Plasma Cell Leukemia (PCL): A Report on 15 Patients

By R. K. Woodruff, J. S. Malpas, A. M. Paxton, and T. A. Lister

Fifteen patients presenting with plasma cell leukemia (PCL) are reported in detail. The clinicopathologic features of PCL differ from typical myeloma and resemble those of acute leukemia: patients with PCL have less bone disease but a much higher incidence of organomegaly and tissue infiltration as well as diffuse marrow involvement and more pronounced pancytopenia. One of the reported patients developed meningeal plasma cell leukemia and is reported in detail. Cytomorphologic assessment of PCL cells showed nuclear immaturity and obvious nuclear/cytoplasmic asynchrony. Despite the use of cytotoxic agents known to be effective in myeloma, the prognosis in PCL is poor, and the median survival of the reported patients was only 2 mo.

PLASMA CELL LEUKEMIA (PCL) is a rare form of presentation of multiple myeloma (MM), and there are sufficient clinical and pathologic differences to warrant its recognition as a distinct subentity. In contrast to typical MM, the clinicopathologic features may resemble those of acute leukemia with more tissue and organ involvement and less bone destruction. In addition, the clinical course may be fulminant, although recent reports of therapy with cytotoxic agents known to be effective in myeloma have produced more promising results in some cases.

This paper details the clinical and pathologic features (including detailed cytologic analyses) of 15 patients with PCL and contrasts them with a much larger series of patients with MM. One patient, who presented with cranial nerve palsies and subsequently developed overt meningeal leukemia, is reported in detail.

MATERIALS AND METHODS

The records of all patients with MM presenting to St. Bartholomew's Hospital during 1957-1977 were reviewed, and 15 patients presenting with PCL were identified (Table 1). MM was diagnosed according to accepted criteria; PCL was defined as more than $0.5 \times 10^9$ liter circulating plasma cells or plasmoblasts at the time of diagnosis, and patients in whom the leukemic phase was transient or developed subsequently are not included. The patients were classified by the criteria of Durie and Salmon into groups with intermediate and high tumor masses (stages II and III, respectively), and subclassified according to the absence (A) or presence (B) of renal impairment (blood urea $\geq 80$ mg/dl).

Cytomorphologic studies. Detailed assessment was made of the bone marrow plasma cells from PLC (ten patients), nonleukemic MM (ten patients), and from ten "normal" patients without plasma cell malignancy. We scored 100 plasma cells from each of the patients with PCL and MM and 50 cells from the controls. The degree of nuclear and cytoplasmic maturity was graded as

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<thead>
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<th>Case</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Presenting Symptoms</th>
<th>Hepatomegaly</th>
<th>Splenomegaly</th>
<th>Enlarged Lymph Nodes</th>
<th>Osseous Lesions</th>
<th>Hb (g/dl)</th>
<th>Platelets (x 10^9/liter)</th>
<th>WBC (x 10^9/liter)</th>
<th>Plasma Cells (%)</th>
<th>Immature Granulocytes and/or NRBCC</th>
<th>Blood Urea (mg/dl)</th>
<th>Serum Calcium (mg/dl)</th>
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<tr>
<td>3</td>
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*C. cyclophosphamide; M, melphalan; P, prednisolone; B, BCHU.*
described by Bernier and Graham with the exception that multiple prominent small nucleoli were interpreted as representing immaturity. Each patient was ascribed an immaturity score (IS) based on nuclear maturity (1, mature; 2, intermediate; 3, immature) and an asynchrony score (AS) as previously described.4

RESULTS

The clinical data and the results of investigation and treatment are shown in Table 1. The mean age at presentation was 58 yr, and there was an even distribution between males and females. The presenting symptoms of PCL were similar to those of MM, except that less than half of the patients had experienced bone pain. Patient 7 presented with progressive quadriplegia, which was shown on myelography to be due to severe cervical spine disc disease. Enlargement of the liver, spleen, and lymph nodes was common, and four patients (all of whom were thrombocytopenic) had signs of abnormal hemorrhage. Investigation showed a high incidence of anemia and thrombocytopenia, although only one patient had absolute neutropenia (2.0 × 10⁹/liter). A leukoerythroblastic peripheral blood picture was seen in two-thirds of the patients at presentation. An erythrocyte sedimentation rate was done in 13 cases and was abnormal in 12, with a mean of 85 mm/hr. Thirteen patients had bone marrow examination and all showed diffuse infiltration (≥45%); ten of them showed marked infiltration (≥70%). Evidence of paraprotein secretion was found in all cases: nine had a serum M band, and Bence Jones proteinuria alone was detected in six. More detailed protein studies were performed on the patients seen more recently (nos. 8–15): five had serum paraproteins (all typed as IgG, range 19–96 g/liter), three secreted only Bence Jones protein (2 λ, 1 κ), and all but one showed decreased levels of normal immunoglobulins.

All but 2 patients had stage III disease, and 8 had evidence of renal impairment at diagnosis. The details of treatment given are shown in Table 1 and in most instances comprised cyclophosphamide or melphalan given in standard continuous or intermittent dosage with or without corticosteroids. The response of the leukemic blood picture was documented in 14 of the patients: in 8 cases (nos. 1–3, 6, 8, 12, 14, 15) there was no significant change, in 3 cases (nos. 5, 9, 11) there was a decrease in circulating plasma cells followed by a recurrence prior to death, and in 3 cases (nos. 4, 10, 13) the leukemic pattern resolved but recurred prior to death in both of the patients whose blood was examined.

The cytologic assessment for immaturity and asynchrony (Fig. 1) showed a clear distinction between “normal” patients and those with plasma cell malignancies. In addition, cells from PCL patients showed slightly more nuclear immaturity and nuclear/cytoplasmic asynchrony than those from MM.

Postmortem examination was carried out in eight cases. Leukemic infiltration of the bone marrow, liver, and spleen was found in all cases, and also in the lymph nodes and kidneys of four. Two showed extramedullary hemopoiesis in the liver and spleen.

CASE REPORT

A 31-yr-old Jamaican male (Table 1, case 13) presented with anemia, rib tenderness, and lymphadenopathy, and PCL was diagnosed on the appearance of the peripheral blood and bone marrow (>80% infiltrated), numerous osteolytic lesions (except in the skull, which was normal)
and κ Bence Jones proteinuria. Neurologic assessment showed palsies of the right VIIth and XIIth cranial nerves without other abnormality, and fundal examination was normal. A cyto-centrifuge preparation of cerebrospinal fluid (CSF) showed $9 \times 10^6/$liter white cells that had the appearance of histiocytes rather than immature plasma cells.

He was given appropriate symptomatic therapy (for uremia, hyperuricemia, and hypercalcemia), systemic chemotherapy (cyclophosphamide, melphalan, and BCNU), and cranial irradiation ($3000$ R over 4 wk). His neurologic signs remained unchanged, but his blood counts returned to normal and plasma cells were no longer seen in the peripheral blood. Three further courses of combination chemotherapy were given over the next 6 mo.

Nine months after presentation he complained of increased bone pain and leg weakness, and examination showed neurologic signs suggestive of nerve root infiltration in both legs. His blood counts were normal and there were no circulating plasma cells, but CSF examination showed large numbers ($880 \times 10^6$/liter) of immature plasma cells. He received radiotherapy to the lumbo-sacral spine in addition to intrathecal methotrexate ($12.5$ mg x 3), which resulted in symptomatic improvement and a fall in the CSF leukocyte count to $30 \times 10^6$/liter. He removed himself from therapy for a month and then re-presented with progressive neurologic signs and multiple subcutaneous tumors. Blood examination showed recurrence of the leukemic appearance (WBC $7.1 \times 10^9$/liter, $6\%$ immature plasma cells), and his marrow was again heavily infiltrated. CSF examination showed a small number of leukocytes ($8 \times 10^6$/liter). He was again given combination chemotherapy and intrathecal methotrexate, but he developed a paraparesis, and CSF examination showed increasing numbers of plasma cells. The numbers of immature plasma cells in the peripheral blood also rose, and he died of septicemia. Permission for postmortem examination was not obtained.

**DISCUSSION**

PCL is an uncommon form of MM, and the 15 patients reported here represent approximately $5\%$ of all cases of MM seen at St. Bartholomew's Hospital during the period 1957–1977. There have been a number of other reports of PCL, but with the exception of two, they mostly relate to single cases.
In contrast to typical MM, patients with PCL show clinicopathologic features similar to those of acute leukemia. Table 2 shows the differences between our patients with PCL and a much larger number of patients with MM. Patients with PCL had a much higher incidence of organomegaly (liver, spleen, lymph nodes), and a lesser proportion had bone pain and osteolytic lesions on x-ray. Peripheral blood examination showed a greater degree of anemia and thrombocytopenia, and there was usually a leukoerythroblastic picture. Bone marrow examination showed diffuse involvement, usually of a high degree, compared with the patchy involvement often seen in MM. In addition, leukemic tissue infiltration in patients with PCL, clinically apparent and occurring early in the disease, has been reported to occur in the lung and pleura, the testes, skeletal muscle, and central nervous system (present case report). Extraosseous infiltration in MM usually occurs later in the disease and is most commonly detected at autopsy. Postmortem examination in PCL usually shows very extensive infiltration, involving typically the marrow, liver, spleen, and lymph nodes, and has been recorded as involving most other organs. That PCL does comprise a distinct clinicopathologic entity is further emphasised by the natural history of the leukemic manifestation of the disease. In the majority of our patients the leukemia persisted, but when it did show response to therapy it always recurred prior to death. In contrast, only 2% of our patients with MM developed a terminal plasma cell leukemic phase.

It is not known why a small number of patients with plasma cell malignancy present with PCL while the majority develop the typical features of MM. Suggestions have been made that the cells in PCL are more immature, and differences have been noted in labeling indices and other cell cycle characteristics. Labeling indices were performed on the marrow cells of only two of our patients and gave unremarkable results (1% and 5%). The balance of reports suggest that there is no difference between the range of abnormal immunoglobulins secreted by PCL and MM, and the relative frequency of PCL with IgD and IgE paraproteins probably reflects selection. Morphologic and ultrastructural abnormalities have been reported in malignant plasma cells, including those from patients with PCL, and these have been shown to correlate

Table 2. Comparison of PCL and Multiple Myeloma

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<th>MM</th>
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<td>212</td>
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<tr>
<td>M:F ratio</td>
<td>7:8</td>
<td>8:7</td>
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<tr>
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<td>61</td>
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<tr>
<td>Bone pain (%)</td>
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<td>75</td>
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<td>Osteolytic lesions (%)</td>
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<td>Hepatomegaly (%)</td>
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<td>Splenomegaly (%)</td>
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<tr>
<td>Lymphadenopathy (%)</td>
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</tr>
<tr>
<td>Hb: &lt;9 g/dl (%)</td>
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<tr>
<td>Mean (g/dl)</td>
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<td>10.3</td>
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<td>Platelets: &lt;60 x 10^9/liter (%)</td>
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<td>Serum calcium (mg/dl) (mean)</td>
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<tr>
<td>Blood urea &gt;80 mg/dl (%)</td>
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with the clinical state in some reports, but not in others. We were able to show nuclear immaturity and nuclear/cytoplasmic asynchrony in both PCL and MM cells. However, immature cells that might not be easily recognized as plasmacytic if seen singly were found within sheets and clumps of recognizable plasma cells in marrows with heavy infiltration, and the comparison is partially invalidated. By the criteria used, the cells showed more immaturity than those from MM and in appearance tended to be more monomorphic.

Neurologic involvement in MM is not uncommon, and careful examination of the CSF in patients with spinal cord compression may show occasional plasma cells. However, diffuse meningeal involvement, not dissimilar to that seen in acute leukemia, is extremely rare: Spaar and Argyrakis reported a patient with cranial nerve palsies and IgA paraproteinemia (but without overt systemic evidence of MM) who subsequently developed diffuse cerebrospinal involvement with plasma cell malignancy, and Ben-Bassat et al. reported a patient with IgD PCL who was neurologically asymptomatic but in whom autopsy revealed severe and diffuse involvement of the meninges.

The prognosis in PCL is poor. A number of single case reports have recorded a good response to chemotherapy, but it is likely that such patients are reported more frequently. The results of therapy in the present series are disappointing. Eleven patients were treated with the cytotoxic agents known to be effective in MM, but the median survival was only 2 mo and only three patients survived more than 1 yr. The majority of our patients presented with the features of a high tumor cell mass (stage III) disease, but their survival was worse than that reported for comparable (nonleukemic) patients. Thus PCL, besides constituting a distinct clinicopathologic subgroup of MM, comprises a particularly bad prognosis group, and future patients should be studied to specifically determine if there are significant differences in cell mass numbers and growth kinetics that may explain these differences. More intensive initial chemotherapy including cycle-specific agents may be indicated, and further cytokinetic and clinical studies are required. In the management of such patients it is obvious that intensive supportive care, such as is used during induction of acute leukemia, should be employed and may improve the prognosis.

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