Chronic Lymphocytic Leukemia (CLL) Terminating in Multiple Myeloma: Report of Two Cases

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Two cases of multiple myeloma (MM) developed late in the course of chronic lymphocytic leukemia (CLL). An 81-yr-old white female developed, after 6 yr of CLL, IgAκ MM with sheets of plasma cells abutting sheets of lymphocytes in the bone marrow, multiple pathologic fractures, and 0.26 g/24 hr free κ light chains in the urine. A 74-yr-old white male developed, after 16 yr of CLL, κ light chain MM with 20% plasma cells in the bone marrow, multiple pathologic fractures, and 3.7 g/24 hr free κ light chains in the urine. In both cases the CLL had responded well to intermittent low-dose chlorambucil therapy, but the MM failed to respond to cyclic melphalan-prednisone therapy. A review of 105 cases of CLL seen at the Geisinger Medical Center failed to turn up any other cases of MM developing during the course of CLL. The suggestion that there is an increased prevalence of MM in CLL is an attractive one because both diseases are B cell neoplasms and because of the increased frequency of asymptomatic monoclonal gammopathies in CLL found by others.

COEXISTENCE of chronic lymphocytic leukemia (CLL) and multiple myeloma (MM) in the same patient is believed to be rare and the development of MM late in the course of CLL still rarer. Because both CLL and MM are seemingly B cell disorders their coexistence takes on more significance than the coexistence of either alone with an unrelated tumor. When two cases of CLL terminating in MM were encountered recently, the question arose as to whether or not MM might occur late in the course of CLL more commonly than appreciated. The development in two elderly patients of documented MM after 6 and 15 yr of CLL is reported.

CASE REPORTS

Case 1. A 75-yr-old white female was admitted to the Geisinger Medical Center (GMC) in January 1965 complaining of malaise, weakness, and weight loss. Several 1-cm lymph nodes in both axillae, a palpable spleen, anemia, and peripheral lymphocytosis were present. A sternal bone marrow aspirate contained 91% well-differentiated lymphocytes but no plasma cells on a careful search of all slides. An intermediate PPD skin test produced 5 mm induration. Chest x-ray, urinalysis, platelet count, reticulocyte count, direct Coombs' test, test for cryoglobulins, and serum tests for glucose, uric acid, urea nitrogen, and bilirubin were normal. A diagnosis of CLL was made, and chlorambucil (CLB) 2 mg daily was prescribed.

Over the subsequent 5 yr she did well as CLB was interrupted when the WBC fell below 20 × 10^9/liter and reinstituted when the WBC reached 40 × 10^9/liter.

In September 1971 she developed pain in the right sixth rib posteriorly, where by April 1972 an expansile lytic lesion was detected. In November 1972 a diagnosis of IgAκ MM was made. Bilateral posterior iliac spine trephine bone marrow biopsies showed on smears 30% lymphocytes and 24% plasma cells containing intracytoplasmic IgA by indirect immunofluorescent staining. The bone marrow sections contained sheets of plasma cells abutting sheets of well-differentiated lymphocytes. Pathologic fractures of the right sixth and left seventh ribs and lytic lesions in several other ribs and the right femoral shaft were noted. The $t_{1/2}$ of the ^{51}Cr red cell survival was 13 days (normal 28 days) without

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Table 1. Comparative Data in Two Cases of CLL Terminating in MM

	Case 1			Case 2		
	At Diagnosis of CLL	At Diagnosis of MM	At Death	At Diagnosis of CLL	At Diagnosis of MM	At Death
Hb (g/dl)	9.1	8.7	7.2	11.6	11.0	10.6
WBC ($\times 10^9$/liter)	102	64	6.7	106	18.7	18.7
Lymphocytes (%)	99	87	19	92	68	80
T cells (%)	—	—	—	—	0	10
M spike (g/dl)	0.67	4.8	6.7	—	—	—
IgG (mg/dl)	—	170	320	—	640	305
IgA (mg/dl)	—	5200	7500	—	115	21
IgM (mg/dl)	—	29	40	—	24	12
Urine κ (mg/24 hr)	—	260	3300	—	0	7000
Urine λ (mg/24 hr)	—	0	0	—	0	0

splenic sequestration. The platelet and reticulocyte counts were normal. The following serum tests were normal: VDRL, direct and indirect Coombs', viscosity, calcium, phosphorus, glucose, urea nitrogen, creatinine, uric acid, alkaline phosphatase, GPT, GOT, LDH, and routine electrolytes. Sputum cytologies and cultures for mycobacteria were negative.

When there was no diminution in the serum IgA or the urinary κ light chains after 3 mo of melphalan 0.25 mg/kg/day and prednisone 2 mg/kg/day for four successive days every 6 wk, daily cyclophosphamide was substituted with no significant decrease in the serum IgA concentration or urinary κ light chain excretion. Until her death of *Escherichia coli* bacteremia and anuria in July 1974 the patient required repeated transfusions, endured several episodes of hypercalcemia, and sustained pathologic fractures of several ribs, vertebral bodies, and, finally, her right femur.

Case 2. A 58-yr-old white male was admitted to GMC May 1958 with weight loss and recurrent oral ulcerations of 3 mo duration. Several 1-cm supraclavicular lymph nodes, anemia, and peripheral lymphocytosis were present. A sternal bone marrow aspirate contained 76% lymphocytes and a few scattered plasma cells. A diagnosis of CLL was made, and triethylenemelamine (TEM) was prescribed until June 1962. CLB 2 mg daily was prescribed between February 1963 and November 1974.

In November 1974 a diagnosis of κ light chain MM was made after two vertebral compression fractures had developed over the preceding 29 mo. Multiple lytic lesions were detected in the skull, ribs, vertebrae, and pelvis. Bilateral posterior iliac bone marrow biopsies showed nodules of plasma cells and increased numbers of lymphocytes in the sections with 20% plasma cells and 57% lymphocytes in the smears. Peripheral lymphocytes purified by Ficoll-Hypaque gradient separation failed to form T cell rosettes with sheep erythrocytes.

Despite melphalan 0.25 mg/kg/day and prednisone 2 mg/kg/day four successive days every 6 wk, pathologic fractures of multiple ribs and vertebrae occurred, the serum creatinine rose, transfusions were required, and eventually the patient died in June 1975 of azotemia and respiratory failure secondary to a flail chest.

DISCUSSION

Previous reports of CLL terminating in MM have emphasized the rarity of the occurrence. However, two cases of this supposedly uncommon occurrence were encountered at the Geisinger Medical Center among 105 cases seen between December 31, 1957 and January 1, 1977. During the same 19 yr, 158 cases of MM were seen.

MM, which was clearly absent when CLL was diagnosed, became manifest late in the course of CLL in both of our cases. In case 1 the symptoms of MM developed 80 mo and the diagnosis of MM was made 95 mo after the diagnosis of CLL. In case 2 the symptoms of MM developed 169 mo and the diagnosis of MM was made 192 mo after the diagnosis of CLL.

The coexistence of CLL and MM at the time of diagnosis has been reported

more frequently than the termination of CLL in MM, and we found no reports of MM terminating in CLL. Vander and Johnson[1] in 1960 reported a 72-yr-old Portuguese male with both CLL and MM present at the time of diagnosis. Stobbe[2] in 1962 reported a 69-yr-old female with both CLL and MM. In 1971 Naidu and Rosner[3] reported a 67-yr-old black male with both CLL and IgAλ (later reported as IgGλ) MM, and Hasper and Macchi[4] reported an 82-yr-old female having both CLL and MM. In 1972 Preud'homme and Seligmann[5] mentioned during a discussion of surface-bound immunoglobulins in lymphoproliferative diseases a case of CLL and coexistent IgAλ MM that had αλ intracytoplasmic staining of plasma cells and μλ and αλ lymphocyte markers. In 1972 Lohrmann et al.[6] described a 69-yr-old male with CLL and coexistent κ light chain MM. In 1974 Reimer[7] described a man with CLL and coexistent IgG MM. Ghosh and Sayeed[8] in 1974 added a case of coexistent CLL and MM. Narasimhan et al.[9] in 1975 reported a 60-yr-old male with CLL and IgGκ MM, described in more detail the previously reported case by Naidu and Rosner,[3] and reported a case of "nodular lymphocytic leukemia" with MM.

A few cases of CLL terminating in MM and one terminating in μ heavy chain disease have been reported. Forte et al.[10] in 1970 reported a case of CLL terminating in μ heavy chain disease, a white male who developed at age 52 yr CLL and at age 58 yr μ heavy chain disease with 45% lymphocytes and 33% plasma cells in the bone marrow, κ light chain proteinuria, amyloidosis, and osteoporosis. In 1971 Shuster and Causing[11] reported a 54-yr-old male with CLL terminating in IgG MM. In 1973 Fitzgerald et al.[12] reported a 68-yr-old female, a carrier of Gp-(Ch^1) constitutional chromosomal abnormality, who developed acute plasma cell leukemia after 8.5 yr of CLL. In 1975 a patient with CLL who developed successively malignant melanoma, IgGκ MM, and terminally acute myelomonocytic leukemia was reported by Cryer and Kissane.[13] In 1977 Hoffman and Rudders[14] reported a 69-yr-old male with CLL who developed IgGκ MM and low concentrations of free λ light chains in the urine, presumably from λ light chain surface markers on the lymphocytes.

Although there have been sporadic reports of coexistent CLL and MM, most studies of second malignancies in CLL list carcinomas (especially of the skin), and soft tissue sarcomas but not MM. Lawrence and Donald[15] in 170 cases of CLL and associated malignancies collected from their own experience and the literature prior to 1959 found no cases of MM. Gunz and Angus[16] found no MM in 23 cases of CLL with second malignancies occurring in New Zealand during a period of 46 mo, 1958–1961. In a prospective study of 420 CLL cases seen at the Memorial Hospital for Cancer and Allied Diseases, New York, Berg[17] found no MM in 19 cases of CLL developing second malignancies. Manusow and Weinerman[18] found no MM in 21 cases of CLL with second malignancies in a retrospective analysis of 102 cases of CLL treated by the Hematology Service of the University of Manitoba from January 1, 1955 to April 1, 1974.

Although systematic studies of CLL have generally failed to show MM as a significant second malignancy, immunologic studies of CLL have shown monoclonal gammopathies at frequencies greater than in age-matched populations of normal people and patients with cancers not lymphatic in origin.[19] Of 266 cases of CLL reported by Alexanian[19] in 1975, 17 had monoclonal gammopathies by serum protein electrophoresis. The monoclonal peaks were IgG in 5, IgM in 11, and not

typed in 1. A 75-yr-old male with CLL and an IgA peak of 1.5 g/dl was not considered further in the analysis by Alexanian. The IgG concentration peaks in the 5 patients with CLL and IgG ranged from 0.7 to 1.6 g/dl, and there were clearly none with MM.

In those cases where MM develops during the course of the CLL, two hypotheses have been offered:[20] (1) a normal B lymphocyte develops into a malignant B lymphocyte, which in turn transforms into a malignant plasma cell; (2) although CLL is present, normal B lymphocytes persist, transform to normal plasma cells, and in turn undergo malignant transformation. The case of Preud'homme and Seligmann[5] in which the light chain subtype of the CLL lymphocytes was the same as that produced by the malignant plasma cells tends to support the first hypothesis but does not exclude the second. On the other hand, the case of Hoffman and Rudders[14] seems to support the second hypothesis. Perhaps there are cases developing by both mechanisms. Unfortunately, in our cases surface immunoglobulins on the lymphocytes were not studied in case 1, and although studies were attempted in case 2 they were inconclusive.

Salmon and Seligmann[20] in 1974 suggested a unifying view of the diverse neoplastic disorders arising from cells of the B cell series of immunocytes. They pointed out that such neoplasms are almost always monoclonal as reflected by the cell-bound or secreted immunoglobulin. In their view, CLL is usually expressed as a disease of the committed B lymphocyte untouched by antigen, the B_1 lymphocyte in their terminology. They postulated further from the work of Preud'homme and Seligmann[5] that although the proliferating B cell seems to be "frozen" at the B_1 level, occasionally cells at all stages of development from B_1 to B_4 (early secretory plasma cell) level proliferate.

We have no explanation for the finding of two cases of MM late in the course of CLL among 105 cases of CLL. However, our experience suggests the need for closer scrutiny of CLL for the development of clinical MM. The suggestion that there is an increased prevalence of MM in CLL is an attractive one because both are B cell neoplasms and because of the increased frequency of asymptomatic monoclonal gammopathies in CLL found by others.[19,21]

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