiple myeloma</td>
<td>56</td>
<td>M</td>
<td>18 g/L</td>
<td>IgG-(\lambda)</td>
<td>22% clonal plasma cells</td>
<td>None</td>
<td>CD3(^+)/CD57(^+)</td>
<td>+</td>
<td>36</td>
<td>None</td>
<td>Stable</td>
<td>Stable</td>
</tr>
<tr>
<td>2, BK-137</td>
<td>Multiple myeloma</td>
<td>71</td>
<td>F</td>
<td>58 g/L</td>
<td>IgA-(\kappa)</td>
<td>50% clonal plasma cells</td>
<td>Lytic bone lesions</td>
<td>CD3(^+)/CD56(^+) and CD3(^+)/CD57(^+)</td>
<td>+</td>
<td>49</td>
<td>Bortezomib + lenalidomide</td>
<td>Complete remission</td>
<td>Stable</td>
</tr>
<tr>
<td>3, BD-470</td>
<td>Multiple myeloma</td>
<td>50</td>
<td>F</td>
<td>34 g/L</td>
<td>IgG-(\kappa)</td>
<td>80% clonal plasma cells</td>
<td>Anemia</td>
<td>CD3(^+)/CD57(^+)</td>
<td>+</td>
<td>30</td>
<td>Lenalidomide</td>
<td>Partial remission</td>
<td>Stable</td>
</tr>
<tr>
<td>4, SG-326</td>
<td>Smoldering multiple myeloma</td>
<td>84</td>
<td>M</td>
<td>6 g/L</td>
<td>IgA-(\kappa)</td>
<td>20%-30% clonal plasma cells</td>
<td>None</td>
<td>CD3(^+)/CD57(^+)</td>
<td>+</td>
<td>121</td>
<td>Cladribine, methotrexate, cyclophosphamide</td>
<td>Stable</td>
<td>Progressed</td>
</tr>
<tr>
<td>5, SC-045</td>
<td>MGUS evolved to multiple myeloma</td>
<td>56</td>
<td>F</td>
<td>30 g/L</td>
<td>IgG-(\lambda)</td>
<td>5.2% clonal plasma cells initially</td>
<td>None, later + anemia</td>
<td>CD3(^+)/CD16(^+)/C56(^+)/CD57(^+)</td>
<td>+</td>
<td>103</td>
<td>Cyclosporin A, cyclophosphamide, methotrexate, bortezomib</td>
<td>Progression</td>
<td>Stable</td>
</tr>
<tr>
<td>6, BA-918</td>
<td>MGUS evolved to multiple myeloma</td>
<td>59</td>
<td>F</td>
<td>23 g/L</td>
<td>IgG-(\kappa)</td>
<td>NA at initial diagnosis; 9 years later, 25% clonal plasma cells</td>
<td>Lytic bone lesions</td>
<td>CD3(^+)/Abeta(^+)/CD8(^+)/CD57(^+)</td>
<td>+</td>
<td>119</td>
<td>Melphalan, prednisone, and thalidomide</td>
<td>Partial remission</td>
<td>Stable</td>
</tr>
</tbody>
</table>

Abbreviations: CRAB = calcium level elevation, renal failure, anemia, and bone lesions (limits defined in note); Ig = immunoglobulin; LGLL = large granular lymphocytic leukemia; MGUS = monoclonal gammopathy of undetermined significance; NA = not applicable; TCR = T-cell receptor.

\(^a\)C: calcium elevation > 1 mg/dL above the reference upper limit, renal dysfunction (creatinine > 2 mg/dL), anemia (hemoglobin 2 g/dL below the reference lower limit, bone lesions (lytic lesions or osteoporosis with compression fracture).

\(^b\)Follow-up in months as of March 2014.
with T-cell LGLs (20%) (Figure 1). Treatment with single-agent bortezomib weekly was started. Six months later, it was changed to oral lenalidomide for the patient’s convenience. Two years later, MM was in complete remission. The LGL cell count decreased from $9.41 \times 10^8$ cells/L to $4.67 \times 10^8$ cells/L while the patient was on bortezomib, and it remained stable on lenalidomide.

**Case 3**
A 50-year-old white woman was diagnosed with MM and LGLL during workup for anemia and persistent leukocytosis (white blood cell count, $1.27 \times 10^{10}$ cells/L). Bone marrow biopsy found 60% cellularity, 80% plasma cells, and positive T-cell receptor (TCR)-γ gene rearrangement. Initial LGLL cell count (CD3-positive [CD3⁺], CD57⁺) was $8.8 \times 10^8$ cells/L. One year after treatment with lenalidomide and dexamethasone, MM reached a partial remission, and LGLL remained stable. She underwent collection of peripheral blood stem cells, and she received an autologous stem cell transplant. The posttransplant evaluation at day 100 found MM in complete remission, whereas the LGLL persisted unaltered in the peripheral blood. After 30 months of follow-up while she has remained on maintenance therapy with lenalidomide and bortezomib, the LGLL cell count has decreased to $1.73 \times 10^8$ cells/L.

**Case 4**
An 84-year-old man was diagnosed with smoldering MM and T-cell LGLL in 2004, during the workup for anemia. The TCR gene rearrangement study was positive for clonality. The patient required therapy for LGLL, and he initially received cladribine, then methotrexate, without improvement. He subsequently received oral cyclophosphamide, 100 mg daily for 1 year, and LGLL achieved complete remission. Eight years later, LGLL relapsed, and he was restarted on cyclophosphamide. In the meantime, MM remained smoldering, and it required no treatment.

**Case 5**
A 56-year-old woman was diagnosed with MGUS and LGLL during workup for anemia and neutropenia. Both peripheral blood smear and marrow biopsy found numerous LGLs, which represented 37% of nucleated cells in the marrow. The TCR gene rearrangement study was positive for an $\alpha/\beta$ clone. She was sequentially treated with cyclosporine A, cyclophosphamide, and methotrexate, but she continued requiring growth factors support with recombinant erythropoietin and G-CSF. A repeat bone marrow biopsy 2 years later found that her cytopenias were in fact due to progression of her MGUS to MM. Therapy with bortezomib and dexamethasone was initiated. Her cytopenias have improved with this treatment.

**Case 6**
A 59-year-old white woman was diagnosed with MGUS. Nine years later, she was found with lymphocytosis, and she was diagnosed with T-LGLL. Three years later, her monoclonal protein had increased to $>3 \text{ g/dL}$, and bone marrow biopsy identified 25% clonal plasma cells. After 2 cycles of chemotherapy with melphalan, prednisone, and thalidomide, both monoclonal protein and lymphocytosis decreased (to $1.7 \text{ g/dL}$ and $3.7 \times 10^9$ cells/L, respectively). After 9 cycles, both diseases are in partial remission, with monoclonal protein at $1.4 \text{ g/dL}$ and the lymphocytic count at $2.4 \times 10^9$ cells/L with 39% LGLL.

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**Figure 1** Immunohistochemical Features of Bone Marrow of Patient 2 Visible are Concomitant Plasma Cells and Cells of the T-cell Type of Large Granular Lymphocytic Leukemia. The Marrow Is Infiltrated by Cells Positive for CD3, CD8, CD57, and CD138 (Original Magnification × 20)
LGL Leukemia and Plasma Cell Dyscrasias

Discussion

This study identified 6 patients with both LGLL and MM from a combined registry of 858 patients with LGLL. The previous medical literature contains 6 similar cases. Because of the very rare incidence of these 2 hematologic disorders, the present authors suspect that the coexistence of LGLL and MM in the present 6 patients is not just coincidental.

The simultaneous occurrence of LGLL and MM in a patient offered the opportunity to report for the first time the effect of novel anti-MM drugs on the LGLL. In the past decade, the treatment of MM has been revolutionized by the introduction of novel agents such as the proteasome inhibitor bortezomib and the immunomodulatory drugs thalidomide and lenalidomide. In patient 2, LGLL cells decreased with bortezomib, and they remained stable with lenalidomide. In patient 3, LGLL cells remained stable on lenalidomide. From this anecdotal experience, the authors speculate that bortezomib may have a more pronounced effect on inhibiting the LGLL clone than lenalidomide. The fact that lenalidomide may not suppress the LGLL clones effectively is not surprising, because this drug is known to activate NK T cells.

Mechanisms responsible for the concurrent development of both LGLL and MM are not known. One theory implies that the clonal cytotoxic T-cell population could play a role, at least temporarily, in antitumor immunosurveillance. In this model, the MGUS, which represents the initial stage of MM evolution, could be controlled by the effector functions of the T-LGLL cells. According to the immunoeediting theory, MM cells can eventually escape this immunosurveillance, leading to the development of symptomatic MM. Thus, LGLL could reflect an exaggerated clonal expansion resulting from a chronic immune response, initially generated against a neoplastic expansion of B cells.

An alternative hypothesis is that the B-cell expansion can result from B-cell dysfunction in the setting of T-LGLL. Indeed, despite being CD8+, T-LGLL does not suppress immunoglobulin synthesis in vivo. Normally, T cells modulate B-cell maturation and differentiation into immunoglobulin-secreting plasma cells through complex interactions involving cell surface molecules and cytokines, but this modulation is disrupted in T-LGLL. Furthermore, a mouse model of B-cell tumor showed that T cells could also influence the differentiation state of transformed B cells. Finally, one cannot exclude, at least from the theoretical point of view, that the B-cell expansion and the T-LGLL could share a common malignant precursor.

Conclusion

In light of the very rare incidence of both LGLL and MM, the present cases suggest that there is an association between these 2 hematologic malignancies. However, the exact pathophysiological mechanism awaits exploration, and the common triggers need to be elucidated.

Several studies have found that clonal T-cell expansions develop in association with monoclonal gammapathies, and the present authors believe that the association between LGLL and MM may be greater than is suspected. In fact, the present study is limited by its retrospective nature, with the inherent collection bias associated with this type of analysis. If the topic is studied in a prospective setting, it is likely that more cases will be discovered, even because both MM and LGLL can be present in patients who are clinically asymptomatic.

Disclosure

The authors have stated that they have no conflicts of interest.

References