

ORIGINAL ARTICLE

Acute lymphoblastic leukaemia of the L3 subtype in adults in the Northern health region of England 1983–99

M R Velangi, M M Reid, N Bown, G H Jackson, G P Summerfield, S J Proctor, P R A Taylor

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See end of article for authors' affiliations

Correspondence to: Dr M Velangi, Department of Haematology, Royal Victoria Infirmary, Newcastle Upon Tyne NE1 4LP, UK; M.R.Velangi@ncl.ac.uk

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Aim: Acute lymphoblastic leukaemia (ALL) with an L3 morphological FAB type is regarded by some as being synonymous with B cell ALL or ALL with a Burkitt-type chromosomal translocation— $t(8;14)$, $t(2;8)$, $t(8;22)$. This paper describes a series from a population based study of 24 patients with L3 ALL presenting over 17 years.

Methods: Clinical data were collected prospectively from all adult patients presenting with acute leukaemia in the Northern region since 1982. Data from all patients diagnosed with FAB type L3 ALL were analysed.

Results: Overall, L3 ALL accounts for 8.6% of all adult ALL and it is more common in the elderly than has hitherto been recognised. In addition to classic Burkitt-type translocations (11 of 24 cases), the $t(14;18)$ translocation, which is characteristically found in lower grade lymphomas such as follicular lymphoma, is frequently present (five of 24 cases).

Conclusion: The presence of L3 ALL is often associated with non-Burkitt-type translocations and the presence of a $t(14;18)$ translocation may indicate that in some cases a clinically non-apparent lymphoproliferative disorder, such as a low grade follicular lymphoma, has transformed to a more aggressive form and, thus, presents as a de novo acute leukaemia.

Chromosomal translocations involving several oncogenes play an important role in B cell neoplasia. L3 acute lymphoblastic leukaemia (ALL) is a morphologically distinct subgroup, which constitutes approximately 1–2% of all cases of ALL,^{1,2} occurs predominantly in children, and has (in children at least) cytogenetic abnormalities usually identical to those found in Burkitt's lymphoma. These are the $t(8;14)(q24;q32)$, $t(2;8)(p12;q24)$ and $t(8;22)(q24;q11)$ translocations,³ in which there is a breakpoint within the immunoglobulin heavy chain (IgH) locus on chromosome 14 or the light chain loci on chromosome 2 (κ) or 22 (λ). c-MYC (located at 8q24)⁴ is relocated to chromosome 14 in $t(8;14)$, but remains on the derivative chromosome 8 in the variant translocations. These changes result in overexpression of c-MYC.⁵ This classic triad of morphology, immunophenotype, and cytogenetic abnormalities has become so closely associated with Burkitt's lymphoma/leukaemia that many are tempted to use morphology or immunophenotype alone or in combination as surrogates for the complete triad.

"L3 acute lymphoblastic leukaemia occurs predominantly in children, and has (in children at least) cytogenetic abnormalities usually identical to those found in Burkitt's lymphoma"

Because morphological diagnosis is the starting point in the complete diagnosis of leukaemia, and because the appearance of L3 blasts is so characteristic, we decided to examine all unselected cases of this morphologically defined entity that arose in adults in our health region to establish a realistic picture of the spectrum and diversity of the associated cytogenetic abnormalities.

METHODS

The Northern Region Haematology Group has prospectively registered all patients with adult ALL in our geographical

region since October 1982. This process is an intrinsic part of population adjusted clinical epidemiology,⁶ a methodology in which aspects of epidemiological study are applied to the clinical arena to overcome the common problems of inadvertent selection of patients when accruing groups of patients for studies. All adults with ALL in the Northern health region of England, excluding Barrow in Furness, have been registered. The population (approximately 3.08 million, predominantly white) has remained largely constant. Details of clinical presentation, treatment, and outcome have been kept prospectively. Between 1983 and 1999, 277 cases of adult ALL were diagnosed. The criteria used to include patients in our study were: (1) bone marrow replacement by > 30% L3 blasts, (2) age > 15 years, and (3) no pre-existing lymphomatous stage. We avoided using the term Burkitt-type ALL in this selection process because some controversy surrounds its definition and the term brings into question the biology of the leukaemia.

Morphological diagnoses were made from Romanowsky stained films of bone marrow. A diagnosis of L3 morphology was made if the following definition was met—moderate large blasts, with finely stippled nuclear chromatin often with one or more nucleoli, deeply basophilic cytoplasm, and prominent vacuolation—as described by the French-American-British Cooperative Group.² All diagnoses were centrally reviewed.

Immunophenotypic analysis was performed by standard immunofluorescent techniques, using fluorescent microscopy up to 1989 and flow cytometry since then, supplemented on occasion by immunocytochemical techniques. A broad panel was used, including antibodies against terminal deoxynucleotidyl transferase, surface membrane Ig (SIg), the common ALL antigen (CD10), the B cell lineage associated antigens

Abbreviations: ALL, acute lymphoblastic leukaemia; B-ALL, B cell ALL; CI, confidence interval; SIg, surface immunoglobulin; T-ALL, T cell ALL

Table 1 Patient details including immunophenotypic and cytogenetic analysis

Patient	Sex/Age	Immunophenotype	CR	Survival (weeks)	Cytogenetic analysis
1	F/66	B+, Sig+	+	Alive	46,XX,t(8;14)(q24;q32)
2	M/40	B+, Sig+	+	5 days	46,XY,t(8;14)(q24;q32)
3	M/79	B+, Sig+	-	1	46,XY,t(8;14)(q24;q32)
4	F/46	B+, Sig+	-	12	46,XX,t(8;14)(q24;q32)/46,idem,dup(1)(q22.1q32)
5	F/58	B+, Sig+	+	Alive	46,XX,t(8;14)(q24;q32)/46,idem,der(4)t(1;4)(q17;q37),der(22)t(7;22)(q11;p17)
6	M/55	ND	-	4 days	46,XY,t(8;14)(q24;q32)/46,idem,dup(1)(q22;q32)
7	F/36	B+, Sig-	-	13	47,XX,t(8;14)(q24;q32),add(12)(p13)
8	F/62	B+, Sig-	-	15	46,XX,del(6)(q7),t(8;14)(q24;q32)/45,idem,-19
9	F/83	ND	-	1	55-56,XX,+X,+X,+add(1)(p10),del(1)(q10),+7,t(8;14)(q24;q32),+11,del(16)(q7),+21
10	M/32	B+, Sig+	-	1	46,XY,dup(1)(q25),t(3;22)(q29;q11),t(8;14)(q24;q32)/idem,add(14)(p11)
11	F/62	B+	-	4 days	47,XX,t(2;8)(p12;q24),+7,t(14;18)(q32;q21)
12	M/41	B+, Sig+	+	41	47,XX,add(1)(p36),add(3)(q27;q7),+7,t(14;18)(q32;q22),t(15;22)(q26;q21),der(19)t(1;19)(q23;p13)
13	F/72	B+, Sig+	+	1	47,XX,t(14;18)(q32;q21),+7
14	M/42	B+, Sig+	+	40	50,XY,t(14;18)(q32;q21),-der(X)t(X;1)(p11;q27),add(4)(p11),+7,add(7)(q22),ins(8;7)(q22-47),add(11)(q23),+12,+20
15	M/69	B+, Sig+	+	3	47,XY,+12,t(14;18)(q32;q22)
16	M/76	ND	+	16	46,XY,dup(1)(q21;q32),add(14)(q32)/48,idem,+7,+12/47,idem,+12,der(13)t(7;13)(q12;q32)
17	F/66	B+, Sig+	+	5 days	45,XX,add(1)(q27),der(13)t(3;22)(q32;q117),add(14)(q32),der(19)t(1;19)(q13;p13.3),-22
18	F/89	B+	-	2 days	48,X,-X,-1,-3,del(6)(q1.75),+add(7)(p7),+18(p21),+9,+11,-13,-14,+15,-16,+add(18)(q22),+19,-20,-21,+4
19	M/46	ND	+	50	46,XY,del(9)(p21)/46,idem,+1,der(1;6)(q10;p10)/46,idem,+der(17)t(1)(q10)
20	M/20	B+	+	20	46,XY
21	M/53	B+	+	40	Failed analysis
22	M/53	ND	+	11	ND
23	F/39	B+, Sig+	+	51	ND
24	F/77	B+, Sig+	-	4 days	ND

B, B lineage markers; CR, complete remission; ND, not done; Sig, surface immunoglobulin. Cytogenetic abnormalities referred to in the text are highlighted in bold.

CD19 and CD20, the T cell lineage associated antigens CD2, CD3, and CD7, the myeloid lineage associated antigens CD13, CD14, and CD33, and the platelet associated antigen CD61. Because of the time period over which the diagnoses were made and the variability in size of samples available for testing, not all patients were tested for all antigens. Cytogenetic studies were carried out by the Northern Region Genetics Service. Standard G banding techniques were used to stain metaphase preparations obtained from unstimulated cultures of bone marrow cells. Chromosome analysis was considered to have failed if fewer than 10 metaphases showing a normal karyotype could be fully analysed. A complete analysis of a "normal" karyotype comprised the full analysis of 20 cells. A clonal abnormality was defined as two or more cells showing identical chromosome gains or structural rearrangements, or three or more cells showing identical chromosome losses. Chromosomal abnormalities are described according to the international system for human cytogenetic nomenclature (1995).⁷

RESULTS

A diagnosis of L3 ALL was made in 24 of the 277 adult patients with ALL. The study population comprised 12 men and 12 women. Their median ages were 53 years and 64 years, respectively (ranges, 20–79 and 36–89, respectively). Five of 24 were 15–40 years, eight of 24 were 41–60 years, and 11 of 24 were > 60 years.

Laboratory features at presentation (full details are shown in table 1)

All patients had > 30% blasts in the bone marrow and abnormal haematological parameters at presentation. The median white blood cell count was 17.4×10^9 /litre (range, 1.8–65) and in nine patients it was greater than 20×10^9 /litre. Circulating blasts were seen in most patients. Anaemia (haemoglobin (Hb) < 120 g/litre) was present in 16 patients but the Hb was lower than 80 g/litre in only three patients. Thrombocytopenia (platelet count < 150×10^9 /litre) was present in 18 cases and the median platelet count was 59×10^9 litre (range, 7–377). Figure 1 shows examples of the L3 cytological features in two of the patients with the t(14;18) translocation (patients 13 and 14).

Immunophenotyping was performed in 19 patients. Typing for SIg was done in 15 patients. In the four other patients a B lineage phenotype was confirmed but no typing for SIg was done. SIg was present on the leukaemic blasts of 13 patients.

Cytogenetics (full details are shown in table 1)

Cytogenetic analysis was attempted in 21 patients. In one patient, culture of the bone marrow failed to produce metaphases of sufficient quality for analysis (patient 10) and in another patient no abnormality was found in all 48 metaphases examined (patient 9). The classic Burkitt translocation t(8;14)(q24;q32) was found in 10 patients and was the only abnormality in three. The t(14;18)(q32;q21) translocation was found in five patients but was never the only abnormality. In one patient (patient 11) t(14;18) was found in combination with the variant Burkitt translocation t(2;8)(p12;q24) and, in another (patient 12), in association with the t(1;19)(q23;p13) translocation,⁸ which is most often found in pre-B-ALL. In two further patients (patients 1 and 17) an abnormality

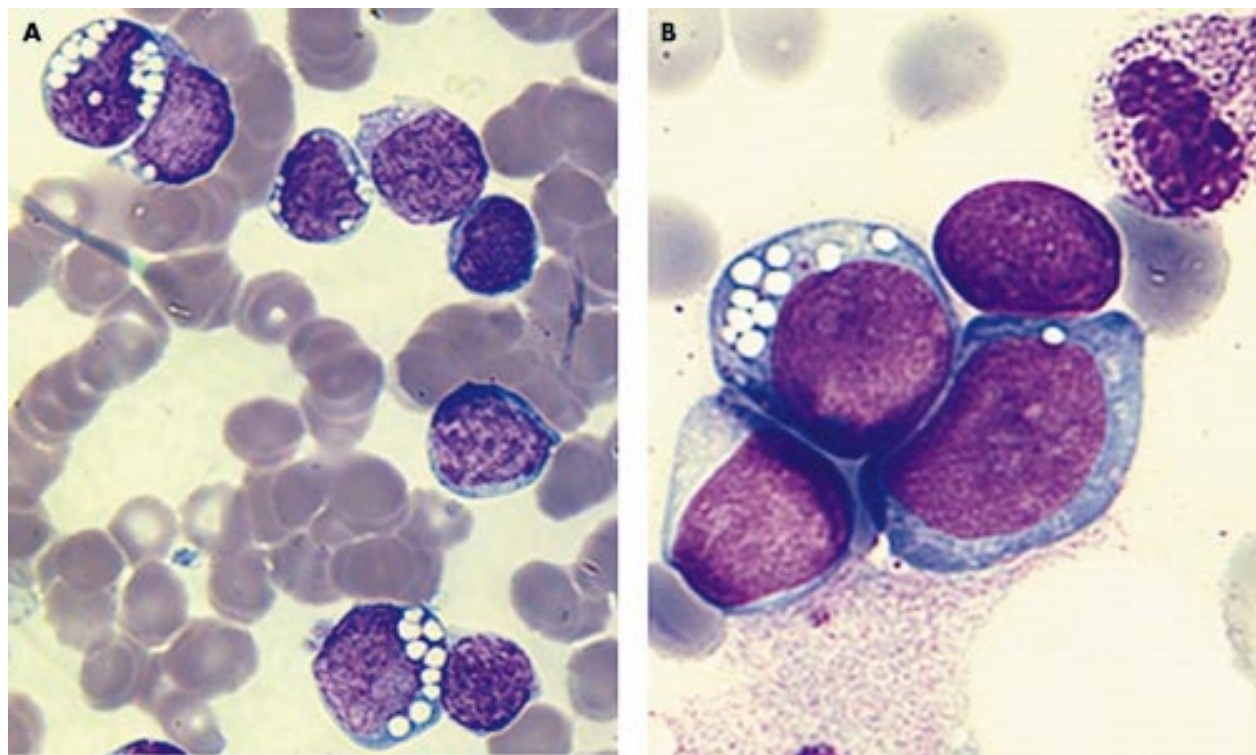


Figure 1 Bone marrow aspirate smears from two patients that demonstrate the characteristic cytological features of L3 acute lymphoblastic leukaemia; (A) low power and (B) higher power.

involving 14q32 was found but this could not be fully characterised. In the two remaining patients a complex karyotype was found. The t(8;14) translocation was found in most age groups and was not restricted to younger patients. The t(14;18) translocation was not found in patients aged < 40 years. Because the number of young patients is small this should not be overinterpreted.

Other abnormalities detected were often part of a complex karyotype. The most common were trisomy 7 (six patients) and structural abnormalities of chromosome 1 (seven patients). Cytogenetic findings in the 13 patients who were shown to be SIg positive reflected those of our entire L3 group—six patients had a t(8;14) translocation, four had a t(14;18) translocation, one had an abnormality involving 14q32, and in the remaining two patients no analysis was performed.

Non-L3 cases

We excluded from our study two patients who expressed sIg but had L1 morphology. Cytogenetic analyses were unfortunately not done on these patients.

One patient with the t(14;18) translocation had L1 morphology and was not included in our study. No patients were found where t(8;14) was associated with morphology other than L3.

Treatment

Five patients received palliative treatment only. The remainder received a variety of regimens: modified MACHO,⁹ NEALL III,¹⁰ CHOP,¹¹ IVE,¹² and others incorporating prednisolone, vincristine, and cyclophosphamide. All but two have died. All died from resistant or relapsed disease. The two survivors (52 and 69 months follow up) received NEALL III and CHOP, respectively, followed in both by a combination of IVE, cranial irradiation, intrathecal methotrexate, and maintenance chemotherapy. Both survivors had t(8;14) at presentation.

DISCUSSION

Acute lymphoblastic leukaemia with FAB L3 morphology is a morphological diagnosis yet there is a tendency to use this term almost interchangeably with the terms “Burkitt’s” or “B” ALL.¹³ For our study, we decided to focus on L3 cases because the morphological diagnosis seems a logical starting point and morphological material and data were available from all patients. We chose not to follow previous criteria¹⁴ in which the definition of Burkitt cell leukaemia requires: (1) initial presentation with bone marrow failure as a result of bone marrow disease, without the presence of massive tumour; (2) bone marrow infiltration with > 50% L3 blasts; and (3) proof of mature B cell features by demonstrating the presence of SIg. Such stringent criteria artificially restrict the scope of our study (for example, by excluding some cases with a bone marrow blast percentage of 31–49%) and also guarantee that some cases of mature B cell ALL (B-ALL) and others with L3 morphology will be excluded. The main purpose, and the effect of our study criteria, is to provide an opportunity to obtain a realistic picture of the incidence, demographic features, cytogenetic, and immunophenotypic diversity of all L3 ALL in adults.

The chief findings are: (1) overall, L3 ALL accounts for 8.6% of all adult ALL (2) L3 ALL is more common in the elderly than has hitherto been recognised; and (3) in addition to classic, Burkitt-type translocations (11 of 24 cases), the t(14;18) translocation, which is characteristically found in lower grade lymphomas such as follicular lymphoma, is frequently present (five of 24 cases). The L3 morphology in our patients with the t(14;18) translocation clearly contrasts with the classic morphology of follicular lymphoma in the leukaemic phase.¹⁵ A previous study reported five L3 cases out of 90 reviewed cases of mixed adult and childhood ALL (5.6%; 95% confidence interval (CI), 1.8% to 12.5%).¹⁶ We found 24 of 277 (8.6% CI, 6% to 13%). Without the t(14;18) cases (n = 5) we would have had 19 L3 ALLs (7%; 95% CI, 4% to 11%), a proportion very similar to that reported by other groups. This

series provides the first unselected demographic data which show that, whether one restricts the focus to SIg positive (that is, mature B-ALL) cases or uses the wider, morphologically based criteria, L3 morphology is strongly associated with both of these disease associated cytogenetic abnormalities.

“The cytogenetic abnormalities found in our patients include a variety of translocations that are not considered to be classic Burkitt translocations”

Although L3 morphology has been reported in association with common ALL¹⁷ and pre-B-ALL^{18,19} this is probably a rare event. Similarly unusual are reports of the pre-B-ALL immunophenotype associated with t(8;14)²⁰ or 14q+ abnormality²¹ and the mature B cell immunophenotype with L1 morphology.²² In the 25% of cases of ALL with a mature B cell immunophenotype,²³ L1 morphology again accounted for a small total number of patients. In addition, L3 morphology has been reported in non-B cell leukaemias—in M6 acute myeloid leukaemia²⁴ and T-ALL.²⁵ We did not find examples of all these phenomena in our study. Only two cases of SIg positive leukaemia without L3 morphology were detected among our 277 cases of ALL, accounting for < 10% of all B-ALL cases. The cytogenetic abnormalities found in our patients include a variety of translocations that are not considered to be classic Burkitt translocations. Although 11 of our series of 24 patients had Burkitt-type translocations, specifically t(8;14) in 10 patients and t(2;8) in one, the only t(2;8) translocation was associated with a t(14;18). This combination of abnormalities has previously been reported in a patient with chronic lymphocytic leukaemia,²⁶ but is not known in acute leukaemia or, as far as we know, in non-leukaemic non-Hodgkin's lymphoma. The t(14;18) translocation, which is most often associated with cases of follicular lymphoma, was found in five patients. This was never the only abnormality and in one patient was associated with the t(1;19) translocation. No molecular analysis was done to investigate whether this was the classic t(1;19) translocation, which is more usually associated with pre-B-ALL.²⁷ A t(1;19) translocation has been described previously in ALL with a mature B cell phenotype, in association with t(14;18)^{22,23} or alone,⁸ and in five patients with L3 ALL.²⁸ One further patient with the t(14;18) translocation was described in our study, but this patient was excluded because the morphology was L1, not L3, and no immunophenotype was available. A normal karyotype was found in one patient in whom 48 metaphases had been examined. This has been reported in three other patients and despite Southern blot analysis in one of these patients no c-MYC rearrangement could be found.^{14,29} Other chromosomal abnormalities were found in our patients. Trisomy 7, observed in six patients, has been associated with a diffuse growth pattern in lymphoproliferative disorders.³⁰ Duplication or other gains of chromosome arm 1q were seen in nine patients and are frequently seen with t(8;14).³¹

The finding of t(14;18) in de novo ALL has been reported previously.^{8,17,18,22,28,32-40} The t(14;18) translocation involves the bcl-2 and IgH chain genes on the long arms of chromosomes 18 and 14, respectively. It is thought to arise as an error during V-D-J recombination in the precursor B cell.⁴¹ Bcl-2 inhibits apoptosis but is not in itself tumorigenic. Bcl-2 and c-MYC act together to produce tumours.⁴² The association of t(14;18) and t(8;14) or a c-MYC rearrangement³³ in ALL has been reported.^{17,20,32,35,36,39,42,43} The t(14;18) translocation is thought to be a primary event that leads to the clonal expansion of a B cell population with increased survival within which a further chromosomal rearrangement, such as activation of c-MYC, occurs as a subsequent event, precipitating the leukaemic illness. This could occur soon after the activation of bcl-2, leading to a clinical picture of de novo ALL, or after a longer interval, as demonstrated clinically by leukaemic transformation of

Take home messages

- L3 acute lymphoblastic leukaemia (ALL) accounts for 8.6% of all adult ALL
- L3 ALL is more common in the elderly than was previously thought
- The classic, Burkitt-type translocations were found in 11 of 24 patients
- In addition, the t(14;18) translocation, which is characteristically found in lower grade lymphomas such as follicular lymphoma, was frequently present (five of 24 patients)
- Classic cytogenetic analysis is a mandatory investigation in L3 ALL for all age groups

an antecedent lymphoma. The absence of Burkitt-type translocations in most of our patients with the t(14;18) translocation suggests that mechanisms other than the activation of c-MYC may be involved in the occurrence of this aggressive leukaemia. The presence of t(14;18) in five of our patients suggests that a subclinical low grade lymphoproliferative disorder, such as a follicular lymphoma, may undergo an aggressive transformation and present as an apparent de novo mature B-ALL. It is well recognised that low grade lymphoproliferative disorders can transform to more aggressive disease and this is often associated with the development of further genetic abnormalities.^{44,45} Transformation of follicular lymphoma to both L3 ALL¹⁷ and pre-B-ALL^{20,42} are documented. In these cases, the presence of the t(14;18) and t(8;14) translocations or 8q+/14q+ abnormalities is noted. In addition, t(14;18) has been found in 25% of patients with high grade non-Hodgkin's lymphoma.⁴⁶ However, because we did not perform c-MYC or bcl-2 studies on our cases, some of which date back nearly 20 years, our suggested model remains speculative and based on circumstantial evidence. It could be tested prospectively.

“Although we found no patients with t(14;18) under the age of 40 years, the numbers are too small for any important conclusions to be drawn from this fact”

Therefore the classic triad of L3 morphology, SIg positivity, and t(8;14) translocation (or its variants) is too restrictive to be useful in the diagnosis of adult ALL. Uncritical use of either morphology or immunophenotype alone, or even both together, as a surrogate for the recommended triad can be even more misleading. It seems likely that for most patients with either L3 morphology or a mature B cell phenotype, at least two biologically distinct malignant processes should be considered: one associated with t(8;14) or its variants as the primary abnormality; the other with t(14;18) as the primary abnormality. It is possible that these diseases may preferentially affect different age groups. Leukaemias with t(8;14) typically occur across the entire age spectrum. Although we found no patients with t(14;18) under the age of 40 years, the numbers are too small for any important conclusions to be drawn from this fact. The response of younger patients to treatment may also differ, but this study contains too many different regimens applied to too few patients to answer such questions; it may be no more than chance that the only two survivors both received consolidation treatment with IVE after their initial chemotherapy and that both had t(8;14). It is certain that we will make it harder to detect any putative differences in behaviour or response if we use morphology or immunophenotype alone, or in combination, without cytogenetic data, when making these diagnoses. In addition, our study emphasises the importance of classic cytogenetic analysis and underlines that it is a mandatory investigation in L3 ALL for all age groups.

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Authors' affiliations

M R Velangi, M M Reid, G H Jackson, G P Summerfield, S J Proctor,
P R A Taylor, Department of Haematology, Royal Victoria Infirmary,
 Newcastle Upon Tyne NE1 4LP, UK
N Bown, Regional Genetics Service, Royal Victoria Infirmary

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