

Module 3: Diagnosis of Mantle Cell Lymphoma (MCL)

START

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MCL Diagnosis

Tutorial



Tutorial

Glossary terms are identified by bold, yellow text.

Glossary terms are identified by bold, yellow text. Select the word to see the definition

Tutorial

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Module Overview

This MCL Diagnosis Module will explain the diagnostic criteria and workup for mantle cell lymphoma (MCL)

- Learning Objectives
- Diagnostic Criteria
- Differential Tests
- Summary
- Progress Check

Upon completion of this module, you should be able to:

- List the diagnostic criteria used to evaluate MCL
- Discuss the diagnostic workup for MCL





This section will present the diagnostic criteria, explain the diagnostic tests available, and discuss the differential diagnoses for MCL.

Upon completion of this section, you should be able to:

DIAGNOSTIC CRITERIA

- List the diagnostic criteria used to identify MCL

DIAGNOSTIC TESTS

- Describe the tests required to establish a definitive diagnosis of MCL

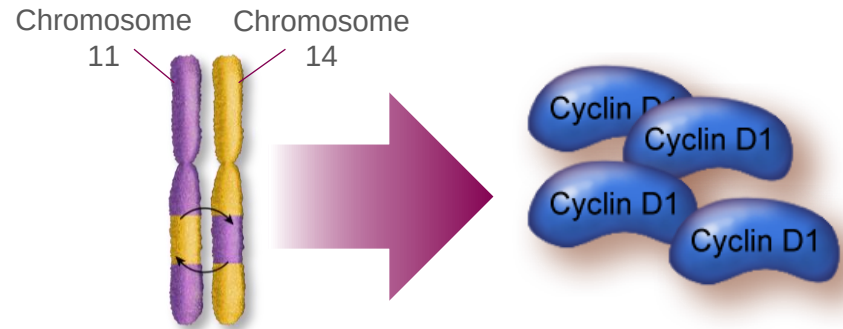
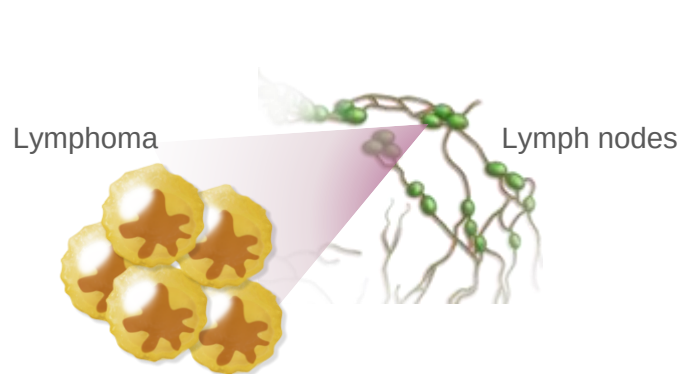
DIFFERENTIAL DIAGNOSES

- Differentiate MCL from other disease states with similar symptoms



MCL can be differentiated from other lymphomas using established diagnostic procedures and tests.¹

A diagnosis of MCL is established if:^{1,2}



- Lymphoma is identified in affected tissues

- Lymphoma cells express characteristic markers of MCL, including:
 - The t(11;14)(q13;q32) **chromosomal translocation**, resulting in overexpression of **cyclin D1**



MCL can be differentiated from other lymphomas using established diagnostic procedures and tests.

A diagnosis of MCL is established if:

Cyclin D1 Overexpression

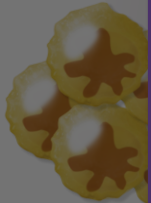
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Less than 5% of MCL cases are negative for cyclin D1 overexpression. Instead, the following abnormalities may be observed:^{1,2}

- Overexpression of cyclin D2
- Overexpression of cyclin D3
- Rearrangements of the *CCND2* or *CCND3* genes

The pathologic and clinical features of cyclin D1–negative MCL appear to be similar to those of cyclin D1–positive MCL.^{1,2}

Lymphoma



- Lymphoma is identified in affected tissues

- Lymphoma cells express characteristic markers of MCL, including:
 - The t(11;14)(q13;q32) **chromosomal translocation**, resulting in overexpression of **cyclin D1**



Diagnostic Procedures

Diagnostic Tests



The diagnostic workup for MCL includes:¹



Physical examination
and medical history



Lymph node and bone
marrow **biopsies**



Blood analysis



Imaging tests



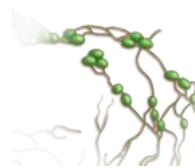
Physical Examination and Medical History

A thorough physical examination is done to evaluate the patient's performance status and to identify the presence of symptoms, which may include the following B (general) symptoms:^{1,3,4}

- Loss of appetite and unexpected weight loss (> 10% of body weight)
- Fever⁵
- Drenching night sweats
- Adenopathy



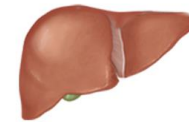
If MCL is suspected, particular attention may be placed on organs likely to be involved:⁴



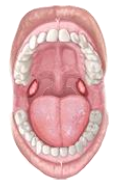
Lymph
nodes



Spleen



Liver



Tonsils

A complete medical history is obtained to assess possible risk factors, family history, and concurrent medical conditions.⁴



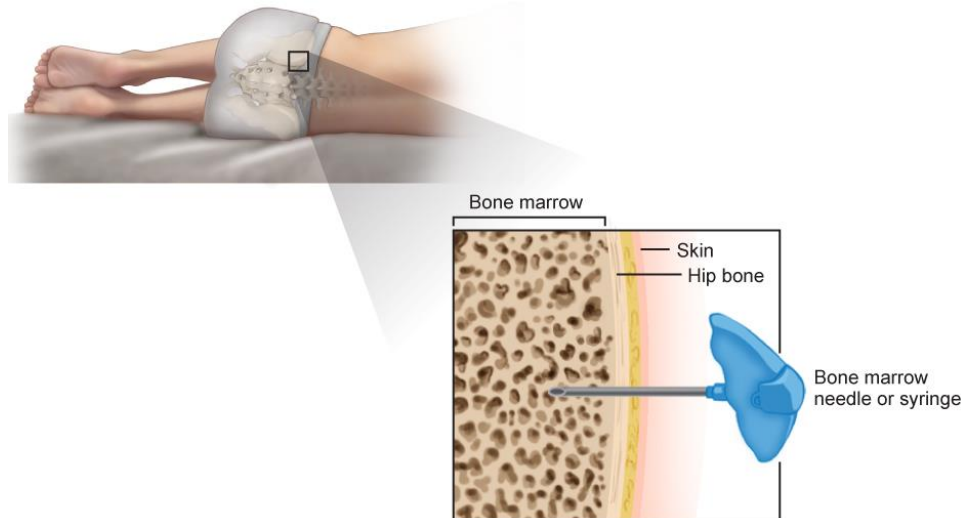
Lymph Node and Bone Marrow Biopsies

A biopsy of the tumour must be done to confirm a suspected diagnosis of MCL:⁴

- A biopsy is performed to remove either the entire lymph node or part of the tumour

Since the bone marrow is frequently involved in MCL, the following 2 bone marrow samples are obtained after diagnosis to determine if malignant B cells are present and to stage the disease:^{1,4}

- Liquid bone marrow can be drawn using a syringe to produce bone marrow **aspirate**
- A biopsy is performed, where a small piece of bone and marrow are removed using a larger needle:



Bone marrow aspiration and biopsy: With the patient lying on their side, a needle is inserted into the hip bone to withdraw liquid bone marrow and/or a small piece of bone and marrow⁴

The biopsy and aspiration samples from the lymph node and bone marrow are assessed using all of the following tests to establish the diagnosis and spread of MCL.¹

Select each test to learn more.

Morphologic examination

Immunophenotyping

Cytogenetic evaluation

- The structure and form of malignant B cells are examined⁶

Morphologic examination alone is generally not enough to diagnose MCL.⁷



- MCL B cells are typically small-to-medium-sized with irregular nuclei:

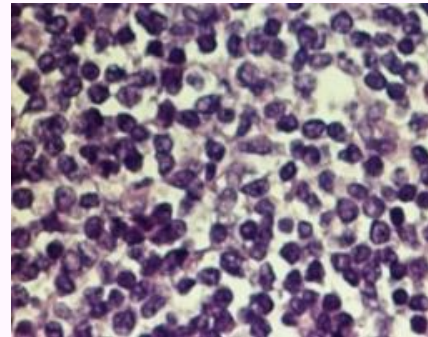


Image credit: © Kella et al, OPENi

- However, morphologic variants may be present, such as small, round cells resembling those of chronic lymphocytic leukaemia (CLL), marginal zone-like, pleomorphic, and blastoid cells



The biopsy and aspiration samples from the lymph node and bone marrow are assessed using all of the following tests to establish the diagnosis and spread of MCL.¹

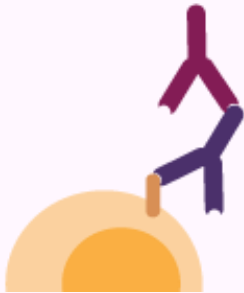
Select each test to learn more.

Morphologic examination

Immunophenotyping

Cytogenetic evaluation

- Antibodies are applied to the sample to identify specific proteins on the surface of certain cells⁴
- Immunophenotyping** can be done using:¹
 - Immunohistochemistry (IHC) ?
 - Flow cytometry ?



- MCL cells typically express cyclin D1 and B-cell lymphoma 2 (BCL2), and have the following expression pattern of **cluster of differentiation (CD) proteins**:¹

Positive	Negative/Positive
- CD5 - CD20 - CD43	- CD10 - CD23

- Ki67** expression is also assessed for prognostic purposes¹



Immunohistochemistry

IHC takes advantage of the fact that antibodies bind most tightly to the antigen that they recognise—**antibody-antigen specificity**. IHC identifies cells expressing a given antigen by using antibodies that emit and change colour when bound to their specific antigen.^{4,6}

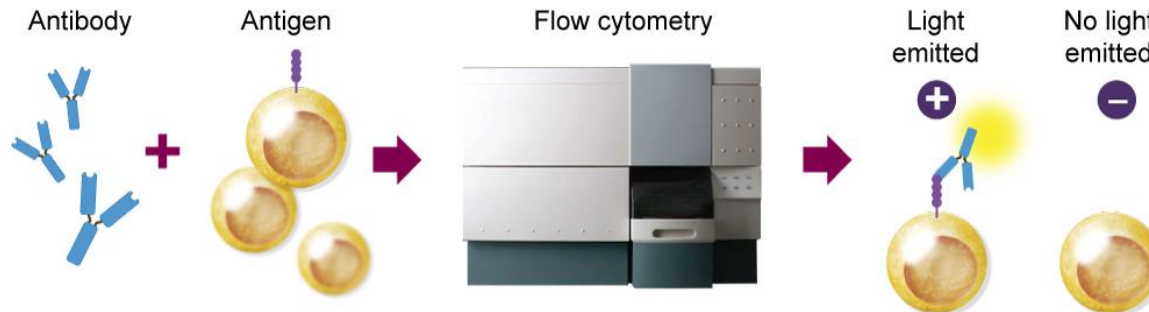


The sample is treated with antibodies. Colour change is observed under a microscope if the antibodies bind to their specific antigen.^{4,6}

- **Ki67** expression is also assessed for prognostic purposes¹

Flow Cytometry

Flow cytometry is a technique that identifies, separates, and counts cells based on antibody-antigen recognition as cells are passed in front of a laser. Cells with bound antigen emit fluorescent light, which is measured and analysed.⁴



The sample is treated with antibodies, and the cells are passed in front of a laser. Light is emitted if the antibodies bind to their specific cell surface antigen.⁴

- **Ki67** expression is also assessed for prognostic purposes¹

The biopsy and aspiration samples from the lymph node and bone marrow are assessed using all of the following tests to establish the diagnosis and spread of MCL.¹

Select each test to learn more.

Morphologic examination

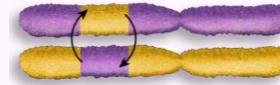
Immunophenotyping

Cytogenetic evaluation

- **Cytogenetics** is the study of the structure of chromosomes under a microscope to identify abnormalities⁴
- Fluorescent in situ hybridisation (FISH) uses fluorescent dyes that attach to specific parts of chromosomes to find chromosomal abnormalities⁴ ?



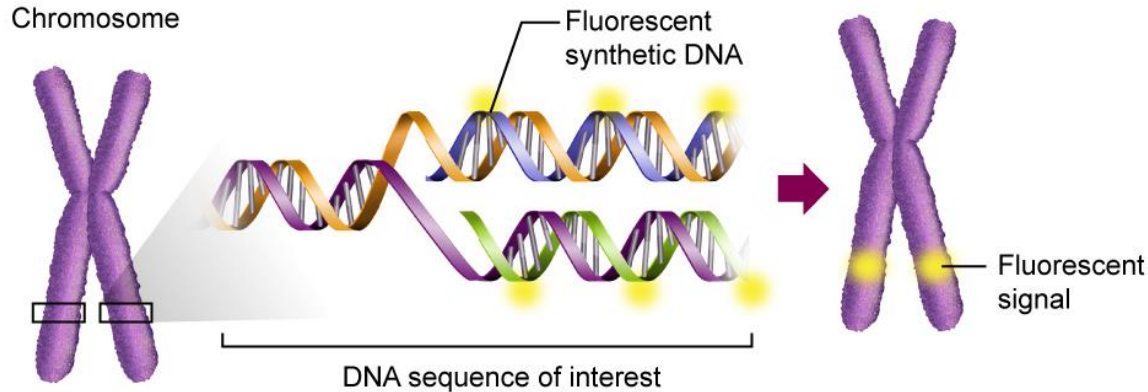
- MCL cells have the t(11;14)(q13;q32) chromosomal translocation^{1,2}



Note that cyclin D1 overexpression, resulting from the t(11;14)(q13;q32) chromosomal translocation, is the hallmark of MCL and is generally required for diagnosis.^{1,2}

Fluorescent In Situ Hybridisation

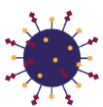
- FISH:
 - Introduces short sequences of fluorescent synthetic DNA that are complementary to and bind a specific DNA sequence of interest, such as the t(11;14)(q13;q32) translocation, within a sample. If the target sequence is present, a fluorescent signal is given off^{1,8}
 - Can be used on regular blood or bone marrow samples to identify chromosomal abnormalities⁴



Fluorescent synthetic DNA binds to the DNA sequence of interest and emits a fluorescent signal.⁸

Blood Analysis

After the biopsy has confirmed diagnosis of MCL, analysis of the patient's blood is done as part of the initial workup to identify the presence of malignant B cells. Tests conducted on the peripheral blood include:^{1,4}

	Laboratory test	Description	Significance
	Complete blood count (CBC) with differential ⁴	Measurement of circulating levels of white blood cells (WBCs), red blood cells (RBCs), and platelets ⁴	- Low platelet and RBC levels may be seen with lymphoma growth in the bone marrow⁴ - WBC count may be elevated⁷
	Lactate dehydrogenase (LDH) measurement ⁴	LDH is an enzyme found in many tissues, including the lungs, kidneys, heart, and liver, that oxidises lactate within cells ⁶	LDH levels are typically increased in patients with lymphoma ⁴
	Metabolic panel ⁹	Measurement of liver and kidney function, including tests of: ⁹ - Electrolyte (eg, calcium, magnesium, potassium, and sodium) balance - Blood protein levels	Abnormal levels of calcium and elevated levels of the protein β -2 microglobulin may indicate lymphoma ^{9,10}
	Hepatitis B screening ¹	Screening for hepatitis B virus infection ¹	Hepatitis B virus may reactivate in infected patients if they are treated with immunotherapy ¹



Imaging Studies

Imaging tests are performed to determine the localisation and spread of MCL.¹ ?

Select each test to learn more.

CT scan

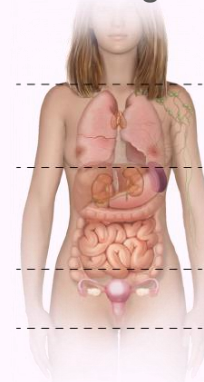
- Computed tomography (CT) is an x-ray test that takes detailed, cross-sectional images by rotating around the body⁴



The patient lies down on the bed of the CT machine while the scanner rotates and captures images of the body.⁴

PET scan

- CT scans show soft tissue details, allowing for the visualisation of enlarged lymph nodes or other organs where lymphoma cells may be found:⁴
 - Both oral and intravenous contrast dyes are used to improve the visualisation of different organs



Chest

Abdomen

Pelvis

Typical areas of interest for CT scanning¹



Imaging Studies

Imaging tests are performed to determine the localisation and spread of MCL.¹ ?

Select each test to learn more.

CT scan

PET scan

- Complete test the imaging

Imaging Studies

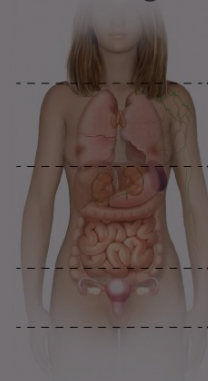
Imaging studies use x-rays, sound waves, or magnetic fields to produce images of the body so it can be examined for the presence of lymphoma.⁴

X



The patient lies down on the bed of the CT machine while the scanner rotates and captures images of the body.⁴

- Both oral and intravenous contrast dyes are used to improve the visualization of different organs¹



Chest

Abdomen

Pelvis

Typical areas of interest for CT scanning¹



Imaging Studies

Imaging tests are performed to determine the localisation and spread of MCL.¹

Select each test to learn more.

CT scan

- Positron emission tomography (PET) uses a radioactive sugar called **fluorodeoxyglucose (FDG)** to visualise the body:⁴
 - Rapidly dividing cells like lymphoma cells absorb large amounts of FDG and can be differentiated from other cells



PET scan

- PET scan images are not as finely detailed as those obtained with a CT scan, but can be combined with CT results for more information⁴

PET scans can be used to:⁴

- Visualise lymphoma in an enlarged lymph node
- Identify small areas with lymphoma that may not be enlarged on a CT scan

After injection with FDG, the patient is moved to the PET scanner, where a camera creates images depicting the areas of radioactivity in the body.⁴



Additional Diagnostic Tests

In addition to the analyses discussed, the following tests may be recommended in certain cases:¹



Endoscopy

- To determine the extent of gastrointestinal (GI) involvement in patients with GI symptoms²



Lumbar puncture

- In patients with blastoid morphology or central nervous system (CNS) symptoms



Differential Diagnoses

MCL shares many similarities with other B-cell lymphomas, but has one of the worst prognoses.¹¹

Diseases similar to MCL	Reasons for differential diagnosis	Distinguishing features
CLL/Small lymphocytic lymphoma (SLL) ¹²	- Both can engage lymph nodes, bone marrow, and blood¹² - Share many morphological and phenotypic characteristics¹² - Less aggressive than MCL¹²	MCL can be distinguished by: ¹² - Presence of the t(11;14)(q13;q32) chromosomal translocation, leading to cyclin D1 expression - Lack of CD23 expression - Expression of the transcription factor SOX11
Marginal zone lymphoma (MZL) ¹¹	- Malignant cells have similar irregular nuclei¹¹ - MZL arises from the marginal zone, but can spread to the germinal center and mantle zone¹¹	MCL can be distinguished by: ¹ - Expression of cyclin D1 and CD5 - A more aggressive disease course than MZL
Follicular lymphoma (FL) ¹¹	- Similar pattern of abnormal growth in the lymph nodes¹¹ - Can be an aggressive lymphoma like MCL¹¹	MCL can be distinguished by: ¹¹ - Morphologically irregular nuclei vs the characteristic large and elongated nuclei of FL - Expression of cyclin D1 and CD5



DIAGNOSTIC CRITERIA

- A diagnosis of MCL is established if:
 - Lymphoma is identified in affected tissues
 - Lymphoma cells express characteristic markers of MCL, including the t(11;14)(q13;q32) chromosomal translocation

DIAGNOSTIC TESTS

- Diagnostic tests for MCL include:
 - Physical examination and medical history
 - Lymph node and bone marrow biopsies
 - Blood analysis
 - Imaging tests
- The following additional tests may be recommended in certain cases:
 - Endoscopy
 - Lumbar puncture

DIFFERENTIAL DIAGNOSES

- Differential diagnoses to consider when MCL is suspected include:
 - CLL/SLL
 - MZL
 - FL





1. Which of the following is a characteristic marker of MCL?

A) Expression of cluster of differentiation 10 (CD10)

B) The t(11;14)(q13;q32) chromosomal translocation, resulting in overexpression of cyclin D1

C) The t(11;14)(q13;q32) chromosomal translocation, resulting in underexpression of cyclin D1

D) The t(13;10)(q13;q32) chromosomal translocation, resulting in overexpression of cyclin D3





1. Which of the following is a characteristic marker of MCL?

A) Expression of cluster of differentiation 10 (CD10)

B) The t(11;14)(q13;q32) chromosomal translocation, resulting in overexpression of cyclin D1

C) The t(11;14)(q13;q32) chromosomal translocation, resulting in underexpression of cyclin D1

D) The t(13;10)(q13;q32) chromosomal translocation, resulting in overexpression of cyclin D3

B) The t(11;14)(q13;q32) chromosomal translocation, resulting in overexpression of cyclin D1, is a characteristic marker of MCL.





2. The diagnostic workup for MCL includes which of the following tests?

A) Blood analysis and lymph node biopsy only

B) Physical examination, lumbar puncture, and blood analysis

C) Physical examination, lymph node and bone marrow biopsies, blood analysis, and imaging tests

D) Physical examination, spleen biopsy, blood analysis, and imaging tests





2. The diagnostic workup for MCL includes which of the following tests?

A) Blood analysis and lymph node biopsy only

B) Physical examination, lumbar puncture, and blood analysis

C) Physical examination, lymph node and bone marrow biopsies, blood analysis, and imaging tests

D) Physical examination, spleen biopsy, blood analysis, and imaging tests

C) The diagnostic workup for MCL includes physical examination, lymph node and bone marrow biopsies, blood analysis, and imaging tests.





3. Which of the following cluster of differentiation (CD) proteins is expressed by CLL cells but not MCL cells?

A) CD5

B) CD20

C) CD23

D) None of the above





3. Which of the following cluster of differentiation (CD) proteins is expressed by CLL cells but not MCL cells?

A) CD5

B) CD20

C) CD23

D) None of the above

C) CD23 is expressed by CLL cells but not MCL cells.





4. Which of the following laboratory assessments can be used to detect the t(11;14)(q13;q32) chromosomal translocation in a lymph node biopsy?

A) Fluorescent in situ hybridisation (FISH)

B) Flow cytometry

C) Immunohistochemistry

D) Morphologic examination





4. Which of the following laboratory assessments can be used to detect the t(11;14)(q13;q32) chromosomal translocation in a lymph node biopsy?

A) Fluorescent in situ hybridisation (FISH)

B) Flow cytometry

C) Immunohistochemistry

D) Morphologic examination

A) FISH can be used to detect the t(11;14)(q13;q32) chromosomal translocation in a lymph node biopsy.





5. Which of the following is a differential diagnosis of MCL?

A) Chronic lymphocytic leukaemia (CLL)/Small lymphocytic lymphoma (SLL)

B) Follicular lymphoma (FL)

C) Marginal zone lymphoma (MZL)

D) All of the above





5. Which of the following is a differential diagnosis of MCL?

A) Chronic lymphocytic leukaemia (CLL)/Small lymphocytic lymphoma (SLL)

B) Follicular lymphoma (FL)

C) Marginal zone lymphoma (MZL)

D) All of the above

D) FL, MZL, and CLL/SLL are all differential diagnoses of MCL.



Glossary

Select the definition to return.



Antibody-antigen specificity

The special affinity between an antigen and its corresponding antibody.¹³

Aspirate

A small amount of fluid filled with blood cells removed from the central core of a bone used to diagnose blood disorders.⁶

Biopsy

A tissue sample collected from the body for examination, usually to establish a diagnosis.⁶

Cluster of differentiation (CD) protein

A protein marker on the surface of white blood cells that is used to classify immune cell types.⁶

Chromosomal translocation

A mutation involving the attachment of part of a chromosome to a different chromosome.¹⁴

Cyclin

A protein that activates CDK enzymes to regulate the progression of the cell cycle. Cyclin protein concentrations within the body fluctuate according to the cell cycle.¹⁴

Cytogenetics

The study of the structure and function of chromosomes.⁶

Fluorodeoxyglucose (FDG)

A fluorinated, radiographically visible glucose molecule used in positron emission tomography scanning to demonstrate glucose uptake in tissues.⁶

Immunophenotyping

Identification of the molecules on the surface of cells.⁶ A laboratory assay assessing immunophenotype may be used to diagnose and classify blood cell malignancies. Blood samples are analysed using predefined antibodies for each type of blood cell malignancy, including acute lymphocytic leukaemia, acute myeloid leukaemia, hairy cell leukaemia, B-cell lymphoma, and T-cell lymphoma.¹⁵

Ki67

An antigen whose expression is associated with cell proliferation.⁷

Lactate

A salt derived from lactic acid. Lactate is formed by muscle cells during strenuous exercise.⁶

Oxidase

Enzyme that catalyses an oxidation reaction.¹⁴

SOX11

A transcription factor that is not expressed in 14% to 32% of MCL cases. SOX11 positivity may be used to identify cyclin D1–negative MCL cases.^{1,2}



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