

IgH-CCND1 by FISH on Formalin-Fixed, Paraffin-Embedded Tissue

DETECTION OF IGH-CCND1 GENE TRANSLOCATION T(11;14) FOR THE DIAGNOSIS OF MANTLE CELL LYMPHOMA BY FLUORESCENT IN SITU HYBRIDIZATION (FISH)

Test Highlights

- FISH analysis provides an analytically more sensitive detection of the t(11;14) gene translocation necessary for the diagnosis of mantle cell lymphoma than the traditional methodologies of conventional cytogenetics or PCR analysis for the translocation.

Disease Overview

Mantle cell lymphoma is a non-Hodgkin lymphoma that originates from malignant B-lymphocytes normally residing in the mantle zone or outer edge of the B-cell follicle. The neoplastic lymphocytes are small in size and have a monoclonal mature B-cell phenotype with co-expression of CD5. Mantle cell lymphoma is highly associated with the specific translocation t(11;14), which causes the over-expression of cyclin D1. Demonstration of cyclin D1 over-expression by immunohistochemistry or the t(11;14) by molecular or cytogenetics methods is essential in making a definitive diagnosis of mantle cell lymphoma. It is also important to identify mantle cell lymphoma and differentiate it from other small B-cell lymphomas that co-express CD5 (such as chronic lymphocytic leukemia/small lymphocytic lymphoma), as mantle cell lymphoma has a much more aggressive clinical course and requires a more aggressive treatment approach.

Epidemiology

Mantle cell lymphoma is an uncommon neoplasm representing about 3–10 percent of all non-Hodgkin lymphomas, with approximately 3,300 new cases diagnosed each year in the United States. It is more common in males and in the elderly population (median age: 58 years old). Both nodal and extranodal (particularly gastrointestinal tract and Waldeyer's ring) disease is seen. Most patients will present with widespread (stage III or IV) disease.

Genetics

Mantle cell lymphoma is strongly associated with a specific translocation, t(11;14)(q13;q32), which juxtaposes the immunoglobulin heavy chain and the cyclin D1 (PRAD-1 or bcl-1) genes leading to over-expression of cyclin D1. A small number of cases may have genetic changes leading to over-expression of other cyclins as an underlying pathogenetic mechanism.

Pathophysiology

The exact cause of mantle cell lymphoma is not known. It is known that most neoplasms result from acquired damage to DNA in the gene(s) of a cell, resulting in malignancy. Most patients with mantle cell lymphoma have an acquired genetic alteration known

as t(11;14) that leads to over-expression of the cyclin D1 protein, which increases the rate of cell division and growth. The distinction of mantle cell lymphoma from other B-cell lymphomas is important and provides prognostic and therapeutically relevant information.

Indications for Ordering

- Diagnosis or suspicion of mantle cell lymphoma from morphology or immunophenotypic studies.
- Non-Hodgkin lymphoma with equivocal or uninterpretable immunophenotyping.

Contraindications

This test is not recommended for detection of minimal residual disease.

Additional Ordering Notes

The biopsy site and fixative used should be provided. The submitted sample should contain sufficient viable tumor.

Interpretation

- Presence of IgH-CCND1 [t(11;14)] translocation is strongly supportive of a diagnosis of mantle cell lymphoma in samples with appropriate morphologic and immunophenotypic features.
- A negative result does not rule out mantle cell lymphoma, since a small percentage of patients may have alternative translocations leading to development of mantle cell lymphoma.

Limitations

Tissues fixed in alcohol-based or non-formalin fixatives have not been tested using this method.

Methodology

The detection of IgH-CCND1 translocation [t(11;14)] in formalin-fixed, paraffin-embedded tissue uses a commercially available DNA FISH probe. FISH is a technique that utilizes fluorescently labeled DNA probes to ascertain the status of specific DNA sequences within the genome. The FISH methodology for recognition of the IgH-CCND1 gene translocation utilizes a SpectrumGreen-labeled IgH probe and a SpectrumOrange-labeled CCND1/MYEOV probe. This test is conducted by noting the probe signal configuration within the nuclei and reporting the result as translocated or normal.

References

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3. Campo E. Genetic and molecular genetic studies in the diagnosis of B-cell lymphomas I: mantle cell lymphoma, follicular lymphoma, and Burkitt's lymphoma. *Hum Pathol* 2003;34:330–5.
4. Frater JL, Hsi ED. Properties of the mantle cell and mantle cell lymphoma. *Curr Opin Hematol* 2002;9:56–62.
5. Lai R, Medeiros LJ. Pathologic diagnosis of mantle cell lymphoma. *Clin Lymphoma* 2000;1(3):197–206;discussion: 207–8.
6. Swerdlow SH. Small B-cell lymphomas of the lymph nodes and spleen: practical insights to diagnosis and pathogenesis. *Mod Pathol* 1999;12:125–40.
7. Torlakovic E, Nielsen S, Vyberg M. Antibody selection in immunohistochemical detection of cyclin D1 in mantle cell lymphoma. *Am J Clin Pathol* 2005;124(5):782–9.
8. Package insert. Vysis® LSI IGH/CCND1-XT Dual Color, Dual Fusion Translocation Probe.

Test Information

0049381

t(11;14) IgH-CCND1 Translocation by FISH

For specific collection, transport, and testing information, refer to the ARUP Web site at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.