Rapidly fatal respiratory failure and angioimmunoblastic lymphadenopathy: possible contributions of immunoblastic leukaemia, chemotherapy, and multiple antibodies directed against mature blood cells

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SUMMARY A patient with angioimmunoblastic lymphadenopathy, immunoblastic leukaemia, pulmonary immunoblastic infiltration, and multiple antihemolytic antibodies in his serum deteriorated rapidly after chemotherapy due to severe progressive respiratory dysfunction. The haematological and immunological changes that accompanied this are described and discussed in the light of the pulmonary changes observed at necropsy of pulmonary oedema, fibrinous thrombi within venules, and immunoblastic infiltration of these thrombi and the venule walls. A pathophysiological mechanism is postulated in an attempt to rationalise these findings, and to act as a guide for the future assessment and management of similar cases.

The major studies of angioimmunoblastic lymphadenopathy (AIL) series incorporating between four and 38 patients¹⁻⁸ have enabled the unique histology of this disease to be clearly defined and have revealed some commonly occurring clinical manifestations, which include progressive lymphadenopathy, rash, fever, autoimmune haemolytic anaemia, and a polyclonal increase of immunoglobulin. The disease can be classified as a hyperimmune disorder of the B-cell system^{3 4 6 9-11} perhaps related to a reduction in suppressor T-cell activity.^{2 6 9 12 13} Levamisole-induced remissions support the latter concept.^{14 15} Others regard the clinical pattern and histological evolution of AIL to be very similar to those of a graft-versus-host reaction.^{1 2 16} Recently, intracytoplasmic virus-like particles have been observed in AIL lymphoid cells.^{17 18}

Less common clinical features of AIL may include the presence of numerous immunoblasts in the peripheral blood,^{2 7 8 19} which we define as immunoblastic leukaemia (IBL) if the concentration exceeds $1.0 \times 10^9/l$ ($1000/mm^3$)—diffuse interstitial pul-

monary infiltration by immunoblasts,^{2 5 13 19-23} and additional immunological aberrations such as the presence of multiple autoantibodies,¹⁰ hypocomplementaemia,^{5 24-26} and cutaneous anergy—all well reviewed by Cullen *et al.*⁸

We report on a case of AIL exhibiting the special features of IBL, pulmonary infiltration, and some previously undescribed serum antibodies directed against neutrophils, lymphocytes, and platelets. The possible interrelations of these features are discussed in detail, and particularly the immunological changes induced by chemotherapy since these may have contributed significantly to the morbidity and death of the patient. A pathophysiological scheme is suggested both to summarise the findings in this case and also to provide a scheme upon which to base the investigation and management of any cases of AIL showing similar features in the future.

Case report

A 53-year-old Caucasian steel-worker had been fit throughout his life until he first noticed a lump in his neck—defined as day 1 of the illness. By day 15 he had become anorectic, slightly dyspnoeic with a dry cough, and had lost 3 kg in weight. Examination show-

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ed enlarged, discrete, painless, rubbery lymph nodes bilaterally in the neck, axillae, and groins ($\frac{1}{2}$ -1 cm in diameter), and a firm smooth non-tender liver extending 6 cm below the costal margin. The spleen was impalpable. A plain abdominal x-ray examination showed the large liver but was otherwise normal. A maculopapular non-pruritic erythematous rash was on the trunk and arms. Some scattered crepitations were audible at both lung bases, and a chest x-ray examination (Fig. 1) showed bilateral hilar lymphadenopathy, with generalised nodular and linear opacities throughout both lung fields, although most prominent at the right base. A significant lymphocytosis was seen in the peripheral blood, but only slight anaemia (Figs 2 and 3), and the blood film cellular morphology appeared normal.

Fig. 1 Chest x-ray film showing bilateral hilar lymphadenopathy and generalised nodular and linear opacities throughout both lung fields in a case of angioimmunoblastic lymphadenopathy with pulmonary immunoblastic infiltration.

On day 22 when the patient was admitted to hospital the lymph nodes had enlarged to a maximum diameter of 2.5 cm, the liver was palpable 8 cm below the costal margin, and the spleen was just palpable. The rash was unchanged, but in other areas the skin and mucous membranes were pale. A strongly positive direct Coombs test (broad spectrum), a raised concentration of hydroxybutyrate dehydrogenase (HBD) in the serum (650 IU/l; normal range 0-360), a low serum haptoglobin concentration < 0.3 g/l (normal range 0.3-2.0 g/l) and increased urine urobilinogen all indicated the presence of autoimmune

Fig. 2 Peripheral blood erythroid changes accompanying the progression of the disease and the initiation of chemotherapy in a case of angioimmunoblastic lymphadenopathy with multiple circulating antihemocytic antibodies.

Fig. 3 Peripheral blood leucocyte and platelet changes accompanying the progression of the disease and the initiation of chemotherapy in a case of angioimmunoblastic lymphadenopathy with immunoblastic leukaemia and multiple circulating antihemocytic antibodies.

extravascular haemolysis, as did the blood film (cold agglutination, spherocytes, increased polychromasia, absence of fragments) and the other haematological indices (Fig. 2). The patient still complained of the same respiratory symptoms as on day 15 although the signs at the lung bases had disappeared. A repeat full physical examination was normal in all other respects, and in particular he was afebrile with a regular pulse rate of 90/min, a blood pressure of 130/70, a normal electrocardiogram, and a respiratory rate of 15/min. There was no history of rigors, night sweats, or recent drug intake. The histology of a cervical lymph node biopsied on day 23 showed alteration of the nodal architecture by a diffuse proliferation of small blood vessels, a pleomorphic mononuclear cellular infiltrate composed of immunoblasts, plasma cells, and lymphocytes, and the presence of PAS-positive intercellular material. This well-established histological triad² enabled a definite diagnosis of AIL to be made (agreed by three histologists).

From day 26 the patient deteriorated clinically with increasing respiratory distress and cough, which paralleled the appearance of definite IBL (Fig. 4) and progressive leucoerythroblastic anaemia (Fig. 2). Thick mucoid sputum was obtained on day 27 only, and treatment for a possible chest infection with oral ampicillin/cloxacillin (days 27, 28), septrin (days 31, 32), and salbutamol and intravenous gentamicin/lincomycin (days 29, 30) were all without clinical benefit, although no bacterial or fungal organism

could be cultured from the sputum of day 27.

A bone marrow aspirate on day 26 was hypocellular but with 25% immunoblasts, in contrast to an extremely cellular trephine biopsy on day 28 that showed gross infiltration by immunoblasts and a considerable increase in small and medium-sized reticulin fibres, as described by Brearley *et al.*²⁷

Throughout the illness the plasma concentrations of alkaline phosphatase and aspartate aminotransferase, and sodium, chloride, potassium, and phosphate ions were all normal. In contrast, however, the plasma concentrations of bilirubin, hydroxybutyrate dehydrogenase, and urea rose slowly throughout the study reaching the following concentrations during the last two days of life: bilirubin 30 $\mu\text{mol/l}$ (1.7 mg/100 ml; normal range 0-17 $\mu\text{mol/l}$ (0-1.0 mg/100 ml)), hydroxybutyrate dehydrogenase 880 IU/l (normal range 0-360 IU/l), urea 12 mmol/l (72 mg/100 ml; normal range 2.5-7.5 mmol/l (15-45 mg/100 ml)). The plasma concentrations of calcium and albumin fell slowly to: calcium 1.90 mmol/l (7.6 mg/100 ml; normal range 2.26-2.60 mmol/l (9.0-10.5 mg/100 ml)), albumin 21 g/l (2.1 g/100 ml; normal range 35-48 g/l (3.5-4.8 g/100 ml)). On day 31 the plasma uric acid concentration was slightly raised at 0.49 mmol/l (8.23 mg/100 ml; normal range 0.15-0.4 mmol/l (2-7 mg/100 ml)).

On day 29 the patient became confused, with a respiratory rate of 40/min, a haemoglobin concentration of 6.2 g/dl, but with a chest x-ray appearance unchanged from that of day 15. The slow transfusion

Fig. 4 A pre-chemotherapy buffy coat preparation from the peripheral blood of a case of angioimmunoblastic lymphadenopathy with immunoblastic leukaemia showing (a) two immunoblasts at the edge of the preparation $\times 1800$; (b) the more mature immunoblasts (including lymphoplasmacytoid cells) predominant in the thinner part of the preparation $\times 500$.

of $4\frac{1}{2}$ units of packed red cells over 36 hours (Fig. 2) did not, however, alter any of these respiratory symptoms or signs. In an attempt therefore to treat the underlying AIL and IBL, chemotherapy was started using cyclophosphamide, corticosteroids, and bleomycin as shown in Figs 2 and 3. This apparently arrested the leukaemic phase of the disease and was accompanied by a reduction in the concentrations of some other cellular components of the blood (Fig. 3).

The patient, however, continued to deteriorate with abnormal blood gases (pH 7.33, PCO_2 29 mm Hg (3.8 kPa), PO_2 50 mm Hg (6.6 kPa), standard

bicarbonate 17 mmol (mEq)/l and base excess—10.0 mmol (mEq)/l; day 30) and increasing confusion, leading to coma and death in respiratory failure on day 32. The low platelet counts before death (days 30, 31, 32, Fig. 3) could not be readily attributed to disseminated intravascular coagulation since the slight rise of fibrin degradation products within the range of 40–80 mg/l was accompanied throughout this period by fibrinogen titres (1/64; normal range 1/32–1/128), one-stage prothrombin times, kaolin-cephalin clotting times, and individual assays for factors V, VII, VIII, IX, X, and XII, which were all

Peripheral blood haematological and immunological changes accompanying the progression of the disease and the initiation of chemotherapy in a case of angioimmunoblastic lymphadenopathy with immunoblastic leukaemia, pulmonary immunoblastic infiltration, and multiple circulating antihaemocytic antibodies

PERIPHERAL BLOOD COMPONENTS			PERIPHERAL BLOOD COMPONENT VALUES ON DAYS INDICATED					DIRECTION OF CHANGE (↓ OR ↑) AND RATE OF CHANGE (A OR B; amount per day) OF COMPONENT VALUES				RATIO OF B / A	
			PRE-CHEMO- THERAPY		POST-CHEMO- THERAPY			PRE-CHEMO- THERAPY		POST-CHEMO- THERAPY			
TYPE	UNITS	NORMAL RANGE	DAY 22	DAY 29	DAY 30	DAY 31	DAY 32	↑/↓	A	↑/↓	B		
IMMUNOBLASTS	x10 ⁹ .l ⁻¹		2.7	15.6	3.1	1.7	0.0	↑	1.9	↓	7.0	R	
LYMPHOCYTES	x10 ⁹ .l ⁻¹	1.5 - 4.0	16.0	4.3	2.7	2.8	1.1	↓	1.7	↓	1.0	0.6	
LYMPHOCYTE SUB-TYPES	T-CELLS	%				37	E - rosettes						
	(B-CELLS)	%				21	EAC - rosettes						
	B-CELLS	%				48	immunofluorescent surface immunoglobulin						
	NULL CELLS	%				15							
IMMUNOGLOBULIN G	g.l ⁻¹	5.0 - 16.0	20.0	26.4	39.0			↑	0.71	↑	12.6	17.6	
IMMUNOGLOBULIN A	g.l ⁻¹	1.25-4.25	4.0	5.0	7.2			↑	0.11	↑	2.2	20.0	
IMMUNOGLOBULIN M	g.l ⁻¹	0.47-1.70	7.5	13.3	15.0			↑	0.64	↑	1.7	2.7	
ANTIBODIES	RED CELL*	40C titre				1/2048	anti-I (reduced to 1/256 at RT)						
	LYMPHOCYTE	%				93	cell kill/80-cell panel/NSA						
	NEUTROPHIL	%				40	agglutination/60-cell panel/NSA						
	PLATELET	titre				1/40	complement fixation						
	PLATELET	titre				1/16	agglutination						
OTHER +						ND							
HAEMOGLOBIN	g.dl ⁻¹	13.0-18.0	8.1	(5.8)	9.6		7.4	↓	0.4	↓	1.1	2.9	
NEUTROPHILS	x10 ⁹ .l ⁻¹	2.0-7.5	5.3	25.5	16.6	10.1	10.5	↑	2.9	↓	7.7	R	
PLATELETS	x10 ⁹ .l ⁻¹	150-400	255	125	40	9	19	↓	18.6	↓	58.0	3.1	
COMPLEMENT COMPONENTS	C3	mg.l ⁻¹				165							
	C3c/C3d					ND	immunoelectrophoresis						
	C4	mg.l ⁻¹				25							
	C4a					ND	immunoelectrophoresis						

R = Reversed direction of change of component values before and after chemotherapy.

Longest horizontal boxes contain a brief indication of the corresponding methods used.

*Pan-reacting antibody also detected at 37°C in saline, albumin, and by indirect Coombs; it was not possible to elucidate whether this represented the established anti-I with a high thermal amplitude, or an additional antibody (or antibodies).

+ Other antibodies directed against nucleus, smooth muscle, mitochondria, parietal cells, thyroid, lung, salivary gland, brucella, influenza, parainfluenza, psittacosis/lymphogranuloma venereum, rickettsia, respiratory syncytial virus, mycoplasma, mumps, and herpes simplex were all tested for but not detected (ND). The Paul-Bunnell test was also negative.

NSA = No specificity assignable.

(5.8) = Data from day 28, not day 29.

Corresponding references describe the methods used for the quantitative or semiquantitative measurement of (i) immunoglobulin classes,²⁸ (ii) lymphocytotoxic antibodies,²⁹ (iii) neutrophil agglutinins,³⁰ (iv) complement fixing antiplatelet antibodies,³¹ (v) platelet agglutinins.³²

entirely normal.

The immunological changes during this patient's illness and their relation to the cellular changes in the blood are of particular interest and are given in the Table, with the technical methods used.

At necropsy the reticuloendothelial system showed marked infiltration by AIL at all the sites examined—cervical, mesenteric, para-aortic, splenic and mediastinal lymph nodes, spleen, bone marrow, and the portal tracts of the liver. The degree of infiltration was considerably less than that seen in the original lymph node biopsy specimen, and there were focal areas of cellular depletion. The upper dermis at the site of the rash showed a similar infiltrate.

Both lungs were firm and heavy (left 1020 g, right 960 g), deep pink on section, and the main bronchi contained a small amount of mucoid material. Microscopically there was severe generalised oedema of both lungs affecting all lobes. A number of small bronchi were obstructed by mucus and although there was some degree of bronchopneumonia in terms of alveolar polymorphic inflammatory exudate this was limited to peribronchial areas of a few airways. A lymphoid infiltrate, which included many plasmacytoid cells, was seen particularly in relation to small bronchi and venules, with very little extension into alveolar walls and alveoli. The walls of some venules were affected by the infiltrate and fibrinous thrombi were often seen. These showed variable degrees of organisation and were themselves sometimes infiltrated by pleomorphic lymphoid cells. Culture of lung tissue showed a scanty growth of *Escherichia coli* only, which was regarded as a post-mortem contaminant; the patient had been treated with antibiotics so any pathogen may not have grown. Viral culture was negative and there was no histological evidence of fungal infection.

A few petechiae were present on the small bowel mucosa and on the subcapular surfaces of the kidneys. Stress changes were seen in the adrenal gland with a few focal medullary lymphoid infiltrates. The heart, thyroid, pituitary, pancreas, testes, and brain were normal and also the remainder of the alimentary and renal tracts.

Discussion

Respiratory death in AIL is usually the result of either pulmonary immunoblastic infiltration (PII)^{2 23} or opportunistic pulmonary infection,^{2 8} or a combination of the two.^{21 22} In the case reported here, however, infection was not found but rather some pulmonary vascular abnormalities that have not previously been described and which may have been secondary, in part at least, to certain immunological abnormalities also peculiar to this patient. The

immediate cause of death in this case of AIL was pulmonary oedema, associated with extensive PII predominantly of the peribronchial tissue, but to a lesser extent of the walls of many pulmonary venules and the fibrinous thrombi occluding some of them.

Others have observed PII in this disease, some having relied upon clinical and radiological findings alone,^{13 19} others having obtained definite histological confirmation of immunoblastic infiltration: focal,² diffuse perivascular,⁵ diffuse interstitial,^{8 20 22 23} diffuse interstitial infiltration associated with infiltration and destruction of the walls of small bronchi.²¹ This report, however, gives the first description of pulmonary venule infiltration and occlusion in AIL. It is not possible for the PII in this case to have arisen by the haematogenous spread of immunoblasts, since the pulmonary lesions were well established before IBL appeared (Figs 1 and 3). This agrees with other descriptions of AIL associated with either IBL^{2 7 8 19} or PII,^{2 5 8 13 19–23} and none of these studies shows an obvious association between IBL and PII in AIL. The lymphocytosis observed at presentation, however, should not be ignored since it is possible that lymphocytes of normal morphology by light microscopy, and perhaps even at normal blood concentrations, are responsible for the haematogenous spread of the disease with further differentiation into immunoblasts occurring at the metastatic site. The future assessment of this possibility will require at least the sequential monitoring of the concentrations of the various lymphocyte subpopulations in the blood, throughout the initial, intermediate, and terminal phases of this disease, particularly since associated abnormalities of the B-cell system^{3 4 6 9 10 11} and the T-cell system^{6 9 12–15 20} have been described. The B-cell and T-cell values obtained in this patient on day 30, were not particularly abnormal, but this further emphasises the need for sequential studies. Nevertheless, it is of particular interest that the patient's respiratory symptoms deteriorated coincidentally with the appearance of IBL and it suggests that the latter may have resulted in the haematogenous dissemination of immunoblasts to lungs already infiltrated by AIL thereby aggravating the severity of the local pathology and likewise the symptomatology. It is conceivable that this mechanism was primarily responsible for the vascular infiltration already discussed with fibrin deposition and thrombus infiltration occurring secondarily, although other possible immunoblast migration routes are indicated in Fig. 5.

As in many cases of the disease red cell auto-antibodies were present and were responsible for severe haemolytic anaemia (Figs 2 and 3, Table). Many additional autoantibodies that have also been

described in this disease (Table 6 of Cullen *et al.*)⁸ were tested for in this case but yielded negative results (Table). Additional studies, however, showed the presence of multiple antihaemocytic antibodies in the serum directed against lymphocytes, platelets, and neutrophils. This is the first description of such a finding, apart from an isolated report of "an apparent lympholytic factor" in the serum of one other case.³ It was not possible to study the specific immunoglobulin classes carrying these separate antihaemocytic activities, nor was it possible to study them by elution from the patients own white cells and platelets, so it is only by inference that they are referred to as autoantibodies.

The neutrophil and platelet antibodies were detected by agglutination without the addition of complement and such agglutination occurring *in vivo* would lead to trapping of some of the neutrophil and platelet aggregates within the pulmonary vasculature, since the lungs form part of the reticuloendothelial system. This could reduce vessel/airway gaseous exchange in the lungs and also predispose to local pulmonary intravascular coagulation causing further reduction in gaseous exchange. It is postulated therefore, that the presence of multiple circulating antihaemocytic antibodies might aggravate defects in pulmonary function in AIL by this mechanism, which is completely separate to that of PII. The impairment of gaseous exchange in the latter would be a direct effect of immunoblastic infiltration of the pulmonary interstitium or walls of small pulmonary vessels, or both. Both fibrin occlusion of pulmonary venules and PII would be expected to predispose to pulmonary oedema due to a combination of vascular occlusion and inflammation. Any inflammatory process due to PII will itself predispose to local intravascular coagulation, and any agglutinating antibodies to neutrophils or platelets, or both, whether released from immunoblasts in the vessel wall or in the interstitium (multiple antihaemocytic antibodies in the tissues) could cross the vessel walls and direct their effects intravascularly, thereby enhancing any local accumulation of neutrophils, platelets, and fibrin. These postulated pathophysiological mechanisms are summarised in Fig. 5 and are in complete agreement with the necropsy findings.

The progressive respiratory dysfunction in this patient was, however, accelerated by chemotherapy, which was itself accompanied by very large increases in the serum concentrations of IgG and IgA (approximately 50% absolute increase; approximately 2000% increase in the rate of increase) relative to the values before chemotherapy (Table). It may be postulated, therefore, that rapid chemotherapeutic destruction of immunoblasts caused the release of preformed intracellular immunoglobulins into the serum,

thereby accounting for this rapid rise in immunoglobulin concentrations. A parallel increase in antihaemocytic antibodies in both the serum and tissues could also be expected if one assumes that these antibodies are produced by the pathological immunoblast population. Any inflammatory effects of PII would be similarly aggravated during such a period of immunoblast destruction. The net result of chemotherapy would therefore be the amplification of the pathophysiological mechanisms already postulated above and in Fig. 5, leading to a rapid deterioration in pulmonary function.

The smaller increase in IgM after chemotherapy (approximately 10% absolute increase; approximately 300% increase in the rate of increase) relative to the IgG and IgA changes (Table) may be explained by transfusion if it is assumed that much of the serum IgM was composed of the anti-I red cell autoantibody known to be of high titre in this case (Table). Any red cell transfusion would therefore tend to obscure a rising serum IgM concentration, as a result of IgM adsorption on to the transfused red cells.

The rate of fall of the peripheral blood lymphocyte concentration slowed progressively from day 22 until death, despite the presence of complement-dependent lymphocytotoxic antibodies in the serum, and despite chemotherapy. The serum complement concentrations, however, had reached very low levels by day 30 (Table), and it may be argued that any modification of peripheral blood lymphocyte concentrations by complement-dependent lymphocytotoxic antibodies would be minimised by the low availability of complement. Similarly, any rise in lymphocytotoxic antibodies after chemotherapy, as postulated for the antihaemocytic antibodies above, would exert a minimal cytotoxic effect. Hypocomplementaemia has been described in other cases of AIL,^{5 24-26} but the findings in this case suggest that lymphocytotoxic antibodies may directly reduce the blood lymphocyte concentration and consume complement in the process so that the resultant low complement concentrations would abrogate further lymphocytotoxic effects. This emphasises the need for serial monitoring in such cases, not only of the total peripheral blood lymphocyte concentrations, but also of the concentrations of different lymphocyte subpopulations, complement levels, and the presence or absence of immune complexes. Unfortunately it was not possible to screen for the latter in this case.

The only haemopoietic cell line that provides evidence for chemotherapy exerting very little effect on normal haemopoiesis in this patient during the short post-chemotherapy period (days 30, 31, 32) is that of erythropoiesis. The two linear but inversely related trends of haemoglobin concentration against

time and reticulocyte percentage against time—as seen between days 15 and 29 in Fig. 2—indicate the pre-chemotherapy level of erythropoiesis in terms of

the reticulocyte responses at various haemoglobin concentrations. These were used to predict the reticulocyte counts for the post-chemotherapy

Fig. 5 Pathophysiological mechanisms that may result in various pulmonary defects in patients with angioimmunoblastic lymphadenopathy, pulmonary immunoblastic infiltration and multiple antihemocytic antibodies in the serum, and the possible amplification of some of these by chemotherapy.

haemoglobin concentrations of days 30, 31, and 32 and gave values of 3%, 3.5%, and 7.5% respectively. The mean predicted reticulocyte count after chemotherapy of 4.7% is slightly less than the mean observed reticulocyte count of 6% (incorporating the separate counts of 7%, 6%, and 5% for days 30, 31, and 32 respectively) and suggests that the erythropoietic levels before and after chemotherapy are very similar. This implies that the threefold increase in the rate of fall in haemoglobin concentration after chemotherapy (Table) is due to a dramatic increase in the rate of haemolysis rather than to a marked decrease in the rate of erythropoiesis, and would therefore support the hypothesis that the chemotherapy primarily destroys immunoblasts and releases preformed antibodies with specific anti-haemocyte activity.

Unfortunately these hypotheses can only be tentative, particularly since it is impossible to be certain that haemopoiesis was relatively unaffected by the cyclophosphamide. Although Cullen *et al.*⁸ advise against the use of corticosteroids alone in the treatment of AIL, it may nevertheless be the best initial treatment when the disease is associated with PII, IBL, and multiple circulating antihemocytic antibodies, since patients could be monitored throughout, in the definite absence of any myelosuppression induced by chemotherapy. Frequent serial immunological, haematological, and pulmonary studies, if performed before and during such treatment, would more readily allow the hypotheses above to be verified or refuted. This would give a much clearer indication of the special dangers of managing patients with AIL who have the associated problems of PII, IBL, and multiple circulating antihemocytic antibodies.

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