IGH-CCND1 Fusion, t(11;14) in Mantle Cell Lymphoma

Indications for Ordering

Diagnosis of mantle cell lymphoma (MCL) particularly when individual presents with
• Atypical morphology
• Aberrant immunophenotype
• Unusual clinical presentation
• Equivocal cyclin D1 staining

Test Description

Cyclin D1
• Immunohistochemistry

IGH-CCND1 Fusion, t(11;14) by FISH
• Fluorescence in-situ hybridization (FISH)
• Dual color, dual fusion probes detect t(11;14)

Tests to Consider

Typical testing strategy
Lymph node biopsy with morphologic and immunohistochemical evaluation
• Cyclin D1
  ○ Surrogate marker for t(11;14)
  ○ Present in 97% of MCL cases

Leukemia/lymphoma phenotyping by flow cytometry
• CD5+, CD10- in combination with bright CD20, CD23-, and high light-chain intensity suggests MCL

Detect cytogenetic abnormalities, if necessary
• IGH-CCND1 fusion, t(11;14) by FISH

Bone marrow (BM) evaluation for staging
Chromosome analysis – sometimes necessary

Primary tests
Cyclin D1, SP4 by Immunohistochemistry 2003842
• Diagnosis of MCL in conjunction with morphology and immunohistochemical studies
• Formalin-fixed, paraffin-embedded (FFPE) tissue specimens only

IGH-CCND1 Fusion, t(11;14) by FISH 2007226
• Aid in diagnosis of MCL if cyclin testing is noninformative
• FFPE tissue specimens

Related tests
Leukemia/Lymphoma Phenotyping by Flow Cytometry 2008003
• Aid in evaluation of hematopoietic neoplasms
• Monitor therapy in patients with established diagnosis of hematopoietic neoplasms

Chromosome FISH, Interphase 2002298
• Specific FISH probe for t(11;14)(q13;q32) must be requested
• Fresh tissue specimens only

Chromosome Analysis, Bone Marrow 2002292
• Diagnosis, prognosis, and monitoring of hematopoietic neoplasms (eg, lymphoma in BM)

Chromosome Analysis, Solid Tumor 2002296
• May identify additional, useful cytogenetic abnormalities in tissues that are not targeted by FISH assays

Disease Overview

Incidence – 3-10% of all non-Hodgkin B-cell lymphomas

Symptoms
• Majority present at advanced stage
• Lymphadenopathy – usually widespread
• Extranodal sites most commonly include
  ○ Gastrointestinal tract
  ○ Waldeyer’s ring

Diagnostic criteria
• Morphology
  ○ Small- to medium-sized lymphoid cells with irregular nuclear contours (centrocyte-like) with dispersed chromatin and inconspicuous nuclei
  ○ Nodular, diffuse, mantle zone pattern has been described
  ○ Associated hyalinized small vessels are common

• Flow cytometry immunoprofile
  ○ Bright CD20, monoclonal light chains, CD5+, CD10-, CD23-

• Immunohistochemistry
  ○ Cyclin D1 expression is present in the majority of cases
Diagnostic issues
MCL is often diagnosed using combination of morphology, immunohistochemistry (cyclin D1), immunophenotyping, and clinical presentation
• Variants of MCL (small cell, marginal-zone-like) that phenotypically resemble other non-Hodgkin lymphomas, such as CLL/SLL may present problems for diagnosis in atypical cases
  o IGH-CCND1 fusion, t(11;14) FISH testing most useful in this setting

Genetics
Gene – IGH-CCND1
Structure/function
• The translocation juxtaposes the CCND1 gene located on the long arm of chromosome 11 (q13) with the IGH gene located on the long arm of chromosome 14 (q32)
• IGH-CCND1 fusion causes overexpression of cyclin D1
  o Overexpression is oncogenic and defines disease
• Cyclin D1 promotes cell division and growth

Test Interpretation
IGH-CCND1 Fusion, t(11;14) by FISH
Sensitivity
• Analytical sensitivity – 20%
Results
• Positive – presence of the t(11;14) translocation supports a diagnosis of MCL
• Negative – absence of the t(11;14) translocation
Limitations
• IGH-CCND1 Fusion, t(11;14) by FISH has not been validated for
  o Tissue fixed in alcohol-based or nonformalin fixatives
  o Decalcified tissue
• Negative result does not exclude the possibility of translocations involving other partners
• Variant is not specific for MCL
  o Results need to be analyzed in conjunction with morphology, immunohistochemistry, and immunophenotyping results