IGH-CCND1 Fusion, t(11;14) by FISH

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

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- 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 3001306
- Aid in diagnosis of MCL if cyclin testing is noninformative
- FFPE tissue specimens

Related Tests

Leukemia/Lymphoma Phenotyping by Flow Cytometry 3001780
- 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 chronic lymphocytic leukemia/small lymphocytic lymphoma may present problems for diagnosis in atypical cases
  - *IGH-CCND1* fusion, t(11;14) FISH testing is 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
  - 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
  - Tissue fixed in alcohol-based or nonformalin fixatives
  - Decalcified tissue
- Negative result does not exclude the possibility of translocations involving other partners
- Variant is not specific for MCL
  - Results need to be analyzed in conjunction with morphology, immunohistochemistry, and immunophenotyping results