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The association of chronic lymphocytic leukaemia and multiple myeloma: a study of eleven patients

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SUMMARY. We present haematological and immunological data obtained in 11 patients with the rare association of chronic lymphocytic leukaemia (CLL) and multiple myeloma (MM). CLL occurred before MM in six cases and both diseases were diagnosed simultaneously in five. With regard to CLL, no peculiar clinical feature was found; in six patients, MM was characterized by extra-osseous lesions. A significant remission (*3–7* years) was obtained in three patients. In six patients, CLL and plasma cells synthesized Ig molecules with different light chains, probably indicating the coexistence of two distinct clonal proliferations. In two cases where monoclonal Ig synthesized by both types of cells had the same type of light chains, studies with anti-idiotypic antibodies showed that the two proliferations were also distinct. The pathophysiology of this rare association is discussed in the light of these findings and of data from the literature.

The Occurrence of both chronic lymphocytic leukaemia (CLL) and multiple myeloma (MM) in the same patient is a rare and noteworthy association of two B cell neoplasias. We report here the clinical course and immunologic features of 11 such cases which were studied in our department during the last 20 years, and review the 24 similar cases previously reported in the literature.

In seven of our patients, a study of both surface and cytoplasmic Ig expressed by CLL and MM cells, including in two cases a search for shared idiotypes, was performed to elucidate whether this association represents the progression and maturation of a pre-existing CLL clone or the occurrence of two distinct malignancies.

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PATIENTS AND METHODS

Case reports

Case 1. In 1955 the diagnosis of CLL was made in this 45-year-old male patient on the basis of moderate splenomegaly, lymph node enlargement and blood and marrow lymphocytosis (Table I). A lymph node biopsy showed a diffuse infiltration by small mature lymphocytes without plasma cells. He received a course of radiation therapy to involved lymph nodes. Two years later, the haematological data were unchanged and several serum electrophoreses were normal. Intermittent chlorambucil therapy was given during the next 4 years. At this time, a tumour of the right upper gum was noted. A biopsy revealed an infiltration by abnormal plasma cells. Skeletal X-rays showed a single lytic lesion of the right maxillary bone. Bone marrow examination disclosed a persisten lymphocytosis (70%) without any plasma cells: serum immunoelectrophoresis showed a decrease of IgG and IgA. Local irradiation therapy was given. Nine months later, several soft tissue tumours appeared. Pertinent haematological data at this time are listed in Table I. E-rays showed a diffuse osteoporosis and multiple lytic lesions. Urinary analysis performed for the first time, identified a κ Bence Jones protein (1 g/l). The patient died 4 months later with extensive bone lesions, Post-mortem examination showed a proliferation of abnormal plasma cells in bone marrow, liver and spleen. Lymphocytic infiltrates were discrete and predominated in liver and lymph node.

Case 2. In 1960 the diagnosis of CLL was made in this 59-year-old woman on the basis of slight lymphadenopathy, splenic enlargement and blood and marrow lymphocytosis (see Table I). Intermittent chlorambucil was started. Four years later the patient had fever, weight loss and back pains. On examination, the liver and spleen were massively enlarged and a pelvic mass was felt. Pertinent laboratory values at this time are listed in Table I. A bone marrow biopsy showed a nodular infiltration by both immature plasma cells and small lymphocytes in distinct foci. Lymph node aspirate contained only abnormal plasma cells as did liver biopsy. Serum immunoelectrophoresis revealed a monoclonal IgAλ and a marked decrease of IgG and IgM. Lambda Bence Jones proteinuria (24 g/l) was found. The disease rapidly progressed, the WBC reached 161×10^9/l with 98% lymphocytes, and the patient died from sepsis. At autopsy, the bone marrow, lymph nodes, liver and spleen were infiltrated predominantly by plasma cells with small focal lymphoid infiltrates. The pelvic mass was plasmacytic.

Case 3. In 1963 this 71-year-old male experienced symptoms of spinal cord compression at the level of the fifth dorsal vertebral body. He was treated by surgery followed by radiation therapy. The vertebral body was heavily infiltrated by small mature lymphocytes without any plasma cells. There was a slight blood lymphocytosis (see Table I). Two years later, the clinical status was unchanged but a marked abnormal plasmacytaxis was found on bone marrow examination (Table I). Bone marrow biopsy showed a hypercellular bone marrow with nodular lesions composed either of mature lymphocytes or of abnormal plasma cells. Serum electrophoresis was normal but the immuno-electrophoretic study disclosed a monoclonal IgAλ. A 1 Bence Jones protein was found (0·35 g/l). Skeletal X-rays were normal

Table I. *Main clinical and laboratory data in 11 patients with CLL and MM*

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11
Age at onset (yr)	45	59	71	55	76	65	62	77	86	70	74
Sex	M	F	M	M	M	F	F	M	M	M	M
Splenomegaly	+	+	0	0	0	0	+	0	0	+	+
Lymph node enlargement	+	+	0	+	+	0	+	0	0	+	0
WBC ($\times 10^9$/l)	26	100	11	12	74	16	25	24	18	27	20
Lymphocytes ($\times 10^9$/l)	24	99	6	7	72	15	24	22	16	25	14
Neutrophils ($\times 10^9$/l)	2	1	4	3·5	1·5	1	2	2	2	2	6
Hb (g/dl)	14	12	14·5	9	12	15	14	12	9·5	11	11
Platelets ($\times 10^9$/l)	250	95	240	150	100	250	200	240	250	150	200
Bone marrow											
Lymphocytes (%)	73	82	32	90	62	60	30	37	45	50	35
Plasma cells (%)	0	1		0	6		2	6	55	50	36
Serum monoclonal Ig	—	ND	ND	IgA	IgMκ	ND	—	IgGκ	IgAκ	IgD	BJλ
Age (yr)	56	63	73	57*	76	78	65	IgAκ 86	70	74	
WBC ($\times 10^9$/l)	40*	13*	6·2	4		7·7	30*				
Lymphocytes ($\times 10^9$/l)	39	14	4	2·5		5·6	27				
Plasma cells ($\times 10^9$/l)	0	0	0	0		0·14					
Neutrophils ($\times 10^9$/l)	1	2	2	1·5		1·2	3				
Hb (g/dl)	12	10	14	9		11·6	8				
Platelets ($\times 10^9$/l)	220	120	250	150		300	200				
Bone marrow											
Lymphocytes (%)	52	82	30–60	20–60		25	18				
Plasma cells (%)	46	9	4–80	10–80		53	20				
Plasma cell tumours	+	+	0	0	+	+	+	0	0	+	0
Osteolytic bone lesions		+	+	+	+	+	0	+	0	+	+
Serum monoclonal Ig	—	IgA	IgA	IgA	IgMκ	BJκ	IgMκ	IgG IgAκ	IgAκ	IgDλ	BJλ
Urinary monoclonal Ig	BJκ	BJλ	BJλ	—	BJκ	BJκ	BJκ	BJκ,BJλ	—	BJλ	BJλ

BJ: Bence Jones protein. ND: not done; M: male; F: female.

* Intermittent chemotherapy with chlorambucil was given for CLL.

except for the vertebral lesions. Chlorambucil therapy was starte 1. During the next years several bone marrow aspirates showed a varying percentage of ymphocytes and plasma cells; a small Ig spike appeared on serum electrophoresis. Skeletal X-rays showed a lytic lesion in the femoral neck. At this time, chlorambucil was stopped and melphalan therapy was given. During the next 6 years the patient remained in good healtl i in spite a progression of bone lesions. No modification of the haematologic or protein pr ofiles was observed. The patient died suddenly of unknown cause.

Case *4.* In 1968 this 55-year-old man was referred because of haemolytic anaemia. Clinical examination was normal. The Coombs test was positive for IgG and complement. The haematologic data were compatible with associated CLL (see Table I). Bone marrow biopsy showed a nodular infiltration by mature lymphocytes. There was a slight hypogammaglobulinaemia (5 g/l) with a monoclonal IgAλ. High dose steroids were required to maintain the haemoglobin level above 10 g/l. One year later X-ray studies showed marked bone demineralization with a lytic lesion of the right tibia. Lymphangiograms were grossly abnormal. A splenectomy was performed as well as abdominal lymph node biopsies, Pathologic examinations disclosed an extensive infiltration by small mature lymphocytes and some foci of plasma cells. During the next year the patient was doing well under steroids and chlorambucil treatment. Bone marrow biopsy and aspirate showed still a purely lymphocytic infiltration. The level of the IgA spike steadily increased to reach 10 g/l. At this time the clinical condition deteriorated with bone pains. X-rays showed several vertebral fractures and lytic lesions of the humerus pelvis and femoral neck. Bone marrow aspirates showed 10% abnormal plasma cells. Despite melphalan chernotherapy, the condition of the patient worsened and a plasma cell leukaemia developed. Post-mortem examination showed a plasma cell infiltration of lymph nodes, bone marrow, liver and spleen.

Case 5. In 1968 this 76-year-old patient was referred for lymphocytosis and back pains. On examination, moderate enlargement of liver and lymph nodes was found. Laboratory data were compatible with both CLL and MM. There was a striking blood and marrow hyperlymphocytosis but abnormal plasma cells were also found in marrow aspirates (see Table I). X-rays showed a diffuse osteoporosis with a collapse of the fifth dorsal vertebral body. Protein studies showed in the serum a small amount of monoclonal IgMκ and a decrease of IgG and IgA. In the urine, there was a large quantity of κ Bence Jones protein. Chlorambucil therapy was given. One year later, the vertebral lesion progressed and a bone marrow biopsy showed a proliferation of both lymphocytes and plasma cells in distinct nodules; melphalan was added. During the next 18 months the clinical condition improved and the laboratory values showed an objective improvement (WBC 7.5×10^9/ml with 80% lymphocytes). There were less than 30% abnormal cells in bone marrow. Bence Jones protein excretion was 3 g/24 h. Thereafter, bone lytic lesions progressed in the pelvis, femur and ribs: the lymph nodes enlarged rapidly and the bone marrow was infiltrated mainly by plasma cells. The patient died from sepsis. Post-mortem examination showed a lymphocytic infiltration of lymph nodes with some foci of plasma cells and a total invasion of bone marrow by plasma cells.

Case *6.* The diagnosis of CLL was made in 1962 in this 65-year-old woman. on the basis of blood and marrow lymphocytosis (see Table I). There was no abnormality on physical

examination. Without chemotherapy, her clinical and haematological status remained unchanged until 13 years later when thoracic pain developed. On examination, there was a slight splenomegaly and a fractured rib. Haematologic data were compatible with both CLL and MM (see Table I). X-rays showed a diffuse osteoporesis. Serum Ig levels were slightly depressed and κ Bence Jones was found in the serum and urine (4 g/l). Intermittent steroids and melphalan therapy gave a good remission. Two years later, a relapse was observed with costal and cutaneous plasma cell tumours and a malignant pleural effusion. The bone marrow was heavily infiltrated by plasma cells.

Case 7. This 62-year-old woman was referred for CLL of the prolymphocytic type. There was a marked splenomegaly. The main laboratory data are listed in Table I. There was no abnormal serum or urinary Ig. The patient was treated by chemotherapy (chlorambucil) and splenectomy. There was only a partial remission during the three following years. At that time, fever, weight loss and skin nodules developed. Laboratory data were compatible with both CLL and MM (Table I). Serum electrophoresis and immunoelectrophoresis disclosed a monoclonal IgM (5 g/l) and there was a massive excretion of κ-type Bence Jones protein (10–20 g/24 h). The patient was treated by combined chemotherapy with cyclophosphamide, adriamycin, prednisone and vincristine. She died from infection 6 months after the beginning of this treatment.

Case 8. This 77-year-old man was referred in 1981 for bone pains and hypercalcaemia. Physical examination revealed an acutely ill patient with weight loss and fever. There was no lymph node, liver or spleen enlargement. Haematological data are listed in Table I. Bone marrow biopsy confirmed the existence of an infiltration by both small lymphocytes and abnormal plasma cells. Serum electrophoresis and immunoelectrophoresis showed the Presence of two monoclonal Ig, one IgGλ (50 g/l) and the other IgAκ (17 g/l). Monoclonal free κ and λ chains were found in urine. There were multiple osteolytic lesions of skull, pelvis and vertebral bodies. The patient died from heart failure 1 month after the beginning of chemotherapy.

Case 9. This 86-year-old man was referred in 1982 for weakness and hypercalcaemia. Physical examination was unremarkable except for long-standing psoriasis. Laboratory data were compatible with CLL and MM (see Table I). Bone marrow biopsy confirmed the existence of an infiltration by both small lymphocytes and plasma cells. Serum electrophoresis and immunoelectrophoresis revealed a monoclonal IgAκ (33 g/l) with a decrease of polyclonal IgM and IgG. Skeletal X-rays were normal. The patient died soon after starting chemotherapy.

Case 10. This 70-year-old patient was referred in 1981, for bone pains and lymphocytosis. Physical examination was unremarkable except for an hepatomegaly. Laboratory data were consistent with both CLL and MM (see Table I). Bone marrow biopsy showed the coexistence of both lymphoid and plasmacytic proliferations in distinct nodules. Serum immunoelectrophoresis revealed a monoclonal IgD λ protein (10 g/l) with a decrease of IgM, IgG and IgA. X-ray showed multiple bone lesions and several rib fractures. The patient died despite chemotherapy with prednisone and melphalan.

Case 11. This 74-year-old man without significant medical past story was referred because of recent discovery of a severe renal failure (plasma creatinine 800 μmol/l). There

was slight splenomegaly on examination. Haematological data (Table I) showed blood lymphocytosis and bone marrow infiltration by abnormal plasma cells and small mature lymphocytes. Skeletal survey revealed multiple lytic lesions. Immunoelectrophoretic studies showed the presence of large amount of a λ Bence Jones protein in serum and urine. The renal failure did not improve and dialysis was necessary. A percutaneous renal biopsy showed features of myelomatosis tubulopathy. Polychemotherapy with cyclophosphamide and melphalan was begun without significant remission.

Surface and cytoplasmic *Ig*

Surface and cytoplasmic Ig expressed by lymphocytes and plasma cells were studied in seven patients by direct immunofluorescence with monospecific antisera to the various light and heavy Ig chains on blood and marrow lymphoid cells as previously reported in detail (Preud'homme& Labaume, 1975).

RESULTS

Surface and cytoplasmic *Ig*

Results are summarized in Table II.

Idiotypic studies

In cases 6 and 8, the relationship between the surface Ig present on the lymphocytes and the serum monoclonal Ig was investigated further with an anti-idiotypic antiserum. These sera were obtained in rabbits immunized with the κ Bence Jones protein (case 6) or purified serum IgGλ and IgAκ (case 8). The immune sera were absorbed on erythrocytes, tonsil lymphocytes and normal serum, IgG, IgA, IgM, κ and λ chains coupled to Sepharose 4B.

The absorbed sera were used by indirect immunofluorescence with a second layer of rhodamine conjugated Fab'2 fragments from IgG antibodies of a sheep antiserum to rabbit IgG. Absorbed sera still stained cytoplasmic Ig from plasma cells of the corresponding patients whereas they were negative with unrelated myeloma plasma cells or normal plasma cells obtained after stimulation of normal peripheral blood by pokeweed mitogen, Likewise, they did not stain normal blood lymphocytes.

Case 6. CLL lymphocytes bearing $\mu\kappa$ molecules were not stained by the anti-idiotypic antiserum raised against urinary κ Bence Jones protein.

Case 8. Two different anti-idiotypic antisera were raised against either the IgGλ or IgAκ serum monoclonal Ig. We could not detect shared idiotypes between the two serum monoclonal Ig (data not shown). The anti-idiotypic serum to the IgGλ component was negative on blood lymphocytes either by surface or cytoplasmic staining. The anti-idiotypic serum to the IgAκ monoclonal Ig stained intracellularly a few blood lymphoplasmacytic cells whereas it was negative by either surface or cytoplasmic staining on small lymphocytes. Positive cells corresponded most likely to the few blood cells (mainly plasma cells) which were similarly stained with anti α and κ reagents.

Reference	Age (yr)	Sex	Monoclonal Ig	Lytic bone lesions or plasma cell tumours	Diagnosis of MM (years after CLL onset)
Vander & Johnson (1960)	72	M	Not identified	+	1
Peters *et al* (1961)	41	M	Electrophoresis: polyclonal Ig at the onset; monoclonal spike 3 months after	0	0
Waldenström (1962)	[illegible]	[illegible]	Electrophoretic spike at the onset	+	1
Stobbe (1962)	69	F	Electrophoretic spike at the onset	+	0
Shuster & Causing (1971)	54	F	IgG	+	3
Naidu & Rosner (1971)	67	M	IgA, BJλ	0	0
Lohrmann *et al* (1972)	68	M	BJκ	+	3
Reimer (1974)	?	M	IgG	?	5
Narasimhan *et al* (1975)	60	M	IgGκ BJκ	+	0
Reinhard *et al* (1975)	56	F	IgGκ	+	4
Bonnazi *et al* (1968)	69	M	IgA	+	0
Spengler *et al* (1961)	72	F	IgA	+	0
Hoffman & Rudders (1971)	69	M	IgGκ	+	2
Fitzgerald *et al* (1973)	68	F	IgMκ	+	8
Tubiana *et al* (1978)	61	M	0	+ (localized plasmocytoma)	4
Jeha *et al* (1981)	64	M	IgGκ, BJλ	+ (osteosclerotic)	0
Kough & Makary (1978)	75	F	IgAκ	+	6
Kough & Makary (1978)	58	M	BJκ	+	15
Crowley *et al* (1976)	80	F	IgAκ	+	0
Zbignew *et al* (1978)	48	F	IgGκ BJκ	+	3
Pedersen-Bjergaard *et al* (1978)	79	F	IgGλ	+	2
Zalcberg *et al* (1982)	69	M	IgMλ	+	−1
Sany *et al* (1976)	49	F	BJκ	+	13
Ghosh & Sayeed (1974)	68	F	IgG	+	0

Table III. Chronic lymphocytic leukaemia and multiple myeloma: membrane markers of malignant cells

	CLL cells surface Ig	Myeloma cells cytoplasmic Ig
Present study		
Case 3	μκ	κλ
Case 6*	μκ	κ
Case 7	μδκ	κ
Case 8*	μδκ	κ
Case 9	μδλ	κ
Case 10	μκ	δλ
Case 11	μλ	λ
Literature		
Hoffman & Rudders (1977)	κλ	κ
Kough & Makary (1978)	None (Fcγ+)	κ
Pedersen-Bjegaard et al (1978)	γκ	λ
Zalcberg et al (1982)	μδκ	κλ
Jeha et al (1981)	μδκ	λ

* No shared idiotypes between SIg and cIg molecules.

DISCUSSION

CLL and MM represent the neoplastic expansion of a single B cell clone. CLL is usually considered as a leukaemic process involving lymphocytes which are frozen at a given stage of the B cell differentiation pathway whereas MM is the expression of the proliferation of most mature B cells (Seligmann et al, 1973). However, some data suggest that in myeloma both some circulating B cells (Seligmann et al, 1973) as well as pre-B cells (Kubagawa et al, 1979) may belong to the neoplastic clone. The occurrence of the two diseases in the same individual is quite rare since only 35 cases, including our own 11 cases, have been identified (Table III).

The clinical picture in such patients is usually a composite of the typical features of both CLL and MM. However, several points deserve emphasis. In a single case, MM antedated the development of CLL (Zalcberg et al, 1982). In contrast, CLL was diagnosed before MM in six out of our 11 cases and in 14 out of 24 cases in the literature; the interval between the two diagnoses ranges from 2 to 15 years. In the other cases the diagnosis of both CLL and MM was either simultaneous or made within 1 year. However, in those cases where CLL preceded MM, detailed haematological and protein studies are available in only a few patients at the time when CLL was diagnosed. In two patients of this series (patients 4 and 7, Table I) detailed studies were performed 2 and 5 years before the diagnosis of MM was suspected. In case 7 neither infiltration by plasma cells nor Ig abnormalities were detectable. In patient 4 blood and marrow examination (including bone marrow biopsies) wert compatible with CLL, without any excess in bone marrow plasma cells. However. serum immunoelectrophoresis disclosed a small amount of monoclonal IgAλ and a decrease of IgG and IgM and, 1 year later,

a lymph node biopsy showed small foci of abnormal plasma cells. The level of the monoclonal protein steadily increased to reach 10 g/l 2 years later. At this time, the marrow was infiltrated by 10% plasma cells and lytic bone lesions developed. From these data, it is hardly possible to determine whether or not latent myeloma is present at the time CLL is diagnosed. Nevertheless it is of note that in five of the 33 cases we reviewed, the clinical phase of MM appeared more than 10 years after the diagnosis of CLL.

The haematological diagnosis of CLL is not questionable in the group of 35 patients with associated myeloma. No peculiar features emerge from the clinical charts. The immunological identification of the leukaemic cells was performed in seven of our cases and in five cases reported in the literature (Table II); it revealed. as in common CIL, a homogenous proliferation of B lymphocytes carrying monoclonal surface Ig.

The circumstances leading to the diagnosis of MM were variable. Six of our patients experienced back pains with vertebral bone lesions whereas in four other cases the diagnosis of MM was based on the finding of a malignant plasma cell infiltration located to the gum, lymph nodes or bone marrow. The onset of MM in five of our patients was also indicated by a sudden deterioration of the clinical status with high fever, sweats, weight loss and a rapidly downhill course. In all reported patients the bone marrow was infiltrated by abnormal plasma cells and, with three exceptions, lytic bone lesions were observed. However, it is of interest than in six of our patients extra-osseous plasma cell tumours were found, especially in skin, pleura and lymph nodes. Pathological studies showed in bone marrow and/or lymph nodes the coexistence of a nodular plasma cell proliferation with a diffuse lymphocytic infiltration without any mixing of the two cell populations.

Only scarce data are available on the evolution and treatment of both diseases. In our series, death occurred less than 1 year after the diagnosis of MM in six patients despite chemotherapy. In three other cases a remission was obtained with chlorambucil and melphalan in two patients and melphalan and prednisone in one. The remission lasted 3 years in two patients and 7 years in the third.

In those cases where MM develops during the course of CLL, two explanations have been offered. First, the malignant B CLL clone may further mature giving rise to MM; second, the two malignancies represent distinct clonal proliferations. In the first hypothesis, one could expect to find several cases of plasma cell tumours secreting IgM, if the process occurs without Ig isotype switching. since most CLL are featured by membrane IgM. In two of our cases serum monoclonal IgM was indeed present. Nevertheless, in these two cases, a large urinary excretion of Bence Jones protein was coincident with the onset of MM. Therefore, the monoclonal IgM most likely corresponded to the product of the CLL clone. Immunologic studies performed in one of these cases showed, however, that the malignant plasma cells contained intra-cellular μ and κ chains, an unreported finding in Bence Jones myeloma (Preud'homme *et al*, 1976), which may suggest that the original CLL clone was also involved in MM. However, in another case where a monoclonal IgM was found in serum, IgM molecules found at the surface of the CLL clone and secreted by the plasma cells possessed different types of light chains (Zalcberg *et al*, **1982).** Therefore, the occurrence of IgM secreting Plasma cells tumours, although distinctly unusual, does not allow firm conclusions. Nevertheless, it is of interest to note that the class distribution of monoclonal serum or

urinary Ig in MM supervening on CLL is rather unusual since IgA cases (10 patients) predominated over IgG (8), light chains (8), IgM (2), IgD (1) or lion-secreting (1) myelomas.

Obviously the comparison of the immunologic phenotype of both CLL and myeloma in a given patient is needed to reach meaningful conclusions. As shown in Table II, such data have been collected in 12 cases only. In six patients, CLL cells and plasma cells synthesized Ig molecules with different light chain types indicating the occurrence of two distinct clonal proliferations. In two cases where monoclonal Ig synthesized by both types of cells had the same type of light chains, we performed a study with anti-idiotypic reagents: in both cases idiotypic determinants expressed by serum (or urinary) and intracellular plasmacytic Ig were not detectable on the surface immunoglobulins synthesized by the CLL B cells. A similar negative study had been reported in another case (Hoffman & Rudders, 1977). In one of our cases there was in addition a second monoclonal spike which was shown to be idiotypically unrelated to both CLL and plasma cells. Taken together these findings strongly argue against the possibility that CLL B cells 'transformed' into plasma cells. These results contrast with those obtained in the Richter's syndrome and in acute crisis of CLL where it has been shown that the phenotype of supervening blast cells is usually identical to that of CLL cells (Brouet *et al*, 1973, 1976).

Having in mind that CLL and MM are most likely not the expression of a single malignant clone, it is of note that oligoclonal lymphoid malignancies may not be so rare. Indeed, examples of biclonal CLL have been observed (Preud'homine & Seligmann, 1972); furthermore, monoclonal serum immunoglobulins with an idiotypic specificity different from that of the Ig molecule synthesized by the leukaemic B cells, are not infrequent in CLL (Seligmann *et al*, 1973). They may well have the same significance as the development of overt MM in CLL patients. In addition, some evidence has been obtained that malignant tumours may be polyclonal at onset (Woodruff *et al*, 1982). Burkitt's recurrence may be due to the emergence of a second malignant clone as assessed by G_6PD phenotype (Fialkow, 1976). Finally, as postulated in chronic myelocytic leukaemia, the target cell for the oncogenic event may be a stem cell with distinct developmental capabilities. This last hypothesis could account for the occurrence of myeloid leukaemias in untreated patients with CLL or MM (Turszet *al*, 1974). Interestingly, it has been recently reported that MM may develop in patients affected with another B cell malignancy, namely hairy cell leukaemia (Catovsky *et al*, 1981). An intriguing possibility would be that, in such cases, the leukaemic B cell (or another cell type) may secrete some factor(s) which may trigger either normal B cells or plasma cells.

REFERENCES

BONNAZI, L., AZZINI, C.F. & FOSTE, P.L. (1968) **Gamrnapathie monoclonale et hypergammaglobulinemie au cours d'une leucemie lyrnphatique maligne.** *Frcastoro.* **61,** 950–959.

BROUET, J.C., PREUD'HOMME, J.L., FLANDRIN, G., CHELLOUL, N. & SELIGMANN, M. (1976) **Membrane markers in so-called 'hystiocytic' lymphomas.** *Journal of the National Cancer Institute.* **56,** 631–633.

BROUET, J.C., PREUD'HOMME, J.L., SELIGMANN, M. & BERNARD, J. (1973) **Blast cells with monoclonal surface immunoglobulins in two cases of acute blast crisis supervening on chronic lymphocytic leukaemia.** *British Medical Journal.* iv, 23–24.

CATOVSKY, D.. COSTELLO. C., LOUKOPOULOS. D., FESSAS, P.R.. FOXLEY. J.M., TRAUB, N.E., MILLS, M.J& O'BRIEN, M. **(1981)** Hairy cell leukemia and myelomatosis: chance association or clinical manifestations of the same B cell diseases spectrum. **Blood, 57, 758–763.**

CROWLEY, J.P.. CHURCHILL, W.H., SIMON. J. & ALBALA, M.M. **(1976)** Absence of lymphocyte immunoglobulin production in chronic lymphatic leukemia and multiple myeloma. **Annals of Internal Medicine, 86, 750.**

FIALKOW. P.J. **(1976)** Clonal origin of human tumors. **Biochimica et *Biophysica* Acta. 458, 283–421.**

FITZGERALD, P.H., RASTRICK, J.M. & HAMER. J.W. **(1973)** Acute plasma cell leukemia following chronic lymphatic leukaemia: transformation or two separate diseases. **British *Journal* of Haematology. 25, 171–177.**

GHOSH, M.L. & SAYEED, A. **(1974)** Unusual cases of myelomatosis. **Scandinavian Journal of *Haematology*, 12, 147–154.**

HOFFMAN. K.D. & RUDDERS, R.A. **(1977)** Multiple myeloma and chronic lymphocytic leukemia in a single individual. Immunologic studies and review of the literature. **Archives of Internal Medicine, 137, 232–235.**

JEHA, M.T., HAMBLIN, T.J. & SMITH, J.L. **(1981)** Coincident chronic lymphocytic leukemia and osteosclerotic multiple myeloma. **Blood, 57, 617–619.**

KOUGH, R.H. & MAKARY, A.Z. **(1978)** Chronic lymphocytic leukemia (CLL) terminating in multiple myeloma. **Blood. 52, 532–535.**

KUBAGAWA, H.. VOGLER, L.B., CAPRA, J.D.. CONRAD. M.E., LAWTON, A.R. & COOPER. M.D. **(1979)** Studies on the clonal origin of multiple myeloma. **Journal of Experimental Medicine, 150, 792–807.**

LOHRMANN, M.P., SCHNEIDER. G.. MERTEN. K. & TENBAUM, A. (1972) Koinzideng von Familias gehauf auftretenden Plasmozytom, chronischer lymphatische Leukämie und rectum Karzinom. ***Blut*, 24, 356–364.**

NAIDU, R.T. & ROSNER, M.O. **(1971)** Combined multiple myeloma and chronic lymphatic leukemia. ***New* England Journal of Medicine. 284, 108.**

NARASIMHAN, P.. KANDHASAMY. J., ELIZALDE. A.M. & ROSNER, F. **(1975)** Chronic lymphocytic leukemia and lymphosarcoma associated with multiple myelcma: report of three cases. **Archives of Internal Medicine, 135, 729–732.**

PEDERSEN-BJERGAARD, J., DRAMINSKY PETERSEN, H., THOMSEN, M., WIIK, A. & WOLFF-JENSEN, J. **(1978)** Chronic lymphocytic leukaemia with subsequent development of multiple myeloma. **Scandinavian journal of Haematology. 21, 256–264.**

PETERS, J.H.. HELLER. P. & VALAITIS. J. **(1961)** Malignant lymphoma, plasmocytosis dysproteinaemia. **Archives of Internal Medicine, 107, 903–907.**

PREUD'HOMME. J.L., HUREZ. D., DANON, F., BROUET, J.C. & SELIGMANN, M. **(1976)** Intracytoplasmic and surface bound immunoglobulins in 'non secretory' and Bence Jones myeloma. **Clinical and Experimental Immunology, 25, 428–436.**

PREUD'HOMME. J.L. & LABAUME, S. **(1975)** Immunofluorescent staining of human lymphocytes for the detection of surface immunoglobulins. **Annals of the New York Academy *of Sciences*, 254, 254–261.**

PREUD'HOMME, J.L. & SELIGMANN, M. **(1972)** Surface-bound immunoglobulins as a cell marker in human lymphoproliferative diseases. Blood. **40, 777–794.**

REIMER, E. **(1974)** Chronische lymphatische Leukaemie und Plasmozytom: kazuistische. langzeitbeobachtung. ***Blut*, 28, 231.**

REINHARD. E.. SAGEL, S., KORNFIELD, S., SCHROER. K., NADLER. P. & LYNCH, R. **(1975)** Multiple malignancies: chronic lymphocytic leukemia, malignant melanoma, multiple myeloma and acute myelo-monocytic leukemia. **American *Journal* of Medicine, 58, 408–416.**

SANY, J., MORLOCK, G., CLOT, J., BALDET. P., CARCASSONNE. Y. & SERRE. H. **(1976)** Leucémie lymphoide chronique et myelome multiple. **Revue du Rhumatisme. 43, 1–9.**

SELIGMANN, N.M., PREUD'HOMME, J.L. & BROUET, J.C. **(1973)** B and T cell markers in human proliferative blood diseases and primary immunodeficiencies. with special reference to membrane bound immunoglobulins. **Transplantation Reviews. 16, 85–113.**

SHUSTER, M. & CAUSING, W.C. **(1971)** Chronic lymphatic leukemia and lymphosarcoma terminating a multiple myeloma. **journal of Medical Society *of New* Jersey. 68. 365–368.**

SPENGLER, G.A.. ROULET. D.L.A., RICCI, C., SCINDER. U., SCHOOP, U., KAPPELER. R. & RIVA, G. (1961) Paraproteinamie bei chronischen Lymphadenose. ***Schweizerische Medizinische Wochenschrift,*** 1025–1029.

STOBBE, M. (1962) Syntropis von chronischen Lymphadenose und Plasmozytom. ***Acta Haematologica***, 27, 180–188.

TUBIANA. N.. ANDRAC. L., **OLIVE,** D. & CARCASSONNE, Y. (1978) Association leucémie lymphoide chronique plasmocytome. *Nouvelle* Presse ***Médicale***, **13,** 967.

TURSZ, T., FLANDRIN. G.. BROUET, J.C.. BRIERE. J. & SELIGMANN, M. (1974) Simultaneous occurrence of acute myeloblastic leukaemia and multiple myeloma without previous chemotherapy. ***British Medical Journal.*** ii, 642–643.

VANDER. J.B. & JOHNSON, H.A. (1960) Chronic lymphatic leukemia and multiple myeloma in the same patient. ***Annals*** of ***Internal Medicine,*** 53,1052–1059.

WALDENSTRÖM. J. (1962) Hypergammaglobulinemia as a clinical iematological problem: a study in the gammapathies. ***Progress in Hematology,*** Vol. 3, pp. 265–293. Grune & Stratton, New York.

WOODRUFF. M.F.A., ANSELL, J.D., **FORBES,** G.M., GORDON, J.C., BURTON, D.I. & MICKLEM. H.S. (1982) Clonal interaction in tumours. ***Nature,*** 299, 822–824.

ZALCBERG, J.R., CORNELL, F.N.. IRETON, J.C., MCGRATH, K.M.. MCLACHLAN, R., WOODRUFF, R.K. & WILEY. J.S. 11982) Chronic lymphatic leukaemia developing in a patient with multiple myeloma. ***Cancer, 50,*** 594–597.

ZBIGNEW, A,, ZADAWADZKI, M.D., KAPADIA. S. & BARNES, A.E. (1978) Leukemic myelomatosis (plasma cell leukemia). ***American Journal of Clinical Pathology.*** **70,** 605–611.