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Mark E. Sobel, MD, PhD, Director of Journal CME Programs

CME January Questions # 1-8

Three articles (on molecular profiling of aggressive B-cell lymphomas, DNA minimal residual disease (MRD) markers in neuroblastoma, and a high-resolution melting (HRM) curve screening test for SRSF2 mutations in myelodysplastic syndromes) were selected for the January 2015 JMD CME Program in Molecular Diagnostics. The authors of the referenced articles, the planning committee members, and staff have no relevant financial relationships with commercial interests to disclose.


Upon completion of this month’s journal-based CME activity, you will be able to:

- Define Burkitt lymphoma (BL) and diffuse large B-cell lymphoma (DLBCL).
- Understand the genetics of BL and DLBCL.
- Describe B-cell lymphoma unclassifiable (BCL-U).
- Understand the characteristics of neuroblastoma.
- Describe qPCR-based minimal residual disease (MRD) detection.
- Define SRSF2.
- Describe the frequency of SRSF2 mutations in different disorders.
- Define the SRSF2 hotspot.

1. Burkitt lymphoma (BL) and diffuse large B-cell lymphoma (DLBCL) are aggressive tumors of mature B cells that are distinguished by a combination of histomorphologic, phenotypic, and genetic features. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2015, 17:19-30.]

   a. The World Health Organization (WHO) classification of tumors defines neoplastic diseases according to unique clinical and biological characteristics.
   b. The reliable differentiation of BL from DLBCL is important, because these tumors are treated with distinct chemotherapeutic regimens.
   c. BL is a neoplasm composed of monomorphic, intermediate-sized lymphocytes that are positive for markers of mature, germinal-center B cells and negative for the anti-apoptotic protein BCL2.
   d. Some BL cells (<60%) are positive for the proliferation marker Ki-67/MIB1.
2. BL and DLBCL are aggressive tumors of mature B cells categorized as individual tumor types. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2015, 17:19-30.]

a. The genetic hallmark of BL is a balanced translocation involving the MYC oncogene and the immunoglobulin heavy chain locus (IGH).

b. Mutations in TCF3 and ID3 are common in BL.

c. DLBCL is composed of pleomorphic, small lymphoid cells and, in general, increased apoptosis and a higher proliferation index than BL.

d. DLBCLs express markers of mature B cells, with or without evidence of germinal center cell derivation, and often express BCL2.

3. A subset of B-cell lymphomas has one or more characteristics that overlap BL and DLBCL, and are categorized as B-cell lymphoma unclassifiable (BCL-U). Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2015, 17:19-30.]

a. Most cases of BL and DLBCL are diagnosed with high confidence using traditional histopathological, immunophenotypic, and targeted genetic analysis.

b. The 2008 WHO Classification of Lymphoid Tumors recognized cases with the novel diagnostic category, BCL-U, as having features intermediate between DLBCL and BL.

c. BCL-U is, by definition, a heterogeneous group, and its diagnosis requires that pathologists make subtle distinctions in histomorphological features, immunophenotype, and genetics that may not be highly reproducible.

d. High co-expression of MYC and TCF3 in tumor cells provides a biological basis for the inferior outcome among patients with the activated B-cell (ABC) type BL when treated with standard chemotherapy.

4. Neuroblastoma is an extracranial solid tumor of childhood, with a broad spectrum of clinical behavior. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2015, 17:43-52.]

a. Despite intensive treatment, high-risk neuroblastoma patients have a poor prognosis, and relapse is a frequent occurrence.

b. Bone marrow (BM) metastases are present in approximately 80% of patients at diagnosis.

c. Quantitative real-time PCR (qPCR) is a sensitive technique to detect small numbers of tumor cells in blood or BM.

d. qPCR-based minimal residual disease (MRD) detection is based on neuroblastoma-specific RNA markers.

5. RNA MRD markers can have disadvantages. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2015, 17:43-52.]

a. The MRD level might be overestimated by using RNA markers.

b. The expression of RNA markers can vary between patients.

c. It is unknown whether RNA markers are stably expressed during treatment.

d. Only paired-like homeobox 2b (PHOX2B) has no expression in hematologic cells.

6. Somatic mutations of the spliceosome machinery have been identified using whole genome analysis in several hematologic diseases and solid tumors. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2015, 17: 85-89.]

a. SRSF2 is a member of the serine/arginine-rich family pre-mRNA splicing factors that is involved in mRNA export from the nucleus and translation.

b. Besides the RNA recognition domain, the SRSF2 protein contains a serine/arginine-rich domain that promotes interaction with other splicing factors.

c. SRSF2 constitutes a critical player in the process of mRNA splicing.

d. The SRSF2 gene is located on the short arm of chromosome 9 subregion 14.2.

7. SRSF2 mutations have been described in several hematologic disorders. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2015, 17: 85-89.]

a. In one study, SRSF2 mutations were detected in 5.5% of refractory anemia with ringed sideroblasts and refractory cytopenia with multilineage dysplasia with ringed sideroblasts.

b. SRSF2 mutations were detected in 28.4% of chronic myelomonocytic leukemias (CMMLs) in one report, whereas another report identified the mutations in nearly half of the cases.

c. A total of 13.3% of SRSF2 mutations have been found in acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS).

d. SRSF2 mutations have been detected in 0.7% de novo AML and in 1.9% of myeloproliferative neoplasms.
8. Most \textit{SRSF2} mutations are located at the amino acid position P95. Based on the referenced article, select the ONE statement that is NOT true: [See J Mol Diagn 2015, 17: 85-89.]

- a. The hotspot localization at P95 corresponds to exon 4 of the \textit{SRSF2} gene.
- b. Most P95 mutations are missense in which proline is substituted by histidine (47.5%), leucine (31.6%), arginine (19.2%), or rarely, alanine or threonine.
- c. In primary myelofibrosis, \textit{SRSF2} monoallelic mutations were reported in 32 of 187 patients, affecting residue P95.
- d. \textit{SRSF2} mutations are significantly associated with advanced age, high-risk category, and worse prognostic outcome compared with nonmutated primary myelofibrosis.