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Editorial

Annual Masquerade of San Diego Hematopathological Celebrities

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Editorial

Nonentity is as glamorous as the Academy Awards ceremony held every year in the "City of Angels". Just 120 miles south to Los Angeles, nothing is as celebrated to the hematopathologists as the Annual Meeting of the San Diego Society of Hematopathology (SDSH). The inaugural SDSH Annual Meeting and CME Activity was called to order at 8:05 AM on November 2, 2013, themed with Lymphoma and Myelodysplasia and featured by two keynote lectures given by Dr. Jonathan Said, Professor and Director of Anatomic Pathology at the University of California Los Angeles, and Dr. Rafael Bejar, Assistant Professor/Physician Scientist at the University of California San Diego (UCSD) Moores Cancer Center. Several local hematopathologists also presented their outstanding works to the audience from all the major pathological institutions of San Diego and Southern California. The morning session focused on the challenges in the diagnosis of malignant lymphomas and histiocytic neoplasms, while the afternoon session probed the molecular discoveries of myelodysplasias. Several celebrated hematopathological entities walked down the "red carpet". This article intends to briefly summarize this one day event.

Malignant Lymphomas and Histiocytic Neoplasms

"Burkitt lymphoma and MYC: what else is new?" vividly described the discovery of Burkitt Lymphoma (BL) by Dr. Denis P. Burkitt and reviewed the milestones in the history of Burkitt lymphoma/leukemia. From the epidemiology to the molecular etiology, EBV had played a major role in the development of Burkitt Lymphoma particularly in the endemic clinical variants. As the most common non-Hodgkin lymphoma in children, adolescents, and adults older than 60 years, BL and the absolute number of BL cases in adults exceeds those in childhood. BL is described as a monomorphic proliferation of medium sized transformed B-cells with round nuclei, clumped chromatin, basophilic cytoplasm, and squared off cell borders, cytoplasmic vacuoles, medium sized paracentral nucleoli, and a starry sky pattern. Translocation involving MYC is characteristic but not specific for Burkitt lymphoma. No single parameter is the gold standard for diagnosis; morphology, cytogenetics, immune phenotype, and gene expression profiles all may contribute to the diagnosis. Dr. Said not only presented the MYC-negative BL, but also discussed other lymphomas with MYC rearrangement. His work suggests that when we encounter a lymphoma with high proliferative index we should always rule out MYC rearrangements. While neither EBV nor MYC are sufficient to cause BL there is increasing information from techniques such as complete RNA sequencing that identify essential pathways that are activated in the pathogenesis of BL. These findings suggest novel opportunities for improving therapeutic intervention.

Mantle Cell Lymphoma (MCL), the most aggressive small B-cell lymphoma, was also the hot topic of this meeting. Dr. Arash Mohtashamian from the San Diego Naval Medical Center presented his research on the minimal residual disease detection in MCL. He gave a thorough review of the past studies on MCL and identified the important molecular biomarkers for the detection of MCL minimal residual disease. He compared several currently used methods in the detection of MCL minimal residual diseases: consensus PCR, real time quantitative PCR, and flow cytometry. With known genetic abnormalities, real time quantitative PCR is the most sensitive and reliable assay. Flow cytometry may be the simpler approach for detecting minimal residual diseases.

Histiocytic and dendritic cell neoplasms are among the rarest tumors of the lymphoid tissue. This group of neoplasms originates from either CD34+ myeloid stem cells, such as histiocytic sarcoma, Langerhans cell neoplasms (Langerhans cell histiocytosis and Langerhans cell sarcoma), interdigitating dendritic cell sarcoma, and blastic plasmacytoid dendritic cell neoplasm, or mesenchymal stem cells, such as follicular dendritic cell sarcoma. With cases of his own and others, Dr. Huan-You Wang of UCSD Hemato pathology Program presented a complete review of all categories of histiocytic and dendritic cell neoplasms outlined by the 2008 WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues. He also updated the new concept of so-called "trans differentiation" used by Andrew Feldman et al. in their publication of 8 cases of patients who have both follicular lymphoma and histiocytic/dendritic cell neoplasms [1]. By employing FISH and molecular tools such as PCR and DNA sequencing, they have convincingly shown that at least some of the histiocytic/dendritic cell neoplasms have a common origin with follicular lymphoma. In fact, this concept has been extended into other histiocytic/dendritic cell neoplasms and mature as well as immature B- and T-cell lymphomas and leukemias. For example, between Langerhans cell histiocytosis and T-acute

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lymphoblastic leukemia, histiocytic/dendritic cell neoplasms and chronic lymphocytic leukemia/small lymphocytic lymphoma, and recently between Langerhans cell sarcoma and follicular lymphoma. It is safe to say that histiocytic/dendritic cell neoplasms have a common cellular origin with a spectrum of B- and T-cell lymphomas or leukemias. These findings are significant in that they not only shed more light on molecular/genetic mechanism in terms of pathogenesis, but also provide guidance to daily diagnostic practices in that a concurrent B-cell lymphoma needs to be excluded at the time of histiocytic/dendritic cell neoplasm diagnosis.

Molecular Aspects of Myelodysplasia and Related Neoplasms

Myelodysplastic syndrome (MDS) and other myeloid neoplasms with dysplastic features comprise a heterogeneous group of hematopoietic malignancies. Since there are so many mimics of myelodysplasia, the diagnosis has to be made in the proper context of other factors, such as infection, lack of nutrition and exposure to toxins or drugs. Dr. Elizabeth Broome summarized all the possible factors that could lead to a misdiagnosis of myelodysplasia which include copper deficiency, vitamin 12 deficiency, alcohol consumptions, lead toxicity, isoniazid and arsenic therapy, etc.

The current WHO classification (2008) relies heavily on morphologic findings and chromosomal abnormalities. In the past several years, with the wide availability of next generation sequencing, tremendous insights has been obtained about molecular genetics of MDS and related diseases. Dr. Rafael Bejar, a pioneer in this field, provides an excellent summary of those findings. It has been shown approximately 80% of all MDS cases have one or more mutations detected, which is more common than known chromosomal abnormalities. The most commonly affected genes fall into several categories: epigenetic regulation (TET2, DNMT3A, ASXL1, etc), transcription factors (RUNX1, ETV6, PHF6, etc), tyrosine kinase pathway (NRAS, JAK2, CBL, etc), splicing regulation (SF3B1, SRSF2, U2AF1, etc) and tumor suppressors and other (TP53, NPM1, etc). During his presentation, Dr. Bejar also reviewed different prognostic scoring systems for MDS and their advantages and limitations, including IPSS (International Prognostic Scoring System), LR-PSS (Lower-Risk MD Anderson Prognostic Scoring System) and IPSS-R (the Revised International Prognostic Scoring System).

While the molecular data are accumulating with a fast pace, physicians are facing some challenges in terms of how to interpret the genetic data. Multiple mutations are often seen in one case. Most mutations detected are in single digit percentage or less. Different type of mutations could have drastically distinct biologic consequences (missense vs nonsense mutations). Regarding frequencies of mutant allele, the data show more of spectral distribution than binary distribution. This observation might reflect that there are many different status of the mutant clone (dominant clones vs subclones). Even more complicated, it remains an open question how to incorporate all these variables with distinct clinical presentation of each individual patient.

There is strong evidence showing mutations of important genes have prognostic values. For example, Papaemmanuil et al showed leukemia-free survival inversely correlated with the numbers of driver mutations [2]. Another example is TP53 mutation, which is known to associate with adverse prognosis. Recent data showed the adverse prognosis associated with complex karyotype is accounted for by TP53 mutation instead. The new knowledge of genetic mutations of MDS could have the following applications in the future: 1) new classification of MDS; 2) being incorporated into prognostic scoring systems; 3) monitoring therapeutic response; 4) identifying "adverse subclones" and monitoring minimal residual disease. Clinical access to many MDS and AML related mutations are available at UCSD.

Recurrent mutations of multiple splicing factors were recently found in significant portion of myeloid neoplasm with dysplasia. This topic is discussed by both Dr. Bejar and Dr. Xu. The mutated splicing factors are seen in approximately one third of all myeloid neoplasms with dysplasia. The mutated genes include SF3B1, SRSF2 (or SC35), ZRSR2, U2AF35 (U2AF1), SF3A1, PRPF40B, U2AF65, SF1. Some of the mutants have high prevalence and strong association in subtypes of MDS. For example, approximately three fourths of MDS with ring sideroblasts are positive for SF3B1 mutation. Another example is SRSF2 or SC35, which is seen in 28% of chronic myelomonocytic leukemias. Interestingly, most of the mutated factors have functions in recognition the 3' splice site during splicing processing and show a mutually exclusive pattern. More studies are needed to understand the potential role of those factors in MDS pathogenesis, their prognostic values in individual diseases and clinical applications.

Integrating Molecular Pathology to Hematopathology Practice

With more and more emerging genetic data and molecular studies associated with the hematological diseases, it remains a challenge to integrate those data and studies into our routine diagnosis. Dr. Ryan Phan using his experience updated us with all the available genetic and molecular assays, critically analyzed all the molecular assays commonly used in the diagnosis of hematological diseases, described how to integrate the data from molecular studies into our clinicalpractice,and pointed out the limitations and interpretation pitfalls. Although he articulated the importance of molecular studies in hematopathology, Dr. Phan stressed that "molecular/cytogenetic analyses must be interpreted in clinical and pathological context".

The SDSH holds symposium and CME activity at least once a year, which is joined by the SDSH members and the pathologists of Greater San Diego and Southern California. This meeting provides an opportunity for both academic and community pathologists with interests in hematopathology to network, exchange ideas, and promote the advancement of hematopathology in San Diego and Southern California.

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