SHORT REPORTS

Dual B and T markers on lymphocytes in fulminant nodular lymphoma

Most lymphomas and leukaemias may be classified according to whether the malignant cells are derived from thymus (T lymphocytes) or bone marrow (B lymphocytes). In a few cases the cells may carry markers of both types,¹⁻⁴ which may indicate a proliferation of the small population of lymphocytes with dual markers present in normal people.⁵ We report such a case in a patient with fulminant lymphocytic lymphoma, in which a sequential study of B and T markers was made.

Case report

An 8-year-old girl presented with bronchitis and pallor of six weeks' duration. She had a pleural effusion, generalised lymphadenopathy, enlarged liver and spleen, and a renal mass. On radiography the anterior mediastinum was seen to be massively widened. The peripheral blood leucocyte count was $105 \times 10^9/l$ ($105\,000/mm^3$), with 78% lymphocytes, mostly of abnormal morphology. The bone marrow was hypercellular, 90% of the cells being abnormal lymphocytes. The pleural fluid also contained many abnormal lymphocytes. Histological examination of a lymph node showed a poorly differentiated, nodular lymphocytic lymphoma.

There was a dramatic response to cyclophosphamide, vincristine, and prednisolone (COP). All clinical evidence of tumour disappeared, and the peripheral blood leucocyte count was normal after six days. A meningeal relapse at six weeks was treated with cranial irradiation and intrathecal methotrexate. At 11 weeks there was a systemic relapse, with a peripheral blood leucocyte count of $210 \times 10^9/l$ ($210\,000/mm^3$; 93% lymphocytes). Partial remission was obtained with COP plus doxorubicin.

Results of tests for lymphocyte surface markers on cells obtained before treatment. Each value represents mean result of duplicate tests

	Patient				Control peripheral blood values
	Lymph node	Bone marrow	Peripheral blood	Pleural fluid	
E rosettes (%)	81.2	82.2	83.5	80.2	55.8
EAC _{hu} rosettes (%)	91.2	79.6	48.3	23.6	12.9
EAC _{mo} rosettes (%)	40.0	36.0	20.9	4.3	3.4

Tests for lymphocyte surface markers—Lymphocytes purified on Isopaque/Ficoll gradients were tested for their ability to form E (spontaneous sheep cell) rosettes (T-cell marker) and EAC (complement receptor) rosettes (B-cell marker), both human and mouse complement being used to sensitise the erythrocytes (EAC_{hu} and EAC_{mo} rosettes respectively). Tests carried out at the time of diagnosis (see table) showed that most of the cells in the lymph node, bone marrow, and peripheral blood had both B and T markers. Most of those in the pleural fluid and some of those in the blood, however, had only the T-cell marker. After COP 29% of the peripheral blood lymphocytes formed E rosettes and 37% EAC_{hu} rosettes. At the time of relapse, 11 weeks later, 92% of the peripheral blood lymphocytes formed E rosettes but only 1% had the complement receptor.

Comment

Although several isolated reports of "double-receptor" lymphoproliferative disorders have appeared,¹⁻⁴ this case is remarkable in two respects: it is the first to be associated with a nodular lymphoma rather than a leukaemia, and it is the first in which surface-marker characteristics were observed to change during the course of the disease. At the time of relapse the cells no longer had the B marker but retained the T marker. Either the double-marker cells must have lost their B marker or a subclone of cells with only the T marker must have evolved from the original double-marker lymphocytes. Interestingly, some of the lymphocytes already present in the pleural fluid and peripheral blood at the time of diagnosis lacked the B marker.

These findings emphasise the need for testing malignant lymphocytes for cell surface markers as soon as possible after the onset of the disease and before chemotherapy if the true origin of the malignant clone is to be determined. Conclusions drawn from testing cells at the time of relapse rather than diagnosis may not be valid.

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Department of Medicine, University of Tasmania, Royal Hobart Hospital Clinical School, Hobart, Tasmania, Australia 7000

S M KIROV, PhD, research fellow

R M LOWENTHAL, MRCP, senior lecturer

T-cell leukaemia in a young boy presenting with central nervous system symptoms

Acute lymphoblastic leukaemia (ALL) can be of T or null cell type. T cell ALL is associated with poor-risk factors including central nervous system (CNS) leukaemia. CNS leukaemia is commonly associated with ALL in relapse and occasionally at presentation in lymphoma with mediastinal involvement.¹ A case of T cell ALL presenting as CNS leukaemia without clinical evidence of other tissue involvement is described.

Case report

A 3-year-old Indian boy born in England presented after 10 days of vomiting, anorexia, and drowsiness. Chest x-ray showed an enlarged thymic shadow with clear lung fields. There was no hepatosplenomegaly or lymphadenopathy. The blood film was normal with a leucocyte count of $8.6 \times 10^9/l$ and a haemoglobin of 11.2 g/dl. The cerebrospinal fluid (CSF) contained 0.14×10^9 lymphocytes/l and gave no growth on culture; protein was 0.2 g/l and glucose 2.7 mmol/l (0.48 g/l). Visual impairment and a 6th nerve palsy occurred on day six after admission, and a provisional diagnosis of post-infectious encephalomyelitis was made. Prednisolone 40 mg/day was given, which was followed by a decrease in size of the thymic shadow on chest x-ray. ACTH was added to the prednisolone, but on day 33 his vision deteriorated and he developed a bilateral 6th nerve palsy. The CSF now contained 4.2×10^9 lymphocytes/l with an abnormal morphology. Air studies excluded the presence of a cranial space-occupying lesion.

On day 45 the lymphocytes in the CSF, blood, and bone marrow were examined for E, Fcγ, and C3 receptor cells and for surface immunoglobulin.² CSF neoplastic cells rosetted with sheep erythrocytes (E) and with C3 sensitised ox cells (see table). These cells did not carry Fcγ receptors or

Immunological investigations on day 45 after presentation

Preparation	10 ⁹ /l Leucocytes	10 ⁹ /l Lymphocytes	% Neoplastic cells	Lymphocyte markers %			
				E	Fcγ	C3	SIg
CSF	—	5.0	>90	95	3	25	0
PB	13.2	3.6	0	60	54	32	40
BM	—	—	0	45	37	21	25

surface immunoglobulin and were characterised by convoluted nuclei and scarce cytoplasm. The cells were 10-15 μ m in diameter and were negative for acid phosphatase, non-specific esterase, Sudan black, and periodic-acid Schiff stains. No abnormal lymphocytes were detected in the blood or bone marrow. Cranial radiation and intrathecal methotrexate were started on day 48, but no systemic cytotoxic therapy was given. Severe visual impairment persisted and his general condition remained unchanged. His spleen, lymph nodes, bone marrow, and peripheral blood remained normal. On day 71 occasional primitive lymphocytes and numerous smear cells were found in his blood; the white count was $2.7 \times 10^9/l$. The patient deteriorated until death on the 81st day after admission. There was no necropsy. Analysis of the bone marrow and peripheral blood at death showed infiltrating neoplastic cells with E and C3 receptors as detected previously in the CSF.

Discussion

This case may be regarded as acute leukaemia or lymphoma with early involvement of the meninges. It is unusual for acute leukaemia to present with CNS symptoms.³ The incidence of meningeal symptoms at diagnosis of non-Hodgkin's lymphoma varies—6/30 children reported from Toronto⁴ and 0/64 by Pinkel *et al.*⁵ This case appears to be the first documented of a T cell lymphoma presenting with CNS symptoms and no clinical evidence for other tissue lesions. The neoplastic cells had convoluted nuclei, but, unlike other cases of T cell ALL, expressed the C3 complement receptor. Tests with unsensitised and IgM-sensitised ox cells were negative.

This case is reported to emphasise that ALL enters into the differential diagnosis of CSF lymphocytosis. This point was not appreciated initially, since there was no indication that the lymphocytes in the first CSF were malignant, and the thymic shadow, although enlarged, was not considered abnormal.

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Correspondence to Dr J L Smith.

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Department of Child Health, University of Southampton General Hospital, Southampton SO9 4XY

M RADFORD, MRACP, MRCP, senior lecturer
J V LEONARD, MRCP, paediatric registrar
I C S NORMAND, FRCP, professor

Immunology Unit, Tenovus Research Laboratory, General Hospital, Southampton SO9 4XY

J L SMITH, PHD, principal scientific officer

Acquired circulating anticoagulant in a 4-year-old child

Acquired inhibitors of coagulation have been reported in several conditions including haemophilia, various autoimmune disorders, elderly patients with no demonstrable underlying disease, and in women post partum. We wish to report a case occurring after infection.

Case report

A 4½-year-old girl presented with a six-week history of spontaneous bruising, anorexia, headaches, and lassitude. She had a recent history of an upper respiratory tract infection, which had been treated with a course of erythromycin. There was no family or previous history of a haemorrhagic diathesis. Clinical examination showed numerous small bruises over the trunk and limbs and one large subcutaneous haematoma in the left parasternal region. Discrete cervical lymphadenopathy was present. At the time of presentation a sibling had proved infectious mononucleosis.

The results of haematological studies were as follows: haemoglobin 12.0 g/dl; total white cell count $6.8 \times 10^9/l$; differential count, neutrophils

62%, lymphocytes 35%, monocytes 3%, no atypical cells seen. The ESR was 30 mm in one hour and the platelet count $171 \times 10^9/l$. A Paul-Bunnell screen (Monospot-Ortho Diagnostics) gave a negative result. Viral serological investigations showed significant titres for adenovirus (1/320), respiratory syncytial virus (1/80), *Mycoplasma pneumoniae* (1/80), and Epstein-Barr virus (IgG-1/128). Cytomegalovirus and rubella titres were 1/8 and 1/5 respectively. The results of immunological investigation were as follows: no antinuclear, gastric parietal cell, smooth muscle, or mitochondrial antibodies were detected; a screen for rheumatoid factor was negative. Serum complement levels were: C3 (65 mg/dl)—slightly reduced levels—and C4 (25 mg/dl) normal levels. The immunoglobulin levels were normal.

Anticoagulant effect of patient's plasma

Test	Patient	Normal range
Prothrombin time (seconds)	14.8	11.8–15.3
Kaolin-cephalin time (seconds)	62.6	33.4–52.4
Kaolin-cephalin time + equal amount normal plasma	61.6	
Thrombin time—5u (seconds)	14.0	12.0–16.0
Factor VIII assay 2-stage method (% normal)	130	50–200
Factor IX assay 1-stage method (% normal)	65	50–200
Factor II assay 1-stage method (% normal)	50	60–200

The anticoagulant effect of the patient's plasma (see table) was confirmed by a modification of the agarose gel inhibitor technique.¹ The degree of inhibition did not appear to be influenced by varying the concentration of phospholipid (Diagen-Bell and Alton platelet substitute). The same reagent was used in the kaolin-cephalin clotting time test. Antibody neutralisation experiments using sheep anti-human IgG and IgM (Burroughs Wellcome) indicated that the inhibitor was an IgG antibody. Initial clotting investigations were limited by the amount of plasma available. Three months after presentation the patient was clinically well and the inhibitor was undetectable. In view of the possible association of this inhibitor with infectious mononucleosis, samples from twenty individuals with serologically proved mononucleosis were tested using the agarose gel technique. Four samples showed a variable degree of inhibition of coagulation but further studies were not possible.

Discussion

The appearance of a circulating inhibitor of coagulation in a child is rarely reported. Lechner² in a review reported only one case of a coagulant inhibitor occurring after infection. The nature of the associated infection in our case is uncertain. The absence of diagnostic haematological and virological findings consistent with recent infectious mononucleosis³ could be due in part to the late presentation of the case. Bleeding problems occurring in this illness are usually associated with thrombocytopenia but abnormalities of coagulation have also been described.⁴

Circulating anticoagulants which do not appear to consume coagulation factors but otherwise interfere with the coagulation process have been described in systemic lupus.⁵ The mechanism of inhibition is poorly understood but may affect interaction of prothrombin with prothrombin activator. An associated variable decrease in prothrombin levels also occurs. Thus our inhibitor resembles the lupus anticoagulant. Inhibition of phospholipid, which has also been suggested for the lupus-inhibitor activity, was not found in our limited experiments.

When bleeding problems occur in association with infectious mononucleosis or other viral infections with a normal platelet count the possibility of an acquired circulating anticoagulant should be considered.

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Lord Mayor Treloar Hospital, Alton, Hants

P J KIRK, MB, CHB, research fellow, Treloar Haemophilia Centre
D S McLELLAN, FIMLS, chief technician, haemophilia laboratory

Basingstoke District Hospital, Park Prewett, Basingstoke, Hants

A ARONSTAM, MB, MRCPATH, consultant haematologist