Hairy Cell Leukemia and Myelomatosis: Chance Association or Clinical Manifestations of the Same B-Cell Disease Spectrum

By D. Catovsky, Christine Costello, D. Loukopoulos, P. R. Fessas, J. M. Foxley, N. E. Traub, M. J. Mills, and Maureen O’Brien

We describe three patients who had typical features of hairy cell leukemia (HCL) and multiple myeloma (MM) at the same time. In two, both diagnoses were made within a short period of time, and in the third, HCL had been present for 2 yr before the appearance of a paraprotein, bone lesions, and plasma-cell infiltrates established the diagnosis of MM. Although this association has not been previously reported, cases of HCL with osteolytic lesions or a paraprotein band have been described. The cases described may represent clinical manifestations of closely related disorders arising from divergent differentiation from a common B-cell precursor rather than a chance association.

Hairy cell leukemia (HCL) and multiple myeloma (MM) are well characterized clinicopathologic entities. HCL affects primarily the bone marrow, blood, and spleen, with pancytopenia being its chief hematologic manifestation. Osteolytic lesions, bone marrow involvement by neoplastic plasma cells, and a serum or urinary paraprotein are characteristic of MM.

The presence of a monoclonal (M) serum immunoglobulin (Ig) band on electrophoresis or Bence Jones proteinuria has been described in some cases of HCL, and recently, four reports have drawn attention to the occurrence of osteolytic lesions in HCL patients.

We report here three patients who had typical manifestations of both HCL and MM at the same time. This may be a chance coexistence of two distinct lymphoid malignancies or the result of a clone(s) of malignant B lymphocytes developing in two directions, one along the plasma cell line and one towards hairy cells. If the second possibility proves to be correct, this association would have important implications for the study of the spectrum of B-cell neoplasia in man.

MATERIALS AND METHODS

Peripheral blood (PB) and bone marrow (BM) films stained with May-Grünewald-Giemsa were examined. Surface marker studies were performed on PB mononuclear cells by direct immunofluorescence with FITC-conjugated antisera to human Ig (SmIg) and by rosetting techniques with sheep and mouse RBC. Transmission electron microscopy (TEM) was carried out on PB and BM cells fixed in 3% glutaraldehyde and processed according to standard techniques. The material was embedded in araldite, and ultrathin sections, stained with lead citrate and uranyl acetate, were viewed with an AEI 6B electron microscope. In PB cells from case 3, SmIg were also demonstrated by the immunoperoxidase technique at TEM level.

Case 1

A 57-yr-old Greek man, admitted for surgery in Athens for a duodenal ulcer, was found to be anemic (Hb 8.2 g/dl) and thrombocytopenic (platelets 60 x 10⁹/liter) and to have an enlarged spleen; there were many typical hairy cells in the blood film (Table 1 and

Table 1. Summary of Findings in the Three Patients

<table>
<thead>
<tr>
<th>Myelomatosis</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteolytic lesions</td>
<td>Femur, tibia and spine</td>
<td>Dorsal spine</td>
<td>Skull and spine</td>
</tr>
<tr>
<td>Paraprotein (serum concentration)</td>
<td>IGA L (10 g/liter)</td>
<td>Two K light chains*</td>
<td>IgG K (35 g/liter)</td>
</tr>
<tr>
<td>Bone marrow plasma cells (%)</td>
<td>12</td>
<td>20†</td>
<td>33</td>
</tr>
<tr>
<td>Hairy Cell leukemia</td>
<td>8 cm</td>
<td>Absent</td>
<td>5 cm</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>7.8</td>
<td>6.2</td>
<td>16.5</td>
</tr>
<tr>
<td>WBC (x 10⁹/liter)</td>
<td>36</td>
<td>15</td>
<td>65</td>
</tr>
<tr>
<td>Hairy cells (%)</td>
<td>84</td>
<td>40†</td>
<td>8</td>
</tr>
<tr>
<td>P blood</td>
<td>IgD K</td>
<td>ND</td>
<td>IgA L</td>
</tr>
<tr>
<td>B marrow</td>
<td>ND</td>
<td>ND</td>
<td>52</td>
</tr>
</tbody>
</table>

*Also present in the urine (Bence-Jones proteinuria).
†Subsequent bone marrow test showed a further increase in plasma cells (55%) and a decrease in hairy cells (5%).

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Submitted September 8, 1980; accepted December 11, 1980.

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HAIRY CELL LEUKEMIA AND MYELOMATOSIS

Fig. 1. Case 1. Electron micrograph of spleen cells showing three hairy cells with a villous and irregular cytoplasmic outline and a normal looking plasma cell (x 6000). The insert shows a peripheral blood hairy cell (x 1200).

Fig. 1 insert. A bone marrow aspirate showed extensive infiltration with hairy cells, which were found to have tartrate-resistant acid phosphatase activity. Serum proteins were normal. A diagnosis of HCL was made, and no treatment was given; the patient’s condition remained stable for 1 yr. Because of further splenic enlargement, he was treated with radiotherapy to the spleen, anabolic steroids, and courses of COP (cyclophosphamide, vincristine, and prednisolone) with little effect. He was then seen at the Hammersmith Hospital where splenectomy was recommended; this was carried out later in Greece. The spleen weighed 1115 g, and the histology was typical of HLC. TEM showed the characteristic hairy cells (Fig. 1) with long villi; some cells contained ribosome lamella complexes. His blood count returned to normal and he remained well for 6 mo. Two years from the initial diagnosis, protein electrophoresis showed an IgA serum paraprotein. He was later admitted with a fractured neck of femur (L), and was found to have multiple osteolytic lesions (Table 1 and Fig. 2) and a further increase in the serum paraprotein concentration. The bone marrow showed hairy cell infiltration and numerous atypical plasma cells. He showed little response to further chemotherapy and died a few months later.

Case 2

A 73-yr-old woman presented with pain in the right shoulder and weight loss. The Hb was 9.8 g/dl and the ESR 113 mm in the first hour. Serum protein electrophoresis revealed two minor paraproteins in the γ region, which were characterized as K light chains by immunoelectrophoresis. Ig levels were normal. The appearances of the bone marrow aspirate and trephine biopsy were consistent with a
Fig. 3. Case 2. Electron micrograph of bone marrow plasma cells illustrating various morphological abnormalities. (A) Poorly developed ER, (B) immature plasmablast, (C) mature form, (D) binucleated cell (×10,000).
diagnosis of HCL but also showed a small plasma cell component (Table 1). Her condition deteriorated and treatment with prednisolone and later chlorambucil was begun. Five months after presentation, Bence Jones protein was detected in the urine and characterized by K light chains; the serum Ig levels were now very depressed. Spinal x-rays showed diffuse osteoporosis with partial collapse of some vertebral bodies with lesions suggestive of MM deposits. A second bone marrow aspirate showed infiltration with both hairy cells and myeloma cells, the latter now being predominant. TEM examination confirmed the presence of both types of abnormal cells. The majority of plasma cells were pleomorphic and immature, with prominent nucleoli, scanty rough endoplasmic reticulum, and binucleated forms (Fig. 3). Treatment with melphalan was begun but the response was poor. The patient is still alive.

Case 3

A 76-yr-old woman presented with a chest infection and was found to have splenomegaly, an ESR \( \cdot 100 \) mm in the first hour, and osteolytic bone lesions. Abnormal plasma cells were seen in a bone marrow aspirate, and MM was diagnosed. Six months later a paraprotein was demonstrated in her serum (Table 1), and a skeletal survey showed punched-out lesions in the skull and collapse of several vertebral bodies. Blood counts showed lymphocytosis (Table 1), the majority of the cells being small hairy cells. Their B-cell nature was demonstrated by surface marker studies (Table 1) and immunoelectron microscopy (Fig. 4). The membrane phenotype of these cells was characteristic of HCL.

A second bone marrow aspirate showed a further increase in large plasma cells with the typical features of MM (Fig. 5) and small proportion of hairy cells (Table 1). The patient improved with local radiotherapy and courses of melphalan and remains well at the present time.

DISCUSSION

This is the first report of an association between HCL and myelomatosis. Case 1 had had typical clinical hematologic and histologic features of HCL for 2 yr when he was found to have a paraprotein and shortly afterwards osteolytic lesions and a pathologic fracture. His bone marrow at that stage showed the coexistence of hairy cells and plasma cells. In cases 2 and 3, both diseases were probably present at diagnosis. In case 2, the first diagnosis made was HCL, based on the presence of hairy cells in the PB and BM, and in case 3, MM was first diagnosed on the basis of the typical triad of osteolytic lesions, paraprotein, and atypical plasma cells in the bone marrow. The evidence supporting both diagnoses in the three patients is summarized in Table 1.

Both osteolytic lesions\(^7\) \(^8\) and serum or urine paraproteins\(^1\) \(^6\) have been documented in patients with HCL. Rhyner et al.\(^7\) described three cases of HCL with osteolytic lesions resembling myeloma deposits developing 1–3 yr postsplenectomy. None of these patients had a serum paraprotein. Weh et al.\(^8\) reviewed
150 patients with HCL seen over the previous 20 yr and found that 5 (3.3%) had radiologic demonstrable demineralization, lysis, and pathologic fractures. Two other cases with bilateral femoral lesions have recently been reported.9,10 It is interesting that in 8 of the 10 HCL cases with bone lesions, the main involvement was, as in our case 1, in the femur.

The presence of a paraprotein in some cases of HCL has been interpreted as resulting from Ig production and secretion by the hairy cells. The heavy and light chains in the serum were the same as those in the cell membrane or in the cytoplasm of the hairy cells.1-4 The presence of light chains in the urine6 may result from the excess of free light-chain synthesis by the hairy cells.5 None of these patients, however, has been reported as having clinical features of MM. In one of the cases reported by Rhyner et al.,7 the biopsy of an osteolytic lesion showed mature and immature plasma cells together with typical hairy cells. A prominent association between plasma cells and hairy cells has also been reported.8

Two possible explanations for the association of HCL and MM should be considered. One is the chance coexistence of two rare lymphoproliferative disorders, a possibility that cannot be excluded. However, the knowledge that this association exists should encourage more detailed clinicopathologic studies in HCL and MM patients, which in time will show its real frequency. Only intensive interhospital consultations and exchange of pathologic material led to the correct diagnosis in our patients.

A second possibility is that the two conditions arise in the same patient by divergent differentiation from a common B-cell precursor. This hypothesis is supported by the incidence, detailed above, of features of MM in typical HCL patients and could also explain the association of HCL with malignant lymphoma recently reported.16,17 Opposing this argument is the fact shown in two of our cases (1 and 3) that the type of Ig found in the membrane of the hairy cells (SmIg) was different from the paraprotein found in the same patient (Table 1), thus suggesting that both processes originated from different malignant clones. On the other hand, biclonal proliferations are well documented in B-cell neoplasias, such as myelomatosis and chronic lymphocytic leukemia.12,18,19 It has been suggested that the various B-cell neoplasias in man derive from cells in different stages of the B-cell differentiation pathway.11 MM originates from Ig-secreting plasma cells, at the end stage of B-cell maturation, and hairy cells from B cells whose maturation has been arrested at a late stage.20,21 We therefore postulate that these closely related cells (hairy cells and plasma cells) could, in their neoplastic state, manifest overlapping clinical features and, in some patients, they may be triggered to proliferate by the same oncogenic agent. The latter will result in biclonal events that could be expressed clinically as two apparently independent B-cell malignancies.

ACKNOWLEDGMENT

We wish to thank Dr. G. Pangalis for the cytochemical studies of patient 1 and Dr. R. J. Mills and M. W. Fahie-Wilson for the protein studies in patient 2.

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