This January 2020 issue of Clinical Cytometry B includes 7 original articles, 2 brief communications, 1 review, and 1 letter to the editor.

The issue is predominated by original study articles in hematolymphoid malignancies

Wang and colleagues (1) reported a large series of extranodal NK/T cell lymphoma, nasal type (ENKTL-N) from the west part of China. The authors showed that flow cytometry immunophenotyping not only could assist in diagnosis but also discriminate cellular lineages (NK- vs T-), evaluate activation status of NK-cells, and assess potential therapy targets of ENKTL-N. Through thorough characterization, the authors identified a number of immunophenotypical characteristics facilitating a ready distinction of ENKTL-N from reactive NK/T cells. We have longed for a simple straightforward T cell clonality assessment, reminiscent Kappa/Lambda for B cell clonality. Currently, TCR \( V_\beta \) repertoire analysis by flow cytometry (2–4) uses 24 antibodies recognizing 70% \( V_\beta \) repertoires, which is labor-intensive, costly, and with limited sensitivity. Shi and colleagues (5) from Mayo Clinic reported their experience in using single anti-TRBC1 antibody for TCR \( \beta \) clonality assessment. The authors showed that all 20 T-cell malignancies (TCR\( \beta \)) exhibited a monophasic TRBC1 expression (100% sensitivity); whereas, 44 patients without T-cell malignancies showed an expected mixture of TRBC1-positive and TRBC1-negative subpopulations (non-clonal). The use of single antibody TRBC1 allows the integration of clonality assessment with immunophenotyping, together, hopefully provides a simple, rapid and reliable method in the detection of T-cell neoplasms. T-cell/histiocyte rich large B cell lymphoma (THRLBCL) is a large B cell lymphoma with rare neoplastic B-cells embedded in a reactive infiltrate that conventional flow cytometry is unable to detect B-lymphoma cells. For the first time, Glynn and colleagues (6) characterized the immunophenotype of lymphoma cells in THRLBCL through flow cytometric cell sorting technology. CD40, CD50 and CD54 were found over-expressed, likely contributing to the predominance of \( T \)-cells in THRLBCL. Cherian et al (7) previously reported frequent CD3+CD4+CD7-bright/CD45-bright T-cell subpopulations in primary mediastinal large B cell lymphoma (PMLBCL). In the letter to editor, Gadgeel and colleagues (8) communicated their observation of CD20+ \( T \) cells in two cases of PMLBCL. CD20+ T cells with highly activated Th17 cells that may contribute to the PMLBCL microenvironment. Apparently, atypical T-cell proliferation is common in PMLBCL, and it is important not to misinterpret as T cell lymphoma.

There are two studies on bone marrow (BM) hematogones (immature precursor B cells) in this issue. Daratumumab is an IgG1-kappa monoclonal antibody that targets CD38, which has obtained FDA approval for refractory myeloma patients, and recently as frontline therapy in combination with bortezomib, melphalan and prednisone for patients ineligible for transplant (9). Due to bright CD38 expression on hematogones, artifactual kappa light chain restriction was observed, and the findings were summarized in the study by Jiang and coauthors (10). Kappa-restricted CD10+ hematogones might result in a false interpretation of a concurrent clonal B cell proliferation. In the era of rapidly growing list of therapeutic monoclonal antibodies, diagnosticians should be aware of potential interferences. On the other hand, hematogones are often markedly decreased or completely absent in the BMs of patients with myelodysplastic syndromes (MDS) (11), and the finding is considered as an important feature for MDS by flow cytometry immunophenotyping. However, preservation of hematogones is observed in some cases of MDS; have you ever wondered if it has any clinical and biological significance? Chen and colleagues (12) studied 160 treatment naïve low grade MDS and reported the perseverance of stage I hematogones in over a quarter of the patients. This biological phenomenon was associated with MDS with

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ring sideroblasts, MDS with no somatic mutation and a favorable prognosis in multivariate analysis. So watch out for hematogones in MDS!

There are two studies on B-lymphoblastic leukemia (B-ALL). For B-ALL patients undergoing allogeneic stem cell transplant (SCT), minimal residual disease (MRD) at pre- or post- SCT has been known to be associated with risk of relapse. Wang and colleagues (13) reported their experience in pediatric B-ALL patients who received haploidentical SCT. They showed that not only pre- or post- but also peri-SCT MRD dynamics, were associated with cumulative incidences of relapse. Based on their findings, they suggest to stratify patients into different risk groups based on peri-transplant MRD kinetics rather than single MRD status. As we all know that one of the disadvantages of flow cytometry in B-ALL MRD detection was a lower sensitivity (0.01%) compared with allele-specific oligonucleotide PCR or next generation sequencing assay (0.001% to 0.0001%). Although the current standard of care is based on a MRD level of 0.01%, it has been shown that lower levels of the MRD (<0.01%) or deeper responses can further stratify risk groups based on peri-transplant MRD kinetics rather than single MRD status. As we all know that one of the disadvantages of flow cytometry in B-ALL MRD detection was a lower sensitivity (0.01%) compared with allele-specific oligonucleotide PCR or next generation sequencing assay (0.001% to 0.0001%). Although the current standard of care is based on a MRD level of 0.01%, it has been shown that lower levels of the MRD (<0.01%) or deeper responses can further stratify relapse risk in childhood ALL, emphasizing the need of MRD techniques with higher sensitivity (14). Tenthrab and colleagues (15) showed that a higher flow cytometry sensitivity (0.0002%) could be easily achieved with a 10-color MRD assay using bulk red cell lysis and acquiring a large number of events (medium 4 million events). The sensitivity was closely related to the events acquired; in fact, they found a 52% and 21.3% false MRD-negative rate in samples with only 500,000 events and 1,000,000 events acquired respectively.

Recently, a unique phenotype, the “RAM phenotype” (16), was described and reported to associate with a poor prognosis within the Children’s Oncology Group (COG) trial AAML0531. A high intensity of CD56 expression was one of the major characteristics of the RAM phenotype. Pedro and coauthors (17) expanded the study on CD56+ AML of the same AAML0531 trial. CD56+ AML was found to cluster with three distinct genotypes of AML, each having a different patient outcome. Plasmacytoid dendritic cells (PDCs) share a common progenitor with monocytic/myeloid cells. Neoplastic cells derived from PDCs, in addition to the well-known blastic plasmacytoid dendritic cell neoplasm (BPDCN), have been known to be associated with various myeloid neoplasms (18), such as chronic myelomonocytic leukemia, rare cases of AML with monocytic differentiation and MDS (19). Hamadeh and colleagues (20) described a third type of PDC proliferation in association with acute leukemia. The blasts exhibited immature markers, but a subset showing a PDC immunophenotype. This type acute leukemia was morphologically indistinguishable from other AML and all had an aggressive clinical course. The authors suggested that these AML should be recognized as AML with PDC differentiation.

Neurotuberculosis (nTB) is one of the commonest HIV associated opportunistic infections of the central nervous system in India, which can lead to markedly altered frequencies of T cell subsets in the study by Rao and colleagues (21). HIV+nTB+ patients were found to have high activation and senescence in the CD8 T cell population and memory subsets, which might influence to the course and progression of the disease.

These are excellent articles with exciting findings and practical, useful tips-enjoy!


