Diagnosis of chronic lymphocytic leukaemia (CLL)

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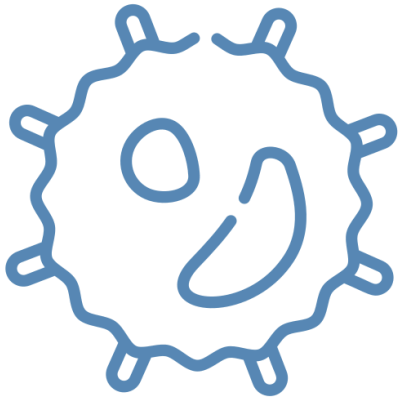
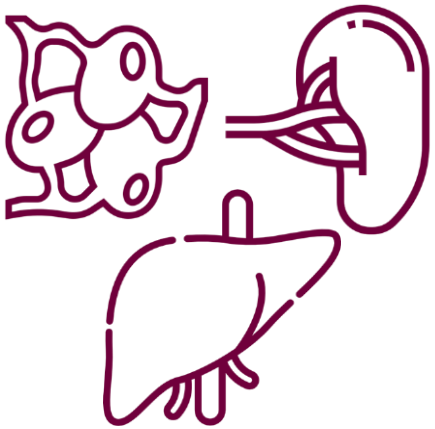
Clinical presentation

Most CLL patients have no symptoms when they present.[1]



The most common presentation is the discovery of **lymphocytosis** on an unrelated blood test[2]



The most common physical signs are **enlarged lymph nodes** (present in 50-90%), **spleen** (25-55%) and **liver** (15-25%)[10]

5-10% of patients present with one or **more B symptom***: fever, weight loss and drenching nights sweats or fatigue[10]

*B symptoms are systemic symptoms related to B-cell malignancies[3]

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Diagnostic tests

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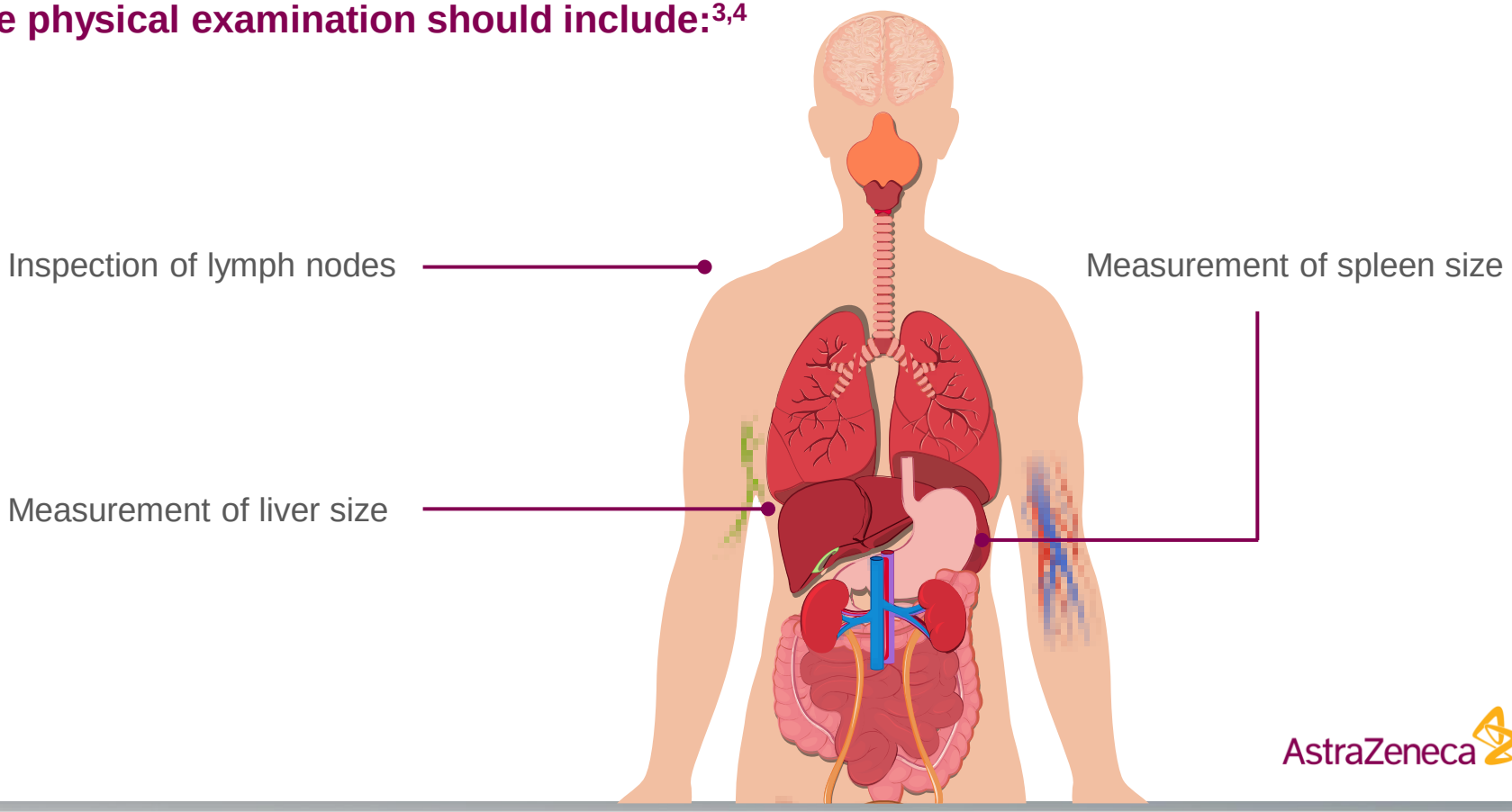
Diagnostic workup – medical history and physical examination

A complete medical history is taken to assess:

- possible risk factors
- family history
- concurrent medical conditions
- how well the patient can carry out daily activities
- whether they have B symptoms[4,5]

The physical examination should include:[3,4]



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Diagnostic workup – blood analysis

	Laboratory test	Characteristic findings in CLL	Significance
	**Complete blood count (CBC)[4,5,6]**	• Lymphocytosis • Decreased red blood cell (RBC) count	• High levels of lymphocytes can indicate that the body is fighting an infection, but they can also indicate a white-cell malignancy • RBCs carry oxygen through the body, so having too few results in fatigue. In CLL, crowding of abnormal lymphocytes in bone marrow can diminish RBC production
	**Blood smear[7,8]**	• Characteristic “smudge cells”	• Distinct CLL B-cell morphology allows for differential diagnosis
	**Immunophenotyping/ Immunohistochemistry (IHC)[9]**	• CLL cells carry distinct cell surface markers	• Antibodies are used to label specific molecules on the surface of B cells that are characteristic for CLL and different from other B-cell malignancies • They are also used to confirm clonality • The expression pattern enables physicians to distinguish CLL from other B-cell malignancies
	**Immunoglobulin concentration measurement[4]**	• Levels of immunoglobulin/antibodies	• Levels may be informative in patients with recurrent infections
	**Cytogenetics**	• Common mutations in CLL (e.g. del17p)[13]	• Cytogenetics is the study of the structure and function of chromosomes[11] • Differentiates CLL from other B-cell malignancies • Predictive of time to progression from diagnosis and of response to treatment[12]

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Blood analysis – recommendations

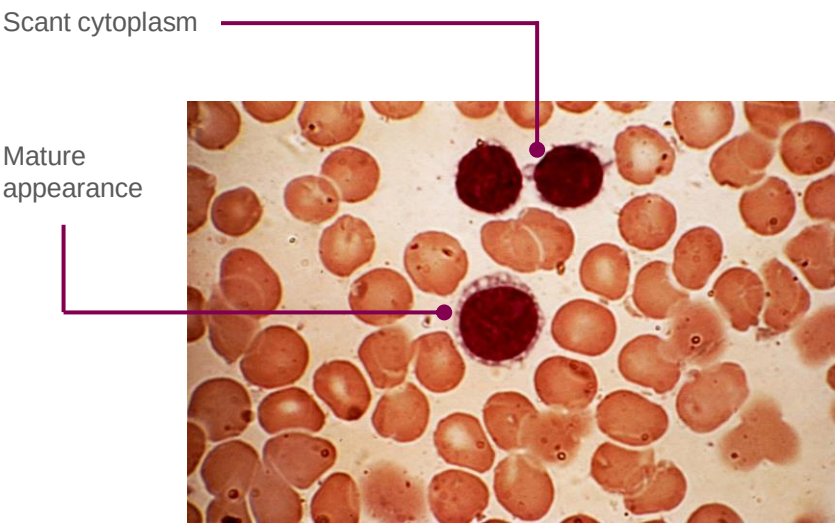
To establish a diagnosis of CLL, The European Society for Medical Oncology **(ESMO)** clinical practice guidelines and the International Workshop on CLL **(iwCLL)** recommend the following:

Complete blood count

The presence of at least 5 x 10^9 monoclonal B cells/litre in the peripheral blood for more than 3 months[4,14]

Blood smear

Cancer cells found in the blood smear should be small, mature-appearing with scant cytoplasm and a dense nucleus lacking visible nucleoli with partially aggregated chromatin[4,14]



Microscopic image of CLL cells[4]
© Image Source/Science Photo Library C0151819(used under license)

Immunophenotyping/IHC

Evaluate the immunophenotype to verify the following expression pattern of cluster-of-differentiation proteins that is characteristic of CLL:[14]

- CLL cells co-express the surface antigen CD5, together with the B-cell antigens CD19, CD20 and CD23
- The levels of surface immunoglobulin, CD20 and CD79b are characteristically low compared with those found on normal B cells
- Each clone of leukaemia cells is restricted to expression of either κ or λ immunoglobulin light chains
- A recent, large harmonization effort has confirmed that a panel of CD19, CD5, CD20, CD23, κ, and λ is usually sufficient to establish the diagnosis
- In borderline cases, markers such as CD43, CD79b, CD81, CD200, CD10 or ROR1 may help to refine the diagnosis

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Genetic testing

Before considering a patient's therapy, it is important to factor in the profile of their malignant CLL cells.[15] The **iwCLL guidelines** recommend consistently testing for the following genetic biomarkers when diagnosing CLL:[14]

Biomarker	Description
***IGHV* mutational status**[14]	• Unmutated *IGHV* is associated with poorer prognosis • Mutated *IGHV* is associated with a more favourable prognosis
***TP53* mutation**[14,18]	• Loss of function of *TP53* disrupts p53-dependent apoptosis, leading to chemotherapy resistance and impaired survival in CLL patients
Cytogenetic abnormalities*[17,18]	• Del(11q) is seen in ~18% patients • Del(13q) is seen in ~55% patients and is associated with a more favourable prognosis • Del(17p) causes a loss of function of *TP53* • This cytogenetic anomaly is seen in ~7% of patients at diagnosis and ~30% at relapse[16] • Trisomy 12 is observed in ~15% of CLL patients[17]

*Based on one study that enrolled primarily untreated CLL patients (n=325)

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Differential diagnosis

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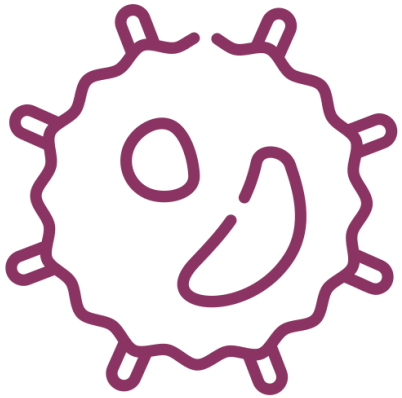
Differential diagnosis

The **ESMO guidelines** and **iwCLL** recommend the differential diagnosis of CLL from other **B-cell malignancies** and the premalignant condition **monoclonal B-cell lymphocytosis (MBL)**, via a combination of blood cell counts, presence or absence of surface molecules, or certain symptoms.[4,14]

Small Lymphocytic Leukaemia (SLL)[4,14]

SLL would present with a lower absolute **monoclonal B-cell** count than **CLL** (i.e. <5 x 10^9/litre)

SLL patients present with swollen lymph nodes and/or an enlarged spleen



Monoclonal B-cell lymphocytosis (MBL)[4,14]

MBL would present with a lower absolute **monoclonal B-cell** count than **CLL** (i.e. <5 x 10^9/litre)

It would also be differentiated by the **absence of any palpable lymphadenopathy** (all lymph nodes in MBL are <1.5 cm)

Additionally, **MBL** could be differentiated from **CLL** based on lack of anaemia and thrombocytopenia (an abnormally low count of platelets)

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Summary

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Diagnosis of CLL - Summary

Clinical presentation	• Patients will often be asymptomatic at initial presentation • Physical examination may reveal enlarged lymph nodes, spleen, and liver • Patients often have high levels of lymphocytes • Patients who present symptomatically may be experiencing fever, weight loss, night sweats or fatigue
Diagnostic tests	• Diagnostic workup includes a physical examination and medical history, as well as several blood tests • Complete blood count will reveal a high number of B cells • Peripheral blood smear will demonstrate B cells with scant cytoplasm that maintain a mature lymphocyte appearance • Evaluate the immunophenotype to verify the expression pattern of cluster-of-differentiation proteins that is characteristic for CLL
Differential diagnosis	• Differential diagnosis may be necessary to distinguish CLL from other B-cell malignancies and the premalignant condition monoclonal B-cell lymphocytosis (MBL)

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Knowledge check

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Knowledge check: questions

1. Which of these might suggest that a patient has CLL?

A. Recurrent migraines and symptoms of fatigue
B. Enlarged lymph nodes and high lymphocyte count
C. High lymphocyte count and loss of memory
D. Enlarged lymph nodes and recurrent migraines

2. Once an HCP suspects that her patient may have CLL, which of the following blood tests is she likely to order?

A. A complete blood count and a blood smear
B. Cholesterol and lipid tests
C. Glucose tests and a complete blood count
D. Lipid and glucose tests

3. A CLL patient's complete blood count would be characterised by what finding?

A. $\geq 5 \times 10^6$ monoclonal B cells/litre
B. $\geq 5 \times 10^7$ monoclonal B cells/litre
C. $\geq 5 \times 10^8$ monoclonal B cells/litre
D. $\geq 5 \times 10^9$ monoclonal B cells/litre

4. A CLL patient's blood smear would be characterised by what finding(s)?

A. Small lymphocyte size
B. Immature-like appearance of lymphocytes
C. Lymphocytes with scant cytoplasm
D. All of the above

5. What is immunophenotyping used for?

A. To sort and separate malignant from nonmalignant cells
B. To examine characteristics of RBCs under the microscope
C. To label specific cell markers on lymphocytes that characterise CLL and to confirm clonality
D. None of the above

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Knowledge check: answers

1. **B:** Enlarged lymph nodes and high lymphocyte count
2. **A**: A complete blood count and a blood smear
3. **D:** ≥5 x 10^9 monoclonal B cells/litre
4. **C:** Lymphocytes with scant cytoplasm
5. **C:** To label specific cell markers on lymphocytes that characterise CLL and to confirm clonality

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