Acute Lymphoblastic Leukaemia

Introduction

- Acute lymphoblastic leukaemia (ALL) is caused by accumulation of lymphoblasts in the bone marrow
- Most common malignancy of childhood
- Incidence is highest at 3-7 years with 75% cases occurring before age 6
- There's a secondary rise after age 40
- 85% are of B-cell lineage and have an equal sex incidence
- There's a male predominance for the 15% of T-cell ALL (T-ALL)

Pathogenesis – 1

- A proportion of cases of childhood ALL are initiated by genetic mutations that occur during development in utero
- Studies in identical twins have shown that both may be born with the same chromosomal abnormality, e.g. the t(12;21), ETV6-RUNX1 translocation
- This has presumably arisen spontaneously in a haemopoietic progenitor cell that has passed from one twin to the other as a result of shared placental circulation
- Environmental exposure during pregnancy may be important for this first event
- One twin may develop ALL early (e.g. at age 4) because of a second transforming event affecting the copy numbers of several genes, including those in B-cell development
- The other may remain well or develop ALL later, perhaps as a result of a different transforming event
- The ETV6-RUNX1 translocation is present in the blood of approximately 10% of newborn infants, but only 1 in 100 of these go on to develop ALL at a later date
- The mechanism of the ‘second genetic hit’ within the neoplastic cell is unclear, but an abnormal response of the immune system to infection is suggested by epidemiological studies
- In other cases, the disease seems to arise as a postnatal mutation in an early lymphoid progenitor cell

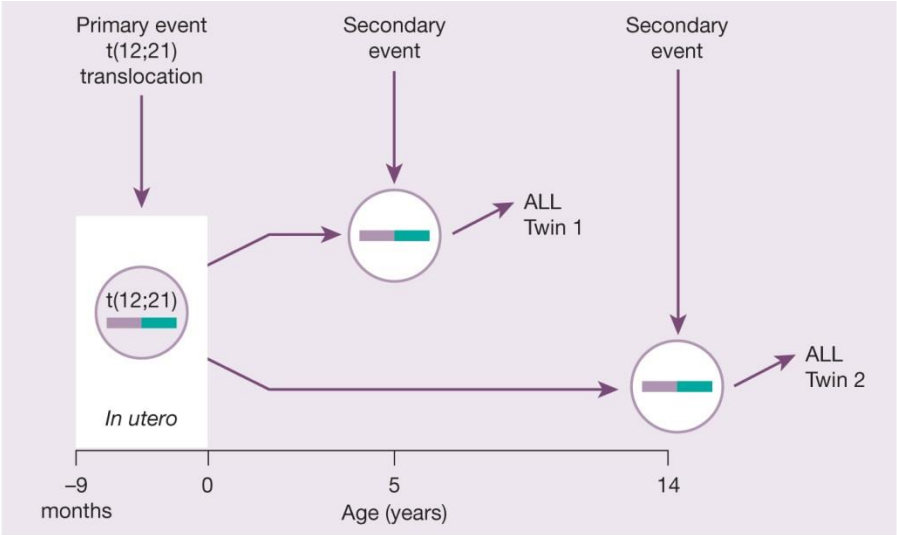


Figure 17.1 Prenatal origin of acute lymphoblastic leukaemia (ALL) in a pair of identical twins. Both tumours had an identical t(12;21) translocation. ALL was diagnosed in the first twin at age 5 years and in the second at age 14 years, indicating probable origin of the leukaemic clone *in utero* and dissemination to both twins via a shared placental blood supply. Because of the prolonged latency of the ALL, it is presumed that a secondary event is required to initiate the development of overt leukaemia. At the time of the diagnosis of ALL in twin 1 the t (12;21) translocation could be detected in the bone marrow of twin 2. It is likely that such a 'fetal origin' of childhood ALL occurs in a significant number of sporadic ALL cases. Source: Adapted from J.L. Wiemels *et al*. (1999) *Blood*, 94(3): 1057–62.

Hoffbrand's Essential Haematology, Eighth Edition. By A. Victor Hoffbrand and David P. Steensma.

Companion website: www.wileyessential.com/haematology

Pathogenesis – 2

- Children with a high level of social activity, notably those attending early nursery daycare, have a reduced incidence of ALL, whereas those living in more isolated communities and who have a reduced exposure to common infections in the first years of life have a higher risk
- Certain germline polymorphisms in a group of genes mainly involved in B-cell development (e.g. IKZF1) appear to predispose to ALL, since they are more frequent in children with B-cell ALL (B-ALL) than controls
- IKZF1 is also deleted in the leukaemic cells in 30% of high-risk B-ALL and 95% of ALL BCR-ABL1 positive cases
- In general, the genomic landscape in ALL is characterized by primary chromosomal abnormalities and a wide range of secondary deletions and mutations involving key pathways implicated in leukaemogenesis
- These are described in more detail below. For childhood ALL, an average of 11 somatically acquired structural variations are present

Classification

- Acute lymphoblastic leukaemia, B cell or T cell, is subclassified by the World Health Organization (WHO 2016) according to the underlying genetic defect
- Within B-ALL there are several specific genetic subtypes, such as those with the t(9;22) [BCR-ABL1] or t(12;21) [ETV6-RUNX1] translocations, rearrangements of the KMT2A(MLL) gene or alteration in chromosome number (aneuploidy)
- The subtype in both B-ALL and T-ALL is an important guide to the optimal treatment protocol and to prognosis

Table 17.1 Classification of acute lymphoblastic leukaemia (ALL)/lymphoblastic lymphoma according to the World Health Organization (modified from WHO 2016); see also Appendix.

B cell
B acute lymphoblastic leukaemia NOS
B-lymphoblastic leukaemia/lymphoma with recurrent genetic abnormalities
B-lymphoblastic leukaemia/lymphoma with t(9;22)(q34.1;q11.2); *BCR-ABL1*
B-lymphoblastic leukaemia/lymphoma with t(v;11q23.3); *KMT2A(MLL)* rearranged
B-lymphoblastic leukaemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
B-lymphoblastic leukaemia/lymphoma with hyperdiploidy (>50 chromosomes)
B-lymphoblastic leukaemia/lymphoma with hypodiploidy (<45 chromosomes)
B-lymphoblastic leukaemia/lymphoma with t(5;14)(q31.1;q32.3); *IL3-IGH*
B-lymphoblastic leukaemia/lymphoma with t(1;19)(q23;p13.3); *TCF3-PBX1*
Provisional entity: B-lymphoblastic leukaemia/lymphoma, *BCR-ABL1*-like
Provisional entity: B-lymphoblastic leukaemia/lymphoma with *IAMP21*
T cell
T-lymphoblastic leukaemia/lymphoma
Provisional entity: Early T-cell precursor lymphoblastic leukaemia

N.B. A minority of patients present with nodal or extranodal masses and <20% blasts in the marrow, and are called lymphoblastic lymphoma if the tumour cells resemble those of ALL. They are approached similarly to ALL.
NOS, not otherwise specified.

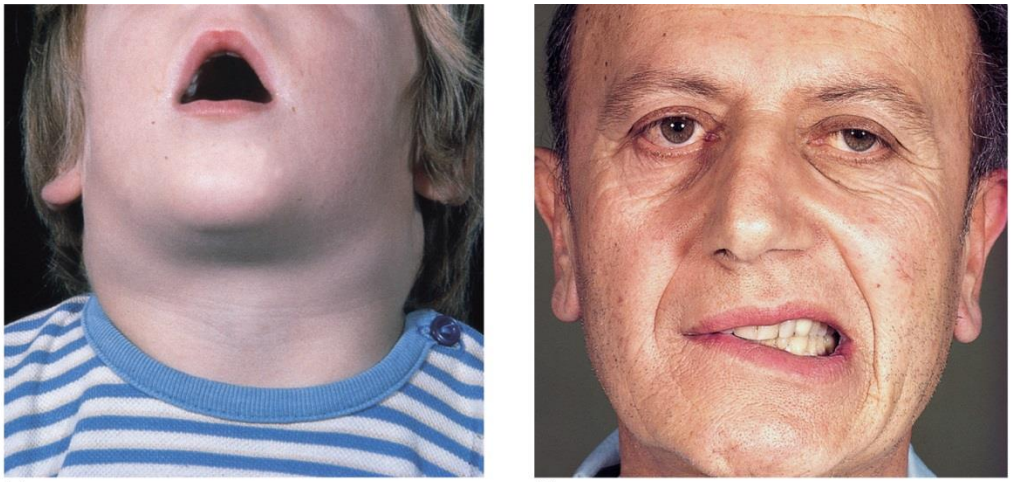
Clinical features

Bone marrow failure

- Anaemia (pallor, lethargy and dyspnoea)
- Neutropenia (fever, malaise, features of mouth, throat, skin, respiratory, perianal or other infections)
- Thrombocytopenia (spontaneous bruises, purpura, bleeding gums and menorrhagia)

Organ infiltration

- Tender bones
- Lymphadenopathy
- Moderate splenomegaly
- Hepatomegaly
- Meningeal syndrome (headache, nausea, vomiting, blurred vision & diplopia
- Testicular swelling
- Mediastinal compression in T-ALL
- If lymph node or solid extranodal masses predominate with <20% blasts in the marrow, the disease can be called lymphoblastic lymphoma, but is treated as ALL

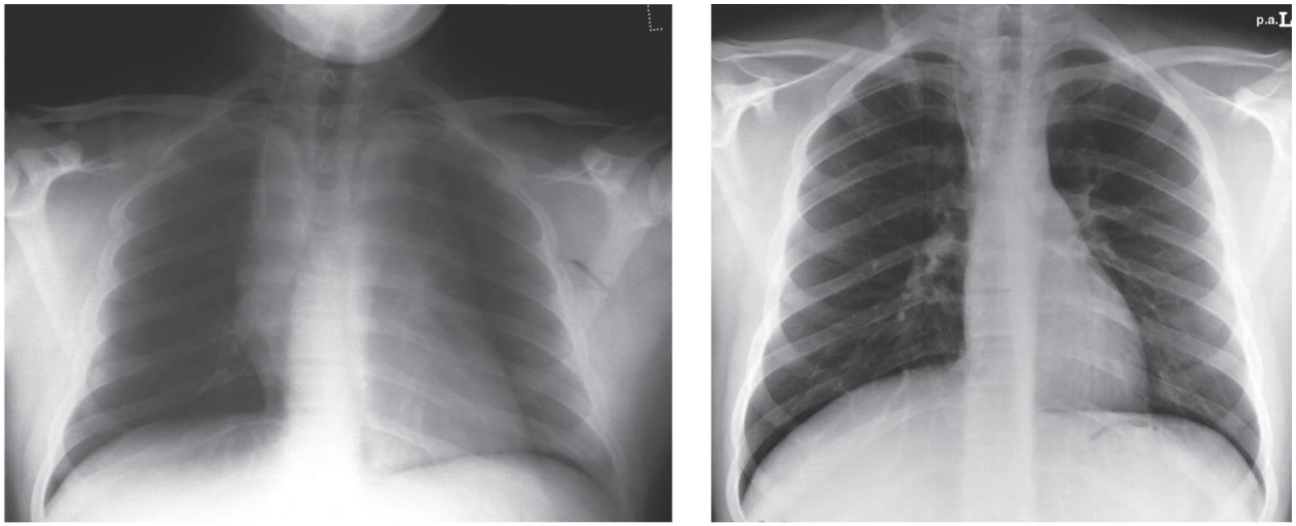


(a) (b)

Figure 17.2 Acute lymphoblastic leukaemia. **(a)** Marked cervical lymphadenopathy in a boy. **(b)** Facial asymmetry in a 59-year-old man due to a right lower motor neurone seventh nerve palsy resulting from meningeal leukaemic infiltration. Source: V.A. Hoffbrand *et al*. (2019) *Color Atlas of Clinical Hematology*, 5th edn. Reproduced with permission of John Wiley & Sons.

Hoffbrand's Essential Haematology, Eighth Edition. By A. Victor Hoffbrand and David P. Steensma.

Companion website: www.wileyessential.com/haematology



(a) (b)

Figure 17.3 Chest X-ray of a boy aged 16 years with acute lymphoblastic leukaemia (T-ALL). **(a)** There is a large mediastinal mass caused by thymic enlargement at presentation. **(b)** After 1 week of therapy with prednisolone, vincristine and daunorubicin, the mass has resolved.

Hoffbrand's Essential Haematology, Eighth Edition. By A. Victor Hoffbrand and David P. Steensma.

Companion website: www.wileyessential.com/haematology

Investigations

Haematological investigations reveal:

i) Normochromic normocytic anaemia
ii) Thrombocytopaenia
iii) Total white cell count decreased, normal or increased
iv) Blood film shows variable numbers of blast cells
v) Bone marrow is hypercellular with >20% leukaemic blasts
vi) Blasts are characterised by morphology, cytochemistry, immunological tests and cytogenetic analysis

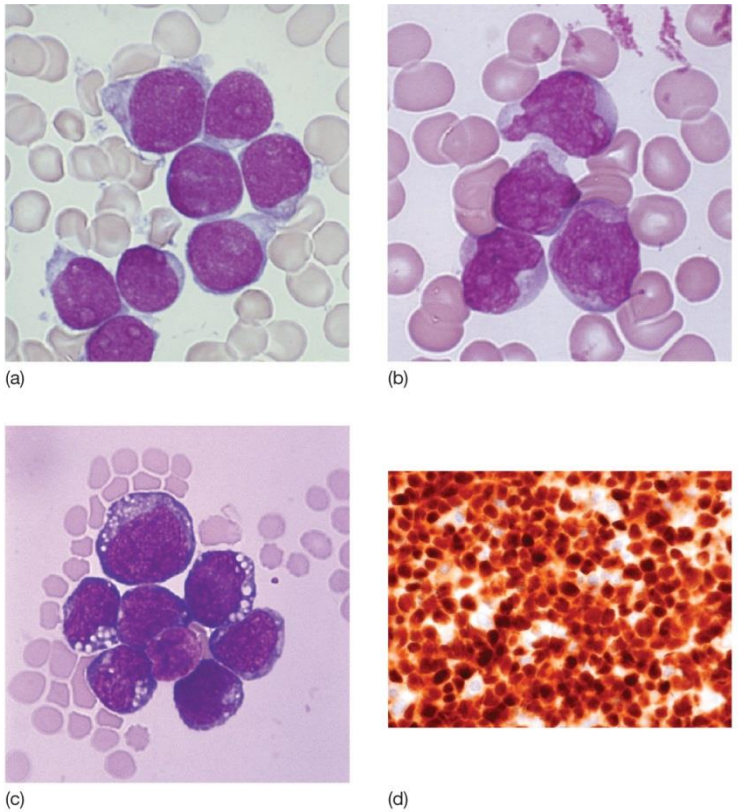


Figure 17.4 Morphology and immunophenotyping of acute lymphoblastic leukaemia. **(a)** Lymphoblasts show scanty cytoplasm without granules. **(b)** Lymphoblasts are large and heterogeneous with abundant cytoplasm. **(c)** Lymphoblasts are deeply basophilic with cytoplasmic vacuolation. **(d)** Acute lymphoblastic leukaemia: bone marrow cells staining positive for TdT by immunoperoxidase. Source: A.V. Hoffbrand *et al*. (2019) *Color Atlas of Clinical Hematology*, 5th edn. Reproduced with permission of John Wiley & Sons.

Hoffbrand's Essential Haematology, Eighth Edition. By A. Victor Hoffbrand and David P. Steensma.

Companion website: www.wileyessential.com/haematology

Table 17.2 Immunological markers for classification of acute lymphoblastic leukaemia (ALL; see also Fig. 11.14). Markers that distinguish the early T-cell precursor subtype are described in the text.

	ALL	
Marker	**B**	**T**
B lineage-associated		
CD19	+	–
cCD22	+	–
cCD79a	+	–
CD10	+ or –	–
cIg	+ (pre-B)	–
sIg	–	–
TdT	+	+
T lineage-associated		
CD7	–	+
cCD3	–	+
CD2	–	+
TdT	+	+
CD1a	–	+
CD4, CD8	–	+
Myeloid or stem cell lineage-associated		
CD34, CD117, HLADR, CD13, CD33, CD11b, or CD65	Negative except in multilineage	Negative except in early T-cell precursor subtype or multilineage

c, cytoplasmic; s, surface.

Table 17.3 Specialized tests for acute lymphoblastic leukaemia (ALL).

Immunological markers (flow cytometry)*	See Table 17.3; Fig. 11.14
*Immunoglobulin and TCR genes**	B-ALL: clonal rearrangement of immunoglobulin genes
	T-ALL: clonal rearrangement of TCR genes
Chromosomes and genetic analysis	See Table 17.1

*Tests needed at diagnosis for subsequent monitoring for minimal residual disease.
B-ALL, B-cell acute lymphoblastic leukaemia; T-ALL, T-cell acute lymphoblastic leukaemia; TCR, T-cell receptor.

Other investigations

- Lumbar puncture (may promote spread of tumour cells to the CNS)
- Biochemical tests (uric acid, LDH, Ca^{+})
- Liver & kidney function tests as baseline before treatment
- Radiography (may reveal lytic bone lesions and a mediastinal mass)

Cytogenetics and Molecular Genetics

- Cytogenetic analysis shows differing frequencies of abnormalities in infants, children and adults, which partly explains the different prognoses of these groups
- Cases are stratified according to the number of chromosomes in the neoplastic cell (ploidy) or by specific molecular abnormalities
- The two parameters define good- and poor-prognosis disease

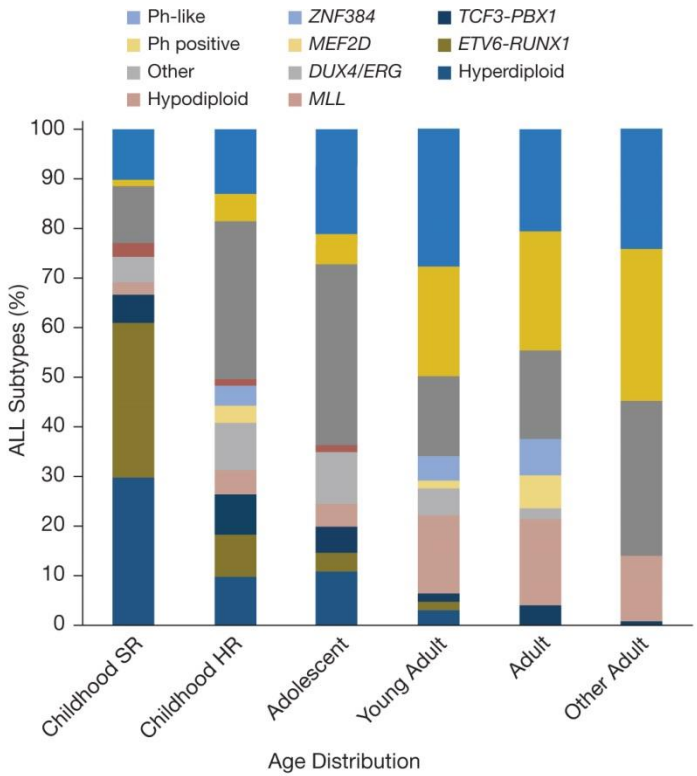


Figure 17.5 Age distribution of cytogenetically or molecularly defined acute lymphoblastic leukaemia (ALL) subtypes. The incidence of Ph-positive and Ph-like increases with ageing; ETV6-RUNX1 and hyperdiploid genotypes dominate in childhood standard-risk disease. *MLL(KMT2A)*, *ZN384*, *MEF2D* and *DUX4/ERG* indicate rearrangements of these genes. Source: I. Iacobucci, C.G. Mullighan (2017) *J. Clin. Oncol.* 35: 975–83. Reproduced with permission of the American Society of Clinical Oncology.

Hoffbrand's Essential Haematology, Eighth Edition. By A. Victor Hoffbrand and David P. Steensma.

Companion website: www.wileyessential.com/haematology

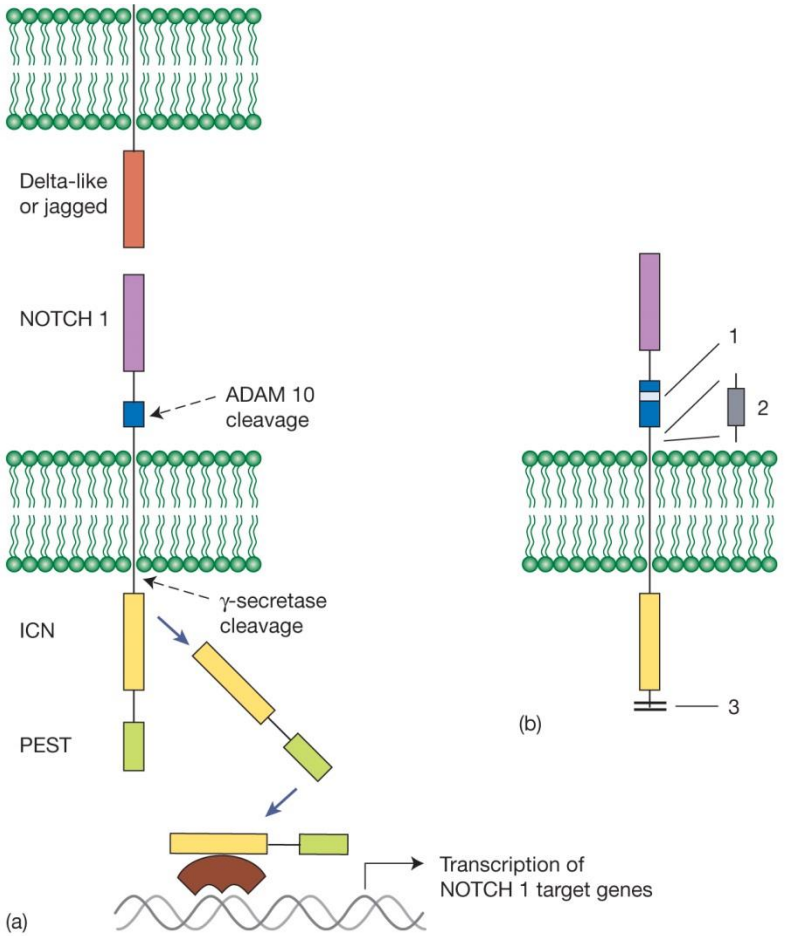


Figure 17.6 The molecular basis of activation of NOTCH signalling in T-cell acute lymphoblastic leukaemia (T-ALL). **(a)** The molecular basis of NOTCH signalling. NOTCH is expressed at the cell membrane and after binding to a ligand (Delta-like or Jagged) on a neighbouring cell, the protein is cleaved in two places – first by extracellular ADAM 10 and then by an intracellular γ-secretase complex. The portion of intracellular NOTCH that is released is then translocated to the nucleus, where it leads to activation of NOTCH1 target genes. **(b)** Several types of genetic abnormalities are seen in the NOTCH signalling pathway in patients with T-ALL. These include (1) mutations in the extracellular cleavage site, (2) insertion of an internal tandem duplications in the juxtamembrane region or (3) deletion of the intracellular PEST domain. The net result of all these mutations is to increase the rate of cleavage and nuclear translocation of the NOTCH domain.

Differential diagnosis

- Acute myeloid leukaemia
- Aplastic anaemia (with which ALL sometimes presents)
- Marrow infiltration by other malignancies (e.g rhabdomyosarcoma, neuroblastoma and Ewing's sarcoma)
- Infections i.e infectious mononucleosis, pertussis, juvenile rheumatoid arthritis
- Immune thrombocytopenic purpura

Treatment

General supportive therapy

- Insertion of central venous cannula
- Blood product support
- Prevention of tumour lysis syndrome
- Infection control & prompt treatment of episodes of fever

Specific therapy

- Chemotherapy – complex treatment protocols
- Radiotherapy – sometimes

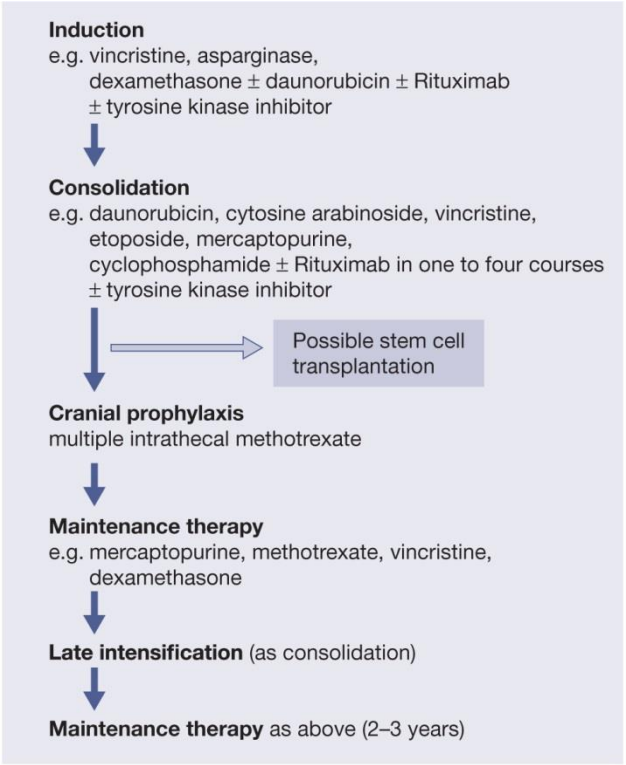


Figure 17.7 Flow chart illustrating typical treatment regimen of acute lymphoblastic leukaemia (ALL).

Hoffbrand's Essential Haematology, Eighth Edition. By A. Victor Hoffbrand and David P. Steensma.

Companion website: www.wileyessential.com/haematology

Table 17.4 Prognosis in acute lymphoblastic leukaemia (ALL).

	Good	Poor
WBC	Low (<50 × 10/9/L)	High (e.g. >50 × 10^9/L B-ALL, >100 × 10^9/L T-ALL)
Sex	Female	Male
Age	Child (1–10 years)	Adult (or infant <1 year)
Immunophenotype (in children)	B-cell	T-cell
Cytogenetics	Normal or hyperdiploidy; *ETV6* rearrangement	t(9;22), most translocations involving 11q23 (MLL), hypodiploidy (<44 chromosomes)
Molecular genetics	Absence of high-risk mutations	Mutations of *TP53*, *NRAS, NR3C1*, *BTG*; Ph-like expression pattern
Time to clear blasts from blood	<1 week	>1 week
Time to remission	<4 weeks	>4 weeks
CNS disease at presentation	Absent	Present
Minimal (measurable) residual disease (MRD)	Negative or <0.01% at 1 month (children); 3 months (adults)	Still positive (>0.01%) at 3–6 months

CNS, central nervous system; WBC, white blood cell count.

Chronic Lymphoid Leukaemias

Introduction

- Several disorders are included in the chronic lymphocytic leukaemias group
- All are characterised by accumulation of mature lymphocytes of either B- or T-cell type
- Overlap with non-Hodgkin lymphomas
- In many cases of non-Hodgkin lymphoma, lymphoma cells are found in blood and the distinction between chronic leukaemia and lymphoma is arbitrary
- In general, these diseases are incurable and tend to run a chronic & fluctuating course

Table 18.1 Classification of the chronic lymphocytic leukaemias (World Health Organization, 2016).

B-cell	T-cell
■ Chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL) ■ B-cell prolymphocytic leukaemia (B-PLL) ■ Hairy cell leukaemia (HCL)	■ T-cell large granular lymphocytic leukaemia (T-LGL) ■ T-cell prolymphocytic leukaemia (T-PLL) ■ Adult T-cell leukaemia/lymphoma (ATLL) ■ Sézary syndrome (see Chapter 20)

Note that this classification includes these disorders within the category of lymphoid malignancies and does not distinguish mature B-cell leukaemias separately (see Appendix).

Diagnosis – 1

- Patients with chronic lymphocytic leukaemias are often asymptomatic and discovered by a full blood count done for another clinical indication
- Alternatively, they may have constitutional symptoms, or may have local signs and symptoms related to lymph node or spleen enlargement
- The usual laboratory finding is chronic persistent blood lymphocytosis, in some cases accompanied by anaemia or thrombocytopenia
- Reactive lymphocytosis should be ruled out
- The clonal nature of the lymphocytosis in chronic lymphocytic leukaemias can be proven with flow cytometry or DNA analysis
- Subtypes of chronic lymphocytic leukaemias are distinguished by morphology, immunophenotype and genetic analysis

Diagnosis – 2

- There is some overlap between chronic lymphocytic leukaemias and the non-Hodgkin lymphomas, as lymphoma cells may be found circulating in the blood, while chronic leukaemias may involve lymph nodes and other lymphatic tissue
- In particular, distinction between chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL) can be somewhat arbitrary, depending on the relative proportion of the disease in soft tissue masses compared to blood and bone marrow; CLL and SLL cells have an identical immunophenotype and genetic abnormalities

Monoclonal B-cell lymphocytosis

- Clonal B cells with the same phenotype as CLL are found at low levels in the blood of many older people
- Indeed, this monoclonal B-cell lymphocytosis (MBL) has been demonstrated in >10% of persons over the age of 50 years and becomes more frequent with advancing age
- It is believed that all cases of clinical CLL progress from this precursor clonal state, which is usually undetected
- Similar genetic changes to these found in CLL may be present in MBL
- If CLL is to be diagnosed, there must be a monoclonal B-cell count of >5 × 10^9/L or tissue involvement outside the bone marrow.

Chronic Lymphocytic Leukaemia

Pathogenesis -1

- Most common of the chronic lymphoid leukaemias
- Peak incidence between 60 and 80 years
- Aetiology unknown
- Common in the Western world and rare in the Far East
- Sevenfold increased risk of CLL in close relatives of patients indicating a genetic predisposition

Pathogenesis – 2

- The CLL neoplastic cell is a mature B cell with weak surface expression of immunoglobulin (IgM or IgD)
- CLL cells exhibit impaired apoptosis and a prolonged lifespan, and this is reflected in their accumulation in the blood, bone marrow, liver, spleen and lymph nodes
- The proliferative rate is usually not markedly increased, but clonal cells accumulate because they survive longer than normal lymphocytes
- SLL is the tissue equivalent of CLL and SLL cells have the same immunophenotype and cytogenetics as CLL
- The difference is that in SLL the neoplastic cells accumulate almost exclusively in the lymph nodes, and by definition there are fewer than 5×10^9/L circulating monoclonal B cells

Clinical features

- The mean age at diagnosis is 72 years, with only 15% of cases before 50 years of age. The male : female ratio is approximately 2 : 1.
- Over 80% of cases are diagnosed from the results of a routine blood test taken for another reason.
- Enlargement of cervical, axillary or inguinal lymph nodes is the most frequent clinical sign. The nodes are usually discrete and non-tender
- Chest X-ray is performed routinely. Abdominal ultrasound may help in evaluation of deep lymphadenopathy, but CT scans are generally not required for initial evaluation or follow-up
- Clinical features of anaemia such as pallor and dyspnea may be present and patients with thrombocytopenia may show bruising or purpura
- Splenomegaly and, less commonly, hepatomegaly are often seen in later stages.
- Immunosuppression is often a significant problem resulting from hypogammaglobulinaemia and cellular immune dysfunction

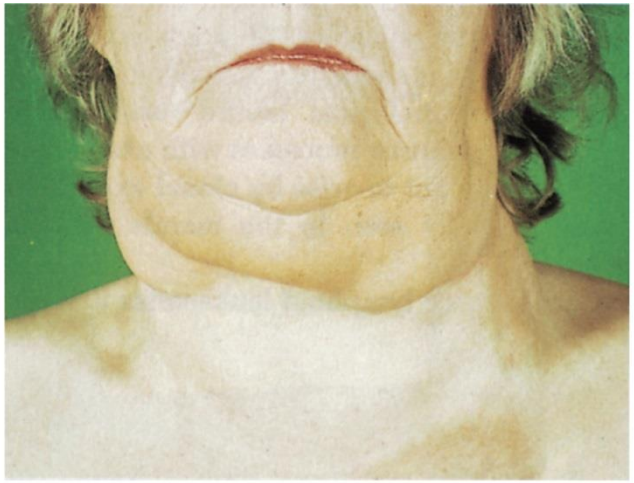


Figure 18.1 Chronic lymphocytic leukaemia: bilateral cervical lymphadenopathy in a 67-year-old woman. Haemoglobin 125 g/L; white blood count 150×10^9/L (lymphocytes 146×10^9/L); platelets 120×10^9/L.

Hoffbrand's Essential Haematology, Eighth Edition. By A. Victor Hoffbrand and David P. Steensma.

Companion website: www.wileyessential.com/haematology

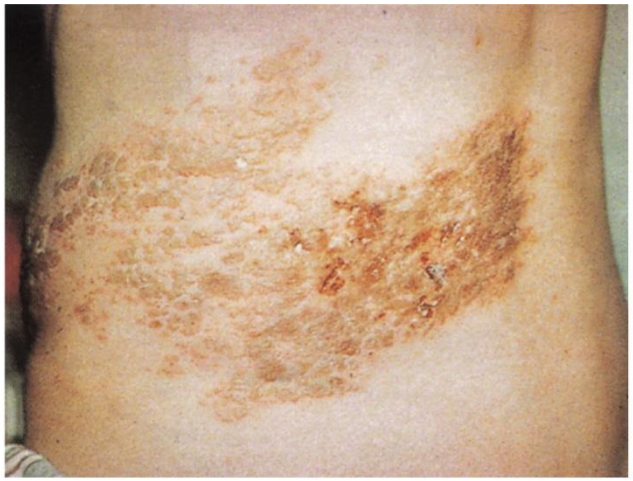


Figure 18.2 Chronic lymphocytic leukaemia: dermatomal herpes zoster infection in a 68-year-old female.

Laboratory findings

- Lymphocytosis. The absolute clonal B-cell lymphocyte count is ≥5 × 109/L by definition and may be 300 × 109/L or more. Typically, between 70% and 99% of white cells in the blood film appear as small lymphocytes. 'Smudge' or 'smear' cells are also present
- Immunophenotyping of the lymphocytes shows them to be B cells (surface CD19+) with expression of only one light chain (known as 'light chain restriction). Characteristically, the cells are also brightly positive for CD5 and CD23, but show low levels of surface immunoglobulin, CD20, CD22 and CD79b
- Two surface proteins that have prognostic significance are CD38, a marker of differentiation, and ZAP70, a protein kinase involved in signalling
- Normochromic normocytic anaemia is present in later stages as a result of marrow infiltration or hypersplenism.
- Bone marrow aspiration shows lymphocytic replacement of normal marrow elements. Trephine biopsy reveals nodular, diffuse or interstitial involvement by lymphocytes
- Reduced concentrations of serum immunoglobulins are found, and this becomes more marked with advanced disease
- Autoimmunity directed against cells of the haemopoietic system is common. Autoimmune haemolytic anaemia is most frequent but immune thrombocytopenia, neutropenia and red cell aplasia are also seen

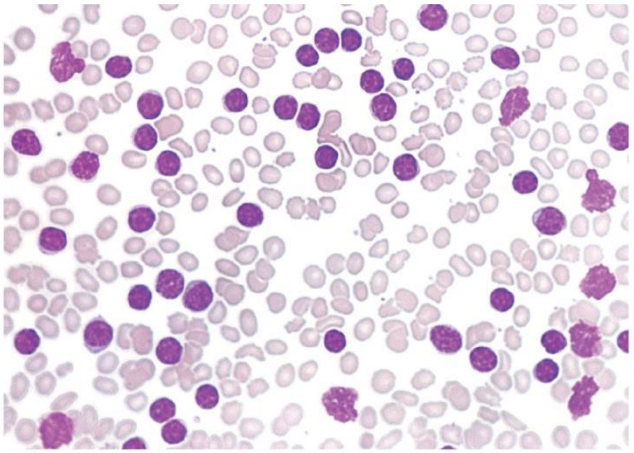


Figure 18.3 Chronic lymphocytic leukaemia: peripheral blood film showing lymphocytes with thin rims of cytoplasm, coarse condensed nuclear chromatin and rare nucleoli. Typical smudge cells are present.

Hoffbrand's Essential Haematology, Eighth Edition. By A. Victor Hoffbrand and David P. Steensma.

Companion website: www.wileyessential.com/haematology

Table 18.2 Immunophenotype of the chronic B-cell leukaemias/lymphomas (all cases $CD19^+$).

	CLL	Hairy cell leukaemia	Follicular lymphoma	Mantle cell lymphoma
SIg	Weak	++	++	+
CD5	+	–	–	+
CD22/FMC7	–	+	+	++
CD23	+	–	–	–
CD79b	–	–/+	++	++
CD103*	–	+	–	–

*CD103 is positive only in classic hairy cell leukaemia (HCL); a variant form of HCL is negative for CD103 (as well as for CD25, also typically expressed in classical HCL).
CLL, chronic lymphocytic leukaemia; SIg, surface immunoglobulin.

Table 18.3 Prognostic factors in chronic lymphocytic leukaemia.

Variable	Good	Bad
Stage	Binet A (Rai 0–I)	Binet B, C (Rai II–IV)
Lymphocyte doubling time	Slow (>12 months)	Rapid
Bone marrow biopsy appearance	Nodular	Diffuse
Chromosomes	Deletion 13q14	Deletion 17p;11q23*
Genetic mutations	High-risk mutations absent	*NOTCH1*, *SF3B1*, *TP53*
VH immunoglobulin genes	Hypermutated	Unmutated; use of VH3.21
ZAP expression	Low	High
CD38 expression	Negative	Positive
LDH	Normal	Raised

*Mutation in the *ATM* gene is also unfavourable if associated with 11q23 deletion.
LDH, lactate dehydrogenase; VH, heavy chain variable. See Table 18.4 for Binet/Rai staging.

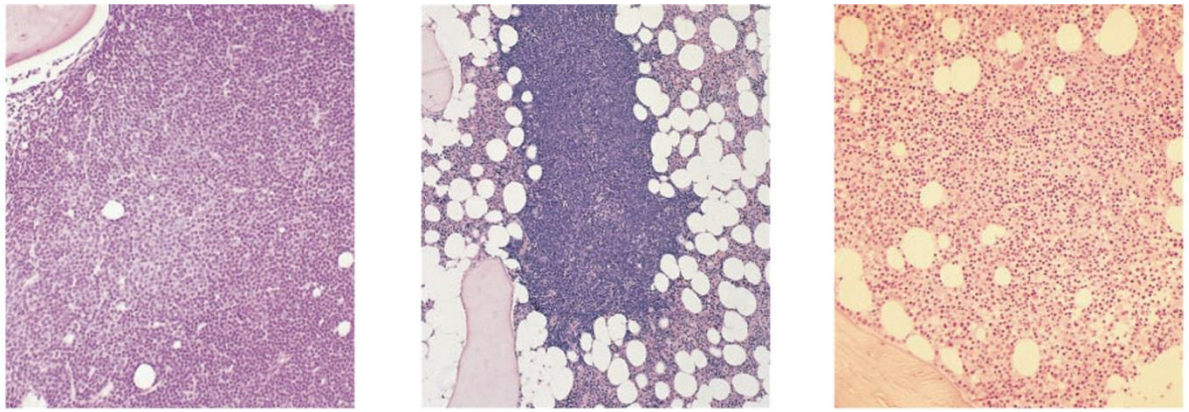


Figure 18.4 Chronic lymphocytic leukaemia: trephine biopsies showing **(a)** a marked diffuse increase in marrow lymphocytes (closely packed cells with small dense nuclei); **(b)** a nodular pattern of lymphocyte accumulation (in a different patient); and **(c)** interstitial infiltration.

Genetics and molecular genetics

- The four most common chromosomal abnormalities in CLL, listed from best prognosis to poorest, are deletion of 13q14, trisomy 12, deletion at 11q23 (involving the ATM gene) and 17p deletion (involving the TP53 gene)
- More than 80% of patients with CLL have one of these findings
- Normal karyotype has an outlook similar to trisomy 12
- The 13q14 deletion leads to loss of microRNAs (see p. 141) that normally control expression of proteins that regulate B-cell survival
- The most common genetic point mutations at presentation are found in ATM, NOTCH1 and SF3B1 (all at around 10% prevalence)
- In addition, point mutations in TP53 can be seen in up to 5% of patients, and these have negative prognostic value and confer resistance to cytotoxic chemotherapy

Somatic hypermutation of the immunoglobulin genes

- When B cells recognize antigen in the germinal centre of secondary lymphoid tissues, they undergo a process called somatic hypermutation in which random mutations occur in the immunoglobulin heavy-chain gene
- In CLL the IGVH gene shows evidence of this hypermutation in approximately 50% of cases, whereas in the other cases the VH genes are unmutated
- CLL with unmutated immunoglobulin genes has an unfavourable prognosis and may respond less well to initial and subsequent therapy

Staging

- It is useful to stage patients at presentation both for prognosis and for deciding on therapy
- The Rai and Binet staging systems are the current international standard
- Typical survival ranged historically from 12 years for Rai stage 0 to less than 4 years for stage IV, but there is considerable variation between patients, and with current therapies survival rates have improved substantially
- Many patients in Rai stage 0 or Binet stage A have a normal life expectancy

Table 18.4 Staging of chronic lymphocytic leukaemia.

(a) Rai classification

Stage	
0	Absolute lymphocytosis ≥5×10^9/L without adenopathy, organomegaly or cytopenias due to replacement of marrow by clonal cells
I	Enlarged lymph nodes (adenopathy)
II	Enlarged liver or spleen ± adenopathy
III	Anaemia (Hb <100 g/L) † ± adenopathy ± organomegaly
IV	Thrombocytopenia (platelets <100×10^9/L) † ±adenopathy ± organomegaly

(b) International Working Party classification (Binet)

Stage	*Organ enlargement**	*Haemoglobin† (g/L)*	*Platelets† (×10^9/L)*
A (50–60% of patients)	0, 1 or 2 areas	≥100	≥100
B (30%)	3, 4 or 5 areas	≥100	≥100
C (<20%)	Not considered	<100	or <100

* One area = lymph nodes >1 cm in neck (including Waldeyer's ring), axillae, groins or spleen, or liver enlargement.
† Secondary causes of anaemia (e.g. iron deficiency) or autoimmune haemolytic anaemia or autoimmune thrombocytopenia must be treated before staging. For example, a patient may have Stage 0 disease but be anaemic due to autoimmune haemolysis.
Hb, haemoglobin.
Source: (b) Adapted from J.L. Binet *et al*. (1981) *Cancer* 48: 198.

Treatment

- Approach to therapy is conservative as cures are rare
- Aim is symptom control rather than normal blood count
- Chemotherapy given too early can shorten life expectancy
- Many patients never need treatment
- Treatment is given for troublesome organomegaly, haemolytic episodes & bone marrow suppression
- Usually patients in Binet stage C will need treatment as will some in stage B

B-cell prolymphocytic leukaemia

- Initially appears similar to CLL on morphology
- Diagnosis made by appearance of a majority of prolymphocytes in the blood
- Prolymphocytes are about twice the size of a CLL lymphocyte with a large nucleolus
- PLL typically presents with splenomegaly without lymphadenopathy & high rapidly rising lymphocyte count
- Anaemia is a poor prognostic feature
- Treatment is difficult

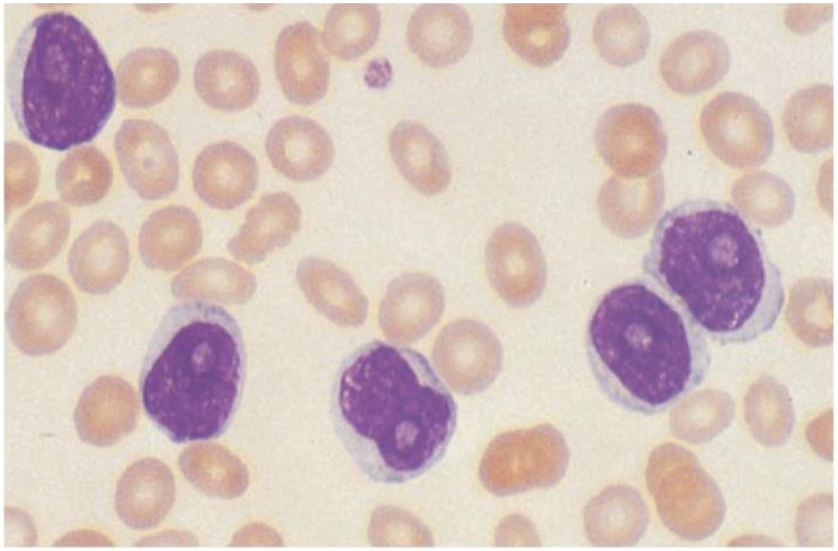


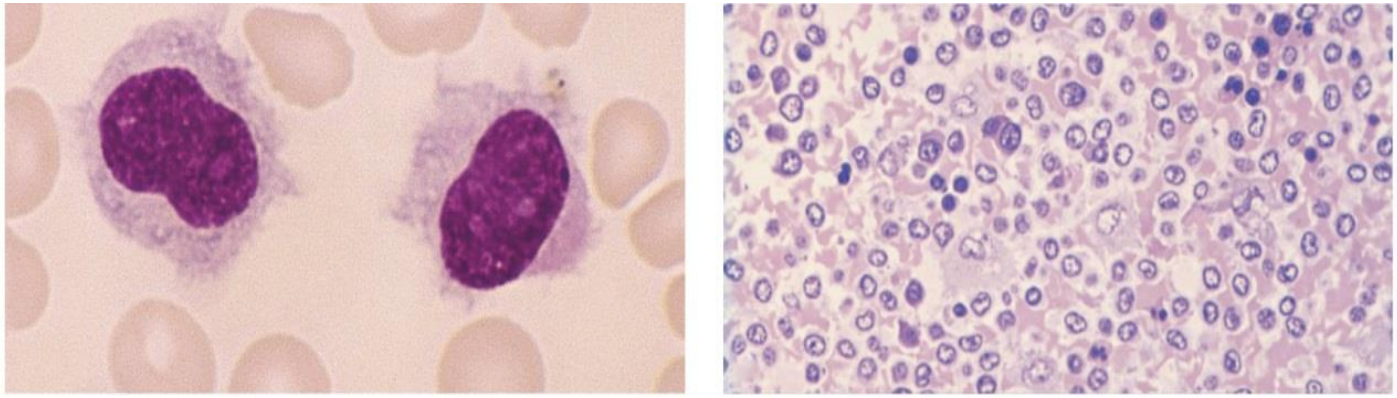
Figure 18.5 Prolymphocytic leukaemia: blood film showing prolymphocytes that have prominent central nucleoli and an abundance of pale cytoplasm.

Hoffbrand's Essential Haematology, Eighth Edition. By A. Victor Hoffbrand and David P. Steensma.

Companion website: www.wileyessential.com/haematology

Hairy cell leukaemia

- Uncommon B-cell lymphoproliferative disease
- Peak incidence at 40-60 years
- Patients typically present with infections, anaemia or splenomegaly
- Lymphadenopathy is uncommon
- Pancytopaenia usual at presentation
- Monocytopenia is a distinctive feature
- HCL was one of the first diseases in which α-interferon was shown to be effective and still remains an excellent treatment



(a) (b)

Figure 18.6 Hairy cell leukaemia: **(a)** peripheral blood film showing typical 'hairy' cells with oval nuclei and finely mottled pale grey-blue cytoplasm with an irregular edge; **(b)** bone marrow trephine.

Lymphocytosis in non-Hodgkin lymphoma

Seen in:

i) Follicular lymphoma
ii) Mantle cell lymphoma
iii) Diffuse large B cell lymphoma
iv) Burkitt lymphoma
v) Splenic marginal zone lymphoma
vi) Lymphoplasmacytoid lymphoma

T-cell diseases

- **T-cell prolymphocytic leukaemia** – presents as B-PLL but lymphadenopathy more marked
- **Large granular lymphocytic leukaemia** – characterised by lymphocytes with abundant cytoplasm and large azurophilic granules
- **Adult T-cell leukaemia/lymphoma** – first malignancy to be associated with a retrovirus, human T-cell leukaemia/lymphoma virus type 1 (HTLV-1). Diagnosis is by morphology & serology. Prognosis is poor

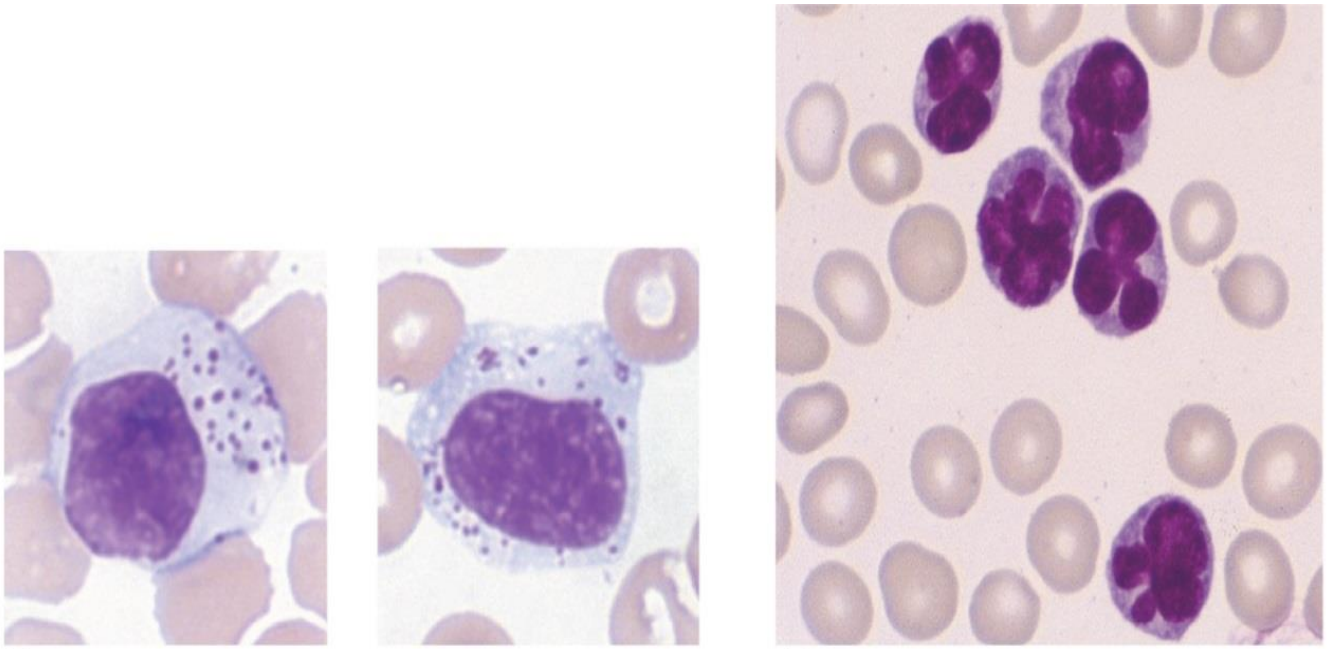


Figure 18.7 **(a)** Large granular lymphocytes in the peripheral blood. **(b)** Adult T-cell leukaemia/lymphoma. Typical convoluted lymphoid cells in peripheral blood.

END OF PRESENTATION