T-CELL LEUKAEMIA-LYMPHOMA VIRUS AND HETEROGENEITY OF CHRONIC T-CELL MALIGNANCIES

SIR,—T-cell chronic lymphocytic leukaemia (T-CCL) is rare in Europe and the U.S.A., accounting for only 2% of all CLL cases.[1] Malignancy of mature T-cells is more frequent in Japan, where this disorder is usually referred to as adult T-cell leukaemia (ATL).[2] Serum antibodies against the structural core protein (p24) of a human C-type leukaemia virus (human T-cell leukaemia-lymphoma virus or HTLV) have been demonstrated in Japanese patients with ATL,[3] suggesting a possible viral aetiology. Catovsky et al.[4] have reported a series of Black patients of West Indian origin with malignancy of mature T cells virtually indistinguishable from Japanese ATL and high titre antibodies against HTLV.

Evidence that HTLV-positive T leukaemia is not confined to Japan prompted us to look for anti-HTLV antibodies in ten patients from Italy with T-CLL; eight of these patients have been described elsewhere.[1,5,6] All patients were born in Italy and they live (or lived) in the Rome metropolitan area or in Padua. Slight hypercalcaemia (a feature of ATL) was observed in patient K while under chemotherapy. Nuclear convolutions, but not pleomorphism,[2] were noted in cells from patients J and K who had skin infiltration.[6] Cells from patients G, H, J, and K displayed the immunological pattern (T3+,T4+,T8−) recorded by Japanese workers for adult T-cell leukaemia.[7]

Coded serum samples from these ten patients were screened[3] and none possessed antibodies to HTLV. One additional patient,[8] from Maryland, U.S.A., with a disease clinically and immunologically indistinguishable from that of the Italian patients was also found to lack anti-HTLV serum antibodies.

Lymphoproliferative disorders of mature T cells represent a small but heterogeneous group of diseases. T-CLL from Europe or the U.S.A. is rare and not yet well defined. Patients with T-CLL sometimes have peripheral and bone marrow lymphocytosis as their main clinical manifestation and a favourable and chronic course even without treatment. Its status as a malignant condition has sometimes been questioned.[6,9,10] On the contrary, adult T-cell leukaemia, which is a more common condition, at least in Japan and the West Indies, is better characterised. Several clinical and morphological findings are present in these patients,[2] the disease behaving as a severe and aggressive malignancy resistant to anti-leukaemic agents. Four of the patients observed by us shared some features with adult T-cell leukaemia patients (skin involvement, nuclear convolutions but not pleomorphism, and/or the presence of T4 antigen on their proliferating cells). These patients also presented with a more aggressive disease and, unlike other T-CLL patients, early treatment was needed in three of them. Yet, the lack of anti-HTLV antibodies in sera from these patients is helpful in distinguishing between these more severe cases of European T-CLL and true cases of adult T-cell leukaemia, and is also suggestive for the different nature of the two diseases.

SUMMARY OF CLINICAL AND IMMUNOLOGICAL DATA OF T-CLL PATIENTS

Patient age, sex	WCC*	Lymphnodes/ liver/spleen enlargement	Skin involvement	Treatment (and survival in mo)	Phenotype of circulating cells†
A 83, M	25 *(88)*	−	−	−/29‡	T3+,T4−,T8+
B 70, F	16 *(96)*	+	−	−/>28	T3+,T4−,T8+
C 52, M	18 *(89)*	++	−	+/>17	T3+,T4−,T8+
D 50, F	19 *(82)*	+	−	+/24	T3+,T4−,T8−
E 33, M	18 *(78)*	−	−	−/>28	T3−,T4−,T8−
F 70, M	20 *(75)*	−	−	−/>20	T3+,T4±,T8±
G 46, F	20 *(94)*	−	−	−/>31	T3+,T4+,T8−
H 67, M	33 *(87)*	+	−	+/20	T3+,T4+,T8−
J 55, M	60 *(90)*	+	+	+/>47	T3+,T4+,T8−
K 78, F	43 *(85)*	+	+	+/35	T3+,T4+,T8−

* White-blood-cell counts in 10^9/l (and % lymphocytes).
† Cells from all cases formed rosettes with sheep erythrocytes. Distribution of surface OKT antigens is reported. For details see Pandolfi et al.[5,6]
‡ Died from an accidental injury while under no treatment for leukaemia.

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ADULT T-CELL LEUKAEMIA-LYMPHOMA WITH UNUSUAL PHENOTYPE

SIR,—Adult T-cell leukaemia-lymphoma is endemic in south-western Japan[1] and has been reported in six Black patients from the West Indies living in the U.K.[2] Three patients with T-cell malignancies similar or identical to the cases in Japan have been reported from the north-western part of the United States.[3] We wish to report another patient from the mid-western United States with T-cell leukaemia-lymphoma cytologically indistinguishable from the previously published cases but whose neoplastic leukaemic cells had a phenotype not previously reported.

A 42-year-old White man presented with generalised lymphadenopathy, splenomegaly, a right-sided pleural effusion, no skin lesions, and a white blood cell count (WCC) of 95×10^9/l. 98% of the white blood cells were pleomorphic lymphocytes with pronounced nuclear lobulations, some nuclei having a mulberry-like appearance (fig. 1). The lymphocytes ranged from small mature-appearing cells with aggregated chromatin to larger blast-like cells with prominent large nucleoli. These cytological features were confirmed ultrastructurally (fig. 2). Most of the cells had diffuse, punctate acid phosphatase activity. Bone marrow biopsy revealed almost complete replacement by neoplastic lymphocytes. Flow cytometric analysis ('EPICS V'; Coulter Electronics, Inc.) of lymphocytes from both peripheral blood and pleural fluid revealed that the cell surface phenotypes of 97% of the cells were T11+ (pan T-cell), T3+ (mature T-cell), T4+ (helper/inducer T-cell), and T8+ (suppressor/cytoxic T-cell). All other monoclonal antibody probes tested were negative, including T10, T9, T6, Ia, J5 (CALLA), Leu 7, B1, B2, and all surface immunoglobulin heavy

1 Pandolfi F, Semenzato G, De Rossi G, et al. Heterogeneity of T-CLL defined by monoclonal antibodies in nine patients *Clin Immunol Immunopathol* 1982; **24:** 330–41.
2 Uchiyama T, Yodoi J, Sagawa K, et al. Adult T-cell leukemia: Clinical and hematological features of 16 cases. *Blood* 1977; **50:** 481–92.
3 Kalyanaraman VS, Sarngadharan MG, Nakao Y, et al. Natural antibodies to the structural core protein (p24) of the human T-cell leukemia (lymphoma) retrovirus found in sera of leukemia patients in Japan. *Proc Natl Acad Sci USA* 1982; **79:** 1653–57.
4. Catovsky D, Greaves MF, Rose M, et al. Adult T-cell lymphoma-leukaemia in Blacks from the West Indies. *Lancet* 1982; i: 639.
5 Pandolfi F, Quinti I, De Rossi G, et al. A population of sheep rosetting cells lacking T- and monocytic-specific antigens, as detected by monoclonal antibodies. *Clin Immunol Immunopathol* 1982; **22:** 331–39.
6 Pandolfi F, De Rossi G, Semenzato G, et al. Immunological evaluation of T chronic lymphocytic leukemia cells: Correlations among phenotype, functional activities, and morphology *Blood* 1982; **59:** 688–95.
7 Hattori T, Uchiyama T, Toibana T, et al Surface phenotype of Japanese adult T-cell leukemia cells characterized by monoclonal antibodies. *Blood* 1981; **58:** 645–47.
8 Pandolfi F, Strong DM, Slease RB, et al. Characterization of a suppressor T-cell chronic lymphocytic leukemia with ADCC but not NK activity. *Blood* 1980; **56:** 653–60
9 Aisenberg AC, Wilkes BM, Harris NL, et al Chronic T-cell lymphocytosis with neutropenia: Report of a case studied with monoclonal antibodies *Blood* 1981; **58:** 818–22.
10 Rumke HC, Miedema F, Ten Berge IJM, et al. Functional properties of T cells in patients with chronic T gamma lymphocytosis and chronic T cell neoplasia *J Immunol* 1982; **129:** 419–26.

1. Uchiyama T, Yodoi J, Sagawa K, Takatsuki K, Uchino H Adult T cell leukemia: Clinical and hematologic features of 16 cases. *Blood* 1977; **50:** 481–91.
2. Catovsky D, Rose M, Goolden AWG, et al. Adult T-cell lymphoma-leukaemia in Blacks from the West Indies *Lancet* 1982; i: 639–43.
3. Kadin ME, Kamoun M. Nonendemic adult T-cell leukemia/lymphoma. *Hum Pathol* 1982; **13:** 691–93

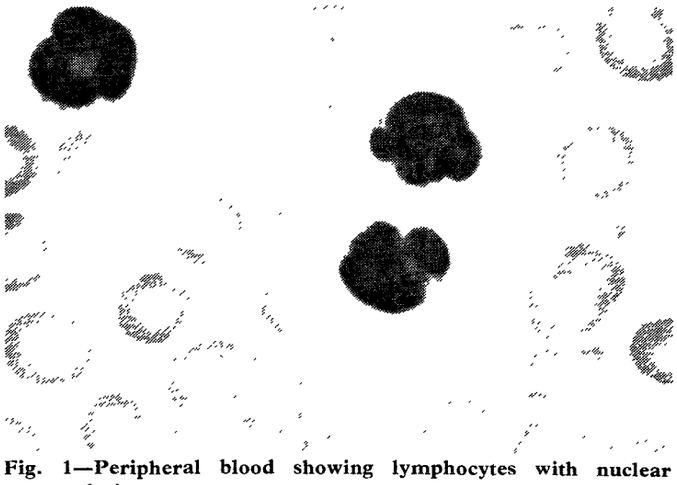

Fig. 1—Peripheral blood showing lymphocytes with nuclear convolutions.

One blastic cell has a large nucleolus (Wright's stain, × 720).

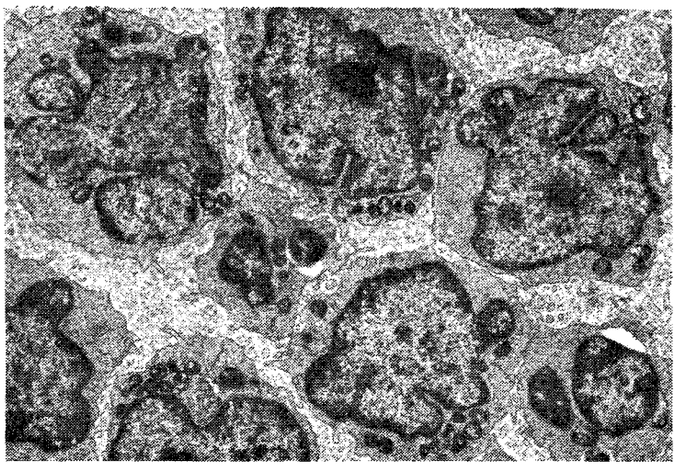

Fig. 2—Electron micrograph showing irregular nuclei of lymphocytes.

(Lead and uranyl acetate stain; × about 4000.)

and light chains. The cells also lacked TdT by immunofluorescence assay. The patient was treated with vincristine, prednisone, and intrathecal methotrexate; the white blood cell count fell but then rose to 140×10^9/l. More aggressive therapy (vincristine, doxorubicin, and prednisone) resulted in a moderate but transient drop of the white blood cell count. The patient died 22 days after the diagnosis of his illness.

Cytologically, the patient's leukaemic cells were indistinguishable from those in previously reported cases of adult T-cell leukaemia-lymphoma.[1-3] Although the neoplastic cells had a mature phenotype and were TdT negative (a characteristic of other reported cases of this disease) the reaction with both T4 and T8 monoclonal antibodies in the absence of T6 and T10 positivity has not been previously described. The neoplastic cells in most previously reported cases have had a helper/inducer phenotype (T4+, T8−). Nor did the patient have hypercalcaemia, which was found in some of the cases reported from Japan and in most of the cases reported by Catovsky et al.[2] Also, the patient's plasma did not have antibodies against disrupted human C-type leukaemia virus (human T-cell leukaemia-lymphoma virus, HTLV), which has been reported in many cases from Japan and in all cases from the West Indies.[2] We believe this patient had a phenotypic variant of adult T-cell leukaemia-lymphoma.

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EFFECT OF CYCLOSPORIN ON RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

SIR,—To explain the renal side-effects encountered during immunosuppressive therapy with cyclosporin[1,2] an antidiuretic hormone (ADH) like activity has been proposed,[3] although this has never been proved by laboratory data. In mice and rats we observed a significant increase in plasma corticosterone levels after single or repeated daily oral administration.[4] This increase was seen at high doses only and has never been confirmed in patients.

Changes in the urinary Na^+/K^+ ratio of animals used in toxicity studies suggested a possible influence of cyclosporin on the renin-angiotensin-aldosterone system (RAAS). Further studies, in beagle dogs, pointed to stimulation of the RAAS, as shown by increased plasma renin activity (PRA) and decreased urinary Na^+/K^+ ratio (table). Similar data were obtained in rats, especially in the genetically hypertension-prone rat, again indicating profound stimulation of the RAAS (table). Adrenalectomy abolished the aldosterone-induced effects on urinary electrolytes (data not shown). The systolic arterial blood pressure and heart rate were, however, slightly raised in both adrenalectomised and intact rats. These data could explain the increased diastolic blood pressure seen in young patients given cyclosporin for bone marrow transplants.[5]

EFFECTS OF CYCLOSPORIN A ON PRA AND URINARY SODIUM/POTASSIUM RATIO IN MALE BEAGLE DOGS AND MALE SPONTANEOUSLY HYPERTENSIVE RATS

Cyclosporin (mg/kg)	Treatment period (days)	PRA (ng/ml)	Urine Na+/K+ ratio
Dogs			
0 (n=3)	1	0·97±0·12	5·9
0 (n=3)	5	1·38±0·29	5·7
25 (n=3)	1	3·39±3·75	2·9
25 (n=3)	5	4·22±1·75*	4·0
Rats			
0 (n=6)	28	4·1±0·3	7·1
20 (n=6)	28	25·1±4·8*	5·2

*$p<0.05$ (Student's test).

Stimulation of renin release and/or production as well as subsequent release of angiotensin II could be responsible for the hypertension. In addition, altered renal haemodynamics might result in hypoxia of the deeper nephrons causing tubular damage. In this situation prednisone, as reported by Durrant et al.,[6] would have a further detrimental effect on blood pressure and tubular function. If this stimulatory effect of cyclosporin on the RAAS does occur in man also, drugs with vasodilatory activity might prevent renin release and/or adverse effects on the kidney.

Another mechanism has been suggested for the capillary glomerular thrombosis seen in a few patients on cyclosporin, in particular after bone marrow transplantation.[7] Experiments suggest that a poorly defined plasma factor (PSF), which stimulates prostacyclin synthesis, is reduced in the plasma of cyclosporin-treated rabbits (Neild GH, Rocchi G, Imberti L, et al. Unpublished).

Baxter et al.[8] have also recently reported increased PRA in rats given cyclosporin.

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1. Hamilton DV, Calne RY, Evans DB, et al The effect of long-term cyclosporin A on renal function. *Lancet* 1981; i: 1218–19.
2. European multicenter trial. Cyclosporin A as sole immunosuppressive agent in recipients of kidney allografts from cadaver donors. *Lancet* 1982; ii: 57–60.
3. Green CJ. Cyclosporin A. Editorial. *Lancet* 1980; i: 110
4. Ryffel B, Deyssenroth H, Borel J. Cyclosporin A: effects on the mouse thymus. *Ag Actions* 1981; **4:** 373–79.
5. Barrett AJ, Kendra JR, Lucus CF, et al. Cyclosporin A as prophylaxis against graft versus host disease in 36 patients. *Br Med J* 1982; **285:** 162–66
6. Durrant S, Chipping PM, Palmer S, Gordon-Smith EC. Cyclosporin A, methylprednisonone, and convulsion. *Lancet* 1982; i: 829–30.
7. Shulman H, Striker G, Deeg HJ, et al. Nephrotoxicity of cyclosporin A after allogeneic bone marrow transplantation. *N Engl J Med* 1981; **305:** 1392–95.
8. Baxter CR, Duggin GG, Willis NS, et al. Cyclosporin A-induced increases in renin storage and release. *Res Comm Chem Pathol Pharmacol* 1982, **37:** 305–11