The chronic lymphoid leukaemias

- Diagnosis

This group is characterized by a chronic persistent lymphocytosis. Subtypes are distinguished by morphology, immunophenotype and genetic analysis. There is some overlap with the non-Hodgkin lymphomas as lymphoma cells may be found in the blood and the distinction between chronic leukaemia and lymphoma can be somewhat arbitrary, depending on the relative proportion of the disease in soft tissue masses compared to blood and bone marrow.

- Several disorders are included in this group and are characterized by accumulation in the blood of mature lymphocytes of either B- or T-cell type. In general, these diseases are incurable but tend to run a chronic and fluctuating course

Chronic lymphocytic leukaemia

Pathogenesis

Chronic lymphocytic leukaemia (CLL) is the most common of the chronic lymphoid leukaemias and has a peak incidence between 60 and 80 years of age. The aetiology is unknown but there are geographical variations in incidence. It is the most common form of leukaemia within Europe and the USA but less frequent elsewhere. There is a seven fold increased risk of CLL in the close relatives of patients, which indicates a genetic predisposition to the disease, although the genes that carry this risk are largely unknown.

The CLL tumour cell is a mature B cell with weak surface expression of immunoglobulin (IgM or IgD). CLL cells typically exhibit impaired apoptosis and a prolonged lifespan, and this is reflected in their accumulation in the blood, bone marrow, liver, spleen and lymph nodes. Small lymphocytic lymphoma (SLL) is the tissue equivalent of CLL and lymphoma cells have the same immunophenotype and cytogenetics as CLL. The difference is that in SLL the tumour cells accumulate almost exclusively in the lymph node and there are fewer than 5 × 109/L circulating monoclonal B cells.

Monoclonal B-cell lymphocytosis

Clonal B cells with the same phenotype as CLL are found at low levels in the blood of many older patients. Indeed, this monoclonal B-cell lymphocytosis (MBL) has been demonstrated in 3% of patients over the age of 50 years and it is believed that all cases of clinical CLL progress from this state. Similar genetic changes to these found in CLL may be present. If CLL is to be diagnosed there must be a monoclonal B-cell count of >5 × 109/L or tissue involvement outside the bone marrow.

Laboratory findings

1. Lymphocytosis. The absolute clonal B cell lymphocyte count is >5 × 109/L and may be up to 300 × 109/L or more. Between 70 and 99% of white cells in the blood film appear as small lymphocytes. ‘Smudge’ or ‘smear’ cells are also present.
2. Immunophenotyping of the lymphocytes shows them to be B cells (surface CD19+) with low levels of surface immunoglobulin and expression of only one light chain (known as ‘light chain restriction’;.Characteristi

cally, the cells are also surface CD5+ and CD23+ but are CD79b− and FMC7−.

3. Two surface proteins that can be detected by flow cytometry and have prognostic significance are CD38, a marker of differentiation, and ZAP70, a protein kinase involved in signalling.

4. Normochromic normocytic anaemia is present in later stages as a result of marrow infiltration or hypersplenism. Autoimmune haemolysis may also occur. Thrombocytopenia occurs in many patients and may also have an autoimmune basis.

5. Bone marrow aspiration shows up to 95% lymphocytic replacement of normal marrow elements. Trephine biopsy reveals nodular, diffuse or interstitial involvement by lymphocytes.

6. Reduced concentrations of serum immunoglobulins are found and this becomes more marked with advanced disease. Rarely, a paraprotein is present.

7. 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

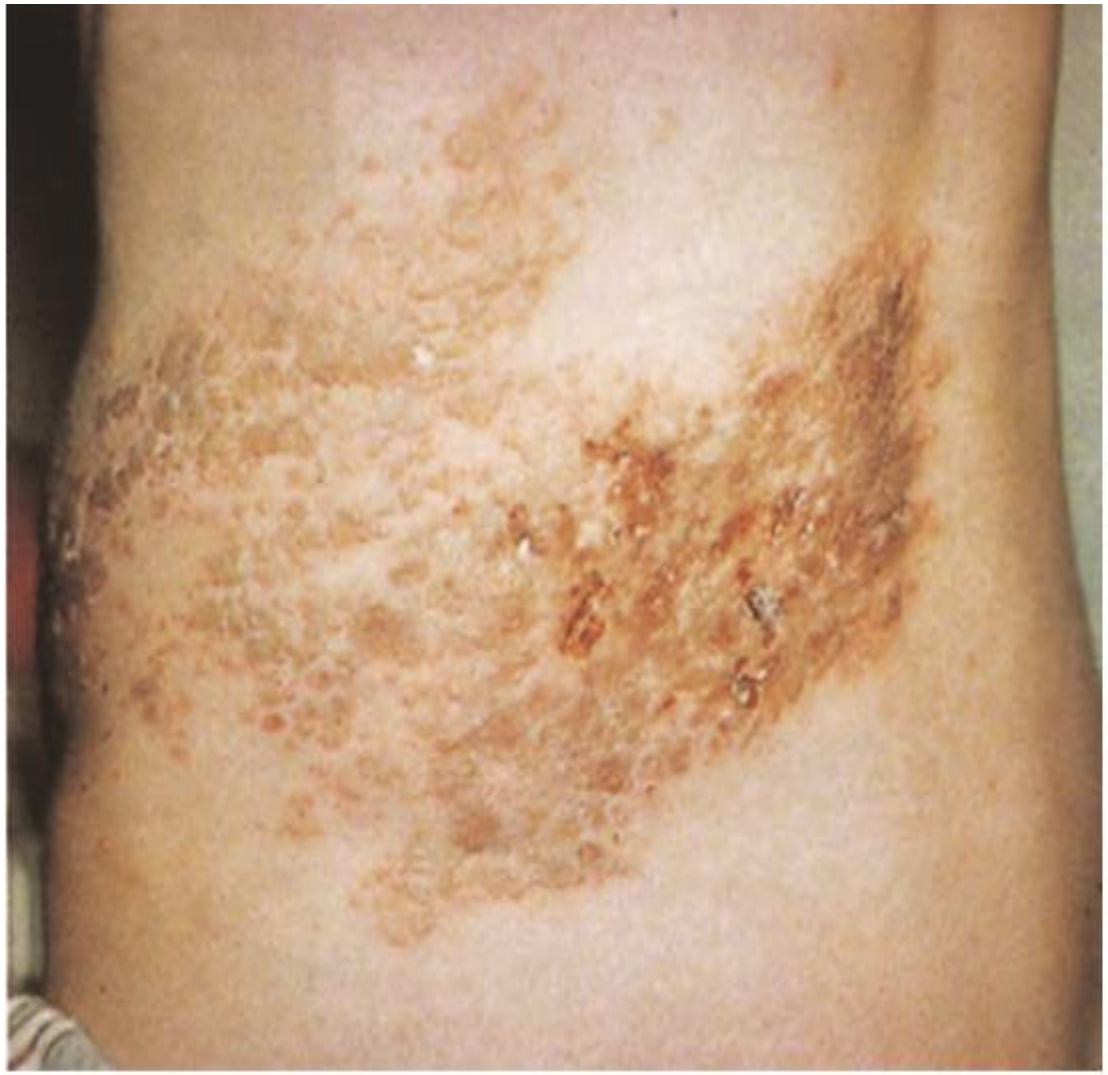

Figure 18.2 Chronic lymphocytic leukaemia: herpes zoster infection in a 68-year-old female.

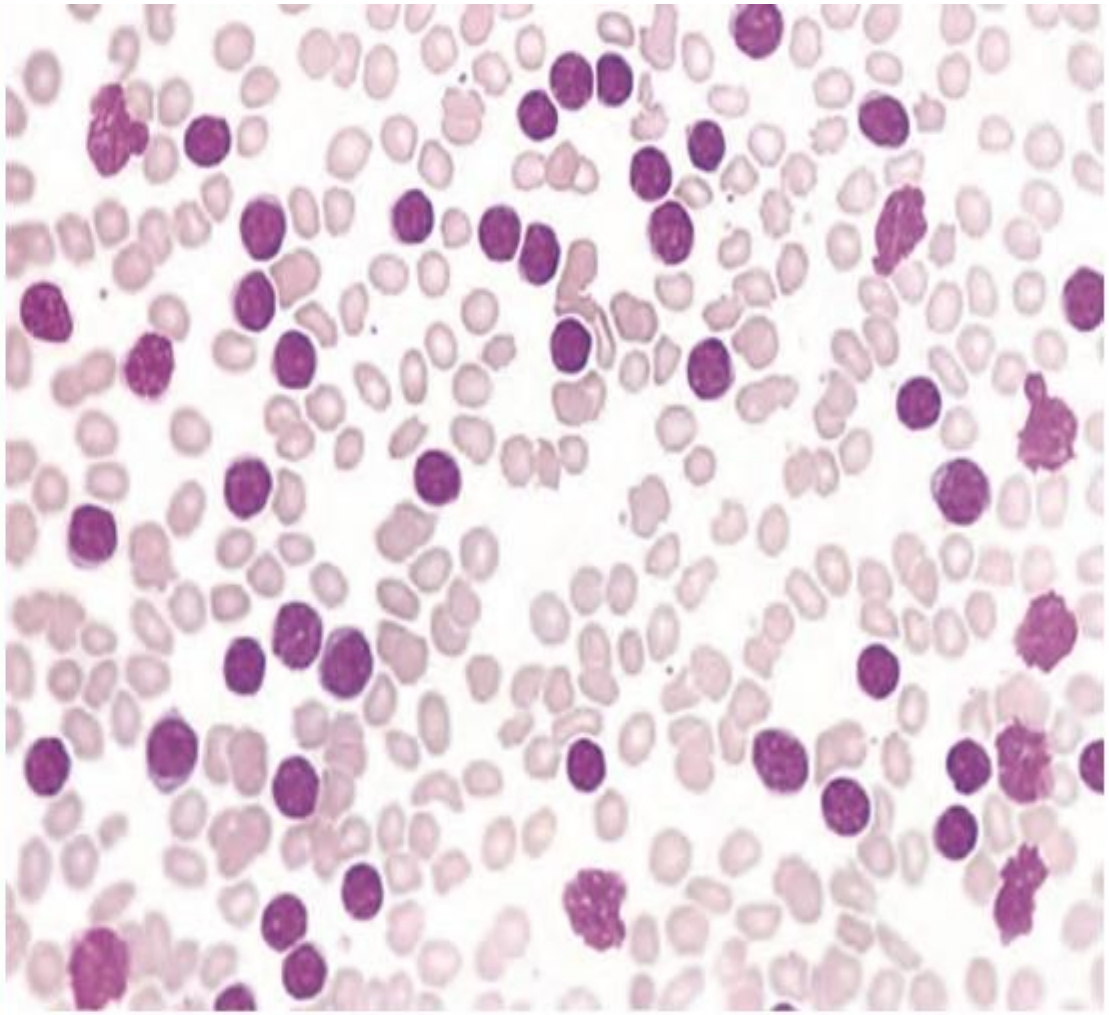

Figure 18.3 Chronic lymphocytic leukaemia: peripheral blood film showing lymphocytes with thin rims of cytoplasm, coarse condensed nuclear chromatin and rare nucleoli. Typical smudge cells are present.

Staging It is useful to stage patients at presentation both for prognosis and for deciding on therapy. The Rai and Binet staging systems. Typical survival ranged 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 are improving. Many patients in stage 0 have a normal life expectancy.

Clinical staging of CLL

(a) Rai classification

Stage	
0	Absolute lymphocytosis >5 × 10^9/L[+]
I	As stage 0 + enlarged lymph nodes (adenopathy)
II	As stage 0 + enlarged liver and/or spleen ± adenopathy
III	As stage 0 + anaemia (Hb <100 g/L)[+] ± adenopathy ± organomegaly
IV	As stage 0 + 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%)	0, 1 or 2 areas	≥100	≥100
B (30%)	3, 4 or 5 areas		
C (<20%)	Not considered	<100	and/or <100

* One area = lymph nodes >1 cm in neck, axillae, groins or spleen, or liver enlargement.

[5] Secondary causes of anaemia (e.g. iron deficiency) or autoimmune haemolytic anaemia or autoimmune thrombocytopenia must be treated before staging.

Source: (b) Adapted from Binet J.L. *et al*. (1981) Cancer 48: 198.

Treatment

It is very difficult to cure CLL and so the approach to therapy is generally conservative, aiming for symptom control rather than a normal blood count. Indeed, chemotherapy given too early in the disease can shorten rather than prolong life expectancy. Another important fact is that many patients never need treatment. Treatment is given for troublesome enlarged lymph nodes or spleen, and constitutional symptoms such as weight loss or bone marrow suppression. The lymphocyte count alone is not a good guide to treatment but if it doubles in <6 months, treatment will usually be needed soon. As a general guide, patients in Binet stage C will need treatment as will some in stage B.

Chemotherapy

For many years the treatment for CLL has based on the combination of cytotoxic drugs (such as fludarabine, chlorambucil and cyclophosphamide or bendamustine) together with a monoclonal antibody against CD20, such as rituximab. However, there are now several effective new drugs which may replace these regimens.. In 2015, the most commonly used first-line treatment for younger patients is R-FC, which combines the antibody rituximab (anti-CD20;) with fludarabine and cyclophosphamide. These agents are given together every 4 weeks and are able to control the white cell count and reduce organ swelling in most cases. Four to six courses are usually given and treatment can be stopped after a satisfactory response has been achieved. The average ‘time to disease progression’ after treatment with R-FC is around 4.5 years. This regimen has a number of potential side-effects, including myelosuppression and immunosuppression. R-B, using bendamustine with rituximab is an alternative approach which is less immunosuppressive.

Poor prognostic factors.

- ♂ sex.
- Advanced clinical stage.
- Initial lymphocytosis >50 × 109/L.
- >5% prolymphocytes in blood film.
- Diffuse pattern of infiltrate on trephine.
- Blood lymphocyte doubling time <12 months.
- Cytogenetic abnormalities 11q–, 17p–, or complex.
- p53 mutations (occurs in 10–15%)—correlates with refractory CLL.
- Unmutated IgVH genes (≤2%)—predicts advanced/progressive disease.
- Cytoplasmic ZAP 70 expression (>20%)—correlates with IgVH status.
- CD38 expression (>30%)—independent of IgVH status.
- increased serum β2-microglobulin—correlates with stage and poor response.
- increased serum LDH.
- Poor response to therapy

Atypical CLL Includes those with >10% prolymphocytes ‘CLL/PLL’ which may show an aberrant phenotype (SmIg strong +ve, FMC7/CD79b +ve) is associated with trisomy 12 and p53 abnormalities and a more aggressive course. Monoclonal B-cell lymphocytosis (MBL) Lymphocyte count <5000/mm3 (but clonal population), no anaemia or thrombocytopenia: observe only.

In older or less fit patients a less intensive treatment plan is used, which still involves chemotherapy and an antiCD20 antibody. Chlorambucil is an oral alkylating agent and is often used in this setting, although bendamustine is also possible. Alemtuzumab is an anti-CD52 monoclonal antibody that is effective at killing B and T lymphocytes by complement fixation but leads to serious infectious complications. It has been used in resistant and relapsed disease but is being replaced by the newer agents.

New Agents in the treatment of B-CLL:

In recent years several new and highly effective therapies have emerged in the treatment of lymphoid disorders. They are used for treating relapsed, resistant patients but trials of their use as initial therapy are in progress.

Other forms of treatment:

■ **Corticosteroids**: Prednisolone is given in autoimmune haemolytic anaemia, thrombocytopenia and red cell aplasia. High-dose steroid therapy alone with alemtuzumab was used in patients with 17q deletion, resistant to chemotherapy. Benefit was temporary and serious infections frequent.

■ **Radiotherapy**: This is valuable in reducing the size of bulky lymph node groups that are unresponsive to chemotherapy. Radiotherapy to the spleen may be valuable in late-stage disease.

■ **Lenalidomide:** is a thalidomide derivative and has therapeutic activity in CLL. Initial treatment is sometimes associated with a disease 'flare' at affected tissue sites and the mechanism of action is uncertain.

■ **Ciclosporin**: Red cell aplasia may respond to ciclosporin.

■ **Immunoglobulin replacement:** Immunoglobulin (e.g. 400 mg/ kg/month by intravenous infusion) is useful for patients with hypogammaglobulinaemia and recurrent infections, especially during winter months.

■ **Stem cell transplantation:** This is currently an experimental approach in younger patients. Allogeneic stem cell transplantation (SCT) may be curative but has a significant mortality rate.

Course of disease:

Many patients in Binet stage A or Rai stage 0 or I never need therapy and this is particularly likely for those with favourable prognostic markers. For those who do need treatment a typical pattern is that of response to several courses of chemotherapy before the gradual onset of extensive bone marrow infiltration, bulky disease and recurrent infection. Molecular and cytogenetic tests show that initially small subclones with, e.g. 17p deletion or P53 mutations, now form the bulk of this resistant disease. The new oral therapies are proving effective even at these late stages. The disease may also transform into a high-grade lymphoma (Richter's transformation) which then requires therapy as for other high-grade B-cell lymphomas.