activated PTT fell from 115 seconds to 100 seconds. Initially factor IX activity did not rise after infusion, owing to binding of factor VIII in the factor-IX deficient substrate by the inhibitor.[1] After eight days' treatment the inhibitor level had fallen to less than one unit/ml; a rise in factor IX activity from 130 to 200% after infusion was then seen. Factor VIII activity remained stable at 3%. No evidence of intravascular coagulation was observed; his platelet count (400-500 $\times 10^9$/l), fibrinogen (3·8-5·7 g/l), and fibrinogen/fibrin degradation products (5-10 μg/ml) remained stable.

Twenty-one days after operation, after Proplex infusion (45 units/kg), the haematoma was removed and the wound resutured. Infusion was repeated next day (15 units/kg) then none was given for two days. The wound started to bleed again, whereupon four units of red cells were transfused, and Proplex (23 units/kg) given daily. Again, wound bleeding rapidly stopped; no further transfusion was required. Proplex (23 units/kg reducing to 15 units/kg daily) was continued for four weeks, until wound healing was complete.

Effect of varying dilutions of three factor IX preparations on partial thromboplastin time (PTT) of normal citrated plasma

Preparation	Proplex (Hyland)	Prothromplex (Immuno)	Factor IX (Edinburgh Protein Fractionation Centre)	Control
Factor IX assay (U/ml)	21·1	17·8	22·1	0·88
PTT (seconds)				133
„ dilution 1/20	145	142	120	
„ dilution 1/40	106	123	123	
„ dilution 1/100	81	129	116	
„ dilution 1/200	82	121	100	
„ dilution 1/400	84	126	123	

Transient hepatitis developed 43 days after operation; all tests for hepatitis B antigen (haemagglutination, immunoelectrophoresis, radioimmunoassay, electron microscopy) remained negative, but the immunoelectrophoresis test for its antibody had become positive. The patient was discharged home eight weeks after operation and has remained well, with an undetectable inhibitor level.

In an in vitro study (see table) dilutions of Proplex were incubated with normal citrated plasma for one minute before determination of the PTT. Shortening at high dilutions was observed, suggesting the presence of activated coagulation factors. Two other factor IX concentrates showed less procoagulant activity. No preparation affected the kaolin-activated PTT in this way.

Discussion

Experience with prothrombin complex concentrates and other factor VIII bypassing fractions in treating bleeding due to factor VIII inhibitors is limited but encouraging. Nevertheless, the effects on bleeding and on coagulation tests are inconstant and not always related.[1-4] In our patient severe external bleeding was seen to cease immediately after treatment, recur after stopping treatment, and again cease on restarting treatment. This therapeutic effect was paralleled by shortening of the PTT in vivo and in vitro, possibly due to bypassing of the factor VIII stage of the coagulation cascade by activated factors (IXa, Xa). Intravascular coagulation due to activated factors has been reported with such concentrates in man and experimental animals but no evidence of this was seen in our patient. Further experience is required to establish their place and dosage.

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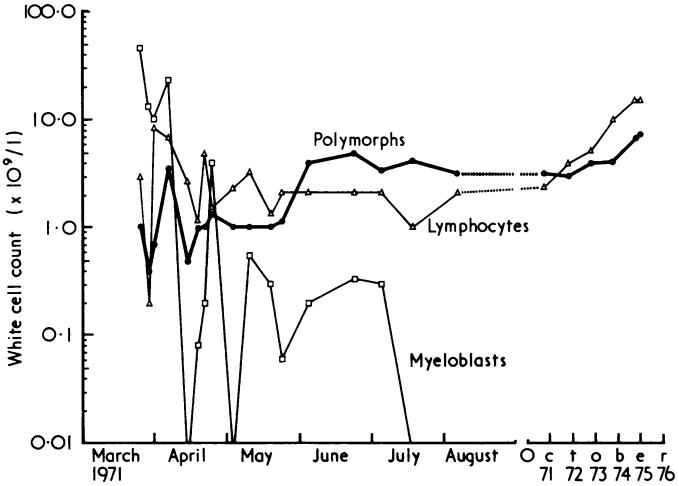
Chronic lymphocytic leukaemia uncovered by successful treatment of acute myeloid leukaemia

Case report

A 59-year-old man presented in March 1971 with a 10-day history of purpura, recurrent haemoptysis, and weight loss. Examination showed lymphadenopathy in the right axilla only, minimal hepatomegaly, and no splenomegaly. Haemoglobin was 12·9 g/dl, and white cell count 52×10^9/l (52 000/mm^3)—blast cells 47×10^9/l, small lymphocytes 3×10^9/l, polymorphs 1×10^9/l, and monocytes 1×10^9/l. Platelet count was 430×10^9/l. The bone marrow was hypercellular, with 85% blast cells and 15% small lymphocytes. The blood and marrow blasts were large, with a moderate nuclear:cytoplasmic ratio and two or three nucleoli, and about half contained Auer bodies in the cytoplasm. Acute myeloid leukaemia (AML) was diagnosed.

A five-day course of once-daily cytarabine intravenously and thioguanine by mouth was followed by two 100-mg doses of daunorubicin intravenously and a further five daily injections of cytarabine. Two weeks after the start of treatment his white cell count was 20×10^9/l, with blast cells 10×10^9/l and small lymphocytes $8{\cdot}8 \times 10^9$/l (see figure). He rapidly went into good remission, although 35% of all nucleated marrow cells were small lymphocytes.



White cell counts during induction and maintenance treatment.

From 1972 to late 1975 he remained in good remission with a normal haemoglobin and platelet count. The white cell count stabilised initially at 7×10^9/l, with small lymphocytes 4×10^9/l and polymorphs 3×10^9/l, but gradually rose. On examination in March 1974 he had a cellular marrow; myelopoiesis looked normal, with blast cells $2{\cdot}9 \times 10^9$/l; erythropoiesis was active; and normal numbers of megakaryocytes were present. Half of all the nucleated cells, however, were small lymphocytes.

Between December 1975 and April 1976 the white cells increased from 25×10^9/l (small lymphocytes 17×10^9/l, polymorphs 7×10^9/l) to 32×10^9/l (lymphocytes 26×10^9/l, polymorphs 6×10^9/l). Membrane marker analysis showed that only 2% of the lymphocytes were T cells (E rosettes) ($0{\cdot}5 \times 10^9$/l), while most mononuclear cells reacted to an anti-B cell serum and carried surface immunoglobulin (surface Ig).[1] The density of surface-Ig staining on most B cells (about 95%) was low. The surface-Ig phenotype of these cells was $\mu+\gamma-\ \alpha-/\kappa-\ \lambda+$. The same mononuclear B-cell population was seen in the bone marrow, which also contained a few T lymphocytes (10%). Thus membrane marker analysis confirmed the diagnosis of overt typical chronic lymphocytic leukaemia (CLL).

Discussion

This patient had an appreciable lymphocytic infiltration of the bone marrow when the AML was diagnosed. It therefore seems likely that he presented with AML and a concomitant lymphoproliferative disorder. Acute leukaemia sometimes occurs with CLL, and CLL may rarely terminate in a blastic phase.[2] It is, however, unlikely that our case would fall into this category because in the few cases in which the blastic cells were analysed in detail they constituted the transformed population of the original CLL alone, expressing the same B-cell surface phenotype.[3] Occasionally, alkylating agents such as

chlorambucil have been implicated in the emergence of a terminal acute leukaemia in CLL.[4]

So far as we know AML and CLL occurring together without previous treatment has only once been reported previously.[5] The CLL was, perhaps, temporarily suppressed but seemed to have been relatively unaffected by the treatment of AML. Indeed, this patient with well documented AML has done extraordinarily well to be still in remission five years after what some would consider to be a mild form of treatment. Any immunological suppression associated with his CLL obviously did not preclude him from keeping the AML in check.

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Association between previous tuberculous infection and glioma

In view of the possible role of depressed immunity in the pathogenesis of neoplasia we investigated 300 patients with cerebral glioma and 300 controls to see if there was any association between previous tuberculous infection and glioma.

Patients, methods, and results

Chest *x*-ray films of 300 consecutive patients with histologically proved glioma of the brain were reviewed for evidence of previous pulmonary tuberculosis. Based on the results the patients were divided into those with only a calcified primary complex or one of its components, and those who had had either progressive primary or postprimary disease. Controls were 300 patients aged over 40 who were seen consecutively during the survey period and examination of whom had excluded any likelihood of malignant disease. Altogether 144 had spinal conditions, of which 111 were either disc lesions or spondylosis; 123 intracranial lesions (the commonest diagnosis being subarachnoid haemorrhage), and 33 peripheral neurological lesions. The table gives the age and sex distribution of the patients and controls.

Of the patients with glioma, 22 (7·3%) had evidence of previous primary tuberculosis, and 28 (9·3%) evidence of either progressive primary or postprimary infection. The corresponding figures among the controls were 28 (9·3%) and 31 (10·3%) respectively (see table).

Discussion

Impaired immunity may predispose to neoplasia in the same way as it does to infections.[1-3] Burnet,[4] for example, pointed out the increased prevalence of cancer in the perinatal period and in old age, when immunity is impaired. Lymphomas have developed in patients receiving immunosuppressives, and there is an increased prevalence of neoplasms in certain genetic immunity deficiency states. It has also been suggested that a neoplasm may form as a result of the immunological responses brought about by a chronic infection such as tuberculosis.[3]

Sutherland[5] reported an increased mortality from malignant neoplasm (including cerebral) in patients who were tuberculin-positive as compared with those who were tuberculin-negative on entry to the tuberculosis vaccines trial, but there was no increased incidence of malignant neoplasm in the group given BCG. He suggested that the higher mortality from neoplasm in those who had had a previous natural mycobacterial infection was therefore more likely to be related to some aspect of the environment in which it occurred than to represent an immunological consequence of that infection.

Ward *et al*[3] reviewed the case histories and chest *x*-ray films of 92 patients with cerebral glioma and compared the findings with those in controls who were over the age of 50 and who had been admitted consecutively to general medical units. They found that 21·7% of the patients with glioma had either a history of previous tuberculosis or evidence of healed fibrotic lesions on their *x*-ray films as compared with 7% of the controls. They suggested that the patients with normal immune responses had dealt rapidly with a primary tuberculous infection, so that it had left no evidence other than perhaps a healed primary focus. Those with impaired immunity had possibly had more difficulty in dealing with the infection, which had therefore taken a more-prolonged course.

In our larger series, in which the controls, like the patients, had neurological complaints and were more nearly comparable in age, there was no evidence to suggest that previous pulmonary tuberculous infection in any form was related to the subsequent development of glioma.

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Age and sex distribution of 300 patients with glioma and 300 controls in relation to evidence of previous pulmonary tuberculosis

	Aged <40			Aged 40–			Aged 50–			Aged ≥60			Total		
	N	P	PP	N	P	PP	N	P	PP	N	P	PP	N	P	PP
Patients with glioma															
Men	36	1	3	25	1	1	35	4	5	50	2	8	146	8 (4·7%)	17 (10%)
Women	22	5	1	23	1	1	28	4	4	31	4	5	104	14 (10·9%)	11 (8·5%)
Total	58	6	4	48	2	2	63	8	9	81	6	13	250	22 (7·3%)	28 (9·3%)
Controls															
Men				43	5	6	44	2	6	48	6	5	135	13 (7·9%)	17 (10·3%)
Women				42	4	8	26	7	4	38	4	2	106	15 (11·1%)	14 (10·4%)
Total				85	9	14	70	9	10	86	10	7	241	28 (9·3%)	31 (10·3%)

N = No evidence of pulmonary tuberculosis. P = Primary pulmonary tuberculosis. PP = Progressive and postprimary pulmonary tuberculosis.